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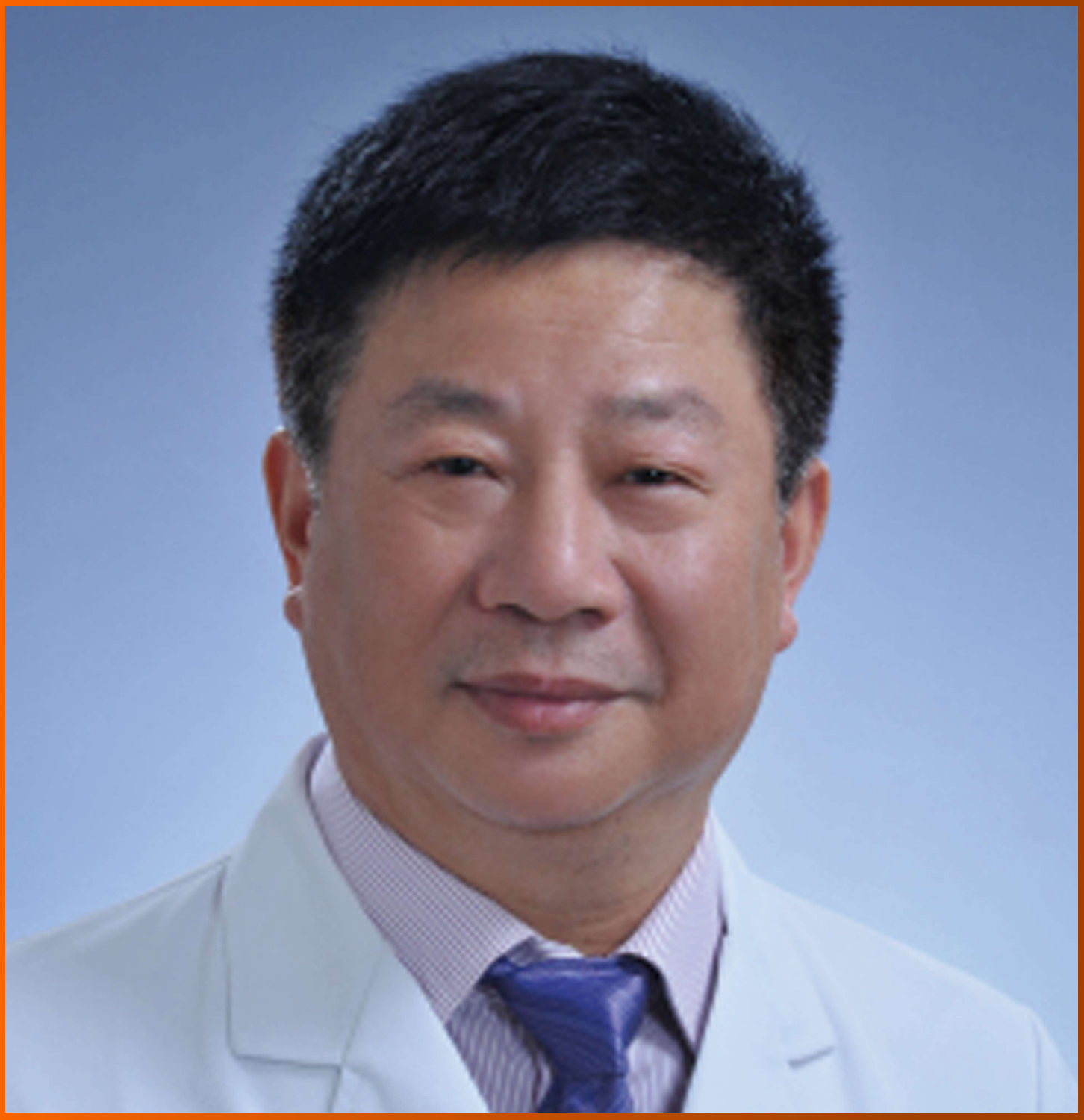

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Contents

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REVIEW

Role of endoscopy in management of gastrointestinal complications of portal hypertension

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Abstract

The management of patients with gastrointestinal complications of portal hypertension is often complex and challenging. The endoscopy plays an important role in the management of these patients. The role of endoscopy is both diagnostic and interventional and in the last years the techniques have undergone a rapid expansion with the advent of different and novel endoscopic modalities, with consequent improvement of investigation and treatment of these patients. The choice of best therapeutic strategy depends on many factors: baseline disease, patient's clinical performance and the timing when it is done if in emergency or a prophylactic approaches. In this review we evaluate the endoscopic management of patients with the gastrointestinal complications of portal hypertension.

Key words: Portal hypertension; Gastrointestinal complications; Bleeding; Esophageal varices; Gastric varices

Core tip: Endoscopy plays a primary role in the staging, diagnosis and treatment of gastrointestinal complications of portal hypertension. In this review, we summarize data from randomized clinical trials or prospective studies together with meta-analytical data, when applicable, to present the most updated recommendations on endoscopic management of the gastrointestinal complications of portal hypertension.

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INTRODUCTION

Portal hypertension is defined as a pathologic increase in portal vein to inferior vena cava pressure gradient greater than 5 mmHg. According to anatomic location,

the diseases causing portal hypertension are classified as pre-hepatic if involve portal, splenic or mesenteric veins, intra-hepatic if cause acute or chronic liver diseases, and post-hepatic if interfere with the venous outflow of the liver. The most prevalent cause of portal hypertension is liver cirrhosis with greater resistance to portal flow. Hepatic venous pressure gradient (HVPG) is an indirect measurement of portal hypertension which is obtained by placing a catheter in the hepatic vein or by occluding a large branch of hepatic vein by inflating a balloon. Portal hypertension likely causes the development of varices and hemodynamic and mucosal changes in the entire gastrointestinal (GI) tract. Varices are present in the 50% of cirrhotic patients[1-4]. Bleeding occurs in approximately 5%-15% of patients, depends on the size of varices. Other predictors of bleeding may be the presence of red wale mark and decompensated cirrhosis[5]. The variceal bleeding mortality is around 20% at 6 wk despite improvement in therapy over the last decade thanks to the development of endoscopical and pharmacological therapies and antibiotic prophylaxis[6-8].

In the patients with portal hypertension the gut mucosa undergoes microcirculatory changes, such as submucosal angiogenesis and vascular ectasia, that impair its integrity and promote its susceptibility to damage. Stomach changes can cause bleeding [portal hypertensive gastropathy (PHG)], usually the involvement of small bowel is asymptomatic (portal hypertensive enteropathy), but sometimes can cause occult blood loss, finally colon involvement (portal hypertensive colopathy) is often associated with bleeding and the symptoms are similar to inflammatory bowel disease[9].

The aim of this paper is to review the interventional and diagnostic role of endoscopy in patients with GI complications of portal hypertension.

ESOPHAGEAL VARICES

Primary prophylaxis

The goal of primary prophylaxis is to prevent first bleeding episode and consequently improve survival through decreasing bleeding-related death. All cirrhotic patients should be screened for varices through endoscopy to detect the patients that need a prophylactic treatment[10,11]. The Child-Pugh (C-P) score suggests that risk factors of bleeding are the presence of red wale marks, the size of varices and the liver disease severity[5].

Typically, one of two approaches is used for primary prophylaxis: pharmacologic prophylaxis using a non-selective beta-adrenergic blockers (NSBBs) or with endoscopic band ligation (EBL).

EBL consists in the placement of rubber rings on variceal columns which are sucked into a plastic hollow cylinder attached to the tip of the endoscope. Endoscopic ligation causes occlusion of the varix and then thrombosis with ischemic necrosis of the mucosa. Multiple-shot devices have largely replaced the original single-shot ligators, since the procedure is much simpler and faster with multi shot devices. Endoscopic variceal ligation is associated with complications such as hemorrhage, chest pain, dysphagia, and odynophagia and ulceration of the mucosa. There are only few studies that have evaluated the risk of bleeding from ligation-induced ulcers. Schepke *et al*[12] found that the incidence of bleeding from ligation ulcers after EBL was 6.7%. Another retrospective data analysis of EBL described hemorrhage from ligation ulcers as 5.7%, irrespective of the indication[13]. Endoscopic variceal ligation sessions are usually repeated at 1-2 wk intervals until complete obliteration[11]. A randomized, controlled trial of bimonthly *vs* biweekly EBL (primary and secondary prophylaxis) found that EBL bimonthly had a higher total eradication rate, lower recurrence rate, and lower rate of additional treatment than biweekly EBL and that the patients treated bi-monthly showed better ulceration healing in the second and third treatments than the patients treated bi-weekly[14]. This approach may decrease the risk of bleeding or perforation.

NSBBs can be used in patients that present cirrhosis, small varices and risk of bleeding according to C-P score[10,11]. It's known that patients with small varices with red signs on its wall or with C-P score class C, have the same risk of bleeding of patients with large varices[5]. In patients with medium/large varices either NSBBs or EBL are an appropriate choice for primary prophylaxis of bleeding[10,11]. A systematic review of 11 randomized controlled trials (RCTs) about prevention of variceal hemorrhage,has compared NSBBs with placebo or non active treatment, and has shown a 9% absolute risk reduction of first variceal bleeding at two years[15]. A significant reduction in mortality was also seen with NSBBs use[16]. The use of NSBBs is limited by their side-effect profile, which includes hypotension, fatigue, lethargy, depression, and dyspnea in patients with associated pulmonary disease. Around 15%-20% of patients suffer from intolerable side effects that require discontinuation of the drug[17].

A meta-analysis of 5 trials comparing prophylactic EBL with controls found that EBL decreases the risk of variceal hemorrhage and the mortality related to hemorrhage[18]. The treatment choice is based on patient preference, local resources and side effects[10]. A Cochrane meta-analysis that included 19 RCTs, has compared prophylactic EBL with NSBBs and has shown a slight beneficial effect for EBL, without different bleeding-related mortality in the two arms[19].

Evolving data suggest novel uses for endoscopic ultrasonography (EUS) in patients with esophageal varices, in fact a RCT has shown that in the treatment of esophageal varices EUS-guided injection sclerotherapy is most safe and efficacious respect to endoscopic injection therapy[20].

In patients treated with NSBBs endoscopic follow-up isn't necessary, conversely in patients treated with EBL, is necessary repeat endoscopy every one or two

weeks until obliteration, 1-3 mo after obliteration and finally every year to check for variceal recurrence[11]. In patients with small varices and who not receive NSBBs, is necessary repeat endoscopy in two years. In the case of hepatic decompensation, endoscopy should be repeated every year and in cirrhotic patients without the presence of varices on the initial endoscopy it should be repeated every three years[10,11].

Acute variceal bleeding

Ruptured esophageal varices cause 70% of all upper GI bleeding episodes in patients with portal hypertension. Therefore, a variceal origin should be suspected in any cirrhotic patient that presents a GI bleeding[7]. In patients with hematemesis or hemodynamic instability, an endoscopic evaluation should be done in the first 12 h after admission[10,11].

The use of new drugs, which are able to decrease portal pressure, the novel and specialized endoscopic endoscopic therapy, the use of antibiotics and the interventional radiologic procedures improved the survival in the last 25 years[6]. Mortality during the bleeding episode remains high and ranges from 24% in unselected cirrhotic variceal bleeders to about 16% among those receiving the current standard of care (band ligation + vasoactive drugs + antibiotics)[21-23]. For the treatment of acute bleeding related to variceal the current recommendation is to combine antibiotic prophylaxis, hemodynamic stabilization, the use of drugs and the treatment through endoscopy[11]. It's important maintaining hemodynamic stability and a hemoglobin of 8 g/dL[11]. The restitution of lost blood causes an increasing in portal pressure to levels higher respect to baseline[24]. A recently RCT showed that a restrictive transfusion strategy in patients with portal hypertensive bleeding reduced further bleeding, need for rescue therapy and length of stay in the hospital. In the restrictive-strategy group the hemoglobin threshold for transfusion was 7 g/dL per deciliter with a target range of 7 to 9 g/dL per deciliter[25]. Antibiotic prophylaxis is a standard practice, in fact it is known that is able to decrease the rate of bacteria infections and the incidence of rebleeding, and increase the survival[26,27]. The combination of endoscopic and pharmacological therapy is the most common approach for treatment of acute variceal bleeding[10,11]. For example a meta-analysis of 8 RCTs has shown that vasoactive drugs enhance the efficacy of endoscopic therapy respect to endoscopic therapy alone, without evidence of side effects or mortality[28].

EBL is the best endoscopic therapy for active bleeding because respect to endoscopic sclerotherapy (ES), allows a greater control of bleeding, the possible adverse events are lower and improves the survival[10,29,30]. When EBL is not technically feasible, endoscopic sclerotherapy is recommended[10]. Endoscopic ultrasound allows a more effective distribution of sclerosant, the injection of sclerosant agents can be realized into esophageal varices, and causes a decrease of the recurrence rate[31].

Emergency injection of acrylate glue could be also an effective method for treat the bleeding of esophageal varices[32]. Vaso-active medications decrease portal blood flow which relate closely to variceal pressure and include vasopressine, somatostatin, and their analogs (terlipressin and octreotide, respectively). Vasoactive therapy should be continued for 5 d to prevent the rebleeding[10], the reason behind this treatment is that a higher portal pressure is associated with a prognosis less favorable[33].

Patients with cirrhosis in Child-Pugh class C or those in class B who have persistent bleeding at endoscopy, are at high risk for treatment failure and a poor prognosis and early use of PTFE-covered TIPS (within 72 h) markedly and significantly reduces failures to control bleeding or rebleeding and improves survival[34].

Secondary prophylaxis

Over 70% of patients experience recurrent variceal bleeding within one year of their index bleed[35,36]. To prevent recurrent bleeding all surviving patients should receive prophylactic treatments[11]. Available treatments for preventing variceal rebleeding include pharmacological therapy, endoscopic therapy, transjugular intra-hepatic porto-systemic shunt (TIPS) and surgical shunting. A recently meta-analysis showed that NSBBs and EBL are similarly able to reduce upper GI bleeding, variceal rebleeding and bleeding-related mortality, but the overall mortality rate was only lowered with NSBBs[37]. The beneficial effect of b-blockers goes beyond the reduction in the variceal bleeding risk and is probably related to an improvement of other complications of portal hypertension.

A combination of NSBBs and endoscopic therapy is the currently recommended first line treatment for the prevention of variceal rebleeding[10,11]. Band ligation is the endoscopic therapy of choice and has replaced injection sclerotherapy because it is safer and more effective[38]. EBL should be repeated every 1-2 wk until obliteration, the first surveillance endoscopy is performed 1-3 mo after obliteration and then every 6-12 mo to check for variceal recurrence and NSBBs should be adjusted to the maximal tolerated dose[10,11].

Recently, a meta-analysis of 9 trials has confirmed that the combination of EBL and drug treatment reduces the risk of overall and variceal rebleeding, but not overall mortality, when compared with b-blockers or EBL alone[39]. However, data evaluating this issue are not very strong. Lo and de la Pena, have shown that adding b-blockers to EBL reduces the risk of rebleeding and variceal recurrence but this effect was not confirmed in a third study[40-42]. Another two trials failed to show a clear-cut benefit from adding EBL to combined pharmacological therapy with nadolol plus isosorbide mononitrate[43,44].

In cirrhotic patients that are unable or that refuse EBL, NSBBs is a valid option, in fact causes a reduction in portal pressure and a slight increase of side effects[11,45].

TIPS should be considered in patients who are Child A or B who experience recurrent variceal hemorrhage despite combination pharmacological and endoscopic therapy[10,11]. The use of polytetrafluoroethylene (PTFE)-covered stents significantly decreased the rates of obstruction and re-intervention[46]. Surgical shunt prevents rebleeding but markedly increases the risk of hepatic encephalopathy[47].

Rescue therapy

In about 10% of patients, despite urgent endoscopic, variceal bleeding cannot be controlled and thus they may be candidates for salvage therapy[11]. A TIPS is suggested in patients with uncontrolled hemorrhage from esophageal varices with bleeding recurs[11,48-50]. Balloon tamponade (BT) is a temporary measure in patients with uncontrollable bleeding[10]. The main complications associated with BT include aspiration pneumonia in unventilated patients, esophageal ulcers, esophageal tears and airway obstruction with fatal complications in 6%-20% of cases[50].

Fully covered self-expanding metal stent (FCSEMS) placement have been recently proposed as rescue therapy[51], their use allow the stabilization of the patients until is performed the definitive therapy. Preliminary studies showed an high success rate, with minor complications[51-54]. Recently the hemostatic powder TC-325 was used as rescue therapy with good results[55].

GASTRIC VARICES

Seventeen percent of patients with hepatic cirrhosis are affected by gastric varices (GV)[56]. Gastric varices are classified according their location in: esophago-gastric varices, *i.e.*, esophageal varices extending either from the gastroesophageal junction to the small curvature of the stomach (GOV1), or to the fundus (GOV2); and isolated gastric varices (IGV), located in the stomach (IGV2) or elsewhere in the fundus (IGV1); GOV1 represent 75% of GV, GOV2, IVG1 and IGV2 represent respectively 21%, 1% and 4% of GV[57]. GOV1 constitute an extension of esophageal varices[10]. GV bleed less frequently than esophageal varices and with a reported incidence of bleeding of about 25% in 2 years. Fundal varices, however, had a significantly higher bleeding incidence (78% for IGV1 and 55% for GOV2), than GOV1 and IGV2 (10%)[56]. Risk factors for GV bleeding include red color spots, larger nodular GV, fundal location and an advanced Child-Pugh class[56,58].

Primary prophylaxis

Little data have been reported about the primary prophylaxis of GV bleeding. Recently a RCT has compared the injection of cyanoacrylate glue with NSBBs in primary prophylaxis of GV bleeding and showed that cyanoacrylate therapy is more efficacious than NSBBs in preventing gastric variceal bleeding[59].

Acute variceal bleeding

Gastric varices bleeding is less frequent, but more severe than esophageal varices bleeding, therefore it can be more challenging to treat. The management of acute GV bleeding is similarly to the management of esophageal varices bleeding, and include antibiotic prophylaxis, management of euvolemic status and early use of vasoactive drugs[10,11]. The use of cyanoacrylate glue injection resulted in an high percentage of success (*i.e.*, bleeding cessation)[60]. A small RCTs compared cyanoacrylate glue injection with EBL and ES and showed that cyanoacrylate injection is as effective as (or more than) ligation in acute bleeding[61,62]. Leaking of glue (4.4%), sepsis (1.3%), systemic embolism (2%-3%) represent the more common complications related to this treatment[63,64].

A new technique of treatment was introduced in last years, EUS-guided therapy of gastric fundal varices with a combination of cyanoacrylate glue and coil injection that reduced the risk of glue embolization. Coils act as a scaffold to sustain the cyanoacrylate glue within the varix and decrease the amount of glue injection. In a retrospective cohort study this technique was successful in all patients without procedure-related complications[65]. A recently study that compared the treatment of GV by using EUS-guided cyanoacrylate injection or EUS-guided coil application showed that both techniques are effective in the obliteration of localized GV. EUS-guided coil required fewer endoscopies and tended to have fewer adverse events compared with EUS-guided cyanoacrylate injection[66].

TIPS is considered in patients with hemorrhage from fundal varices that can't be controlled or with bleeding that recurs despite the therapy[11]. Fibrin sealant (a solution of fibrinogen and thrombin) has been injected for arrest of variceal bleeding in small uncontrolled series[67,68]. Thrombin has been evaluated for use in endoscopic hemostasis of variceal bleeding. In 2 retrospective studies, thrombin achieved hemostasis in bleeding gastric varices in 75% to 94%[69,70].

Secondary prophylaxis

Cyanoacrylate injection is the most frequent treatment for secondary prophylaxis of GV[10]. Rebleeding rates after an acute GV bleeding episode treated with tissue adhesives range from 7%-65%[71]. After initial hemostasis with tissue adhesives, repeated sessions are performed from two to four weeks until is achieved the endoscopic obliteration. Two RCTs compared cyanoacrylate injection with variceal band ligation, showing that cyanoacrylate injection reduced the rebleeding rates[61,62]. Another study compared cyanoacrylate injection with sclerotherapy and showed a greater control of initial hemostasis and a lower rebleeding rates with cyanoacrylate[72]. TIPS is considered when patients show hemorrhage that can not be controlled or in whom bleeding recurs[11,73].

PHG

The prevalence of PHG, in patients with severe liver disease, ranges between the 11% and 80% and is a potential cause of bleeding[74]. PHG is classified as mild when the only change consists of a snakeskin mosaic pattern, and it is classified as severe when in addition to the mosaic pattern, flat or bulging red or black-brown spots are seen, and/or when there is active hemorrhage[75]. Acute bleeding from PHG is a rare event, with an incidence less than 3%, the incidence of chronic bleeding is around 10%-15%[76]. At the current time, there is not enough data to recommend primary prophylaxis of bleeding from PHG in cirrhotic patients[77].

In the case of acute haemorrhage are administered vasoactive drugs such as vasopressin and its analogue and terlipressin, this drugs are able to control haemorrhage[78-80]. In rare cases, the medical therapy is unable to control bleeding and in this cases limited data suggests the endoscopic thermal therapy[81]. Moreover TIPS is employed in the treatment of PHG with improvement of both mild and severe forms and reduction in endoscopic severity as well as transfusion requirement[82]. Recently haemostatic powder (Hemospray) has been evaluated in patients with acute bleeding due to PHG. This haemostatic powder, which acts by forming a barrier over them bleeding site and enhancing the concentration of clotting factors, was successfully used in four patients actively bleeding from PHG[83]. In patients who have previously experienced clinically significant GI blood loss, NSBBs should be used for prevention of recurrent bleeding[10].

GASTRIC ANTRAL VASCULAR ECTASIA

Gastric antral vascular ectasia (GAVE) is a disorder of the stomach that is characterized by the presence of dilated and fragile blood vessels. In patients with cirrhosis GAVE is less detected compared to PHG[84,85]. There are 2 types of GAVE based on distinctive endoscopic appearances. The classic manifestation consists of appearance of multiple flat, linear, erythematous strips of ectatic vessels radiating from the pylorus to the antrum. The second type is punctate, with punctate red spots scattered throughout the antrum and tends to be more associated with liver cirrhosis[86]. It is reasonable to not treat GAVE lesions that are asymptomatic[77]. Neodymium-yttrium-aluminum garnet laser coagulation is used to control GAVE-related bleeding, in fact is able to reduce the need of blood transfusions in 50%-80% of cases. The disadvantages of this technique are the high cost and the need of a long training period[87-89].

Argon plasma coagulation (APC) is a thermoablative method, which produces thermal coagulation by the use of electric current with high frequency that is passed through with argon gas without contact with the mucosa. APC treatment have an efficacy ranging from 90% to 100%, without the need of blood transfusions with an increase of hemoglobin level in most patients[90,91]. The most frequently complication of APC treatment is the intestinal gas distension, more serious adverse events are antral stenosis and upper GI hemorrhage[91]. Argon plasma coagulation is frequently associated with recurrence of bleeding in 30%-60% of cases, in the medium to long term period[91,92]. The use of EBL has been recently demonstrated for GAVE treatment[93].

EBL may more reliably obliterate vascular structures in the deep mucosa and submucosa, thus reducing the need for further treatments. Ligation bands are applied to abnormal-appearing mucosa in the antrum. First is treated the distal antrum, after the ligation bands are applied more proximally until most of the abnormal mucosa is treated. Wells *et al*[93], in a retrospective study, found that EBL reduced recurrent bleeding and required less treatment sessions and hospital admissions compared to APC treatment[93]. This finding is in accordance with other two studies[94,95].

Recently studies examined the use of radiofrequency ablation (RFA) for the treatment of GAVE[96,97]. These two studies suggests that endoscopic mucosal ablation by using the RFA with HALO system is a viable option for the treatment of chronic bleeding related to GAVE[96,97]. Additional therapy for GAVE includes cryotherapy, cyanoacrylate spray and surgical antrectomy[98-101].

ECTOPIC VARICES

Ectopic varices are those varices which are not located in the gastro-esophageal area, are less common and occur in different sites, such as in the jejunum or ileum (18%),in the duodenum (17%) or in the colon (14%), in the rectum (8%), and finally in the peritoneum (9%)[102,103].

Duodenal varices

Duodenal varices (DV) were reported to be the second cause of ectopic variceal bleeding after the rectal location[104]. They are most commonly noted in the duodenal bulb followed by the second part of the duodenum[102,104]. Bleeding due to DV is usually massive, with a mortality rate around the 40% at the first episode[105,106]. Different sclerosant agents are used for endoscopic injection therapy, for example Seo *et al*[107] have been shown how bleeding duodenal varices can be eradicated with injection of ethanolamine. Liu *et al*[106] in a five-year retrospective study reported the successful treatment with cyanoacrylate injection in 4 patients with bleeding due to DV. Some authors have reported also the successful EBL of DV bleeding[108-110]. If rebleeding occur after endoscopic therapy, and TIPS are used as rescue therapy with good results[111,112].

Small-bowel varices

An uncommon, difficult to treat and sometimes fatal manifestation of portal hypertension is the hemorrhage associated with small-bowel varices. In fact, 8.1% of patients with portal hypertension who underwent to capsule endoscopy present small-bowel varices[113]. When

the terminal ileum is intubated on colonoscopy the 18% of patients with portal hypertension, present terminal ileal varices[114]. Double-balloon enteroscopy (DBE) allows to display whole small bowel and perform endoscopic surgeries in patients with bleeding small-bowel varices. Enteroscopic and colonscopic sclerotherapy of jejunal and ileal varices has been described[115-118]. TIPS is the first line treatment for refractory variceal bleeding[119].

Colonic varices

The most common sites of colonic varices are the rectum and cecum[105]. The rate of colonic variceal bleeding in liver cirrhosis is approximately 1%-8%[120]. Several interventional therapies like endoscopic variceal ligation, glue injection, TIPS, BRTO, colonic resection have been reported[121-126].

Rectal varices

Rectal varices are one of the most important causes of bleeding in portal hypertension, they occur in 44% to 89% of cirrhosis[127-129]. The endoscopic options for treatment of rectal varices are injection therapies using sclerosants or cyanoacrylate glue and band ligation[130-133]. Recently EUS-guided approach has been used in management of rectal varices. The advantages to use EUS-guided therapy are different and include the ability to treat directly the varix and visualize deeper collateral vessels. The EUS-guided therapy with sclerosant or coil embolization showed good results[134-136].

PORTAL HYPERTENSIVE BILIOPATHY

Portal hypertensive biliopathy (PHB) is an abnormalities of all biliary tract including intra-hepatic and extra-hepatic bile ducts, cystic duct and gallbladder. The frequency of PHB in patients with extra-hepatic portal venous obstruction (EHPVO), is greater respect to patients with cirrhosis[137]. EUS could be useful in patients with cirrhosis to identify CBD varices or bile duct stones[138].

The extraction of CBD stones by endoscopic sphincterotomy is the normally treatment applied in patients with CBD stones. Endoscopic treatment is the best treatment for patients with dominant biliary stricture, but without a shuntable vein. Porto-systemic shunt is performed in patients with dominant biliary strictures with a shuntable vein[139,140].

PORTAL HYPERTENSIVE ENTEROPATHY

Portal hypertensive enteropathy (PHE) is defined as the presence of several red spots like arterovenous malformations, patchy hyperemia of the mucosa, diffuse mucosal edema, spontaneous bleeding from the mucosa or small bowel varices[141-143]. Due to the difficult access to the small bowel, in the past the diagnosis of PHE was very difficult, but with the introduction of capsule endoscopy and DBE, PHE seems more common and has been seen that in cirrhotic patients may cause chronic GI bleeding with portal hypertension[144,145]. PHG is mostly asymptomatic, although it may bleed acutely leading to hematemesis and/or melena.

PORTAL HYPERTENSIVE COLOPATHY

Portal hypertensive colopathy (PHC) is characterized by erythema of the colonic mucosa and vascular lesions including telangiectasias, cherry-red spots and angiodysplasia-like lesions. The prevalence of PHC in patients with cirrhosis ranging between 25%-70%[146-148]. Portal hypertension seems to play an important role, and there is an association with a hyperkinetic circulatory state[149]. Lower GI bleeding due to PHC is estimated up to 9%[150-152]. In patients with chronic lower GI bleeding secondary to PHC, as reported the treatment with NSBBs is effective[153]. In patients with acute bleeding, vasoactive medications, such as octreotide or terlipressin, could be effective[153]. TIPS has been used as a rescue therapy in patients with refractory GI bleeding[154].

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REVIEW

Small bowel capsule endoscopy: Where are we after almost 15 years of use?

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Abstract

The development of capsule endoscopy (CE) in 2001 has given gastroenterologists the opportunity to investigate the small bowel in a non-invasive way. CE is most commonly performed for obscure gastrointestinal bleeding, but other indications include diagnosis or follow-up of Crohn's disease, suspicion of a small bowel tumor, diagnosis and surveillance of hereditary polyposis syndromes, Nonsteroidal anti-inflammatory drug-induced small bowel lesions and celiac disease. Almost fifteen years have passed since the release of the small bowel capsule. The purpose of this review is to offer the reader a brief but complete overview on small bowel CE anno 2014, including the technical and procedural aspects, the possible complications and the most important indications. We will end with some future perspectives of CE.

Key words: Capsule endoscopy; Small bowel; Preparation; Procedure; Technology; Complications; Features; Enhancements; Indications; Future

Core tip: This review covers all the relevant aspects of small bowel capsule endoscopy anno 2014. The current techniques, procedures, analyses, indications and future perspectives are discussed thoroughly. Easy-to-use flowcharts are provided to help the readers in their decision-making when confronted with small bowel pathology.

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INTRODUCTION

Wireless Video capsule endoscopy (CE) was invented by Gavriel Iddan[1] in the mid-1990s. Being able to visualize the entire small bowel in a noninvasive, well-tolerated way, CE has closed the diagnostic gap between conventional gastroduodenoscopy and colonoscopy. Since the official release of CE in 2001, almost 15 years have passed, and CE has revolutionized the diagnosis and treatment of

various small intestinal diseases. This review aims to provide state of the art on CE in gastrointestinal diseases. Both the evolution in technique and in indications will be discussed.

TECHNICAL PRINCIPALS, PROCEDURE AND ANALYSIS

Capsule definition

The wireless CE system consists of 4 main parts: (1) the single-use wireless Video Capsule; (2) sensor arrays or a sensor belt attached to the patient; (3) the data recorder attached to the belt; and (4) the computer workstation with the application software[2-4] as can be seen in Figure 1 by Pan *et al*[4].

The capsule weighs less than 4 g and measures about 11 mm in diameter × 26 mm in length. It is made of plastic, biocompatible and resistant to digestive fluids. The capsule contains a short focal lens and a miniature video camera: a charge-coupled device or Complementary Metal Oxide Semiconductor, which focuses the image. The gastrointestinal tract is illuminated by white light LEDs. The capsule is powered by two mercury free silver oxide batteries with a life span of 8-12 h. More than 5000 images are transmitted during this battery life at a rate of 2-6 fps. Capsule features have evolved since the release of the first capsule and nowadays standards are a 156-170° field of view, a high resolution and sharpness with a minimum size of detection of 0.07 mm, a 1:8 magnification, a more homogenous light exposure and a depth of view of at least 20-30 mm[5]. The captured data are sent to the sensor arrays and belt worn by the patients by either ultra-high frequency band radio telemetry or human body communications, using the human body as conductor.

At present, there are three main companies supplying wireless CE systems by approval of the FDA. Given Imaging (Ltd, Yoqneam, Israel) supplying the PillCam® SB 3, Olympus America (Inc, Center Valley, Pennsylvania) supplying the EndoCapsule® and Intromedic Company (Ltd, Seoul, South Korea) manufacturing the MiroCam®. Although not approved by the FDA, another Chinese company, Jianshan Science and Technology (Group) Co., Ltd., Chongqing, has developed its own capsule: the OMOM capsule. The capsule has been approved by the State Food and Drug Administration of the People's Republic of China in March 2004 and is since then being used in China, Southeast Asia and some European countries[6]. The first large clinical trials have reported a yield and completion rate similar to the PillCam, but the major advantage of the OMOM capsule is without doubt its price, which could be reduced by fifty percent[6,7] (Table 1 and Figure 2).

Even though the three main capsules approved by the FDA differ in technical specifications, several trials have shown that they offer a comparable diagnostic yield, image quality and completion rate, as was stated in the systematic review by Koulaouzidis *et al*[8].

Small bowel preparation

To ensure a clear view on CE, the patient is asked to start fasting 12 h before the small bowel CE procedure[2,3]. However, due to bubbles, small intestinal fluid and biliary secretions coming from the major duodenal papilla, the visualization by the VCE can deteriorate. Furthermore, limited battery life span can hamper a complete intestinal examination in patients with delayed gastric emptying and small bowel transit, which necessitates the use of additional small bowel preparation[3]. However, not all patients are eligible for small bowel cleaning. The 2012 Consensus guidelines for the safe prescription and administration of oral bowel-cleansing agents[9] states that small bowel preparation is contraindicated in patients with gastrointestinal obstruction, perforation, ulceration, ileus, gastric retention or inflammatory bowel diseases (IBD), in patients with a reduced level of consciousness, swallowing disorders, hypersensitivity to the used agent and in patients having an ileostomy. The use of small bowel cleansing agents is relatively contraindicated in patients with chronic kidney disease or undergoing dialysis, in patients with a renal transplant, congestive heart failure, liver cirrhosis or ascites and in patients taking Renin-angiotensin blockers, diuretics or nonsteroidal anti-inflammatory drugs (NSAIDs). In these patients the utility of small bowel cleaning should be reconsidered and the choice of cleaning agent is of main importance: polyethylene glycol (PEG) is normally preferred over Sodium Phosphate. Patients taking Renin-angiotensin blockers, diuretics or NSAIDs are advised to discontinue their medication temporarily and their hydration and electrolyte status should be checked prior to the small bowel preparation. In a recent systematic review, Kotwal *et al*[10] compared the results of various randomized-controlled trials regarding improvement of vision quality (VQ), diagnostic yield (DY) and completion rate (CR) by small bowel preparation. In this review, administration of 2L polyethylene glycol (PEG) the evening before VCE was found to be superior to two doses of 45 mL Sodium Phosphate before VCE regarding VQ and DY improvements. Another study by Kantianis *et al*[11] showed that 2 L as well as 4 L PEG did not differ in small bowel cleansing and CR. Therefore 2 L should be preferred as regimen before VCE. Furthermore Kotwal *et al*[10] stated that simethicone, an antifoaming agent, significantly improved the VQ by decreasing the bubbles without implications on CR. Yet no significant improvement in VQ and DY were observed by combining Simethicone with PEG. After meta-analysis prokinetics did not show a significant improvement in CR, so they are not recommended.

Procedure

After bowel preparation, the patient gets eight sensor arrays attached to his body and a sensor belt fastened around his waist. The data recorder is attached to the belt before capsule ingestion. The capsule is ingested with a glass of water and fluid restriction is needed till 2

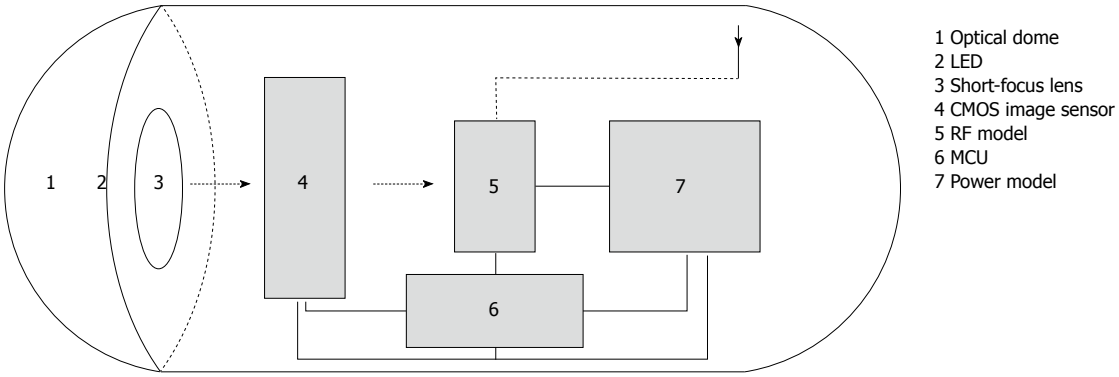

Figure 1 Main parts of the wireless capsule endoscope.

Table 1 Comparison between commercially available capsule endoscopy devices

Capsule	PillCam® SB 3 Given Imaging	EndoCapsule® Olympus America	MiroCam® Intromedic Company	OMOM® Jianshan Science and Technology
Size	Length: 26.2 mm Diameter: 11.4 mm	Length: 26 mm Diameter: 11 mm	Length: 24.5 mm Diameter: 10.8 mm	Length: 27.9 mm Diameter: 13 mm
Weight	3.00 g	3.50 g	3.25-4.70 g	6.00 g
Battery life	8 h or longer	8 h or longer	11 h or longer	6-8 h or longer
Resolution	340 x 340 30% better than SB2	512 x 512	320 x 320	640 x 480
Frames per second	2 fps or 2-6 fps	2 fps	3 fps	2 fps
Field of view	156°	145°	170°	140°
Communication	Radio Frequency Communication	Radio Frequency Communication	Human Body Communication	Radio Frequency Communication
FDA approval	Yes	Yes	Yes	No
Price per capsule	$500	$500	$500	$250

h after ingestion. After 4 h, fasting can be stopped. Daily activities do not need to be interrupted during CE.

Capsule propulsion needs to be followed by real-time viewing during the first hour to make sure the capsule passes the stomach. If not, gastroscopy is performed to deposit the capsule in the duodenum.

The sensor arrays and belt are removed once the capsule has been expelled into the colon (as verified by real-time viewing), or when the battery life has expired. Images can be downloaded from the recorder to the workstation. The capsule itself passes naturally with bowel movement and is usually excreted within 24 to 72 h.

Analysis

After downloading the data from the recorder to the workstation, images can be reviewed by gastroenterologists using the application software. Reading time and interpretation are around 40-120 min[2,12] which can be, compared to conventional endoscopy, a time-consuming activity. A solution to this problem might be to train nonphysicians in pre reading the images. A study by Bossa *et al*[12] found that a nurse with expertise in endoscopy might be able to shorten the time needed by the endoscopist to read a capsule. Moreover the pre reading of the CE by the nurse endoscopist led to a more careful approach of the physician in the flagged areas, which enhanced the accuracy of the CE investigation. Another recent study by Dokoutsidou *et al*[13] confirmed these findings and stated that despite a longer reading time, a nurse is perfectly capable of pre reading and subsequently flagging aberrant images. However, another possibility to lower reading time is the use of special software to select aberrant images, which can be revised afterwards. With the introduction of Quickview by Given Imaging, reading time could be reduced significantly. The Quickview software samples sites of interest for review at a chosen rate, but unfortunately missed lesions occur far more often, which is unacceptable[14]. However, in certain clinical settings, such as overt obscure gastrointestinal bleeding (OGIB) in an urgent inpatient setting and suspected Crohn Disease or occult OGIB in outpatient setting, Koualouzidis *et al*[15] found that Quickview could be used confidently without clinical consequences. To enhance the yield of CE, virtual chromoendoscopy was developed by adding colour filters to the images. Fuji Intelligent Colour Enhancement (FICE) was seen to be superior in detecting small bowel lesions and in particular angioectasias compared to conventional CE[16]. In another trial by Krystallis *et al*[17] Blue Mode (BM) was found superior to FICE in detecting lesions of the small bowel. Adding BM to Quickview studies however did not show any diagnostic advantage and is therefore not recommended[15].

Figure 2 Types of small bowel capsule endoscopes. A: PillCam SB 3 (Given Imaging, Yoqneam, Israel); B: MiroCam (IntroMedic, Seoul, South Korea); C: Endo Capsule (Olympus America, Center Valley, PA); D: OMOM (Jinshan Science and Technology, Chongqing, China).

COMPLICATIONS AFTER CE

Capsule retention

Although very popular for its non-invasive character, CE can be the cause of unnecessary treatment due to complications. One of the most feared complications is capsule retention. It is defined as the presence of the capsule in the bowel lumen for a minimum of 2 wk after ingestion, or when the capsule is retained for an unspecified period of time unless targeted medical, endoscopic or surgical intervention is started[18].

According to a systematic review by Liao *et al*[19] overall retention rates are as low as 1.4%, which makes the procedure acceptable, regarding the high overall diagnostic yield of 59.4%. Furthermore, the retention rate differs according to the underlying pathology, with up to 2.6% in known Crohn's disease (CD) and 2.1% in patients with Neoplastic Lesions[19]. This can be explained by the fact that capsule retention is usually caused by masses, strictures and stenotic areas resulting from neoplastic lesions, CD, NSAID consumption or post-operative adhesions, which narrow the small bowel lumen and favors retention[20]. In this regard, known small bowel obstruction, strictures and extensive CD are a contraindication for CE[21]. In a large study by Höög *et al*[22] risk factors for capsule retention were identified. OGIB and suspected CD were associated with the lowest chance of capsule retention, whereas known CD and small bowel tumors had a higher chance of retention. These findings were also confirmed by other authors[19,23].

Most of the time, retained capsules are asymptomatic, but intestinal obstruction, partial or complete, may occur, especially in case of known CD or neoplastic lesions. In the 2009 consensus by the European Society of Gastrointestinal Endoscopy it is recommended with a grade B evidence level to precede the CE by small bowel imaging or a patency capsule (PC) (cf. infra) in patients with suspected or established CD to rule out potential strictures. As said earlier, known small bowel obstruction is a contraindication for CE and patients at risk for a small bowel obstruction should therefore be carefully investigated by their physician before a CE procedure[24].

Evacuation of the retained capsule can be spontaneously, medically or by surgery. The latter is unfortunately the most frequent intervention, but is on the other hand safe and can be seen as a required diagnostic and therapeutic tool for treating the underlying small bowel condition. With the surgery, not only the capsule is removed, but also the responsible lesion can be resected, which reliefs the patient's symptoms. However retention can also lead to unnecessary surgery of lesions caused by, *e.g.*, NSAID or CD, for which a medical solution would also have been an option[25].

In recent years, an endoscopic approach of capsule retention has become more popular as a less invasive alternative for surgery. Before capsule retrieval a radiographic localization of the capsule is done to determine whether an upper or lower gastro-intestinal and a standard (gastroduodenoscopy, Push Enteroscopy or colonoscopy) or advanced endoscopic approach

(device assisted enteroscopy) is needed. In this regard, surgery can be considered when endoscopic approaches did not manage to retrieve the capsule or when the patient presents with symptoms of toxicity[26]. In a study by Van Weyenberg *et al*[27] DBE showed to be an adequate tool to retrieve a retained capsule. Moreover the DBE was capable to aid in pre-operative staging by histological sampling. In conclusion DBE can prevent unnecessary surgery as well as determine the cause of the capsule retention before the operation, which is beneficial both for physician and patient.

Capsule perforation

Another yet very rare complication is perforation of the small bowel. Usually it results from capsule retention. In the few cases that are reported, CD was the most frequent underlying pathology causing the perforation[20,28-31]. In a study by Repici *et al*[28] a possible explanation for this complication is given. CD affects the tissue of the small bowel wall and makes it vulnerable. By the complete luminal occlusion due to the entrapment of the capsule and the high peristaltic activity the fragile tissue of the small bowel wall distends just above the capsule and leads to fissuration and possible perforation of this area. One study by Gonzalez Carro *et al*[32] reported perforation after CE in a patient with a history of surgery with subsequent adhesions. Because of the major implications, perforation should be acknowledged as a possible complication after CE in patients with known or suspected CD.

Capsule interference

One of the relative contra-indications for CE is the presence of implantable cardiac devices, such as pacemakers, ICDs, pulsatile and nonpulsatile LVADs. Interference may arise during the CE procedure resulting in an alteration of atrial or ventricular assistance[33]. This is however a theoretical assumption without clinical significance, because few studies show actual interference between cardiac devices and CE. Moreover, previous studies have already suggested that CE can be used safely in patients with these devices[34-41]. Only one study by Dubner *et al*[42] reported oversensing of an ICD due to interference with the CE procedure, which resulted in an inappropriate shock by the cardiac device. In another case report by Guyomar *et al*[37] interference between pacemaker and video capsule occurred, resulting in a failure of recording by the capsule when close to the pulse generator. Harris *et al*[43] found similar results in a 2013 study: all implantable devices proved to be safe for the patient, but LVAD had the tendency to interfere with image capture and therefore a CE lead position as far away from the LVAD as possible is required. On the other hand, in the article by Cuschieri *et al*[40] no loss of images was observed. In conclusion, close monitoring is recommended in patients with implantable cardiac devices but the risk for complications seems to be extremely low.

Capsule aspiration

Some cases have reported the existence of bronchial aspiration of the capsule. It is a very rare complication, which occurs in one out of every 800 investigations and can be asymptomatic[44]. CE aspiration can resolve spontaneously[45], but often necessitates immediate radiological investigations to localize the capsule, followed by bronchoscopy to retrieve it with the aid of a Roth Net[44]. To prevent this unnecessary invasive procedure, screening for patients at risk should be done. Risk factors include aging, neurological or swallowing disorders and patients with a weak or absent cough[46,47]. Direct placement of the capsule in the gastrointestinal tract should be considered in these patients[44-46,48]. If not, the Real Time Viewer should be used during the ingestion of the capsule to make sure that the capsule reaches the gastrointestinal tract[46-48].

Until now, only one fatality has been reported due to intracerebral haemorrhage resulting from capsule aspiration[47]. The reason for this low mortality rate is hypothesized in a study by Lucendo *et al*[44] stating that the size of the capsule is not capable to block the total lumen of the trachea and therefore still allows adequate oxygenation after capsule aspiration. However Koulaouzidis *et al*[49] found that the CE size might be correlated with the chance of aspiration.

ADDITIONAL FEATURES AND ENHANCEMENTS IN THE FIELD OF CE

Suspected blood indicator

In 2003 Given Imaging introduced the Suspected Blood Indicator (SBI) as an aid in diagnostics. The new feature highlights images suspected for redness or blood, which makes it easier for physicians to identify possible bleeding sites accurately. The software is activated when the capsule has reached the duodenum and operates only during its stay in the small bowel[50].

Sensitivity of the SBI software is determined by the presence of active bleeding. In studies, sensitivity ranges from 20% to 56.4% and increases up to 58.3% to 93% in case of active bleeding[50-52]. However, sensitivity and specificity of SBI remains too low, so complete review by a gastroenterologist is still required and the SBI only serves as rapid screening tool for actively bleeding lesions[51,52].

The detection rate of the SBI is affected by background color of the small bowel as by velocity of the capsule[50]. This is also a possible explanation for the variation in sensitivity observed among different studies. The background of the small bowel differs according to patient's condition and small bowel preparation[50]. In experimental small intestine models, a very pale magenta background showed the highest detection rate, followed by burnt sierra and yellow. Lowest detection rates were observed in small bowel sites with colors significantly different from the normal small bowel color or when the capsule reached a high velocity. In an interesting study by

Buscaglia *et al*[53] SBI was found to be an inferior screening tool for sites of potential bleeding with a sensitivity below 60% even in active bleeding. Yet they found that in CD the SBI could be used as a screening tool for detection of aberrant mucosa with high sensitivity. Another study by D'Halluin *et al*[54] also rejected the SBI software as a useful tool for screening the small bowel stating that the detection rate was poor, independent of the type of lesion. Furthermore they found that the SBI missed certain lesions while tagging few others and that irrelevant flagging might unnecessarily prolong the reading time of the CE. However, in a recent study Tal *et al*[55] stated that SBI is a reliable aid in excluding active bleeding or major lesions, but that the role of the endoscopist could not be neglected. In summary we can conclude that SBI might improve the interpretation and thereby the yield of CE by tagging areas for a second review, but can certainly not replace the gastroenterologist's review.

PC

To address the problem of capsule retention, the Agile PC was developed by Given Imaging. The PC with the same size as a video capsule, serves as dummy to assess the patency of the small bowel prior to CE examination. As one of the major contraindications for CE is suspicion of small bowel stenosis, routine administration of PCs could enable safe CE use in a larger patient population by ruling out possible stenoses[56]. The PC system consists of two main parts: the capsule itself with a radiofrequency identification tag (RFID tag) and an external detector system to capture radio-frequency signals.

The PC is made of lactose and 10% barium, which dissolves when coming into contact with intestinal fluids through the window at the edge of the capsule, also known as timer plug. To insure that the timer plug is not blocked by capsule impaction in a stricture, the second generation PCs consist of two timer plugs. If excretion does not occur, dissolution starts at 30 h. After 35 h, 38 percent of the capsules are dissolved and all are dissolved within 72 h[57]. After dissolution, the remains of the capsule encounter no difficulties to pass the small bowel strictures.

The detector system receives the radio-frequency signals coming from the RFID tag and reconstructs the exact capsule position. This can also be done by using radiography, which visualizes the PC by its radiopaque RFID tag or 10% barium[56]. Localization can be complicated by overlap of intestines so subsequent fluoroscopy or CT scan can be warranted. One drawback of the RFID tag system is the probability of impaction in a stricture, which can lead to small bowel ileus[58]. Recently a new tag-less PC was developed by Given Imaging to overcome this issue and proved its usefulness as found by Nakamura *et al*[58].

The PC procedure is not as strict as the CE procedure. The capsule can be swallowed without previous food restrictions. If the capsule is not excreted in 33 h, further examination is warranted to localize the PC and make a distinction between a small bowel and a colonic localization. The latter is still an indication for VCE. The subsequent CE has to be done quickly after PC so a possible change of stricture status and subsequent capsule retention is avoided[56].

The use of the PC still remains controversial. Although some authors have reported its utility[59-61], others have found that the capsule was not capable of confirming stenoses, which were found on CT or small bowel follow through[62]. In conclusion, patients still benefit from a CT investigation prior to CE to exclude possible stenosis and strictures.

CapsoCam capsule

Over the last decade, a new player entered the field of CE. CapsoCam by Capsovision renewed the concept of CE by offering a capsule with a 360° view and on-board storage, which enables the retrieval of images wire-free after interception of the capsule in the feces. The capsule contains four cameras, which offer high resolution images and a frame rate up to 20 fps max. Furthermore, two new technologies were developed, Smart Motion Sense Technology and Auto Illumination Technology. Smart Motion Sense Technology enables the capsule to activate its cameras only during capsule motion. When the capsule is stationary, a sensor is used to compare the current frame with the previous frame to control reactivation. Auto Illumination Technology controls the 16 white LEDs to provide the optimal level of illumination. When the capsule is located nearby the walls, a low light intensity is optimal to capture the best images. A position further away from the wall necessitates a higher light intensity. By adding these software features, battery life is sustained up to 15 h. The first clinical trial that used the CapsoCam accepted it as a safe and efficient tool in small bowel evaluation[63]. In a recent French study by Pioche *et al*[64] the concordance between the PillCam SB2 and CapsoCam was evaluated in terms of diagnostic yield and image quality. A kappa value of 0.63 was obtained, which confirms the good concordance between the two capsules. Although the reading time of the CapsoCam was longer, the CapsoCam detected significantly more lesions in a per lesion analysis.

Three-dimensional representation

In recent years, three-dimensional representation is becoming a hot issue. By reproducing the depth information lost by camera recording, diagnosis can be facilitated, because the texture and the abnormalities of the mucosa are highlighted. 3-D rendering can be software- or hardware-based. The latter is limited by the technological possibilities of the capsule, so software based 2-D to 3-D conversion is used[65,66]. Software-based 3-D rendering uses algorithms to recreate the third dimension. In a study by Karargyris *et al*[67] four Shape-from-Shading (SfS) algorithms were compared. The Tsai's SfS algorithm excelled the other algorithms in

visualization improvements, but we may not forget that the evaluation criterion was subjective in origin. However, the Tsai's SfS algorithm is especially adapted to bright and round surfaces, therefore perfectly applicable in small bowel endoscopy.

Lesion localization

Apart from the image quality, accurate lesion localization is one of the key elements of CE, because further therapeutic steps, non-invasive and invasive, can depend on the exact localization of the lesion[68]. Lesion localization is currently estimated according to the transit time and the use of pylorus and caecum as landmarks, but lacks precision.

Exact localization can be determined by using a capsule emitting a magnetic field or electromagnetic waves. Both methods have their advantages and drawbacks. Magnetic-field-strength-based localization is not attenuated by the human body and the capsule does not have to be aligned with the detectors to be detected. As a drawback, interference of the magnetic fields for capsule localization and the magnetic fields for active capsule movement in the future (cf. infra) may occur. On the other hand electromagnetic waves localization, such as the previously mentioned RFID tag, is based on radio-frequency waves, which are attenuated by the human body and therefore may lose precision. A promising step forward in capsule localization is the development of a new software by Olympus Medical Systems Corporation (Tokyo, Japan), which uses a 3D-triangulation. The exact capsule position is calculated by determining its distance from the 6 radiofrequency sensors using radiofrequency signal strength. In the study by Marya *et al*[69] an average localization error of 13.26 cm^3 by attenuation was observed, especially in patients with an increased BMI.

Finally, in 2010 the Capsule-odometer, a conceptual CE design, was proposed by Karargyris *et al*[70] which in theory offers a more accurate lesion localization. The capsule has two protruding wheels attached to a spring-mechanism, so the wheels can adapt to the diameter of the intestinal lumen, serving as a micro-odometer with subsequent accurate lesion localization, calculated from the onset of the capsule investigation. This design also offered a greater stability, avoiding non-forward movement through the gastrointestinal tract. Further experiments and research are needed on this subject.

MAJOR INDICATIONS FOR SMALL BOWEL CE

CE has been approved for various indications. These include (1) overt and occult obscure gastrointestinal bleeding; (2) suspected CD; (3) surveillance in patients with polyposis syndromes and detection of small bowel tumors; (4) screening and evaluation of NSAID side-effects; and (5) suspected malabsorptive syndromes such as celiac disease. These indications will be explained further on in this paper. Relative contra-indications for CE include, like mentioned before: (1) known or suspected GI obstruction, strictures or fistulas; (2) cardiac devices; (3) swallowing disorders; and also (4) pregnancy.

Obscure gastrointestinal bleeding

Obscure gastro intestinal bleeding (OGIB) is defined as bleeding of unknown origin that persists or recurs following a bidirectional negative endoscopic evaluation of the gastrointestinal tract. OGIB is a common problem encountered by gastroenterologists, and accounts for approximately 5% of all GI bleedings[71]. OGIB can be overt (melena, hematochezia, hematemesis) or occult (iron-deficiency anaemia, IDA, with or without a positive fecal occult blood test). OGIB is mostly caused by a lesion located in the small bowel, but can also originate from a lesion in the other parts of the GI tract as well, missed with conventional endoscopy because of intermittent bleeding or by human error[72]. The underlying pathology is age dependent. Under the age of 40, the most frequently detected lesion is a small bowel tumor, followed by Meckel's diverticulum, Dieulafoy's lesion and CD. Above the age of 40, vascular lesions such as angiodysplasia are most frequently observed, counting for up to 40% of the underlying lesions. NSAID-induced lesions (cf. infra) are the second most frequent finding on CE[71].

Since its development in 2000, CE has mainly been used for the indication of OGIB, accounting for 60%-70% of the patients[8]. CE has proven superiority to all other diagnostic modalities in OGIB, such as barium contrast radiology, small bowel computed tomography (CT), magnetic resonance imaging (MRI), push enteroscopy and angiography, as can be seen in Table 2. The American Society for Gastrointestinal Endoscopy (ASGE) confirmed these findings in their guidelines presented in 2007[71]. Before using CE as a diagnostic tool, at least one gastroduodenoscopy and ileocolonoscopy have to be performed to rule out upper and lower gastrointestinal tract abnormalities. Repeating gastroscopies or colonoscopies immediately prior to CE in patients who have not had endoscopic investigations for more than 6 mo, tends to have a low diagnostic yield and is not cost-effective[73]. Therefore, CE is recommended as the first-line investigation after negative bidirectional endoscopies. Younger patients however have a higher chance of IBD or tumours and a CT abdomen is indicated prior to CE to rule out stenosis[20]. A gynaecological etiology has to be considered in young females.

The overall yield of CE is between 35% and 83% for OGIB[19,71,72,74-80] with its mean around 60%[81,82]. Diagnostic yield is influenced by the type of bleeding. Patients with ongoing overt bleeding usually present with a higher diagnostic yield than patients with obscure-occult bleeding, presenting as IDA[72,83]. More factors associated with a higher diagnostic yield have been identified, including low hemoglobin measurements, transfusion need, older age and a short interval of less

Table 2 Comparison of different diagnostic modalities in obscure gastrointestinal bleeding

Ref.	Country	Design	No. of patients	Comparator	Yield of CE, (%)	Yield of Comparator, (%)	Significant difference? (yes/no)	CE superior? (yes/no)	Other
Triester *et al*[80]	United States	Meta-analysis and Systematic review	396	PE	63	28	Yes	Yes	NNT = 3 to yield one additional clinically significant finding with CE
			88	SB radiography (barium contrast and enteroclysis)	67	8	Yes	Yes	NNT = 3 to yield one additional clinically significant finding with CE
Leighton *et al*[82]	United States	Meta-analysis and Systematic review	396	PE	63	28	Yes	Yes	Yield of significant findings: CE = 56% *vs* PE = 26%, NNT = 3 to yield one additional clinically significant finding with CE
			88	Barium radiography	67	8	Yes	Yes	Yield of significant findings: CE = 42% *vs* SB barium radiography = 6%, NNT = 3 to yield one additional clinically significant finding with CE
			42	Intraoperative enteroscopy	83	83	No	No	
			17	Mesenteric angiography	47	53	No	No	
Chen *et al*[205]	China	Meta-analysis and Systematic review	277	DBE	61	56	No	No	CE was superior if no combination of oral + anal approach <-> DBE was superior when a combination of the two insertion approaches was done
Pasha *et al*[95]	United States	Meta-analysis and Systematic review	397	DBE	24	24	No	No	CE should be the initial diagnostic test for determining insertion route of DBE
Arakawa *et al*[76]	Japan	Retrospective Study	162	DBE	54	64	No	No	
Teshima *et al*[77]	Canada, The Netherlands	Meta-analysis and Systematic review	651	DBE	62	56	No	Yes	Yield of DBE after positive CE = 75.0% <-> yield after negative CE = 27.5%
Leung *et al*[206]	China	RCT	60	Mesenteric angiography	53	20	Yes	Yes	No significant difference in the long-term outcomes (transfusion need, hospitalization for rebleeding,mortality)
Wang *et al*[207]	China	Meta-analysis and Systematic review	279	CT	53	34	Yes	Yes	Complementary role to CE and can be used as a triage tool prior to DBE in evaluating OGIB

PE: Push enteroscopy; CE: Capsule endoscopy; SB: Small bowel; NNT: Number needed to treat; DBE: Double balloon enteroscopy; RCT: Randomized controlled trial.

than 3 d between admission and the CE procedure[84-88]. CE is recommended in all cases of OGIB because of its diagnostic value and its impact on further management. A study by Albert *et al*[75] found that CE was able to determine the therapy in 66% of the cases and led to an alteration in management in 32.3% of the cases. This is in line of previous studies, which reported that CE could alter subsequent management in 23%-66% of the cases[79,85,89-91]. Sidhu *et al*[84] found that this management alteration could be predicted by patient comorbidity or angiodysplasia findings on CE.

The reason why CE has been recommended as first-line examination tool over DBE after initial negative upper and lower endoscopies is its noninvasive nature and ease of use, which makes it well-tolerated and feasible in an outpatient setting[92]. Furthermore its ability to visualize the whole small bowel in more than 80%-85% of the cases[93,94] and the ability to determine the initial DBE approach makes it a helpful tool in OGIB diagnostics[92,95]. However, CE often fails to visualize lesions in the proximal small bowel, in a Roux-en-y loop and in patients presenting with diverticula[76].

If necessary, a CE procedure can be followed by a double balloon enteroscopy (DBE) procedure[72]. DBE is the only diagnostic tool showing a similar diagnostic yield for OGIB as VCE, as can be seen in Table 2. However, the DBE procedure is more invasive, can be time-consuming, requires training, needs sedation or general

anesthesia and can have a complication rate of up to 4.3% in therapeutic procedures as was reported by Mensink *et al*[96]. Moreover DBE is not always able to visualize the whole small bowel. A completion rate of only 62.5% was achieved in DBE, compared to 90.6% in CE as reported by Nakamura *et al*[94]. Yet, DBE is preferred over CE in patients requiring a biopsy or a therapeutic intervention such as argon plasma coagulation (APC). Also DBE tends to have an acceptable yield in patients with an initial negative CE and suspicion of a small bowel lesion[95,97], although it has been reported being much lower than the yield of DBE following a positive CE, respectively 28% and 75%[77].

Not only clinically, but also economically is CE recommended as first line investigation of OGIB. It has shown to be more cost-effective than DBE when only visualization of the small bowel is needed[98]. Negative CE investigations usually do not require further diagnostic work-up, which saves money in the long term, because reimbursement for CE is less than for DBE[93]. A mean cost-saving of €1738.07 was reported by Marmo *et al*[99] when CE was preferred over other modalities in OGIB and turned out to be positive. However, only reimbursement costs were evaluated, so the cost of the hospital and the personnel was not taken into account.

If a therapeutic intervention is needed with a probability of more than 25%, gastroenterologists should consider the use of DBE as initial therapeutic option to minimize costs[93]. Furthermore, cost equalization of DBE and CE was reached at 100 procedures for diagnostic DBE and 79 procedures for therapeutic DBE, which suggests that DBE is especially cost-effective in large-scale hospitals, with a substantial number of DBE procedures per year. Another study by Gerson *et al*[100] found that, regardless of the cost, DBE procedure was more cost-effective than CE-guided DBE procedure, because no additional costs were charged regarding further examinations and therapy could be given instantly. However, the workload for physicians would significantly increase if an initial DBE would be done and we may not forget that DBE is correlated with a higher rate of complications compared to CE. CE-guided DBE was associated with better outcomes in the long term because of fewer potential complications and fewer utilization of endoscopic resources. This can be explained by the high negative predictive value of CE, which leads to a reduction in the subsequent DBE procedures[92,100].

When CE is negative, the chance of rebleeding is low, so that further investigations can be deferred, even when a second test might be diagnostic[101-103]. Rebleeding was reported to be higher in CE-positive patients and patients using anticoagulants[103]. Nonetheless, gastroenterologists should consider close monitoring, alternative modalities in suspicious cases because the chance of rebleeding has been reported up to 28.4% and 35.3% during a median follow-up of respectively 23.7 mo and 31.7 mo[104,105]. Repeating the CE procedure however should only be considered if the bleeding presentation switches from occult to overt bleeding or the hemoglobin level drops with more than 4 g/dL[106]. Diagnostic yield of a repeated CE was reported to be between 35% and 75% and a subsequent management change was reported in 39% to 62.5% of the patients[107,108].

To conclude this chapter about OGIB, we have made a flow-chart to represent the current knowledge in this field. For this purpose we included the reviewed articles in previous flow charts[18,109] (Figure 3).

CD

Non-stricturing CD is the second main indication for CE. CD is a type of chronic IBD which may affect the whole gastrointestinal tract and lead to mucosal and transmural damage. Categorization of patients with CD is done based on the disease presentation: solely the small bowel (30%-35% of the patients), the small bowel and the large bowel (45%-50%) or only the large bowel (20%)[110]. So even though it primarily affects the terminal ileum, the ileocecal region and the large bowel, one third of the patients presents with only small bowel inflammation which challenges gastroenterologists to diagnose the disease. Traditionally small bowel involvement was diagnosed by radiological procedures, small bowel barium radiography, CT, colonoscopy with ileoscopy or enteroscopy. But with the invention of CE, new possibilities in CD diagnostics have become available.

CE can be very helpful in the diagnosis of new cases of Crohn and in the evaluation of known CD, with regard to the activity and extent of the disease. CE is reserved however for cases with unexplained symptoms, when other investigations remain inconclusive or when CE would affect the management of the patient[111]. So both in suspected as established CD, CE usually is performed third after a negative colonoscopy and ileoscopy, thereby replacing the traditional modalities. CE is considered positive for CD when more than 3 ulcerations are identified in the absence of NSAID use[111-113] or when 4 or more obvious clear ulcers, erosions, or a region with clear exudate and mucosal hyperemia and edema are seen[114].

Like in OGIB, CE also has shown a superior yield for detecting early inflammatory lesions in the small bowel comparing to all other modalities as can be seen in Table 3. The yield of CE in non-stricturing CD has been reported to be between 18% and 96%[81,95,115-119]. Triester *et al*[81] only found a significant difference in yield between CE and other modalities for diagnosing non-stricturing small bowel CD. However, a distinction should be made between suspected and established CD. The reported superior yield was only significant for evaluating established CD and was not reported for diagnosis of small bowel CD in patients with a suspected initial presentation of the disease. This was contradicted by Dionisio *et al*[115], who found that CE has a superior yield compared to small bowel radiography (SBR), CT enterography (CTE) and colonoscopy with ileoscopy in the diagnosis of suspected CD patients. Although the

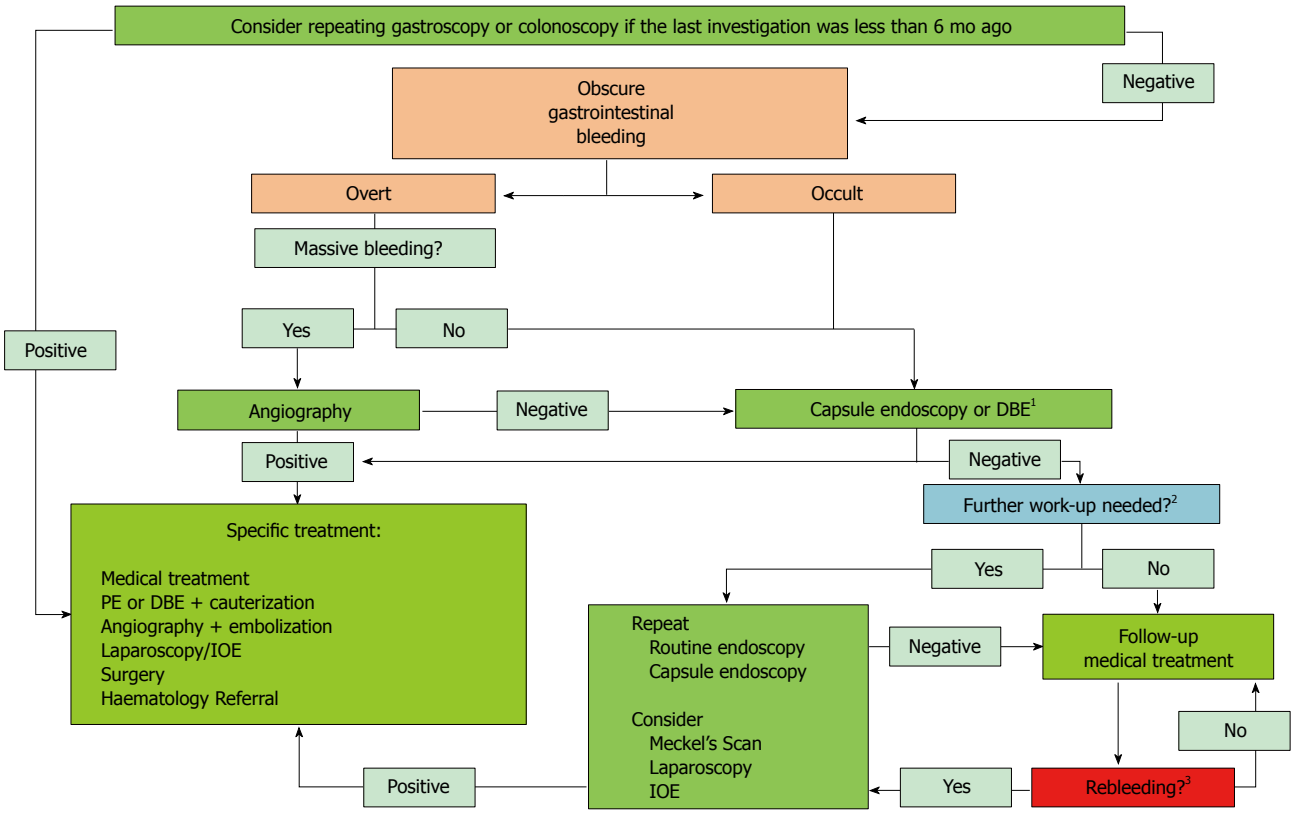

Figure 3 Recommended approaches for diagnosis and treatment of obscure gastrointestinal bleeding. [1]DBE is recommended in (1) patients requiring a biopsy or a therapeutic intervention (2) patients with an initial negative CE and suspicion of a small bowel lesion (3) large scale hospitals or (4) hospitals where CE is not available; [2]If a lesion is suspected, further work-up is needed; [3]Rebleeding was defined as a change from occult to overt bleeding or a hemoglobin level drop more than 4 g/dL. DBE: Double balloon enteroscopy; PE: Push enteroscopy; IOE: Intraoperative enteroscopy; Routine endoscopy: Uni/bidirectional endoscopy.

yield of CE in CD is high, the proportion of CD patients diagnosed with CE is rather low (0%-4%). Only in young patients presenting with abdominal pain plus diarrhea a 30% chance of diagnosing CD was achieved[114]. In established CD patients, CE was reported to be superior compared to SBR, CTE and PE, which was the same according to previous findings[115]. When compared to CT enterography and MR enterography, CE shows superior yields in the first two-thirds of the small bowel, but loses this superiority in the last portion of the small bowel by showing a yield similar to the comparators[120,121]. However, we may not forget that MR enterography is also capable of visualizing the small bowel surroundings, so that transmural and extra-intestinal manifestations can be diagnosed[122]. A recent study by Leighton *et al*[123] found that a combination of colonoscopy with ileoscopy and CE achieved a far more high yield than patients investigated with a combination of colonoscopy with ileoscopy and small-bowel follow-through (SBFT). They confirmed the role of CE as valuable third diagnostic option in diagnosis of suspected CD, when colonoscopy and ileoscopy turned out to be negative or inconclusive.

In patients with suspected CD, Girelli *et al*[119] found that, presuming a pre-test probability of CD of 50%, a positive CE was capable to raise the post-test probability up to 85% and if the CE was negative, it was capable to lower the probability to only 5%. In patients with established CD, the use of small bowel CE in monitoring therapy response is still a controversial issue. Many reports found that the clinical and biological response to treatment is not correlated with mucosal healing, which is monitored on CE, so it has not proven useful in this respect[124].

Caution should be taken when evaluating CEs positive for small bowel lesions. Because of the potential of CE to detect early lesions, CD-induced lesions are often non-specific and can be confused with NSAID-induced lesions. Both CD and NSAID-induced small bowel injury show endoscopically similar lesions and because of the inability of CE to take biopsies, the differential diagnosis remains inconclusive. Pathognomonic however for NSAID-induced lesions are the concentric diaphragmatic strictures in the ileum seen on endoscopy, which can lead to small bowel obstruction[125]. According to Doherty *et al*[126] the problem of false positive capsules also overestimates the incremental yield of CE compared to other modalities, necessitating a diagnostic golden standard to overcome the problem of premature CD diagnoses. Currently, there are two scores available to assess and monitor mucosal disease activity on CE. The CE CD Activity Index (CECDAI or Niv score) and the Lewis score are only recently developed and still have to prove their usefulness in standardizing the diagnosis of CD on CE before being widely accepted in clinical

Table 3 Comparison of different diagnostic modalities in Crohn's disease

Ref.	Country	Design	No. of patients	Comparator	Yield of CE, (%)	Yield of Comparator, (%)	Significant difference? (yes/no)	CE superior? (yes/no)	Other
Marmo *et al*[117]	Italy	RCT	31	SB radiography (enteroclysis)	71	26	Yes	Yes	Terminal ileum: yield 89% *vs* 37% Proximal SB: yield only 46% *vs* 13%
Chong *et al*[208]	Australia	Blinded prospective trial	43	SB enteroclysis	77	19	Yes	Yes	Results are in patients with a history of CD
				PE	77	14	Yes	Yes	
Triester *et al*[81]	United States	Meta-analysis and Systematic review	250	SB barium radiography	63	23	Yes	Yes	NNT = 3 to yield one additional diagnosis with CE
			114	Colonoscopy with ileoscopy	61	46	Yes	Yes	NNT = 7 to yield one additional diagnosis with CE
			93	CT enterography/CT enteroclysis	69	30	Yes	Yes	
			84	PE	46	8	Yes	Yes	
			18	MR enterography	72	50	No	Yes	
Solem *et al*[118]	United States	Blinded prospective trial	41	CT enterography	83	83	No	No	Specificity of CE (53%) was significantly lower than the other tests
				Colonoscopy with ileoscopy	83	74	No	Yes	
				Small bowel follow-through	83	65	No	Yes	
Pasha *et al*[95]	United States	Meta-analysis and Systematic review	343	DBE	18	16	No	No	
Dionisio *et al*[115]	United States	Meta-analysis and Systematic review	428	SB barium radiography	52	16	Yes	Yes	
			236	Colonoscopy with ileoscopy	47 (71)[1]	25 (36)	Yes	Yes	Suspected CD (Established CD)
			119	CT enterography	68 (71)	21 (39)	Yes	Yes	Suspected CD (Established CD)
			102	PE	66	9	Yes	Yes	Established CD
			123	MR enterography	55 (70)	45 (79)	No	Yes (no)	Suspected CD (Established CD)
Lu *et al*[116]	China	Retrospective Study	50	Colonoscopy with ileoscopy	96	66	Yes	Yes	Combination of two methods showed a higher yield, but no significant differences were reported between each two examinations
			34	CT enterography	96	85	Yes	Yes	
			39	Small bowel follow-through	96	67	Yes	Yes	

[1]Extra information between brackets is specific for Established Crohn's disease. PE: Push enteroscopy; CE: Capsule endoscopy; SB: Small bowel; NNT: Number needed to treat; DBE: Double balloon enteroscopy; RCT: Randomized controlled trial.

practice as an objective tool of mucosal inflammation measurement[127,128]. Although the yield of CE has been questioned by these diagnostic problems, CE still remains a valuable tool in the diagnosis of CD: a recent study by Hall *et al*[129] found a very high negative predictive value in the long term despite the questioned yield in patients with suspected CD, which makes it capable of safely ruling out suspected CD.

As mentioned before, capsule retention is especially feared in patients with CD because of possible strictures and stenosis. The reported 2.6% by Sharaf *et al*[130] has made small bowel imaging a standard exam previous to the CE procedure[19]. MR is a useful tool to asses patency of the small bowel[131]. Another possibility is the use of the previously discussed Pillcam PC (Given Imaging, Yoqneam, Israel), which indicates patency if the capsule is excreted intact or the scan has lost the RFID tag signal 30 h after ingestion[132], so the CE procedure can be done to evaluate the mucosal surface of the small bowel.

Cost analyses for CE in CD have been made and showed that colonoscopy with ileoscopy followed by a CT enterography was the most cost-effective choice

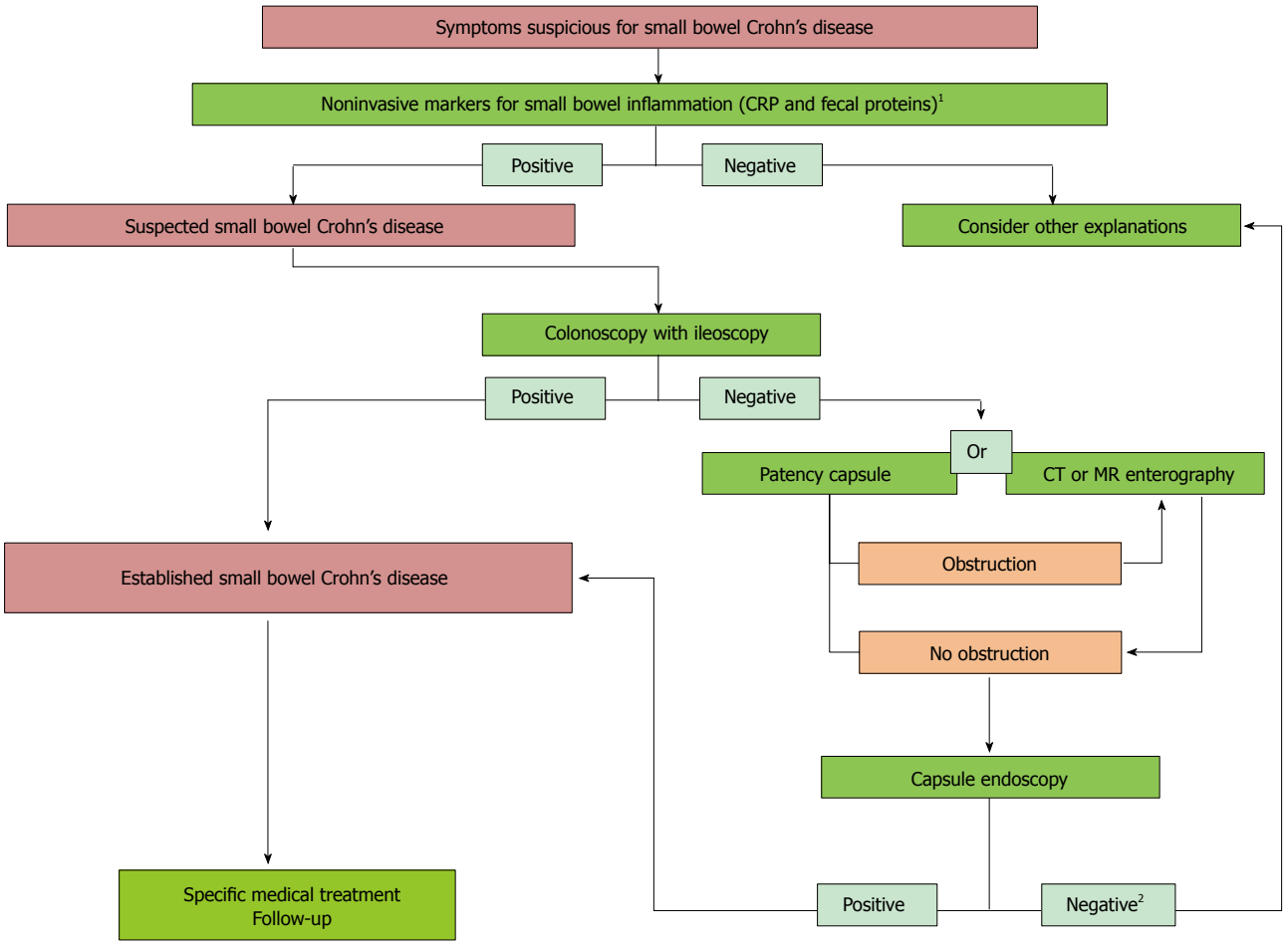

Figure 4 Recommended approaches for diagnosis and treatment of Crohn's disease. [1]Non-invasive markers have proven to be useful in giving baseline information about the presence of small bowel inflammation; [2]If capsule endoscopy (CE) is negative, Crohn's disease can be ruled out due to the high negative predictive value of CE. In that case, other explanations should be considered. CRP: C reactive protein.

among the different diagnostic options in patients suspected of CD[133]. Moreover, CE was proven to be not cost-effective as third diagnostic option, because of the high false positive rate, the diagnostic yield and the low pre-test probability of CD. Sharaf *et al*[130] confirmed these findings and concluded that CE is not a valuable option in patients with suspected CD. However, Leighton *et al*[134] found that CE did play a significant role in early diagnostics of CD, because it did not necessitate repeated procedures, physician visits and hospital stays, so direct costs could be reduced. Further investigation on this matter is needed.

In summary, CE has a superior diagnostic yield when compared to other modalities in suspected as well as established small intestinal CD. However, the question if this superior yield is due to false positive results remains unanswered. With the development of two scoring systems, this problem might be solved in the near future. Still, CE is a promising tool in CD diagnostics because of its capability to early diagnose small bowel lesions. We conclude with a flow chart based on the ICCE flowchart[131] and Mergener *et al*[109] with incorporation of new evidence[124,129] (Figure 4).

Surveillance of polyposis syndromes and detection of small bowel tumors

Small bowel tumors make up only 3%-6% of the gastrointestinal neoplasm cases despite the 90% of the gastrointestinal tract surface the small bowel covers, which makes it a difficult entity to diagnose[135,136]. The most frequently observed tumors are adenocarcinoma, gastrointestinal stromal tumor, carcinoid, lymphoma and sarcoma[137-140]. Symptoms are rather unspecific and include anaemia or overt OGIB and later abdominal pain, nausea, vomiting, weight loss and anorexia[141,142]. Thereby tumors are mostly found on CE or DBE when investigating patients with OGIB[80,139,140,143]. A study by Singeap *et al*[137] reported a detection rate for small bowel tumors of 4.9% in patients presenting with OGIB or other nonspecific symptoms. Other studies have found a tumor detection rate of 6%-12% on CEs done for OGIB[144]. The insidious process often is responsible for the delayed diagnosis of a patient, which impacts the further management of the patient[145]. Fast tumor detection is therefore very important, since management can be changed accordingly and outcomes can be improved even in malignant lesions if metastasis is

absent[146]. Small bowel tumors can be benign, potentially malignant, malignant or metastatic. However the majority, 60%, of these tumors are malignant[144], and differentiation between benignant and malignant cannot be made on CE. Tumors mostly appear as masses or polyps, but also can present as ulcers and stenoses in a minority of the cases. Hereditary polyposis syndromes like Familial Adenomatous Polyposis (FAP) and Peutz-Jeghers Syndrome (PJS), are another entity and apart from the colon polyposis, patients often develop benignant small bowel pathology with a high tendency to evolve into cancer[147].

CE was evaluated for small bowel tumors and hereditary polyposis syndromes and turned out to be a valuable diagnostic tool[148,149]. The pooled detection rate of CE was 55.9%[19]. Therefore, In patients with suspected small bowel tumors, CE can be the first choice in diagnostics[137]. In a study by Schulmann *et al*[147] it was stated that CE was capable of detecting small bowel polyposis, located in the distal jejunum and ileum beyond the reach of PE. These polyps could subsequently be removed by DBE, so surgery was avoided. However, most FAP patients with distal polyposis also presented with proximal polyposis, which was equally detected by CE as well as PE. Proximal jejunal polyposis is significantly correlated with the presence and severity of duodenal disease, which is one of the main locations for adenocarcinoma and subsequent mortality. Because CE was capable of detecting proximal small bowel polyposis and given its superior sensitivity and non-invasive nature, it was recommended as a surveillance tool in a subgroup of FAP patients with severe duodenal polyposis[147]. Duodenal polyposis itself is difficult to detect by CE, due to the rapid transit of the capsule in this part of the gastrointestinal tract. Another study by Plum *et al*[150] confirmed the superiority of CE compared to other modalities such as PE, ileoscopy and enteroclysis in patients with FAP. However, they also stressed on the fact that CE did not replace the other modalities, because CE sometimes missed lesions and did not manage to precisely localize the small bowel lesions. Also a study by Wong *et al*[151] confirmed the fact that CE could underestimate the number of small bowel polyps in FAP and a review by Koornstra[152] stated that CE cannot totally replace standard endoscopy in the surveillance of the proximal small bowel. A tool to overcome missed lesions might be the recently developed CICE tool, which enhances the contrast of the CE images and thereby improves the visibility in patients with small bowel polyposis. Although further evaluation is needed, a first trial showed that half of the adenomatous polyps could be better visualized and hamartomatous polyposis was better visible[153].

In PJS, CE was capable of detecting lesions with direct impact on further management. CE is the most accurate diagnostic tool to detect small bowel polyposis throughout the whole small bowel and can be seen as a safe alternative for the traditional modalities, such as PE and MR enteroclysis used in PJS and FAP[147]. The superiority of CE over MR enterography was also confirmed by Liao *et al*[19] who found that CE was capable of detecting smaller small bowel lesions. Urgesi *et al*[143] stated that CE could detect more lesions than the traditional endoscopy and radiological imaging in patients suspected for small bowel tumors. They concluded that CE played an important role in the diagnostic work-up of these patients[143]. Similarly another very recent study by Urquhart *et al*[154] found that CE was able to identify significantly more small bowel polyps compared with MRE in patients with PJS. Furthermore, Rahmi *et al*[155] found that CE was also useful in planning the DBE approach in patients in need of polypectomy. DBE, which achieves a similar yield as CE, is useful when biopsy, exact pre-operative localization or local therapy, such as stenting or balloon dilatation is needed[156].

CE also has its limitations in the detection of small bowel tumors. First of all it is not useful in an emergency setting, such as obstruction and peritonitis, because of the risk of capsule retention[145]. Furthermore, CE is not capable of treating locally or taking biopsies, needed to differentiate between benignant and malignant[157]. Finally CE is not able to differentiate a mucosal bulge from a smooth-walled tumor. To overcome the latter problem, the scoring system SPICE (Smooth, Protruding lesion Index on CE) has been developed. A score greater than 2 is suggestive of small bowel malignancy, but further validation is needed[158].

Just like in CD, the risk of capsule retention is present. Yet the rate is lower in patients with intestinal tumors compared to patients with CD[19]. Moreover, Bailey *et al*[146] stated that obstructions due to neoplasms were a positive complication because, since the tumor anyway needed to be treated by enteroscopy or surgery, the impacted capsule could serve as a guide. Like in CD, if the patient is suspicious for obstruction, imaging should be done before CE. Management of malignant small bowel tumors is primarily surgical. In selected cases, this can be performed laparoscopically. Adjuvant chemotherapy and radiotherapy may be needed, depending on the histology of the tumor[135].

We can conclude by stating that CE is a diagnostic tool with a big value regarding its yield in diagnosis and surveillance of small bowel tumors/polyps. However, it is complementary to the traditional modalities and can not substitute them. CE is recommended third after negative bidirectional endoscopy in patients with OGIB or other unspecific symptoms indicating a possible small bowel tumor. It can be used first as a complementary diagnostic tool in patients with established hereditary polyposis syndromes. We summarized the evidence in two flow-charts based on the Consensus statements for small–bowel CE, 2006/2007 by Mergener *et al*[109] and a study by Plum *et al*[150] (Figures 5 and 6).

NSAID side-effects

NSAIDs can inflict injury along the whole gastrointestinal tract, when used for a prolonged time. Although many

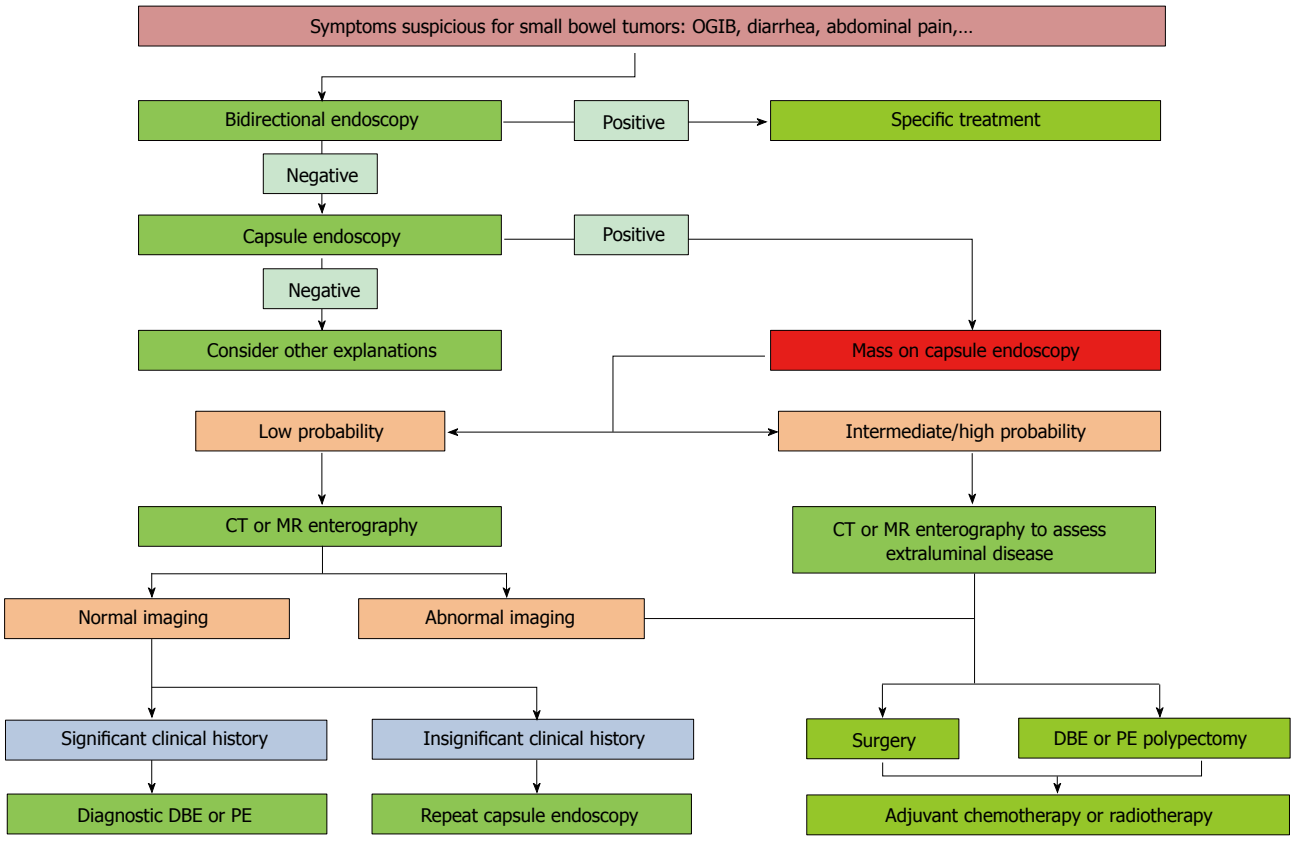

Figure 5 Recommended approaches for diagnosis and treatment of small bowel tumors. DBE: Double balloon enteroscopy; PE: Push enteroscopy; OGIB: Obscure gastrointestinal bleeding.

publications have emphasized on the incidence of upper gastrointestinal lesions, fewer have mentioned lower gastrointestinal ones. However, as mentioned before, NSAIDs can also induce small bowel lesions, which can be observed on CE. In fact, these lesions are far more common than the NSAID-induced gastropathy[159]. Furthermore, complications in the lower gastrointestinal tract, such as perforation, bleeding, or obstruction are currently increasing while upper GI complications are decreasing[160], which necessitates the need of small bowel diagnostics in the field of NSAID side-effects.

In seventy percent of the patients using NSAIDs continuously, mucosal damage of the small intestine has been reported on CE or DBE[161,162]. Even a two-week NSAID-regimen with slow-release diclofenac resulted already in macroscopic injury of the small intestine in 68%-75% of the volunteers[163]. Different types of lesions have been observed ranging from mucosal redness and multiple petechiae to erosions, ulcers, loss of villi, diaphragm-like strictures, which are pathognomonic for NSAID-induced enteropathy, and even severe bleeding[164,165]. Most symptomatic patients present with OGIB with or without obstruction symptoms and are accordingly diagnosed[166,167].

Both CE and DBE have been evaluated for NSAID-induced lesions. They show a similar yield of 60% in diagnosis[166,168]. CE however is preferred for screening of NSAID-induced lesions and evaluation of further treatment because of its non-invasive character. DBE on the other hand is the first choice in patients suspicious of strictures. NSAID-use has been recognized as a risk factor for capsule retention and CE should therefore be avoided in these patients[19]. Furthermore DBE is preferred when further examination of the lesion, endoscopic or histologically, is needed or when local therapy has to be given, such as balloon dilatation of a stricture or endoscopic coagulation, clipping or injection of the bleeding site. Balloon dilatation of a stricture seems to be safe, since the muscularis propria remains intact and perforation is subsequently rarely observed[156]. A recent study by Tacheci *et al*[169] confirmed the high sensitivity of CE and further stated that subclinical small bowel damage also could be observed on CE. If NSAID enteropathy is found on CE or DBE, further investigation can be done using other modalities such as radiological examination, the permeability test, scintigraphy, the fecal excretion with ^{111}In white blood cells and measurement of the calprotectin concentration in the feces[164].

Just like in CD, scoring systems are available to classify lesions and to consider and evaluate further treatment[127,161,163,168]. However, no standard scoring system is thoroughly evaluated. Different therapeutic options are available. The first choice of therapy is a discontinuation in the use of NSAIDs, which in most cases is not possible due to the underlying pathology[161]. Cyclooxygenase-2 (COX-2) selective inhibitors, prostaglandin derivatives, a combination of NSAIDs and

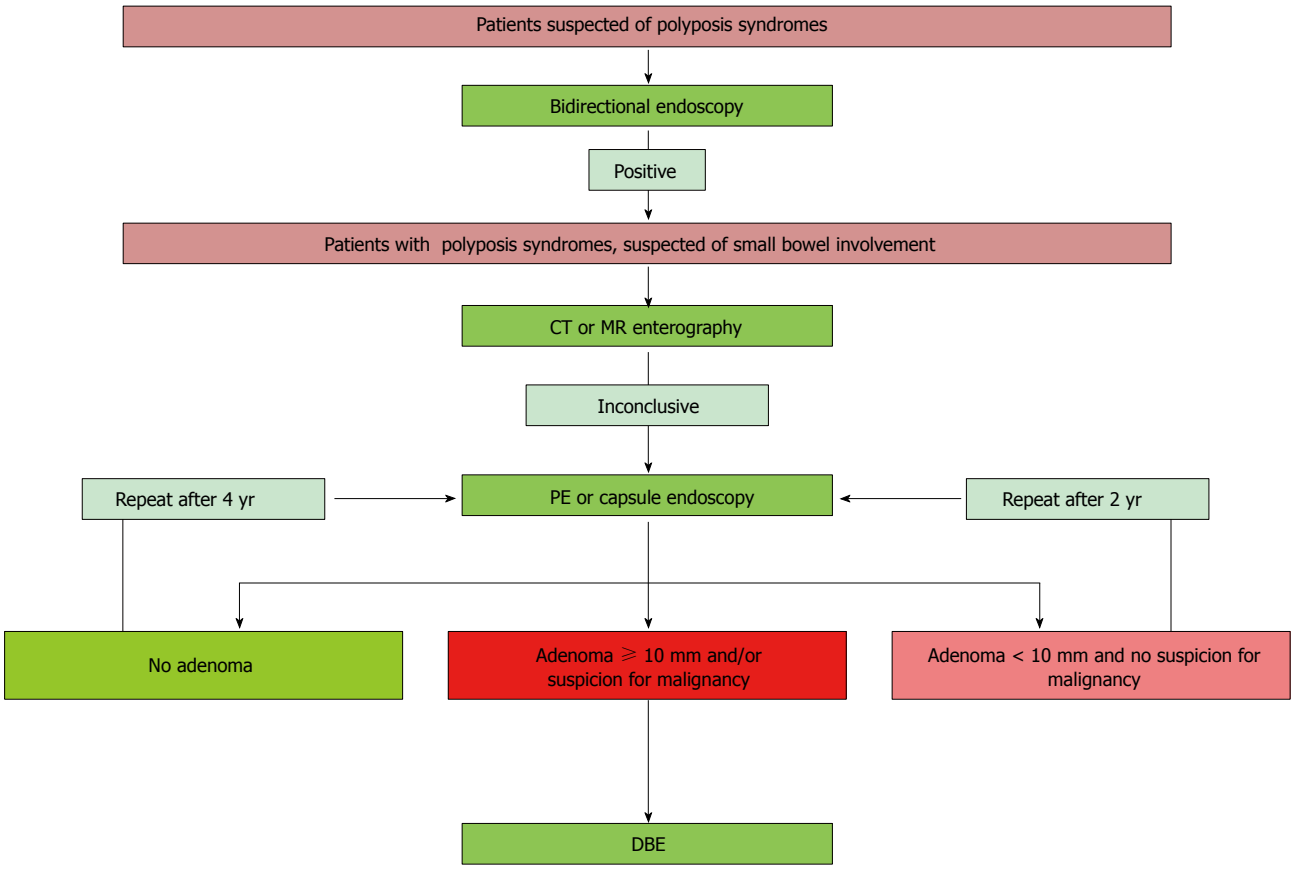

Figure 6 Recommended approaches or diagnosis of small bowel hereditary polyposis. DBE: Double balloon enteroscopy; PE: Push enteroscopy.

phosphatidylcholine, cytoprotective drugs and probiotics are all useful for the treatment of NSAID-induced small intestinal injuries[159]. Yet controversy remains around the use of selective COX-2 agents. A trial by Goldstein *et al*[170] reported that a 2-wk regimen of selective COX-2 agents caused fewer small intestine injuries than treatment with a nonspecific NSAID. This was confirmed in a big RCT by Chan *et al*[171]. However, Maiden *et al*[172] showed that COX-2 selective inhibitors caused the same amount of small bowel damage as long-term NSAIDs, which is interesting given the fact that they affect the gastroduodenal mucosa to a lesser extent[170]. So COX-2 might play a significant role in the maintenance of the small bowel integrity. We can conclude that it remains unclear whether selective COX-2 inhibitors truly prevent NSAID-induced enteropathy.

Also chronic Low-dose aspirin (LDA) users are at risk of small bowel enteropathy. The phenomenon was first described by Leung *et al*[171] in 2007 and the study by Endo *et al*[165] was the first to report the characteristics of the small bowel damage associated with long-term LDA use. The use of LDA however was less harmful than other types of NSAIDs[166]. These findings may have implications on treatment of the large group of patients requiring anti-inflammatory or antithrombotic drugs.

Celiac disease

Celiac disease is caused by an chronic auto-immune response of the intestines to gliadins in the diet and occurs in approximately 1% of the population in genetically susceptible persons[174]. It is characterized by duodenal folds, scalloping of folds, mucosal fissures, crevices or grooves, visible submucosal vessels, micronodules in the duodenal bulb and a mosaic pattern in the small bowel mucosa[175]. The lesions are visible on CE, which makes CE therefore a perfect tool to assess small bowel damage in these patients. In a large meta-analysis by Rokkas *et al*[176] sensitivity and specificity of CE in celiac disease have been reported up to 89% and 95% respectively. This was similar to a previous meta-analysis by El-Matary *et al*[177] which reported a sensitivity of 83% and a specificity of 98%. However, to confirm celiac disease in patients with positive serologic markers, a biopsy is needed, which is not possible with the current capsules. Therefore, the gold standard for the diagnosis of celiac disease remains the histological findings of a small bowel specimen obtained through gastroduodenoscopy.

The main indications to use CE are serological positive patients, who are unwilling to undergo gastroduodenoscopy or patients with antibody-negative villous atrophy. The latter group showed a higher yield on CE, compared with CE in serological positive patients with biopsy-proven celiac disease and persisting symptoms as was found by Kurien *et al*[178]. Also in patients with non-responsive celiac disease, defined by persistent or recurrent symptoms under treatment with a gluten-free diet, CE showed to be of use to detect

complications, such as multiple erosions, ulcerations, ulcerative jejunitis and adenocarcinoma[179]. Tennyson *et al*[180] confirmed these findings, but emphasized that CE was not a necessary tool in the evaluation of non-responsive celiac disease when no alarm symptoms are present, such as weight loss and abdominal pain, or when no loss of T-cell antigens on intraepithelial lymphocytes or loss of clonality of the T-cell receptor gene was observed. In the latter situations, a combination of CE and CT or MR enterography should be performed. In all other cases, upper gastroduodenoscopy with biopsy remains the gold standard. A recent study by Van Weyenberg *et al*[181] found similar results stating that CE could be used in patients with non-responsive celiac disease to identify the cases who are at risk of complications. CE might also be useful in the follow-up of patients with celiac disease under treatment with a gluten-free diet, regarding mucosal healing, because the follow-up of duodenal histology is not representative for the mucosal healing more distally[182]. Finally, Akin *et al*[183] confirmed other authors by stating that CE was useful as an alternative to duodenal biopsy in patients unable or unwilling to undergo gastroduodenoscopy and further stated that CE could be of use in the diagnosis of celiac disease in elderly patients with unspecific symptoms.

In conclusion, gastroduodenoscopy remains the diagnostic tool of choice for celiac disease, but CE shows to be a useful adjunctive tool in specific situations.

UPCOMING CHALLENGES

To conclude this paper about the current knowledge of CE, we would like to offer an insight in its bright future. Since its release in 2001, optics, battery life, visualization and software have been improved, with consequences on yield, completion rate and reading time. We have already discussed some technological advances in CE, but we will now shortly focus on future expectations of this technology.

One major field of advancement will be the maneuverability. If a capsule endoscope would be steerable and could approach a site of interest, this could be a big step forward in the diagnosis and treatment of diseases of the whole gastrointestinal tract. With efficient movement, battery life could sustain during movement through the whole gastrointestinal tract and thereby could increase completion rate. Various studies have been done and many prototype active capsules, using different locomotion techniques are currently under investigation for human use[184-188]. However, in the near future, remote manipulation using magnetic forces will be the first to be commercially available. These capsules contain a magnet, which can then be mobilized with an externally handled magnetic paddle or with a joystick. Perspective of the camera also can be adjusted with this magnet, rendering the desired image[189]. Swain *et al*[190] was the first to document the use of a magnetic field to guide a capsule through the human oesophagus and stomach. Since this article, many studies have followed, especially focusing on investigation of the stomach[191-194]. To overcome the problem of capsule impaction and to improve mucosal visualization, especially in the colon, insufflation techniques have recently been described by several authors using a capsule with a magnetic controlled drug release system to create a basic chemical reaction forming CO_2 in the lumen[195-197]. Another very interesting topic is a novel wireless platform able to measure and locate the force opposing capsule motion as a reflection of the gastrointestinal tract resistance[198]. It is the first platform for magnetic control of CEs that implemented this intermagnetic force measurement feature.

Another advancement might be the availability of a controlled drug release feature. This could help gastroenterologists in the local treatment of various gastrointestinal diseases, such as medical treatment of CD or even hemostasis in OGIB. Only one study introduced a capsule able to microposition a needle and to deliver 1 mL of a targeted medication, while resisting peristalsis with its holding mechanism[199].

The inability of taking biopsies is a third challenge CE faces. Together with an accurate maneuverability, this could enable CE to completely take the place of DBE in diagnostic and even therapeutic endoscopy of the small bowel. In 2008, Valdastri *et al*[200] was the first to successfully report an *in vivo* experiment with a capsule with built-in clip-releasing mechanism. The VECTOR project by the European Commission is currently developing a capsule for diagnosis and treatment of gastrointestinal cancer[201]. Another study also investigated the use of a large number of thermo-sensitive microgrippers in CE for this purpose of grabbing and retrieving tissue samples, which showed promising results[202].

Finally, to end this paper, we would like to reflect on the environmental consequences of capsule endoscopies, a subject that will become more important in the future, given the growing importance of CE. Although the ASGE consensus states that the capsule is "disposable and designed to be excreted"[3], considerations around this topic should be made, since the capsule contains many particles with potential biohazards[203]. Pezzoli *et al*[204] was the first to publish a small article on this matter in 2011. They found that it was possible, after retrieval and cleaning, to reactivate used capsules with a 10 min procedure and a new battery cost of only 2 euro. Recycled capsules could then be given a second life in, *e.g.*, veterinary procedures[205].

CONCLUSION

This paper gives a brief but complete overview on small bowel CE anno 2014. As the technology is still evolving and new insights are still being published every year, we emphasize that healthcare-providers should continue to monitor the medical literature for recent data, in order to provide the best evidence-based care for their patients.

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REVIEW

Endoscopic ultrasound-guided biliary drainage as an alternative to percutaneous drainage and surgical bypass

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Abstract

Endoscopic retrograde cholangiopancreatography had been a treatment modality of choice for both benign and malignant biliary tract obstruction for more than half century, with a very high clinical success rate and low complications. But in certain circumstances, such as advanced and locally advanced pancreatobiliary malignancies (pancreatic cancer, cholangiocarcinoma, ampullary tumor) and tight benign strictures, endoscopic retrograde cholangiopancreatography (ERCP) fails. Up to this point, the only alternative interventions for these conditions were percutaneous transhepatic biliary drainage or surgery. Endoscopic ultrasound guided interventions was introduced for a couple decades with the better visualization and achievement of the pancreatobiliary tract. And it's still in the process of ongoing development. The inventions of new techniques and accessories lead to more feasibility of high-ended procedures. Endoscopic ultrasound guided biliary drainage was a novel treatment modality for the patient who failed ERCP with the less invasive technique comparing to surgical bypass. The technical and clinical success was high with acceptable complications. Regarded the ability to drain the biliary tract internally without an exploratory laparotomy, this treatment modality became a very interesting procedures for many endosonographers, worldwide, in a short period. We have reviewed the literature and suggest that endoscopic ultrasound-guided biliary drainage is also an option, and one with a high probability of success, for biliary drainage in the patients who failed conventional endoscopic drainage.

Key words: Endoscopic ultrasound; Endoscopic ultrasound; Biliary drainage; Choledochoduodenostomy; Hepaticogastrostomy; Technique

Core tip: Failure of endoscopic retrograde cholangiopancreatography occurs in 5%-10% of the cases from many etiologies. However, there are few alternative options for biliary drainage up to the present time. Percutaneous biliary drainage and surgical bypass have their own drawbacks. Endoscopic ultrasound guided biliary drainage (EUS-BD) is a new platform with a very high technical and clinical success rate with

an acceptable complications. This review focused on the techniques, instruments including tips and tricks of this treatment modality. EUS-BD would become another alternative options for biliary drainage for both benign and malignant conditions in the future.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) was first introduced by Demling and Classen[1] in 1970 and is now the treatment of choice for pancreatobiliary diseases. It was originally used as a diagnostic tool, but since the development of magnetic resonance imaging (MRI) and computed tomography (CT), which provide superior soft tissue details of the pancreatobiliary tract, ERCP has been used exclusively for therapeutic purposes. Pancreaticobiliary obstructions are the most common cause of pancreatobiliary disease. Because of the development of ever better endoscopy instruments and technologies, the overall success rate of ERCP is now 90% to 95% with a complication rate of 5% to 7%[2-16]. Selective bile duct cannulation, if performed by experienced endoscopists, is an effective treatment for over 90% of cases of pancreatobiliary disease without anatomical obstructions. It is not effective in only 3% to 5% of cases, usually due to gastroduodenal obstruction, failed cannulation, distorted ampullae, altered anatomy, a periampullary diverticulum, or previous enteral stents. In cases of failed ERCP, patients are usually referred for either percutaneous transhepatic biliary drainage (PTBD) or surgical bypass. Both these procedures have high rates of undesirable complications. Endoscopic ultrasound-guided biliary drainage (EUS-BD) is a new technique that was developed within the last decade. It is an attractive alternative to PTBD or surgery when ERCP fails, but there is no strong evidence-based data on which procedure is best in this setting. We have reviewed the literature and summarize the advantages and disadvantages of PTBD, surgical bypass, and EUS-BD, including which technique is best for different clinical situations and how to maximize procedural success and reduce complications for each method.

Percutaneous transhepatic biliary drainage

Percutaneous transhepatic biliary drainage (PTBD) is a treatment option for patients for whom ERCP was not successful. The first report on PTBD was in 1961 by Catalano *et al*[17], and it was the treatment of choice for biliary drainage for more than two decades. The technical success rate for PTBD ranges from 75% to 100% and the clinical success rate ranges from 65% to 92%. The complication rate ranges from 9% to 31%[18-21]. Ho *et al*[22] published a review article on why PTBD should be considered first-line treatment for biliary drainage. Data showed that PTBD was superior than endoscopic biliary drainage in malignant hilar biliary obstruction with a technical success rate of 89% *vs* 41%, respectively ($P < 0.001$) and complication rates of 52% and 18%, respectively ($P = 0.04$). The data on the best type of drainage for distal CBD obstruction was inconclusive. PTBD is successful even in patients who have poor performance status. It also takes less procedural time and has few complications. The drawbacks are that it cannot be used in the presence of moderate to marked ascites and the fact that bile drainage is external, which impairs the patient's quality of life and involves difficulty in taking care of the catheter.

Surgical bypass

Surgical bypass is another treatment option after failed ERCP or unresectable hilar cholangiocarcinoma. Glazer *et al*[23] published a meta-analysis of randomized controlled trials of immediate stent placement *vs* surgical bypass in the palliative management of malignant biliary obstruction and found that there was significantly less recurrent biliary obstruction after surgical bypass than after stent placement (RR 0.14, 95%CI: 0.03-0.63, $P < 0.01$). The technical success rates (RR 0.99, 95%CI: 0.93-1.05; $P = 0.67$) and complication rates (RR 1.54, 95%CI: 0.87-2.71; $P = 0.14$) were not significantly different. Despite the more invasive approach, surgery produced better drainage; the drainage was internal, which had less effect on the patient's quality of life; and the interval to recurrent biliary occlusion was longer. Unfortunately, this technique is only suitable for patients who are good surgical candidates, which limits its use in cases of advanced malignant biliary obstruction.

EUS-BD

EUS-BD has been increasingly used as a minimally invasive alternative to surgery or radiologic intervention for biliary drainage after failed ERCP. EUS-BD can be performed *via* the papillary or gastrointestinal lumen. In the transpapillary route, rendezvous retrograde or antegrade stenting is used. For gastrointestinal luminal access, choledochoduodenostomy or hepaticogastrostomy is used, depending on the desired site of access. Artifon *et al*[24] conducted a randomized trial of EUS-guided choledochoduodenostomy or percutaneous drainage for unresectable distal biliary obstruction after failed ERCP. Technical success and clinical success were 100% in both groups. The complication rate for PTBD was 15.3% and the complication rate for EUD-BD was 25% ($P = 0.2$), and the cost of the procedures was similar (7570 USD and 5573 USD respectively, $P = 0.39$). Khashab *et al*[25] also conducted a trial of PTBD ($n = 51$) and EUS-BD ($n = 22$) after failed ERCP. Their technical success rate was higher in the PTBD group than the EUS-BD

Table 1 Advanvtage and disadvantage of puncturing sites

Route of access	
Extrahepatic route	Intrahepatic route
Easy approach (especially for large-caliber CBD)	The duct to be punctured is far from the scope
The puncture site is close to the scope	Easier scope positioning to achieve desired direction from the punctured duct
More difficult scope positioning to achieve desired direction from the punctured duct (rendezvous)	Easy scope handling
Easy guidewire negotiation and neo-tract creation (EUS-BD)	Difficult guidewire negotiation and neo-tract creation
Difficult scope handling	Higher risk of bleeding
	Higher risk of bile leakage

CBD: Common bile duct; EUS-BD: Endoscopic ultrasound guided biliary drainage.

group (100% *vs* 86.4%, $P = 0.007$), and their clinical success rates were 92.2% *vs* 86.4%, $P = 0.40$. PTBD was associated with higher adverse events (index procedure: 39.2% *vs* 15.7%), but stent patency and survival rate were equivalent in both groups. PTBD cost more than twice as much to perform as EUS-BD ($P = 0.004$), mainly because the re-intervention rate was higher (80.4% *vs* 15.7%, $P < 0.001$). Multicenter studies and other cases reports and case series[26-41] have confirmed the safety and efficacy of EUS-BD alone. In the authors' opinions, there was no one best approach among these three platforms for patients who failed ERCP. We recommend surgical bypass for patients with both duodenal and biliary obstructions who are good surgical candidates, but EUS-BD might be better than PTBD in patients with a large volume of ascites or patients who refuse external drainage. First-line treatment options depend on each institution's facilities, the clinician's expertise, and the patient's preferences after receiving enough information to accurately evaluate each procedure's strengths, weaknesses, and impact on quality of life.

EUS-guided biliary drainage

The use of endoscopic ultrasound-guided cholangiography was initially described by Wiersema *et al*[42] in 1996. The first EUS-guided biliary drainage was reported by Giovannini *et al*[43] in 2001. In 2004, Mallory *et al*[44] reported the first case of EUS-guided ERCP using the rendezvous technique.

Endoscopic ultrasound-guided biliary drainage can be classified into two major groups: the transpapillary approach (rendezvous retrograde and antegrade stent insertion) and the transmural approach (choledochoduodenostomy and hepaticogastrostomy)[45-48].

When to use the transpapillary rendezvous route

EUS-guided biliary drainage should be reserved for patients for whom ERCP was not successful. Some experts recommend the transpapillary (rendezvous) approach before the transmural approach[49-51]. Rendezvous technique is impossible if the ampulla is not accessible; but, even in patients with accessible ampullae, the rendezvous procedure can be difficult because it is necessary to change from the echoscope to the duodenoscope and the railroad technique during guide wire grasping is not always easy. In the authors' opinion, the advantage of the procedure is that it's not necessary to create a bilo-entereic tract, which can sometimes produce leakage and bleeding. In patients with surgically altered anatomy in which the anastomotic opening could not initially be seen and the access to the opening was not too difficult. When the position of the echoscope is good enough and dilatation and the guidewire can be passed down to the duodenum easily, rendezvous is a good option. If access is through the intrahepatic ducts (left lobe segments Ⅱ or Ⅲ) or extra-hepatic duct [common bile duct, (CBD)] the route depends on the location of the obstruction and the expertise of the endoscopist. If the site of obstruction is located above the proximal to mid-CBD, the intra-hepatic route is best. For distal obstruction with large CBD caliber, the extrahepatic route is the ideal choice.

Each route has advantages and disadvantages. It is easier to make the puncture using the extra-hepatic route, but the echoscope is in an upward curving position that makes it more difficult to control and easier to slip out. The puncture and guidewire placement are more difficult in the transmural route, but handling the scope is easier.

When to use the transmural route

The transmural route of EUS-guided biliary drainage can be achieved through an EUS-guided choledochoduodenostomy or an EUS-guided hepaticogastrostomy. The site of puncture depends on the location of the obstruction. If the obstruction site is distally located, choledochoduodenostomy is procedure of choice, while hilar obstructions are best served by a hepaticogastrostomy. It is easier to perform the puncture and handle the scope in segment Ⅱ of the left lobe of the liver[52,53] and the endoscopist who performed the procedure has to confirm that the puncture site is not in the esophagus in order to avoid higher risk of mediastinitis. Even though some experts use the right lobe[54], it is not yet standard of practice.

Tips for EUS-guided biliary drainage

Where to puncture: We summarized the advantages and disadvantages of extrahepatic and intrahepatic duct puncture in Table 1.

Table 2 Compare the two neo-tract creation methods

Neo-tract creation methods	
Cauterization	Non-cauterization
Easy neo-tract creation with no need for forceful manipulation	More difficult and forceful manipulation, especially when the intervening tissue is thick or the direction is inappropriate
More tissue injury from thermal burn	Less injury, smaller diameter of the neo-tract
The procedure takes less time	Lower risk of bile leakage or bleeding
More complications, especially bile leakage or perforation	

Table 3 Compare the two neo-tract dilation methods

Dilatation methods	
Balloon dilation	Graded dilation
Radial force leads to bigger neo-tract diameter (easier but greater risk for bile leakage, bleeding and perforation)	Axial force creates a smaller neo-tract. More difficult, but less leakage and less bleeding)
Easier stent insertion	Stent insertion can be more difficult
Only a single dilation session is needed and there are fewer guidewire exchanges	More sessions of dilation are needed and there are more frequent guidewire exchanges

How to create the bilo-enteric tract

There are two major ways to create a bilo-enteric tract: cauterization with a needle knife or small caliber cystotome especially 6 Fr in diameter[55-66] and non-cauterization with a tapered-tip catheter[67] or Soehendra stent retriever[68]. Neo-tract creation is followed by neo-tract dilation. The advantages and disadvantages of these two approaches are summarized in Table 2.

Neo-tract dilation can also be performed two ways: balloon dilation or graded dilation. Both methods are evaluated in Table 3.

There is no best approach. The technique of choice depends on the individual endoscopist's expertise. If balloon dilation must be used, the authors recommend the small size (4 mm diameter) balloon dilator.

What is the best stent?

In the early years of EUS-guided biliary drainage, the most commonly used stent was plastic; but many experts used fully covered, self-expandable metal stents (FCSEMS) instead of plastic stents and reported good outcomes[69-71]. Many types of metallic stents were developed for this purpose. Even though metal stents create a wider lumen with better drainage ability, they are more expensive and there is a risk of migration. Recently, Galasso *et al*[72] developed a stent suitable for EUS-guided hepaticogastrostomy called the Gio-Bor stent. It is a half-covered SEMS stent (Figure 1). The authors recommend an FCSEMS or partial CSEMS stent 40 to 60 mm in length for EUS-CD and 80 to 100 mm in length for EUS-HG. The small introducer (7 Fr) FCSEMS and partial CSEMS are shorter procedures and need fewer guidewire exchanges. However, there was a multicenter Japanese study[38] demonstrate that higher bile leakage was associated with plastic stent placement, therefore there was a trend towards to preference of using covered SEMS to prevent this complication.

What are the commonly encountered problems?

How to locate the puncture site: The site of puncture should be evaluated both endosonographically and fluoroscopically. Endosonographic tracing of the left intrahepatic bile duct was important in guiding the tip of needle and helping the endoscopist select the segment most suitable for puncture and easy guidewire negotiation. The fluoroscopic view can also help the endoscopist assess the best angle for bile duct puncture and easy neo-tract creation. Interestingly, if the scope's tip is perpendicular to the gastroduodenal wall, it will make the dilation process more difficult, so we recommend a slightly tangential angle. If the tip of the scope is too angulated, it will make the puncture more difficult. The distance between the punctured duct and the probe should be no more than 1-2 cm. Before starting the puncture, check Doppler color flow to avoid the intervening vessel.

DIFFICULT GUIDEWIRE NEGOTIATION

Using a 0.025 stiff guidewire (VisiGlide) or a 0.035 hydrophilic tip guidewire will make guidewire negotiation easier. The direction of the needle tip will directly affect guidewire manipulation. If the direction of the needle is opposite to the desired guidewire direction, manipulation will be really difficult. Moving the guidewire back and forth just a little bit (jiggling maneuver) will help change the guidewire direction. Using guidewires designed for manual twisting maneuvers or that have accessories, such as Terumo or ViziGlide guidewires, will make guidewire manipulation easier.

Guidewire shearing or knotting

Most endoscopists who perform EUS-guided biliary drainage have experience with guidewire shearing or knotting during the procedure. Saxena *et al*[73] and

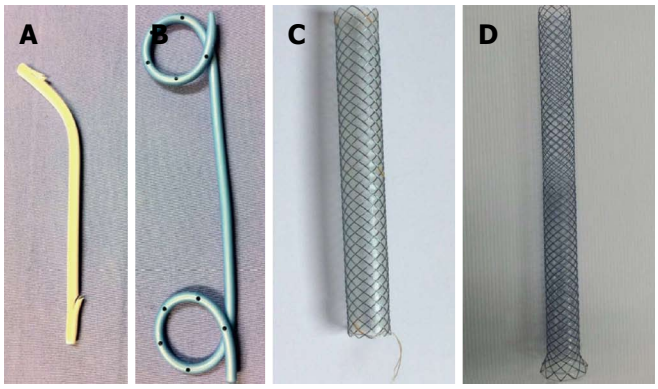

Figure 1 The different types of stents used in Endoscopic ultrasound guided biliary drainage. A: Plastic stent; B: Double-pigtail plastic stent; C: Fully covered, self-expandable metal stent; D: The Gio-Bor stent.

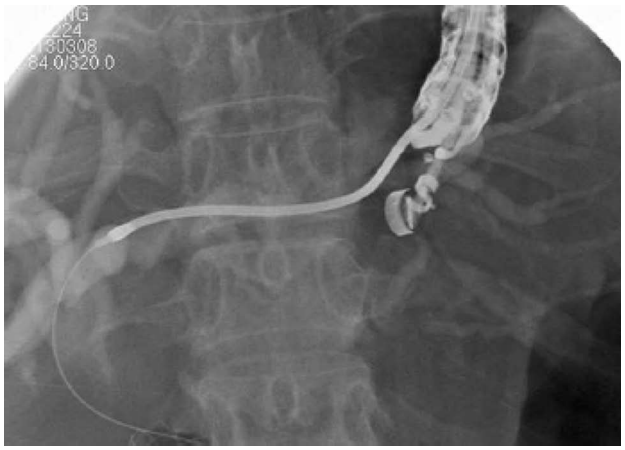

Figure 2 The Soehendra stent retriever was used in neo-tract creation.

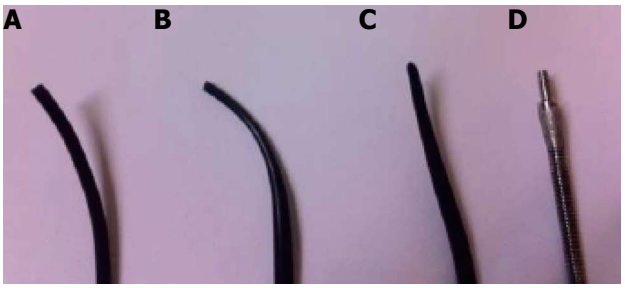

Figure 3 Different types of catheter tips. A: Soehendra stent dilator; B: Tapered tip catheter; C: Sharp tip catheter (self-made); D: Soehendra stent retriever.

Khashub *et al*[74] recommend flushing the channel with water and using a special type of needle, such as an access needle, which is designed to resolve these problems. However, in the authors' experience, this specially designed needle was not sharp enough in some situations and did not prevent guidewire shearing. We found that the way to prevent shearing and knotting was to push, not pull, the guidewire back, even if the desired duct was not yet punctured, and to exchange the needle for the small-sized dilator or tapered-tip catheter after the guidewire was looped and continue the guidewire negotiation later on. We have had no problem with shearing or knotting if we followed these guidelines.

How to deal with thickened soft tissue between the puncture site and bile duct

The distance between the puncture site and the desired duct is a very important factor in neo-tract creation. If the distance is longer, it is more difficult to penetrate through the tissue and pierce the bile duct. Another factor is the stiffness of the tissue between the puncture site and the bile duct. If the patient has liver fibrosis, the tissue is stiffer and this can make creation of a neo-tract more difficult. If difficulty is encountered, we recommended that the endoscopist should, firstly, re-check the position of the scope tip to make sure it is not perpendicular to the gastric wall. If graded dilation is being performed, change the dilating catheter to a smaller size or a catheter with a tapered tip, use a tapered-tip cannulation catheter, or re-shape the tip of the catheter by cutting it to a needle shape. Dilating with a Soehendra stent retriever, which has a drilling effect, might also be useful (Figure 2). If all of the above methods fail, cauterization may be necessary. Different types of catheter tips are shown in Figure 3.

Complications can occur if the needle knife is used with the Odd ratio of 12.4[75]. To minimize possible tissue damage during neo-tract creation, only open the knife half of its full length and cauterize until it enters the duct. In process of dilation, the dilator should be inserted after the knife is used. For cystotome usage, it very important to push the cystotome catheter against the mural and bile duct wall firmly, before starting the cauterization (this technique would help to enter the bile duct easily).

HOW TO MINIMIZE THE COMPLICATIONS DURING NEO-TRACT DILATION

Generally, the least chance of bile leakage and bleeding if the diameter of neotract is as small as possible. Therefore, the authors recommend not to dilate the neo-tract larger than the size of stent introducer (always not more than 8.5 Fr). For graded dilation technique, 8.5 Fr size is suitable for Soehendra dilator and only 7 Fr size is suitable for Soehendra stent retriever whereas smaller balloon especially not more than 4 mm in diameter is suitable for balloon dilation.

FUTURE RESEARCH AND DEVELOPMENT

The development of single step device which might be more suitable to each specific procedure would be helpful the help endoscopist to overcome the cubersome techniques such as multiple guidewire exchanges and would make the procedure time shorter; Smaller introducer (7 Fr) of smaller sized covered SEMSs (6 or 8 mm in diameter) would be benefit for less complications and shorter procedure time; Randomized control trial that EUS-BD as the treatment of choice in some particular conditions such as surgical altered anatomy would be interesting; The possibility of using EUS-BD as the preferable options than transpapillary drainage should be widely discussed and prospective study should be conducted.

CONCLUSION

EUS-guided biliary drainage is safe and effective when performed by an experienced endoscopist, and is an alternative to PTBD and surgical bypass after failed ERCP. Unfortunately, it use is still limited to tertiary care hospitals with advanced-complex endoscopy units. Clinicians will need to choose a treatment method based on each patient's status, preferences, and the facilities of the hospitals in their area.

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Self-expandable metal stents for achalasia: Thinking out of the box!

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Abstract

Achalasia is a primary motor disorder of the esophagus diagnosed manometrically in the clinical setting of dysphagia to both solids and liquids. Currently established treatment options include pneumatic dilation, laparoscopic Heller myotomy, botulinum toxin injection performed endoscopically, oral agents that relax the lower esophageal sphincter and esophagectomy for refractory, end-stage disease. Despite their effectiveness, a significant proportion of patients eventually relapses and needs retreatment. In this setting, several new techniques are under investigation promising future enrichment of our therapeutic armamentarium for achalasic patients. Among them, peroral endoscopic myotomy and self-expandable metal stents placed across the gastro-esophageal junction represent the most encouraging modalities, as initial studies assessing their efficacy and safety indicate. This review highlights the role of self-expandable metal stents in the management of patients with achalasia. Their possible position in the therapeutic algorithm of achalasia along with established and novel techniques is also assessed. Finally, the need for large prospective randomized trials is underlined in order to elucidate the numerous relevant issues.

Key words: Achalasia; Self-expandable metal stents; Dysphagia; Endoscopy; Treatment

Core tip: Recommended treatment of patients with achalasia are associated with significant clinical relapse over subsequent months or years. Therefore, numerous innovative techniques are under evaluation. Self-expandable metal stents may represent a promising alternative according to initial studies. They may gain a place in the therapeutic algorithm of achalasia in the view of its different types and stages, patients' characteristics and other emerging modalities.

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INTRODUCTION

Achalasia is a primary esophageal motility disorder characterized by aperistalsis in the distal portion of the esophageal body and incomplete or absent relaxation of the lower esophageal sphincter (LES). It is a disease of unknown cause; it pathophysiologically results primarily from the degeneration of ganglion cells in the myenteric plexus of the esophageal wall[1,2].

Achalasia is a rare clinical entity with annual incidence and prevalence of approximately 1.6 and 10 cases per 100000 individuals, respectively. Both sexes are affected equally, there is no racial predilection and the age of diagnosis ranges between 25 and 60 years[3,4]. Onset is rather insidious and disease progression gradual accounting for high rates of delayed diagnosis. The predominant symptom of achalasia is dysphagia to solids and liquids. Other symptoms include regurgitation of undigested food or saliva occasionally leading to aspiration and pneumonia, sub sternal chest pain, weight loss and heartburn[5].

The diagnosis of achalasia when clinically suspected is suggested by barium esophagram and established by manometry. On barium swallow supporting findings include aperistalsis, dilation of the esophagus, bird-beak appearance of the gastro-esophageal junction and delayed contrast medium emptying[6]. Manometry typically reveals incomplete or absent LES relaxation in response to a swallow and aperistalsis in the distal 2/3 of the esophagus[7]. Recently high resolution manometry classifies achalasia in 3 subtypes namely I (classic), II (with panesophageal pressurization) and III (spastic or vigorous)[8]. This classification possibly correlates with the final outcome of treatment[9,10]. Endoscopy may be normal or reveals a dilated esophagus with retained saliva and undigested food particles along with difficulty in passing the gastro-esophageal junction. Of importance, endoscopic examination and, when indicated, imaging studies are mandatory to exclude focal malignancy mimicking primary achalasia[11,12].

CURRENT TREATMENT OPTIONS AND THEIR LIMITATIONS

Treatment modalities for achalasia aim at reducing LES resting pressure thus relieving dysphagia and regurgitation and preventing the long-term development or mega-esophagus. This goal is accomplished by either mechanical disruption of the LES muscular fibers (*e.g.*, pneumatic dilation, myotomy either laparoscopic or peroral endoscopic) or by pharmacological decrease in LES pressure (*e.g.*, botulinum toxin injection, oral nitrates and calcium-channel blockers)[13,14].

Pneumatic dilation (PD) represents a highly-accepted first-line therapy for primary achalasia due to its cost-effectiveness and low complication rates. PD is performed in a gradual fashion by experienced endoscopists using standard-diameter balloons. Initial success rates are high and up to 90% of patients report symptomatic relief. Favorable predictors include older age (> 45 years), female gender, narrow esophageal lumen, post-dilation pressure < 10 mmHg and type II pattern on high-resolution manometry[10,15,16]. However, improvement is often not sustainable in the medium - to long-term period, since prospective studies suggest that approximately two thirds of patients eventually relapse and need additional dilations and possibly surgery[17]. Moreover, subsequent dilations seem less effective and patients referred for myotomy are at increased risk for intra-operative complications. Mostly feared complication is esophageal perforation with an overall median rate of 1.9% (range 0%-16%)[18]. Additionally gastroesophageal reflux disease occurs in 15%-35% of patients necessitating antisecretory medications[19].

Laparoscopic Heller myotomy (LHM) coupled with Dor fundoplication is the primary alternative to PD for achalasia. Initial clinical remission is achieved to nearly 90% of patients but this excellent outcome seems to wane over time[18,20]. Long-term studies show that 18% of patients require PD and 5%-10% of them repeat myotomy or esophagectomy 5-11 years post-operatively[21,22]. Nevertheless, a meta-analysis published in 2013 favored LHM over PD in terms of both short- and long-term efficacy[23]. Being more invasive, surgery is associated with a protracted recovery period and numerous complications including gastro-esophageal reflux disease (GERD), dysphagia associated with the fundoplication that may require dilations, perforation, bleeding, leaks and infections which affect negatively its cost-effectiveness[20]. Despite these imperfections, LHM is preferred over PD for patients younger than 40 years as they frequently need more re-dilations than older subjects[5]. To note, very recently, Nau *et al*[24] suggested that LHM should be used as a benchmark against which other treatments for achalasia are judged, given its outstanding results[24].

Developed by Inoue in Japan peroral endoscopic myotomy (POEM) is the most fascinating new treatment option for achalasia currently being extensively studied in the United States and in Europe. This approach involves endoscopic dissection of the esophageal submucosal space and the creation of a tunnel eventually allowing LES circular muscle bundles dissection[25,26]. Initial studies in a total of 1000 procedures with a mean follow-up from 3 to 12 mo report excellent short term results (clinical success 82%-100%) and only minor self-limited adverse events (mainly tense capnoperitoneum) in less than 10% of patients[27]. The most serious complication is mediastinitis due to esophageal leak, although its incidence seems remarkably low. On the other hand, recent studies show that objectively-measured gastroesophageal reflux disease prevalence after POEM varies from 20% to 46%, higher than that in early reports and similar to those following LHM with Dor fundoplication[28,29]. No procedure-related death has been reported. In all circumstances, further studies with long-term follow-up, as well as randomized trials comparing POEM with LHM and PD are warranted before POEM

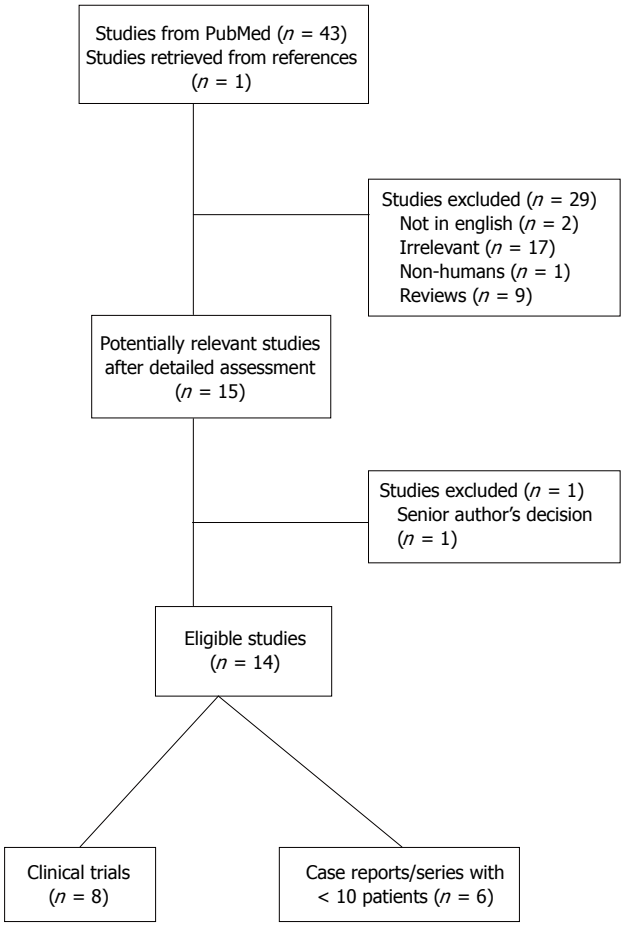

Figure 1 Flow diagram of the literature search strategy and valuation of studies identified for review.

can be recommended[25] as the procedure of choice.

Intrasphincteric botulinum toxin injection (BTI) can be easily performed during routine endoscopy in poor surgical candidates. Using a sclerotherapy needle, 100 units of the toxin are administered just above the squamocolumnar junction in at least 4 quadrants. Its initial efficacy reaches those of PD and LHM. Unfortunately, symptoms relapse in more than 50% of patients necessitating additional injections at 6-24-mo intervals[30]. Main complications are post-procedural chest pain, heartburn and allergic reactions[19]. In addition, BTI may increase the technical difficulty of subsequent myotomy either surgical or endoscopic[31].

Oral pharmacologic agents indicated for primary achalasia include calcium-channel blockers and nitrates. They represent the least effective means of treatment[32]. Traditionally, they are administered 30 to 60 min prior to meals and act by decreasing basal LES pressure and tone. Their efficacy is variable and their use is limited to those who are not suitable to receive invasive therapies. Moreover, side effects such as headache, hypotension and peripheral edema, as well as tachyphylaxis, diminish their application[19].

Finally, for patients with end-stage achalasia (megaesophagus, or sigmoid-esophagus) who have failed PD and/or LHM, esophagectomy should be considered[33]. Esophageal resection results in symptomatic improvement in more than 80% of patients; however, it is associated with significant mortality reaching 5.4% in uncontrolled studies and recurrence of dysphagia in up to 50% of patients[34].

As shown, all currently available therapeutic modalities for primary achalasia remain of palliative nature, given that the underlying mechanism cannot be reversed. Moreover, a good proportion of patients will experience symptom recurrence and require retreatment. In this context, several new endoscopic treatments are under evaluation over the last years. This review aims to highlight the role of self-expandable metal stents (SEMS) in the management of patients with achalasia.

USED MATERIALS AND METHODS

Using PubMed we carried out a thorough review of the literature to identify all articles published between January 1995 and July 2014 referring to the use of SEMS in achalasia. The search was initially performed using the term "achalasia and stents" as a free text. A total of 43 studies were retrieved and one additional was identified by a manual search of the references cited in the key articles. Each manuscript was subsequently cross-checked by two authors (AS, CM) to achieve a maximum completeness of the reports chosen for inclusion. In case of disagreement, a third senior author (KT) made the final decision. Eventually, 14 studies were considered suitable for review. The article selection process is presented in Figure 1.

SEMS FOR ACHALASIA TREATMENT

Early reports regarding the use of SEMS in the treatment of achalasia were published in 1998 by De Palma *et al*[35] A nitinol coil stent (InStent Inc., Eden, Praire, United States), 10 cm long, was placed in 4 patients with long-standing disease who were unresponsive to conventional treatment such as LHM, PD and BTI. Stent placement was successful in all cases and the patients achieved clinical remission during the follow-up period up to 12 mo. One of them developed reflux esophagitis treated medically[35].

Three years later the same authors presented their extended experience in 8 patients followed for a period ranging from 29 to 44 mo. Nitinol coil and Ultraflex (Microvasive, Boston Scientific, Natick, MA, United States) stents were placed across the gastro-esophageal junction. Although stent implantation was technically successful and all patients experienced complete remission of dysphagia, a significant complication rate was noted both in the early (within 30 d) and in the late (after 30 d) phase. In particular, 62.5% of patients had early complications (mainly stent migration, 37.5%) and 57.1% late complications (mainly chest pain, 28.5%). As a result the investigators concluded that the use of SEMS in achalasia should not be generalized but reserved only for carefully selected cases[36].

Unlike the rather promising experience of De Palma *et al*[35], a case series published in 2000 announced extremely disappointing results. Three different SEMS types, namely Gianturco Rosch Z stent (Wilson Cook Medical, Winston Salem, NC, United States) and Wallstent I and Ⅱ (Schneider USA, Plymouth, MN, United States) were inserted in 4 achalasic patients. Placement was technically feasible and uneventful. Symptomatic remission before further intervention varied between 2 wk and 10 mo. However, complications such as stent migration and dysphagia recurrence secondary to either food bolus impaction or inflammatory stricture occurred in all cases. Most serious, one patient died from bleeding due to an aorta-enteric fistula developed from a penetrating gastro-esophageal junction ulcer adjacent to the stent. The authors recommended that alternative to SEMS options should be preferred in the management of patient with refractory achalasia[37].

Thereafter, a center from the United States and one from Spain reported few cases of achalasic patients treated with SEMS insertion. The former used metal coil stents (Esophacoil, InStent Inc., MN, United States) in 2 patients with complicated refractory achalasia. Technical and clinical success was achieved; nevertheless, hematemesis secondary to severe erosive esophagitis and small bowel obstruction due to stent migration were encountered a few months after stent placement[38]. The Spanish center announced the use of SEMS (Hanarostent, MI Tech, IZASA, Seoul, South Korea) as an effective short-term bridging therapy in 2 achalasic patients, one pregnant and one with newly diagnosed pituitary tumor[39].

In 2009 Zhao *et al*[40] reported the results of a prospective study assessing the long term efficacy and safety of a specifically designed partially-covered SEMS, 30 mm in diameter, placed for 3-7 d in 75 achalasic patients. Both technical and post-procedural clinical success was 100%. During the long follow-up period (up to 13 years) the overall remission rates remained extremely high reaching 100% and 83.3% at > 5 and > 10 years, respectively. These excellent results, as well as the low rates of complications including stent migration and perforation (5.3% and 0%, respectively) were attributed to the large-diameter stent that had been used. On the other hand, the same factor was possibly responsible for the relative high rates of chest pain (38.7%), gastro-esophageal reflux (20%) and bleeding (12%). It was therefore suggested that temporary SEMS placement is effective and safe and could serve as an alternative or complementary method in the management of esophageal achalasia[40].

The importance of stent diameter in terms of clinical efficacy was evaluated in a prospective study with long-term follow-up conducted by Cheng *et al*[41] As the results indicate, the overall cumulative clinical remission rate was significantly higher for patients who underwent a 30 mm stent placement as compared with those who received a 25 mm and 20 mm one (87% *vs* 73% *vs* 47%, respectively). Similarly, the wider the stent, the lower the migration rate (6.6% *vs* 13.3% *vs* 26.7%) and the higher the chest pain rate (40% *vs* 33% *vs* 17%, respectively)[41].

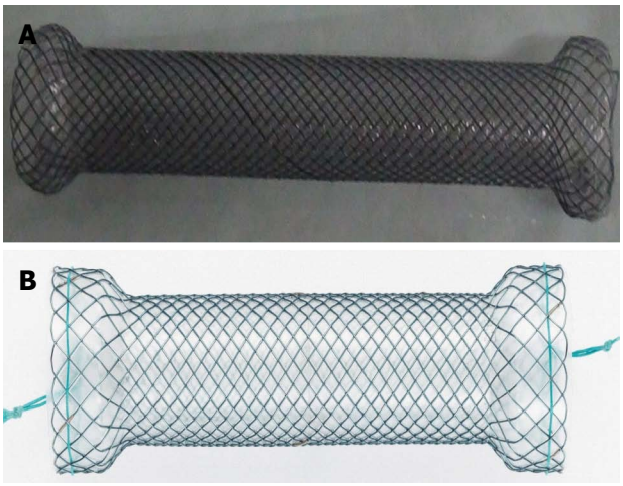

Figure 2 Large-diameter self-expandable metallic stent for achalasia. A: Self-expandable metal stents similar to that used by Coppola *et al*[43]. Picture is provided by courtesy of Mr. Kuhn D, Micro-Tech Europe GmbH, Dusseldorf, Germany; B: Niti-S stent. Picture is provided by courtesy of Mr. Bekzat M, TaeWoong Medical, Seoul, South Korea.

A recent study by Zeng *et al*[42] assessed for the first time the efficacy of fully-covered SEMS, 20-25 mm in diameter, in achalasia (Z-stent, Sigma, Huaian, China). Fifty-nine patients with no prior treatment were enrolled and underwent stent placement for a 1 mo period. The cumulative remission rates after 6, 12, 18, 24, 30 and 36 mo were 90.9%, 81.8%, 76.4%, 69.1%, 65.%% and 49.1%, respectively. Sub sternal chest pain was the most common complication (25.5%), followed by heartburn (10.6%) and stent migration (8.5%)[42].

Apart from Eastern countries, a study from Italy published a few months ago evaluated the safety and efficacy of SEMS as a temporary treatment in patients with achalasia. Seven patients underwent a 30 mm partially-covered stent (Micro-Tech, Nanjin, China) placement for 6 d and were followed thereafter for a mean period of 19 mo. Beneficial effects on dysphagia were excellent in 5 and good in 2 patients during the follow-up. No serious complication was observed. The authors concluded that large stent placement may permanently disrupt the muscular fibers of the cardia and possibly represents a safe and effective option for patients not fit for more invasive interventions[43]. A stent similar to the one used in this study as well as, a nitinol-covered stent are illustrated in Figure 2. Major points of the above mentioned studies are presented in Table 1.

SEMS *VS* PD AND BTI IN THE TREATMENT OF ACHALASIA

Several studies compare SEMS *vs* established treatment options such as PD and BTI in the management of patients with achalasia, as presented in Table 2. Of note,

Table 1 Published series using self-expandable metallic stents for achalasia treatment

Ref.	Coppola *et al*[43] (2014)	Zeng *et al*[42] (2014)	Cheng *et al*[41] (2010)	Zhao *et al*[40] (2009)	De Palma *et al*[36] (2001)	Mukherjee *et al*[37] (2000)	De Palma *et al*[35] (1998)
Baseline characteristics and effectiveness							
Patients, *n*	7	59	90	75	8	4	4
SEMS diameter, mm	30	20/25	20/25/30	30	18	18/20	18
Time to removal, d	6	30	4-5	3-7	?	?	?
Technical success, %	100	100	100	100	100	100	100
Initial remission, %	100	100	100	100	100	100	100
Major complications							
Stent migration, *n*	0	4	14	4	4	1	0
Perforation, *n*	0	0	0	0	0	1	0
Bleeding, *n*	0	0	14	9	0	1	0
30-d mortality, *n*	0	0	0	0	0	1	0

Table 2 Published comparison studies

Ref.	Li *et al*[47] (2010)	Li *et al*[46] (2010)	Zhu *et al*[45] (2010)	Cheng *et al*[44] (2003)	Cai *et al*[48] (2013)
Compared methods	PD *vs* SEMS (20, 25, 30 mm)	PD *vs* SEMS (30 mm)	PD *vs* SEMS (30 mm)	PD *vs* SEMS (permanent, temporary)	BTI *vs* SEMS (25 mm)
Patients, *n*	30/30/30/30	80/75	38/63	60/8/65	51/59
Technical success, %	100/100/100/100	100/100	100	100/100/100	100/100
Initial remission, %	100/100/100/100	100/100	100	100/100/100	94.1/100
Remission at maximum follow-up, %	0/0/28.6/83.3	0/83.3	42.1/88.9	10/33.3/85.5	4.17/49.1
Major complications					
Migration, *n*	NA/8/4/2	NA/4	NA/2	NA/0/0	NA/4
Perforation, *n*	0/0/0/0	0/0	0/0	0/0/0	0/0
Bleeding, *n*	2/3/5/6	4/9	3/10	6/3/8	0/0
30-d mortality, *n*	0/0/0/0	0/0	0/0	0/0/0	0/0

PD: Pneumatic dilation; SEMS: Self-expandable metallic stent; NA: Not applicable.

no randomized trials are currently available.

In 2003 Cheng *et al*[44] compared PD with permanent uncovered or ant reflux covered SEMS and temporary partially-covered SEMS. The latter stents, sized 20-30 mm in diameter, were inserted and withdrawn successfully after 3-7 d. According to the results, temporary partially-covered SEMS exhibited significantly superior long-term therapeutic efficacy as compared to the rest interventions, although immediate symptomatic relief was equally excellent. Interestingly, permanently uncovered metal stent dilation proved to be unsuitable for patients with achalasia due to high rates of gastro-esophageal reflux and stent occlusion secondary to hyperplasia of granulation tissue[44].

To overcome the limitations of their previous study (*e.g.*, relatively short follow-up and great variety in stent diameters) the same investigators reported the results of a retrospective trial comparing PD and temporary partially-covered SEMS (Zhiye Medical Instruments, Guangzhou, China and Youyan Yijin Advanced Materials, Beijing, China). The diameter of the balloon or stent used was 30 mm. The stent was removed within 7 d after placement and the patients were followed both clinically and manometrically for more than 10 years. The results showed that both interventions are very efficacious in the immediate post-procedural period. However, the total symptom scores in patients treated with SEMS were statistically better than those treated with PD throughout the follow-up period ($P < 0.05$). LES pressure did not exhibit significant differences apart from one time frame (after 8-10 years). As expected, complications such as pain and bleeding occurred more frequently in the stent group compared to the balloon one (42.9% *vs* 23.6% and 15.9% *vs* 8%, respectively)[45].

Similar results were obtained by an uncontrolled prospective study with a long-term follow-up comparing SEMS and PD of the same diameter (30 mm). Temporary (3-7 d) SEMS placement was associated with significantly higher clinical remission rates in all follow-up periods (up to > 10 years). Notably, the long-term efficacy of SEMS seems to be comparable with that of LHM. Although of no statistical significance, complications like chest pain and bleeding were more common in the SEMS group, whereas stent migration occurred in 5.3% of patients[46]. Additionally, the same medical group showed prospectively that temporary SEMS with a diameter of 30 mm achieved significantly higher clinical remission rates after more than 10 years of follow-up as compared to patients treated with PD with a 30 mm balloon or SEMS with diameters of 20 or 25 mm (83.3% *vs* 0%, 0% and 28.6%, respectively). Surprisingly, the clinical remission rate with PD in the long-term was extremely poor suggesting a possible study limitation[47].

The only study that compares BTI and SEMS for

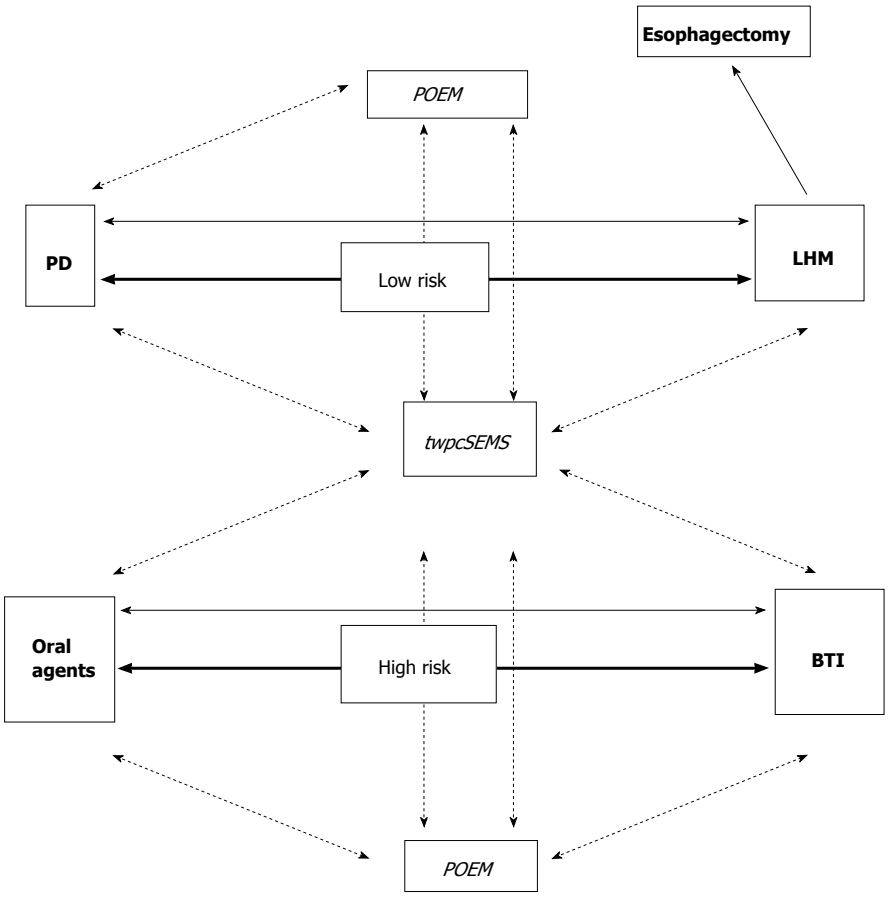

Figure 3 Proposed therapeutic algorithm for achalasia based on surgical risk. Currently established treatments are in bold. Investigational ones are in italics. Arrows indicate current first-line treatments. Lines binding different treatments indicate management of failures. Dotted lines indicate assumed steps in management, while solid lines the to-date recommended[11]. PD: Pneumatic dilation; LHM: Laparoscopic Heller myotomy; BTI: Botulinum toxin injection; twpcSEMS: Temporal, wide, partially covered, self-expandable metallic stent; POEM: Peroral endoscopic myotomy.

the treatment of achalasia has been published by Cai and colleagues in 2013. A partially-covered SEMS 25 mm in width was applied and retrieved after 4 wk. The mean duration of follow-up was 28 mo (range 10-36 mo). Based on the results, the patients in the SEMS group achieved significantly better improvements regarding global symptoms scores, dysphagia and LES pressure. Moreover, differences in remission rates after 12 mo gained statistical significance favoring SEMS placement. No adverse events were observed in the BTI group, whereas 13 episodes of chest pain, 9 cases of regurgitation and 4 stent migrations were captured in the SEMS group[48].

SEMS IN THE NEW ERA

Achalasia treatment should be individualized taking into account both patients characteristics and available expertise. Although current established treatments are effective, emerging techniques such as SEMS placement are being developed, as presented. Nevertheless, what could be the exact position of SEMS in the therapeutic plan of achalasia, especially in the era of very promising interventions like POEM?

As shown in Figure 3, temporal placement of wide, partially covered SEMS could potentially serve as an alternative first-line treatment in both low and high surgical risk patients. This could be of great value mainly for the latter ones, given that the unique currently recommended treatment option (*e.g.*, BTI) exhibits short-term, only, efficacy. Temporal wide partially covered SEMS may also be preferred for all cases of treatment failures, irrespective of the initial therapy, offering an efficacious, well-tolerated choice. It may be hypothesized, that SEMS could possibly serve on a short-term basis as a bridging therapy until surgery is performed.

One could argue that POEM will eventually predominate in achalasia treatment due to its efficacy and safety profile according to initial studies. However, POEM is still a quite invasive procedure compared to SEMS placement. Additionally, it is by far more technically demanding, requires specific training and can be feasible only in centers of excellence worldwide[49,50]. General anesthesia requirements, time consumption and cost should be undoubtedly considered. Long-term results and adverse events in patients who have undergone POEM are still pending. Given the above, temporal placement of wide, partially covered SEMS seems able to maintain a role in the management of achalasic patients, even in the advent of POEM. Comparative randomized trials are

surely appreciated before achalasia therapeutic algorithm takes its definite form.

CONCLUSION

Treatment remains palliative since its neuronal defect seems to be irreversible. In this setting, temporal, wide, partially covered SEMS placement may represent a safe and effective alternative therapy for carefully selected patients. Several technical issues including stent type, stent diameter and length, optimal time for removal and prevention of complications are still open for discussion. Small size of treated population, low quality of studies' design and the majority of studies performed in Asia also preclude the generalizability of the reviewed evidence.

Additionally, the advent of self-expandable biodegradable stents used in the management of refractory benign esophageal strictures, as well as drug-eluting stents could provide an area for further innovation, in the field of stents in achalasia. Large, multicenter, randomized trials are warranted - while not always feasible - to elucidate the exact position of stent placement in the therapeutic armamentarium for the different profiles of achalasic patients.

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Intragastric surgery using laparoscopy and oral endoscopy for gastric submucosal tumors

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Abstract

We review the techniques and outcomes of the intragastric resection for gastric submucosal tumors (GSTs) using laparoscope and oral endoscope. In the literature, the mean operation time, intraoperative blood loss, pathological size of the tumor and postoperative hospital stay were 134 min, minimal, 31 mm and 6.4 d, respectively. There were no particular perioperative complications during the follow-up period (mean: 121.3 mo). Intragastric surgery using laparoscopy and oral endoscopy can be considerably beneficial for patients with GSTs locating in the upper third of the stomach between 2-5 cm in diameter and < 8 cm^2 in cross-sectional area and located in the upper third of the stomach.

Key words: Laparoscopic surgery; Intragastric resection; Gastric submucosal tumor; Oral endoscopy

Core tip: The laparoscopic approach for gastric submucosal tumors (GSTs) depends on the characteristics of the submucosal tumors including its location or size. In particular, GSTs located close to the esophagogastric junction or pyloric ring cannot be easily applied the laparoscopic local resection. Therefore, the intragastric approach is adopted for those tumors. This review evaluates the technique and outcomes of the intragastric resection for GSTs using laparoscopy and oral endoscopy. Intragastric surgery using laparoscopy and oral endoscopy can be considerably beneficial for patients with GSTs less than 5 cm in diameter and locating in the upper third of the stomach.

Tagaya N, Tatsuoka T, Kubota Y, Takegami M, Sugamata N, Saito K, Okuyama T, Sugamata Y, Oya M. Intragastric surgery using laparoscopy and oral endoscopy for gastric submucosal tumors. *World J Gastrointest Endosc* 2015; 7(1): 53-58 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i1/53.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i1.53

INTRODUCTION

Techniques for the resection of gastric submucosal tumors (GSTs) have seen a shift from an open to an endoscopic approach, and from gastrectomy to local resection[1]. Endoscopic approaches can be divided into oral endoscopic resection and laparoscopic resection. The latter may include the resection from outside, inside or both side, depending on the characteristics of the GST, including its location or size. In particular, GSTs located close to the esophagogastric junction (EGJ) or pyloric ring are not amenable to laparoscopic local resection, and instead an intragastric approach is adopted[2-5]. This review evaluates the techniques and outcomes of intragastric resection for GSTs using laparoscopy and oral endoscopy in a series of patients treated at our institution.

PREOPERATIVE EVALUATIONS

We preoperatively investigated the tumor conditions including the size, location and distance from the EGJ to proximal side of the tumor using an upper gastrointestinal radiological series and endoscopy. Furthermore, endoscopic ultrasound (EUS) was also added to evaluate the location and growing formation of the tumor within the gastric wall[6]. And, EUS-guided fine-needle aspiration biopsy examination was performed when necessary. Computed tomography with contrast medium was added to clarify whether there was any liver metastasis, dissemination, ascites, lymphadenopathy or other comorbidities, as well as the relationship between the tumor and the whole stomach.

INDICATION

The criteria for the use of laparoscopy and oral endoscopy for intragastric resection of GSTs were a tumor between 2-5 cm in diameter and < 8 cm^2 in cross-sectional area with the aim of possible removal *via* the mouth, or an endoscopically evident tendency of the tumor to grow in size during follow-up, and location of the tumor on the posterior wall of the upper third stomach or close to the EGJ[4].

SURGICAL TECHNIQUES

Standard technique[4,5]

The patient was placed in the supine position under general anesthesia. Initially a 12-mm port was initially introduced into the peritoneal cavity at the umbilicus, using the open laparotomy method. After creating a pneumoperitoneum by Carbon dioxide (CO_2) insufflation, and the operative field was kept at 8-10 mmHg of intra-abdominal pressure. The stomach was inflated to confirm the tumor condition using an oral endoscope. When we approached an intragastric technique, the anterior wall of the stomach was lifted up to the abdominal wall using a double-straight needle device (Ideal Lifting: Olympus Medical Systems Co., Tokyo, Japan) to insert the port easily. After this preparation, 5-mm and 12-mm ports were directly inserted into the stomach at the left upper quadrant of the abdominal wall, depending on the tumor location, under the observation of oral endoscope. To obtain the better intragastric operative field, CO_2 insufflation was added into the stomach. A linear stapler to minimize the deformity of the stomach and avoid the stenosis of EGJ carried out local resection of the stomach including the lesion with an adequate margin in all directions. The first fire of linear stapler was put on the normal gastric wall near the distal side of the tumor. The direction of the resection line was modified so as not to close the EGJ. The resected specimen with a plastic bag was removed from the mouth by an oral endoscope. If the tumor removal is complicated orally, we made a small gastrostomy enlarging 12-mm port site, and then the specimen extracted from the stomach. We immediately ensured the free margins around the lesion. The entry holes in the stomach were closed using a linear stapler or hand sewing intracorporeally. Finally, the stomach was re-inflated to check the air leakage or bleeding from the closed sites and confirm no stenosis at the EGJ. Abdominal port sites were closed without drainage tube.

In a modified technique, an initial 12-mm port was introduced at the umbilicus. After checking the intra-abdominal cavity by laparoscope during stomach inflation, the anterior wall of the stomach was pulled out through an umbilical incision, and a 12-mm gastric opening was made. This hole was used for insertion of an Endo-GIA linear stapler or a 10-mm laparoscope. Subsequently a 3-mm port was inserted into the stomach at the left upper quadrant to allow manipulation of the normal gastric mucosa near the tumor (Figure 1). The tumor was resected using a linear stapler under endoscopic guidance (Figure 2). The specimen was retrieved *via* the mouth. The entry hole in the stomach was directly closed extracorporeally, and the 3-mm hole of the stomach was closed inside the stomach by clipping using an oral endoscope (Figure 3). The skin was only closed at the umbilicus.

Single-site technique[7,8]

Initially a 2.5 cm vertical skin incision was made at the umbilicus, and a X small Alexis Wound Protector (Applied Medical, Rancho Santa Margarita, CA, United States) was attached to the incision. The stomach was pulled out through that incision, and a 2-cm opening was made in the anterior wall of the stomach by laparoscopic coagulating shears. A single port device or surgical glove with 3 or 4 working ports was introduced into the gastric orifice. After the stomach was inflated with CO_2 gas, intragastric pressure was maintained between 8 and 10 mmHg. A 10- or 5-mm laparoscope was inserted, and the target tumor was identified. The normal mucosa adjacent to the tumor was initially pulled up with a curved grasper

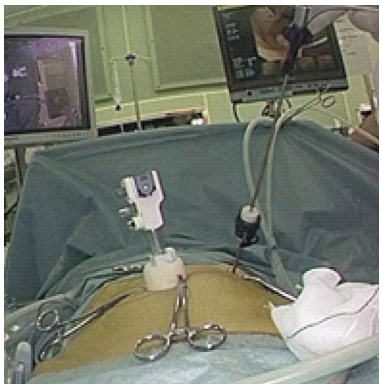

Figure 1 Intraoperative outside view of one 12-mm port and 3-mm port.

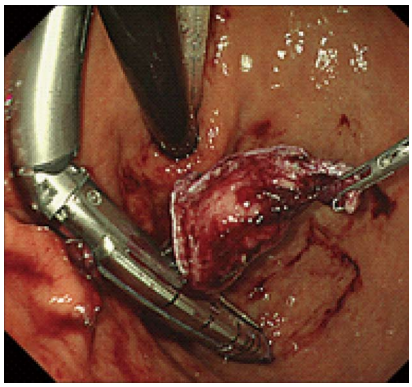

Figure 2 The tumor was resected by an Endo-GIA stapler under the guidance of oral endoscope.

and resected using a 30-mm linear stapler not to expose the tumor itself. Subsequently, the remaining main tumor area was resected continuously using a 45- or 60-mm linear stapler. The specimen was put into the plastic bag and retrieved from the single port site. After the single port device or surgical glove had been removed, the gastric orifice was closed using absorbable sutures. The stomach was re-inflated to confirm no bleeding or air leakage from the repaired site. The umbilical wound was closed without drainage tube.

POSTOPERATIVE EVALUATION

We postoperatively evaluated the passage condition at the EGJ and the deformity of the residual stomach in all patients on the postoperative day 1 by an upper gastrointestinal radiological series, and followed by gastroscopy every 6 mo thereafter. Further treatment for gastrointestinal stromal tumors (GISTs) was considered according to the results of immunohistochemical tumor staging.

DISCUSSION

Surgical resections for GSTs are classified into open, endoscopic or laparoscopic procedures. The selection

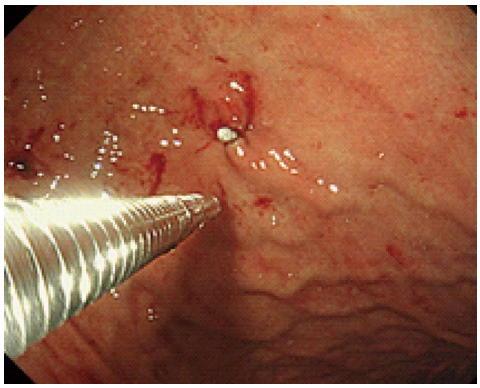

Figure 3 The hole of 3-mm port site was closed by a clip from the inside of the stomach.

of the procedure depends on the characteristics of the tumor, including its size, location and growth condition. In particular, laparoscopic intragastric resection can be modified for tumors located near the EGJ or pyloric ring, in order to avoid gastrectomy or stomach deformity after resection. From the viewpoint of minimal surgical invasiveness, several laparoscopic intragastric approaches have been reported, but the role of oral endoscopy for intragastric resection of GSTs has been emphasized.

The indications for intragastric resection also depend on the characteristics of the tumor. In general, tumors amenable to this technique are 2-5 cm in size and located on the posterior wall of the upper third of stomach, or close to the EGJ. In our experience, tumors more than 5 cm in size or 8 cm^2 in cross-sectional area require an additional gastrostomy for removal of the specimen from the stomach, because those sizes cannot be passed through the EGJ using an oral endoscope. However, when the tumor is less than 2 cm in size, resection depends on the results of FNA. Furthermore, when the tumor is more than 5 cm in size, a transgastric approach is selected for removal[4,5].

The actual resection method involved the use of an endo-linear stapler, coagulating shears or electrocautery. Stapled resection is more beneficial to provide with less operation time and blood loss, and can omit the suture of the resected area. In the resection process using an endo-linear stapler, if the 12-mm port is relatively close to the tumor, or if a tumor is larger than 5 cm, application of an endo-linear stapler is not easy, even if the stomach is inflated, because of the practical movable length of the stapler or the small opening of the stapler jaw[4,5]. Therefore we often use a minimum-length (30-mm) linear stapler, and place the 12-mm port on the greater curvature of the distal stomach under the guidance of oral endoscope. However, for any tumor located on the level of Z-line, submucosal dissection is applied circumferentially using electrocautery to prevent stenosis of the EGJ[9].

For successful intragastric resection of a GST, the use of an oral endoscope is mandatory for defining

Table 1 Basic data of the literature

Ref.	Year	Case	Gender (M/F)	Age (mean)	Location (U/M/L)	Distant from EGJ (mm)	Size (mm)
Choi and Oh[12]	2000	9	NA	NA	9/0/0	NA	NA
Matthews *et al*[13]	2002	3	NA	NA	3/0/0	NA	NA
Walsh *et al*[14]	2003	11	NA	NA	11/0/0	NA	24-85
Pross *et al*[15]	2003	5	NA	NA	5/0/0	NA	34 (28-41)
Uchikoshi *et al*[16]	2004	7	NA	NA	7/0/0	NA	27-75
Li *et al*[17]	2008	3	0/3	77	2/1/0	37 (30-50)	28 (20-40)
Na *et al*[7]	2011	7	3/4	65	6/1/0	NA	27 (23-38)
Sahm *et al*[18]	2011	7	NA	NA	NA	NA	38 (28-48)
Shim *et al*[9]	2011	6	3/3	48	7/0/0	NA	27 (15-40)
Tagaya *et al*[5]	2013	13	5/8	61	10/3/0	40 (10-70)	27 (10-65)
de Vogelaere *et al*[19]	2013	3	NA	68	3/0/0	NA	38 (27-68)
Dong *et al*[20]	2014	8	3/5	51	6/2/0	NA	28 (15-45)

NA: Not available.

Table 2 Clinical data of the literature

Ref.	Year	Operation time (min)	Complication	POHS (d)	Recurrence	Follow up (mo)
Choi and Oh[12]	2000	100-140	Open conversion: 1	5.9	None	Up to 42
Matthews *et al*[13]	2002	NA	NA	NA	NA	NA
Walsh *et al*[14]	2003	186 (120-320)	None	3.0-8.0	None	16.2 (1-32)
Pross *et al*[15]	2003	85-105	None	4.0-7.0	None	NA
Uchikoshi *et al*[16]	2004	141 (95-200)	Open conversion: 1	7.6	1 in 2 yr	14-99
Li *et al*[17]	2008	192 (140-240)	Staple line bleeding: 1	7.7	None	8-57
Na *et al*[7]	2011	86 (70-105)	Wound bleeding: 1	5.7	None	8.5 (1-23.3)
Sahm *et al*[18]	2011	NA	None	6.1	NA	NA
Shim *et al*[9]	2011	128 (105-145)	None	4.3	NA	NA
Tagaya *et al*[5]	2013	176 (132-217)	None	7.5	None	121.7 (1-192)
de Vogelaere *et al*[19]	2013	75 (67-82)	None	5.0	None	NA
Dong *et al*[20]	2014	85 (60-130)	None	7.4	None	NA

POHS: Postoperative hospital stay; NA: Not available.

precisely the location of the tumor, for determining the port placement site in the stomach, for assisting intragastric resection, for confirming hemostasis at the staple line, for retrieval of the specimen *via* the mouth, and for checking the presence of any air leakage from the resected area after re-inflation of the stomach. Schubert *et al*[10] have also reported that intraoperative flexible endoscopy has several advantages including facilitation of the trans-illumination of the gastric lesion during laparoscopic observation, elimination of preoperative tattooing of the lesion, and evaluation of the repaired gastric opening for any leakage after resection. Recently, Hiki *et al*[11] have reported laparoscopic and endoscopic cooperative surgery (LECS) for resection of GISTs. This method makes it possible to obtain an adequate cutting line independently of tumor location, eliminate an unnecessary resection of the gastric wall around the tumor in the setting of exogastric resection, and minimize any deformity of the stomach after resection. However, its indications are limited to intragastric growth-type tumors less than 5 cm in size, those with no direct tumor exposure, and those with no ulceration, in view of the attendant risk of dissemination. It is anticipated that oral endoscopy during laparoscopic procedures will become increasingly important in order to achieve minimal surgical invasiveness.

There are 18 reports covering laparoscopic intragastric resection of GSTs published between 2000 and 2014[5-10,12-23]. Six of them were excluded because their data were mixed with those for exogastric and transgastric procedures, or for single cases. We reviewed previous reports describing laparoscopic intragastric surgery (LIS) for GSTs (Tables 1 and 2)[5,7,9,12-20]. The number of cases ranged from 3 to 13, with a mean of 7 cases. The mean patient age was 62 years (range: 48-77 years). The tumor was located in the upper stomach in almost all cases (96.3%), with the exception of 3 cases. The mean size of the tumor was 31 mm (range: 27-38 mm). The common indications for intragastric resection of GSTs were a tumor location in the upper third of the stomach and posterior wall, intragastric growth, and a tumor diameter of less than 5 cm. The mean operation time was 134 min (range: 75-192 min). There were 4 complications (5.2%), including conversion to open laparotomy in 2 cases, bleeding from the staple line and wound in one case each, respectively. The mean postoperative hospital stay was 6.4 d (range: 4.3-7.7 d). The mean follow-up period was 48.8 mo (range: 8.5-121.7 mo), and only one case of tumor recurrence was recorded. However, the recurrence rate appears to depend on the size of the tumor: Nakamori

et al[22] reported that the recurrence rate increased with tumor size, and that the average period until recurrence was 23.6 mo. Evaluation of recurrence required a follow-up period of more than 2 years. This procedure has one limitation of consuming the number of linear staples, approximately 3 being necessary per procedure. When considering the possibility of recurrence, intragastric resection of GSTs using laparoscopy and oral endoscopy is suitable for tumors less than 5 cm in size and located in the upper third of the stomach.

Transumbilical single-incision laparoscopic abdominal surgery was introduced in 2007 and has since become disseminated worldwide. We have also applied single-incision laparoscopic local resection of the stomach for GSTs showing extragastric growth. There are a few reports[7,8] describing single-port access using a single port devices for tumors showing intragastric growth. Na *et al*[7] reported that a single-incision intragastric approach did not require the use of intraoperative oral endoscopy or pneumoperitoneum, and that the technique differed in three ways from the conventional approach: the operation time was reduced because of the use of a single gastrostomy and extracorporeal repair, the specimen was easily retrieved from the gastric opening without using an endoscope, and a better cosmetic outcome was achieved at the umbilicus. Morales-Conde *et al*[8] also reported intragastric endoscopically assisted single-incision surgery for GST at the EGJ. The single-site approach avoids multiple punctures of the stomach, and allows retrieval of larger specimens. However, this approach should be limited to selected cases involving tumors less than 5 cm in diameter without ulceration because of possible tumor rapture due to the complicated procedures employed.

In conclusion, intragastric surgery using laparoscopy and oral endoscopy can be considerably beneficial for patients with GSTs located in the upper third of the stomach. From the viewpoint of minimal surgical invasiveness, the significance of oral endoscopy during laparoscopic procedures is expected to increase for tumors in the stomach.

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MINIREVIEWS

Current status of single-balloon enteroscopy: Insertability and clinical applications

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Abstract

The single-balloon enteroscopy (SBE) system was launched in 2007, proposed as a simpler method than double-balloon enteroscopy (DBE). Controversy surrounds whether the SBE system has the same insertability as DBE. However, many methods have been proposed to improve the depth of insertion with the SBE system, involving several techniques and endoscopic accessories. SBE is used for investigating not only small bowel diseases, but also diseases of the pancreatobiliary and colonic structures. SBE is a necessary advancement for many endoscopic procedures and applications in modern clinical practice. In our review, we summarized the current literature concerning the insertability of SBE and described the technical aspects of improving the rate of deep insertion in SBE procedures. In addition, the recent applications of SBE to diseases besides those of the small bowel are described.

Key words: Single-balloon enteroscopy; Double-balloon enteroscopy; Small-bowel endoscopy; Endoscopic retrograde cholangiopancreatography; Endoscopic submucosal dissection

Core tip: The insertability of the single-balloon enteroscopy (SBE) system can be improved by technical innovations and by using endoscopic accessories such as carbon dioxide insufflation equipment. SBE is used not only useful for small bowel diseases, but also for colonic lesions and pancreatobiliary diseases. The SBE system is a necessary advancement for many endoscopic procedures in modern clinical practice.

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INTRODUCTION

Double-balloon enteroscopy (DBE) was developed by Yamamoto *et al*[1]. Since then, endoscopic observation of the entire small intestine has been possible without surgical intervention. The single-balloon enteroscopy

(SBE) system was launched in 2007 by Olympus Medical Systems (Tokyo, Japan) as an alternative to DBE[2-5]. SBE is a simpler method because the second balloon at the tip of the enteroscope is not present. However, controversy surrounds whether the SBE system offers the same insertability and diagnostic yield as DBE.

The purpose of this review was to summarize the current literature concerning the insertability and diagnostic yield of SBE and to describe the technical aspects of improving the depth of insertion in SBE procedures. In addition, recent applications to diseases besides those of the small bowel are described. While spiral enteroscopy is another alternative method of DBE[6-8], this method is not widely used in Japan; therefore, we did not discuss spiral enteroscopy in the present article. Details of the instruments used, and the basic principles of the insertion technique of SBE, have already been reviewed by Manno *et al*[9] in 2012.

INSERTABILITY OF SBE

Insertability compared with DBE

Total enteroscopy can be achieved using SBE. Usually, total small bowel visualization is confirmed by inserting the enteroscope through both the oral and anal routes and marking the midway point with an Indian ink tattoo or endoscopic clipping (Figures 1 and 2). The initial experience reports of SBE in Japan have been characterized by total enteroscopy rates of 12.5% to 71.4% (Table 1)[2-5].

Three randomized, controlled trials thus far have compared the rates of total small bowel visualization by DBE and SBE[10-12]. May *et al*[10] reported that complete enteroscopy was achieved with the DBE technique in 66% (33/50) of cases and only 22% (11/50) with the SBE technique ($P < 0.0001$). However, this study had a number of significant limitations. One was that the SBE system used in this study was not the original system produced by Olympus, but a DBE system made by Fujifilm Corporation (Tokyo, Japan) without the tip balloon attached. In 2011, Takano *et al*[12] also reported worse results for the insertability of the SBE system developed by Olympus compared to those for the DBE system developed by Fujifilm. The total enteroscopy rate was 0% in the SBE group and 57.1% in the DBE group ($P = 0.002$). This result suggested that the insertability of SBE might be inferior to that of DBE. However, Domagk *et al*[11] reported that DBE and SBE have comparable performance in the evaluation of the small bowel. Their study revealed that complete visualization of the small bowel was achieved in 18% and 11% of procedures in the DBE and SBE groups, respectively. These randomized control studies yielded conflicting results concerning the insertability of SBE compared to that of DBE.

We have discussed the insertability of SBE using total enteroscopy rate as a comparative parameter, because none of the currently known methods of estimating insertion depth are ideal[13]. However, the clinical impact of total enteroscopy rate is controversial, because in majority of the patients the fact whether total enteroscopy is achieved is not necessary to diagnose small bowel diseases[14]. Lenz *et al*[8] indicated that the first-choice enteroscope should be selected according to availability, physicians' experience, and clinical implications.

In the next section, the many methods of improving the insertability of SBE will be discussed.

Methods of improving the depth of insertion

The most important difference between SBE and DBE is the manner in which the small intestine is held by the tip of the enteroscope during sliding tube insertion. If the holding force is not sufficient, the enteroscope will slip back. Ohtsuka *et al*[15] discussed the method of improving the holding force in the small intestine using the SBE technique. To prevent the scope from slipping back during sliding tube insertion, it is important to use both upward and left angulation, as this helps to increase the holding force applied by the tip of the enteroscope. Furthermore, they recommended the use of a distal attachment to assist the fixation of folds in the small intestine.

A recent study suggested the usefulness of carbon dioxide insufflation during the SBE procedure in improving intubation depth[16,17]. Li *et al*[17] reported that the total enteroscopy rate of the carbon dioxide insufflation group was significantly higher than that of the air insufflation group (34.9% *vs* 17.6%; $P = 0.006$). Lenz *et al*[16] reported that oral intubation depth was significantly higher in the carbon dioxide group than in the air group (258 ± 84 cm *vs* 192 ± 42 cm; $P < 0.05$) in patients with previous abdominal surgery.

By using the techniques described above alongside carbon dioxide insufflation, the depth of SBE insertion devices can be improved. Interestingly, Ohtsuka *et al*[15] reported several cases of total enteroscopy using only the anal approach.

Complications

SBE is a safe diagnostic endoscopic procedure. However, serious complications such as acute pancreatitis[18,19] and perforation[20] could occur, although the rates of these complications are very low. Aktas *et al*[21] reported that while post-SBE hyperamylasemia occurred in 16% (13/81) patients, no acute pancreatitis was observed in 105 consecutive patients undergoing peroral approach SBE. Lenz *et al*[22] reported that the rate of severe adverse events after SBE procedures was only 0.6% (2/298) and did not differ significantly from that after DBE procedures in their large case series.

CLINICAL APPLICATIONS OF SBE

SBE for small bowel diseases

Parikh *et al*[23] summarized the clinical applications of SBE for small bowel diseases in 615 patients reported

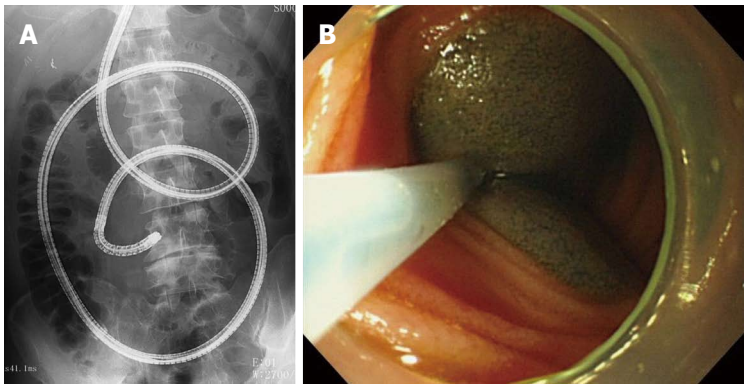

Figure 1 Case of total enteroscopy. A: Single-balloon enteroscope inserted orally; B: Indian ink was used as a tattoo in the deepest part of the intestine.

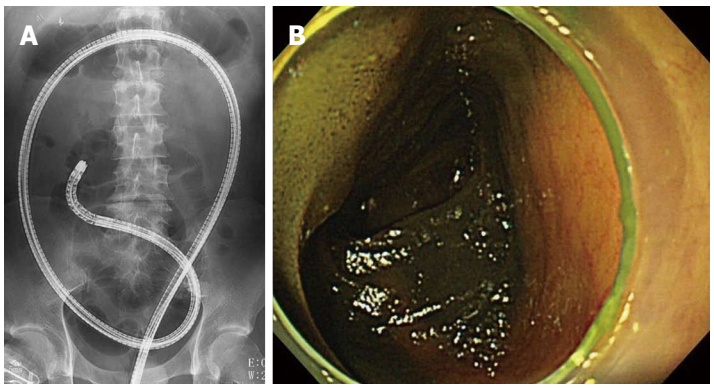

Figure 2 Case of total enteroscopy (continued). A: Single-balloon enteroscope inserted anally; B: Tattoo marked when enteroscope was inserted orally was confirmed.

Table 1 Rates of total enteroscopy using the single-balloon enteroscope

Ref.	Study design	No. of cases	Rate of total enteroscopy	Year
Tsujikawa *et al*[5]	Case series	78 exams in 41 pts	6/24 (25%)	2008
Kawamura *et al*[2]	Case series	37 exams in 27 pts	1/8 (12.5%)	2008
Ohtsuka *et al*[4]	Case series	48 exams in 30 pts	5/7 (71.4%)	2008
Kobayashi *et al*[3]	Case series	50 exams in 40 pts	3/5 (60%)	2008
Ramchandani *et al*[24]	Case series	131 exams in 106 pts	5/20 (25%)	2009
May *et al*[10]	RCT	50 pts	11/50 (22%)	2010
Domagk *et al*[11]	RCT	65 pts	7/65 (11%)	2011
Takano *et al*[12]	RCT	14 pts	0/14 (0%)	2011
Li *et al*[17]	RCT (CO_2 use)	106 pts	37/106 (34.9%)	2014
Li *et al*[17]	RCT (air use)	108 pts	19/108 (17.6%)	2014

RCT: Randomized controlled trial; pts: Patients.

thus far in their review article. The most common indication of SBE was obscure gastrointestinal bleeding (51%), followed by evaluation for Crohn disease (13%) and polyp/mass (8%). The most common lesions of the small bowel were angioectasias (22%), ulcers (15%), and polyp/mass (10%), and the most common interventions included hemostasis with argon plasma coagulation (22%), followed by polypectomy (3%) and dilation (3%).

Although there were conflicting results regarding the insertability of SBE compared with that of DBE, the diagnostic yield of small intestinal lesions using SBE was reported as equal to that of DBE. Diagnostic yields were 41%-65% in initial experience reports[2,5,24] and 37%-50% in randomized control studies[10-12], which were almost same as the rates of the DBE system.

Recently, SBE for disease in regions other than the small bowel has been reported. In the next session, the clinical applications of SBE for colonic and pancreatobiliary lesions are discussed.

SBE for colonic lesions

There are two main reasons for performing SBE for colonic lesions: One is when colonoscopy fails, and another is when endoscopic submucosal dissection (ESD) is required in difficult positions.

An elongated colon and adhesion would make it

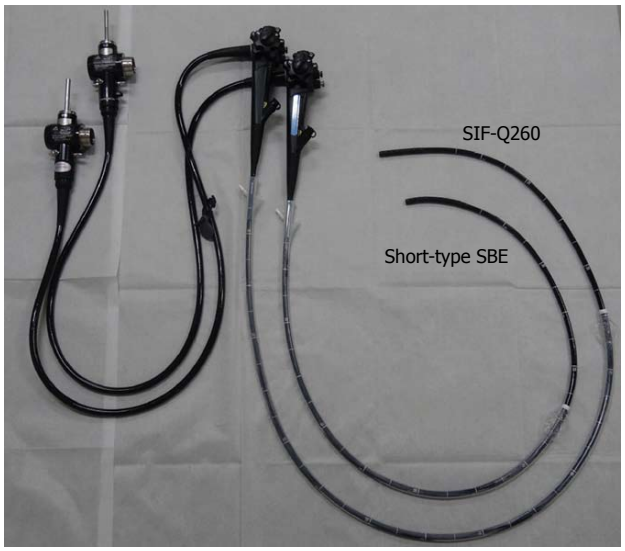

Figure 3 Short-type prototype single-balloon enteroscope. This scope has a working length of 1520 mm and an inner channel of 3.2 mm, which are compatible with those of many endoscopic accessories. SBE: Single-balloon enteroscopy.

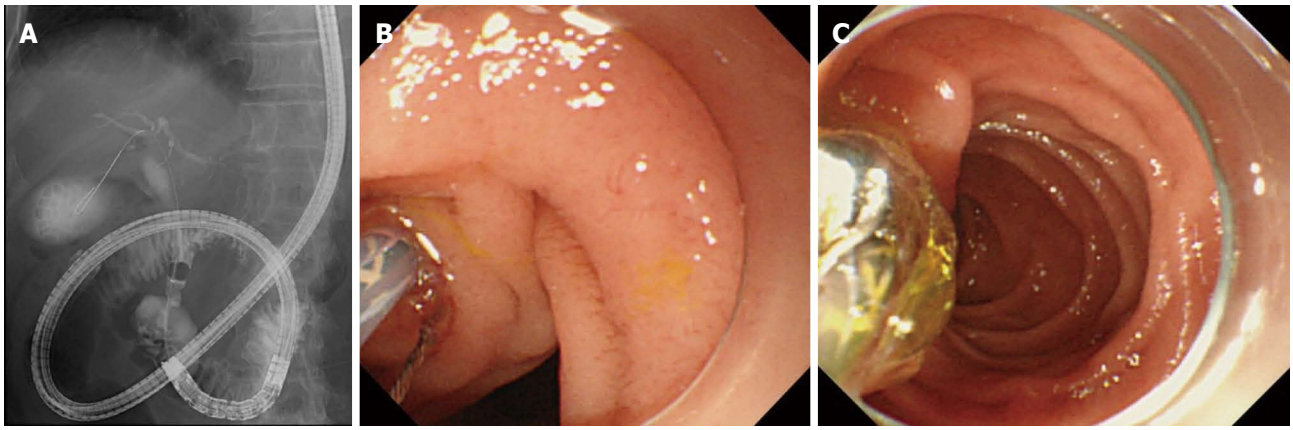

Figure 4 Case of common bile duct stones treated using a short-type prototype single-balloon enteroscope. Conventional endoscopic accessories such as retrieval balloon catheter (A), endoscopic sphincterotomy catheter (B), and endoscopic balloon dilation catheter (C), were used in this procedure.

difficult to achieve total colonoscopy. SBE is used to prevent stretching of the intestine. A case series suggested that the SBE system is successful in almost all patients in whom the cecum cannot be reached[25-27]. A randomized control trial revealed that the utility of SBE and DBE for colonoscopy seemed comparable in patients with incomplete previous colonoscopy using a conventional colonoscope[28].

ESD for colonic neoplasm is a technically challenging procedure, especially if the target neoplasm resides in a difficult to reach position. An overtube with a balloon is used to stabilize the endoscope during the ESD procedure. Ohya *et al*[29] reported the usefulness of a therapeutic gastroscope (GIF-Q260J; Olympus Medical systems, Tokyo) with an SBE overtube for colonic ESD. The SBE overtube was too long to use with the gastroscope, so a modified and shortened overtube of 70 cm from the distal end was used.

Endoscopic retrograde cholangiopancreatography for patients with surgically altered gastrointestinal anatomy

SBE is useful for both small bowel diseases and pancreatobiliary diseases in patients with altered gastrointestinal anatomy. Many studies have reported the usefulness of the SBE system for endoscopic retrograde cholangiopancreatography (ERCP) with altered gastrointestinal anatomy, especially in patients with Roux-en-Y anastomosis[30-43]. However, a limited number of ERCP accessories are compatible with the SBE system because of its narrow inner channel diameter and working length compared to those of a conventional duodenoscope. Recently, the usefulness of the short-type SBE prototype (SIF-Y0004; Olympus medical systems, Tokyo) has been reported[44-49]. The short-type SBE has a working length of 1520 mm and an inner channel diameter of 3.2 mm (Figure 3), which are both compatible with many conventional ERCP accessories (Figure 4). In the future, this short-type SBE system may become the first-choice endoscope for ERCP in patients with altered gastrointestinal anatomy.

Other applications of SBE

Recently, the efficacy and safety of SBE for children with Crohn disease and Peutz-Jeghers syndrome have been

reported[50-52]. SBE is expected to be as useful in children as in adult patients.

Endoscopic removal of foreign objects, diagnosis of parasite infestation, and SBE-assisted direct percutaneous endoscopic jejunostomy are reported as uncommon uses of SBE[53-56]. In cases in which the target regions lies in the small bowel, not far from the ligament of Treitz or the terminal ileum, the balloon at the tip of the enteroscope may not be needed. SBE might have advantages compared to DBE in such cases because of SBE involves a greater ease of preparation.

FUTURE PERSPECTIVES

In the future, detailed diagnosis will become more important and the optimal therapy after reaching the target region will be essential. For example, the usefulness of high-resolution enteroscopy, image-enhanced enteroscopy, magnified enteroscopy, and endoscopic ultrasonography[57-59] by using SBE will need to be discussed. Furthermore, several endoscopic accessories for ERCP and ESD performed using SBE will be required. Endoscopic procedures and applications using the SBE system are promising.

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ORIGINAL ARTICLE

Observational Study

Treatment of dysplastic Barrett's Oesophagus in lower volume centres after structured training

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Author contributions: Hoare J designed the study; Vlavianos P and Hoare J performed all the endoscopies, and collected all the specimens; Goldin R analysed all the specimens; Chadwick G, Faulkner J and Ley-Greaves R extracted all the results from the endoscopy database for analysis; Chadwick G wrote the manuscript with input from Faulkner J and Ley-Greaves R; the manuscript was critically reviewed and edited by Hoare J, Vlavianos P and Goldin R; all authors approved the final manuscript.
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Informed consent: The study was a retrospective observational study using routinely collected hospital data, and as such did not require informed consent.
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Abstract

AIM: To investigate whether dysplastic Barrett's Oesophagus can be safely and effectively treated endoscopically in low volume centres after structured training.

METHODS: After attending a structured training program in Amsterdam on the endoscopic treatment of dysplastic Barrett's Oesophagus, treatment of these patients was initiated at St Marys Hospital. This is a retrospective case series conducted at a United Kingdom teaching Hospital, of patients referred for endoscopic treatment of Barrett's oesophagus with high grade dysplasia or early cancer, who were diagnosed between January 2008 and February 2012. Data was collected on treatment provided (radiofrequency ablation and endoscopic resection), and success of treatment both at the end of treatment and at follow up. Rates of immediate and long term complications were assessed.

RESULTS: Thirty-two patients were referred to St Marys with high grade dysplasia or intramucosal cancer within a segment of Barrett's Oesophagus. Twenty-seven met the study inclusion criteria, 16 of these had a visible nodule at initial endoscopy. Treatment was given over a median of 5 mo, and patients received a median of 3 treatment sessions over this time. At the end of treatment dysplasia was successfully eradicated in 96% and intestinal metaplasia in 88%, on per protocol analysis. Patients were followed up for a median of 18 mo. At which time complete eradication of dysplasia was maintained in 86%. Complications were rare: 2 patients suffered from post-procedural

bleeding, 4 cases were complicated by oesophageal stenosis. Recurrence of cancer was seen in 1 case.

CONCLUSION: With structured training good outcomes can be achieved in low volume centres treating dysplastic Barrett's Oesophagus.

Key words: Barrett's Oesophagus; Oesophageal cancer; Endoscopic treatment; Radiofrequency ablation; Endoscopic resection

Core tip: With structured training endoscopic treatment of dysplastic Barrett's Oesophagus with endoscopic resection and radiofrequency ablation can be provided in lower volume centres with good safety and efficacy outcomes.

Chadwick G, Faulkner J, Ley-Greaves R, Vlavianos P, Goldin R, Hoare J. Treatment of dysplastic Barrett's Oesophagus in lower volume centres after structured training. *World J Gastrointest Endosc* 2015; 7(1): 66-72 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i1/66.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i1.66

INTRODUCTION

Barrett's Oesophagus is a significant risk factor for oesophageal cancer[1], with studies suggesting it develops through a dysplasia-carcinoma sequence[2]. As it does the risk of progression to cancer increases from 0.1% per year for a non-dysplastic segment of Barrett's Oesophagus[3], to 5.6% per year if high grade dysplasia (HGD) is present[4].

United Kingdom guidelines recommend that Barrett's Oesophagus should be regularly surveyed, with prompt intervention if there is progression to HGD or cancer[5]. Until recently esophagectomy has been considered the treatment of choice, but this is associated with significant morbidity and mortality even in high volume centres[6]. Over recent years significant progress has been made in the endoscopic treatment of Barrett's Oesophagus with dysplastic changes. This has resulted in the most recent United Kingdom guidelines recommending endoscopic treatment of HGD in preference to oesophagectomy, given the lower treatment related morbidity[5].

Endoscopic treatment of dysplastic Barrett's oesophagus has two important stages. First, removal of any visible dysplastic lesions. This is usually achieved by endoscopic mucosal resection (EMR) of the lesion; this provides definitive staging information and ensures that lesions extending into the submucosa are not missed. Once this is done, it is recommended that any remaining segment of Barrett's Oesophagus is treated, this minimises the risk development of cancer in the future in the remaining Barrett's segment[7]. Two distinct approaches can be taken to do this, stepwise radical endoscopic resection (SRER) or ablation of the affected mucosa. Over the last five years radiofrequency ablation (RFA) has become the most widely used ablative technique. A recent systematic review demonstrated that while SRER and RFA have similar efficacy in treating dysplastic Barrett's Oesophagus, RFA is associated with a significantly lower rate of complications[8]. Furthermore while SRER appears to be a relatively complex technique to learn[9], learning to perform RFA does not appear to be associated with such a significant learning curve[10]. Ablation is therefore generally accepted as the preferred treatment modality in Europe.

To date most of the studies looking at the endoscopic treatment of Barrett's Oesophagus have come from high volume research centres, with only one small retrospective study coming from a community hospital in the United States[11]. This study reported 100% success in eradication of dysplasia at follow up in 10 patients with HGD, suggesting that dysplastic Barrett's Oesophagus can be managed successfully outside of large volume research centres. But larger studies performed outside high volume research centres are still needed.

Given the rapidly rising incidence of oesophageal cancer and Barrett's Oesophagus in the United Kingdom[12,13], several smaller centres have established treatment programs for dysplastic Barrett's Oesophagus. Recognising this fact the Academic Medical Centre in Amsterdam (AMC) created a multidisciplinary European Training Program for the treatment of neoplasia within Barrett's Oesophagus[14]. The aim of this course was to improve the quality of detection and treatment of dysplastic Barrett's Oesophagus in these lower volume centres.

This study aims to assess whether with the structured training, endoscopists with little experience in ablative techniques can be taught to manage dysplastic Barrett's Oesophagus safely and effectively in lower volume centres.

MATERIALS AND METHODS

Study design and patient population

In 2008 a centre for the treatment of dysplastic Barrett's oesophagus was established at St Mary's, a United Kingdom teaching hospital and regional centre for upper gastro-intestinal surgery. Patients were included in this retrospective consecutive case series, if they were diagnosed with Barrett's Oesophagus with HGD or intramucosal cancer (IMC) between January 2008 and February 2012 and were referred to St Marys for endoscopic treatment.

All patients had their pre-treatment histological diagnosis confirmed by a specialist pathologist (RG), and were discussed at the local specialist multi-disciplinary team (MDT) meeting, to determine the most appropriate treatment course. Any further staging investigations including CT and EUS recommended by the MDT to rule out invasive cancer, were performed at this stage.

Patients were identified for inclusion in the study by searching the hospital's electronic endoscopy database (Ascribe), records were cross checked against pathology

records and MDT meeting reports to ensure no cases were missed. Patients were excluded from this study if there was evidence of sub-mucosal invasion on resection of any visible nodules, or if they were considered unfit for repeated therapeutic endoscopies.

Teaching program at the AMC

Prior to the commencement of the study period, a multi-disciplinary team from St Marys, consisting of an endoscopist (JH), a pathologist (RG) and an endoscopy nurse attended the European training program for Barrett's Oesophagus with neoplasia at the AMC. The course consisted of three two day workshops, these combined theoretical lectures, live demonstrations by experts and finally hands on supervised training sessions. The hands on sessions were staged, starting treatment on explanted pig tissue, before progressing to live pigs and then human cases. A variety of different endoscopic techniques were taught including EMR-cap, multiband mucosectomy and RFA.

Endoscopic procedures

All endoscopic procedures were performed by one of two experienced endoscopists (JH, PV) on an outpatient basis under conscious sedation. All procedures were performed using an Olympus H260Z series endoscope, with narrow band imaging and zoom features used at the operators discretion.

Visible areas of dysplasia were resected first, using the Duette™ Multiband Mucosectomy (Cook Medical, Winston-Salem, NC). Patients with evidence of sub-mucosal invasion on the resected specimen were referred back to the MDT, and excluded from the study at this stage. Remaining patients had a repeat endoscopy two months later, where a further resection was performed if required. Otherwise patients were considered for ablation of any residual Barrett's Oesophagus using RFA. Patients with dysplasia detected within a segment of flat Barrett's Oesophagus on initial endoscopy started treatment with RFA immediately.

RFA was performed using the HALO system (BARRX Medical, Sunnyvale, CA). Circumferential RFA (HALO^{360}) was usually applied first, using standard energy settings (12 J/cm^2, 40 W/cm^2). This was repeated after repositioning the balloon, until the entire Barrett's Oesophagus segment was ablated. The catheter was then removed, so debris could be scraped off the balloon and coagulum could be removed from the ablation zone. The process was then repeated, before ablating the segment a second time. If there was only a short segment of non-circumferential Barrett's Oesophagus present initially or on follow up procedures, focal ablation was applied using the HALO^{90} device. RFA was then delivered twice in quick succession to each area (12-15 J/cm^2, 40 W/cm^2), then the probe and the mucosa were cleaned, the area was then ablated again twice. In the interest of costs, argon plasma coagulation (APC) was used at the endoscopist's discretion to treat small islands (< 5 mm) of residual Barrett's Oesophagus. Patients received treatment at 2-3 monthly intervals until all visible Barrett's Oesophagus was eradicated.

At this stage treatment was considered complete and targeted biopsies were taken of any endoscopic abnormalities in the oesophagus, and quadrantic biopsies were taken from just distal (< 5 mm) to the neo-squamocolumnar junction (NSCJ).

Histological analysis

All histological specimens were analysed by a specialist gastrointestinal pathologist (RG), and if there was evidence of dysplasia the diagnosis was confirmed by a second pathologist. Biopsies were assessed using the revised Vienna classification[15].

Data collection

Data was collected retrospectively from endoscopy reports and pathology records, up to August 2013. Information was collected on patient demographics, length of the Barrett's Oesophagus segment treated, the number and type of procedures each patient had had, duration of follow up and complications related to the procedure. Histology records provided information on pre and post treatment histology.

Endpoints

The primary outcome assessed was success of complete eradication of dysplasia (CE-D) and intestinal metaplasia (CE-IM) after completion of treatment. This was defined as absence of any endoscopically visible Barrett's Oesophagus (confirmed on available oesophageal biopsies), combined with the absence of dysplasia on biopsies taken from just distal to the NSCJ.

Secondary endpoints: (1) Rate of CE-D/CE-IM at most recent follow-up endoscopy, more than 6 mo after completion of treatment. Follow-up duration was defined as the time between completion of treatment and the most recent follow up endoscopy; (2) Rates of short term complications, related to initial endoscopic procedure, *e.g.*, bleeding or perforation; and (3) Rates of long term complications associated with the endoscopic treatment, *e.g.*, oesophageal stenosis.

Results are presented on both a per protocol (PP) and an intention to treat (ITT) basis, for the primary outcome and complication rates. But follow up results are presented on intention to follow up basis, after excluding patients who did not complete endoscopic treatment (due to patient choice or failure of endoscopic treatment) and patients who had not completed 6 mo follow up.

Statistical analysis

The study did not use any biostatistics mathods.

RESULTS

Between January 2008 and February 2012, 32 patients were referred for endoscopic treatment of Barrett's Oesophagus with HGD or IMC.

Twenty-one of these patients had a nodule visible

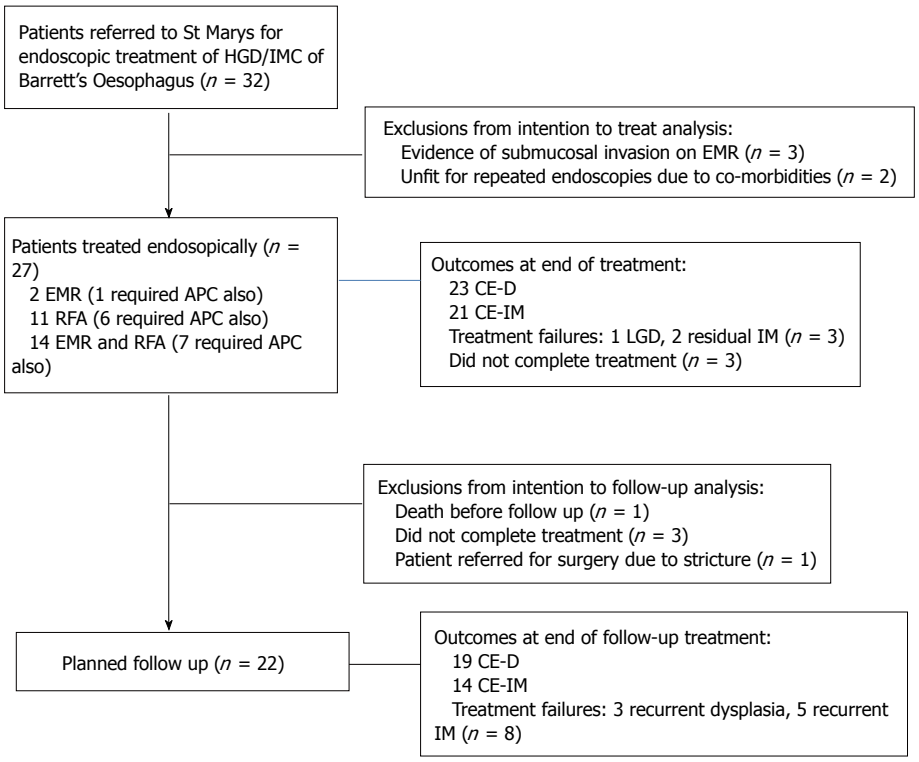

Figure 1 Selection of analysis cohort and outcomes. HGD: High grade dysplasia; LGD: Low grade dysplasia; IMC: Intramucosal cancer; APC: Argon plasma coagulation; EMR: Endoscopic mucosal resection; CE-D: Complete eradication of dysplasia; CE-IM: Intestinal metaplasia.

endoscopically at referral. Of these, 3 patients were found to have lesions extending deep into the submucosa, and an additional 2 patients were considered unfit for repeated endoscopic therapy due to severe co-morbidities. As a result these 5 patients were excluded from analysis.

This left 27 patients who met the inclusion criteria, and were considered for this study (Figure 1). Patient demographics are summarised in Table 1.

Treatment received

Patients received treatment over a median of 5 mo. During this time the median number of treatment sessions required was 3 (range 1-9). Where RFA was used, patients required a median of 1 focal and 1 circumferential ablation.

Sixteen patients (59%), including all those with a known diagnosis of IMC, had a nodule visible at initial endoscopy which was resected. Four of these patients required a further endoscopic resection, during the treatment period. Following successful endoscopic resection, 14 patients received additional treatment with RFA to treat the remaining Barrett's Oesophagus.

While 11 patients were found to have evidence of dysplasia within a flat segment Barrett's Oesophagus, they were treated with RFA alone as the primary therapy.

Following EMR and RFA, additional treatment with APC was needed in 14 patients, to treat small areas of residual Barrett's Oesophagus.

Primary outcomes

On an ITT basis CE-D at the end of treatment was achieved in 85% (23/27) CE-D, while 78% (21/27) achieved CE-IM. But 3 patients did not complete treatment as planned, so for the 24 patients who completed treatment as planned CE-D was achieved in 96% (23/24), with only 1 patient having evidence of residual low grade dysplasia (LGD). A further 2 patients who completed their planned treatment had evidence of visible non-dysplastic Barrett's Oesophagus after completing treatment, so CE-IM was achieved in 88% (21/24) of the cohort on PP analysis.

One patient who did not complete planned treatment was lost to follow up, after failing to attend several appointments. He represented 2 years later with a T2 oesophageal cancer, this was treated with an oesophagectomy but he subsequently died. The other two patients were lost to follow up, despite multiple attempts to re-engage them.

Secondary outcomes

Follow up results: 22 patients were considered for analysis in the follow up cohort. The 5 patients who were dropped from this cohort included the 3 patients who had failed to complete treatment, 1 who died from pancreatic cancer before starting follow up and 1 patient was referred for surgery after endoscopic treatment failed and resulted in a severe stricture refractory to endoscopic dilatation. The median follow up duration was 18 mo (range 7-34 mo).

During follow up 3 patients had recurrence of dysplasia. One patient had recurrent IMC, this has been retreated endoscopically and the patient is awaiting follow up. One patient who had LGD at the end of treatment

Table 1 Patient demographics

Male: female	25:2
Median age (yr) (range)	66 (53-89)
Median length Barrett's (cm) (range)	5 (1-10)
Worst diagnosis on biopsy or ER specimen	9 IMC/18 HGD

HGD: High grade dysplasia; LGD: Low grade dysplasia; IMC: Intramucosal cancer.

progressed to HGD during follow up. This patient is now undergoing regular surveillance instead of further treatment, on account of their co-morbidities and wishes. The final patient who developed LGD during follow up is undergoing more intense surveillance, but has not received further treatment. So overall 19/22 (86%) patients achieved CE-D at the most recent follow up.

A further 5 patients had recurrence of visible non-dysplastic Barrett's Oesophagus during follow up, so CE-IM was maintained in 14/22 (64%).

Complication rates

Overall 6 patients suffered from complications related to the procedure (22%). Two patients suffered acute bleeding post EMR, both were successfully treated endoscopically.

A further four (14.8%) patients developed oesophageal stenosis during follow up, all had had a prior EMR. This was treated successfully with endoscopic dilatation in three patients (two patients required a single dilatation, but one patient required three dilatations). The final patient, treated midway through the study, had five attempts at dilatation but the stricture was refractory to treatment, this patient was referred for an oesophagectomy which confirmed there was no evidence of residual disease.

There were no fatalities or oesophageal perforations related to treatment.

DISCUSSION

Given the high morbidity and mortality associated with oesophagectomy, endoscopic treatment for Barrett's Oesophagus with HGD or IMC is now considered the treatment of choice in most patients[5,16]. To date these treatments have been provided predominantly by high volume research centres. However, with the increasing prevalence of oesophageal cancer and Barrett's Oesophagus in Europe[12], an increasing number of lower volume treatment centres are being established. As a result the AMC in Amsterdam developed a specialised training program aimed at optimising the recognition and treatment of dysplastic Barrett's Oesophagus in these centres. It is therefore important to establish whether similar outcomes, in terms of both treatment efficacy and complication rates, can be achieved in lower volume centres after attending such a program.

This retrospective case series started with the first case of dysplastic Barrett's Oesophagus treated at our institution after attending the course, and demonstrates that EMR and RFA for dysplastic Barrett's Oesophagus can be safely performed in lower volume institutions outside of a research setting.

Analysis of outcomes focused on the rates of eradication of dysplasia and intestinal metaplasia at the end of treatment and at follow up. For this analysis we considered presence of dysplasia on biopsies taken below the neo-squamocolumnar junction as evidence of treatment failure, because studies have suggested the risk of recurrence of dysplasia is highest in this area and may predict development of neoplasia[17,18]. But presence of intestinal metaplasia alone below the NSCJ was not considered significant, as the relevance of this finding is debatable. Morales *et al*[19] demonstrated the presence of intestinal metaplasia in routine biopsies taken from the cardia in 25% of a healthy population, suggesting the finding is not clinically relevant[19].

Overall treatment was very successful in patients who completed treatment as planned, with 100% success in eradication of HGD and IMC, 96% success in eradication of any dysplasia and 88% success in eradicating visible Barrett's Oesophagus. These results are comparable to previous studies, with prospective studies from large volume tertiary referral centres reporting between 81%-100% CE-D and 74%-100% CE-IM at the end of treatment[20-24].

One of the major drawbacks of studies to date has been the short follow up periods reported, between 14 and 22 mo[20-24]. This study provides a median follow up of 18 mo. Overall durability of eradication of dysplasia was good, with 86% of patients maintaining complete eradication of dysplasia at the end of treatment. Previous studies had reported 79%-100% CE-D at follow up[20-22,25,26].

Currently St Marys is a relatively low volume centre, with only 32 new patients considered for treatment during the 4 year study period (equating to less than 1 new patient per month). So our patient volumes are likely to be similar to those reported by centres involved in the United Kingdom HALO registry. This registry collected data from 216 patients recruited from 14 United Kingdom centres, and reported the following outcomes at the end of treatment: 83% CE-HGD, 76% CE-D and 50% CE-IM[27]. It is uncertain what initial training endoscopists had at each centre involved in this study. But our comparatively favourable results suggest that access to a specialised training program may have a beneficial impact on treatment outcomes, and allow lower volume centres to provide access to high quality endoscopic treatment for dysplastic Barrett's Oesophagus.

Throughout this series there were no reported deaths or perforations, but two patients required endoscopic treatment for bleeding post EMR. A further four patients (14.8%) suffered late complications, due to oesophageal stenosis. Our overall rates of oesophageal stenosis was slightly higher than rates reported in previous studies (0%-14%)[20-23,26,28,29]. This can be explained by two factors,

firstly the relatively high proportion of patients (59%) who required EMR prior to use of RFA (it should be noted that all strictures in this study occurred in patients who had had a previous EMR) and secondly this series started with the first case treated by our endoscopists. Van Vilsteren *et al*[9] previously demonstrated that there is a significant learning curve associated with learning to perform oesophageal EMR, and noted that complication rates were highest for the first few therapeutic endoscopies performed[9].

In conclusion, this study demonstrates that following structured training good outcomes can be achieved in the endoscopic treatment of dysplastic Barrett's Oesophagus in lower volume centres. While our rate of oesophageal stenosis was slightly higher than previously reported, it must be noted that these results represent the start of our learning curve. We therefore expect this rate to fall as the endoscopist's experience increases.

COMMENTS

Background

Barrett's Oesophagus is a pre-malignant condition which progresses through a dysplasia-carcinoma sequence. As it does the risk of progression to cancer increases rapidly. It is therefore important to treat patients with evidence of high grade dysplasia as they are at higher risk of developing oesophageal cancer. Until recently oesophagectomy has been the mainstay of treatment this is associated with significant risk, and therefore used predominantly in younger fitter patients. But recently newer endoscopic techniques have been developed with proven safety and efficacy in treating dysplastic Barrett's Oesophagus.

Research frontiers

With the increasing incidence of Barrett's Oesophagus in the United Kingdom it is important to assess whether these endoscopic techniques can be used safely and effectively outside of research centres, where the majority of the current literature is derived.

Innovations and breakthroughs

Several large studies have already demonstrated the safety and efficacy of endoscopic resection and radiofrequency ablation in dysplastic Barrett's Oesophagus (as summarised in a review by Chadwick *et al*). But these studies have come from high volume research centres. This is the first study to demonstrate that with structured training clinicians can achieve good outcomes in the endoscopic treatment of dysplastic Barrett's Oesophagus in low volume centres.

Applications

The results of this study suggest that with structured training, endoscopic treatment of dysplastic Barrett's can be used safely and effectively in lower volume hospitals.

Terminology

Barrett's Oesophagus: This is the replacement of the normal stratified epithelium lining of the lower oesophagus with columnar cells. This is important because it puts the person at increased risk of development of oesophageal cancer; Dysplasia: Refers to the development of abnormal epithelium, which in the case of Barrett's Oesophagus is at risk of progression to cancer; Intramucosal oesophageal cancer: Cancer affecting the very superficial layer of the oesophagus. This stage of cancer is at low risk of spreading to the regional lymph nodes and distant organs; Endoscopic Mucosal Resection: A procedure to remove cancerous or other abnormal tissues (lesions) using an endoscope which is passed down the oesophagus. Radiofrequency ablation is the use of high frequency current to destroy areas of abnormal tissue.

Peer review

This article is really very interesting.

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CASE REPORT

Russell body duodenitis with immunoglobulin kappa light chain restriction

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Abstract

Russell bodies are eosinophilic intracytoplasmic globules which are likely the result of disturbed secretion of immunoglobulins that accumulate within the plasma cell. Russell body collections have been identified within the stomach, known as Russell body gastritis. Similar lesions within the duodenum are referred to as Russell body duodenitis, which is rare. Several Russell body gastritis case reports are associated with *Helicobacter pylori*. However, the etiology of Russell body duodenitis remains unclear. Here we report the first case of Russell body duodenitis with immunoglobulin light chain restriction in a background of peptic duodenitis.

Key words: Russell body duodenitis; Russell bodies; Immunoglobulin

Core tip: Russell body duodenitis is rare and the etiology is unclear. We report a case of Russell body duodenitis with immunoglobulin light chain restriction in a background of peptic duodenitis.

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INTRODUCTION

Russell bodies are eosinophilic intracytoplasmic globules which were first described by Russell *et al*[1] in 1890. These globules are likely the result of disturbed secretion of immunoglobulins that accumulate within the plasma cell. Sixteen case reports have identified abundant collections of Russell bodies in the stomach, known as Russell body gastritis. Similarly, three cases have been reported to occur within the duodenum, with the first in 2011[2]. All three cases presented clinically with upper gastrointestinal symptoms with the subsequent identification of polytypic, Russell body containing plasma cells in the duodenum referred to as Russell body duodenitis[2-4]. Several of the Russell body gastritis case reports are

associated with *Helicobacter pylori* (*H. pylori*). However, the etiology of Russell body duodenitis remains unclear. Here we report the first case of asymptomatic Russell body duodenitis. Additionally, this is the first reported case showing immunoglobulin light chain restriction.

CASE REPORT

Clinical, endoscopic and pathologic findings

A 78-year-old female with a past medical history of congestive heart failure, atrial fibrillation, chronic obstructive pulmonary disease, and chronic renal injury, presented to hospital with shortness of breath and lower extremity edema. Past medical history was also significant for diabetes, and hypertension. Past surgical history included sigmoid resection for diverticulitis, rotator cuff repair, and carpal tunnel release. The patient denied alcohol use, and had a history of smoking over sixty pack-years. Upon admission for shortness of breath, the patient was treated with intravenous diuresis and her symptoms subsequently improved.

Further laboratory investigation revealed concomitant iron deficiency anemia and chart review showed progressive decline in hemoglobin over a nine-month period. There was no clinical or laboratory evidence to suggest monoclonal gammopathy.

Esophagogastroduodenoscopy and colonoscopy were performed to evaluate the source of anemia. The patient had no prior history of upper or lower gastrointestinal symptoms. Upper endoscopy revealed a few scattered gastric fundic sub-centimeter polyps, and prominent gastric antral folds without evidence of inflammation. In the duodenum, clusters of lobulated polyps (Figure 1A) were located in the duodenal bulb, with a normal appearing second portion of the duodenum. No ulceration was present. Colonoscopy revealed a three centimeter ulcerated, sessile mass at the distal ascending colon, concerning for malignancy.

Random stomach biopsies from the body and antrum showed normal morphology and no evidence of *H. pylori*. Duodenal biopsies of the lobulated polyps at the duodenal bulb showed numerous eosinophilic globules, or Russell bodies, as well as gastric surface foveolar metaplasia (Figure 1B). CD138 immunostain was positive in plasma cells containing Russell bodies (Figure 1C). Immunoglobulin kappa light chain immunostain showed a dark peripheral rim with light center staining pattern in the Russell bodies (Figure 1D) while lambda immunostain was negative (not shown). The surrounding plasma cells with mature morphology showed polytypic light chain staining pattern. IgH gene rearrangement was negative. Biopsies of the ulcerated, sessile distal colonic mass revealed invasive adenocarcinoma.

DISCUSSION

Russell bodies are eosinophilic inclusions located in the cytoplasm of plasma cells. While they are typically identified in the setting of several malignancies of hematopoietic origin, they can be seen in some reactive conditions as well. The plasma cells containing Russell bodies, referred to as Mott cells, are often found in the setting of plasma cell myeloma, MALT lymphoma, plasmacytoma, or lymphoplasmacytic lymphoma. Russell body gastritis is a rare reactive condition in which Russell bodies are found within the lamina propria of the gastric mucosa, and so far without a definitive association with *H. pylori* or malignancy.

Of the sixteen reported cases of Russell body gastritis, several identified monoclonality[5-7]. In these cases, there were no clinical and pathologic features of MALT lymphoma or significant plasma cell neoplasia[5]. One case did show lambda restricted Mott cells, positivity for *H. pylori*, and concomitant monoclonal gammopathy of undermined significance (MGUS); however, eradication of *H. pylori* caused the Russell body gastritis to subside while the paraproteinemia remained unaffected[7]. Thus, these cases of monoclonal Mott cell proliferations are either reactive in nature, or possibly, precursor proliferations to more significant conditions, such as MALT lymphoma or plasmacytoma.

Interestingly, the phenomenon of Russell body monoclonality in the presence of mature polytypic plasma cells, as in our case, has been observed before, although outside the gastrointestinal tract. In a biopsy of labial mucosa, Matthews *et al*[8] identified a patient with monoclonal Russell bodies restricted to IgG and kappa chains in a background of mature plasma cells. Of the twelve patients in their study, this was the only patient diagnosed with a significant medical pathology, namely, Sjogren's syndrome. B-cell clonality in Sjogren's syndrome has been hypothesized to alter the salivary or lacrimal gland microenvironment, enabling the progression to lymphoma[9]. Indeed, approximately 5% of patients with Sjogren's syndrome will develop lymphoma, an incidence 40 times that of the general population[10]. It could be postulated that monotypic Mott cells are similar to monoclonal B-cells in this setting, such that the finding indicates a transient or intermediate step between an inflammatory condition, such as Sjogren's syndrome, and the progression to malignancy, such as lymphoma.

Further evidence supporting monoclonal Mott cells as an intermediary between inflammatory conditions and malignancy comes from a rare case of gastric Mott cell tumor associated with *H. pylori*[11]. In this case, abundant monotypic IgG kappa Mott cells were found on gastric biopsy with features suggestive of MALT lymphoma[11]. Furthermore, Mott cells were found in regional lymph nodes[11]. It is possible that *H. pylori* gastritis, a chronic inflammatory condition, over time stimulated an intermediary monoclonal Mott cell proliferation that subsequently developed malignant transformation and lymph node involvement. Whatever the sequence of events, it may be inferred from this example that monotypic Mott cells harbor malignant potential.

To summarize, the present case shows a unique

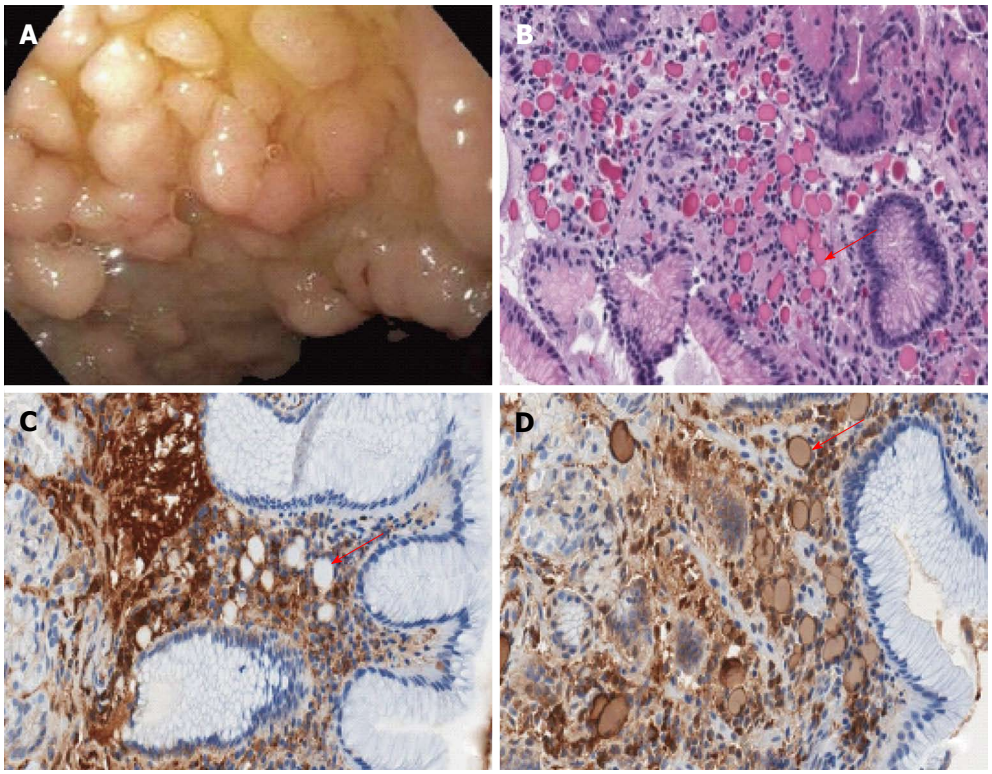

Figure 1 Endoscopic findings of duodenum. A: Endoscopic image shows a cluster of lobulated polyps in duodenal bulb; B: Numerous eosinophilic inclusions (Russell bodies, arrow) in the lamina propria and gastric foveolar metaplasia of the duodenal surface epithelium. H and E, 400 ×; C: CD138 immunohistochemistry highlights numerous mature plasma cells. The Russell bodies are round to ovoid clear spaces (arrow) within the lamina propria. Immunohistochemistry, 400 ×; D: Immunoglobulin kappa light chain immunohistochemistry shows a dark-rim staining and light internal staining pattern of Russell bodies (arrow). Immunohistochemistry, 400 ×.

type of Mott cell monoclonality for several reasons. First, the monoclonal Mott cells were located within the duodenum, of which this is the first reported case at this site. To date, only three cases of Russell body duodenitis have been reported, none of which demonstrate monoclonality[2-4]. Secondly, the monoclonal cells are present in a background of mature, polytypic plasma cells, a finding which is infrequently reported. Lastly, our patient was asymptomatic, the findings of Russell body duodenitis was incidental, and work up for *H. pylori* was negative. In this case, Russell body duodenitis likely originated from peptic duodenitis, indicated by gastric surface foveolar metaplasia of the overlying duodenal epithelium, and independent of *H. pylori*. Over time, chronic inflammation at this site may have caused Mott cells to accumulate, which subsequently progressed to monoclonality. It has been suggested that monoclonality of Mott cells may occur secondary to alternations at the immunoglobulin locus, and may be induced by chronic inflammation[7]. Given the low grade nature of MALT lymphomas in the stomach and duodenum, and the likelihood that monotypic Russell body duodenitis is either reactive or pre-malignant, treatment beyond eradication of *H. pylori* (if present) is likely unnecessary. Further investigation, and the accumulation of additional cases, will be necessary to better understand the clinical significance of monoclonal Russell body duodenitis.

COMMENTS

Case characteristics

The patient presented with shortness of breath and lower extremity edema. Further laboratory investigation revealed concomitant iron deficiency anemia.

Clinical diagnosis

Iron deficiency anemia.

Differential diagnosis

Cause of iron deficiency is unknown. Considering patient's age, the possibility of gastrointestinal blood loss due to ulcer or malignancy should be ruled out. Esophagogastroduodenoscopy and colonoscopy were performed to evaluate the source of anemia.

Endoscopic diagnosis

Gastric fundic polyps, duodenal polyps and a 3 cm ulcerated, sessile mass at the distal ascending colon.

Pathological diagnosis

Russell body duodenitis and colonic invasive adenocarcinoma.

Related reports

Three cases of polytypic Russell body duodenitis have been reported. Here we report the first case of Russell body duodenitis with immunoglobulin light chain restriction in a background of peptic duodenitis.

Experiences and lessons

Russell body duodenitis is uncommon and the etiology remains unclear. The monotypic Russell body duodenitis is either reactive or pre-malignant, treatment beyond eradication of *Helicobacter pylori* (if present) is likely unnecessary. Further investigation, and the accumulation of additional cases, will be necessary to better understand the clinical significance of monoclonal Russell body duodenitis.

Peer review

This is a case report of a rare disease (Russell body duodenitis) described to

occur in the duodenum first in 2011.

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REVIEW

Reappraisal of endoscopic papillary balloon dilation for the management of common bile duct stones

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Abstract

Although endoscopic sphincterotomy (EST) is still considered as a gold standard treatment for common bile duct (CBD) stones in western guideline, endoscopic papillary balloon dilation (EPBD) is commonly used by the endoscopists in Asia as the first-line treatment for CBD stones. Besides the advantages of a technical easy procedure, endoscopic papillary large balloon dilation (EPLBD) can facilitate the removal of large CBD stones. The indication of EPBD is now extended from removal of the small stones by using traditional balloon, to removal of large stones and avoidance of lithotripsy by using large balloon alone or after EST. According to the reports of antegrade papillary balloon dilatation, balloon dilation itself is not the cause of pancreatitis. On the contrary, adequate dilation of papillary orifice can reduce the trauma to the papilla and pancreas by the basket or lithotripter during the procedure of stone extraction. EPLBD alone is as effective as EPLBD with limited EST. Longer ballooning time may be beneficial in EPLBD alone to achieve adequate loosening of papillary orifice. The longer ballooning time does not increase the risk of pancreatitis but may reduce the bleeding episodes in patients with coagulopathy. Slowly inflation of the balloon, but not exceed the diameter of bile duct and tolerance of the patients are important to prevent the complication of perforation. EPBLD alone or with EST are not the sphincter preserved procedures, regular follow up is necessary for early detection and management of CBD stones recurrence.

Key words: Common bile duct stones; Complications; Endoscopic balloon dilation; Endoscopic large balloon dilation; Endoscopic sphincterotomy

Core tip: Indication of endoscopic papillary balloon dilation is now extended from removal of small common bile duct stones to large or difficult stones by using large balloon. Balloon dilation itself is not the cause of pancreatitis. Avoidance of unnecessary pancreatic contrast injection, use the suitable balloon and pressure, slowly balloon inflation and adequate ballooning time to achieve a widely opened papillary orifice are the important steps to perform a safe endoscopic papillary large balloon dilation and successful clearance of bile duct.

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INTRODUCTION

In the laparoscopic era, endoscopic retrograde cholangiopancreatography (ERCP) is as efficient as laparoscopic surgery in the treatment of common bile duct (CBD) stones[1]. Since the introduction of endoscopic sphincterotomy (EST) in 1974 by Classen *et al*[2] and Kawai *et al*[3], EST is widespread used for removal of CBD stones in the following 40 years. Although the success rate of EST is high, this procedure may cause pancreatitis, hemorrhage, perforation and other complications. In a prospective cohort study of EST in 2347 patients[4], the overall complications of EST was 9.8%, including pancreatitis 5.4% (severe 0.4% and one patient died), hemorrhage 2% (severe 0.5% and 2 patients died), perforation 0.3% (severe 0.5%, one patient died), cholangitis 1% (severe 0.1% and one patient died), cholecystitis 0.5% (severe 0.1% and one patient died). The risk factors of pancreatitis included dysfunction of sphincter of Oddi, young age, difficulty in cannulating the bile duct, and number of pancreatic contrast injections; whereas the risk factors of hemorrhage included coagulopathy, anticoagulation therapy, cholangitis, mean case volume of endoscopist $\leqslant$ 1/week, and bleeding during the procedure. Thus, the risk of complications was influenced by the technique of endoscopist in the process of bile duct cannulation and cutting the papilla[4].

In 1981, Centola *et al*[5] presented a case with CBD stones who was successfully treated by percutaneous transhepatic balloon dilation of papilla of Vater. Staritz *et al*[6] also reported his experience by using a 15 mm diameter balloon catheter for endoscopic papillary dilation in 10 patients with CBD stones and one patient with benign papillary stenosis in the next year. Six of the ten patients were successfully cleared the bile tract soon after endoscopic papillary balloon dilation (EPBD) and four patients needed mechanical lithotripsy for stone retrieval. There were no complications in this report. For the purpose of preserving the function of sphincter of Oddi and avoidance of late complication, most endoscopists used the smaller balloon catheters (8 mm or less) to dilate the biliary sphincter for removal of the small stones, or combination use of the smaller balloon with lithotripter to treat the larger stones in the following twenty years. The success rate of EPBD was comparable with EST and reduced risk of bleeding was found[7-13]. Higher incidences of pancreatitis after EPBD by using the 8 mm balloon catheter were reported in some studies[14-16]. Although most of the patients with post-EPBD pancreatitis recovered after conservative treatment, a multi-center study from United States and Ireland disclosed two patients with fatal pancreatitis after EPBD[16]. The impact of this report discouraged the use of EPBD as the first line modality for the treatment of CBD stones by some western endoscopists, particularly in United States[17-20]. However, EPBD was still a popular procedure in Asia and parts of Europe[21]. Tsujino *et al*[22] found that 4.8% of their 1000 patients developed pancreatitis after EPBD, but all of them recovered later.

In 2003, Ersoz *et al*[23] reported their retrospective analysis for using the enteric balloon catheter (previously used for esophageal or pyloric dilation) with the diameter 12-20 mm, to treat 58 patients who had received complete endoscopic sphincterotomy but failure to clear the CBD stones. Of the 58 patients, 18 patients had tapered distal bile duct, and another 40 patients had the large, square and barrel shaped stones. Successful stone removal at the first session was 82.8%, and the other 10 patients also achieved clearance of bile duct after second dilation or mechanical lithotripsy. Complications occurred in 15.5%, including moderate bleeding in three patients (5.2%) and mild pancreatitis in two patients (3.4%). In 2004, Lin *et al*[24] from Taiwan reported a randomized controlled study comparing 51 patients receiving EPBD alone by using the enteric balloon catheter (diameter 10-12 mm) with 53 patients receiving EST for removal of CBD stones. The ballooning time was increased to 5 min to avoid the continuous blood oozing after balloon deflation. The successful bile duct clearance rates and the frequencies of mechanical lithotripsy were comparable between two groups. The minor bleeding episodes were more frequent in EST group (2% *vs* 26.4%, $P < 0.001$), but no other adverse effects such as pancreatitis and perforation were reported. Since then, endoscopic papillary large balloon dilation alone (EPLBD) or after sphincterotomy (ESLBD) became popular use for removal the large or difficult CBD stones, the results are satisfactory and even superior to EST in most studies and literatures of meta-analysis[25-61]. Although lethal pancreatitis is rare, life-threatened complications such as perforation and bleeding have been reported after ESLBD or EPLBD[62,63]. In the era of EPLBD/ESLBD, several previous concepts about EPBD, such as the indications, methodology, short-term and long-term complications should be amended.

INDICATIONS OF EPBD/EPLBD

Staritz *et al*[6] firstly reported the good clinical results of EPBD for removal of CBD stones by using the large balloon catheter, but most endoscopists shifted to the smaller balloon catheter (8 mm) for papillary dilation later[9-16,22]. Because of high incidence of post-procedural pancreatitis in a few studies[15,16], the indica-

tions of EPBD was confined to the vulnerable patients (*e.g.*, coagulopathy, cirrhosis), or altered anatomy (*e.g.*, Billroth Ⅱ gastrectomy, Roux-en-y anastomosis, juxtapapillary diverticulum), and the stones were lesser than 1 cm in diameter[19,20]. After ESLBD and EPLBD were widely used to remove the large or difficult stones with good results, the indications extend to the patients with large stones, tapered or stricture of distal bile duct[21,23,25,31,36,41,44,58,61]. As perforation is more likely to occur in those patients with distal bile duct stricture, some studies suggest that the target of EPLBD/ESLBD should include the patients with CBD dilation but without stricture of distal CBD[25,63]. Since stricture of distal bile duct is also a problem after EST, other studies recommend limited EST, gradually inflation of balloon and early use of lithotripter to remove the CBD stones safely[23,63-66].

SUCCESS RATE OF EPBD/EPLBD FOR REMOVAL OF CBD STONES

The overall success rate of EPBD by using the conventional balloon catheter was comparable (94.3% *vs* 96.5%) with EST in a meta-analysis of eight studies[17], another similar analysis of thirteen studies reported that EPBD being less successful overall in regard to stone removal (90.1% *vs* 95.3%)[18]. Both two above studies showed that patients undergoing EPBD were more likely required mechanical lithotripsy for stone extraction (20.9% *vs* 14.8% and 20.0% *vs* 13.3%, respectively)[17,18]. The contradictory results of meta-analyses in clinical trials may be due to diverse nature of the studies in design and methods[67]. Most of the trials excluded the patients with coagulopathy, cirrhosis, distal bile duct stricture, big stones or difficult cases, the detailed methods including the ballooning time and medications were different. The heterogeneity of the trials may interfere the assessment of overall results.

The initial success rate of ESLBD was 91% (75.5%-100%), overall success rate was 98% (88.6%-100%), mechanical lithotripsy was necessary in 9.3% (0-33%)[68]. The overall success rate ESLBD was comparable with EST in most studies, but the need of mechanical lithotripsy was less frequent in ESLBD[25,31,41,44,58]. In patients received EPLBD alone, the overall success rate of CBD stones removal ranged from 92.7%-97.5%, the need for mechanical lithotripsy ranged from 15.8%-21.2%[45,51,69-72]. Minakari *et al*[69] found that there were no significant difference between the success rate of EPLBD alone and EST (97.5% *vs* 96.2%). Hwang et al reported that the overall success rate of CBD stone removal and the needs of mechanical lithotripsy were similar between the patients received EPLBD alone or ESLBD (96.8% *vs* 95.7% and 19.4% *vs* 26.1%, respectively)[57].

METHODS OF EPBD/EPLBD

The diameter of the balloon depends upon the injection pressure inside the balloon according to the manufacturer's instruction[24,45]. A multicenter study demonstrated the efficacy and safety of EPBD by inflating the balloon until its waist disappears, rather than inflating to a prespecified pressure[72,73]. The balloon should be slowly inflated to avoid sudden tearing of the ampullary roof. After EST, the shape of papillary orifice will be triangular and the distal CBD will be narrow in shape. In contrast, the papillary orifice will be shaped as a large round hole with cylindrical configuration without a narrowing at distal bile duct after adequate balloon dilation, the relative stiff accessory instruments such as basket and lithotripter will enter easily into bile duct for stones removal[47]. The traditional balloon catheter (8 mm in diameter, 3 cm in length) was used to remove the small CBD stones and to preserve the integrity of the sphincter[13,74]. The large balloon (≥ 10 mm to 20 mm) is used to remove the big difficult stones without consideration of sphincter preservation[44].

The choice of balloon depends on the size of the largest stones and the CBD diameter[44]. The size of balloon should not exceed the maximal diameter of bile duct. In the patients with a stricture or tapered distal bile duct, gradual dilation with smaller balloon until disappearance of the waist is suggested, and EPBD should be terminated if the patient is intolerant to the dilating procedure.

The ballooning time is heterogeneous in different reports. In several controlled studies, the short ballooning time 20-30 s had the comparable results with the ballooning time 60-120 s[55,72,75]. In the study of Choi *et al*[76] they demonstrated the favorable outcome of immediate balloon deflation method in ESLBD for the extraction of difficult CBD stones. In a randomized trial from Taiwan, Liao *et al*[77] showed that 5-min EPBD improved the efficacy of stone extraction and reduces the risk of pancreatitis in comparison with conventional 1-min EPBD. A meta-analysis also demonstrated the duration of EPBD is inversely associated with pancreatitis risk[60]. Long EPBD can result in adequate loosening of the intact sphincter and less blood oozing, the widely opened papillary orifice may facilitate the insertion of accessary instruments into bile duct, and decrease the injury of pancreas[24,45,77,78]. In the patients who received ESLBD, shorter ballooning time may be enough because the sphincter is partially severed. The longer ballooning time may probably prevent bleeding complication, particularly in the flail patients with bleeding tendency, cirrhosis, uremia or under anti-platelet therapy[37,63,65].

Attasaranya *et al*[38] suggested that EPLBD after EST may result in separation of the pancreatic and biliary orifices and the balloon dilation forces are away

from the pancreatic duct. According to his theory, many endoscopists performed ESLBD to remove the CBD stones recently[26-30,32-35,37,39,40,42-44,46-48,53,54]. Significant bleeding was reported in 2.8% (0-8%) after ESLBD[68]. Hwang *et al*[57] conducted a study of 131 patients to compare the clinical effect of EPLBD alone and ESLBD. The successful stone removal (EPLBD 96.8%, ESLBD 95.7%), need of mechanical lithotripsy (EPLBD 19.4%, ESLBD 26.1%), postprocedural pancreatitis (EPLBD 6.5%, ESLBD 4.3%), perforation (EPLBD 0%, ESBD 1.4%) were no significant differences between two groups[57]. The recent prospective controlled study by Kogure *et al*[77] also demonstrated the similar findings. Another two single-institution retrospective studies reported that the EPLBD alone had the overall success rate 92.7%-97.4%, required the help of mechanical lithotripsy 15.8%-21.1%, postprocedural mild pancreatitis 0-0.8%, and no major bleeding[45,71]. Therefore, EPLBD alone is a simple safe and effective method in patients with large CBD stones, precut sphincterotomy may be unnecessary except in those patients with difficult cannulation of bile duct.

ADVERSE EVENTS AFTER EPBD/EPLBD

Pancreatitis

EPBD is categorized as one of the important causes of pancreatitis since the report of multicenter study from Disario *et al*[16]. From the result of recent studies, pancreatitis is more frequent in the patients using the traditional balloon (8 mm) and short duration (< 3 min) than the patients using the large balloon and long duration[6,12,14-17,24,25,31,36,45,52,58,60,65,71,77,79]. In 2000, Gil *et al*[80] from Spain reported their results by using percutaneous balloon dilation of sphincter of Oddi to clear the bile duct in the 38 patients with CBD stones. The success rate was 94.7% and no patient developed pancreatitis[80]. Another study from Argentina applied similar method in 300 patients, no patients developed pancreatitis after antegrade balloon dilation of biliary sphincter with maximal diameter 20 mm[81]. A Korean retrospective study compared the efficacy and adverse event in 56 patients underwent percutaneous transhepatic papillary dilation (PTPD) with 208 patients underwent retrograde EPBD for removal of CBD stones[82]. Complete bile duct clearance was achieved in 97.1% of EPBD and 98.2% of PTPD. Fourteen (6.7%) of 208 EPBD group *vs* 0% of PTPD developed pancreatitis after the procedure (P = 0.046). Hyperamylasemia occurred in 29.8% of EPBD group and 7.1% of PTPD group (P = 0.0005). These studies disprove the previous concept of balloon dilation being the cause of pancreatitis. The balloon is innocent and the pancreatitis may actually result from the traumatic injury of major papilla or pancreatic duct at the time of selective cannulation of bile duct, or the procedures of stone extraction after balloon dilation. In the patients with difficult cannulation, papillary edema after repeated cannulation, accidental trauma by diagnostic catheter or excessive injection of contrast medium to the pancreatic ducts are not uncommon, particularly in the patients with small papillary orifice or not widely opened orifice after inadequate balloon dilation. The pathogenesis of pancreatitis after EPBD appears multifactorial, only the superfluous injection of contrast medium into pancreatic duct is certainly considered to lead to increasing the risk of pancreatitis[83]. Once the head portion of pancreatic duct filled with contrast, we should stop the contrast medium injection immediately and withdraw the catheter in order to minimize the pancreatic injury. In addition, adequate dilation of papilla to create a large opening of bile duct may facilitate the accessory instruments enter the bile duct easily and to avoid further injury of pancreas[45]. Routine use of pancreatic stent may help for decrease the risk of pancreatitis by experienced endoscopists, but the indication and detailed methodology are not established yet[84].

Bleeding

Less bleeding is believed to be one of the advantages for EPBD in the treatment of CBD stones up to now. In the early meta-analysis from Baron *et al*[17], no patients developed bleeding after EPBD in 8 controlled studies using the traditional balloon for dilation, but 2% of patients had bleeding after EST. In DiSario's study, self-limited or endoscopically controlled bleeding occurred in 27% of the patients undergoing EST and 10.5% of patients undergoing EPBD[16]. Minor oozing after EPBD commonly occurs due to microvascular rupture accompanied by stretching of the mucosa, particularly in the patients receiving EPLBD, but most of them are self-limited and does not considered as a bleeding complication in most studies[44,65]. Park *et al*[85] had conducted a study to compare the results of EPBD using traditional balloon with EST in patients with cirrhosis and coagulopathy. Significant bleeding occurred in six (30%) patients who received EST and three of them died of bleeding related complications. No bleeding episode was reported in patients received EPBD[85]. Unlike the EPBD using a traditional balloon, the bleeding episodes were ranged from 0-16.7% in patients who received the ESLBD for treatment of CBD stones[44], one patient died of bleeding in a multi-center study who received EPLBD after a full EST[63]. Patients who received EPLBD alone had less frequent or less severe bleeding episodes in both prospective and retrospective reports[45,57-71,77]. Lin *et al*[24] prolonged the duration of balloon inflation to 5 min because of continuous oozing after short duration balloon inflation in the initial two cases. Most of published reports excluded the patients with coagulopathy in their protocols, and there is no consensus for the methodology of EPBD or EPLBD in the present

time. To prolong the duration of balloon inflation and the use of EPLBD alone may probably reduce the risk of significant bleeding to the patients with potential coagulopathy[24,65], but it needs further controlled studies to confirm.

Perforation

The incidence of perforation was 0-2% in patients after EPBD, 0-1.7% in patients after ESLBD[17,44], 0-2.5% after EPLBD alone[30,45,57,71,77,86]. Mortalities after EPBD or ESLBD were also reported[7,63,86]. Distal CBD stricture and over-inflation of balloon may be responsible for the fatal perforation[63]. In the patients with stricture or tapered distal bile duct, gradual balloon dilation with a smaller balloon initially and application of lithotripter may help for safely extraction of CBD stones[23,66]. Strong resistance, persistence of notch, and intolerable pain development during balloon inflation indicated stricture of bile duct, additional pressure should not be applied to avoid perforation[63]. In such cases, it should convert to drainage procedure or other stone extraction modalities[63].

Infection

Incidences of infection after endoscopic treatment for CBD stones are heterogeneous in the published reports. They range from 0-8% in EST, 0-10% in EPBD, 0-3.3% in ESLBD and 0-5% in EPLBD alone [30,44,45,57,61,71,77,86,87]. Biliary infection after endoscopic treatment may relate to the concomitant disease and general condition of the patients, contamination during the procedure and incomplete drainage of bile after the procedure. However, even under strict clean and disinfection protocol, biliary infection still occurred in 0.28%[88]. Some endoscopists routinely used the prophylactic antibiotics to the patients who received endoscopic therapy, but Cotton *et al*[88] suggested that prophylactic antibiotics should restrict to patients with predictably undrainable biliary systems or likely to have infected bile (*e.g.*, immunocompromised, prior sphincterotomy, and/or stent). Besides the strict cleaning and disinfection protocol, aspiration of bile from the proximal bile duct above the obstruction level before the contrast injection and to avoid over-filling of intrahepatic ducts during the procedure may reduce disseminating infection[88].

Late complications

The recurrent CBD stones ranged from 0-25% in the patients using traditional EPBD[9,12,22,87,89-91], 4.4%-21% in ESLBD[79,92-95], 4%-14.5% in EPLBD alone[45,70,79]. Tsujino *et al*[22] reported the long term outcome of 1000 patient after traditional EPBD; the recurrence rate was 8.8%. In subgroup analysis, the recurrent rate was highest in the patients with gallbladder left *in situ* with stones (15.6%), followed by cholecystectomy before EPBD (10.8%), gallbladder left *in situ* without stone (5.9%) and elective cholecystectomy after EPBD(2.4%)[22]. Kojima *et al*[92] and Ohashi *et al*[90] reported the highest recurrent rate of CBD stones in patients with cholecystectomy before EPBD (22%, 17.6%). The recurrent rates in other subgroups were gallbladder *in situ* with gallstones 8.9% and 0%, gallbladder *in situ* without stone 4.9% and 4.9%, cholecystectomy after EPBD 4.3% and 7.4%[90,92]. However, the incidences of acute cholecystitis in the patients with intact gallbladder and gallstones were higher than other three groups (4.5%-7.7%)[22,90]. Most of the primary CBD stones and recurrent stones from Asian patients are belonged to loose bilirubinate stone[22,50,86,90,94,96], the small fragments of these stones missed by cholangiography may remain in the bile duct and act as nidi for early recurrent stones[90]. Poor biliary emptying is responsible to the formation of primary and recurrent stones[97]. Gallbladder contraction after meal may flush the bile duct and expel the small stone particles into duodenum. Patients with prior cholecystectomy may lose this flushing function and increase the risk of stone recurrence. In patients with an intact gallbladder and stones, the stone may migrate to cystic duct and CBD resulting to cholecystitis and recurrent CBD stones[22].

In the recent meta-analysis by Zhao *et al*[93], they found that the overall long-term complications were significant lower if patients were treated by EPBD rather than EST. Compared to EST, EPBD markedly decreased the incidence of acute cholecystitis. Although there were no significant difference between EPBD and EST in the incidences of acute cholangitis and recurrent CBD stones, but a study with follow-up for more than one year indicated that the stones recurrence rate decreased significantly in the EPBD group[95]. Tanaka et al found that the recurrent rate of CBD stones within one year was higher in EPBD than EST (25% *vs* 6.3%), but the incidence of recurrent CBD stones was lower in EPBD than EST after follow up for 1-6 years (6.3% *vs* 26.7%)[12]. Similar late complication and stone recurrence rate in patients after ESLBD and EST was reported by Kim *et al*[94]. During a median 22 mo (range, 1-56 mo) follow up, Kogure *et al*[79] found that the incidence of recurrent CBD stones was higher in patients received ESLBD than the patients received EPLBD alone (21% *vs* 11%).

SPHINCTERIC FUNCTION AFTER EPBD/EPLBD

Most endoscopists emphasized the advantage of EPBD in preservation of sphincteric function and the prevention of late complications in the last century, so the traditional balloon (8 mm) was commonly used with this purpose. Sato *et al*[74] had used the microtransducer catheter to check the sphincter of Oddi (SO) function before and after traditional EPBD. The mean SO basal pressure dropped from 13.6 mmHg to

6.3 mmHg at one week after EPBD and increased to 9.3 mmHg after one month[74]. Yasuda *et al*[13] used the same method as Sato *et al*[74] and found that the preservation of SO function was not completed but remained somewhat reduced (SO basal pressure before, one week and one year after EPBD were 9 mmHg, 3.3 mmHg and 4.2 mmHg respectively)[13]. In addition, EPBD caused less pneumobilia than EST (86% *vs* 40%, $P < 0.01$) but the incidences of recurrent CBD stones did not have significant difference between two methods[13]. Both two studies did not include the pharmacological test in manometry[98,99], the incidences of paradoxical response after cholecystokinin or ceruletide in their patients were not known. Failure to relax the sphincter after meal or SO dysfunction may hinder the spontaneous passage of residual stones particles, resulting in recurrent stone formation[12]. In the patients who received EPLBD (> 1 cm), the SO function was not preserved[100]. The Asian patients with CBD stones are male predominant, older age, high percentage of juxtapapillary diverticulum and bilirubinate stones, their characteristics are different from the Western patients[7-10,13-16,30,35,63,83,91]. A recent retrospective study indicates that EPLBD is helpful to prevent re-recurrence of CBD stones after previous EST[101], but further controlled studies are needed to clarify the role of sphincteric function in the Asian patients with CBD stones.

LIMITATION OF EPBD/EPLBD

In patients with papillary stenosis, severe stricture of distal bile duct or impacted stones in papilla, it is difficult to insert the guidewire deeply into bile duct, precut sphincterotomy is necessary to assist EPBD or EPLBD. In patients with non-dilated bile duct or tapered distal bile duct, EPBD should be started with a small balloon and gradual inflation. In the patients with biliary stricture and unsuitable for surgical intervention, EPBD can be tried but the risk of perforation is high[63]. If patient feels intolerable pain during the procedure or the waist of balloon does not disappear after inflating the balloon to 75% of the maximum recommended pressure, balloon pressure should be reduced or change to other modalities[65]. Although EPBD is recommended in the patients with coagulopathy, details of the method for safely handling these high risk patients is not yet established. As non-significant bleeding is common in EPBD/EPLBD, avoid precut sphincterotomy and increased the duration of balloon dilation may be necessary to prevent the lethal bleeding complication. EPBLD alone or with EST are not the sphincter preserved procedures, the patent papillary orifice can facilitate the free drainage of small stone particles into duodenum, but also allows the reflux of duodenal content, regular follow up is necessary for early detection and management of CBD stones recurrence[102].

CONCLUSION

The methods in endoscopic treatment of CBD stones should be individualized. Both EST and EPBD/EPBLD can be safely used in the routine practice to remove the CBD stones by the experienced endoscopists. EPBD/EPLBD is preferred in the patients with difficult CBD stones, altered anatomy, tapered or mild stricture of distal bile duct, and coagulopathy. EST is superior to EPBD in the patients with stones impaction, difficult deep cannulation, and small CBD diameter without stricture. EPLBD is a safe procedure if it is performed according to the following steps: (1) avoidance of unnecessary pancreatic contrast injection; (2) use of suitable balloon and pressure; and (3) slowly balloon inflation and adequate ballooning time to achieve a widely opened papillary orifice. EPLBD alone is as effective as ESLBD but this point needs more controlled studies to confirm. EPLBD as well as EST is not the sphincter preserved procedure, regular follow-up may be necessary for early detection of recurrent CBD stones.

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MINIREVIEWS

Current status of minimally invasive endoscopic management for Zenker diverticulum

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Abstract

Surgical resection has been the mainstay of treatment of pharyngoesophageal (Zenker) diverticula over the past century. Developments in minimally invasive surgery and new endoscopic devices have led to a paradigm change. The concept of dividing the septum between the esophagus and the pouch rather than resecting the pouch itself has been revisited during the last three decades and new technologies have been investigated to make the transoral operation safe and effective. The internal pharyngoesophageal myotomy accomplished through the transoral stapling approach has been shown to effectively relieve outflow obstruction and restore physiological bolus transit in patients with medium size diverticula. Transoral techniques, either through a rigid device or by flexible endoscopy, are gaining popularity over the open surgical approach due the low morbidity, the fast recovery time and the fact that the procedure can be safely repeated. We provide an analysis of the the current status of minimally invasive endoscopic management of Zenker diverticulum.

Key words: Zenker diverticulum; Endoscopic stapling; Cricopharyngeal myotomy; Diverticulectomy; Interventional flexible endoscopy

Core tip: Developments in minimally invasive surgery and interventional endoscopic techniques have led to profound changes in the management of Zenker's diverticula. Transoral techniques, either through a rigid or flexible endoscopic device, have gained popularity due to the low morbidity, fast recovery time and safe repeatability. However, the choice of treatment is still based on phisician's expertise, personal preferences, and area of specialty. Endostapling through rigid endoscopy remains the most frequently performed approach. Interventional flexible endoscopy is an attractive minimally-invasive treatment option. However, due to heterogeneity of data and lack of standardized protocols, a direct comparison of the various techniques is difficult. Prospective clinical studies are required to establish treatment guidelines for Zenker diverticulum.

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INTRODUCTION

The management of Zenker diverticulum is far from being standardized in current clinical practice. Impaired opening of the upper esophageal sphincter due to increased hypopharyngeal bolus pressure and reduced wall compliance[1,2] are the main physiological determinants of this "pulsion" diverticulum which is more frequent in elderly male patients. It s likely that the prevalence of this disorder will increase in the future due to the increased aging population. Common symptoms are dysphagia, weight loss, regurgitation, halitosis, and aspiration with possible episodes of pneumonia. Preoperative workup should include a videofluoroscopic swallowing study and an upper endoscopy to rule out concomitant esophagogastric disease, and treatment should be reserved for symptomatic patients.

Interestingly, the first surgical resection and the first endoscopic approach with punch forceps were performed before World War I; both procedures were soon abandoned because of the high mortality rate. Between 1950 and 1960 both surgical and endoscopic procedures were revisited and restored to favour: surgeons recognized the importance of adding a cricopharyngeal myotomy to resection, whereas endoscopists introduced the CO_2 laser to divide the septum[3].

Nonetheless, more than 50 years later, despite the revolution of minimally invasive surgery and the introduction of disruptive technologies, we are still left in doubt regarding the choice of the ideal therapy. In the real world, a minimally invasive endoscopic operation may sometimes be the only reasonable choice, especially in elderly patients with multiple comorbidities deemed unfit for conventional open surgery. A tailored approach that takes into account the size of the diverticulum and the patient physiological status seems also reasonable, but clinical evidence is still lacking[4,5].

CURRENT THERAPEUTIC OPTIONS

Treatment options for Zenker diverticulum include open surgery through a left cervical incision (cricopharyngeal myotomy with or without resection), and transoral division of the septum through rigid endoscopy (with stapler, CO2-laser, or harmonic scalpel) or interventional flexible endoscopy (free hand or assisted). No controlled trials have been performed to demonstrate the superiority of one technique over another and, as a consequence, there is no accepted guideline for patient management[6].

Open surgical procedures

Surgical repair of Zenker diverticulum is usually performed under general anaesthesia through a left neck access and consists of stapled diverticulectomy with cricopharyngeal myotomy. Myotomy alone may be preferred for small diverticula. The patient is placed supine with a small pillow under the shoulders and the head hyperextended and turned to the right side. The incision is made parallel to the anterior border of sternocleidomastoid muscle. The pharynx and cervical esophagus are exposed by retracting the sternocleidomastoid and carotid sheath laterally, and the larynx and thyroid medially. Cricopharyngeal and proximal esophageal myotomy is performed after dissecting the pouch from the surrounding loose connective tissue. The diverticulum can be surgically excised with a linear stapler (diverticulectomy), uplifted and suspended to the prevertebral fascia (diverticulopexy), or invaginated into the lumen (Table 1). The results of diverticulectomy have been uniformly satisfactory. In the largest series of 888 patients from the Mayo Clinic, the operative mortality was 1.2%. The most frequent complications were recurrent nerve palsy (3.2%), wound infection (3%), and salivary fistula (1.8%). The reported recurrence rate was less than 5%[7]. A similar outcome with no operative mortality, minimal morbidity, and very good to excellent results has been reported in Europe[8]. Reoperation can represent a technical challenge after open diverticulectomy because of the risk of fistula and recurrent nerve injuries[9].

Transoral procedures

Rigid endoscopy: A transoral technique using an endoscopic stapler introduced through a rigid scope was first proposed in 1993[10-12]. The patient is placed supine with the neck hyperextended; the surgeon is sitting behind the patient's head. The operation is performed under general anaesthesia with orotracheal intubation. The Weerda diverticuloscope is introduced into the esophageal inlet in the closed position, under direct 0° telescopic vision, and it is slowly withdrawn to expose the septum between the diverticulum and the esophageal lumen. The two valves of the diverticuloscope are placed inside the esophagus and the diverticulum, respectively. An endoscopic linear stapler with a 35 mm blue cartridge is introduced through the diverticuloscope down to the septum. One or two cartridges are usually necessary to divide the septum depending on the length of the pouch. The stapler allows safe simultaneous cutting and sealing of the septum. By creating this delta-shaped anastomosis the diverticulum and the esophagus become a common cavity.

The procedure is generally not indicated in small diverticula (< 3 cm)[3]. In case of borderline diverticulum size, traction sutures applied at the apex of the septum with a laparoscopic endostitching device can help to engage the septum between the stapler jaws and allow a more complete septal division[13,14]. Transoral septum stapling is the preferred initial treatment for Zenker diverticulum in many centers and it has been shown to be a safe and effective proce-

Table 1 Outcome of open surgical procedures for Zenker diverticulum

Ref.	No. pts	Technique	Satisfactory outcome (%)	Overall morbidity (%)	Salivary fistula (%)
Orringer[46]	12	M, DM	85	25	8
Ellis *et al*[47]	10	DM	100	0	0
Konowitz *et al*[48]	20	DM	100	20	5
Barthlen *et al*[49]	43	M, DM	82	7	0
Payne *et al*[7]	888	D	93	30	1
Morton *et al*[50]	15	DM	100	40	13
Bonafede *et al*[51]	87	D, DM, DpM	78	24	NA
Fraczek *et al*[52]	37	DM, DpM	93	23	5
Van Eeden *et al*[53]	17	M, DM, DpM	59	6	14
Zbären *et al*[54]	66	DM	77	15	12
Busaba *et al*[55]	9	DM	100	0	0
Leporrier *et al*[56]	40	DM, DpM	92	10	3
Sydow *et al*[57]	13	M, DM, DpM	NA	27	23
Gutschow *et al*[58]	101	M, D, DM, DpM	98	13	13
Zaninotto *et al*[59]	34	DM, M	100	12	6
Colombo-Benkmann *et al*[60]	79	D, DM	99	4	4
Bonavina *et al*[3]	116	DM	94	0.8	0.8
Rizzetto *et al*[4]	77	DM, DpM, M	95	13	4

M: Myotomy; DM: Diverticulectomy/myotomy; D: Diverticulectomy; DpM: Diverticulopexy/myotomy; NA: Not available.

dure[15-17].

The harmonic scalpel (Ultracision, Ethicon Endo-Surgery, Cincinnati, Ohio), operated through the Weerda diverticuloscope, has been used to divide the septum as an alternative to stapling[18-20]. The device is able to cut and simultaneously coagulate tissue with minimal lateral thermal spreading and optimal haemostasis. The small diameter of the scalpel allows an easy maneauverability and the cutting surface extends to its distal tip allowing a distally extended miotomy in small diverticula that could not be suitable for endoscopic stapling.

CO2-laser division of the septum, first introduced in 1981 by van Overbeek[21], represents another alternative or a complementary technique to endoscopic stapling. The operation is generally performed under narcosis with endotracheal intubation. An operating microscope with a 400-mm lens and attached CO_2 laser micromanipulator is introduced and focused on. Using the laser on continuous mode the septum is transected on the midline down to the bottom[22,23]. The CO_2 laser technique is precise but strictly operator-dependent, and the risk of perforation and mediastinitis should not be underestimated. Table 2 shows the results of the transoral procedures through rigid endoscopy.

Interventional flexible endoscopy: Flexible endoscopy was proposed in 1995 for the treatment of Zenker diverticulum[24,25]. Some centers offer this option to all patients, although most authors recommend the endoscopic flexible approach for a selected subset of highly morbid patients who are unfit for surgery or for rigid endoscopy under narcosis[26,27].

Patients are placed in a left lateral decubitus position. The operation is performed either in conscious sedation or under narcosis. The technique can be "freehand" or a variety of different accessories (capo, hood, overtube) can be used to improve septum exposure, stabilize its position, and protect the esophagus and the pouch from thermal injury[28,29]. A novel device for improving the operative field and fixing the septum is the soft diverticuloscope (Zenker overtube; Cook Endoscopy, Winston-Salem, North Carolina, United States)[30,31]. Similar to the Weerda diverticuloscope, this transparent soft-rubber overtube has two distal flaps that protect the esophagus anteriorly and the diverticulum posteriorly. The overtube is advanced over the endoscope and the septum is properly displayed under direct endoscopic vision. Different cutting devices can be used (needle-knife, monopolar forceps, hook-knife, argon plasma coagulation)[32]. Hondo *et al*[33] have recently described the use of the harmonic scalpel introduced through a soft diverticuloscope.

With the needle-knife, the septum is generally divided through a midline incision directed distally towards the bottom of the pouch. The wound edges of the septum separate immediately after the incision. The risk of mediastinal perforation associated with the procedure has led some operators authors to use a clip-assisted (clip and cut) technique where, prior to dissection, two endoclips are placed on either side of the septum[34,35]. Other operators place one or more metal endoclips at the bottom of the incision to secure the margins and prevent microperforations[31].

An incomplete cricopharyngeal myotomy may account for the high recurrence rates associated with single session flexible endoscopy diverticulotomy. A step-wise approach with a limited initial incision followed by multiple repeat procedures could improve the overall clinical outcome and further reduce the risk of perforation[26]. Table 3 shows the results of the transoral procedures through interventional flexible endoscopy.

CLINICAL OUTCOME AND FUTURE PERSPECTIVES OF TRANSORAL PROCEDURES

The obvious advantages of endoscopic stapling over the conventional open surgical approach are the absence of cutaneous incision, shorter operative time, reduced postoperative discomfort, faster return to oral feeding, and shorter length of hospital stay. An additional advantage is expected in patients who had

Table 2 Outcome of transoral rigid procedures for Zenker diverticulum

Ref.	No. pts	Technique	Satisfactory outcome	Overall morbidity	Salivary fistula	Conversion rate
Fremling *et al*[61]	6	Stapling	100%	0%	0%	0%
Peracchia *et al*[36]	95	Stapling	93%	1%	0%	3%
Narne *et al*[62]	102	Stapling	100%	0%	0%	4%
Philippsen *et al*[15]	14	Stapling	100%	0%	0%	21%
Cook *et al*[16]	74	Stapling	97%	3%	2%	8%
Lüscher *et al*[63]	23	Stapling	96%	1%	4%	0%
Jaramillo *et al*[64]	32	Stapling	80%	4%	0%	16%
Thaler *et al*[65]	23	Stapling	87%	0%	0%	30%
Counter *et al*[66]	31	Stapling	95%	10%	10%	0%
Chang *et al*[22]	24	CO_2 laser	90%	8%	0%	0%
Fama *et al*[18]	25	Harmonic Scalpel	96%	12%	0%	0%
Sharp *et al*[19]	48	Stapling/Harmonic Scalpel	88%	12%	2%	0%
Helmstaedter *et al*[23]	40	CO_2 laser	NA	10%	NA	NA
Wasserzug *et al*[67]	55	Stapling	90%	4%	2%	7%
Peretti *et al*[68]	28	CO_2 laser	85%	7%	4%	4%
Nicholas *et al*[13]	7	Stapling	100%	14%	0%	0%
May *et al*[20]	7	Harmonic Scalpel	100%	0%	0%	0%
Bonavina *et al*[14]	91	Stapling	80.8%	5%	1%	13.2%
Adam *et al*[69]	128	Stapling/CO_2 laser	NA	4.6%	0%	NA

NA: Not available.

previous surgical procedures on the left side of the neck in whom the recurrent laryngeal nerve is more likely to be injured at conventional reoperation[36].

Despite all these features and the proof of safety and efficacy, transoral stapling has not been widely accepted as first-line treatment for Zenker diverticulum for a number of reasons: (1) lack of long-term audit; (2) lack of controlled clinical studies; (3) lack of technical expertise and dedicated equipment in many hospitals; (4) lack of confidence or proper training with the transoral access by surgical specialists other than otolaryngologists; and (5) fear of carcinoma arising within the non resected pouch.

Collective data from retrospective or prospectively recorded case series consistently show that a satisfactory outcome with endoscopic stapling is obtained in more than 90% of patients, with a 6% recurrence or persistence rate[37]. A recent article by Leong *et al*[38] reviewed the experience with transoral stapling in England where this technique is performed by the majority of otolaryngologists and is endorsed by the National Institute for Clinical Excellence (NICE). Out of 585 patients reviewed, 540 (92.3%) successfully underwent transoral stapling with an intraoperative conversion rate of 7.7%, an overall complication rate of 9.6%, and an overall recurrence rate of 12.8%. Most of the patients in whom the procedure failed underwent repeat endoscopic stapling.

Small diverticula (< 3 cm) have indeed represented a major cause of long-term failure of transoral stapling[3]. This is due to the difficulties in accommodating of the 30-35 mm anvil. However, in most patients with borderline diverticulum size, the application of traction sutures the apex of the common septum can improve the engagement of the spur in the stapler jaws with a net gain of about 1 cm of stapled tissue[14]. In case of recurrent symptoms, the procedure can be successfully repeated through a transoral approach (rigid or flexible). CO_2 laser or ultrasonic cutting techniques may have a complementary role in some circumstances[39].

Interventional flexible endoscopy is an attractive therapeutic alternative, especially in elderly patients unfit for surgery, and may overcome some of the physical limitations of rigid endoscopy. Flexible endoscopy can be performed in the endoscopic suite, under conscious sedation with midazolam. The procedure allows quick resumption of oral feeding and fast hospital discharge. In patients with persistent or recurrent symptoms the procedure is easily repeatable, and appears to be safe even after failure of endostapling. A recent study has reported similar outcomes for flexible and rigid endoscopy regarding hospital stay, dysphagia score improvement and complication rates[40]. Several case series have shown the safety and efficacy of interventional flexible endoscopy with clinical success rates ranging from 56% to 100%. Perforations and bleeding have been reported in up to 27% and 10% of cases, respectively[27].

Interventional flexible endoscopy for Zenker diverticulum is not standardized, and different cutting techniques can be combined with different accessories depending physicians' personal experience and preferences. The needle-knife is the most frequently used device, often in combination with a transparent cap, hood or soft diverticuloscope. No significant differences in clinical outcomes have emerged by using of one or the other accessory[41,42]. An overall clinical recurrence rate of 25% has been reported in the literature[43]. It is generally recommended that the incision should be carefully balanced in order not to cause mediastinal perforation; on the other hand, a too

Table 3 Outcome of transoral flexible procedures for Zenker diverticulum

Ref.	No. pts	Incision device	Accessories	Satisfactory outcome	Overall morbidity	Salivary fistula
Mulder *et al*[25]	20	Coagulation	Forceps	NA	0%	0%
Ishioka *et al*[24]	42	Needle Knife	Mix	93%	1%	2%
Hashiba *et al*[70]	47	Needle Knife	Mix	96%	2%	13%
Mulder[71]	125	Argon Plasma	None	100%	2%	15%
Sakai *et al*[28]	10	Needle Knife	Hood	100%	1%	0%
Costamagna *et al*[31]	28	Needle Knife	Cap	43%	14%	18%
Rabenstein *et al*[72]	41	Argon Plasma	Cap	95%	0%	3%
Christiaens *et al*[32]	21	Monopolar forceps	Hood	100%	0%	5%
Vogelsang *et al*[34]	31	Needle Knife	Cap	84%	3%	23%
Tang *et al*[35]	6	Needle Knife	Hood/Endoclips	100%	0%	0%
Case *et al*[73]	22	Needle Knife	Cap	100%	32%	27%
Repici *et al*[29]	32	Hook knife	None	88%	6%	3%
Al-Kadi *et al*[74]	18	Needle Knife	None	78%	12%	6%
Hondo *et al*[33]	6	Harmonic scalpel	Soft diverticuloscope	100%	0%	0%

short transection may lead to incomplete myotomy and higher clinical recurrence rates. Unfortunately, when the incision is made in a proximal to distal direction it may be difficult to identify secure landmarks other than the muscular fibres. This has prompted some investigators to assess the safety and efficacy of the hook-knife by directing the incision from bottom to top. The more controlled and precise cut appears to reduce the risk of perforations[29]. More recently, an insulated-tip needle (IT-Knife 2), originally developed for endoscopic submucosal dissection has been tested in a series of 19 patients. The authors noted a more controlled septum incision and no adverse events. Over a median follow-up of 27 mo, dysphagia relapsed in two patients[44]. Finally, a diverticulum cap prototype with a swinging needleknife that is similar in principle to the device used for biliary sphincterotomy has been described and may provide in the future more precise and efficient septum dissection[45].

CONCLUSION

Treatment of Zenker diverticulum has evolved thanks to a better appraisal of the pathophysiology of the disease and the implementation of new techniques in the field of minimally invasive surgery and interventional flexible endoscopy. Over the past three decades the transoral approach has been revisited and, once again, the emphasis of research has shifted from diverticulectomy to myotomy. However, heterogeneity of data and lack of standardized protocols preclude a direct and meaningful comparison of the techniques. No randomized trials nor retrospective case series have demonstrated the superiority of single treatment modalities and, therefore, the choice still depends on physician's expertise and personal preferences. Interventional flexible endoscopy is indeed an attractive treatment option, but at present transoral stapling has a longer follow-up and has been associated with significantly improved quality of life[75]. Further investigation and prospective clinical studies are eagerly awaited to define treatment guidelines for Zenker diverticulum.

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Colonoscopy appropriateness: Really needed or a waste of time?

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Abstract

Technical and quality improvements in colonoscopy along with the widespread implementation of population screening programs and the development of open-access units have resulted in an exponential increase in colonoscopy demands, forcing endoscopy units to bear an excessive burden of work. The American Society for Gastrointestinal Endoscopy appropriateness guideline and the European panel appropriateness of gastrointestinal endoscopy guideline have appeared as potential solutions to tackle this problem and to increase detection rates of relevant lesions. Inappropriate indications based on either guideline are as high as 30%. Strategies based on these clinical criteria or other systems may be used to reduce inappropriate indications, thus decreasing waiting lists for outpatient colonoscopy, saving costs, prioritizing colonoscopy referrals and subsequently decreasing interval times from diagnosis to treatment. Despite the potential role of appropriateness guidelines, they have not been widely adopted partly due to fear of missing significant lesions detected in inappropriate indications. We review the main appropriateness and prioritising systems, their usefulness for detecting relevant lesions, as well as interventions based on those systems and cost-effectiveness.

Key words: Colonoscopy appropriateness; European panel appropriateness of gastrointestinal endoscopy Ⅱ; National Institute for Health and Clinical Excellence; Colonoscopy prioritisation; Open access endoscopy unit

Core tip: There is increasing worldwide demand for colonoscopy referrals, overburdening endoscopy units. Controlling the appropriateness of colonoscopy referrals has been proposed to decrease the increased workload. The American Society for Gastrointestinal Endoscopy appropriateness and the European panel appropriateness of gastrointestinal endoscopy guidelines, and prioritisation criteria such as those of the National Institute for Health and Clinical Excellence and the Scottish Intercollegiate Guidelines network are good candidates for this task. We review the available systems and interventions designed to rationalize colonoscopy demand.

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INTRODUCTION

During the last decade we have witnessed a gradual increase of endoscopic procedures and a reduction of radiological techniques to examine the gastrointestinal tract such as esophagus-gastro-duodenal transit or barium enema. Some significant quality improvements have contributed to the widespread diffusion of endoscopic techniques, including conscious sedation[1], safety[2] and technological developments.

Furthermore, the implementation of screening programs for the early detection of colorectal cancer (CRC) and the development of open-access endoscopy units may further increase the demand for outpatient colonoscopy and the overall workload of endoscopy units. These factors are particularly worrisome in universal insurance health care systems.

In this setting, rationalization of the demand is mandatory to prevent overburdening endoscopy units, to improve efficiency in colonoscopy and to reduce costs and potential risks arising from inadequate colonoscopy referrals.

This review analyses, firstly, the causes of increasing workload of endoscopy units, with greater emphasis on especially focusing on population screening programs and open-access endoscopy units; secondly, strategies developed to control colonoscopy appropriateness and their results, including appropriateness criteria and adherence to guidelines, and finally criteria for prioritising referrals with higher risk of advanced colorectal neoplasms. Table 1 shows the highlights of this review.

Table 1 Summary box

Appropriateness guidelines and prioritising criteria have been developed to lessen colonoscopy workload in endoscopy units
The sensitivity of EPAGE Ⅱ criteria is higher than that of EPAGE Ⅰ criteria for detecting significant colorectal lesions (especially CRC); however, specificity should be further improved. Since these criteria are not perfect, in clinical practice, they should be used to assist the clinician before requesting a colonoscopy but they should not be the sole criteria for the decision
Although EPAGE Ⅱ criteria might be used to cancel inappropriate colonoscopy referrals, in clinical practice they should be used with caution, because some life-threatening lesions are missed, even in inappropriate requests
NICE criteria used for prioritising colonoscopy are not accurate enough for detecting advanced colorectal neoplasms, but may be improved in combination with other markers (*i.e.*, immunochemical fecal occult blood tests)
Adherence to guidelines required to decrease inappropriate indications and colonoscopy waiting lists

EPAGE: European panel appropriateness of gastrointestinal endoscopy; CRC: Colorectal cancer; NICE: National Institute for Health and Clinical Excellence.

INCREASING WORKLOAD OF ENDOSCOPY UNITS: SCREENING COLONOSCOPY AND OPEN ACCESS ENDOSCOPY UNITS

A recent survey carried out in the United States found that the number of colonoscopies performed had risen three to four times between 1998 and 2004[3], with colonoscopy being the most demanded endoscopic procedure. Similar patterns have been found in Europe[4]. Furthermore, the European Commission has recommended the implementation of programs for the detection of CRC in all countries of the Union[5]. A recent report assessed the amount of colonoscopies generated by a population screening program, depending on the screening strategy and uptake. Assuming a participation rate of 60%, screening might double the annual workload of endoscopy units[6]. Another source of additional referrals arising from screening programs are subsequent surveillance colonoscopies required after the resection of colorectal adenomas and CRC. Notably, surveillance colonoscopy after resection of colorectal adenomas is the most frequent indication in patients aged over 74 years in the United States, accounting for 28.9% in women and 37.9% in men[7]. Furthermore, according to a recent meta-analysis, more than 30% of the average-risk population may have colorectal adenomas[8]. Similar data have been reported in European studies[9-11]. Such a volume of colonoscopies represents a substantial burden.

A potential source of inappropriate referrals is open-access endoscopy units, increasingly frequent in both the United States and Europe. In open-access endoscopy units, any physician (not only a gastroenterologist) may request an endoscopic procedure[12]. These units emerged in an effort to save costs, preventing unnecessary office consultations with the gastroenterologist. Open-access endoscopy units may also be useful as a "shortcut", decreasing waiting times between consultation and colonoscopy. In fact, time off work for appointments is a problem for patients and open-access endoscopy units may expedite the diagnosis of severe diseases, and decrease empirical treatments[13]. However, one wonders whether the ease of access would not also increase the workload of endoscopy units resulting from a higher rate of inappropriate referrals, further increasing waiting lists and total costs. Thus, rationalization of the indication is considered essential.

Open access endoscopy units can be roughly classified as simple or censored. While no control system is applied in the former, in the latter, referral appropriateness is continuously checked by trained staff[14].

Table 2 Main indications for colonoscopy according to European panel appropriateness of gastrointestinal endoscopy Ⅱ (www.epage.ch)

Iron deficiency anemia
Hematochezia
Discomfort or pain in the lower abdomen persisting ⩾ 3 mo
Uncomplicated chronic diarrhea
Assessment of ulcerative colitis
Assessment of Crohn disease
Colorectal cancer screening
Colorectal cancer screening in patients with inflammatory bowel disease
Surveillance colonoscopy after polypectomy
Surveillance colonoscopy after colorectal cancer resection
Miscellaneous

APPROPRIATENESS CRITERIA FOR IMPROVING COLONOSCOPY INDICATION

A procedure is deemed appropriate as long as health advantages outweigh the theoretical risks by a wide margin of safety[15]. As resources are limited, adherence to the appropriate indications for colonoscopy is necessary. Appropriateness guidelines may be useful not only to prevent unnecessary colonoscopies and potential risks resulting from them, but also to prioritize colonoscopy[10,16].

American Society for Gastrointestinal Endoscopy and European panel appropriateness of gastrointestinal endoscopy Ⅰ criteria

The first guideline was developed by the American Society for Gastrointestinal Endoscopy (ASGE)[17]. It consists of 27 general indications for colonoscopy. This guideline has been adopted with some modifications by the Italian Society of Gastrointestinal Endoscopy which uses wider criteria and includes some indications unlisted by the original guideline, such as significant weight loss and changes of bowel habit[18]. The application of these modified criteria slightly increases the rates of appropriateness and detection of significant lesions, especially CRC[19]. In 1999, European experts, including gastroenterologists, surgeons and family physicians, designed the criteria of the European panel appropriateness of gastrointestinal endoscopy (EPAGE-Ⅰ)[20]. These criteria are based on a detailed review of the literature. The European panel established 12 main indications for colonoscopy, including 309 different clinical scenarios. Each clinical situation is scored from 1 to 9 (appropriate 7-9; 1-3 inappropriate; 4-6 uncertain). Colorectal cancer, adenomas, inflammatory bowel disease, stenosis and angiectasia are usually considered "significant lesions". Compared with ASGE criteria, EPAGE-Ⅰ criteria are more specific and detailed. With regard to the prediction of appropriateness, the two systems have been shown to be similar[19,21-28]. The rate of inappropriate referrals ranged from 20%-30% for both guidelines[21-24,26,27,29]; however, they have never been compared for colonoscopy referrals. One factor that might influence appropriateness is the role of physician specialty. In this regard, results are controversial; in some studies no differences between gastroenterologists and other specialists were found[21,23], in others, the data were favourable to gastroenterologists[28].

It must be said that neither set of criteria is perfect. First, significant lesions are detected in about 30% of inappropriate colonoscopies[22]. This has been attributed to incidental findings of asymptomatic lesions. In fact, one meta-analysis showed the suboptimal sensitivity of alarm symptoms for CRC detection, ranging from 5%-64% across the studies[30]. Second, it is well-known that some alarm signs and symptoms are also frequent in other diseases, leading to poor specificity. A recent meta-analysis assessed the performance of ASGE and EPAGE-Ⅰ criteria for the detection of significant lesions (as defined in each manuscript)[31]. Sensitivity, specificity, positive and negative likelihood ratios were: 89% (95%CI: 82%-93%), 26% (95%CI: 21%-31%), 1.16 (95%CI: 1-1.3), 0.44 (95%CI: 0.25-0.8), respectively. These data were similar to those reported for CRC. The authors concluded that a more effective strategy is needed and that both sets of criteria need further refinement to increase sensitivity (especially for CRC) and positive predictive value, and to minimize the number of colonoscopies in patients without significant lesions.

The most frequent cause of inappropriateness identified by both sets of criteria is surveillance colonoscopies after polypectomy or CRC surgery that are performed too early[25,27,28]. In a study involving more than 3000 colonoscopies, the most frequent causes of inappropriate indication were surveillance colonoscopies performed by general practitioners (GPs), surgeons and internists, and by gastroenterologists in the context of inflammatory bowel disease[26].

EPAGE Ⅱ criteria

EPAGE-Ⅰ and ASGE appropriateness guidelines are not sufficiently widespread. As mentioned, there are some concerns regarding safety when using these criteria, as a significant percentage of relevant lesions are detected in improperly requested colonoscopies.

More recently, an updated version of the EPAGE-Ⅰ criteria for colonoscopy has been published (EPAGE-Ⅱ criteria), after a comprehensive review of the literature from 1998 to February 2008 (Table 2)[32]. To date, four studies have assessed the benefit of EPAGE-Ⅱ criteria for predicting appropriateness and diagnostic yield of significant lesions (Table 3)[9-10,16,33]. Only in the largest study was the design fully prospective[10]. Three studies were carried out in Spain[9-10,33] and one in Norway[16]. Although statistical performance with confidence intervals of EPAGE-Ⅱ studies were described in only two of the studies[10,16], enough information was available in the other two for

Table 3 European panel appropriateness of gastrointestinal endoscopy Ⅱ studies addressing appropriateness and diagnostic yield

Ref.	Design[1] (referrals)	EPAGE Ⅱ[2] (% appropriate)	S[3] (95%CI)	Sp (95%CI)	PPV (95%CI)[4]	NPV (95%CI)
Carrión *et al*[33] (2010)	R 655	82.0	80.3 (74.0-84.3)	16.8 (14.9-18.5)	24.8 (23.1-26.4)	71.3 (63.1-78.6)
Arguello *et al*[9] (2012)	R 619	82.6	78.3 (73.8-82.4)	34.4 (31.3-37.3)	45.2 (42.6-47.6)	69.6 (63.4-75.4)
Gimeno García *et al*[10] (2012)	P 968	89.5	93.1 (90.0-96.3)	12.7 (10.0-15.0)	38.8 (36.0-42.0)	75.5 (67.0-84.0)
Eskeland *et al*[16] (2014)	R 295	91.0	92.6 (84.8-96.6)	22.9 (17.8-29.0)	31.3 (25.3-37.3)	89.1 (80.7-97.5)

[1]Study design: R (retrospective); *P* (prospective); [2]Appropriate and uncertain referrals jointly analysed; [3]S (sensitivity); Sp (specificity); [4]PPV (positive predictive value); NPV (negative predictive value).

calculation[9,33]. Taking into account the pooled results of the four studies, 75.4% of colonoscopy referrals were deemed appropriate, 13.9% inappropriate and 10.7% uncertain.

A validation study of these criteria showed that significant lesions were more prevalent in appropriate colonoscopies than in those considered inappropriate (38.8% *vs* 24.5%; OR = 1.95, 95%CI: 1.22-3.13; $P < 0.005$)[10]. This study also reported the performance for significant neoplastic lesions (advanced adenoma and CRC), showing sensitivity, specificity, positive and negative predictive values of 98% (95%CI: 95-100), 11.5% (95%CI: 9-14), 11.2 (95%CI: 9-13) and 98% (95%CI: 95-100) respectively. In accordance with other studies, an appropriate indication was more frequent in patients over 50 years compared with younger individuals (92.9% *vs* 76.7%; OR = 3.98, 95%CI: 2.60-6.09, $P < 0.001$). In fact, 50% of inappropriate referrals were found in patients younger than 50 years, despite constituting only 20% of referrals. In studies carried out in Spain, the indication with the highest rate of inappropriateness was surveillance colonoscopy, ranging from 41% to 76%[9-10,33], whilst in the Scandinavian study, this was lower abdominal symptoms (49%)[16]. In one study, inappropriateness in subjects younger than 50 years was separately analyzed. CRC screening at a younger age than usually recommended (33.3%) followed by surveillance colonoscopy at shorter intervals than recommended (20.8%) were the most frequent causes of colonoscopy overuse[10].

Recent evidence has shown that the application of EPAGE-Ⅱ criteria decreases rates of inappropriateness compared with EPAGE-Ⅰ criteria and, more importantly, decreases the rate of missed significant lesions[9,16]. In both studies, the specificity of EPAGE-Ⅱ criteria was lower than that of the first version, theoretically decreasing the impact of EPAGE-Ⅱ criteria on saving colonoscopies. Nevertheless, EPAGE-Ⅱ might be considered safer than EPAGE-I with respect to missed significant lesions. Some authors have suggested jointly calculating uncertain and inappropriate colonoscopies, as opposed to what is usually done (combining appropriate and uncertain together)[16]. In fact, no significant differences in diagnostic yield were found in two studies that compared different combinations[9,16]. However, some CRC might be missed with this approach. Of 109 CRC diagnosed in the 4 series, 2 were diagnosed in inappropriate referrals (1.83%) and 3 more in uncertain ones (2.75%). Therefore, it seems safer to consider uncertain and appropriate referrals together to prevent missing significant lesions. Recently, the combination of EPAGE criteria with blood or fecal biological markers was tested with the purpose of increasing appropriateness and improving diagnostic yield of significant lesions[34]. In one study, fecal calprotectin[34], which has shown its capacity to distinguish organic diseases (*i.e.,* inflammatory bowel disease) from functional disorders, was tested with EPAGE criteria in 224 consecutive patients with abdominal discomfort. Diagnostic yield for significant lesions was significantly higher when the combined strategy was used (70.2%) compared with either EPAGE or calprotectin alone (diagnostic yield 23.6% and 57.4% respectively). The combined strategy also improved re-classification of patients with a higher rate of appropriateness.

In summary, the refined EPAGE Ⅱ criteria are more sensitive than the old EPAGE Ⅰ, and may be an effective strategy to assist the clinician to decide whether a colonoscopy should be requested or not. They may also be a useful tool for decreasing colonoscopy overuse, as well as increasing diagnostic yield.

INTERVENTIONS BASED ON APPROPRIATENESS CRITERIA

Several studies have suggested that the medical specialty of the referring physician may influence colonoscopy appropriateness[9,10,21,28], with surveillance after polypectomy at shorter intervals than recommended being the most inappropriate indication. Therefore interventions based on audits and training of referring physicians are warranted to increase appropriateness.

Using EPAGE Ⅱ criteria[10], 91% of the inappropriate referrals corresponded to CRC screening, surveillance of neoplastic lesions (adenomas or CRC) or to subjects younger than 50 years. Subjects with any of these conditions had a lower rate of significant lesions and advanced neoplastic lesions than those who did not meet these conditions (31.2% *vs* 46.6%, $P < 0.001$; OR = 1.9, 95%CI: 1.47 to 2.51 and 5.1% *vs* 18.1%, $P < 0.001$; OR = 4.1, 95%CI: 2.60 to 6.41, respectively). In an interventional prospective study[35], 451 patients with high probability for inap-

propriateness (age < 50 years, surveillance colonoscopy or screening colonoscopy) were attended in an appropriateness outpatient clinic. EPAGE Ⅱ criteria along with current Spanish Association of Gastroenterology guidelines[36-38] were applied and colonoscopy was finally requested when deemed appropriate. In patients with an inappropriate indication, a different approach was carried out; a more suitable examination was requested, (*i.e.,* biochemical tests, abdominal ultrasonography) or treatment was prescribed when a functional disorder (intestinal bowel syndrome or functional dyspepsia) was suspected. Appropriateness was compared with a historical cohort of 968 patients who underwent colonoscopy and to whom EPAGE-Ⅱ criteria were applied. The intervention achieved a significant reduction of inappropriateness (5.2% *vs* 10.5%, OR = 0.46, 95%CI: 0.27-0.81) and, furthermore, increased the diagnostic yield of significant lesions (50.7% *vs* 37.3%, OR = 1.73; 95%CI: 1.33-2.25). However, these encouraging results of a censored open access unit should be taken with caution as the cost-effectiveness of this strategy has not been evaluated yet.

In another interventional study[19], involving 133 GPs, a tailored educational program was assessed using ASGE/SIED appropriateness guidelines. Fifty GPs finally attended the course and completed a multiple choice test to assess the level of learning. The rest received a brief summary of the ASGE/SIED appropriateness criteria by regular mail. Colonoscopy appropriateness was compared before and after the intervention. In this study, appropriate referrals significantly increased from the first to the second period, resulting in a mere 7% of inappropriateness (23% *vs* 7% respectively; $P < 0.001$). Although the effect was more striking among attendants, appropriateness also increased in those GPs who did not attend the course but received the ASGE/SIED criteria by mail. Furthermore, the authors also reported long-term efficacy of the intervention, with the benefit being maintained 1 year later. Therefore, this study encourages greater diffusion of the current guidelines on the main colonoscopy indications and the usefulness of periodic educational programs in an open access unit setting.

ADHERENCE TO GUIDELINES

Several studies have addressed the impact of compliance with the current surveillance guidelines after adenoma or CRC resection on colonoscopy waiting lists[39,40]. One study evaluated the effect of good compliance with the guidelines proposed by the American Gastroenterology Association (AGA) for surveillance after resection of colorectal adenomas on improving appropriateness and decreasing the waiting list[40]. Compliance with guidelines not only improved appropriateness in this indication but also increased the interval between surveillance colonoscopies by 0.73 years, with a 14% reduction of annual colonoscopies for this indication. Another work assessed the impact of compliance with the guidelines of the British Society of Gastroenterology and the Association of Coloproctology of the United Kingdom and Ireland for screening and surveillance after endoscopic polypectomy[39]. In this multicenter study, researchers from a tertiary care referral center applied these guidelines to the waiting list of several hospitals, recommending the exclusion of patients with an inappropriate referral. Overall, in 78% of cases the indication was inappropriate. The appointment was delayed in 27% on them, whilst the indication was deemed inappropriate in the remaining 51% and were cancelled. The authors therefore concluded that adherence to the guidelines could reduce waiting times for diagnostic colonoscopy, but might trigger ethical and moral debate.

CLINICAL IMPACT AND COST-EFFECTIVENESS OF APPROPRIATENESS GUIDELINES

The educational-based intervention study reported by Grassini *et al*[19], noted above, estimated a saving of 19500 euros per year in a low-volume endoscopy unit (1700 colonoscopies per year) and a 15% reduction on the waiting list for outpatient colonoscopy. A recent systematic review assessed the impact of ASGE and EPAGE-Ⅰ criteria on the cost-effectiveness of colonoscopy based on the appropriateness of an indication in selecting patients who were referred ~~to~~ for colonoscopy[41]. Appropriateness studies reported until 2007 were considered for inclusion. In a decision-analysis model, a relatively high prevalence of CRC was found in inappropriate referrals (1.1%; 95%CI: 0.7%-1.4% *vs* 5.6%; 95%CI: 5.1%-6%) along with a significant reduction in survival because of CRC diagnostic delay. Therefore, the authors recommended refining the current criteria before using them in routine clinical practice. However, only the first version of EPAGE criteria was used in the studies included, but not the more recent EPAGE Ⅱ criteria, which as previously mentioned are significantly more sensitive, especially for CRC.

STRATEGIES FOR PRIORITIZING PATIENTS

Some systems have been developed to prioritise patients with alarm signs or symptoms. The most well-known is the one developed in the United Kingdom by the National Institute for Health and Clinical Excellence (NICE), implemented in 2000 (Table 4)[42]. Based on this system, patients meeting certain clinical criteria are referred for consultation with the gastroenterologist within two weeks in order to decrease waiting times for CRC diagnosis[43]. This guideline was updated in 2005, with the goal of reducing death

Table 4 Clinical criteria for prompt colonoscopy referral (2 wk) according to the National Institute for Health and Clinical Excellence in the United Kingdom[44]

Patients ⩾ 40 yr with rectal bleeding and change of bowel habit persisting ⩾ 6 wk
Patients ⩾ 60 yr with rectal bleeding persisting ⩾ 6 wk without a change in bowel habit and without anal symptoms
Patients ⩾ 60 yr with a change of bowel habit persisting ⩾ 6 wk without rectal bleeding
Patients with right lower abdominal mass
Patients with palpable rectal mass
Patients with unexplained iron deficiency anemia (⩽ 11 g/100 mL in men and ⩽ 10 g/100 mL in women)

rates by 20% in people under 75 years in 2010[42]. The United Kingdom National Health Service later developed the "straight to test" approach for suspected CRC, in order to delete time-wasting visits and therefore delays in the diagnosis phase[44]. The Scottish Intercollegiate Guidelines network (SIGN) has also developed referral criteria which are less strict than NICE criteria. They are also based on alarm signs and symptoms of CRC[45] (Table 5).

Beggs *et al*[46], compared the effect of the two week-referral pathway for colonoscopy with the traditional pathway (referring the patient firstly to the gastroenterologist) on colonoscopy waiting lists and direct costs (only consultation and colonoscopy). The former strategy was less costly (saving more than £ 26.000), and also significantly reduced colonoscopy waiting list numbers compared with the usual care process (by 166.6 d, $P < 0.01$). Another study assessed the time intervals between referral for colonoscopy, diagnosis and treatment in a fast referral group compared with the usual care process[47]. As expected, delay to endoscopic and histological diagnosis was significantly lower for the fast referral group ($P < 0.0001$), but also to treatment ($P = 0.048$). One study showed that the "straight to test" strategy was also an effective strategy for CRC detection at early stages compared with the standard of care[48].

A recent Spanish multicenter study highlighted the limited accuracy of NICE criteria in a prospective cohort of 787 symptomatic patients referred for colonoscopy[49]. NICE and SIGN criteria were compared with the immunochemical fecal occult blood test (FIT) at 100 ng/ml threshold for CRC detection. FIT was significantly more sensitive than NICE criteria (87.6% *vs* 61.9% respectively; $P < 0.001$) but similar to SIGN criteria (82.5%, $P = 0.4$). However, the specificity of FIT was significantly higher than either NICE or SIGN criteria (77.4%, 65.2% and 42.7% respectively; $P < 0.001$). These data support the idea that, in isolation, NICE criteria lack sufficient diagnostic accuracy and should be used in combination with other markers. Studies using a combination of clinical, blood and fecal markers are currently ongoing in order to improve the accuracy of the clinical criteria[50].

Recently, risk scores based on demographic and clinical information have been developed for either symptomatic or asymptomatic patients in order to prioritise outpatient colonoscopy[51,52]. Law *et al*[52], with 1013 symptomatic Asian subjects, showed that a score higher than 17 predicted CRC with a specificity of 96%. The area under the curve of the risk score was 0.83, proving that the model had a good discrimination, leading the authors to conclude that this model might be useful to prioritise colonoscopy. Another recent study, carried out in asymptomatic Caucasian patients[51], validated a model for detecting advanced colorectal neoplasia based on demographics and family history of CRC. The authors suggested that this model might help health care providers to make decisions about screening.

Table 5 Scottish Intercollegiate Guidelines network referral criteria[45]

1 Persistent rectal bleeding without anal symptoms
2 Persistent change in bowel habit (> 6 wk)
3 Significant family history
4 Right-side abdominal mass
5 Palpable rectal mass
6 Unexplained iron deficiency anemia
7 Persistent diarrhea

CONCLUSION

Although appropriateness criteria (ASGE and EPAGE Ⅱ criteria) enable a better selection of colonoscopy referrals and increase the rate of significant lesions detected, further refinement is required since some relevant lesions are still missed even when the more sensitive EPAGE Ⅱ criteria are used. Prioritising systems such NICE criteria seem to accelerate CRC diagnosis and treatment, without increasing the waiting list for outpatient colonoscopy, but they might not be sensitive enough for selecting patients with CRC. Educational programs on surveillance colonoscopy and adherence to the current guidelines are warranted to reduce inappropriate referrals. Finally, the combination of clinical criteria (appropriateness or prioritising criteria) with blood or fecal markers might be a better approach than isolated clinical criteria to increase the diagnostic yield of significant lesions.

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Sedation in gastrointestinal endoscopy: Where are we at in 2014?

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Abstract

Gastrointestinal endoscopies are invasive and unpleasant procedures that are increasingly being used worldwide. The importance of high quality procedures (especially in colorectal cancer screening), the increasing patient awareness and the expectation of painless examination, increase the need for procedural sedation. The best single sedation agent for endoscopy is propofol which, due to its' pharmacokinetic/dynamic profile allows for a higher patient satisfaction and procedural quality and lower induction and recovery times, while maintaining the safety of traditional sedation. Propofol is an anesthetic agent when used in higher doses than those needed for endoscopy. Because of this important feature it may lead to cardiovascular and respiratory depression and, ultimately, to cardiac arrest and death. Fueled by this argument, concern over the safety of its administration by personnel without general anesthesia training has arisen. Propofol usage seems to be increasing but it's still underused. It is a safe alternative for simple endoscopic procedures in low risk patients even if administered by non-anesthesiologists. Evidence on propofol safety in complex procedures and high risk patients is less robust and in these cases, the presence of an anesthetist should be considered. We review the existing evidence on the topic and evaluate the regional differences on sedation practices.

Key words: Hypnotics and sedatives; Propofol; Conscious sedation; Endoscopy; Gastrointestinal

Core tip: Sedation in endoscopy is a hot topic. There is a wide range of practices depending on the countries and even regionally at a national level. These differences range from no sedation to traditional sedation or propofol based sedation (with or without an anesthetist) and are the result of several factors which include cultural aspects, medical training, legal responsibility and societal lobbying. Herein we review the most important evidence regarding the sedation aspects in the endoscopy suite and compare practices which vary among several countries.

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INTRODUCTION

Sedation is a fundamental aspect of gastrointestinal (GI) endoscopy. Although some patients can perform diagnostic esophagogastroduodenoscopy (EGD) and colonoscopy without sedation, the use of sedation is associated with a higher patient satisfaction[1,2] and procedural quality[3]. There is also an increasing demand for sedation by the patients and all endoscopists should be in position to comply with such demand.

There are several options for sedation which range from light sedation (anxiolysis) to general anesthesia depending on the procedure being performed, the center expertise and the individual patient. Still, the most commonly used sedation is moderate-deep sedation achieved by midazolam with or without an opioid (meperidine/pethidine, fentanyl or alfentanyl), which is commonly designated as "traditional sedation", with the other option being propofol which can also be used alone or in combination with analgesic opioids or midazolam. This review revolves around the value of sedation, the most common options and the similarities and differences between them. We also aim to discuss the role of anesthesia providers in the equation.

SEDATION AND PHARMACOLOGY

Midazolam is a short acting, water soluble, highly lipophilic benzodiazepine that was approved in the 80's. The agents of this class act by binding to the type A γ-aminobutyric acid (GABA) receptor and enhancing its' inhibitory actions on the central nervous system. Midazolam has anxiolytic, hypnotic, anticonvulsant, muscle relaxant and antegrade amnestic properties[4]. It's 1.5-3.5 times more potent than diazepam and it has a shorter onset (1-2 min) and duration of action (15-80 min) when compared to other benzodiazepines[5,6]. Midazolam is metabolized by the liver and its' metabolites are excreted by the kidney.

Intravenous midazolam allows for moderate (conscious) sedation with commonly used doses in endoscopy ranging from 2 mg to 6 mg[7] but frequently a state of deep sedation is inadvertently achieved, at least when used in combination with an opioid[8].

The major side effect is respiratory depression but it may also cause cardiovascular effects (hypotension and dysrhythmias) and occasionally "paradoxical" reactions occur with hostility and aggression occurring after administration. This reaction has been described to have an incidence of 1.4% and while it usually doesn't preclude completion of the procedure it renders it more difficult. The combination of pethidine has been suggested, in an observational study, to lower the risk for such reactions[9].

Midazolam action can be reversed by the administration of flumazenil (a benzodiazepine antagonist) which has an onset of action of 1-2 min with a duration of 60 min, a little shorter than midazolam explaining why the sedation level may deepen again after some time.

Propofol (2, 6-diisopropofol) is a hypnotic drug with minimal analgesic properties. Propofol also exerts its effect through potentiation of the GABA by reducing the rate of GABA-receptor dissociation[10].

It is highly lipophilic which enables it to have a quick onset, corresponding to one arm-brain circulation time (30-45 s) and a short, predictable duration of action (4-8 min)[11]. Propofol is metabolized in the liver and excreted by the kidney. Several factors significantly alter its' pharmacokinetic profile and clinical effects with the major ones being age, weight and sex, with the elderly being significantly more sensitive to low doses.

Propofol formulations vary but usually they contain soybean oil and purified egg phosphatide and it should be avoided in patients with known allergies/hypersensitivity to egg and soy products.

Propofol induces respiratory depression in a dose-response fashion and it has a negative cardiac inotropic effect causing a decrease in cardiac output, systemic vascular resistance and arterial pressure[7]. Transient pain on injection site is common, affecting up to 50% of patients[12]. Apart from these clinically non-significant effects, serious adverse events leading to death are very rare and the risk is estimated to be even slimmer in low risk patients (ASA Ⅰ-Ⅱ), ranging from 1:10000 to 1:300000[13].

The most common agents used for sedation and their pharmacologic profile are shown in Table 1.

HISTORICAL AND GLOBAL PERSPECTIVE

GI endoscopies are invasive, unpleasant and sometimes painful experiences. To overcome such unpleasantness, we have been searching for ways to minimize it since the introduction of the fiberscope in the 50's.

The technological advances in endoscopy have improved the diagnostic and therapeutic capabilities throughout the GI tract but they have also allowed for faster and less painful examinations. Advances like the utilization of thinner endoscopes[14], variable stiffness colonoscopes[15], CO_2 insufflation[16] and water immersion techniques (in colonoscopy)[17] allow for less painful procedures. Although helpful, these options are probably not as effective as medical sedation has been shown to be.

There has been a continuous evolution on sedation practices for endoscopy since the early 60's when pentobarbital use was described in conjunction with a transtracheal xylocaine injection[18]. The use of meperidine as an analgesic was an initial strategy and it was followed by the widespread adoption of the combination with diazepam, which was shown to improve the rate of "satisfactory examinations" by 20% comparing to meperidine alone[19]. This set the *rationale*

Table 1 Pharmacologic profile of commonly used drugs for procedural sedation

Drugs	Onset of action (min)	Duration of action (min)	Usual doses	FDA pregnancy category	Adverse effects
Pethidine	3-6	60-180	25-100 mg	C	Respiratory depression, vomiting
Fentanyl	1-2	30-60	50-200 μg	C	Respiratory depression, vomiting
Alfentanyl	< 1	30-60	0.250-2 mg	C	Respiratory and cardiovascular depression
Midazolam	1-2	15-80	1-6 mg	D	Respiratory depression, disinhibition
Propofol	< 1	4-8	40-400 mg	B	Respiratory and cardiovascular depression
Flumazenil	1-2	60	0.1-1 mg	C	Agitation, withdrawal symptoms
Naloxone	1-2	30-45	0.2-1 mg	B	Narcotic withdrawal

for the so called traditional sedation.

After almost two decades there was the advent of midazolam[6]. Midazolam had a very good acceptance in the endoscopy community in virtue of its faster induction time, higher effectiveness and shorter duration of action comparing to diazepam while keeping the safety feeling provided by the existence of a reversal agent. However, there were several (71) death reports in the 80's with midazolam based sedation and the Food and Drug Administration (FDA) issued a warning on this topic. Later, a more systematic epidemiological approach, led by a joint effort from the FDA and the American Society of Gastrointestinal Endoscopy (ASGE), failed to show an increased risk of death with midazolam compared with diazepam[20]. At the present time, midazolam is considered a safe agent and is commonly used as a sedative in gastrointestinal endoscopy.

Propofol, an ultra-short acting hypnotic agent, entered the arena a few years after midazolam[12] but it had a much slower uptake due to its use mostly as an anesthetic agent and as a sedative for critically ill patients and its' product label states that it "should be administered by persons with training in general anesthesia" in the United States and by anesthetists and intensive care physicians in some European countries. Because of this, most endoscopists feel untrained to administer propofol. Still, from a pharmacokinetic/pharmacodynamic point of view, propofol is superior to midazolam as it has a faster onset and a shorter predictable duration of action[11]. Propofol has since been proved to be a better sedative for endoscopy when compared to traditional sedation, improving both patient and endoscopist satisfaction, procedural quality indicators (such as cecal intubation time), induction, wake up and psychomotor recovery times[1,2,21-23]. These improvements are achieved without an increased risk for adverse events as shown in several meta-analyses of randomized controlled trials (RCT)[1,2,24]. These characteristics may have significant impact in procedural quality, patients' acceptance (especially for screening procedures) and endoscopic unit productivity.

One important concern regarding sedation in colonoscopy is the theoretical increase in perforation risk. In two observational but robust population based studies in the United States it has been shown that propofol sedation is not associated with an increased perforation risk[25,26]. It may, however, be associated with a slightly higher risk for aspiration pneumonia[26]. Another recent observation study showed an increased risk for perforation but only in therapeutic colonoscopy and when adjusted for confounders the odds ratio was 1.34 with a *P* value of 0.04[27]. Obviously, it is hard to detect small effect sizes for rare outcomes such as colonic perforation, but so far, the available evidence suggest that sedation doesn't play a significant role in perforation rates.

Despite the advantages of propofol and the endorsement of propofol sedation by several national and international societies[28-32], it is still underused in most settings, because of medico-legal aspects, namely the requirement of an anesthesiologist and, consequently, increased costs[33].

The non-availability of NAAP seems to be a limiting step for the availability of propofol sedation and it significantly increases costs in a non-reasonable tradeoff. This has been shown in a recent cost-effectiveness analysis by Cesare Hassan, with a calculated cost of 1.5 million USD/life year gained[34].

There is wide variability in sedation practice worldwide. In the United States the number of endoscopic procedures in increasing[35], as a result of the increased uptake of colorectal cancer screening colonoscopy. The participation of an anesthesiologist in endoscopy has doubled from 14% in 2003 to 30% in 2009[36] and it's expected to pass the 50% mark by 2015[37]. On the other hand, non-anesthesiologist administration of propofol (NAAP) is becoming less common, as a result of Medicare reimbursement change in 2009[38], although this policy has been rejected by several states.

In Europe the variability is even bigger. In most countries routine diagnostic EGDs are performed without sedation[39] with colonoscopies being more likely to receive some form of sedation[33]. The countries with highest rates of propofol sedation are probably Switzerland[40] and Germany[41] with high rates of NAAP. In the latter, over 90% of the colonoscopies are performed with sedation, 97% of them with propofol and only 2% of those with support of an anesthesiologist. These data were acquired from a German national survey in 2011 with 732 respondents and showed an increase in sedation and propofol rates

comparing to the first survey, 4 years earlier.

NAAP is also a common practice in Denmark, Austria, Spain, Italy, Greece, the Netherlands and Sweden[32,42-45].

In other countries, like France and Portugal, virtually all endoscopic sedation with propofol is performed with an anesthesiologist. Unpublished data from our group regarding a national survey performed in Portugal in 2014, showed less than 3% of endoscopists perform NAAP and that propofol is used in less than half of the colonoscopies.

SEDATION IN SPECIAL POPULATIONS

There are populations that require specific considerations[46], especially the elderly, the obese, patients with cirrhosis, pregnant women, patients with pulmonary disease and acutely ill patients.

In the elderly one must be aware of the slower onset of sedation and the higher sensitivity to sedatives. These patients are at an increased risk for cardiopulmonary events and aspiration syndrome. The recovery times are also increased due to slower hepatic and renal clearance and a higher fat body mass. Sedatives should be titrated at a slower pace and smaller doses should be generally used[47].

Obesity is a growing pandemic, especially in the United States. Obesity is frequently associated with other comorbidities and is considered an independent risk factor hypoxemia and the need for airway permeabilization maneuvers[48]. Still, even though these patients are at a higher risk for minor events, it's considered safe to perform sedation for endoscopic procedures by trained personnel[46].

Cirrhosis is a comorbid condition with significant impact on a patient's health status. Cirrhotic patients are supposed to undergo surveillance EGDs for esophageal varices and frequently undergo endoscopic procedures for indications such as anemia, bleeding, liver transplant evaluation or adenoma surveillance. Sedation in these patients pose some concerns due to hepatic dysfunction, decreased drug clearance and risk for hepatic encephalopathy. Several studies looked into this effect. Riphaus *et al*[49] performed a RCT that showed that propofol sedation was superior to midazolam in terms of recovery times and cognitive impairment after EGD[49]. A larger RCT comprising 211 patients confirmed these findings[50]. In a more recent RCT, in South Korea, propofol was shown to be safe in cirrhotic patients comparing to healthy controls[51]. Propofol is, therefore, considered the best option for sedation in patients with cirrhosis.

Pregnant women seldom need endoscopic procedures and common sense dictates that elective procedures should be postponed if possible. However, in some instances endoscopy has to be performed. While sedation is considered safe for the woman, there isn't high quality evidence to confirm it and some considerations have to made because of the possible risks to the fetus and are discussed in a ASGE guideline[52]. Among narcotics, meperidine is the favored agent. Benzodiazepines are classified as FDA pregnancy class D and are best avoided. Propofol is class B and may be used during pregnancy and preferably by an anesthesiologist. All agents are best avoided during the first trimester due to higher theoretical risks to the fetus. During lactation propofol and fentanyl are considered safe options with no need to withhold breastfeeding.

Acutely ill or decompensated patients are best managed by an anesthesiologist and most guidelines recommend considering anesthesiologist support for ASA $\geqslant$ Ⅲ patients, since most evidence on NAAP is on low risk patients and death have been reported only in ASA $\geqslant$ Ⅲ patients[44].

EVIDENCE

There is high quality evidence comparing propofol to traditional sedation, which includes several RCTs and five systematic reviews (4 of them with meta-analysis - Table 2)[1,2,21,23,24]. The results are very consistent in showing a similar rate of adverse events with propofol versus traditional sedation. The advantages of propofol are shorter recovery and discharge periods, higher post-anesthesia recovery scores, better sedation, and greater patient cooperation. One limitation of the majority of the RCTs included in the meta-analysis is the lack of anesthesiologist participation. This may limit the generalizability of the data but it's unlikely that there would be a decrease in the safety or quality of this sedation when performed by an anesthesiologist.

The big question is therefore who should be responsible for the administration of propofol[53].

To address this issue there is only one RCT[54]. This study by Poincloux *et al*[54] randomized 90 low risk patients undergoing colonoscopy for sedation by anesthesiologist using a target control infusion (TCI) or by the endoscopist using a modified patient controlled sedation pedal. In this study patients who were sedated by anesthesiologists had more frequent side events (16% *vs* 3%; P = 0.008), had higher doses of propofol (94 mg *vs* 260 mg), less pain but similar satisfaction levels.

Currently, we are performing a non-inferiority randomized trial addressing the safety of NAAP by comparing it no anesthesiologist sedation in low risk patients (ClinicalTrials.gov - NCT02067065). The interim analysis (100 patients) did not show a significant difference in the incidence of adverse events (primary endpoint) between the two groups (ref).

Apart from randomized controlled trials, there's significant experience with NAAP and extensive prospective evaluation on the safety and effectiveness of this type of sedation, especially for low risk patients. Rex *et al*[38] published in 2009 a sum of all published evidence on NAAP and collected unpublished prospective and retrospective records from several centers all

Table 2 Meta-analysis of randomized controlled trials of propofol *vs* traditional sedation in endoscopy

Ref.	Procedures	Sedation compared	No. of studies (cases)	OR (95%CI) for adverse events
Qadeer *et al*[23], 2005	EGD/colonoscopy/ERCP/EUS	Propofol *vs* traditional sedation	12 (1161)	0.74 (0.44-1.24)
Singh *et al*[2], 2008	Colonoscopy	Propofol *vs* traditional sedation	22	Hypoxia: 0.69 (0.25-1.89); Hypotension: 1.03 (0.28-3.83)
Bo *et al*[21], 2011	ERCP	Propofol *vs* traditional sedation	6 (663)	1.69 (0.82-3.50)
Garewal *et al*[24], 2012	ERCP	Propofol *vs* traditional sedation	4 (510)	Narrative
Wang *et al*[1], 2013	EGD/colonoscopy/ERCP	Propofol *vs* traditional sedation	22 (1798)	0.90 (0.70-1.17)

EGD: Esophagogastroduodenoscopy.

Table 3 Existing societal guidelines for non-anesthesiologist administration of propofol

Scientific society	Limitations	Consider anethesiologist
Sociedad Española de Endoscopia Digestiva, 2014	Complex procedure; ASA Ⅲ	ASA ≥ Ⅲ; long/complex procedure; difficult airway
Austrian Society of Gastroenterology and Hepatology (OGGH), 2007	NA	NA
Canadian Association of Gastroenterology, 2008	NA	ASA ≥ Ⅲ; long/complex procedure; difficult airway
German S3 guidelines - DGVS/DGAI, 2008	ASA ≥ Ⅲ; long/complex procedure; difficult airway	ASA ≥ Ⅳ; long/complex procedure; difficult airway
European Society of Gastrointestinal Endoscopy (ESGE/ESGENA), 2010/2013	NA	ASA ≥ Ⅲ; long/complex procedure; difficult airway
American multisociety guideline - AGA/ACG/ASGE/AASLD, 2009/2012	NA	ASA ≥ Ⅲ; long/complex procedure; difficult airway

ASGE: American Society of Gastrointestinal Endoscopy; NA: Not available.

around the world, totaling 646080 cases out of which 4 patients died and 11 were intubated. These numbers are not very different from published mortality rates for general anesthesia which is 1:13322 (overall) and 1:200200 in ASA Ⅰ-Ⅱ[13]. Recently, a large German experience of 24 441 cases on propofol and propofol with midazolam has been published[55]. The data was collected prospectively and severe adverse events were reported in only 4 patients, with no severe outcomes (death or permanent neurologic damage).

With such a track record it will be very difficult to design a RCT powered to detect a difference in mortality or even in the need for endotracheal intubation (EOT). If we consider a probability of 1:20000 for EOT (3 times higher than published by Rex), then we would need a sample size of 17 133802 patients to exclude a 20% difference (of the expected incidence) between the groups with a confidence of 90% and a one-sided confidence interval of 95%.

COST-EFFECTIVENESS

In the study by Hassan *et al*[34], the authors calculated the costs of training of nurses for EDP and assuming the published mortality rate of 0.0008% for EDP-colonoscopy and 0% for anesthesiologist sedation they concluded that the incremental cost-effectiveness ratio was 1.5 million USD/life year gained in the United States, 31 times above the accepted value of $50000 USD. This means that to make it cost effective a reduction in anesthesiologist reimbursement (for Medicare) from $95 to $6 would have to take place.

This study is based on the assumption that the presence of an anesthesiologist is 100% effective in avoiding death in these procedures.

GUIDELINES

As a consequence of the advantages provided by propofol sedation and the difficulty in adopting its use due to logistical, financial and medico-legal issues, several national and international guidelines have been published in the last decade and are shown in Table 3[28-32,45,56,57]. These guidelines help to provide the framework to allow endoscopists to perform NAAP in their countries.

Of note, the German guidelines were the result of a collaboration between the GI endoscopy and anesthesia national societies and are therefore a valuable evidence based consensus document made by the country that has the highest level of propofol sedation in endoscopy in the world.

An interesting aspect is what occurred with the ESGE/ESGENA guideline. This one was also a joint effort with the European Society of Anesthesia (ESA) and was published in the November 2010 with the ESA support in both Endoscopy[29] and the European Journal of Anesthesiology[58]. Following this guideline, several national Anesthesiology societies declared to be against such endorsement and that position as was made public in a "Special Article" in the *ESA* journal in June 2011 by Perel[59] and undersigned by 21 national societies. The argument used was the concern for patient safety based on the manufacturer's package insert that states that "DIPRIVAN Injectable

Emulsion should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure". As a consequence of this pressure there was a vote at the ESA General Assembly to retract the support of the ESA for the guideline that had been previously evaluated and approved by the ESA guidelines committee and Board of Directors. As of April 2012, without significant new evidence to support the change, or any kind of review of the same evidence, the ESA retracted the support[60].

CONCLUSION

Propofol is currently considered the best candidate drug for sedation in endoscopic procedures. Still, we are in need for well-designed randomized clinical trials (with meaningful primary endpoints) to provide the definite proof of safety comparing to traditional sedation when used by non-anesthesiologists.

This kind of high quality evidence will help the different professional societies to overcome their differences and determine a robust, evidence-based, approach for safe and cost-effective sedation and monitoring in endoscopy.

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MINIREVIEWS

Narrow-band imaging with magnifying endoscopy for the evaluation of gastrointestinal lesions

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Abstract

Narrow band imaging (NBI) endoscopy is an optical image enhancing technology that allows a detailed inspection of vascular and mucosal patterns, providing the ability to predict histology during real-time endoscopy. By combining NBI with magnification endoscopy (NBI-ME), the accurate assessment of lesions in the gastrointestinal tract can be achieved, as well as the early detection of neoplasia by emphasizing neovascularization. Promising results of the method in the diagnosis of premalignant and malignant lesions of gastrointestinal tract have been reported in clinical studies. The usefulness of NBI-ME as an adjunct to endoscopic therapy in clinical practice, the potential to improve diagnostic accuracy, surveillance strategies and cost-saving strategies based on this method are summarized in this review. Various classification systems of mucosal and vascular patterns used to differentiate preneoplastic and neoplastic lesions have been reviewed. We concluded that the clinical applicability of NBI-ME has increased, but standardization of endoscopic criteria and classification systems, validation in randomized multicenter trials and training programs to improve the diagnostic performance are all needed before the widespread acceptance of the method in routine practice. However, published data regarding the usefulness of NBI endoscopy are relevant in order to recommend the method as a reliable tool in diagnostic and therapy, even for less experienced endoscopists.

Key words: Narrow band imaging magnifying endoscopy; Premalignant; Early cancer; Mucosal patterns; Vascular patterns

Core tip: The article summarizes recent data regarding the potentials of one of the most advanced endoscopic technique used in clinical practice. There are many classification systems of mucosal and vascular patterns already reported in literature, therefore a review could be useful for a better systematization of data. Strategies and challenges in the application of the method in routine practice represent another issue of interest in this article. The picture selection actually reflects the work in the endoscopy department and could serve as a tool in the learning process.

Boeriu A, Boeriu C, Drasovean S, Pascarenco O, Mocan S, Stoian M, Dobru D. Narrow-band imaging with magnifying endoscopy for the evaluation of gastrointestinal lesions. *World J Gastrointest Endosc* 2015; 7(2): 110-120 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i2/110.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i2.110

INTRODUCTION

Narrow band imaging (NBI) represents an advanced endoscopic technique consistings in the assessment of surface patterns and microvascular architecture by utilization of a narrowed spectrum light. Blue and green wavelengths are selected by optical filters, with the elimination of red light[1]. These lights with narrowed bandwidths penetrate the superficial mucosal structures and are better absorbed by hemoglobin, providing an enhancement of mucosal features and blood vessels (capillaries from superficial mucosal layer, deeper mucosal and submucosal vessels)[2,3].

Clinical studies have shown the ability of NBI method to evaluate lesions and to estimate their histology in real time. The combination between NBI and magnification endoscopy (NBI-ME) enables an accurate assessment of lesions in the gastrointestinal (GI) tract, the differentiation between premalignant and malignant lesions, and the detection of early neoplasia by emphasizing neovascularization. The visualization of vascular details by magnification allows the early detection of changes associated with malignant transformation. Different classification systems including mucosal and vascular patterns were proposed to differentiate preneoplastic and neoplastic lesions and also to predict the depth of invasion in superficial cancer.

APPLICATIONS OF NBI-ME IN ESOPHAGEAL LESIONS

Magnifying endoscopy with NBI of normal esophagus enables visualization of capillary vessels of mucosa (intra-epithelial papillary capillary loop, IPCL) and submucosal vascularity (branching vessels) (Figure 1A). In reflux esophagitis, dilated, elongated IPCLs have been detected on NBI endoscopy[4]. The examination of the gastroesophageal (GE) junction and lower esophagus using NBI and magnification in patients with symptomatic GERD has allowed the detection of modified mucosa and vascularity: microerosions, an increased vascularity at the GE junction, an increased number, and dilatation and tortuosity of IPCLs[5].

Five different IPCL patterns have been described in association with different esophageal features, from normal mucosa to modified mucosa due to inflammation, dysplasia or cancer: type Ⅰ corresponds to normal mucosa (Figure 1A), type Ⅱ to inflammation, type Ⅲ corresponds to borderline lesions, often related to low-grade intraepithelial neoplasia, type Ⅳ (Figure 2A) and Ⅴ corresponds to high-grade intraepithelial neoplasia (HGIN) or carcinoma[6]. Dilation, tortuosity, irregularity in vessels caliber and form, destruction of IPCLs and replacement with tumor vessels are vascular features associated with esophageal carcinoma. The assessment of IPCLs and submucosal vascularity allows the detection of superficial squamous carcinoma and also the prediction of the depth of invasion[7]. The utility of the estimation of submucosal invasion in clinical practice influences the decision of performing endoscopic therapy.

Magnifying NBI endoscopic diagnosis of Barrett's esophagus

The surveillance of Barrett's esophagus (BE) for early detection of adenocarcinoma continues to represent a challenge in clinical practice due to the large number of random biopsies required and to sampling errors. New endoscopic techniques improve the visualization of Barrett mucosa and improve the detection of dysplasia and early cancer by targeting biopsies from areas with modified pattern. Numerous reports have described mucosal and vascular features displayed in BE.

Chromoendoscopy and magnifying endoscopy has been used for better detection of specialized intestinal metaplasia (SIM) and early neoplasia in BE[8-10]. However, the dye application alters the visualization of vascular patterns. Additional time is required for better fixation of the dye on the tissue surface, followed by repeated water rinses and suctions to remove excess dye. NBI technique has the advantage of identification of both vascular and mucosal patterns without dye application, is easier to perform, and adds useful information about the mucosal morphology.

Different mucosal patterns have been described that can be detected at the GE junction during magnifying NBI endoscopy: rounded, circular (Figure 1C) or oval crypts (columnar mucosa), flat (Figure 1D), villous (Figure 1E), and gyrus-shaped patterns [intestinal metaplasia (IM)][11]. Apart from these regular

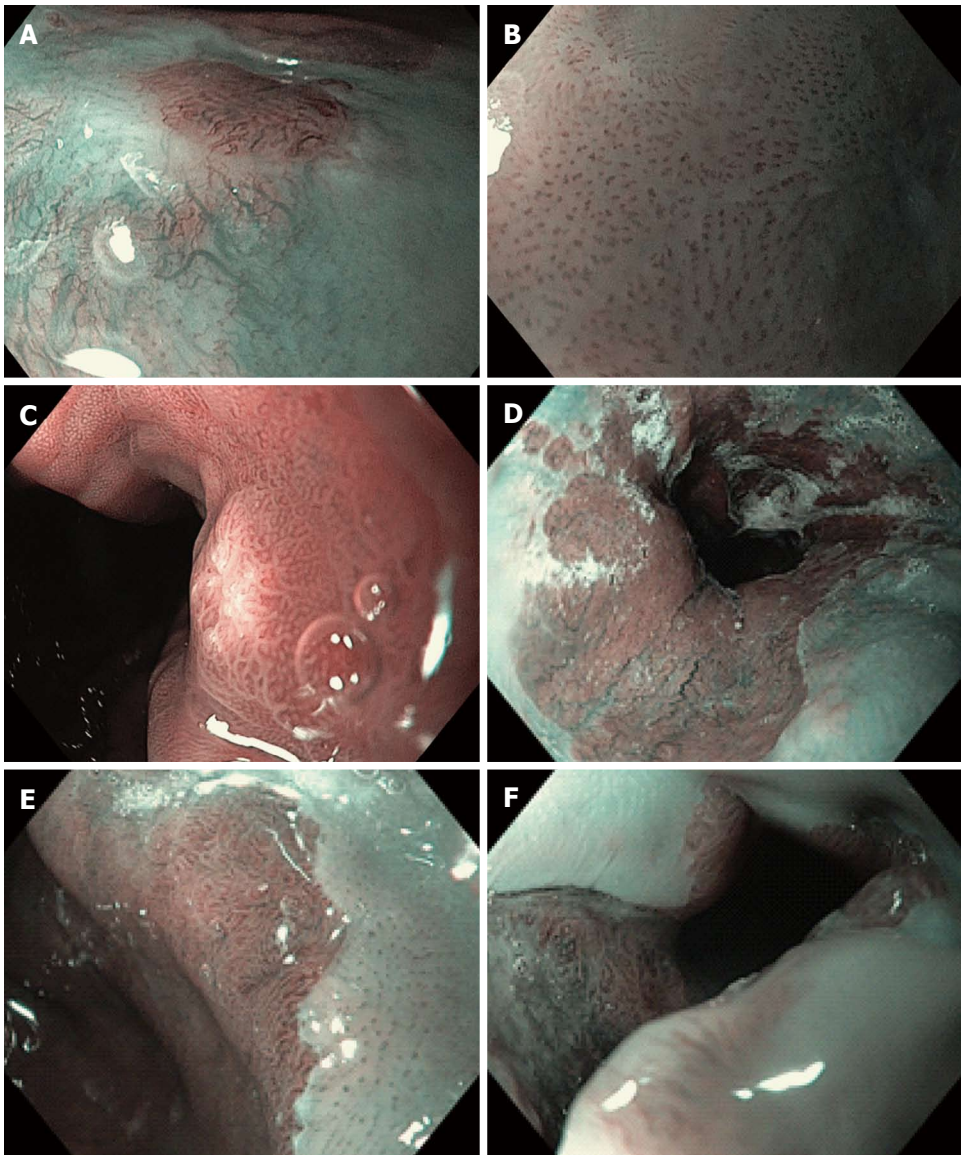

Figure 1 Narrow band imaging with magnification endoscopy images of the esophagus. A: Normal esophageal mucosa: branching vessel network and intra-epithelial papillary capillary loop (IPCL) surrounding an island of Barrett's esophagus (BE); B: IPCL type V1: dilatation of intra-epithelial papillary capillary loop, irregular caliber, and form variation; C: Round pits with regular microvasculature corresponding with columnar mucosa; D: Non-dysplastic BE: flat-type mucosa with regular long branching vessels; E: Non-dysplastic BE: regular villous/ridge mucosal pattern; F: Dysplastic BE: distorsion of mucosal pattern and irregular vascular pattern.

patterns, the identification of an irregular, disrupted mucosal pattern raises the suspicion of a dysplastic/cancerous lesion. The second element that should be evaluated is the vascular pattern: the presence of a regular pattern with normal-appearing vessels or an irregular pattern with abnormal blood vessels. In non-dysplastic BE a regular vascular pattern is associated with the regular villous/gyrus-like pattern or with flat-type mucosa (Figure 1D, E). Areas presenting an irregular mucosal pattern or abnormal blood vessels (irregular, dilated, corkscrew type vessels) are suspicious for the presence of high-grade dysplasia (HGD) or cancer (Figure 1F).

The significance of the detection of irregular mucosal and vascular patterns and abnormal blood vessels for the diagnosis of HGIN by using NBI-ME was previous outlined by Kara *et al*[12] (94% sensitivity, 76% specificity, 64% PPV and 98% NPV for HGIN). Other studies have reported the sensitivity, specificity and positive predictive value (PPV) of ridge/villous pattern for diagnosis of IM (93.5%, 86.7% and 94.7% respectively) and the sensitivity, specificity and PPV of irregular/distorted pattern for HGD (100%, 98.7% and 95.3% respectively), but also have emphasized the inability to differentiate areas of IM from areas with low-grade dysplasia[13].

The reproducibility and repeatability of a simplified classification of mucosal and vascular patterns visualized in BE by experts and non-NBI-experts endoscopists was reported by Singh *et al*[14]. They have

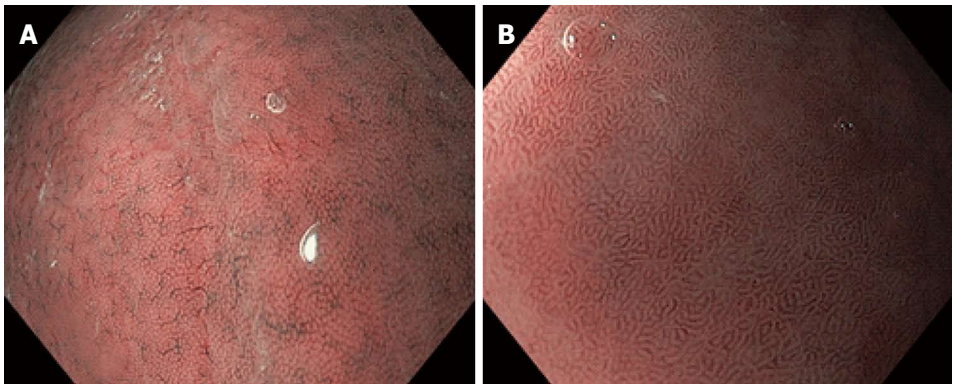

Figure 2 Narrow band imaging with magnification endoscopy images of normal gastric mucosa. A: Round pits surrounded by the subepithelial capillary network (SECN) and collecting venules (CVs) in normal corporeal mucosa; B: Coil-shaped appearance of SECN, without the visualization of the CVs in normal antral mucosa.

described four different patterns on NBI-ME: type A-round pits with regular microvasculature (Figure 1C) corresponded with columnar mucosa without IM (PPV and NPV were 100% and 97% respectively); type B-villous/ridge pits with regular microvasculature and type C-absent pits with regular microvasculature (Figure 1D, E) corresponded with IM (PPV and NPV were 88% and 91% respectively); type D-distorted pits with irregular microvasculature (Figure 1F) was associated with HGD (PPV and NPV were 81% and 99% respectively)[14].

Due to the multiplicity of classification systems, the clinical utility of NBI-ME in the assessment of BE is still under evaluation. In a study performed by Alvarez Herrero *et al*[15], a simplified classification of mucosal and vascular patterns (regular patterns in nondysplastic BE, irregular patterns in dysplastic BE) has shown a moderate interobserver agreement and a disappointing rate for correctly identifying HGIN/early cancer (67% and 71% of the images with HGIN/early cancer were correctly identified). The limitations of the available classification systems concerning accuracy in identification of SIM and dysplasia, as well as limited interobserver agreement, are arguments that the surveillance protocol of BE based on random 4-quadrant biopsies and biopsies from suspicious areas, cannot be yet replaced[16]. A targeted NBI-ME examination of suspicious areas previously identified on white light endoscopy (WLE), such as mucosal irregularities, depressed areas, ulcerations, or nodules, is useful for the delineation of modified mucosal or vascular patterns and for the guidance of directed biopsies.

NBI-ME has also successfully been used as an adjunct for therapeutic procedures. The method has proved to be helpful in targeting and delineating areas with early Barrett's neoplasia, previously identified by high-resolution endoscopy and autofluorescence imaging, for endoscopic mucosal resection[17]. The trimodal imaging evaluation, which combines high-resolution WLE, autofluorescence, and NBI could be an alternative to dye-spraying techniques for the detection and the lateral spread assessment of early cancer before endoscopic therapy.

Applications of NBI-ME in gastric lesions

The normal gastric mucosa displays particular features in the corpus and antrum on NBI-ME. A regular arrangement of small, round pits surrounded by the subepithelial capillary network (SECN) with a honeycomb appearance and the collecting venules (CVs) are detected in the gastric body (Figure 2A). A coil-shaped appearance of SECN, without the detection of the CVs are specific features associated with normal antral mucosa (Figure 2B). Modified patterns should be evaluated by comparison with these normal mucosal and vascular features. The detection of modified patterns due to inflammatory and atrophic changes of the corporeal mucosa and the interpretation of such endoscopic features could represent a challenge in clinical practice: the enlargement of pits with irregular SECNs in *Helicobacter pylori* gastritis (Figure 3A), or the detection of oval or tubulovillous pits with coiled or wavy vessels in IM (Figure 3B) and atrophic gastritis (AG)[18]. Targeted biopsies from areas with modified patterns are mandatory for a proper evaluation of the lesions.

The detection of blue whitish slightly raised areas, described as the "light blue crest sign" (Figure 3C) was reported to have a good sensitivity (89%), specificity (93%) and accuracy (91%) for the diagnosis of IM[19]. This sign could represent a marker for global gastric atrophy[20]. The detection of extensive and severe atrophy and IM and the detection of dysplasia are important steps in the identification of patients at risk for gastric neoplasia. According to European guidelines, these patients should be included in a surveillance program[21]. Targeted surveillance and directed biopsies guided by NBI-ME for IM and AG mapping could represent a better alternative to a surveillance protocol based on randomly taken biopsies.

Different mucosal and vascular patterns have been

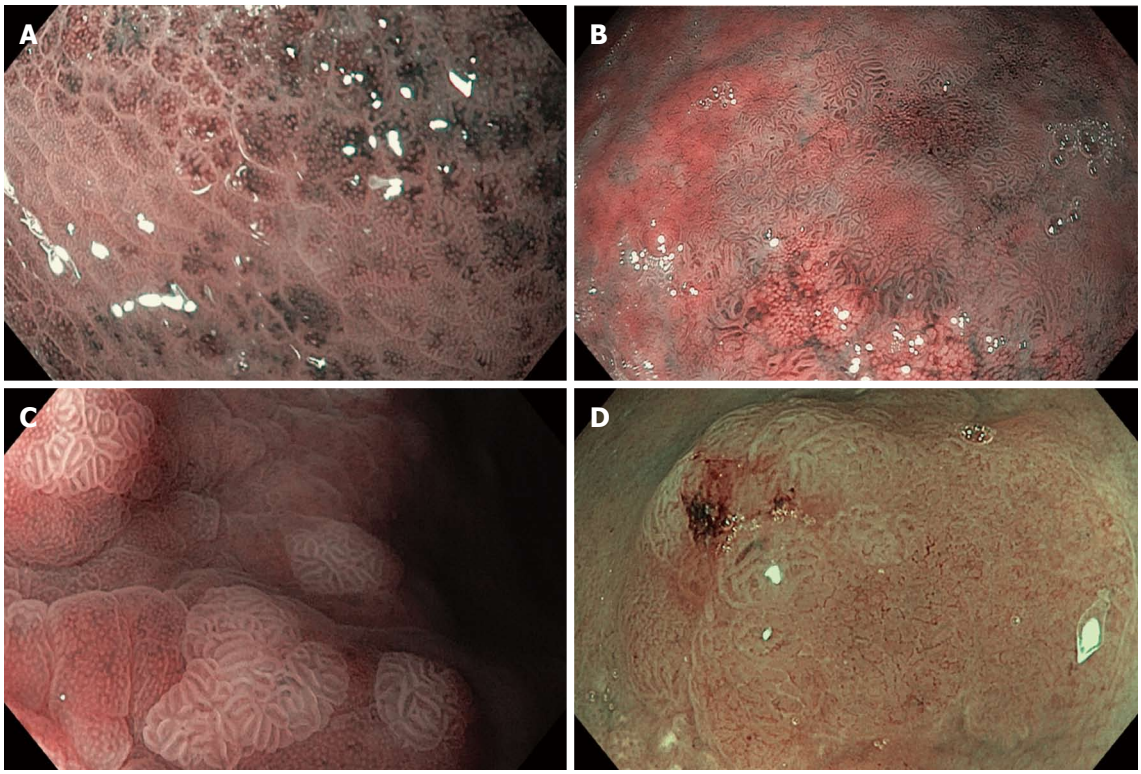

Figure 3 Narrow band imaging with magnification endoscopy images of gastric lesions. A: *Helicobacter pylori* gastritis: enlargement of pits, variable vascular density (alternation of lighter and darker areas); B: Extensive areas of intestinal metaplasia (tubulovillous mucosal pattern) and remnant normal gastric body mucosa (small regular and circular pits); C: Areas of intestinal metaplasia: blue whitish slightly raised areas (the light blue crest sign) with regular, tubulovillous mucosal pattern; D: Dysplasia: area with architectural loss of mucosal pattern and irregular vascular pattern.

reported in association with normal gastric mucosa, preneoplastic and neoplastic gastric lesions. Pimentel-Nunes *et al* have proposed a classification system for the diagnosis of gastric preneoplastic lesions: pattern A (regular and circular mucosal patterns with regular vascular patterns - Figure 2A) corresponds with normal mucosa (accuracy 83%; 95%CI: 75%-90%), pattern B (regular, ridge or tubulovillous mucosal patterns with regular vessels - Figure 3C) corresponds with IM (accuracy 84%; 95%CI: 77%-91%), and pattern C (absent or irregular mucosal patterns with irregular vascular patterns - Figure 3D) corresponds with dysplasia (accuracy 95%; 95%CI: 90%-99%)[22].

Magnifying NBI endoscopic diagnosis of early gastric cancer

Diagnostic accuracy for early gastric cancer was improved by the development of NBI-ME, which allows the detection of subtle mucosal changes. The estimation of the histology and the delineation of the lateral spread of gastric cancer are possible during endoscopic examination[23-25]. An estimation of the deep of invasion of early gastric cancer was also achieved by NBI endoscopy. The superiority of NBI-ME over WLE for the diagnosis of superficial gastric lesions in a population at high risk of gastric cancer was demonstrated in clinical studies[26].

Three criteria have been use by Kaise *et al*[27] for the detection of superficial gastric cancer: the disappearance of fine mucosal structure, microvascular dilation and heterogeneity in shape of vessels. The sensitivity of these criteria for the diagnosis of cancer was 92.9%, with 94.7% specificity[26]. Yao *et al*[28] have used a "VS classification", based on the assessment of microvascular pattern (V) and microsurface pattern (S). They have identified the irregular microvascular pattern and/or the irregular microsurface pattern and the demarcation line as hallmarks of early gastric cancer (Figure 4). The delineation of the lateral margins of differentiated carcinoma prior to endoscopic resection has been performed using NBI-ME[28].

Yamada *et al*[29] have recently reported that the demarcation (DL) line and an irregular microvascular pattern (IMVP) on NBI-ME represent reliable criteria for the diagnosis of small, depressed, early gastric cancer. An irregular margin and a spiny depressed area on conventional WLE represent diagnostic criteria for depressed cancer. The diagnostic accuracy increases by using both methods: the initial detection of a depressed lesion on conventional WLE, followed by magnifying NBI assessment for the presence of DL and IMVP[29]. The combination of conventional WLE with NBI-ME in clinical practice has proved to enhance diagnosis accuracy of small, depressed gastric mucosal cancer (96.6% accuracy, 95.0% sensitivity, and

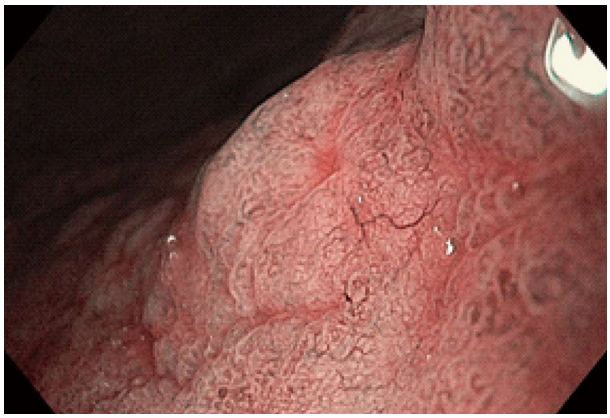

Figure 4 Superficial gastric cancer: Disappearance of microsurface pattern, irregular microvascular pattern with a demarcation line.

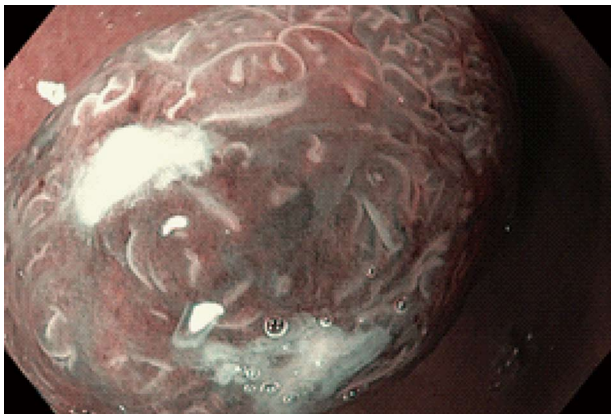

Figure 5 Gastric adenoma: White opaque substance with regular distribution obscures the subepithelial microvascular pattern.

96.8% specificity)[30].

Regarding the application of NBI-ME in the assessment of elevated gastric lesions, a regular microsurface and microvasculature was detected in adenomas, while the microvascular changes (irregular caliber, meandering, heterogeneity) and the line of demarcation were associated with carcinoma[31]. There are situations when an estimation of the microvascular pattern is difficult, due to a white opaque substance (WOS) within the neoplastic epithelium, which obscures the microvessels (Figure 5). Yao *et al*[32] have identified the WOS in 0-Ⅱa type neoplasms, and more frequently in adenomas (78%) than in carcinomas (43%). A regular distribution of WOS was detected within adenomas, whereas an irregular distribution was found in carcinomas. Besides the assessment of the microvascular pattern, morphologic analysis of the WOS could represent a valuable optical sign discriminating between adenoma and carcinoma[32].

The demarcation line could also be identified in focal gastritis, but in this situation the regular mucosal and vascular patterns differentiate the lesion from early cancer. Doubtful lesions are better sent for pathologic assessment after endoscopic submucosal dissection.

Distinct vascular patterns are related to different histologic types of cancer. The fine network pattern, appearing as mesh microvessels, correlates with well-differentiated adenocarcinoma, whereas the corkscrew pattern, with isolated and tortuous microvessels, corresponds with undifferentiated adenocarcinoma[33]. Li *et al*[34] have reported a good sensitivity, specificity, and accuracy of NBI-ME in distinguishing between differentiated from undifferentiated adenocarcinoma (92.3%, 89.7%, and 90.4%, respectively) and in differentiation between cancerous and noncancerous lesions (97.3%, 84.4% and 90.2% respectively). The authors have described three distinct patterns associated with different type of gastric lesions and with the depth of cancer invasion. A regular surface and microvascular pattern (type A pattern) corresponds with noncancerous lesions. The type B pattern, consisting of thickened, dilated, irregular vessels, with an asymmetrical distribution, and an irregular surface pattern, corresponds with differentiated adenocarcinoma and intramucosal/superficially invasive cancers. The type C pattern, consisting of the disappearance of the surface pattern, with markedly distorted, sparse, isolated microvessels, or with avascular areas, is indicative of undifferentiated adenocarcinoma or differentiated cancer with deep submucosal invasion[34].

In a recent report, Yagi *et al*[35] have also emphasized the usefulness of NBI-ME in the evaluation of the depth of submucosal invasion of the carcinoma. They have described the blurry mucosal pattern (BMP) and the irregular mesh vascular pattern (IMP) as endoscopic features suggestive of submucosal invasion of gastric differentiated adenocarcinoma (Figure 6). A mucosal cancer could be estimated by correlating the absence of these NBI-ME criteria (BMP, IMP) with the absence of conventional endoscopic criteria for invasion (extremely uneven or depression, nodularity at the verge, obvious hardening of the wall and unusual elevated non-cancerous mucosa on the verge)[35]. When the margins of early gastric cancer are difficult to identify using chromoendoscopy, NBI-ME represents a reliable alternative to delineate the horizontal extent of the differentiated carcinoma. The difficulty in determining the real extent of undifferentiated cancer still remains a problem, and a proper evaluation by biopsies from the apparently normal mucosa around the lesion is recommended in these situations[36].

Applications of NBI-ME in colonic lesions

The ability of NBI for the prediction of a polyp's histology has been reported in different studies. Kudo's classification system of mucosal pit pattern detected on magnification has included 5 different types: type Ⅰ - round pits, type Ⅱ - stellar or papillary pits, type Ⅲ L- large tubular or roundish pits, type Ⅲ s-

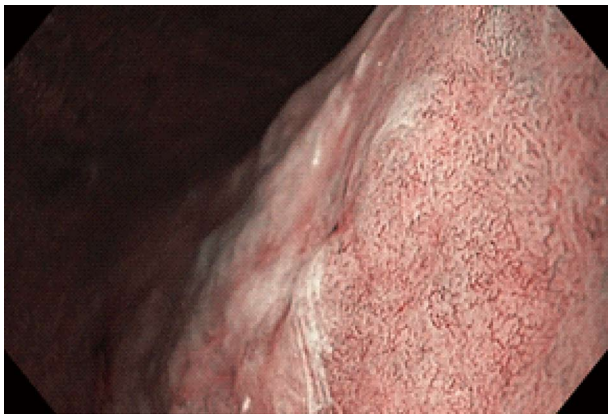

Figure 6 Gastric cancer with submucosal invasion: Blurry mucosal pattern and irregular mesh vascular pattern.

small tubular or roundish pits, type Ⅳ- branch-like or gyrus-like pits and type Ⅴ- non-structural pits[37]. A proper evaluation of a colonic lesion consists in the assessment of mucosal pattern and also of vascular pattern. Sano *et al*[38] have proposed an evaluation of "capillary pattern" by using NBI colonoscopy with magnification for the differential diagnosis of colorectal lesions: type Ⅰ - absent meshed brown capillary network (MBCN) in hyperplastic polyps (Figure 7A), type Ⅱ - regular pattern in adenomatous polyps (Figure 7B), and type Ⅲ- irregular pattern in cancerous lesions (Figure 7C).

According to these diagnostic criteria for mucosal and vascular patterns, specific features on NBI-ME have been described, corresponding with different colonic lesions: type Ⅰ or Ⅱ mucosal pattern (round, stellar or papillary pits) and type Ⅰ vascular pattern (absence of vascular structure) in hyperplastic polyps (Figure 7A); type Ⅲ or type Ⅳ mucosal pattern (tubular or branching pits) and type Ⅱ vascular pattern (regular vessels) in adenoma (Figure 7B); type Ⅴ mucosal pattern (disappeared pits) and type Ⅲ vascular pattern (irregular vessels) in adenocarcinoma (Figure 7C). This combined classification system, based on mucosal and vascular patterns assessment, was used for the prediction of polyp histology. The accuracy of the NBI-ME method has proven to be superior to high-resolution WLE for the prediction of polyp histology[39].

The NBI International Colorectal Endoscopic (NICE) classification has been proposed by an international expert group for the diagnosis of colonic lesions[40]. The classification is based upon the evaluation of lesion color, microvascular architecture, and surface pattern, and can be applied for NBI observation either with or without use of magnification. The similar or lighter color of the polyp compared with the background mucosa, with no vessels or isolated vessels coursing across the polyp surface, the homogenous lack of mucosal pattern, the detection of dark or white spots of uniform size, are features corresponding with hyperplastic polyps (Figure 7A). A browner color of the polyp relative to the background mucosa, the visualization of brown vessels surrounding oval, tubular or branched white structures are features mainly associated with colonic adenomas (Figure 7B). A brown color of the lesion relative to background, sometimes with patchy whiter areas, an absent or amorphous mucosal pattern, and a vascular pattern with disrupted or missing vessels, all represent endoscopic criteria for the diagnosis of deep submucosal invasive colorectal carcinomas according to NICE classification (Figure 7D)[41].

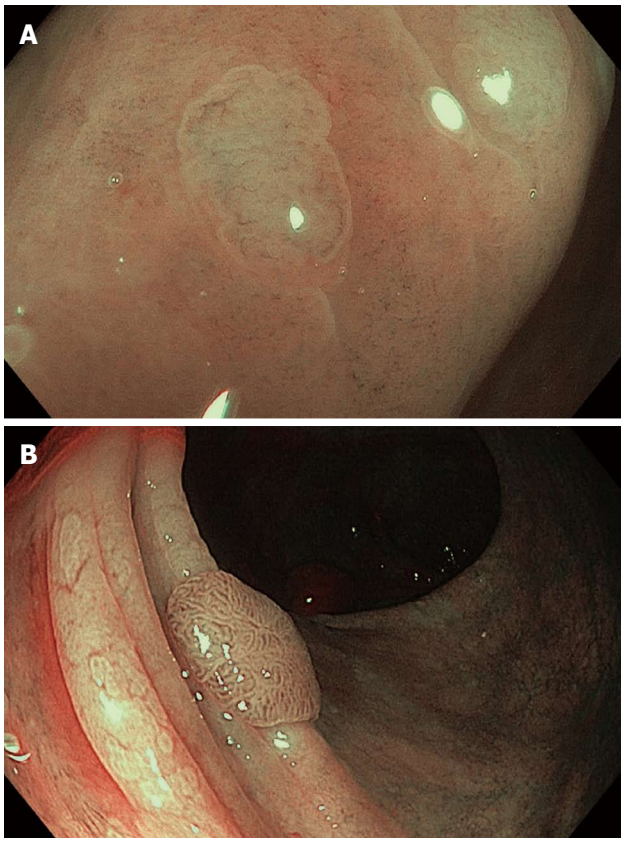

Figure 7 Assessment of colonic lesions by narrow band imaging with magnification endoscopy according to different classification systems. A: Hyperplastic polyp: absent mesh brown capillary network (Type Ⅰ MBCN) (Sano classification); a lighter color of the polyp than the background, isolated vessels coursing across the lesion (NICE criteria); B: Adenomatous polyp: regular mesh brown capillary network (Type Ⅱ MBCN) and Kudo's Type Ⅳ mucosal pattern; the brown color relative to background, thick brown vessels surrounding white structures (NICE criteria); C: Cancerous colonic lesion: irregular mucosal and vascular patterns (Type Ⅲ MBCN); D: Deep submucosal invasive colorectal cancer: amorphous surface pattern and disrupted vessels (NICE criteria).

The real time estimation of polyp histology could play an important role in clinical decisions regarding the therapeutic strategy for polyps ≤ 5 mm in size and for the duration of post-polypectomy surveillance intervals. Different cost-saving strategies were previously proposed in this setting. A "resect-and discard" policy was proposed for polyps ≤ 5 mm, which consists in a real-time estimation of polyp histology by NBI, followed by resection without pathologic as-

sessment[42]. The "resect and discard" strategy for diminutive adenomatous polyps could decrease the cost of colonoscopy. The post-polypectomy surveillance intervals could be recommended on the basis of the estimation of polyp histology by NBI and of the pathologic assessment of the larger polyps submitted to histology[43].

The accurate estimation of the histology of the polyps (real-time optical biopsy) could prevent unnecessary polypectomies in cases of diminutive rectosigmoid hyperplastic polyps ("do-not-resect" strategy). On the basis of the evaluation of polyp histology by NBI criteria (color, vessels, pit pattern), experts have demonstrated that leaving diminutive distal hyperplastic polyps in place without pathologic assessment could be a reliable approach in clinical practice[44].

According to the Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) statement, developed by The American Society for Gastrointestinal Endoscopy (ASGE), the thresholds of endoscopic technology for the assessment of polyps histology are: optical diagnosis for diminutive colorectal polyps combined with pathologic assessment of all other polyps should provide $\geqslant$ 90% agreement in determining post-polipectomy surveillance intervals when compared with decisions based on pathology assessment of all polyps, and the recommended NPV for adenomatous histology in diminutive rectosigmoid polyps should be $\geqslant$ 90%. After the achievement of PIVI thresholds, the NBI technology could be used to guide the "characterize, resect and discard" strategy in clinical practice[45]. Recent studies have focused on the ability of NBI diagnosis to meet these ASGE thresholds[46,47]. The incorporation of real-time histology in clinical practice still represents a matter of debate[48].

Regarding the widespread use of the aforementioned strategies in clinical practice, the lack of accurate criteria for the differentiation between sessile serrated adenomas (SSAs) and hyperplastic polyps on NBI could represent a real challenge. A type Ⅱ open-pit pattern (Type Ⅱ-O), characterized by wider and rounded pits, was identified on magnification to be specific to SSAs[49]. Recent reports from community gastroenterologists have showed that endoscopic features of SSAs under NBI according to NICE classification were intermediate to the patterns observed in hyperplastic polyps and adenomas[50]. The misclassification of SSAs could affect clinical decisions regarding therapeutic strategy and surveillance intervals. The approach to serrated polyps in clinical practice should take into account their malignant potential[51].

Another problem regarding the global use of optical biopsy in practice is related to the level of training and expertise. A high performance level of the optical diagnosis of the polyps using NBI-ME was reported by the experts[47], but these studies were mainly performed in academic centers. Recent studies investigating optical biopsy performance in community practice have shown that the results are not as good as those obtained in the academic setting: only 25% of gastroenterologists assessed polyps with $\geqslant$ 90% accuracy. The thresholds for optical biopsy recommended by ASGE were achieved for identification of adenoma (NPV $\geqslant$ 90%), but not for the surveillance interval agreement[46]. The level of performance in clinical practice might be improved by training programs including the evaluation of frozen images or videos, real-time optical diagnosis during NBI colonoscopy, as well as creation of computer-aided diagnostic tools[52].

CONCLUSION

A tremendous development in the applications of NBI endoscopy with magnification has been reported in recent years. The method has made significant contributions to diagnostic accuracy, screening, surveillance, and cost-saving strategies. The method is used for better characterization of GI tract lesions by focusing the endoscopic examination on modified areas in which to perform targeted biopsies from suspicious lesions. The distinction between neoplastic and non-neoplastic lesions *in vivo* represents an important tool in clinical decisions regarding surveillance or therapy. Looking for the best therapeutic strategy in early cancer, the estimation of the depth of invasion and the delineation of the horizontal extent of carcinoma are mandatory before a therapeutic procedure such endoscopic therapy or surgical resection can be recommended. NBI-ME has been successfully applied in practice to select the optimum therapy and to guide endoscopic resections.

The good results already reported regarding clinical applicability of NBI represent arguments that the method could become an increasingly reliable tool in diagnostic and therapy, even for inexperienced endoscopists. Whether or not NBI will become a standard in endoscopy practice, it entirely depends on the widespread use of the technique in current practice by endoscopists with varying levels of experience, after a proper training.

Despite all these advances, there are still challenges in application in clinical practice, particularly regarding the standardization of endoscopic criteria in order to achieve a simplified and accurate descriptive system of mucosal and vascular patterns. The validity of the different classification systems is still under evaluation and further randomized multicenter studies are needed to confirm their clinical utility. The adoption of real-time optical diagnosis in routine practice requires training and expertise in the recognition of endoscopic features on the basis of standardized NBI-ME criteria.

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Circumstance of endoscopic and laparoscopic treatments for gastric cancer in Japan: A review of epidemiological studies using a national administrative database

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Abstract

Currently, endoscopic submucosal dissection (ESD) and laparoscopic gastrectomy (LG) have become widely accepted and increasingly play important roles in the treatment of gastric cancer. Data from an administrative database associated with the diagnosis procedure combination (DPC) system have revealed some circumstances of ESD and LG in Japan. Some studies demonstrated that medical costs or length of stay of patients receiving ESD for gastric cancer had become significantly reduced while length of hospitalization and costs were significantly increased in older patients. With respect to LG, some recent reports have shown that this has been a cost-beneficial treatment for patients compared with open gastrectomy while simultaneous LG and cholecystectomy is a safe procedure for patients with both gastric cancer and gallbladder stones. These epidemiological studies using the administrative database in the DPC system closely reflect clinical circumstances of endoscopic and surgical treatment for gastric cancer in Japan. However, DPC database does not contain detailed clinical data such as histological types and lesion size of gastric cancer. The link between the DPC database and another detailed clinical database may be vital for future research into endoscopic and laparoscopic treatments for gastric cancer.

Key words: Gastric cancer; Endoscopic submucosal dissection; Laparoscopic gastrectomy; Diagnosis Procedure Combination; Administrative database; Epidemiological studies

Core tip: Currently, endoscopic submucosal dissection (ESD) and laparoscopic gastrectomy (LG) have become accepted for treatment of gastric cancer and increasingly played important roles on the treatments of gastric cancer in Japan. Using the database on national administrative database associated with the diagnosis procedure combination (DPC) system, the various studies with regards to ESD and LG for gastric cancer have been revealed. We herein describe the circumstance of ESD and LG for gastric cancer in Japan based on reports using Japanese administrative database associated in the DPC system in this review.

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INTRODUCTION

Gastric cancer is one of the most frequent cancers and causes of cancer-related deaths[1,2]. Although a trend of declining incidence has been observed, gastric cancer still causes a great health care burden[3]. According to the report by the Ministry of Health, Labour and Welfare of Japan (MHLW), roughly 50000 Japanese people die due to gastric cancer annually, representing 15% of cancer-related deaths[2]. Therefore, health care policies for gastric cancer are increasingly focused on detection and treatment in the early stage because the 5-year cancer survival in the early stage of gastric cancer has been reported to be greater than 90%[4,5]. Almost half of gastric cancers have been discovered at an early stage because of early detection measures[6].

Regarding the endoscopic treatments for early gastric cancer, endoscopic mucosal resection (EMR) was standard practice[6]. However, significant progress in endoscopic treatment has contributed to more effective resection of early gastric cancer. Endoscopic submucosal dissection (ESD) has achieved a high rate of histologically curative en bloc resection for early gastric cancer regardless of size, permitting the resection of previously non-resectable tumors. The ESD technique has spread rapidly owing to its excellent eradication rate compared with EMR[6-8]. ESD is recognized as an established endoscopic therapy for the treatment of early gastric cancer[8-10].

Although almost early gastric cancers can be treated by ESD, the number of surgical operation for gastric cancer still remains high. Also in the field of surgical treatments, recent advances have allowed more effective and safe procedure for gastric cancer. Laparoscopic gastrectomy (LG) is significantly less invasive than open gastrectomy (OG), with lower mortality and morbidity rates[11-13]. Furthermore, LG is now performed not only as distal gastrectomy but also as proximal and total gastrectomy[11-13]. Currently, LG has been accepted for the treatment of gastric cancer, with the number of patients requiring this surgical procedure increasing in Japan, as well as other developed countries[13-15].

Currently, endoscopic and laparoscopic treatments such as ESD and LG are increasingly playing important roles for the treatment of gastric cancer. In this review, we report the circumstances of ESD and LG for gastric cancer in Japan, based on reports using Japanese administrative database associated with the diagnosis procedure combination (DPC) system.

ADMINISTRATIVE DATABASE ASSOCIATED WITH THE DPC SYSTEM

History of the DPC system

The health care system of Japan has severe problems owing to the expense of new medical technology and extended hospitalizations of patients[16]. To solve these problems, the MHLW started to investigate whether the case-mix classification system can be adopted to standardize medical profiling and payment[16-20]. In 2003, Japanese case-mix projects based on the DPC system were introduced to 80 university and 2 national hospitals.

DPC participating hospitals have adopted a unique reimbursement system, whereby the paid medical treatment fees become proportionally higher as the length of stay (LOS) becomes shorter. Therefore, a shorter hospitalization leads to an increase in income for the hospitals. Furthermore, payment per hospitalization is strictly determined by the DPC payment system. Currently, the number of DPC-participating hospitals has been increasing. Enormous amounts of data on hospitalization of patients have been collected annually, covering roughly 55% of the total hospitalizations, according to the report from the MHLW in 2014[21].

Component of data in the DPC system

This system collects important data during hospitalization in addition to the characteristics of the unique reimbursement system. Each patient's background information or discharge summary, which includes principal diagnosis, complications, comorbidities, and outcomes are recorded in the administrative database associated with the DPC system. These patient data are coded using the International Classification of Diseases and Injuries 10th Revision (ICD-10th) code. Also, this database includes the hospital information, number and date of clinical procedures, such as operations or drug therapies that are indexed in the original code determined by the MHLW[16-20]. Detailed contents of data in the database of the DPC system are shown in Table 1[22].

Collection and use of DPC data

Comprehensive surveys of DPC-participating hospitals are conducted by the DPC research group that has worked on the DPC data utilization project for research purposes, independently of the MHLW. DPC-participating hospitals sent the anonymized and provided detailed data to the DPC research group, which then sent to the server in the DPC research group. Using the sent data from DPC-participating hospitals, many studies have been reported in the various fields of medical research[16-20,23-26].

Table 1 Contents of data in the national administrative database[22]

Hospital information
Location of hospital
Number of beds
Patient background information
Age
Sex
Zip code
Diagnoses
Main diagnoses (coded with International Classification of Diseases and Injuries 10th Revision (ICD-10th) code)
Main diagnoses (coded with the ICD-10th codes)
Complications after admission (coded with the ICD-10th codes)
Procedures for patients
Surgery, anesthesia and other procedures (coded with the Japanese original codes)
Drugs and devices (coded with the Japanese original codes)
Dates of each procedure
Dates of use for each drug and device
Admission and discharge data
Urgent or elective admission
Ambulance service use
Dates of admission and discharge; length of stay
Discharge status (discharge to home, rehabilitation hospital or other facility, or death)
Claim data
Total charge
Itemized charges for hospitalization, medication, examination, surgery and others
Other clinical data
Height/body weight
Smoking index
Pregnancy
Japan Coma Scale at admission
TNM classification of malignant tumors
Activity of Daily Living scale
Modified Rankin scale
Hugh-Jones classification of respiratory status
New York Heart Association classification of heart failure symptoms
Canadian Cardiovascular Society classification of angina pectoris
Killip classification of acute myocardial infarction
Severity classification of community-acquired pneumonia
Child-Pugh classification of liver cirrhosis
Severity classification of acute pancreatitis
Burn index
Global Assessment of Functioning scale

EPIDEMIOLOGICAL STUDIES ON ESD FOR GASTRIC CANCER USING DPC DATABASE

ESD for gastric cancer (Table 2)

Time trend of outcomes of ESD in Japan: According to the report about the time trend of outcomes of ESD in Japan, the rate of ESD-related complications was stable (3.2% in 2009 *vs* 3.5% in 2010 *vs* 3.3% in 2011, $P = 0.496$) between 2009 and 2011[27]. In the early 2000s, some clinical studies in single centers reported that the complication rate of ESD was from 5% to 8%[28,29]. However, the complication rate of ESD based on an administrative database was approximately 3% between 2009 and 2011, which indicated that complications of ESD remained low. Therefore, the decrease in complication rates may suggest that the number of experienced endoscopists has been increasing between the early and late 2000s, and their technical skill level in ESD has been favorably stable from 2009 to 2011. In addition, the LOS and medical costs of patients had become significantly reduced in Japan (10.5 d in 2009 *vs* 9.8 d in 2010 *vs* 9.5 d in 2011 and 6768.4 US dollars in 2009 *vs* 6507.7 US dollars in 2010 *vs* 6427.6 US dollars in 2011; $P < 0.001$, respectively)[27]. The efficiency of ESD for gastric cancer as well as stable technical skills has been progressing in Japan.

Outcomes of ESD in high-volume hospitals: With respect to the report about hospital characteristics such as hospital volume, ESD-related complications were significantly lower in higher-volume hospitals (> 100 cases between 2009 and 2011) than lower- (< 50 cases) or medium-volume hospitals (50-100 cases) in upper gastric cancer (6.5% in lower-volume hospitals *vs* 5.2% in medium-volume hospitals *vs* 3.4% in higher-volume hospitals; $P = 0.017$)[30]. Multivariate logistic regression analysis also revealed that high-volume hospitals were significantly associated with a decrease of relative risk of ESD-related complications in upper gastric cancer [odds ratio (OR) for higher-volume hospitals 0.51; 95% confidence interval (CI), 0.32-0.81, $P = 0.005$]. Meanwhile, no significant differences for ESD-related complications were seen for middle and lower gastric cancers among the different hospital volume categories ($P > 0.05$)[30]. Some previous studies also pointed out that a higher skill level with ESD is required for upper gastric cancers than for middle or lower gastric cancers[31-33]. Higher volume hospitals were more likely to have experienced endoscopists can provide sufficient treatment, which significantly contributed to fewer complications or shorter LOS[34,35]. Thus, it is reasonable that the decreases in ESD-related complications and in LOS of patients with upper gastric cancer were observed at higher-volume hospitals.

Comparison between non-elderly and elderly patients treated by ESD: A comparison between elderly (80 years or more) and non-elderly patients (less than 80 years) regarding outcome of ESD was also reported[36]. A recent study revealed that there was no statistically difference with regard to ESD-related complications (3.9% *vs* 4.3%, $P = 0.152$)[36]. The findings about complications of ESD has been consistent with those of some previous studies in Japan[37,38]. Kakushima *et al*[37] showed that the complication rate of ESD in elderly patients was not significantly different from that in non-elderly patients, while Tokioka *et al*[38] also reported that the occurrences of perforations during ESD were similar in non-elderly and elderly patients. However, length of hospitalization and direct costs during hospitalization

Table 2 Reports of endoscopic and laparoscopic treatments for gastric cancer using national administrative database

	No. of patients	No. of hospitals	Study period	Investigated outcomes
Endoscopic submucosal dissection				
Murata *et al*[27]	32943	907	2009-2011	Complications, length of stay, and medical costs
Murata *et al*[30]	27385	867	2009-2011	Complications and length of stay
Murata *et al*[36]	27385	867	2009-2011	Complications, length of stay, and medical costs
Laparoscopic gastrectomy				
Yasunaga *et al*[40]	9388	805	2010	Complications, length of stay, medical costs, in-hospital mortality and 30-d readmission rates
Kuwabara *et al*[41]	17761	258	2006-2008	Length of hospital stay, medical costs and operative time
Murata *et al*[42]	14006	744	2009-2011	Complications, length of stay, medical costs and in-hospital mortality
Kuwabara *et al*[46]	3054	420	2007	Complications and operative time
Kuwabara *et al*[47]	3914	258	2006-2008	Complications, length of stay, medical costs, in-hospital mortality and blood transfusions
Ryu *et al*[48]	209	5	2007-2008	Length of hospital stay (pre and post operative) and duration of antibiotic administration and post operative fasting

were significantly increased in elderly patients requiring ESD for gastric cancer, compared with non-elderly patients (12.2 d *vs* 9.3 d and 7346.3 US dollars *vs* 6295.6 US dollars; $P < 0.001$, respectively). The growing life expectancy and an aging population will unavoidably lead to an increasing number of elderly patients in Japan[39]. Therefore, providing appropriate care in endoscopic treatments for elderly patients is becoming significantly important in Japan. More efficient medical implementation for elderly patients with gastric cancer treated with ESD will be required in the future.

LG for gastric cancer

Comparison between LG and OG for gastric cancer: Using the data in 2010, Yasunaga *et al*[40] reported that patients treated by LG had shorter LOS compared with those with OG (13 d *vs* 15 d, $P < 0.001$) while no significant difference was observed in mortality and occurrence of postoperative complications (LG *vs* OG, 0.36% *vs* 0.28%, $P = 0.80$ and 12.9% *vs* 12.6%, $P = 0.73$, respectively). Kuwabara *et al*[41] also reported that LG offered a significant economic advantage over OG (14405 US dollars *vs* 17260 US dollars, $P < 0.001$). These results show that LG has been a beneficial treatment for patients who require surgical resection for gastric cancer.

Influence of additional laparoscopic cho-lecystectomy on outcomes of LG for gastric cancer: A recent report revealed that adding laparoscopic cholecystectomy did not influence to outcomes of patients undergoing LG for gastric cancer (OR for laparoscopy-related complications 1.02, 95%CI: 0.84-1.24, $P = 0.788$ and OR for in-hospital mortality 1.16, 95%CI: 0.49-2.76, $P = 0.727$)[42]. These results have been consistent with previous studies in other developed countries[43,44]. The greater surgeon's experience and continuing technical progress for laparoscopic resection has resulted in expanded indications in Japan[42]. Besides, there has been an increase in the types of surgical operations together with laparoscopic procedure, and the number of surgeons interested in simultaneous laparoscopic procedures has increased[45]. Thus these results indicate that the combined LG and cholecystectomy is safe procedure for patients with both gastric cancer and gallbladder stones.

Impact of hospitals and regional differences for outcomes of LG for gastric cancer in Japan: With regard to hospital characteristics in LG for gastric cancer, several studies reported that higher-volume hospitals had shorter operation times and postoperative LOS of patients compared with low case-volume hospitals[46,47]. In an analysis of regional differences in LG for gastric cancer, Ryu *et al*[48] reported that there were significant differences with respect to rate of laparoscopic resection or duration of antibiotic administration between cancer centers of different regions. In addition, their report revealed that significant variation in pre- or postoperative LOS was observed between hospitals. Such reports could contribute to the quality of medical care for patients, which could have significant implications for decision making of health care policy in Japan.

ADVANTAGE OF EPIDEMIOLOGICAL STUDIES USING DPC DATABASE

Unlike the single center study, these studies have been conducted based on a nationally representative sample of patients in a community setting. One of the advantages of the clinical epidemiological studies using DPC data is that they facilitated evaluation of a large sample of patients in unbiased manner[16-20]. Usually, ESD and LG are performed in hospitals that have more experienced endoscopists or surgeons as well as more resources or availa-ble facilities. The DPC participating hospitals play important roles in providing advanced care or me-dical studies, as well as educating students and medical residents[16-20]. Furthermore, medical data with regards to proce-

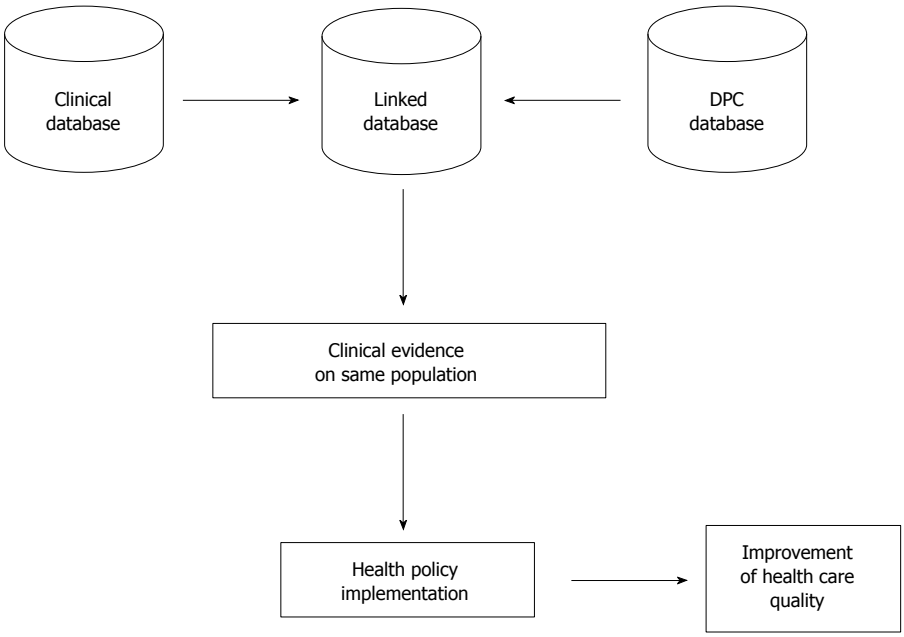

Figure 1 Framework for future clinical epidemiological studies. DPC: Diagnosis procedure combination.

dures or medications have been extensively indexed with original codes[16-20]. These data are recorded on a daily basis for each patient[16-20]. Therefore, this administrative database also enables to evaluate the clinical outcomes with detailed medical treatments, in particular for medical economic outcomes. The epidemiological studies using the DPC database directly reflect the present circumstances of endoscopic or surgical treatment for gastric cancer in Japan.

LIMITATIONS OF EPIDEMIOLOGICAL STUDIES USING DPC DATABASE

Some potential limitations of clinical epidemiological studies using DPC data also should be acknowledged. This database does not contain patient data such as lesion size, histological type and staging of gastric cancer. It is reasonable that the lack of these data may influence the results of the studies using the DPC database. In addition, the types of devices for ESD or the kinds of stapling devices used for laparoscopic resection have not been included in the DPC database. Therefore, DPC data may be currently unsuitable to the detailed clinical investigation of ESD and LG for gastric cancer.

FUTURE IMPLEMENTATION

To resolve the lack of detailed clinical data, a link between our database and the other database may be vital for future research about ESD and LG for gastric cancer in Japan. The Japanese Gastric Cancer Association (JGCA) began a project to register patients who were treated by ESD since 2011[49]. In addition, some studies has been reported using the data of the National Clinical Database (NCD)[50,51]. The results from the database of this project will be useful information for the quality of ESD and LG for gastric cancer in the near future. However, we consider that more valuable information can be produced by a link between our administrative database and the database in this project. For example, the Surveillance, Epidemiology and End Results program of cancer registries, which is a cancer registry database in the United States, has been linked to the Medicare Claim Database, a payment system for medical services. As a result, many clinical studies have reported using these linked databases[52]. Therefore, we believe that a link between our database and the database of the JGCA or NCD may be vital for future research for ESD and LG for gastric cancer in Japan. If this is carried out, more valuable information showing the favorable quality of ESD for gastric cancer can be expected in patients who undergo ESD and LG for gastric cancer (Figure 1).

CONCLUSION

From recent studies using the national administrat-ive database, the various circumstances of endosco-pic and laparoscopic treatments for gastric cancer are revealed. These findings are useful for future studies of the treatments of gastric cancer, which could in turn have important implications for care of patients with gastric cancer in Japan. However, this administrative database is still lacking detailed clinical data of gastric cancer. The link between the administrative database and the other detailed clinical database may be vital for future research into endoscopic and laparoscopic treatments for gastric cancer in Japan.

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ORIGINAL ARTICLE

Retrospective Study

Endoscopic retrograde cholangiopancreatography for suspected choledocholithiasis: From guidelines to clinical practice

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Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at jmagalhaes@chaa.min-saude.pt. The consent of the participants was not obtained but the presented data are anonymized and risk of identification is low.

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Abstract

AIM: To study the practical applicability of the American Society for Gastrointestinal Endoscopy guidelines in suspected cases of choledocholithiasis.

METHODS: This was a retrospective single center study, covering a 4-year period, from January 2010 to December 2013. All patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) for suspected choledocholithiasis were included. Based on the presence or absence of predictors of choledocholithiasis (clinical ascending cholangitis, common bile duct (CBD) stones on ultrasonography (US), total bilirubin > 4 mg/dL, dilated CBD on US, total bilirubin 1.8-4 mg/dL, abnormal liver function test, age > 55 years and gallstone pancreatitis), patients were stratified in low, intermediate or high risk for choledocholithiasis. For each predictor and risk group we used the χ^2 to evaluate the statistical associations with the presence of choledocolithiasis at ERCP. Statistical analysis was performed using SPSS version 21.0. A P value of less than 0.05 was considered statistically significant.

RESULTS: A total of 268 ERCPs were performed for suspected choledocholithiasis. Except for gallstone pancreatitis (P = 0.063), all other predictors of cho-

ledocholitiasis (clinical ascending cholangitis, $P = 0.001$; CBD stones on US, $P \leqslant 0.001$; total bilirubin > 4 mg/dL, $P = 0.035$; total bilirubin 1.8-4 mg/dL, $P = 0.001$; dilated CBD on US, $P \leqslant 0.001$; abnormal liver function test, $P = 0.012$; age > 55 years, $P = 0.002$) showed a statistically significant association with the presence of choledocholithiasis at ERCP. Approximately four fifths of patients in the high risk group (79.8%, 154/193 patients) had confirmed choledocholithiasis on ERCP, *vs* 34.2% (25/73 patients) and 0 (0/2 patients) in the intermediate and low risk groups, respectively. The definition of "high risk group" had a sensitivity of 86%, positive predictive value 79.8% and specificity 56.2% for the presence of choledocholithiasis at ERCP.

CONCLUSION: The guidelines should be considered to optimize patients' selection for ERCP. For high risk patients specificity is still low, meaning that some patients perform ERCP unnecessarily.

Key words: Choledocholithiasis; Endoscopic retrograde cholangiopancreatography; Cholangitis; Common bile duct stones; Dilated common bile duct

Core tip: The American Society for Gastrointestinal Endoscopy (ASGE) proposes a stratification of patients according to the risk for choledocholithiasis, influencing subsequent management. Our study shown that the risk stratification, according to ASGE guidelines, may improve risk estimation of choledocholithiasis and should be considered to optimize patients' selection for endoscopic retrograde cholangiopancreatography (ERCP). However, even in the "high risk group" the specificity was low. Thus, at this point, it seems advisable that also "high risk" patients undergo further testing before being submitted to ERCP, similarly to those patients with "intermediate risk", while for patients with "low-risk" of choledocholithiasis a watchful waiting strategy seems adequate.

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INTRODUCTION

Choledocholithiasis is the most common cause of biliary obstruction. Approximately 5% to 22% of the Western population has gallstones[1] and common bile duct stones occur in 8%-20%[2,3] of those patients. Patients suspected of having choledocholithiasis are diagnosed with a combination of laboratory tests and imaging studies[4]. The first imaging study obtained is typically a transabdominal ultrasonography (US). When the ultrasound findings are not enough for a diagnosis a magnetic resonance cholangiopancreatography (MRCP) or an endoscopic ultrasound (EUS) should be considered.

The diagnosis of choledocholithiasis usually should be followed by some therapeutic intervention to remove the stones[4-7]. Endoscopic retrograde cholangiopancreatography (ERCP) is the standard method for the diagnosis and therapy of bile duct stones, however it is an invasive procedure not free of complications[8-11].

According to the results of laboratory tests and US, the American Society for Gastrointestinal Endoscopy (ASGE) proposes to stratify a patient in low, intermediate or high risk for choledocholithiasis. Subsequent management will vary depending on the patient's level of risk[12]. The purpose of this study was to evaluate the practical applicability of the American Society for Gastrointestinal Endoscopy guidelines in a population of patients undergoing ERCP for suspected choledocholithiasis.

MATERIALS AND METHODS

Patients

We performed a retrospective single center study, covering a 4-year period, from January 2010 to December 2013. Patients referred for ERCP for suspected bile duct lithiasis were consecutively included. Patients presenting for stent exchange or follow-up of known and incompletely removed stones on previous ERCP were excluded.

Clinical data recorded from disease onset (age, gender, symptoms at presentation, laboratorial values) to the time of the ERCP (therapeutic procedures and related complications) were collected.

Predictors of choledocholithiasis

According to ASGE guidelines[12], cholangitis, total bilirubin > 4 mg/dL and common bile duct (CBD) stone on US were considered very strong predictors. Total bilirubin 1.8-4 mg/dL and dilated CBD on US were considered strong predictors and abnormal liver biochemical tests, age > 55 years and gallstone pancreatitis were considered moderate predictors. Patients with strong predictors or any very strong predictor were considered at high risk for choledocholithiasis. Patients without any predictor and all other patients were considered low and intermediate risk for choledocholithiasis, respectively. The diagnosis of cholangitis was established by the presence of Charcot's triad (fever, abdominal pain and jaundice). The diagnosis of CBD stone on US was considered when an intraductal echogenic focus with distal acoustic

Table 1 Baseline characteristics of the study population *n* (%)

Variable	Total (*n* = 268)
Gender, female	161 (60.1)
Age, mean ± SD	66.8 ± 16.8
Very strong predictors	
Clinical ascending cholangitis	36 (13.4)
Common bile duct stone on US	109 (40.7)
Total bilirubin > 4 mg/dL	102 (38.1)
Strong predictors	
Total bilirubin 1.8-4 mg/dL	84 (31.3)
Dilated common bile duct on US	195 (72.8)
Moderate predictors	
Abnormal liver function test	231 (86.2)
Age > 55 yr	197 (73.5)
Gallstone pancreatitis	63 (23.5)

US: Ultrasonography.

shadow was identified. Dilated CBD on US was considered when bile duct diameter was > 6 mm in a patient without cholecystectomy. Abnormal liver biochemical tests were considered when aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (AP) presented elevated laboratory values, considering the reference lab values in our institution. Gallstone pancreatitis was considered when patients presented with abdominal pain (epigastric pain often radiating to the back), lipase (or amylase activity) at least 3 times higher than the upper limit of normal, stones or biliary sludge within gallbladder and no history of alcohol abuse.

Endoscopic retrograde cholangiopancreatography procedure

Every ERCP was performed using Olympus® TJF 160 VR or TJF 145 side-viewing endoscopes. All patients provided written consent to undergo ERCP and were informed of the risks and benefits of the procedure. Patients were under propofol sedation assisted by an anaesthesiologist. Stone size and number were documented on the initial diagnostic cholangiogram at ERCP. Endoscopic sphincterotomy was performed over a guide wire. Some patients underwent papillary balloon dilation using a through-the-scope balloon catheter for oesophageal/pyloric dilation, gradually inflated to 12-18 mm according to the size of the largest stone and the maximal diameter of the distal bile duct on the cholangiogram. Stones were removed using a retrieval balloon catheter and/or a Dormia basket. When necessary, mechanical lithotripsy was performed to fragment the stones prior to removal. Complete clearance of the bile duct was documented with a balloon catheter cholangiogram at the end of the procedure. In the case of residual lithiasis, a biliary 7 Fr double pigtail plastic stent was placed and a second ERCP was planned within 10-12 wk. At the end of each ERCP, 100 mg rectal indomethacin was routinely given, to prevent post-ERCP pancreatitis. Prophylactic antibiotics were not routinely administered.

Statistical analysis

Statistical analysis was performed using SPSS version 21.0 (SPSS® Inc., Chicago, IL, United States).

Quantitative data were described as mean ± SD and qualitative data as proportions. For each predictor and risk group the χ^2 was used to access differences between presence *vs* absence of choledocolithiasis on ERCP. A P value < 0.05 was considered statistically significant.

For each risk group and their predictors the sensitivity, specificity, positive predictive values (PPV) and negative predictive value (NPV) were assessed.

RESULTS

From January 2010 to December 2013, a total of 268 patients were referred for ERCP for suspected choledocholithiasis. Patients included in our study were predominantly female (60.1%), with a mean age of 66.8 ± 16.8 years. Choledocholithiasis was present in 179 ERCPs (66.8%). The predictors more often seen in our patients were the presence of abnormal liver biochemical tests (86.2%), age > 55 years (73.5%) and dilated CBD on US (72.8%). Main clinical features of the study population are shown in Table 1.

Predictors of choledocholithiasis

Except for gallstone pancreatitis (P = 0.063), all other predictors showed a statistically significant difference between presence *vs* absence of choledocholithiasis on ERCP (cholangitis, P = 0.001; CBD stone on US, P < 0.001; total bilirubin > 4 mg/dL, P = 0.035; total bilirubin 1.8-4 mg/dL, P = 0.001; dilated CBD on US, P < 0.001; abnormal liver function test, P = 0.012; age > 55 years, P = 0.002) (Table 2).

The risk of choledocholithiasis, as shown by *odds ratio*, was increased for patients who presented with cholangitis (OR: 6.48, 95%CI: 1.93-21.80), common bile duct stone on US (OR: 11.25, 95%CI: 5.32-23.81), total bilirubin > 4 mg/dL (OR: 1.79, 95%CI: 1.04-3.08), total bilirubin 1.8-4 mg/dL (OR:3.15, 95%CI: 1.63-6.08), dilated common bile duct on US (OR:5.06, 95%CI: 2.85-8.99), abnormal liver function test (OR:2.43, 95%CI: 1.20-4.90) and age > 55 years (OR:2.37, 95%CI: 1.36-4.15) (Table 2).

Risk group for choledocholithiasis

Of the 268 patients included in this study, 72% were stratified into the high risk group. Of the remaining patients, 27.2% e 0.8% were stratified into the intermediate and low risk groups, respectively. Approximately four fifths of patients in the high risk group (79.8%, 154/193 patients) had confirmed choledocholithiasis on ERCP. The presence of choledocholithiasis was identified in 34.2% (25/73) of intermediate risk patients. Any patient into the low risk group had choledocholithiasis on ERCP. There was a statistically significant association between

Table 2 Predictors of choledocholithiasis - univariate analysis *n* (%)

Variable	Choledocholithiasis on ERCP	No Choledocholithiasis on ERCP	OR	95%CI	*P* value
Very strong predictors					
Clinical ascending cholangitis	33 (91.7)	3 (8.3)	6.48	1.93-21.80	0.001
Common bile duct stone on US	100 (91.7)	9 (8.3)	11.25	5.32-23.81	< 0.001
Total bilirubin > 4 mg/dL	76 (74.5)	26 (25.5)	1.79	1.04-3.08	0.035
Strong predictors					
Total bilirubin 1.8-4 mg/dL	63 (75.0)	21 (25.0)	3.15	1.63-6.08	0.001
Dilated common bile duct on US	150 (76.9)	45 (23.1)	5.06	2.85-8.99	< 0.001
Moderate predictors					
Abnormal liver function test	161 (69.7)	70 (30.3)	2.43	1.20-4.90	0.012
Age > 55 yr	142 (72.1)	55 (27.9)	2.37	1.36-4.15	0.002
Gallstone pancreatitis	36 (57.2)	27 (42.8)	0.58	0.32-1.03	0.063

ERCP: Endoscopic retrograde cholangiopancreatography; US: Ultrasonography.

Table 3 Risk group for choledocholithiasis - univariate analysis *n* (%)

Variable	Total	Choledocholithiasis on ERCP	No Choledocholithiasis on ERCP	*P* value
High risk group	193 (72.0)	154 (79.8)	39 (20.2)	< 0.001
Intermediate risk group	73 (27.2)	25 (34.2)	48 (65.8)	
Low risk group	2 (0.8)	0 (0)	2 (100)	
Very strong predictors				
None	97 (36.2)	39 (40.2)	58 (59.8)	< 0.001
One	104 (38.8)	80 (76.9)	24 (23.1)	
Two	58 (21.6)	51 (87.9)	7 (12.1)	
Three	9 (3.4)	9 (100)	0 (0)	
Strong predictors				
None	27 (16.4)	3 (11.1)	24 (88.9)	< 0.001
One	78 (47.3)	50 (64.1)	28 (35.9)	
Two	60 (36.4)	50 (83.3)	10 (16.7)	

ERCP: Endoscopic retrograde cholangiopancreatography.

the presence of choledocholithiasis on ERCP and the risk group ($P < 0.001$) (Table 3). The odds ratio (OR) for choledocholithiasis in high risk patients was 7.89 (95%CI: 4.36-14.32). The combination of any two or all very strong predictors elevated the probability of choledocholithiasis for 87.9% (51/58) and 100% (9/9), respectively. The combination of both strong predictors presented 83.3% (50/60) of probability of choledocolithiasis.

Sensitivity, specificity, positive predictive values and negative predictive values for choledocolithiasis

Cholangitis was the parameter that had the higher specificity (96.6%), however for the same parameter the sensitivity was low. Total bilirubin > 4 mg/dL or the presence of CBD stones on US also presented a good specificity (89.9% and 70.8%, respectively). The PPV was high for very strong predictors, mainly clinical ascending cholangitis (PPV 91.7%) and CBD stones on US (PPV 91.7%). The high risk group had a high sensitivity (86%) and PPV (79.8%), but low specificity (56.2%) for the presence of CBD stones (Table 4).

DISCUSSION

According to ASGE guidelines, a patient stratified as high risk has > 50% of probability of choledocholithiasis[12]. In our study, patients stratified as high risk following ASGE criteria had 79.8% probability of choledocholithiasis. These results are consistent with those presented in the study by Rubin *et al*[13]. All the very strong predictors (clinical ascending cholangitis, CBD stones on US or total bilirubin > 4 mg/dL) presented a statistically significant association with the presence of choledocholithiasis. The combination of any of two or three very strong predictors increased the probability of choledocholithiasis for 87.9% and 100%, respectively.

Transabdominal ultrasound is the most commonly used initial imaging modality for suspected biliary stones. In our study, the presence of CBD stones detected during the US evaluation presented an OR of 11.25 for choledocholithisis. The diagnosis of choledocholithiasis is often difficult, with the sensitivity for the detection of CBD stones by US ranging from 20% to 80%[14]. The diagnostic accuracy of US is operator dependent but it is also influenced by some clinical features of patients (shadowing from bowel gas, overweight and stone size)[14].

In our study, the combination of strong predictors (dilated CBD on US, total bilirubin 1.8-4 mg/dL) presented 83.3% of probability of choledocholithiasis confirmed at ERCP. Strong predictors presented a sta-

Table 4 Sensitivity, specificity, positive predictive values and negative predictive values for choledocolithiasis

Variable	Sensitivity	Specificity	PPV	NPV
Very strong predictors				
Clinical ascending cholangitis	18.4	96.6	91.7	37.0
Common bile duct stone on US	55.9	89.9	91.7	50.3
Total bilirubin > 4 mg/dL	42.5	70.8	74.5	37.8
Strong predictors				
Total bilirubin 1.8-4 mg/dL	61.1	66.6	75	51.2
Dilated common bile duct on US	83.8	49.4	76.9	60.3
Moderate predictors				
Abnormal liver function test	89.9	21.3	69.7	51.3
Age > 55 yr	79.3	38.2	72.1	47.9
Gallstone pancreatitis	20.1	69.7	57.1	30.2
High risk group	86	56.2	79.8	66.7
Intermediate risk group	13.9	46	34,2	21

PPV: Positive predictive values; NPV: Negative predictive values; US: Ultrasonography.

tistically significant association with the presence of choledocholithiasis, which is in line with other previously published data[15-18]. The OR for choledocholithiasis in a patient with a CBD dilation was 5.06. However, the CBD dilation should always be interpreted according to patient characteristics, particularly previous cholecystectomy and age[19-21]. Previous studies[15-17,22,23] have reported some utility of serum bilirubin levels as a predictor of CBD stones. In this study, a bilirubin value between 1.8-4 g/dL had an OR of 3.15 and a specificity of 66.6% for choledocolithiasis. The specificity increased to 70% when the bilirrubin value was > 4 mg/dL. These results are in agreement with those previously reported by ASGE guidelines[12].

Individually, moderate predictors, such as abnormal liver function test and age > 55 years, presented a statistically significant association with the presence of choledocholithiasis in our series and a sensitivity of 89.9% and 79.3% for the prediction of choledocholithiasis on ERCP. In a study by Barkun *et al*[16], abnormal liver function tests, such as alkaline phosphatase > 300 units/L and AST > 120 units/L present a sensitivity of 79% and 81% to predict choledocholithiasis, respectively. At the same study, age > 55 years, only presented a sensitivity of 57%, however, when combined with other predictors (elevated bilirubin and CBD dilation on US) the model predicted with 94% of probability the presence of choledocholithiasis.

As previously reported by other authors[13,24], also in our results the diagnosis of gallstone pancreatitis was not related with the presence of choledocholithiasis at ERCP ($P > 0.05$). Stone size may be an explanation, as larger stones are less likely to migrate[24] and the small gallstones, that most commonly are the source of pancreatitis[25], frequently pass spontaneously. Some studies have reported that in the absence of cholangitis, patients with gallstone pancreatitis do not benefit from early ERCP[26,27].

In patients stratified into the intermediate and low risk group, the probability of choledocholithiasis is 10%-50% and < 10%, respectively[12]. In this study, the probability of choledocholithiasis was 34.2% (25/73) and 0 (0/2) for intermediate and low risk groups, respectively. For these risk groups the sensitivity, specificity, PPV and NPV did not show values with clinical interest. In the intermediate risk group, ASGE guidelines[12] recommended less invasive options for detecting choledocholithiasis, such as MRCP or EUS. The two techniques showed a good sensitivity and specificity for choledocholithiasis[28,29], so deciding which test should be performed first depends on various factors such as availability, cost, patient-related factors and the suspicion for a small stone. Because it is noninvasive, MRCP is the first test performed to look for CBD stones. However, for small CBD stones (< 5 mm) the sensitivity of MRCP is lower[30], so, if the MRCP is negative, but the suspicion for a common bile duct stone remains moderate to high, EUS is an appropriate next step.

In conclusion, our study confirms that the combination of choledocolithiasis predictors, according to ASGE guidelines[12], enables risk stratification of patients based on the likelihood for the presence of choledocholithiasis. However, for high risk patients the specificity was still low (56.2%), with 39 patients (20%) false positive, meaning that a significant proportion of patients will be submitted to ERCP unnecessarily. In the future, the inclusion of new predictors or different combinations of previous predictors will be essential to improve the classification of patients as high risk, obviating the need of other imaging tests (MRCP/EUS) before ERCP. However, at this point, it seems advisable that also "high risk" patients undergo further testing with MRCP and/or EUS before being submitted to ERCP, similarly to those patients with "intermediate risk", while for patients with "low-risk" of choledocholithiasis a watchful waiting strategy seems adequate.

COMMENTS

Background

Patients suspected of having choledocholithiasis are diagnosed with a combination of laboratory tests and/or imaging studies. Endoscopic retrograde cholangiopancreatography (ERCP) has been established as the standard method for the management of bile duct stones, but it may be associated with substantial morbidity and mortality. In the evaluation of suspected choledocolithiasis, the American Society for Gastrointestinal Endoscopy (ASGE) proposes to stratify a patient as high risk, intermediate risk or low risk for having choledocholithiasis. Subsequent management will vary depending on the patient's level of risk.

Research frontiers

In this study, the authors aimed to assess the practical applicability and to validate the current ASGE guidelines in a population of patients undergoing ERCP for suspected choledocholithiasis.

Innovations and breakthroughs

The study confirms that the combination of choledocolithiasis predictors, according to ASGE guidelines may improve risk estimation of choledocholithiasis and should be considered to optimize patients' selection for ERCP. However, even in the "high risk group" the specificity was low (56.2%), meaning that a significant proportion of patients will still perform ERCP unnecessarily.

Applications

The results of this study suggest that the inclusion of new predictors of choledocholithisis or different combinations of previous predictors will be essential to improve the classification of patients as high risk, obviating the need of other imaging tests before endoscopic retrograde cholangiopancreatography. Thus, at this point, it seems advisable that also "high risk" patients undergo further testing before being submitted to ERCP, similarly to those patients with "intermediate risk", while for patients with "low-risk" of choledocholithiasis a watchful waiting strategy seems adequate.

Terminology

Choledocholithiasis is defined as the occurrence of stones in the bile duct and has a propensity for life-threatening complications such as cholangitis and acute pancreatitis. Endoscopic retrograde cholangiopancreatography is a technique that combines the use of endoscopy and fluoroscopy to diagnose and treat problems of the biliary or pancreatic ductal systems. It has evolved from a diagnostic procedure to an almost exclusively therapeutic technique.

Peer-review

Title and running title accurately reflects the topic and contents of the paper key words.

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SYSTEMATIC REVIEWS

Clinical outcomes of self-expandable stent placement for benign esophageal diseases: A pooled analysis of the literature

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Data sharing: All data in this systematic review were extracted from the original articles and are presented in the literature Tables 1 and 4. No additional data are available.

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Abstract

AIM: To analyze the outcomes of self-expandable stent placement for benign esophageal strictures and benign esophageal leaks in the literature.

METHODS: The PubMed, Embase and Cochrane databases were searched for relevant articles published between January 2000 and July 2014. Eight prospective studies were identified that analyzed the outcomes of stent placement for refractory benign esophageal strictures. The outcomes of stent placement for benign esophageal leaks, perforations and fistulae were extracted from 20 retrospective studies that were published after the inclusion period of a recent systematic review. Data were pooled and analyzed using descriptive statistics.

RESULTS: Fully covered self-expandable metal stents (FC SEMS) (n = 85), biodegradable (BD) stents (n = 77) and self-expandable plastic stents (SEPS) (n = 70) were inserted in 232 patients with refractory benign esophageal strictures. The overall clinical success rate was 24.2% and according to stent type 14.1% for FC SEMS, 32.9% for BD stents and 27.1% for SEPS. Stent migration occurred in 24.6% of cases. The overall complication rate was 31.0%, including major (17.7%) and minor (13.4%) complications. A total of 643 patients were treated with self-expandable stents mainly for postsurgical leaks (64.5%), iatrogenic perforations (19.6%), Boerhaave's syndrome (7.8%) and fistulae (3.7%). FC SEMS and partially covered SEMS were used in the majority of patients. Successful closure of the defect was achieved in 76.8% of patients and according to etiology in 81.4% for postsurgical leaks, 86.0% for perforations and 64.7% for fistulae. The pooled stent migration rate was 16.5%. Stent-related complications occurred in 13.4% of patients, including major (7.8%) and minor (5.5%) complications.

CONCLUSION: The outcomes of stent placement for refractory benign esophageal strictures were poor. However, randomized trials are needed to put this into perspective. The evidence on successful stent placement for benign esophageal leaks, perforations

and fistulae is promising.

Key words: Self-expandable stents; Benign esophageal strictures; Esophageal perforation; Esophageal fistula; Anastomotic leak; Systematic review

Core tip: After a systematic search of the literature, we performed a pooled analysis on the clinical outcomes of self-expandable stent placement for benign esophageal diseases. We analyzed the clinical success, adverse events and removal outcome of stent placement in 232 patients with refractory benign esophageal strictures and 643 patients with benign esophageal leaks, perforations and fistulae. Additional analyses were performed for clinical outcomes according to stent type and etiology.

van Halsema EE, van Hooft JE. Clinical outcomes of self-expandable stent placement for benign esophageal diseases: A pooled analysis of the literature. *World J Gastrointest Endosc* 2015; 7(2): 135-153 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i2/135.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i2.135

INTRODUCTION

Esophageal self-expandable stent placement is a well-established, evidence-based treatment for the palliation of malignant dysphagia. By the end of the 90's self-expandable metal stents have replaced the traditional rigid plastic tubes, because of their superiority in safety and cost-effectiveness[1-6]. Ever since the stent designs have evolved in order to improve their efficacy, durability and safety, and to expand their use for different clinical indications.

Besides malignant indications, esophageal self-expandable stents are nowadays used for refractory benign strictures, benign perforations, postoperative anastomotic leaks and benign fistulae[1,7]. To define the heterogeneous group of patients with refractory benign esophageal strictures Kochman *et al*[8] have proposed a uniform definition that has been widely accepted. According to Kochman's criteria an esophageal stricture is refractory or recurrent when it cannot be remediated to a diameter of 14 mm over 5 dilatation sessions at 2-wk intervals, or when a satisfactory luminal diameter cannot be maintained for 4 wk once the target diameter of 14 mm has been achieved[8]. The definition only applies in the absence of active inflammation and neuromuscular dysfunction. In this subgroup of patients with refractory strictures self-expandable stent placement is performed to extend the dysphagia-free period and to reduce the number of dilatations (Figure 1A and B).

There is a varied offer of esophageal self-expandable stents, that can be divided into four main groups: (1) removable fully covered metal stents (FC SEMS); (2) removable partially covered metal stents (PC SEMS); (3) removable covered plastic stents (SEPS); and (4) biodegradable stents (BD stents). In this literature review we aim to provide an overview of the clinical outcomes of self-expandable stent placement for benign esophageal diseases including a by clinical indication and by stent design breakdown.

MATERIALS AND METHODS

The PubMed, Embase and Cochrane databases were searched for publications from January 2000 to July 2014. Key words that were used included esophagus, stent and benign. Articles were screened by title and abstract for their relevance. Studies were considered for inclusion when they reported on the clinical outcomes of esophageal self-expandable stent placement for benign strictures, benign perforations, anastomotic leaks and/or benign fistulae. The exclusion criteria and search results are shown in Figure 2. The primary endpoint was clinical success, which was defined as the absence of dysphagia at end of follow-up after single stent placement in case of esophageal strictures and successful closure of the defect after single or multiple stent placements in case of an esophageal leak, perforation or fistula. Clinical failures were defined as recurrent dysphagia in case of esophageal strictures and persistent leak or death during stent therapy in case of esophageal leaks, perforations and fistulae. Secondary endpoints were the technical success rates of esophageal stent placement, morbidity rates, mortality rates and stent removal outcome. Technical success was defined as stent placement across the lesion at the end of the procedure, including successful stent repositioning after immediate migration. Successful stent removal was defined as uneventful endoscopic stent extraction without the need for additional interventions or procedures. So stent removal by the stent-in-stent procedure, which is used to induce pressure-necrosis of granulation tissue to facilitate the removal of an embedded stent, was considered an adverse event.

Statistical analysis

This manuscript contains descriptive statistics. Data were pooled and presented as frequency and percentage, so no biostatistical tests were used.

RESULTS

Refractory benign esophageal strictures

After searching the literature no randomized controlled trials (RCTs) were found that studied the outcomes of stent placement for refractory benign esophageal strictures. Twelve prospective, nonrandomized studies were identified that reported on the outcomes of esophageal stent placement for benign strictures

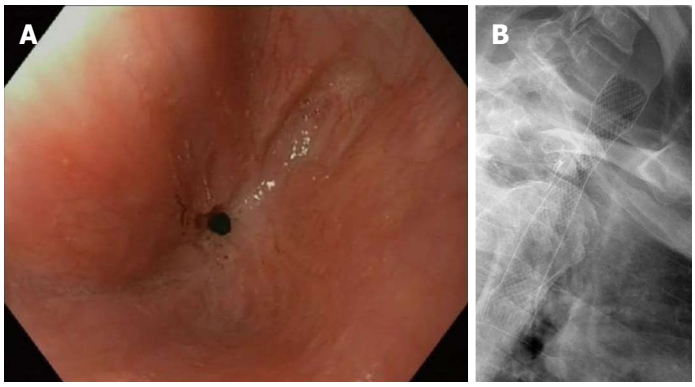

Figure 1 Refractory benign anastomotic stricture after esophagectomy (A) and fully covered self-expandable metal stent placement for a refractory benign esophageal anastomotic stricture (B).

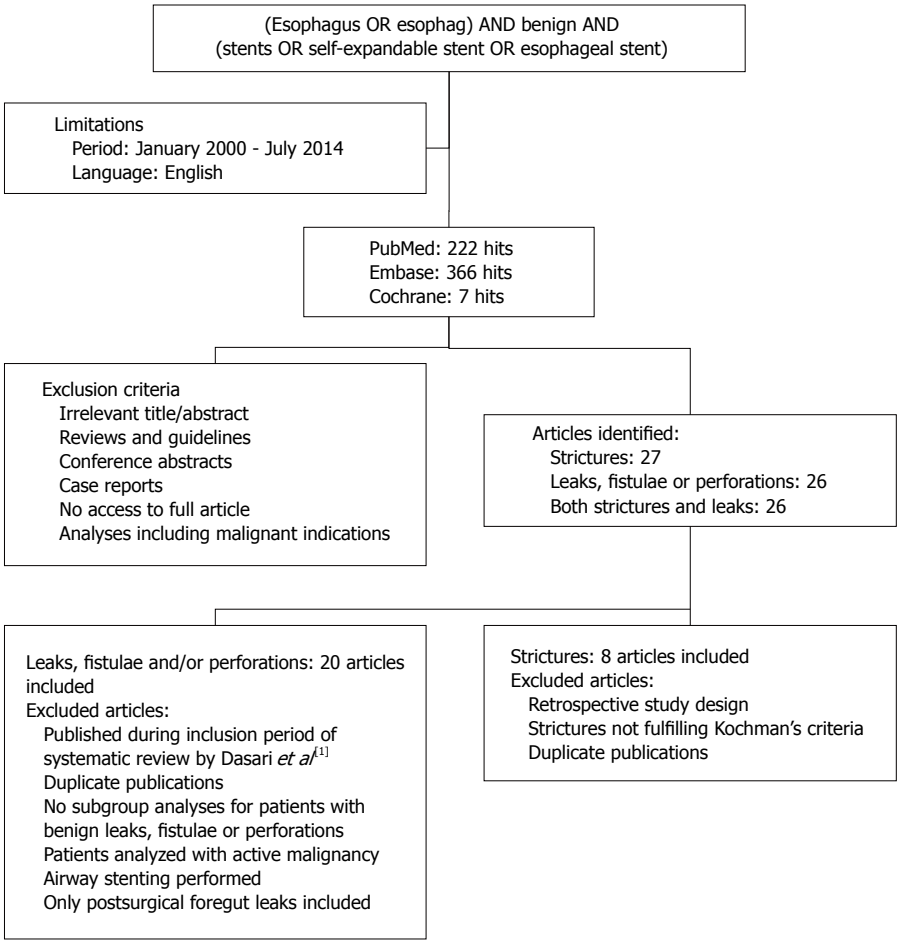

Figure 2 Literature search.

(Table 1)[9-20]. One was excluded because of a duplicate publication[20]. To create a homogeneous population only the studies were analyzed that included patients with refractory benign esophageal strictures according to Kochman's criteria[8]. A total of eight prospective cohort series were included that reported on 232 patients with refractory benign esophageal strictures[9-16]. In 85 patients a FC SEMS was placed, 77 patients received a BD stent and a SEPS was inserted in 70 patients. No PC SEMS were used in any of the included articles. The overall pooled technical success rate of esophageal stent placement was 98.7%. Details on stricture etiology, stent type and clinical outcomes are summarized in Table 2. Analyses by stricture etiology were not possible due to lacking data.

Clinical success: The overall clinical success rate after single stent placement was 24.2%. The clinical success rates per type of stent are presented in Table 2. The time to recurrence of dysphagia after failed stent therapy varied widely. Stricture recurrence after FC SEMS removal was reported by three studies after median periods ranging from 15 d to 1.7 mo[9,10,12]. Recurrence of dysphagia after SEPS removal was re-

Table 1 Literature on self-expandable stent placement for refractory benign esophageal strictures

Ref.	Study design	Patients, indications	Stent type, technical success rate, scheduled removal	Follow-up median (range)	Complications	Successful stent removal	Clinical success (dysphagia-free)
Prospective cohort studies including patients with RBES according to Kochman's criteria							
Chaput *et al*[9] 2013	Prospect	Patients with recurrent benign strictures after more than 3 dilatations to more than 15 mm during the previous 12 mo: *n* = 41 1 Anastomotic stricture: 29% (12/41) 2 Peptic stricture: 39% (16/41) 3 Caustic stricture: 7% (3/41) 4 Radiation stricture: 20% (8/41) 5 Others: 5% (2/41)	Standard FC SEMS: 100% (24/24) - 4 wk Multilayer silicone FC SEMS: 100% (17/17) - 3 mo	24 mo	Overall complications: Stent migration: 29.3% (12/41) Chest pain requiring stent removal or repositioning: 9.8% (4/41) Chest pain resolved with conservative management: 2.4% (1/41) Vomiting: 2.4% (1/41) Pneumonia: 2.4% (1/41)	FC SEMS: 100% (41/41)	Overall clinical success: 9.8% (4/41)
Canena *et al*[10] 2012	Prospect	Patients with RBES according to Kochman criteria: *n* = 30 1 Anastomotic stricture: 43% (13/30) 2 Peptic stricture: 23% (7/30) 3 Caustic stricture: 10% (3/10) 4 Radiation stricture: 7% (2/30) 5 Idiopathic stricture: 17% (5/30)	BD stent: 100% (10/10) SEPS: 100% (10/10) - 12 wk FC SEMS: 100% (10/10) - 12 wk	23.4 (8-66) mo	Patients with complications (P = 0.38): BD stent 50%, SEPS 70%, FC SEMS 60% Stent migration (P = 0.16): BD stent 20%, SEPS 60%, FC SEMS 30% Tissue hyperplasia (P = 0.09): BD stent 30%, SEPS 0%, FC SEMS 0% Associated with one major bleeding and recurrent dysphagia in two patients Minor complications in 17% (5/30) of patients: 1 Globus sensation: BD stent 0%, SEPS 0%, FC SEMS 10% 2 Moderate chest pain: BD stent 0%, SEPS 20%, FC SEMS 10% 3 Reflux: BD stent 0%, SEPS 10%, FC SEMS 10% Major complications in 7% (2/30) of patients: 1 Major bleeding: BD stent 10%, SEPS 0%, FC SEMS 0% 2 Severe chest pain: BD stent 10%, SEPS 0%, FC SEMS 0%	SEPS: 100% (10/10) FC SEMS: 100% (10/10)	Overall: 27% (8/30) Stent type (P = 0.27): 1 BD stent: 30% (3/10) 2 SEPS: 10% (1/10) 3 FC SEMS: 40% (4/10)
Hirdes *et al*[11] 2012	Prospect	Patients with RBES according to Kochman criteria: *n* = 28 1 Peptic stricture: 32% (9/28) 2 Anastomotic stricture: 25% (7/28) 3 Radiation stricture: 11% (3/28) 4 Caustic stricture: 7% (2/28) 5 Others: 11% (3/28) 6 Unknown origin: 14% (4/28)	Single BD stent: *n* = 15 Sequential BD stent: *n* = 13 Technical success: 100% (28/28) In total 59 BD stent placed	630 (21-1121) d	Stent migration: 10.7% (3/28) Food impaction: 10.7% (3/28) Major complications of 59 stent placements in 28 patients: 29% (8/28) of patients 1 Retrosternal pain and vomiting: 7.1% (2/28) 2 Retrosternal pain: 7.1% (2/28) 3 Bleeding: 7.1% (2/28) 4 Fever and vomiting: 3.6% (1/28) 5 Aspiration pneumonia: 3.6% (1/28) Minor complications of 59 stent placements in 28 patients: 14% (4/28) of patients 1 Retrosternal pain: 7.1% (2/28) 2 Reflux: 3.6% (1/28) 3 Vomiting: 3.6% (1/28) One patient (3.6%) died of aspiration pneumonia, relation to stent unclear	Not applicable	At 6 mo after: First stent: 25% (7/28) Second stent: 15% (2/13) Third stent: 0% (0/7)

Hirdes *et al*[12] 2012	Prospect	Patients with RBES according to Kochman criteria: *n* = 15 1 Peptic stricture: 40% (6/15) 2 Caustic stricture: 20% (3/15) 3 Radiation stricture: 13% (2/15) 4 Other: 7% (1/15) 5 Unknown cause: 20% (3/15)	FC SEMS: 100% (15/15) 109 d (87-222)	After stent removal: 86 (14-330) d	Stent migration: 33% (5/15) Tissue overgrowth: 20% (3/15) Major complications in 20% (3/15) of patients: 1 Severe pain requiring stent removal: 7% (1/15) 2 Severe persistent odynophagia: 7% (1/15) 3 Nausea/vomiting: 13% (2/15) 4 Aspiration pneumonia: 7% (1/15) Minor complications: 1 Pain: 20% (3/15)	93% (14/15) Stent-in-stent: 7%	0% (0/15)
Eloubeidi *et al*[13] 2011	Pro- and retrospect	Patients with benign esophageal lesions treated with Alimaxx-E stent: *n* = 35 Leaks/fistulae: *n* = 12 Perforations: *n* = 4 RBES: *n* = 19 1 Anastomotic stricture: 37% (7/19) 2 Peptic stricture: 21% (4/19) 3 Caustic stricture: 11% (2/19) 4 Radiation stricture: 11% (2/19) 5 Others: 21% (4/19)	FC SEMS: 100% (19/19) In situ for: 64 ± 74 d (range 6-300)	161 ± 111 (range 24-360) d	Stent migration: 36.8% (7/19) Minor complications in patients with RBES: 1 Stent infolding/invagination: 16% (3/19) 2 Chest pain: 5% (1/19) 3 Abdominal pain: 11% (2/19) 4 Globus sensation: 5% (1/19) 5 Fever: 5% (1/19) Major complications in patients with RBES: 1 Arrhythmia: 5% (1/19)	97% (34/35) Stent fracture: 3%	21% (4/19)
Van Boeckel *et al*[14] 2011	Prospect	Patients with RBES according to Kochman criteria: *n* = 38 1 Anastomotic stricture: 34% (13/38) 2 Peptic stricture: 18% (7/38) 3 Radiation stricture: 18% (7/38) 4 Caustic stricture: 16% (6/38) 5 Others: 11% (4/38) 6 Unknown etiology: 3% (1/38)	BD stent: 100% (18/18) SEPS: 95% (19/20) - 6 wk	BD stent: 166 (21-559) d SEPS: 385 (77-924) d	Major complications: 15.8% (6/38) 1 Hemorrhage: SEPS 5%, BD stent 11% 2 Perforation: SEPS 5%, BD stent 0% 3 Severe pain requiring opiates: SEPS 0%, BD stent 11% Minor complications: 10.5% (4/38) 1 Reflux: SEPS 0%, BD stent 6% 2 Nausea/vomiting: SEPS 5%, BD stent 11% Stent migration: SEPS 25% (5/20), BD stent 22% (4/18) Food impaction: SEPS 0%, BD stent 11% (2/18) Tissue in-/overgrowth: SEPS 0%, BD stent 11% (2/18) A FC SEMS was placed in both patients	SEPS: 100% (16/16)	Stent type (*P* = 0.83): 1 SEPS: 30% (6/20) 2 BD stent: 33% (6/18)
Repici *et al*[15] 2010	Prospect	Patients with RBES according to Kochman criteria: *n* = 21 1 Peptic stricture: 33% (7/21) 2 Anastomotic stricture: 24% (5/21) 3 Radiation stricture: 24% (5/21) 4 Caustic stricture: 10% (2/21) 5 Other: 5% (1/21) 6 Idiopathic stricture: 5% (1/21)	BD stent: 100% (21/21)	53 (25-88) wk	Stent migration: 9.5% (2/21) Severe thoracic pain requiring analgesics: 14.3% (3/21) Minor bleeding: 4.8% (1/21) Dysphagia caused by hyperplastic tissue: 4.8% (1/21)	Not applicable	45% (9/20)
Dua *et al*[16] 2008	Prospect	Patients with RBES according to Kochman criteria: *n* = 40 1 Anastomotic stricture: 30% (12/40) 2 Caustic stricture: 20% (8/40) 3 Radiation stricture: 18% (7/40) 4 Peptic stricture: 5% (2/40) 5 Others: 28% (11/40)	SEPS: 95% (38/40) 4 wk	53 (11-156) wk	Stent migration: 22.2% (8/36) Severe chest pain requiring medication: 11.1% (4/36) Fistula: 2.8% (1/36) Perforation: 5.6% (2/36) Gastroesophageal reflux: 5.6% (2/36) Bleeding: 8.3% (3/36) Stent-related mortality: 2.8% (1/36) Massive bleeding probably due to stent eroding into major vessel	94% (31/33) Inability to remove stent: 6% (2/33)	30% (12/40)
Remaining prospective cohort studies							

Van Hooft *et al*[17] 2011	Prospect	Patients with an esophagogastric anastomotic stricture who did not have had any endoscopic treatment: n = 10	BD stent: 100% (10/10)	6 mo	Food impaction: 10% (1/10) Hyperplasia-induced obstruction: 20% (2/10)	Not applicable	60% (6/10)
Evrard *et al*[18] 2004	Prospect	SEMS-induced stricture: n = 5 Esophagocolonic anastomotic stricture: n = 4 Refractory benign strictures after a median of 6 (range 1-12) dilation sessions per year: n = 8 Anastomotic leak: n = 4	SEPS: 100% (21/21) Range 2 d–18 mo	After stent removal: 21 (8-39) mo	Stent migration: 57.1% (12/21) Stridor due to tracheal compression: 4.8% (1/21) Inflammatory epiglottic stenosis: 4.8% (1/21)	100% (21/21)	76% (13/17)
Repici *et al*[19] 2004	Prospect	Patients with persisting benign esophageal strictures after at least 6 dilation sessions: n = 15 1 Caustic stricture: 33% 2 Anastomotic stricture: 27% 3 Radiation stricture: 27%	SEPS: 100% (15/15) 6 wk	Mean: 22.7 (19-27) mo	Severe chest pain requiring analgesics: 33% (5/15) Mild/moderate mucosal hyperproliferation: 27% (4/15) Stent migration: 7% (1/15)	100% (15/15)	80% (12/15)

RBES: Refractory benign esophageal strictures; SEPS: Self-expandable plastic stent; BD stent: Biodegradable stent; FC SEMS: Fully covered self-expandable metal stent.

ported by one study after a mean of 4 (range 2-9) wk[10]. After BD stent placement dysphagia recurred after mean periods ranging from 4 wk to 19 wk[10,15].

Stent migration, reactive tissue formation and food impaction: The overall pooled stent migration rate was 24.6% (57/232). By stent type migration rates were 31.8% (27/85) for FC SEMS, 14.3% (11/77) for BD stents and 27.1% (19/70) for SEPS.

Tissue hyperplasia was reported in 4.3% (10/232) of patients, causing recurrent dysphagia in 5 patients (2.2%) who all had received a BD stent. Hyperplastic tissue growth according to stent type was 3.5% (3/85) for FC SEMS, 7.8% (6/77) for BD stents and 1.4% (1/70) for SEPS. Food impaction was reported in 2.2% (5/232) of patients and occurred only in patients with a BD stent (6.5%, 5/77).

Adverse events: Excluding stent migration, reactive tissue formation and food impaction which were analyzed separately, 72 (31.0%) patients suffered a total of 77 complications due to stent placement. Major complications were reported in 17.7% of patients and minor complications in 13.4%. Major and minor complication rates per stent design are presented in Table 3. There was one (0.4%) stent-related death from a massive bleeding probably due to SEPS erosion into a major vessel[16]. Another patient with a BD stent died of aspiration pneumonia, which may have been caused by stricture recurrence[11].

Stent removal: Removal of SEPS or FC SEMS was scheduled after 4 to 12 wk and BD stents were left in place to dissolve. Stent removal was attempted in 92.9% (144/155) of patients with a SEPS or FC SEMS. Successful stent removal was achieved in 97.2% (140/144) of patients; FC SEMS (97.6%, 83/85) and SEPS (96.6%, 57/59). Two SEPS were removed during surgery, because one migrated SEPS could not be pulled through the ileocecal valve in a patient with a colon – ileocecal valve – terminal ileum interposition, and one was partially embedded by granulation tissue above the stent[16]. One FC SEMS had to be removed by a stent-in-stent procedure due to severe reactive tissue growth through the disrupted cover of the stent[12]. Another FC SEMS fractured during removal and was retrieved in two pieces[13].

Benign esophageal leaks, perforations and fistulae

The literature search revealed a recently published systematic review that analyzed the clinical outcomes of self-expandable stent placement for benign esophageal leaks and perforations in the literature published from 1990 to 2012[1]. Therefore, the studies published after the systematic review of Dasari *et al*[1] were considered for analysis. No RCTs that focused on the outcomes of stent placement for benign esophageal leaks, perforations or fistulae were identified. A total of 28 studies were selected from the literature, but after more careful reading of the articles eight more studies were excluded because they analyzed patients with active malig-

Table 2 Pooled analysis of 232 patients with refractory benign esophageal strictures according to Kochman's criteria treated with self-expandable stent placement *n* (%)

Stricture etiology	
Anastomotic strictures	69 (29.7)
Peptic strictures	58 (25.0)
Radiation strictures	36 (15.5)
Caustic strictures	29 (12.5)
Others	26 (11.2)
Unknown	14 (6.0)
Stent type	
FC SEMS	85 (36.6)
BD stent	77 (33.2)
SEPS	70 (30.2)
PC SEMS	0 (0)
Technical success	
Overall	229 (98.7)
FC SEMS	85 (100)
BD stent	77 (100)
SEPS	67 (95.7)
Clinical success	
Overall (*n* = 231)	56 (24.2)
FC SEMS (*n* = 85)	12 (14.1)
BD stent (*n* = 76)	25 (32.9)
SEPS (*n* = 70)	19 (27.1)

FC SEMS: Fully covered self-expandable metal stent; BD stent: Biodegradable stent; SEPS: Self-expandable plastic stent; PC SEMS: Partially covered self-expandable metal stent.

nancy[21], performed a double stent strategy including airway stenting[22-24], included only postsurgical foregut leaks[25], did not perform subgroup analyses for patients with benign esophageal leaks, perforations or fistulae[26,27], or because of duplicate publication[28]. Ultimately, 20 studies were included for analysis, all with a retrospective study design (Table 4)[13,29-47]. A total of 643 patients with benign esophageal leaks, perforations and fistulae were considered for analysis. A total of 852 stents were inserted in 573 patients. In the remaining 70 patients the number of stents used was not reported. The main indications for self-expandable stent placement were postsurgical leaks (64.5%), iatrogenic perforations (19.6%), Boerhaave's syndrome (7.8%) and fistulae (3.7%). The majority of inserted stents were FC SEMS (41.0%) and PC SEMS (37.7%). Stent placement was technically successful in 99.9% of cases. Further details are summarized in Table 5. Data on concurrent drainage of fluid collections were available for 425 patients, of whom 57.4% (244/425) underwent drainage procedures.

Clinical success: The overall clinical success rate of esophageal stent placement for benign leaks, perforations and fistulae was 76.8% (480/625). Subgroup analysis according to etiology was possible for 358 patients. The highest clinical success rate was achieved in patients with perforations (86.0%), followed by postsurgical leaks (81.4%) and fistulae (64.7%) (Table 5). When solely FC SEMS were used, clinical success was achieved in 73.0% (135/185) of patients. Solely PC SEMS were used in two studies with a pooled clinical success rate of 78.2% (68/87). Only one study focused on the outcomes of SEPS placement and reported clinical success in 90% (27/30) of patients with anastomotic leaks.

Table 3 Pooled analysis of adverse events in patients with refractory benign esophageal strictures *n* (%)

Overall complications	72 (31.0)
Overall major complications	41 (17.7)
FC SEMS (*n* = 85)	9 (10.6)[1]
Severe retrosternal pain	5 (5.9)
Severe nausea and vomiting	2 (2.4)
Aspiration pneumonia	2 (2.4)
Arrhythmia	1 (1.2)
Percutaneous endoscopic gastrostomy because of impaired intake caused by severe, persistent odynophagia	1 (1.2)
BD stents (*n* = 77)	22 (28.6)[1]
Severe retrosternal pain	10 (13.0)
Hyperplasia-induced stenosis	5 (6.5)
Bleeding, hematemesis	5 (6.5)
Severe nausea and vomiting	3 (3.9)
Aspiration pneumonia	1 (1.3)
SEPS (*n* = 70)	10 (14.3)
Severe retrosternal pain	4 (5.7)
Perforation	3 (4.3)
Bleeding, hematemesis[2]	2 (2.9)
Stent-induced fistula	1 (1.4)
Overall minor complications	31 (13.4)
FC SEMS (*n* = 85)	15 (17.6)[1]
Retrosternal pain	6 (7.1)
Stent infolding/invagination	3 (3.5)
Abdominal pain	2 (2.4)
Globus sensation	2 (2.4)
Reflux symptoms	1 (1.2)
Vomiting	1 (1.2)
Fever	1 (1.2)
BD stents (*n* = 77)	8 (10.4)
Nausea and vomiting	3 (3.9)
Retrosternal pain	2 (2.6)
Reflux symptoms	2 (2.6)
Minor bleeding	1 (1.3)
SEPS (*n* = 70)	8 (11.4)
Reflux symptoms	3 (4.3)
Retrosternal pain	2 (2.9)
Minor bleeding	2 (2.9)
Nausea and vomiting	1 (1.4)

[1]Patients can have more than one complication; [2]Including one stent-related death from massive bleeding. FC SEMS: Fully covered self-expandable metal stent; BD stent: Biodegradable stent; SEPS: Self-expandable plastic stent; PC SEMS: Partially covered self-expandable metal stent.

Stent migration, reactive tissue formation and food impaction: Stent migration could be analyzed in 320 patients who received a total of 468 self-expandable stents. The overall pooled stent migration rate was 16.5% (77/468). By stent type migration rates were 21.8% (53/243) for FC SEMS and 10.6% (23/218) for PC SEMS. Data were insufficient to analyze the stent migration rate of SEPS.

Pooled analysis of tissue hyperplasia was possible for 384 patients in whom 530 stents were inserted.

Table 4 Literature on self-expandable stent placement for benign esophageal leaks, perforations and fistulae

Ref.	Study design	Patients	Stent type, technical success (%) and time to removal	Additional sepsis-related procedures, follow-up	Complications and mortality	Successful stent removal	Clinical success
Dua *et al*[29] 2014	Pro- and retrospect	Patients treated with a non-foreshortening FC SEMS for benign esophageal leaks: *n* = 6 1 Postsurgical leaks: *n* = 5 2 Esophagopericardial fistula: *n* = 1 Single stent: 83% (5/6) Multiple stents: 17% (1/6)	FC SEMS: 100% (7/7) Median time to removal: 50 (49-56) d	Unknown FU: unknown	Minor complications: Pneumoperitoneum during endoscopy secondary to air insufflation: 17% (1/6) Stent migration: 17% (1/7) Mortality rate: 33.3% (2/6) - cerebral embolism: 16.7% (1/6) - sepsis-related: 16.7% (1/6)	FC SEMS: 100% (4/4)	Overall: 67% (4/6) -Postsurgical leaks: 80% (4/5) -Fistula: 0% (0/1)
El Hajj *et al*[30] 2014	Retrospect	Patients with attempted stent placement for esophageal leaks, fistulae and perforations: 1 Postsurgical leaks: *n* = 29 Single stent: 72% (21/29) Multiple stents: 28% (8/29) Excluded from analysis because patients were included with active malignancy: 1 Perforations: *n* = 10 2 Fistulae: *n* = 15	PC SEMS: 100% (19/19) - 4 to 6 wk FC SEMS: 100% (30/30) - 6 to 8 wk SEPS: 100% (15/15) - 6 to 8 wk	Not analyzed for subgroup of patients with anastomotic leaks ≥ 3 mo FU: 100%	No subgroup analysis for patients with esophageal leaks 1 Chest pain 2 GI Bleed 3 Pneumothorax 4 Increase size of leak during deployment 5 Breakage of stent 6 Dysphagia 7 Aspiration pneumonia Stent migration not analyzed for subgroup of patients with esophageal leaks Mortality rate: 0% (0/29)	No subgroup analysis for patients with postsurgical leaks -Stent-in-stent procedure: 2 -Breakage of stent: 1	Overall: 82.8% (24/29) -Primary closure rate: 72% (21/29) -Secondary closure rate: 38% (3/8)
Freeman *et al*[31] 2014	Retrospect	Patients with intrathoracic leak after surgical repair of an acute iatrogenic esophageal perforation: *n* = 29 Single stent: 100% (29/29)	SEPS: 100% (24/24) FC SEMS: 100% (5/5) Mean time to removal: 22 (13-41) d	PEG: 10.3% (3/29) Thoracoscopic decortication: 10.3% (3/29) Jejunostomy: 3.4% (1/29) Median FU: 6 wk	No stent-related complications. Stent migration: 17.2% (5/29) - not analyzed according to stent type Mortality rate: 0% (0/29)	100% (25/25) Not analyzed according to stent type	86.2% (25/29)
Gubler *et al*[32] 2014	Retrospect	Patients with benign (gastro)esophageal leaks, fistulae or perforations: *n* = 85 1 Iatrogenic perforations: *n* = 32 2 Anastomotic leaks: *n* = 31 3 Fistulae: *n* = 7 4 Boerhaave: *n* = 7 5 Other perforations: *n* = 8 Single stent: 78% (66/85) Multiple stents: 22% (19/85)	Total SEMS: *n* = 113 PC SEMS: *n* = 72 FC SEMS: *n* = 28 Unknown: *n* = 13 Technical success: 100% Average time to removal: 15 (1-111) d	Percutaneous/ thoracoscopic drainage: 55.3% (47/85) OTSC: 2.4% (2/85) Vacuum-therapy: 2.4% (2/85) FU: at least 4 wk after stent removal	Stent migration: 8.8% (10/113) - not analyzed according to stent type Food bolus obstruction: 0.9% (1/113) - not analyzed according to stent type Mortality rate: 9.4% (8/85) 1 Unrelated to in situ stent: 3.5% (3/85) 2 Multi-organ failure: 2.4% (2/85) 3 Acute respiratory distress syndrome: 1.2% (1/85) 4 Heart insufficiency: 1.2% (1/85) 5 Aortic dissection: 1.2% (1/85)	98.2% (107/109) - Irremovable: 2 - Spontaneous passage after migration: 1 Not analyzed according to stent type	Overall: 79% (67/85) -Postsurgical leaks: 74% (23/31) -Fistulae: 43% (3/7) -Iatrogenic: 94% (30/32) -Boerhaave: 71% (5/7) -Others: 75% (6/8) PC SEMS: 68% (49/72) FC SEMS: 54% (15/28)

Orive-Calzada *et al*[33] 2014	Pro- and retrospect	Patients treated with FC SEMS for benign upper gastrointestinal fistulae and perforations: *n* = 56 1 Postsurgical leaks: *n* = 44 2 Iatrogenic perforations: *n* = 6 3 Boerhaave syndrome: *n* = 4 4 Other perforations: *n* = 2 Single stent: 59% (33/56) Multiple stents: 41% (23/56)	FC SEMS: 100% (87/87) PC SEMS: 100% (1/1) Median time to removal: 42 (9-1460) d	Surgical drainage: 30% (17/56) Percutaneous drainage: 41% (23/56) FU: unknown	Minor complications: Atrial fibrillation: 1.8% (1/56) Major complications: Stent-related perforation: 5.4% (3/56) Stent migration: 20.5% (18/88) - FC SEMS: 20.7 (18/87) - PC SEMS: 0% (0/1) Mortality rate: 16% (9/56) - cerebrovascular accident: 1.8% (1/56) - nosocomial pneumonia: 1.8% (1/56) - neoplasia: 1.8% (1/56) - secondary to sepsis: 10.7% (6/56)	FC SEMS: 100% (87/87) PC SEMS: 0/1 -Stent-in-stent procedure: 1	Overall: 79% (44/56) -Postsurgical leaks: 78% (36/46) -Perforations: 80% (8/10)
Persson *et al*[34] 2014	Retrospect	Patients with benign spontaneous, iatrogenic or traumatic esophageal perforations: *n* = 40 1 Iatrogenic perforation: *n* = 16 2 Boerhaave syndrome: *n* = 23 3 Other perforations: *n* = 1 Single stent: missing Multiple stents: missing	Total No. of stents missing Stent type missing Time to removal: 4-6 wk	Unknown FU: unknown	No stent-related complications Stent migration not analyzed according to stent type Mortality rate: 7.5% (3/40) 1 Multi-organ failure: 5% (2/40) 2 Respiratory insufficiency without sepsis: 2.5% (1/40)	Stent type and no. of stents removed missing -Removal during second procedure: 1	82.5% (33/40) No subgroup analysis according to etiology
Sharaiha *et al*[35] 2014	Retrospect	Patients treated with stent placement for benign upper GI leaks: *n* = 18 1 Postsurgical leaks: *n* = 12 2 Iatrogenic perforation: *n* = 1 3Other fistulae: *n* = 5 Single stent: 28% (5/18) Multiple stents: 72% (13/18)	Total stents: *n* = 47 1 FC SEMS 2 PC SEMS 3 SEPS 4 Uncovered Technical success: 100% Mean time to removal: 54 (18-118) d	Clip/endoloop: 27.8% (5/18) Dilation: 33.3% (6/18) Surgery: 16.7% (3/18) FU: median 283 d (IQR 38-762)	Overall 9 complications in 5 patients 5 minor complications in 4 patients: - reflux/esophagitis: 16.7% (3/18) - abdominal pain: 5.6% (1/18) - collapsed stent: 5.6% (1/18) 4 Major complications in 3 patients: - aspiration pneumonia: 11.1% (2/18) - perforation: 5.6% (1/18) - stricture: 5.6% (1/18) Tissue hyperplasia: 5.6% (1/47) - stent type unknown Food impaction/bezoar: 11.1% (2/47) - stent type unknown Stent migration not analyzed for subgroup of patients with esophageal leaks Overall mortality rate: 5.6% (1/18) Not specified	No subgroup analysis for patients with benign leaks -Stent-in-stent procedure: 7 -Irremovable uncovered stent: 1	Overall: 47% (7/15) -Postsurgical leaks: (5/11) -Fistula: 67% (2/3) -Iatrogenic: 0% (0/1)
Shim *et al*[36] 2014	Retrospect	Patients who underwent endoscopic treatment for anastomotic leakage after total gastrectomy: *n* = 27 1 FC SEMS: *n* = 13 2 Non stent therapy: *n* = 14 Single stent: 85% (11/13) Multiple stents: 15% (2/13)	FC SEMS: 100% (15/15) PC SEMS: 100% (1/1) Median time to removal: 38 (0-69) d	Concurrent fluid drainage: 61.5% (8/13) FU: unknown	Minor complication: Stent malposition: 6.3% (1/13) Stent migration: 25% (4/16) - FC SEMS: 26.7% (4/15) - PC SEMS: 0% (0/1) Tissue in- or overgrowth: 6.3% (1/16) - FC SEMS: 6.7% (1/15) Mortality rate: 15.4% (2/13) - sepsis related: 7.7% (1/13) - non-stent related bleeding: 7.7% (1/13)	FC SEMS: 100% (11/11) PC SEMS: 100% (1/1)	Overall: 67% (8/12) -Primary closure rate: 67% (8/12) -Secondary closure rate: 0% (0/4)

Brangewitz *et al*[37] 2013	Retrospect	Patients with esophageal defects treated with stent placement: *n* = 39 1 Postsurgical leaks: *n* = 31 2 Iatrogenic perforations: *n* = 6 3 Boerhaave syndrome: *n* = 2 Single stent: 100% (39/39)	FC SEMS: 100% (39/39) Median time to removal: 33 (9-132) d	Unknown FU: unknown	Minor complications: - stent-related ulcers: 12.8% (5/39) Major complications: - severe bleed at upper end of stent: 2.6% (1/39) - death due to esophageal necrosis at proximal end of stent: 2.6% (1/39) Stent migration: 15.4% (6/39) Mortality rate: 25.6% (10/39) - esophageal necrosis at proximal stent end: 2.6% (1/39) - not specified: 23.1% (9/39)	FC SEMS: 90.3% (28/31) -Self-limiting bleed: 2 -Migrated stent requiring surgical removal: 1	53.8% (21/39) No subgroup analysis according to etiology
Leenders *et al*[38] 2013	Retrospect	Patients with anastomotic leakage after esophageal resection or bariatric surgery: *n* = 26 Single stent: 81% (21/26) Multiple stents: 19% (5/26)	FC SEMS: 100% (31/31) PC SEMS: 100% (2/2) Mean time to removal: 11 (1-63) wk	Unknown FU: range 2-144 wk	Minor complications: - stent disintegration all with FC SEMS: 11.5% (3/26) Major complications: - stent-related perforation with FC SEMS: 3.8% (1/26) Stent migration: 24.2% (8/33) - FC SEMS: 25.8% (8/31) Tissue ingrowth: 6.1% (2/33) - PC SEMS: 100% (2/2) Mortality rate: 19.2% (5/26) - sepsis-related: 19.2% (5/26)	FC SEMS: 100% (26/26) PC SEMS: 0% (0/2) -Traumatic removal due to tissue ingrowth: 2	80.8% (21/26)
Wilson *et al*[39] 2013	Retrospect	Patients treated with FC SEMS placement for benign esophagogastric diseases: *n* = 33 1 Perforation: *n* = 7 2 Anastomotic leak: *n* = 14 3 Sleeve gastrectomy leak: *n* = 6 4 Fistula: *n* = 6 Single stent: missing Multiple stents: missing	FC SEMS: 100% (40/40) Average time to removal: 47 d	Drainage procedure: 66.7% (22/33) VATS/open: 36.4% (12/33) Tube thoracostomy: 21.2% (7/33) Percutaneous: 9.1% (3/33) FU: unknown	Major complications: - severe hemorrhage from aorta-esophageal fistula: 3.0% (1/33) No subgroup analysis for patients with esophageal leaks, fistulae and perforations: - stent migration - food impaction Mortality rate: 0% (0/33)	No subgroup analysis for patients with esophageal leaks, fistulae and perforations -Stent fracture: 2	94% (31/33) avoided open repair -Postsurgical leaks: 95% (19/20) -Perforations: 86% (6/7) -Fistulae: 100% (6/6)
Van Boeckel *et al*[40] 2012	Retrospect	Patients treated with a SEMS or SEPS for sealing a benign esophageal rupture or anastomotic leak: *n* = 52 1 Anastomotic leak: *n* = 32 2 Iatrogenic perforation: *n* = 13 3 Boerhaave syndrome: *n* = 4 4 Others: *n* = 3 Single stent: missing Multiple stents: missing	PC SEMS: 98% (60/61) FC SEMS: 100% (15/15) SEPS: 100% (7/7) Median time to removal: 25 (1-197) d	Concurrent fluid drainage: 46.2% (24/52) Median FU: 470 (25-1200) d	Major complications: Severe retrosternal pain: 3.8% (2/52) - all PC SEMS Hemorrhage: 3.8% (2/52) - FC SEMS: stent-related death 1.9% (1/52) - PC SEMS: required adrenaline injections: 1.9% (1/52) Ruptured stent cover: 7.2% (6/83) - PC SEMS: 9.8% (6/61) Tissue in-/overgrowth: 9.6% (8/83) - PC SEMS: 13.1% (8/61) Stent migration: 12.0% (10/83) - FC SEMS: 20% (3/15) - PC SEMS: 10% (6/61)	88.7% (63/71) Tissue in- and/or overgrowth at removal of 8 PC SEMS -Stent-in-stent procedure: 4 -Esophageal rupture: 2 -Second endoscopic procedure: 1 -Esophagectomy: 1 Not analyzed according to stent type	65.4% (34/52) *No subgroup analysis according to etiology* PC SEMS: 69% FC SEMS: 56% SEPS: 71%

					- SEPS: 14% (1/7) Food obstruction: 3.6% (3/83) - PC SEMS: 4.9% (3/61) Mortality rate: 13.5% (7/52) - severe stent-related hemorrhage: 1.9% (1/52) - sepsis related: 7.7% (4/52) - malignancy: 1.9% (1/52) - active euthanasia: 1.9% (1/52)		
Buscaglia *et al*[41] 2011	Retrospect	Patients treated for benign esophageal conditions by FC SEMS placement: - fistula or leak: *n* = 15 Single stent: 67% (10/15) Multiple stents: 33% (5/15)	FC SEMS: 100% (24/24) Median time to removal: 42.5 (3-122) d	Unknown FU: unknown	Stent migration: 33.3% (8/24) Further complications not analyzed for subgroup of patients with fistulae and leaks - chest pain - globus sensation Mortality rate: 6.7% (1/15) - paraspinal abscess related to persistent fistula	No subgroup analysis for patients with esophageal leaks and fistulae -Removal during surgery: 1 -Stent-in-stent procedure: 1	79% (11/14) No subgroup analysis according to etiology
Dai *et al*[42] 2011	Retrospect	Patients treated with SEPS for: - postoperative esophageal anastomotic leaks: *n* = 30 Single stent: missing Multiple stents: missing Excluded from analysis because patients were included with active malignancy: - esophageal perforations: *n* = 6 - fistulae: *n* = 5	Total no. of SEPS missing Technical success: 100% Mean time to stent removal: 30 (7-62) d	Interventional drainage: 40% (12/30) Tracheotomy: 43% (13/30) Mean FU: 12.8 (1-61) mo	Major complications: - stent dislocation and inability to place new stent requiring rethoracotomy: 3.3% (1/30) Stent migration not analyzed for subgroup of patients with esophageal leaks Mortality rate: (2/30) - persistent sepsis and multi-organ failure: 6.7% (2/30)	No. of removed stents missing One migrated stent in a patient with an esophago-colonic anastomotic leak could not be removed	90% (27/30)
David *et al*[43] 2011	Pro- and retrospect	Patients treated with SEMS for esophageal or gastric perforation and intrathoracic contamination: *n* = 30 - postsurgical leak: *n* = 13 - boerhaave syndrome: *n* = 6 - iatrogenic perforation: *n* = 6 - fistulae: *n* = 4 - other perforation: *n* = 1 Single stent: 50% (15/30) Multiple stents: 50% (15/30)	At least 62 stents - FC SEMS - PC SEMS Technical success: 100% Average duration of stenting: 29 d	Chest tube thoracostomy: - Alone: 23.3% (7/30) - Additional intervention: 76.7% (23/30) Pleural decortication: 56.7% (17/30) Muscle-flap reinforcement: 36.7% (11/30) Average FU: 8.1 mo	Minor complications: - pain: 6.7% (2/30) - hiccups: 3.3% (1/30) - nausea: 3.3% (1/30) Major complications: - bowel obstruction: 6.7% (2/30) - erosion: 3.3% (1/30) - left atrial compression: 3.3% (1/30) Stent migration: 6.7% (2/30) - not analyzed according to stent type Mortality rate: 10% (3/30) - multi-organ failure: 3.3% (1/30) - multiple emboli caused by esophago-atrial fistula: 3.3% (1/30) - aspiration during contrast study: 3.3% (1/30)	No. of removed stents missing Not analyzed according to stent type	76.7% (23/30) No subgroup analysis according to etiology

Eloubeidi *et al*[13] 2011	Pro- and retrospect	Patients with benign esophageal lesions treated with Alimaxx-E stent: *n* = 16 - postsurgical leaks: *n* = 11 - fistula: *n* = 1 - iatrogenic perforations: *n* = 3 - other: *n* = 1 Single stent: 81% (13/16) Multiple stents: 19% (3/16)	FC SEMS: 100% (16/16) In situ for: 51 ± 45 d (range 9-163)	Dilation: 6.3% (1/16) PEG placement: 6.3% (1/16) FU: unknown	Minor complications: 1 Stent infolding/invagination: 6.3% (1/16) 2 Chest pain: 6.3% (1/16) 3 Dysphagia: 6.3% (1/16) 4 Globus sensation: 6.3% (1/16) Major complications: 1 Respiratory compromise: 6.3% (1/16) 2 Aspiration pneumonia: 12.5% (2/16) Stent migration: 31.3% (5/16) Mortality rate: 0% (0/16)	FC SEMS: 100% (16/16) One stent was retrieved in two pieces	43.8% (7/16) *No subgroup analysis according to etiology*
Freeman *et al*[44] 2011	Unknown	Hospitalized patients with an anastomotic leak after esophagectomy: *n* = 17 Single stent: 100% (17/17)	SEPS: 100% (14/14) FC SEMS: 100% (3/3) Mean time to removal: 17 (12-27) d	VATS pleural drainage: 29.4% (5/17) Pharyngostomy: 5.9% (1/17) Tube jenunostomy: 5.9% (1/17) FU: at least 3 mo after stent removal	No complications associated with stent placement or removal Stent migration: 17.6% (3/17) - not analyzed according to stent type Mortality rate: 0% (0/17)	SEPS: 100% (14/14) FC SEMS: 100% (3/3)	94% (16/17)
Nguyen *et al*[45] 2011	Retrospect	Patients who developed postoperative leaks after minimally invasive esophagectomy: *n* = 18 - conventional treatment: *n* = 9 - FC SEMS placement: *n* = 9 Single stent: 100% (9/9)	FC SEMS: 100% (9/9) Removal after 6 wk	Percutaneous drainage: 22% (2/9) Tracheostomy: 11% (1/9) FU: unknown	No stent-related complications Mortality rate: 0% (0/9)	FC SEMS: 100% (9/9)	100% (9/9)
Schweigert *et al*[46] 2011	Retrospect	Patients treated with stent placement for intrathoracic leak after esophagectomy: *n* = 12 Single stent: 100% (12/12)	PC SEMS: 100% (12/12) Median time to removal: 48 (16-99) d	Tube thoracostomy: 100% (12/12) FU: unknown	Major complications: 1 Death by hemorrhage from stent-related erosion into the aorta: 8.3% (1/12) 2 Stent-related fistula after removal: 8.3% (1/12) Stent migration: *n* = missing Mucosal hyperproliferation: *n* = missing Mortality rate: 16.7% (2/12) 1 Stent-related death by hemorrhage: 8.3% (1/12) 2 Pulmonary aspiration after stent removal and successful healing of the leak: 8.3% (1/12)	PC SEMS: 100% (10/10)	81.8% (9/11)
Swinnen *et al*[47] 2011	Retrospect	Patient treated with PC SEMS placement for benign upper GI leaks or perforations: *n* = 88 - postsurgical leaks: *n* = 65 - boerhaave syndrome: *n* = 4 - iatrogenic perforation: *n* = 14 - other perforations: *n* = 5	PC SEMS: 100% (153/153) Median time to removal for 33 PC SEMS: 23 d Median time to removal for 99 PC SEMS: 69 d	Drainage of collections: 47.7% (42/88) - Surgical: 26.1% (23/88) - Percutaneous: 15.9% (14/88) - Endoscopic: 5.7% (5/88)	Minor complications: - transient stent-related dysphagia: 11.4% (10/88) Major complications: - bleeding requiring intervention: 5.7% (5/88) - stent-related perforation: 1.1% (1/88)	PC SEMS: 24.4% (33/135) Stent-in-stent procedure: 73.3% (99/135) Removal during surgery: 2.2% (3/135)	77.6% (59/76) No subgroup analysis according to etiology

Single stent: 58% (51/88) Multiple stents: 42% (37/88)	Follow-up after removal: 3 mo: 83% 7 mo: 81% 1 yr: 72%	- tracheal compression: 1.1% (1/88) - dysphagia due to tissue hyperplasia: 18.2% (16/88); PC SEMS: 10.5% (16/153) Stent migration: 11.1% (17/153) of PC SEMS mortality rate: 10.2% (9/88) 1 Sepsis related: 3.4% (3/88) 2 Pulmonary embolism: 1.1% (1/88) 3 Full-blown AIDS: 1.1% (1/88) 4 Cardiac disease: 1.1% (1/88) Three additional deaths during first 3 mo after treatment: 1 Sepsis after surgery: 1.1% (1/88) 2 Tension pneumothorax: 1.1% (1/88) 3 Pneumonia: 1.1% (1/88)

FC SEMS: Fully covered self-expandable metal stent; FU: Follow-up; PC SEMS: Partially covered self-expandable metal stent; SEPS: Self-expandable plastic stent; VATS: Video-assisted thoracic surgery; PEG: Percutaneous endoscopic gastrostomy; OTSC: Over-the-scope-clips; IQR: Interquartile range.

Tissue hyperplasia was directly reported or deduced out of context (*e.g.*, stent-in-stent procedure for removal) in 111 cases (28.9% of patients and 20.9% of stents). The rate of reactive tissue formation according to stent type was 0.4% (1/267) for FC SEMS, 50.5% (110/218) for PC SEMS and 0% (0/45) for SEPS.

Of the 812 stents that were inserted in 540 patients, food impaction was reported in 6 cases (1.1% of patients and 0.7% of stents). Data were insufficient to analyze food impaction according to type of stent.

Adverse events and mortality: Two studies including 44 patients and 88 stent placements could not be analyzed because of missing subgroup analyses for patients with benign esophageal leaks[30,41]. So adverse events were evaluated for 599 patients. Excluding stent migration, reactive tissue formation and food impaction, which were analyzed separately, 80 (13.4%) patients suffered a total of 82 complications due to stent placement. The overall pooled major and minor complication rate were 7.8% and 5.5%, respectively. Complication rates according to stent type are presented in Table 6.

Mortality during the course of stent therapy was reported in 10.0% of all patients with benign leaks, perforations and fistulae. Stent-related mortality was reported in three cases (0.5%). One was caused by severe bleeding in a patient treated with a FC SEMS who refused further interventions[40]. In another case esophageal necrosis at the proximal end of a FC SEMS resulted in a fatal outcome[37]. The third stent-related death was due to massive hemorrhage caused by erosion of a PC SEMS into the aorta[46]. Other non-stent-related causes for mortality are summarized in Table 7.

Stent removal: The outcome of stent removal could be analyzed in 13 studies in which 555 of the 615 inserted stents were subsequently removed. The overall pooled successful removal rate was 78.7% (437/555). Causes of failure were stent embedding by granulation tissue requiring stent-in-stent procedures for removal (n = 104, 18.7%), surgical removal (n = 5, 0.9%), esophageal ruptures (n = 2, 0.4%), irremovable stent (n = 2, 0.4%), self-limiting bleedings (n = 2, 0.4%), traumatic removal due to tissue ingrowth (n = 2, 0.4%) and additional endoscopic procedures (n = 1, 0.2%). When uneventful stent-in-stent procedures were considered as successful removals, the overall successful stent removal rate increased up to 97.5% (541/555). Stent removal outcome could be analyzed for 187 FC SEMS of which 84% (158/187) were removed after a median period of 5 to 7 wk. FC SEMS removal was successful in 98.4% (184/187) of procedures, including one fractured stent that was retrieved in two pieces. There were two cases of a self-limiting bleeding and one migrated FC SEMS required surgical removal. The majority of PC SEMS (73%, 109/149) were removed after a median period of 7 to 10 wk. One study accounted for 91% (135/149) of the PC SEMS removals[47]. Successful endoscopic removal of PC SEMS was achieved in 29.5% (44/149) of cases and in 96.6% (144/149) after stent-in-stent procedures. Three PC SEMS were removed during surgery and two removals were traumatic due to tissue ingrowth. The two cases of esophageal rupture also occurred during the removal of PC SEMS, but could not be included

Table 5 Pooled analysis of 643 patients with benign esophageal leaks, perforations and fistulae treated with self-expandable stent placement

Etiology	
Postsurgical leaks	415 (64.5)
Iatrogenic perforations	126 (19.6)
Boerhaave's syndrome	50 (7.8)
Fistulae	24 (3.7)
Others/not specified	28 (4.4)
Stent type of 852 stents used in 573 patients[1]	
FC SEMS	349 (41.0)
PC SEMS	321 (37.7)
SEPS	60 (7.0)
Stent type unknown	122 (14.3)
Technical success	
Overall	851 (99.9)
FC SEMS	349 (100)
PC SEMS	320 (99.7)
SEPS	60 (100)
Stent type unknown	122 (100)
No. of stents per patient	
Single stent placement	357 (55.5)
Multiple stents inserted	131 (20.4)
Unknown	155 (24.1)
Clinical success	
Overall (n = 625)	480 (76.8)
According to etiology (n = 358)	
Postsurgical leaks (n = 247)	201 (81.4)
Perforations[2] (n = 86)	74 (86.0)
Fistulae (n = 17)	11 (64.7)
Others/not specified (n = 8)	6 (75.0)

[1]In two studies including 70 patients the total number of stents used was not reported; [2]Including iatrogenic and spontaneous perforations. FC SEMS: Fully covered self-expandable metal stent; PC SEMS: Partially covered self-expandable metal stent; SEPS: Self-expandable plastic stent.

in the pooled analysis because the overall number of removed PC SEMS was not reported[40]. The ruptures were successfully treated with another stent. The outcome of SEPS removal could be extracted from one study and was successful in 100% (14/14) of cases after a mean stent time of 17 d[44].

DISCUSSION

This pooled analysis of the literature showed that the overall clinical success rate of self-expandable stent placement was 24.2% for refractory benign esophageal strictures and 76.8% for benign esophageal leaks, perforations and fistulae. With regard to refractory benign strictures, the meta-analysis by Thomas *et al*[7] found sustained improvement of dysphagia in 46.2% of patients treated with self-expandable stents, which is almost twice as high as the clinical success rate (24.2%) in this pooled analysis. Also the systematic review by Repici *et al*[48] reported a much higher clinical success rate of 52% after SEPS placement for benign esophageal strictures. The difference in clinical success between our pooled analysis and the aforementioned systematic reviews may be explained by the etiology and the severity of the strictures. The study population of Thomas *et al*[7] mainly included corrosive (43%), postsurgical (25%) and radiation (11%) strictures. The etiologies of the patients in the systematic review on SEPS treatment mainly included postsurgical (38%), corrosive (25%) and radiation (15%) strictures[48]. In our analysis, peptic strictures accounted for 25.0% of patients, while corrosive strictures represented only 12.5%. However, the literature data were insufficient to analyze the clinical outcomes of stent placement according to stricture etiology. With regard to the severity of the strictures, Thomas *et al*[7] included three studies, that accounted for 50% of weight in the meta-analysis, in which patients had a history of two or less dilatations before stent placement. The review by Repici *et al*[48] did not provide details on the number of previous dilatations, but included mainly retrospective studies with heterogeneous definitions of refractory or recurrent strictures. We think that the more homogeneous population included in this analysis of prospective studies, that fulfilled Kochman's criteria[8], had more severe strictures and therefore a poorer outcome of stent therapy. Thomas *et al*[7] reported a significantly higher clinical success rate for Polyflex stents (55.3%) compared with nitinol stents (36.7%). Our results also showed a lower clinical success rate with the use of FC SEMS (14.1%) compared with SEPS (27.1%) and BD stents (32.9%). We do not have a good explanation for this finding. Complication, stent migration and tissue response rates were not significantly higher with the use of FC SEMS.

Safety analyses in patients treated with self-expandable stents for refractory benign strictures showed an overall complication rate of 31.0%, including a major complication rate of 17.7%. That complications are frequent during the course of stent therapy has also been demonstrated by several retrospective studies that were not included in our analyses[49-53]. The major complication rate of BD stents (28.6%) was twice as high as those of SEPS (14.3%) and FC SEMS (10.6%), because they caused more retrosternal pain, hyperplasia-induced stenoses and bleedings. Severe retrosternal pain occurred in 13.0% of patients who received a BD stent. Pain after stent placement has been postulated to be caused by the radial force of the stent against the tight stricture and is mainly reported within the first week after stent placement[9,11,15,49,53]. However, *in vitro* analysis of the radial and axial forces of 23 esophageal stent models showed that BD stents had a relatively low radial force and high axial force[54]. Therefore, it is more likely that because of the rigid stent design BD stents interact less well with the peristalsis of the esophagus causing more spasm and pain. In this analysis clinically relevant hyperplastic tissue growth was reported in 7.8% of BD stents. Two case series not included in this review also showed that reactive tissue formation is common after BD stent placement (Figure 3)[17,55]. The occurrence of tissue growth may be explained as a reaction to the chemical processes of degradation,

Table 6 Pooled analysis of adverse events in patients with benign esophageal leaks, perforations and fistulae

Total number of patients analyzed: *n* = 599	No. of patients (*n* = 599)	No. of FC SEMS (*n* = 295)	No. of PC SEMS (*n* = 302)	No. of SEPS (*n* = 75)[1]	Stent type unknown (*n* = 162)[2]
Overall complications	80[3] (13.4)	26 (8.8)	38 (12.6)	1 (1.3)	17 (10.5)
Overall major complications	47[3] (7.8)	11 (3.7)	28 (9.3)	1 (1.3)	8 (4.9)
Hyperplasia-induced stenosis	16 (2.7)	0	16	0	0
Hemorrhage[4]	8 (1.3)	2[4]	6	0	0
Stent-related perforation	6 (1.0)	4	1	0	1
Aspiration pneumonia	4 (0.7)	2	0	0	2
Respiratory compromise/ tracheal compression	2 (0.3)	1	1	0	0
Severe retrosternal pain	2 (0.3)	0	2	0	0
Bowel obstruction	2 (0.3)	0	0	0	2
Erosion[4]	2 (0.3)	0	1[4]	0	1
Hemorrhage from aorta-esophageal fistula	1 (0.2)	1	0	0	0
Stricture formation	1 (0.2)	0	0	0	1
Stent-related fistula	1 (0.2)	0	1	0	0
Stent dislocation and inability to place new stent requiring rethoracotomy	1 (0.2)	0	0	1	0
Left atrial compression	1 (0.2)	0	0	0	1
Death due to esophageal necrosis at proximal stent end	1 (0.2)	1	0	0	0
Overall minor complications	33[3] (5.5)	15 (5.1)	10 (3.3)	0 (0)	9 (5.6)
Transient stent-related dysphagia	11 (1.8)	1	10	0	0
Stent-related ulcers	5 (0.8)	5	0	0	0
Reflux/esophagitis	3 (0.5)	0	0	0	3
Chest pain	3 (0.5)	1	0	0	2
Stent disintegration	3 (0.5)	3	0	0	0
Stent collapse/invagination	2 (0.3)	1	0	0	1
Pneumoperitoneum during endoscopy secondary to air insufflation	1 (0.2)	1	0	0	0
Atrial fibrillation related to sedation	1 (0.2)	1	0	0	0
Stent malposition	1 (0.2)	1	0	0	0
Abdominal pain	1 (0.2)	0	0	0	1
Nausea	1 (0.2)	0	0	0	1
Globus sensation	1 (0.2)	1	0	0	0
Hiccups	1 (0.2)	0	0	0	1

[1]Including 30 patients in whom the number of SEPS used was not reported; [2]Including 40 patients in whom the number of stents used was not reported; [3]Patients can have more than one complication; [4]Including one stent-related death. FC SEMS: Fully covered self-expandable metal stent; PC SEMS: Partially covered self-expandable metal stent; SEPS: Self-expandable plastic stent.

Table 7 Overall mortality in 643 patients treated with self-expandable stents for benign esophageal leaks, perforations and fistulae *n* (%)

Overall mortality	64 (10.0)
Stent-related	3 (0.5)
Sepsis-related	23 (3.6)
Multi-organ failure	5 (0.8)
Cerebral embolism/cerebrovascular accident	2 (0.3)
Heart insufficiency/cardiac disease	2 (0.3)
Pneumonia	2 (0.3)
Malignancy	2 (0.3)
Non stent-related bleeding	1 (0.2)
Respiratory insufficiency without sepsis	1 (0.2)
Pulmonary embolism	1 (0.2)
Acute respiratory distress syndrome	1 (0.2)
Pulmonary aspiration after healing of leak	1 (0.2)
Aortic dissection	1 (0.2)
Tension pneumothorax	1 (0.2)
Paraspinal abscess related to persistent fistula	1 (0.2)
Full-blown AIDS	1 (0.2)
Aspiration during contrast study	1 (0.2)
Multiple emboli caused by esophago-atrial fistula	1 (0.2)
Active euthanasia	1 (0.2)
Not specified	13 (2.0)

which may also trigger bleedings from the affected esophageal mucosa. So one should be aware that the higher efficacy of BD stent placement is attended by an increased risk of complications.

The clinical success rate (76.8%) of self-expandable stent placement for benign esophageal leaks, perforations and fistulae found in this pooled analysis is comparable with the 81% of the systematic review by Dasari *et al*[1] (Figure 4A and B). In contrast to our analysis, the latter review excluded patients with leaks from the gastric staple line after sleeve gastrectomy and did not analyze patients with fistulae. In our study clinical success according to etiology was 81.4% for postsurgical leaks, 86.0% for perforations and 64.7% for fistulae. Though derived from retrospective series, these results seem promising. Patients with esophageal leaks or ruptures are usually in poor condition with elevated septic parameters and require invasive management, like drainage procedures, surgery and ICU care. This is reflected by the increased mortality rate of 7.2%-25.8% after postsurgical esophageal leakage[56-58]. Several treatment strategies have been described for the management

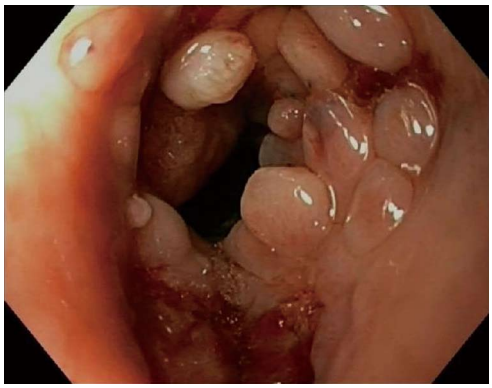

Figure 3 Endoscopic image of granulation tissue growth 4 mo after biodegradable stent placement for a refractory benign esophageal anastomotic stricture.

of esophageal leaks, such as endoscopic vacuum therapy, nose fistula tube drainage, surgical repair and conservative management[59-61]. Retrospective comparison of 41 patients with an anastomotic leak after esophagectomy who were matched by clinical status, showed that endoscopic vacuum therapy resulted in a lower mortality rate (12%, 2/17) compared with surgical treatment (50%, 9/18) and stent placement (83%, 5/6) in systemically ill patients[58]. Another retrospective study reported a significantly higher closure rate after endoscopic vacuum therapy (84%) compared with stent therapy (53.8%) in 71 patients with esophageal defects[37]. However, one should keep in mind that success of stent placement depends on the size of the esophageal lesion, the delay between diagnosis and stent placement and if the patient has elevated septic parameters[30,33,34,47]. Stent placement is most likely to fail in a large lesion (> 15 mm), that exists for several weeks in a septic patient. Therefore, patients with an esophageal leak should receive a multidisciplinary patient-tailored approach.

The removability of self-expandable stents was safe and feasible with an overall successful removal rate of 97.2% in patients with refractory strictures and 78.7% in patients with esophageal leaks. The fact that PC SEMS were used in 38% of patients with esophageal leaks resulted in a lower overall successful removal rate. PC SEMS removal was often complicated by stent embedding requiring stent-in-stent procedures to induce pressure-necrosis of the granulation tissue to facilitate the removal procedure. The vast majority of stent-in-stent procedures were reported in the study by Swinnen *et al*[47]. The removal of FC SEMS and SEPS removal was much safer with successful removal rates of 96.6% up to 98.4%. The relation between the use of PC SEMS and complicated stent removal has also been demonstrated by several large retrospective series[62,63].

This pooled analysis of the literature has several limitations. The prospective data on the outcomes of stent placement for refractory benign esophageal strictures reflect a patient population with various

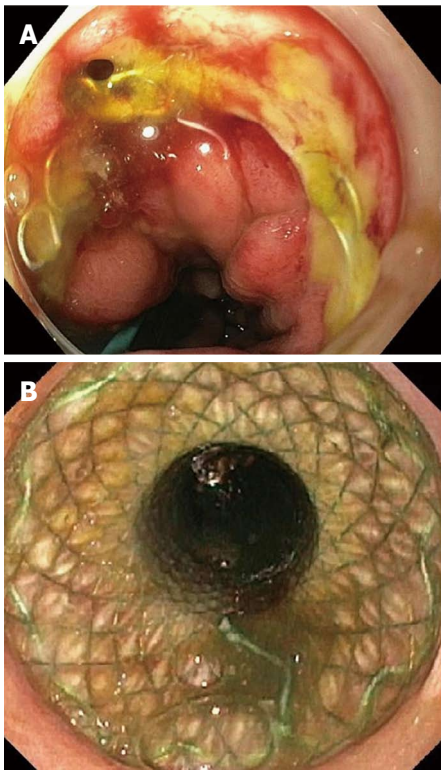

Figure 4 A small leak at the anastomosis of the esophagus and the gastric tube 5 d after esophagectomy (A) and esophageal fully covered self-expandable metal stent placement for a small anastomotic leak (B).

causes for stricture formation. Data were insufficient to provide analyses according to stricture etiology. The studies that were analyzed on the outcomes of esophageal stent placement for benign leaks, perforations and fistulae were all retrospective, causing heterogeneity and underreporting of adverse outcomes.

In conclusion, the outcomes of self-expandable stent placement for refractory benign esophageal strictures were poor with a clinical success rate of 24.4% and a major complication rate of 17.7%. However, randomized trials are needed to put these outcomes into perspective. Although derived from retrospective series, the evidence on stent placement for benign esophageal leaks, perforations and fistulae is promising with an overall clinical success rate of 76.8%.

COMMENTS

Background

Self-expandable stents in various types are increasingly being used for the treatment of refractory benign esophageal strictures and benign esophageal leaks, perforations and fistulae.

Research frontiers

It is hypothesized that esophageal stent placement for benign refractory strictures prolongs the dysphagia-free period compared with conventional dilatation therapy. Besides application for the treatment of strictures, esophageal stents are also used to seal leaks, perforations and fistulae.

Innovations and breakthroughs

The literature on esophageal stent placement for benign indications is heterogeneous and usually includes small samples. In this systematic review

we performed a pooled analysis on the treatment outcomes of 232 patients with refractory strictures and 643 patients with leaks, perforations and fistulae.

Applications

This pooled analysis may be helpful for the endoscopist in the decision-making on the indication for esophageal stent placement and also to inform the patient on the risks and benefits of stent therapy.

Terminology

Biodegradable stents are only used for strictures, because they have the property to dissolve. Nitinol metal stents (SEMS) have an outer membrane of silicone or polytetrafluoroethylene to prevent hyperplastic tissue ingrowth. Because they are covered, they are removable and can also be used to seal leaks. Partially covered SEMS usually become partially embedded by granulation tissue, which prevents stent migration, but makes them harder to remove. Self-expandable plastic stents consist of plastic instead of metal and are fully covered.

Peer-review

This review is well-written and comprehensive review about this subject.

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CASE REPORT

Rare case of dysphagia, skin blistering, missing nails in a young boy

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Author contributions: Makker J and Bajantri B contributed equally in writing the manuscript; Remy P edited and approved the final version of manuscript.

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Informed consent: Informed written consent was obtained prior to writing this case report.

Conflict-of-interest: Authors have no conflicts of interests to declare.

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Abstract

Epidermolysis bullosa is a group of genetic disorders with an autosomal dominant or an autosomal recessive mode of inheritance and more than 300 mutations. The disorder is characterized by blistering mucocutaneous lesions and has several varying phenotypes due to anchoring defect between the epidermis and dermis. The variation in phenotypic expression depends on the involved structural protein that mediates cell adherence between different layers of the skin. Epidermolysis bullosa can also involve extra-cutaneous sites including eye, nose, ear, upper airway, genitourinary tract and gastrointestinal tract. The most prominent feature of the gastrointestinal tract involvement is development of esophageal stricture. The stricture results from recurrent esophageal mucosal blistering with consequent scarring and most commonly involves the upper esophagus. Here we present a case of a young boy with dominant subtype of dystrophic epidermolysis bullosa who presented with dysphagia, extensive skin blistering and missing nails. Management of an esophageal stricture eventually requires dilatation of the stricture or placement of a gastrostomy tube to keep up with the nutritional requirements. Gastrostomy tube also provides access for esophageal stricture dilatation in cases where antegrade approach through the mouth has failed.

Key words: Epidermolysis bullosa; Dysphagia; Esophageal stenosis; Gastrostomy; Blistering

Core tip: Epidermolysis bullosa is a genetic disorder with four main types. The most prominent feature of the disease is extensive skin blisters. Extra-cutaneous manifestations like dysphagia vary among different subtypes. Recessive type of dystrophic epidermolysis bullosa is the subtype most commonly associated with esophageal strictures. Treatment of dysphagia secondary to esophageal stricture involves changing diet texture, dilatation of the stricture and placement of a gastrostomy tube.

Makker J, Bajantri B, Remy P. Rare case of dysphagia, skin blistering, missing nails in a young boy. *World J Gastrointest Endosc* 2015; 7(2): 154-158 Available from: URL: http://www.

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INTRODUCTION

Epidermolysis bullosa is a multisystem inherited disorder with extensive skin blistering as the most prominent feature. Four distinct types of epidermolysis bullosa recognized are epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB), dystrophic epidermolysis bullosa (DEB) and kindler syndrome. Severity and extent of cutaneous and extra-cutaneous features can vary among different subtypes and depends on the type of skin structural protein affected.

CASE REPORT

A 15-year-old boy with blistering skin disease since birth presented to this hospital complaining of worsening dysphagia for 3 d. He had been generally well till the age of 9 years when he started experiencing dysphagia. He described his symptoms as gradually worsening difficulty in swallowing solids for past 6 years. He mostly consumed liquids and soft consistency meals during these years. He reported an episode of worsening swallowing difficulty with inability to swallow liquids as well about 6 mo prior to presentation. At that time, he was admitted to another hospital and a barium esophagogram was obtained which showed upper esophageal stenosis. He also reported a failed endoscopic attempt at that time. Subsequently, he improved spontaneously in 2-3 d and resumed his liquid diet until 3 d ago when he again experienced difficulty swallowing liquids and solids both. He described his symptoms as inability to swallow and the food being stuck in his throat. He also claimed to have a choking sensation when he tried to drink milk. He denied chest pain, shortness of breath, fever and drooling of saliva. He denied any worsening of his skin condition.

He had an extensive skin blistering disease since birth and was advised by his pediatric dermatologist to use a moisturizing cream on the raw skin areas exposed by ruptured blisters. Review of his skin lesion biopsy done previously revealed the diagnosis of dystrophic epidermolysis bullosa dominant type. He denied any prior surgeries. He did not smoke, use alcohol or any illicit drug. He lived with his mother who was apparently healthy without any chronic skin disease. His mother was separated from his father and did not have any details about his father's medical conditions.

On examination, he appeared comfortable, afebrile with pulse 93 beats per minute, blood pressure 111/68 mmHg, respiratory rate 18 per minute and body mass index (BMI) was 16.1 kg per square meter. He had extensive erosions and crust formation with whitish papules involving face, neck, trunk, and extremities (Figure 1). On examination of his extremities, many of his finger and toenails were missing (Figure 1). His oral cavity examination and the systemic examination including chest, cardiac, abdomen and neurological examination were unremarkable.

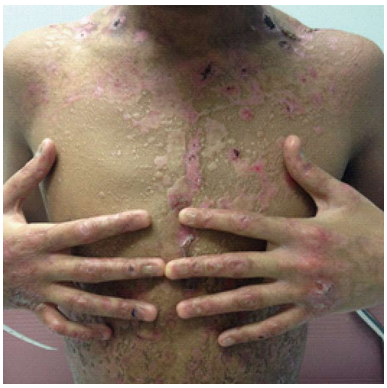

Figure 1 Extensive erosions, crusts, scars on the skin and missing nails.

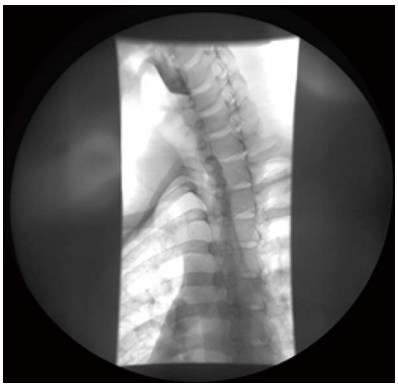

Figure 2 Upper esophageal stenosis as seen on an esophagogram.

During his hospital stay, an esophagogram was done which showed tight stenosis at the level of cervical esophagus (Figure 2). An upper gastrointestinal endoscopy was performed which showed a tight stenosis involving the upper esophagus (Figure 3). Stenosed region of the upper esophagus could not be traversed even with the use of an extra slim 5.5 mm diameter endoscope. Patient eventually underwent a percutaneous gastrostomy tube placement.

DISCUSSION

A German dermatologist Heinrich Koebner coined the term epidermolysis bullosa in 1886[1]. Epidermolysis bullosa comprises a group of hereditary disorders characterized by recurrent mucocutaneous blisters that result from minor trauma. Due to several genotypic and phenotypic variants of epidermolysis bullosa, classifying this group of disorder was challenging. In 1962, Epidermolysis bullosa was first classified by Pearson based on the detailed structures of dermo-

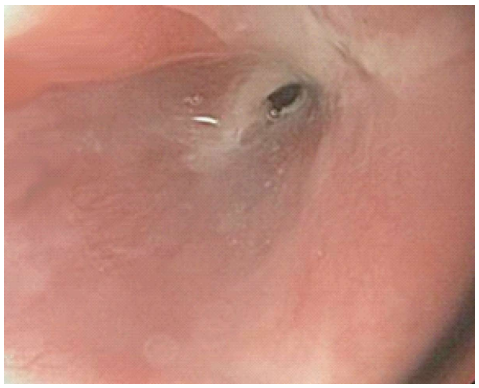

Figure 3 Upper esophageal stenosis as seen on an esophagogastroduodenoscopy.

epidermal junction as seen on the electron microscope[2]. Since then the group of experts have had four international consensus meetings on diagnosis and classification of epidermolysis bullosa to include all the subclasses under one classification system.

The last international consensus meeting results were released in 2014 and the expert group continues to recognize epidermolysis bullosa into four major types based on the level of cleavage in the skin layers[1]. Skin is composed of an outer epidermis, inner dermis and an intermediate layer called basement membrane zone, which lies between the epidermis and dermis. Basement membrane zone has been further divided into four layers - hemidesmosome, lamina lucida, lamina densa and sub-lamina densa[3]. Four major types (Figure 4) of epidermolysis bullosa with their level of cleavage are – EBS (intra-epidermal cleavage), JEB (intra-lamina lucida cleavage), DEB (intra sub-lamina densa cleavage) and kindler syndrome (multiple levels of cleavage)[1].

Epidemiology

Epidermolysis bullosa has a variable worldwide prevalence. The variability is likely due to genetic differences between different populations but the differences in recognizing and reporting of the disease are also contributory. In countries where epidermolysis bullosa registries have been established, epidemiological data is slowly emerging but is still underestimated. Prevalence of 10 per million in Australia[4], 49 per million in Scotland[5], 32 per million in Ireland[6] and 10.1 per million in Italy[7] has been reported. In United States, National Epidermolysis Bullosa Registry (NEBR) was founded in 1986 and since then it has emerged as the largest registry of epidermolysis bullosa in the world. According to 1990 estimates of NEBR, the prevalence of epidermolysis bullosa was 8 per million in United States[8].

Etiopathogenesis

Epidermolysis bullosa is inherited as an autosomal dominant or an autosomal recessive disease. Mutations in genes encoding for structural proteins of epidermis, dermis and basement membrane zone are responsible for the fragility of the skin. Phenotypic heterogeneity of epidermolysis bullosa depends on the structural protein involved. Various proteins implicated in different subtypes of epidermolysis bullosa are shown in Figure 4[9].

Clinical features

Cutaneous manifestations: Skin blisters are the most prominent manifestations of epidermolysis bullosa. Blisters may involve oral mucosa as well. Besides skin blisters, other skin lesions described in literature are erosions, milia (small white papules), deformity or absence of finger and toenails, scarring and extensive granulation tissue. Skin lesions vary in severity and extent among different subtypes.

EBS is the predominant type prevalent in western countries and in general has milder skin lesions as compared to JEB or DEB. The herlitz subtype of JEB is less prevalent than the non-herlitz JEB, but both can have characteristic enamel hypoplasia. Skin scarring is a predominant feature of herlitz subtype JEB. In addition, involvement of the mucosal surfaces of esophagus, upper airway and cornea with subsequent scarring can also be seen with herlitz subtype JEB. The non-herlitz JEB has fewer tendencies to develop extracutaneous manifestations. Dominant form of DEB develops skin blisters at birth. Recurrent involvement of esophagus with subsequent scarring and stenosis can be seen among these patients. Recessive form of DEB is the most severe form of epidermolysis bullosa and leads to disfiguring skin scars, hand and foot deformities, growth retardation and failure to thrive. Kindler syndrome is characterized by photosensitivity and skin pigmentation besides skin blistering[8].

Extra-cutaneous manifestations

Epidermolysis bullosa, in addition to skin involvement, may involve extra-cutaneous sites leading to significant morbidity and mortality. It can involve eye, oral cavity, nose, gastrointestinal tract, genitourinary tract, respiratory tract and heart. Involvement of eye may manifest as conjunctival edema, keratitis, corneal erosions, corneal ulcerations and scarring. Genitourinary involvement may manifest as scarring of glans penis or vaginal vestibule, urethral strictures leading to hydroureter and hydronephrosis. Repeated blisters involving nose, oral cavity and ear may lead to scarring and occlusion of external nares, oropharynx and external auditory canal. Blisters may involve larynx and upper respiratory tract epithelium leading to scarring and respiratory compromise[10]. Musculoskeletal involvement in recessive DEB is characterized by extensive blistering and scarring that eventually leads to fusion of fingers and toes (mitten deformity). Other features of musculoskeletal involvement are contractures involving multiple

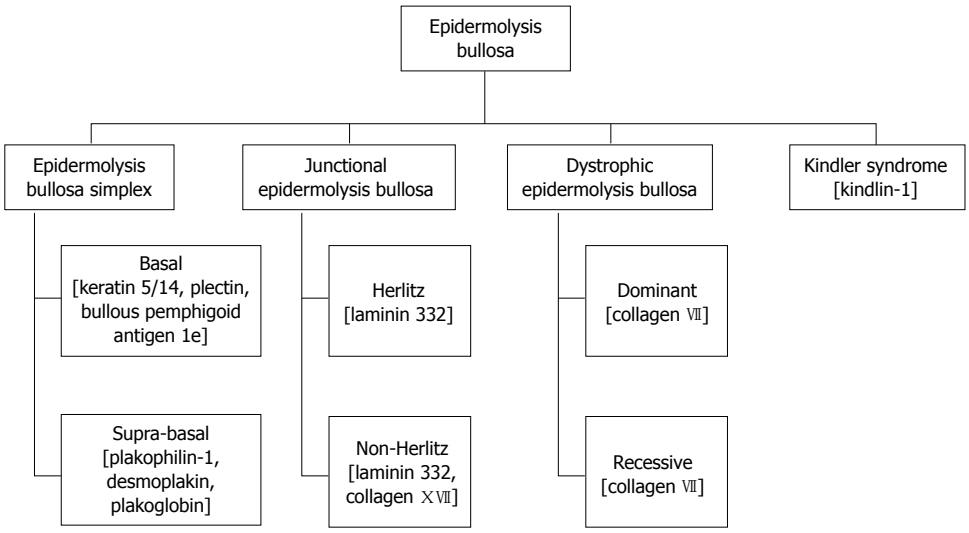

Figure 4 Major types and subtypes of epidermolysis bullosa with affected structural skin proteins in parenthesis.

joints, muscular dystrophy and osteoporosis.

Anemia is commonly seen in patients with JEB and recessive DEB. Cardiomyopathy secondary to micronutrient deficiencies, anemia and transfusion related iron overload has been uncommonly seen in recessive DEB. Skin cancers like squamous cell carcinoma, basal cell carcinoma and melanoma are also known to occur in patients with epidermolysis bullosa[11]. Squamous cell carcinoma is the leading cause of mortality in several subtypes of epidermolysis bullosa. It most commonly affects recessive form of epidermolysis bullosa and the cumulative risk increases with age[12].

Gastrointestinal manifestations

The gastrointestinal tract is commonly involved in different subtypes of epidermolysis bullosa. Repeated blistering of the esophageal mucosal surface most commonly leads to scarring and stenosis of the upper esophagus. The resulting strictures can vary in length and may involve multiple sites. Recessive type of DEB is the subtype most commonly associated with esophageal strictures, however other types including dominant DEB, JEB and EBS may also show similar findings[13]. Analysis of 3280 epidermolysis bullosa patients enrolled in National Epidermolysis Bullosa Registry showed the highest cumulative risk of esophageal strictures in the recessive subtype of DEB. Cumulative risk of about 95% and 35% were seen respectively in patients with recessive DEB and herlitz JEB[14].

Patients usually present with symptoms of dysphagia, odynophagia and malnutrition. Strictures, though commonly affect the upper esophagus, may involve mid and lower esophagus as well. Lower esophageal strictures can be precipitated by gastroesophageal reflux disease (GERD) besides blistering of the mucosa. The other common gastrointestinal problems affecting epidermolysis bullosa patients are constipation and fecal impactions, which result from painful perianal blistering or anal canal stenosis. Pyloric atresia that mostly involves JEB patients is another serious gastrointestinal problem that manifests early in life[11].

Treatment

Currently there is no effective therapy available for curing epidermolysis bullosa. However, over the last decade several potential future therapies including protein replacement and gene therapies have been explored. Model systems using these approaches show promise for significant advances in future. Gene therapy for non-Herlitz junctional epidermolysis bullosa has been performed and shown to be efficacious[15]. In the absence of a definite therapeutic modality to cure or modify epidermolysis bullosa disease course, management is largely symptomatic. Management of skin lesions focuses on avoiding further skin trauma and secondary bacterial infections[8].

Dietary modification with fiber supplementation is an effective initial approach to manage constipation. Osmotic laxatives can also be tried if dietary measures fail. GERD symptoms usually respond to histamine type 2 receptor antagonists or proton pump inhibitors.

Treatment of an esophageal stricture begins with modification of diet texture to soft, puree and liquids. Supplementation of multivitamins and minerals is an additional important measure. Despite these measures, patients may not be able to keep up with the required caloric intake resulting in malnutrition and growth retardation. Severe strictures eventually may require esophageal dilatation that can be done either with the use of a balloon catheter or a bougie. Both the methods have comparable efficacy, however balloon catheters are preferred due to their relative safety over bougies. Single or multiple sessions of esophageal dilatations may be needed. Usually an antegrade approach is used where a balloon catheter

is inserted from the mouth under endoscopic or fluoroscopic guidance. In cases with microstomia due to oropharyngeal scarring, a retrograde approach from the gastrostomy tube may also be tried. With each dilatation small but definite risk of esophageal perforation exists[16]. Rarely, colonic interposition or transposition has also been used. Management of most of these complications of epidermolysis bullosa requires a multi-modality approach with multi-disciplinary coordination.

COMMENTS

Case characteristics

A 15-year-old boy with blistering skin disease since birth, dysphagia since age nine presented with worsening dysphagia for 3 d.

Clinical diagnosis

He had extensive skin erosions and crust formation involving face, neck, trunk, and extremities and many of his finger and toenails were missing.

Differential diagnosis

Four main types of epidermolysis bullosa: epidermolysis bullosa simplex, junctional epidermolysis bullosa, dystrophic epidermolysis bullosa and kindler syndrome.

Laboratory diagnosis

Skin lesion biopsy showed dominant type dystrophic epidermolysis bullosa.

Imaging diagnosis

Esophagogram showed tight stenosis at the level of cervical esophagus and an upper gastrointestinal endoscopy showed a tight stenosis involving the upper esophagus.

Pathological diagnosis

Gene mutation affecting collagen VII leads to skin blisters involving uppermost part of dermis.

Treatment

Management of skin lesions is largely symptomatic but protein and gene replacement therapies are emerging. Worsening dysphagia may require esophageal stricture dilatation or gastrostomy tube placement.

Related reports

Recessive type of dystrophic epidermolysis bullosa (DEB) is the subtype most commonly associated with esophageal strictures, however other types including dominant DEB, junctional epidermolysis bullosa and epidermolysis bullosa simplex may also show similar findings.

Term explanation

Epidermolysis bullosa comprises a group of hereditary disorders characterized by recurrent mucocutaneous blisters that result from minor trauma.

Experiences and lessons

This case report highlights the association of skin blisters, missing nails and dysphagia in patients with epidermolysis bullosa.

Peer-review

This is a very nice case report.

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Contents

Monthly Volume 7 Number 3 March 16, 2015

EDITORIAL

REVIEW

MINIREVIEWS

Contents

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EDITORIAL

Laparoscopic liver resection: Toward a truly minimally invasive approach

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Abstract

In the surgical treatment of hepatocellular carcinoma and colorectal liver metastasis, it is important to preserve sufficient liver volume after resection in order to avoid post-hepatectomy liver sufficiency and to increase the feasibility of repeated hepatectomy in case of intrahepatic recurrence. Parenchyma-sparing approach, which minimizes the extent of resection while obtaining sufficient surgical margins, has been developed in open hepatectomy. Although this approach can possibly have positive impacts on morbidity and mortality, it is not popular in laparoscopic approach because parenchyma-sparing resection is technically demanding especially by laparoscopy due to its intricate curved transection planes. "Small incision, big resection" is the words to caution laparoscopic surgeons against an easygoing trend to seek for a superficial minimal-invasiveness rather than substantial patient-benefits. Minimal parenchyma excision is often more important than minimal incision. Recently, several reports have shown that technical evolution and accumulation of experience allow surgeons to overcome the hurdle in laparoscopic parenchyma-sparing resection of difficult-to-access liver lesions in posterosuperior segments, paracaval portion, and central liver. Laparoscopic surgeons should now seek for the possibility of laparoscopic parenchyma-sparing hepatectomy as open approach can, which we believe is beneficial for patients rather than just a small incision and lead laparoscopic hepatectomy toward a truly minimally-invasive approach.

Key words: Laparoscopy; Liver resection; Hepatectomy; Minimally-invasive; Parenchyma-sparing; Laparoscopic surgery; Hepatocellular carcinoma; Liver metastasis; Liver lesion; Colorectal carcinoma

Core tip: In the surgical treatment of hepatocellular carcinoma and colorectal liver metastasis, it is important to preserve sufficient liver volume after resection in order to avoid post-hepatectomy liver sufficiency and to increase the feasibility of repeated hepatectomy in case of intrahepatic recurrence. Parenchyma-sparing hepatectomy has been developed for the best remnant liver function as well as sufficient surgical margins and

may have positive impacts on morbidity and mortality. Surgeons should overcome the technical difficulty and seek for the possibility of laparoscopic parenchyma-sparing hepatectomy, which will lead laparoscopic hepatectomy toward a truly minimally-invasive and beneficial approach.

Ogiso S, Hatano E, Nomi T, Uemoto S. Laparoscopic liver resection: Toward a truly minimally invasive approach. *World J Gastrointest Endosc* 2015; 7(3): 159-161 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i3/159.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i3.159

TOWARD A TRULY MINIMALLY-INVASIVE LIVER RESECTION

I remember the words, "small incision, big resection", in the keynote lecture by Professor Henri Bismuth at the European Association for Endoscopic Surgery meeting in 2011, which cautioned laparoscopic surgeons against an easygoing trend to seek for a superficial minimal-invasiveness of hepatectomy rather than substantial patient-benefits.

Laparoscopic hepatectomy has become popular[1-4] and is the standard of care[3] to treat lesions in the left lateral section[5] or peripheral anteroinferior segments[6,7] with better short-term outcomes compared to open hepatectomy, including less blood loss, less pain, and earlier recovery[8,9]. In addition, increasing number of laparoscopic major hepatectomy is actively performed in specialized centers all over the world[2,10], based on the recognition that such benefits may confirm the superiority of laparoscopic hepatectomy as a minimally-invasive surgical treatment compared to open hepatectomy. However, now is the time to reconsider if laparoscopy is truly minimally-invasive and advantageous for patients. Hepatectomy is different from other visceral surgery with regard to the importance of postoperative remnant organ function. Post-hepatectomy liver sufficiency is a life-threatening complication, mainly observed in hepatocellular carcinoma (HCC) patients with cirrhosis or colorectal metastases (CLM) patients after prolonged chemotherapy. Even after successful hepatectomy, both HCC and CLM patients may develop intrahepatic recurrence and then the possibility of repeated hepatectomy depends on the liver functional reserve. As Professor Bismuth cautioned, "big resection with small incision" should not be beneficial for patients compared to "small resection with big incision".

In seeking for both sufficient surgical margins and the best remnant liver function, parenchyma-sparing hepatectomy, including mono-segmentectomy[11] and combination of minor resections[12], has been developed in open hepatectomy. On the other hand, parenchyma-sparing approach is not popular in laparoscopic hepatectomy. This is because laparoscopy has a significant limitation of forceps manipulation so that making intricate curved transection planes for parenchyma-sparing hepatectomy is much more demanding in laparoscopic approach than in open approach. In our opinion, major hepatectomy with a single and straight transection plane, such as right and left hepatectomy, is easier and more suitable for laparoscopy, compared to anatomical or non-anatomical minor resection. For this reason, large resection, which excises non-tumorous parenchyma more than required to obtain sufficient surgical margins, is often performed by laparoscopy for small-to-intermediate-sized lesions in difficult-to-access areas. Recently, several reports have shown that technical evolution and accumulation of experience allow surgeons to overcome the hurdle in laparoscopic parenchyma-sparing resection of difficult-to-access liver lesions[13] in posterosuperior segments[14,15], paracaval portion[16], and central liver[17]. We believe laparoscopic surgeons should now reconsider the importance of parenchyma-sparing hepatectomy and try to minimize the extent of resection by laparoscopy as open approach can. "Small incision, minimum resection required for oncologic principles" should lead laparoscopic hepatectomy toward a truly minimally-invasive and beneficial approach.

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REVIEW

Intentional ingestions of foreign objects among prisoners: A review

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Abstract

The intentional ingestion of foreign objects (IIFO) is described more commonly in prison populations than in the general population, with an estimated annual incidence of 1 in 1900 inmates in our state correctional facilities. Incidents often involve ingestion of small metal objects (*e.g.*, paperclips, razor blades) or other commonly available items like pens or eating utensils. Despite ingestion of relatively sharp objects, most episodes can be clinically managed with either observation or endoscopy. Surgery should be reserved for those with signs or symptoms of gastrointestinal perforation or obstruction. For those with a history of IIFO, efforts should focus on prevention of recurrence as subsequent episodes are associated with higher morbidity, significant healthcare and security costs. The pattern of IIFO is often repetitive, with escalation both in frequency of ingestions and in number of items ingested. Little is known about successful prevention strategies, but efforts to monitor patients and provide psychiatric care are potential best-practice strategies. This article aims to provide state-of-the art review on the topic, followed by a set of basic recommendations.

Key words: Ingestion; Foreign body; Endoscopy; Prisoner; Swallower; Prevention; Recurrence

Core tip: Intentional ingestion of foreign objects typically involves ingestion of small objects (*e.g.*, paperclips, razor blades, pens, eating utensils). Most episodes can be managed with either observation or endoscopy. Surgery should be reserved for those with signs or symptoms of gastrointestinal perforation or obstruction. Due to the documented pattern of escalation, efforts should focus on prevention of recurrence as subsequent episodes are associated with higher morbidity, and significant healthcare and security costs. There are no proven prevention strategies, but efforts to closely monitor patients and provide early psychiatric intervention are among recommended best-practice strategies.

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INTRODUCTION

Intentional ingestion of foreign objects (IIFO) is a

serious problem that chronically affects the United States prison population. Although other non-prisoner patients, specifically those with severe psychiatric conditions, have been reported to have the propensity toward IIFO, the prison population seems unique in that the magnitude of the problem is especially high[1-3]. It has been estimated that up to 1500 deaths may be attributable to IIFO annually in the United States alone[4]. IIFO is a seemingly preventable phenomenon that is associated with high costs of care as well as security costs for transporting and guarding inmates while hospitalized[5]. Health care costs associated with IIFO accounted for $6.5 billion of the $36.8 billion spent to manage the correctional system budgets of 44 states[6]. In a recent study, IIFO episodes were associated with healthcare-related median charges between $4683 and $7698 for those evaluated in the emergency department and admitted[5]. Male sex, incarceration, and psychiatric disease are the predominant factors associated with IIFO[7].

The management of IIFO was revolutionized by the widespread adoption of endoscopic techniques that can be used for retrieval of accessible ingested objects[8]. The prisoner population presents unique challenges due to the multifactorial interaction of psychiatric disease, the (less likely) potential for secondary gain, and the escalating nature of recurrent IIFO. Inmates treated for IIFO often return after variable time intervals having ingested larger, more dangerous, or more toxic objects[2]. These extenuating factors should prompt careful consideration of treatment options as overly aggressive treatment can often lead to disastrous complications.

LITERATURE SEARCH

An exhaustive literature search was performed using the terms "foreign body ingestion", "foreign object ingestion", "intentional ingestion", "swallowed object", and "ingestion". We utilized the United States National Library of Medicine NIH PubMed service, as well as Google™ Scholar to identify as many pertinent English literature sources as possible. After narrowing down the publication list to case reports, case series, reviews, retrospective and prospective studies, the search was further focused on epidemiology, diagnosis, management, and prevention as additional search terms. Results were tabulated, with all major studies on the topic published to date and compiled into a comprehensive, definitive list (Table 1).

EPIDEMIOLOGY

The epidemiology of intentional foreign object ingestions continues to be poorly understood. Most literature focusing on foreign object ingestions is in the pediatric literature, where the size of the gastrointestinal (GI) tract is smaller and many objects become lodged in the pharynx or esophagus posing an aspiration, toxicity, or erosion risk[9-11]. Psychiatric and prison populations account for the majority of adults presenting with foreign object ingestions, the vast majority of which were non-accidental[2]. Due to the unique characteristics of these populations, relatively few of these patients tend to present to community hospitals. In the United States these patients are typically cared for in "safety net" hospitals, making IIFO a relatively high-frequency occurrence in select hospitals. While a general IIFO incidence in the community is not known, the annual incidence of IIFO requiring evaluation in the emergency room or hospital from 2006-2010 in the prison population in the State of Ohio was 0.0528% or approximately 1 in 1900 inmates, making the disease quite rare in this high risk population (see Table 1). Unfortunately in the prison population, recurrent ingestions are also relatively more common[2,5]. The epidemiology of recurrent IIFO is less well understood. Grimes *et al*[7] found no evidence that conscious sedation, esophageal pathology, or age had any statistical significance as a significant predictor of recurrent ingestion. Repeat ingestors are more likely to ingest foreign objects and less likely to experience food impaction[7]. Impulsivity, secondary gain, or an undiagnosed psychiatric disorder are possible explanations for ingestions in the prison population[7].

Table 1 Incidence of Ingestions 2006-2010 in the Ohio Department of Rehabilitation and Corrections

Year	IIFO incidents seen (*n*)	Total prisoners incarcerated[12] (*n*)
2006	17	48534
2007	20	49691
2008	22	50371
2009	47	50371
2010	26	50944
	132	249911 (5-yr census)

Several case series and observational studies of IIFO in adults have been published[1-4,7,8,13-20]. Many of these studies included prisoners, but some included a mix of general psychiatric patients as well. Table 2 summarizes the world published literature on adult IIFO. While children commonly ingest toys, coins, and loose household items, inmates and psychiatric patients are much more likely to ingest sharp and relatively dangerous objects such as blades, improvised shanks, and metal hardware and instruments. Table 3 reviews the types of objects frequently ingested in the published literature.

HEALTHCARE COSTS

The costs of IIFO in the inmate population are high, especially when compared to the non-incarcerated population[21]. It has been estimated that the overall cumulative annual costs of IIFO in the majority (44 out of 50) United States states exceed $6 billion[6].

Table 2 Published series of intentional ingestion of foreign objects with patient treatment plans when available *n* (%)

Ref.	Year	Patients (*n*)	Not undergoing intervention	With psych dx	Surgery	Endoscopy	Objects ingested (*n*)
O'Sullivan *et al*[1]	1996	36 (20 prisoners)	31 (86)	6 (16)	2 (6)	4 (11)	308
[1]Dalal *et al*[2]	2013	30 (141 episodes)	33 (23)	27 (19)	11 (7)	97 (68)	649
[1]Weiland *et al*[3]	2002	22 (256 episodes)	23 (9)		10 (4)	64 (25)	256
Barros *et al*[4]	1991	167 (39 prisoners)	14 (8)	6 (3)	51 (30)	117 (70)	167
Selivanov *et al*[8]	1984	100	42 (42)	4 (6)	12 (12)	42 (42)	101
Blaho *et al*[13]	1998	8	8 (100)	6 (75)			14
Velitchkov *et al*[14]	1996	542 (379 prisoners)	410 (75)	124 (23)	26 (5)	19 (3)	1203
Karp *et al*[15]	1991	19		18 (95)			
[1]Lee *et al*[17]	2007	33 (52 episodes)	0		6 (12)	46 (88)	104
Bisharat *et al*[18]	2008	11	7 (63)		3 (27)	2 (18)	
Huang *et al*[19]	2010	33	4 (12)	27 (81)	2 (6)	299	305
Ribas *et al*[20]	2014	82	142	62 (75)	5 (6)	15 (18)	162
Grimes *et al*[7]	2013	159 (23 prisoners)		34 (21)	5 (3)	231	254
Total		2613	1014 (39)	317 (12)	190 (7)	1129 (43)	3153

[1]Many presented with multiple episodes. Not all studies reported all data. Some studies may include some non-intentional ingestions.

Table 3 Most common types of objects ingested

O'Sullivan *et al*[1]	Batteries, sharp metal objects (nails, razor blades, pins)
Dalal *et al*[2]	Pens, razor blades, spoons, sporks[1], toothbrush, screws, bolts
Weiland *et al*[3]	Metal bezoars
Barros *et al*[4]	Wires, needles, balloons (filled with narcotics)
Selivanov *et al*[8]	Coins, bones, food, razor blades, safety pins
Blaho *et al*[13]	Razor blades
Velitchkov *et al*[14]	Screws, pins, spoons
Huang *et al*[19]	Pens, batteries, knives
Karp *et al*[15]	Razors, glass, toothbrush
Lee *et al*[17]	Metal wires, pens, toothbrush, needles
Bisharat *et al*[18]	Razors, batteries
Ribas *et al*[20]	Razor blades, cylindrical batteries, mattress springs
Grimes *et al*[7]	Toothbrush, pencil

[1]Spork: Functional combination of a spoon and a fork.

The majority of IIFO care costs can be broken down into nursing care (56%), endoscopy services (14%), emergency department care (10%), and surgical services (6%)[19]. Considering the above, IIFO episodes were associated with healthcare-related median charges between $4683 and $7698 for both emergency department evaluations and hospital admissions[5]. In the subset of patients who required hospital admission, median per-episode charges exceeded $14000[5]. Moreover, when repeated episodes of IIFO are factored in, estimated cumulative "lifetime" charges for patients studied in the same cohort were nearly $50000[5]. In addition there are the costs of security and transportation to the prison system because these patients have to be transported in a secure fashion, typically with multiple guards. While hospitalized, a guard must remain at the patient bedside. Hospitals also cover the cost of around-the-clock security for non-prisoner psychiatric patients. The estimated cost not reimbursed by third party payers for security was $278806 in Rhode Island over an eight year span[19].

DIAGNOSIS (VERIFICATION)

Actual ingestions

Most ingestions are either self-reported by the inmate or witnessed by security staff. Patients presenting typically receive a plain X-ray to localize the object. Patients with normal vital signs and normal physical exam typically do not require additional imaging, even in the setting of sharp or other seemingly more dangerous objects.

Plain abdominal X-ray demonstrating free air is considered diagnostic for perforation. However, free air under the diaphragm is rarely seen because perforations are most commonly caused by impactions that have slowly eroded through the intestinal wall. These erosions are covered by fibrin, omentum, or adjacent loops of bowel limiting the passage of free air into the peritoneal cavity[22].

Patients with abdominal pain, fever, gastrointestinal bleeding, or other symptoms typically require CT scanning to evaluate for the presence of bowel perforation or other pathology. It has been shown that prisoners sometimes choose objects that will be visible on radiographs, wrap them in plastic or other materials to reduce the risk of injury, and then feign gastrointestinal symptoms[20]. Most objects are located in the stomach at the time of initial presentation (Figure 1). After initial X-ray, no additional workup is typically performed for radiolucent objects unless mandated by abnormal physical exam findings or vital signs.

Fictitious ingestions

Claimed or fictitious ingestions have been reported[13]. Although speculative, there are three possible explanations for this observed pattern: (1) some form of secondary gain may be present when an ingestion is claimed; (2) an actual ingestion may have occurred but the object ingested is not readily detectable or has already passed through the gastrointestinal system; or (3) the patient may be contemplating ingestion, but has

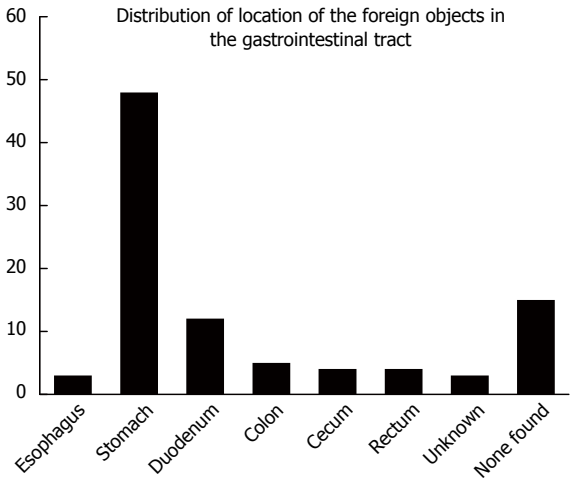

Figure 1 Distribution of intentional ingestion of foreign objects in the gastrointestinal tract in inmate. (From Dalal *et al*[2] Figure 2, permission pending).

not yet committed to this self-destructive behavioral pattern. It is important to note that healthcare-related median charges associated with verified (*i.e.*, proven) ingestions are higher ($5860) than charges associated with claimed (*i.e.*, fictitious) ingestions ($3997)[5].

MANAGEMENT

General principles

Like any surgical emergency, initial management is typically based on physical examination and patient physiology. Patients with peritonitis typically require immediate surgical exploration[2]. Selective endoscopy is appropriate for many intragastric objects and can prevent progressive peristalsis of the object (with its associated dangers)[2,4,8]. In inmate and psychiatric populations surgical exploration should be avoided when possible as the benefits of operative removal often do not outweigh the risks of surgery. Drug and contraband smuggling, known as "body packing," is another event that should be recognized. Ribas *et al*[20] reported on 36 patients attempting to smuggle cocaine by ingesting packets containing the drug. These "body packers" usually do not undergo endoscopy for fear of rupture and surgery is usually only performed if the patient develops symptoms. The operative course itself may be difficult due to the adhesions of previous laparotomies, often due to prior such incidents, and patients with the associated psychiatric comorbidities may have a difficult postoperative course.

In our practice there is a high rate of wound complications, self-inflicted wound mutilation (including self-inflicted evisceration of the midline laparotomy site), and non-compliance with physician orders (such as violation of nothing-by-mouth orders resulting in aspiration of gastric contents). Prisoners who develop complications of surgery for IIFO are at risk for the development of intestinal fistula and we have observed generally poor outcomes of both operative and non-operative management of fistulas in this population, with high rates of readmission, parenteral nutrition-associated line infections, abdominal wall infections, and non-healing wounds. In our previous work we reported the various management strategies employed for 141 episodes of IIFO in inmates (Table 4)[2].

Table 4 Relative frequency of intentional ingestion of foreign objects management strategies employed in 141 episodes of intentional ingestion of foreign objects

No intervention	16%
Hospital admission	10%
Surgery alone	5%
Endoscopy + surgery	3%
Endoscopy alone	12%
Endoscopy (successful)	54%

Observation

In the vast majority of cases (approximately 67%-80%) expectant management will suffice, including watchful waiting and serial physical exams, with or without concurrent radiographic assessments[1,8,14]. Most of the foreign bodies that clear the stomach will spontaneously pass through the gastrointestinal system, frequently within a week[3,8]. Fortunately, many of the IIFO episodes end up being self-limited, and do not require formal hospital admission[22]. The need for admission is present in 7%-33% of patients[1,13]. In one series of 141 ingestions, the risk of hospital admission was independently associated with elevated white blood cell count [odds ratio (OR) 1.4] and increasing number of items ingested (OR 1.3)[2].

Endoscopy

Endoscopy has revolutionized the management of IIFO. In fact, the forward-viewing flexible endoscope is the first option for retrieval of foreign objects in the stomach and duodenum[23]. Most ingested objects can be retrieved endoscopically, as long as they have not progressed beyond the ligament of Treitz. Successful endoscopic retrieval of IIFO has been reported in 19.5%-53.9% of cases[2,14]. Some of the more common objects retrieved by endoscopy are coins, bones, and impacted food[8]. In one study, the successful performance of endoscopy with retrieval of the IIFO has been found to reduce the risk of surgery by over 85%[2]. Having said that, endoscopy has also been associated with high failure rates and complications by others, thus warranting careful consideration when implementing this therapeutic option[3]. Grimes *et al*[7] found first time ingestors were more likely to have a food impaction compared to recurrent ingestors who were more likely to have ingested metal objects; however, recurrent ingestors experienced food impactions as well, commonly due to esophageal stricture[7]. In the same study one patient was found to be responsible for 67 ingestions (22%)

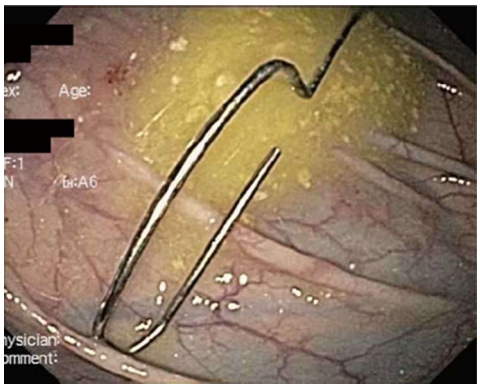

Figure 2 Paperclip in the ascending colon noted on colonoscopy (image rights belong to the authors).

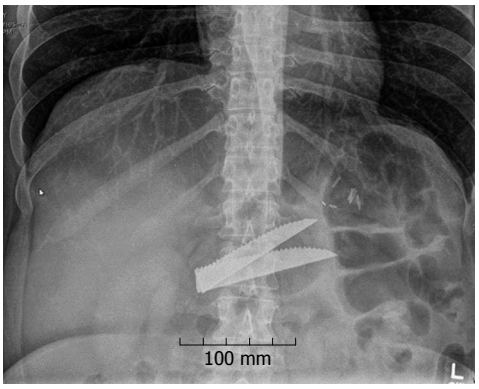

Figure 3 Steak knife blades in the stomach (image rights belong to the authors).

of the ingestions. On average there were 9.2 episodes per patient. They also found that endoscopy was more successful in single ingestion patients, supporting the idea that the more times a patient ingests an object the more complex the ingestion becomes. Most objects that pass the ligament of Treitz are likely to pass through the entire GI tract. Rarely, small objects can become impacted in the colon. Endoscopy is frequently successful in removing those small objects such as the paperclip that was removed by the author (D.C.E.) depicted in Figure 2. While some sharp objects such as small razor blades can be removed endoscopically, particularly with the use of hoods, available endoscopic equipment and local practices may vary and we cannot draw any conclusions regarding recommendations for specific strategies for objects of various shapes, sizes, or sharpness.

Surgery

Operative intervention is required in up to 30% of IIFO cases[1,2,4,8,14], although more recent series report lower rates (*i.e.*, < 15%) of operative intervention in this population[1,2]. In one large retrospective study, factors independently associated with risk of surgery in the setting of IIFO included elevated white blood cell count (OR 1.6) and increasing number of ingested items (OR 1.1 per item)[2]. Not surprisingly, failure of endoscopy has been associated with the need for subsequent operative intervention[4]. It has been noted that thinner, sharper foreign objects mandate a higher index of clinical suspicion due to higher perforation risk[14]. Also, surgery may be more likely in cases of proximally located IIFO, especially when the object is > 6-7 cm in largest dimension[14]. Previous surgery, obstruction, and narrowing all predispose to impaction of an object and increase the possible need for surgical intervention[22]. Long objects, such as the intragastric steak knife blades shown on abdominal X-ray (Figure 3), frequently require laparotomy. The author (D.C.E.) retrieved one blade endoscopically but the other became impacted at the esophageal hiatus and required laparotomy with gastrotomy for removal.

Figure 4 Balls of narcotics wrapped in plastic wrap. These required surgical removal in a prisoner who was engaged smuggling activities by "body packing" (image rights belong to the authors).

IIFO impaction is also possible, particularly in the ileo-cecal area[14]. The ileocecal region is particularly prone to obstruction by objects less than 6 cm that are able to maneuver through the duodenum[22]. Velitchkov *et al*[14] advocate an appendicostomy approach to retrieval of IIFO impacted in this location, however, most surgeons would prefer a simple enterotomy with foreign object retrieval, followed by repair of the enterotomy[14]. Figure 4 depicts small plastic-wrapped balls of narcotics removed from the terminal ileum by the author (D.C.E.) in a prisoner who was smuggling drugs by body packing. The patient developed an acute complete small bowel obstruction requiring emergent laparotomy. We performed a simple enterotomy in the ileum that was closed with interrupted silk sutures.

When it comes to IIFO-related gastrointestinal tract perforations, certain generalizations can be borrowed from the cumulative experience with non-intentional foreign object ingestions. In that setting, perforations

of the stomach, duodenum, and large intestine tend to present with slow onset of non-specific clinical signs while perforations of the ileum and jejunum typically are severe and acute[22]. This is likely due to foregut and hindgut perforations occurring in retroperitoneal spaces where perforations are often contained. In contrast, midgut perforations are more likely to result in free spillage of enteric contents into the abdomen.

PREVENTION

Recently published data reinforce the critical importance of prevention in the setting of IIFO, especially when repeated episodes of ingestion are present[2,5]. It has been difficult to prevent psychologically ill patients from ingesting foreign bodies and psychiatric medication has proven ineffective. Prisoners typically receive mental health care in their institution and do not require admission to the hospital for psychiatric care. Many of these patients are not suicidal and their psychiatric illness is not acute in nature, so psychiatric hospital admission is typically of little value[19]. Prevention strategies suggested include decreasing access to objects in the environment, increasing psychotherapy, changing diet for those with a history of food impaction, and dilating the esophagus for those with stricture[7].

The impetus for prevention primarily stems from the association between escalating psychiatric illness and repeated ingestion episodes. The fact that patients with recurrent ingestion episodes tend to have more severe psychiatric illness (as evident by the increasing number of formal psychiatric diagnoses) supports the contention that early and aggressive psychiatric intervention may help curtail the escalation of this self-damaging behavioral pattern. Gitlin *et al*[24] present a fascinating discussion of the psychiatric aspects of IIFO and found that most IIFO cases in the general population are associated with malingering, psychosis, pica, or personality disorders[24]. Treatment should be tailored to the patient's specific psychiatric diagnosis[25]. Prisons may employ closely monitored units in combination with psychiatric care in an attempt to reduce this type of behavior.

Another impetus for aggressive prevention is that finding that the financial burden of IIFO also tends to escalate as this repetitive self-destructive behavior continues to recur[5]. As the complexity of care and frequency of surgical intervention increases in patients with a history of prior ingestions, so does the cost of care.

CONCLUSION

IIFO is a rare but complex and expensive disease in prisoners. Observation and endoscopy are common appropriate management strategies and surgery should be avoided when possible. For those patients who present with their first episode of IIFO, an intensive monitoring and prevention plan should be developed to reduce the risk of recurrent episodes. While more data on the types of prevention interventions and their effectiveness is needed, the pattern of escalation among the IIFO population certainly warrants organized, proactive approaches.

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REVIEW

Therapeutic upper gastrointestinal tract endoscopy in Paediatric Gastroenterology

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Abstract

Since the first report of use of endoscopy in children in the 1970s, there has seen an exponential growth in published experience and innovation in the field. In this review article we focus on modern age therapeutic endoscopy practice, explaining use of traditional as well as new and innovative techniques, for diagnosis and treatment of diseases in the paediatric upper gastrointestinal tract.

Key words: Child; Pediatrics; Endoscopy; Gastroscopy; Intestinal polyps; Hemorrhage; Caustics; Gastrostomy; Mitomycin; Gastroesophageal reflux

Core tip: This is a comprehensive review on use of therapeutic upper gastrointestinal endoscopy for emergency and elective procedures in paediatric gastroenterology.

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INTRODUCTION

Significant advances have occurred in diagnostic and therapeutic paediatric endoscopy since the first report of its use in children in the 1970s. The last two decades has seen an exponential growth in published experience and innovation in the field of paediatric therapeutic endoscopic intervention in the upper gastrointestinal (GI) tract and is the subject of this review.

HISTORY

The first attempt to observe the living human body

directly through a tube was in 1805 when Philip Bozzini created an instrument known as a Lichtleiter (light guiding instrument) to examine the urinary tract, rectum and pharynx[1,2]. In 1853, Antoine Jean Desormeaux of France developed an instrument specially designed to examine solely the urinary tract and the bladder; he named it the "endoscope", and it was the first time this term was used in history[3,4].

The first gastroscopy is accredited to Adolf Kussmaul in 1868, a German physician, who enlisted the help of a professional sword swallower to pass a 47 cm long metal tube with a 13 millimetre diameter into his stomach[5]. It was not until 1881, that Johann von Mikulicz and his colleagues created the first rigid gastroscope for practical applications; unfortunately these gastroscopes were not flexible at all. Finally in 1932, Dr. Rudolph Schindler invented the first flexible gastroscope that allowed examinations even while the tube was bent[4]. However, the significant breakthrough in endoscopy occurred in the 1950s with the advent of glass fiber, with Basil Hirschowitz being credited with development of the first flexible fiber-optic endoscope in 1957[6]. Following these adaptations, endoscopy of the GI tract became a routine diagnostic and therapeutic tool throughout gastroenterology units around the world.

With reduction in its size in the early 1970s, a few paediatricians began to adopt this new tool to examine the upper digestive tract[7]. During the late 1970s, the diagnostic value of endoscopy was slowly replacing the requirement of contrast radiology in the paediatric setting[8,9]. Subsequently, the first commercially available slim scope became available, the Olympus GIF-P, which was used in a few select paediatric centres around the world. However it was not till 1981 when the first European workshop on paediatric gastrointestinal was held, that a dedicated scope for paediatric use was developed, Olympus GIF-XP, which had an outer diameter of 7.8 mm. Consequently, other models by Fuji and Pentax were developed for the developing paediatric market.

PAEDIATRIC ENDOSCOPES

There are no published data to guide recommendations for endoscope choice, so decisions are made on standard practice and experience. The techniques in paediatric gastroscopy are principally the same as in the adult field specific consideration needs to be given to the slight anatomical variations. The oesophagus of the newborn is about 10 cm in length and about 0.5 cm in diameter and the trachea that sits in front of this is easily compressible during gastroscopy. The antrum and proximal duodenum are also more angulated requiring a greater degree of tip deflection before intubation into the empty duodenum which has a diameter of 1 cm[10].

Endoscopes for paediatric cases are chosen on the basis of age and weight of the patient. Table 1 illustrates this, reflecting practice in paediatric gastroenterology units in Southampton and Sheffield. Table 2 shows the current paediatric scopes available.

Table 1 A guide to use of paediatric scopes according to weight

Weight (kg)	OGD	ERCP
< 2.5	⩽ 6 mm gastroscope	7.5 mm duodenoscope
2.5-10	⩽ 6 mm gastroscope preferred. Standard gastroscopy may be considered particularly if endotherapy required	7.5 mm duodenoscope
10-35	Slim or Paediatric Gastroscope	*Via* slim or paediatric gastroscope
> 35	Standard	Most will tolerate standard therapeutic duodenoscope

INDICATIONS

Over the past few years, many organisations have attempted to identify selected criteria to create a list of indications for paediatric patients most likely to benefit from upper gastrointestinal tract endoscopy[11,12]. Because children undergo endoscopy less frequently than adults, the volume of evidence for its practice is limited compared to adults, nevertheless, there does remain a need for such guidelines. In essence, the decision to perform an endoscopy is based on whether it will alter diagnosis, treatment or prognosis. However, local expertise and availability of the test along with its cost can play an influential part in the decision making process. The most common indications for diagnostic and therapeutic endoscopy in the paediatric setting are listed in Table 3.

Recurrent abdominal pain or upper gastrointestinal bleeding account for the most common indications in the "Eastern" world[13-15] and abdominal pain and failure to thrive in the Western world[16-18].

INTERVENTIONAL ENDOSCOPY

The role of therapeutic intervention in the paediatric upper gastrointestinal tract can be divided broadly into (1) emergency and (2) elective procedures.

Emergency procedures

The two most common scenarios faced by the paediatric gastroenterologist is foreign body ingestion in the upper gastrointestinal tract (for example inanimate objects or food bolus and upper gastrointestinal tract bleeding. We discuss this further below.

Foreign body removal (Figures 1 and 2): As the child grows, explores and interacts with their local habitat they inevitably put foreign bodies into their mouths, ingesting a small proportion of them. Of over a 100000 cases of foreign body ingestion in the United

Table 2 Current paediatric endoscopes available

Manufacturer	Model	Insertion tube length/diameter (mm)	Definition/magnification/colour enhancement	Biopsy channel diameter (mm)
Olympus	GIF-N180	1100/4.9	Standard/none/NBI	2.0
	GIF-XP180N	1100/5.5	Standard/none/NBI	2.0
Fujinon	EG530N	1100/5.9	High-definition/zoom/none	2.0
	EG530NP	1100/4.9	High-definition/zoom/none	2.0
Pentax	EG1690K	1100/5.4	Standard/zoom/iSCAN	2.0
	EG1870K	1050/6.0	Standard/zoom/iSCAN	2.0

Adapted table from ASGE equipment for paediatric endoscopy status evaluation report.

Table 3 Indications for upper gastrointestinal endoscopy

Diagnostic
Recurrent abdominal pain (differentiation from FGIDs is important)
Weight loss/failure to thrive not just due to lack of nutrition
Dysphagia
Diarrhoea/malabsorption (differentiation from FGIDs is important)
Continued vomiting/haematemesis other than a simple
Mallory-Weiss tear
Investigation for iron deficiency anaemia
Suspected enteropathy-coeliac (new guidelines)/autoimmune
Part of investigations for inflammatory bowel disease
Therapeutic
Foreign body removal
Insertion of feeding tube
Dilation of strictures
Injection/banding varices
Treatment with Botox
Excision of polyps

States each year, more than 80% occur in children, mainly between the ages of 6 mo and 3 years[19-21]. Fortunately most foreign bodies that enter, pass through the gastrointestinal tract spontaneously, with only about 10%-20% requiring endoscopic removal and less than 1% require surgical removal[19,22]. Deaths are extremely rare but they have been reported[21,23]. The types of objects vary with geography but in the western world, coins are the most frequently encountered foreign body, while in the eastern world, fish bones account for a greater percentage[21,24]. Objects such as batteries or safety pins can add a degree of complexity and risk to foreign body retrieval.

After initial workup with a detailed history and biplane X-rays (antero-posterior and lateral), intervention depends on three factors; (1) the object ingested (2) location of the object and (3) the age of the patient. The location is often in areas of physiological narrowing; the upper oesophageal sphincter, the level of the aortic arch, lower oesophageal sphincter or the dependent part of the stomach, usually the gastric fundus[22,25]. It is important to note that the location of the pain or symptom does not always correlate with the associated site of impaction (visceral innervation)[26]. In the very young, due to the compressibility of the trachea, endoscopists need to be aware that even relatively small objects can potentially cause serious tracheal compression leading to respiratory compromise[10].

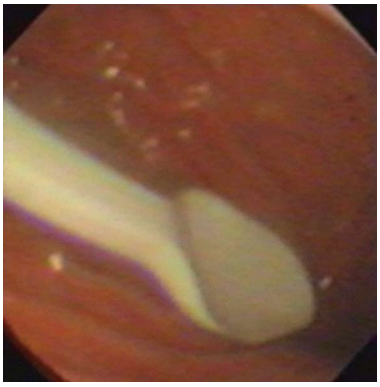

Figure 1 Foreign body (a plastic spoon) in the stomach of a child. Ingestion of coins and small lithium batteries tend to be much more common.

There are various methods to remove foreign bodies, with the flexible gastroscope being preferred as it allows direct visualisation, manipulation and observation of any potential injury to the adjacent mucosa[27,28]. The endoscopist should have an array of equipment readily available including polyp snares, alligator forceps, rat-tooth forceps, net baskets and overtubes.

Magill forceps, angled forceps commonly used in anaesthesia, are sometimes sufficient to remove a variety of objects in the oropharynx or upper oesophagus providing direct vision is possible. This may require the use of general anaesthesia and a laryngoscope to gently open up the oesophagus[29].

The use of a rubber or plastic dilator (Bougienage) may be used for foreign bodies impacted beyond the reach of forceps in the oesophagus to aid their passage into the stomach. However, careful consideration needs to be taken to assess that the object is judged able to pass along the oesophagus into the stomach without causing significant mucosal injury (*e.g.*, blunt and small objects such as coins) The use of this technique is thus limited and most endoscopists would only advocate this in experienced hands and only in patients where there has been witnessed ingestion within 24 h without existing oesophageal disease[30,31].

An alternative method is extracting the object impacted in the oesophagus with the use of a Foley catheter. This technique involves passing the Foley catheter past the foreign body and inflating the balloon with radio-opaque dye, then with fluoroscopic

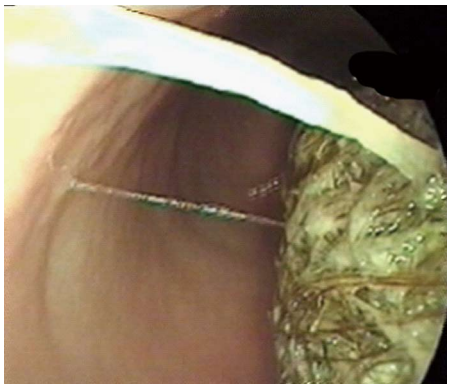

Figure 2 Bezoar seen at endoscopy. Endoscopic removal wasn't possible.

guidance, gently pulling on the catheter so the object is drawn back into the oral cavity and retrieved[32]. Many endoscopists do not advocate this technique in inexperienced hands as there is the risk of perforation or inadvertent placement of the foreign body into the trachea[33].

Pragmatically, foreign objects beyond the reach of forceps require intubation of the oesophagus with a flexible gastroscope. On entering the oesophagus, occasionally air insufflation or water flush alone may be sufficient to dislodge certain foreign objects to pass the lower oesophageal sphincter into the stomach. Smooth, round objects such as coins or flat batteries can often, more easily, be grasped with alligator jaw forceps. Rubber tipped or specialised alligator forceps are available for the paediatric 2 mm channel.

Special mention needs to be made regarding "button" batteries which are now ever more increasingly being swallowed[34]. Although standard batteries can cause problems due to their size and from the leakage of caustic material, button batteries have the added risk of conducting electricity (as both poles are in direct contact with the mucosa) which can cause significant necrosis and potential perforation[35]. Hence, even if these small batteries are not causing direct impaction, if found anywhere in the upper gastrointestinal tract, they should be removed. The preferable technique is to use a Roth Net® and retracting the basket as far back into the endoscope as possible and removing the endoscope and the foreign body together in one sweep.

Up to 30% of objects ingested are "sharp" such as needles and pins[21]. Unfortunately, the majority of sharp pointed objects are not radio-opaque. Hence, if there is a clinical suspicion of ingestion of these objects, it is of the authors' opinion that they should all proceed to having an endoscopic assessment and retrieval. Forceps and snares are often suitable as retrieval devices, minimising potential mucosal injury on retraction. This can be achieved by either retrieving the foreign body with the sharp end trailing, using an overtube or even novel devices such as protector hoods on the end of the endoscope[36].

Food bolus: This does not occur as frequently as it does in the adult population (the most common cause of oesophageal foreign body in this group)[37]. The likelihood of there being an underlying oesophageal pathology is higher such as eosinophilic oesophagitis, achalasia or strictures[38].

The indications for intervention is the same as that of other foreign bodies and inability to swallow saliva always requires emergency endoscopy, otherwise there is a risk of aspiration.

The use of medication, for example glucagon, buscopan and proteolytic enzymes, although still being used in current practice lack any evidence and the true likelihood is that the bolus would have passed naturally anyway. Therefore, authors, do not advocate their use considering the associated side effect profile[39]. An overtube may facilitate multiple passes of the endoscope that may be required, but caution with its use needs to be considered, as mentioned earlier.

Methods of removal can be broken into two actions of either "pushing" of the bolus into the stomach or "extraction" of the bolus into the oral cavity. With each method the food may be extracted preferably whole or "piecemeal". Both methods have been proven to be effective but the former "pushing" method is less preferable considering the unknown potential of pathology distal to the food bolus[40,41]. "Piecemeal" removal can be achieved using alligator forceps, rat-tooth forceps or tripod forceps down the accessory channel facilitating safer "pushing" of contents into the stomach.

Certain food boluses are not easily broken down into smaller pieces, in which case suction can be used with the aid of a cap on the end of an endoscope. If one is not readily available, the friction fit adaptor from an oesophageal band ligation kit can be used, allowing suction to stabilise the food bolus at the distal end more securely before pulling it into the oral cavity[42]. The authors have a preference of using a Roth Net®, with the catheter gently placed alongside the bolus with the net then opened in direct vision carefully in a "to and fro" manner to accommodate the food bolus before angling the net from one wall to the other to then allow the bolus to be caught in the net and retrieved.

Upper gastrointestinal tract bleeding: Life threatening gastrointestinal bleeding in paediatrics is rare but it is important for the endoscopist to recognise when it occurs and act promptly. As this is encountered infrequently in most endoscopy units, much of the evidence for the use of various haemostatic methods in children is inferred from the adult population. It is the common practice for the authors to collaborate with adult gastroenterologists and paediatric surgeons in the case of a serious gastrointestinal bleed.

Bleeding in the upper gastrointestinal tract can arise from peptic ulcers, varices, Mallory-Weiss tears,

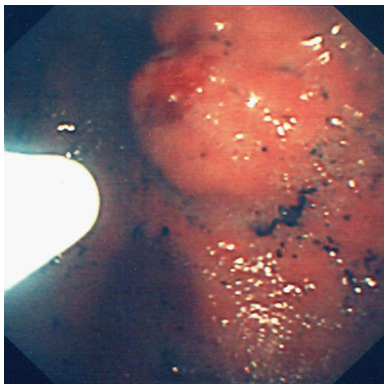

Figure 3 Injection of glue into a gastric varix.

dieulafoy lesions and angioectasia[43,44]. Unfortunately, there are no large series looking into gastrointestinal bleeding in children overall, with most large prospective studies assessing the incidence in the specialised paediatric intensive care setting[45]. Case series from Asia and developing countries show a higher incidence of variceal bleeding (mainly from extrahepatic portal hypertension) and those in developed countries having a higher incidence of erosive/peptic ulcer bleeding (mainly in the context of a a critically ill state)[45,46].

It is important for the endoscopist to be aware of the different modalities of endoscopic haemostasis available and it is just as important to know when these modalities would be required. Several scoring systems have been created in adults, although not validated in children, that can be used (after certain parameters are adjusted), to ascertain the need for endoscopic intervention. Blatchford and Rockall scores are used worldwide although there has been recent debate on their validity in the prediction of re-bleeding and 30 d mortality[47,48].

For peptic ulcers, the Forrest criteria was created for high-risk bleeding stigmata found during endoscopy. The presence of active bleeding, a non-bleeding visible vessel (re-bleeding rate of 40%-100%) or adherent clot (re-bleeding rate of approximately 25%) are indications for endoscopic treatment. While clean based ulcers do not require endoscopic therapy as the risk of re-bleeding is low (5%)[49,50]. Varices that are not actively bleeding can still be considered at high risk if there are signs of engorged protuberant vessels or a prominent red petechial mark on the vessel (cherry red spot) and therefore therapy should be considered.

The type of therapy used is dependent on the size of child, the type of lesion, the site of bleeding and the judgement and ability of the endoscopist. Three modalities are available to the endoscopist, which can be divided into 3 categories: injection, mechanical haemostasis or thermo-coagulation. Ideally, if the patient size permits, a two channel scope is preferable so that haemostasis can be achieved with concurrent use of flushing of the target area with saline for better visualisation.

(1) Injection therapy: Most injection needles have a small enough diameter to pass through a 2 mm channel in a paediatric gastroscope. Vasoactive agents, sclerosing agents and tissue adhesives can all be delivered by these needles.

Adrenaline is typically available in 1:10000 dilution and its action is *via* local vasoconstriction, platelet aggregation and mechanical tamponade[51]. In the case of an ulcer, it is important to wash the area, even if it is for a temporary view, in order to visualise the ulcer and identify a possible bleeding vessel. The scope is advanced near to the ulcer and the needle catheter fed through the channel. It is important to have the gastroscope close to the lesion or vessel as the extra length of catheter may predispose it to "kinking". Ideally, one should aim to inject 1-2 mls aliquots in 4 quadrants around the ulcer or near the vessel (so theoretically to exhibit its 3 effects circumferentially around the bleeding point). Unfortunately, no data exists for exact volumes in children as it does in adults where large volumes of 13-20 mls have been shown to be more efficacious[52].

Sclerosing agents such as sodium tetradecyl sulphate and ethanol act by inducing localised thrombosis over the bleeding vessel. In the past, sclerosing agents had been used for treatment of peptic ulcers and dieulafoy lesions[53]. In the last 2 decades, their role has been more confined to dealing with varices. Although band ligation is more efficacious in the adult population, the benefit of sclerosing agents in children is that they can be used in scenarios where band ligators are too large to pass through the oropharynx of a young child. The exact dose to use is not clear, but recent ASGE (American Society of Gastrointestinal Endoscopy) suggest the use of a quarter to half of what would be used in adults in children under the age of 12 years[54]. Injection can be delivered directly into the varix causing direct thrombosis or para-varix causing tamponade and submucosal fibrosis. Complications can occur including chest pain, mucosal ulceration and stricture formation. The largest case series to date was by Poddar *et al*[55] who demonstrated the use of alcohol injection in 257 children with varices and showed successful eradication in 95% of patients with a mean of 4.5 sessions (mean volume of 8 mls of absolute alcohol used). In this series 1.4% (n = 3) had perforation and 18% (n = 38) had stricture formation[55].

Tissue adhesives such as fibrin glue have emerged as being successful in adult treatment particularly for gastric varices (Figure 3)[56]. There is only one pilot study, to date, in the paediatric population by Rivet *et al*[57] where 8 infants were treated successfully for varices with fibrin glue. There are technical challenges with this agent, as there is a risk of the needle sticking to the varix or blocking the endoscope channel and causing serious damage. The authors' preference is to inject between 1-2 mls and flush thoroughly with

water and instead of bringing the injection needle back up the channel, to withdraw it together with the endoscope and cut the tip, hence preventing any adhesion to the scope.

(2) Mechanical therapy: Mechanical therapy in the form of clips is ever increasingly being utilised as it has the ability to effectively tamponade areas of bleeding. Its efficacy has been excellent in non variceal bleeding in adults, however published experience in the paediatric setting is lacking. Interestingly, a Japanese series has shown its benefit in prophylaxis. Eighty two children who underwent clipping of their varices, showed a prevention of variceal progression in 90%[58]. One of the limiting factors for its use is that all current brands on the market today need a channel size of 2.8 mm, therefore it is not compatible with paediatric gastroscopes. The jaw length of haemoclips range from 9-11 mm. Each brand has a slightly different clip deployment method, with the option of opening and closing the clips several times as well as clip rotation before deployment.

It is imperative that the endoscopist becomes familiar with the deployment technique. In the authors' experience, it is often the lack of communication between the endoscopist and assistant that leads to unsuccessful clip deployment. Indications for clip deployment are mainly for a bleeding vessel in an ulcer base, dieulafoy lesion or bleeding from Mallory-Weiss tears. It is the authors' preference to use a set of commands consisting of: (1) expose (exposing the clip from sheath); (2) open (opening jaws of clip); (3) close (closing of jaws); and (4) deploy (deploying the clip from the shaft). A useful pneumonic to remember is Extreme OCD (expose-open-close-deploy). In a case of severe bleeding that subsequently requires angiography, the radiologist finds the clip a useful aid to identify the site of the bleeding vessel before coil placement.

Band ligation has been the mainstay of treatment for oesophageal variceal haemorrhage for the last 3 decades. It can be utilised for primary haemostasis or for prophylactic measures. The device consists of a cylindrical friction fit adapter cap which has a number of elastic ligating bands fitted around it. The adaptor is placed on the end of an endoscope (minimum tip of 8.5 mm required) and a thread connected to these bands is fed through the channel of the endoscope to a deploying handle positioned on top of the biopsy channel. After the endoscope is placed in the desired location, suction is applied to draw the varix (or other lesion) into the adaptor. The bands are deployed by rotation of the handle, ideally suction should be held for a further 2-3 s to allow the band to fully reach its maximum tension capacity. For varices, this should ideally occur near the GOJ and proceed proximally to avoid obstruction of views by the bands or inadvertent displacement. In contrast to adult studies, randomised control studies are lacking and when they have been undertaken, the sample sizes have been small. As such, there is no consensus on the best modality, although reports suggest fewer complication rates with bands than with sclerotherapy[59].

(3) Thermo-coagulation: Thermo-coagulation devices deliver thermal energy causing coagulation and desiccation which can lead to haemostasis. There are 2 types available, monopolar and bipolar. With monopolar devices, *e.g.*, hot biopsy forceps, an electrical current is passed through the probe tip and conducted through the patient through a grounding pad and back to the diathermy unit. The probe can be applied directly to a vessel until bleeding stops. However, the authors do not use this routinely for haemostasis as the depth of burn is difficult to regulate and a deep thermal injury or perforation is possible[60].

A preferable method is bipolar coagulation. Here, the probe delivers thermal energy by creating an electrical circuit between 2 electrodes on the probe tip. Therefore, the electrical current passes through the affected tissue only, so tissue penetration is less deep. There are 5-French heater probes that can be used with paediatric gastroscopes. Bipolar probes have 6 points through which current can be passed and hence good tissue contact can be made, whether it is used en face or tangentially. As it has less tissue penetration, more pressure is required for deeper penetration and application time is longer. From the authors' experience when haemostasis is not achieved, it is often when the endoscopist has not taken enough time to place the tip on the bleeding point, which should be a minimum of about 10 s for a bleeding vessel or 3-4 s for angioectasia.

Heater probes have an electrical heated coil inside a Teflon-covered insulated cylinder. Coagulation is performed by directly applying heat through the probe over the bleeding vessel with pressure. There is very little experience of this in paediatrics and currently no probe available for paediatric scopes.

Argon plasma coagulation (APC) is a non-contact form of coagulation in which current is transmitted in an arc of electricity through an ionised gas (argon). It has been shown to be useful in adults for non-variceal bleeding and is commonly used in the treatment of radiation-induced proctitis[61]. The degree of coagulation is dependent on several factors: the power settings, duration of application, distance between tip and tissue and flow rate of the argon gas. Its advantages are that as the tissue coagulates, the conductivity decreases which hence limits the depth of injury and it is available in a 1.5 mm diameter probe for the paediatric gastroscope. There is only one case series of its use in children by Khan *et al*[62] where 13 children with upper GI lesions (ulcers, haemangiomas and erosions) were successfully treated with APC (flow rate of 0.9 L/min and power at 55 w). Care should be taken to aspirate the argon gas frequently which is potentially combustible in large volumes.

Elective procedures

As experience grows in this evolving field, the range of indications for "chronic" conditions suitable for therapeutic intervention increases. We list a few of these used in common practice as well as some novel therapies.

Percutaneous endoscopic gastrostomy

This is now very commonly used since it was first performed by Gauderer *et al*[63] in 1979. To this day, it is still an effective method of feeding *via* the stomach where the oral route may not be possible, providing hydration and nutrition[64]. Endoscopic gastrostomy placement compared to surgical placement was developed to avoid surgical intervention. The most common indications for its use in the paediatric setting are neurological impairment or failure to thrive[65,66]. Percutaneous endoscopic gastrostomy (PEG) use is based around the fact that the continuous, suture-less approximation of the stomach to the peritoneum and anterior abdominal wall by a feeding tube leads to the formation of adhesional attachments which subsequently leads to the formation of a tract around the tube[66].

Several modifications of the technique have been introduced since it was first described. The "pull" technique is the most commonly used. This involves performing a gastroscopy to identify the anterior stomach and using sufficient air insufflation to oppose the anterior stomach with the anterior abdominal wall, pushing aside any possible visceral organs that may be inadvertently punctured. The area for insertion of the tube is ascertained by visualisation of trans-illumination of the gastroscope through the abdominal wall and visualisation of a clear finger indentation within the stomach lumen. This area is marked and sterilised before infiltration of local anaesthesia. A skin incision of approximately 0.5 cm is made (only few mm depth required) which can be made horizontally so the scar can be hidden within skin creases for aesthetic purposes. A trocar/angiocath is pushed through this point into the stomach under endoscopic vision. A soft guide wire is then inserted through this so that it just appears within the gastric lumen. This threading wire is then snared through the endoscope and the whole apparatus, scope, snare and thread are withdrawn together. After the guide wire is out, a suitable feeding tube is attached to it and pulled through the mouth and out of the incision. An external bolster/stopper is then placed on the skin to hold this in place. It is at discretion of the endoscopist whether it is necessary to re-intubate the scope to confirm placement of the tube.

The authors would advocate that the distance on the PEG tube is documented, *i.e.,* the distance from the "button/stopper" in the gastric end to that on the skin surface, markings which are available on all feeding tubes. This distance varies according to the size of the child, however, it may be a guide in cases where a larger than expected distance is noted to suggest a possible additional inadvertent visceral attachment. Antibiotics should always be given although the optimal timing, whether pre, post or peri can be left to local microbiology policies.

Oesophageal dilatation: Unlike in adults, where malignancy is the major cause of upper gastrointestinal structuring, in children it is almost always caused by benign disorders. Techniques and equipment used in adult patients can be applied to children, *i.e.*, bougienage, balloon dilatation and self-expanding stents (seldom used). The approach will be determined as with many cases where adult skills are transferred to the paediatric setting by characteristics of the stricture, position, size (both radial and longitudinal), availability of equipment, expertise of the endoscopist and patient size.

The most common cause of oesophageal stricturing worldwide is the ingestion of caustic liquids from around the house, with the other major causes falling into peptic or post-surgical strictures (mainly corrective surgery for oesophageal atresia)[67]. Rarer conditions involve the consequences of prolonged ingestion of certain foreign bodies, strictures associated with eosinophilic oesophagitis, post variceal sclerotherapy and congenital abnormalities.

Dilatation is indicated in patients with symptomatic obstruction. Anastomotic strictures post oesophageal atresia are common, with an incidence of up to 44% in some series[68,69]. Koivusalo *et al*[70] demonstrated that a watch and wait policy based on symptomatology was superior to routine dilatations as greater than half did not require any subsequent dilatations[70].

The purpose of oesophageal dilatation is to alleviate symptoms, permit free intake of enteral nutrition and reduce complications such as pulmonary aspiration. This must be weighed up against the risk of perforation. This has been reported as 0%-5% after balloon dilatation and 8%-9% after bougienage[71,72].

Bougie dilators come in a range of makes and diameters. However, in the paediatric setting experience is mainly with Savary-Gillard type systems, *i.e.,* a long tapered, radio-opaque, wire-guided and poly-vinyl hollow tubes designed for use in the oesophagus. The bougie system is naturally limited to the oesophagus in the upper GI tract as transmission of the force more distally would be more difficult. Bougie dilators apply axial as well as radial forces[73]. They come in sizes of 5-20 mm diameter and 70-100 cm in length. The technique involves feeding a guide wire through the lumen of the stricture either endoscopically, fluoroscopically or both. When done solely endoscopically, it is worthwhile to note the distance of the stricture from the incisors. After the endoscope is retracted, it is imperative, particularly if fluoroscopy is not used, to maintain the guide wire in a fixed position by an assistant so it does not inadvertently move out of position. The bougie is lubricated well and passed over the guide wire until the maximal diameter has passed

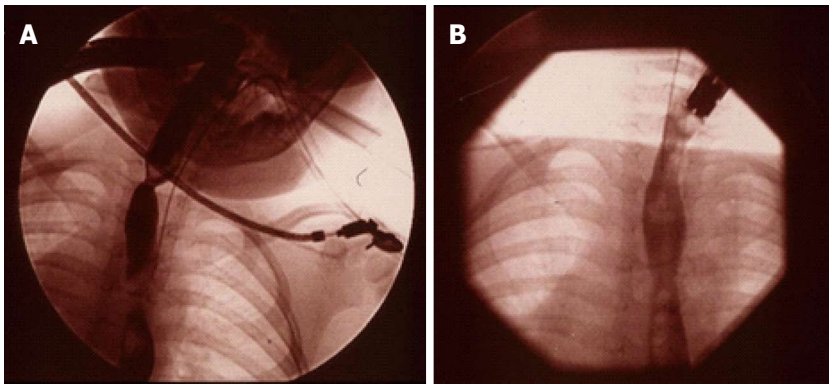

Figure 4 (A) Videofluoroscopy image of a proximal and a distal stricture in the oesophagus and (B) resolution of the strictures in the same child 3 mo after treatment with Mitomycin C.

over the area of the stricture (as estimated from the previous incisor distance). In adults, it is advocated that only 3 dilators or a maximum increment of 3 mm from initial dilatation occurs in a single session to minimise risk of oesophageal perforation[74]. This data is lacking in children and hence an estimate of the diameter of the adjacent normal calibre oesophagus should be used.

Balloon dilators have the benefit of potentially being used under direct vision and delivering direct radial force across the entire stricture, while controlled manometrically by a hand held device by an assistant. It cannot be passed down the standard 2.0 mm channel of a paediatric scope but in these scenarios, guide wires can be placed *via* fluoroscopy to enable the balloon catheter to pass over this[75,76]. Balloons are available in 4-40 mm diameter and length varying depending on location used. With this range is mind, in infants, larger length balloons may traverse unnecessarily the entire length of the oesophagus so shorter lengths, pyloric or colonic, should be used in this group. The ideal length of time the balloon is inflated is not known but it is the authors' experience to leave it inflated for at least 1 min.

One of the issues with caustic strictures is the frequency of stricture recurrence after dilatation. The authors reported the first use of Mitomycin-C, an antifibrotic agent, for treatment of caustic strictures (Figure 4)[77]. Following the initial report, a case series was reported from 8 paediatric gastroenterology centres around the world about its successful use[78] and it has now been adopted as standard practice in many units[78,79].

Choice of methods for dilatation is largely down to the experience of the endoscopist and it is not known if one method is better over another for any particular indication. In retrospective data of oesophageal atresia patients, balloons were found to be more effective than bougienage and required fewer dilatations[79]. However, another report showed those with peptic and caustic strictures did better with bougienage[80]. Balloon dilatation does seem to offer a better safety profile and better efficacy[79]. Perforations are a risk although this can be minimised by cautious and gentle dilatation, and avoidance of excessive manipulation that may cause potentially damaging shearing axial forces.

Gastroesophageal reflux disease-novel therapies: The burden of gastro-oesophageal reflux (GORD) is well established in adults with all its associated symptoms including chest discomfort, recurrent cough, chronic respiratory disorders and regurgitation. In the paediatric setting, the additional sequelae of failing to thrive are seen which reduces the threshold for intervention. Those children with frequent symptoms under the age of 2 are more likely to have symptoms later in their childhood[81].

The predominant mechanism causing GORD, as in the adult population, is transient lower oesophageal sphincter (LES) relaxation. This is defined as an abrupt and transient decrease in LES pressure to the level of intra-gastric pressure, unrelated to swallowing and of relatively longer duration than the relaxation triggered by a swallow[82].

The aim of treatment for GORD is to achieve symptom relief whilst preventing complications. Those patients who fail to achieve control with medical therapy or not wishing to be dependent on long term anti-reflux medications may warrant an anti-reflux surgical procedure[83,84].

A variety of endoscopic techniques have been developed for treatment of GORD. These methods can be divided in three broad categories: (1) methods that attempt to create a fundoplication/gastroplication (plicating techniques); (2) methods that create a controlled stricture (radio frequency); and (3) methods that bulk the gastro-oesophageal junction (injecting bulking agents)[85]. There is only experience in the paediatric setting with the first two methods. The ideal procedure should be safe, effective over a long term and should not compromise future surgical options.

Endoluminal gastroplication (Figures 5-7): Endoluminal plication uses mechanical techniques to decrease reflux by approximation of tissue at

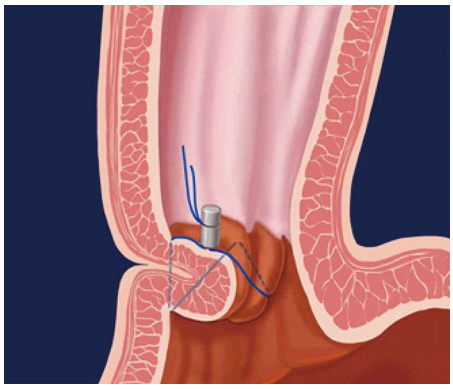

Figure 5 Endoscopic gastroplication. This figure the pattern of a zig-zag stich when applied with an Endocinch® sewing maching.

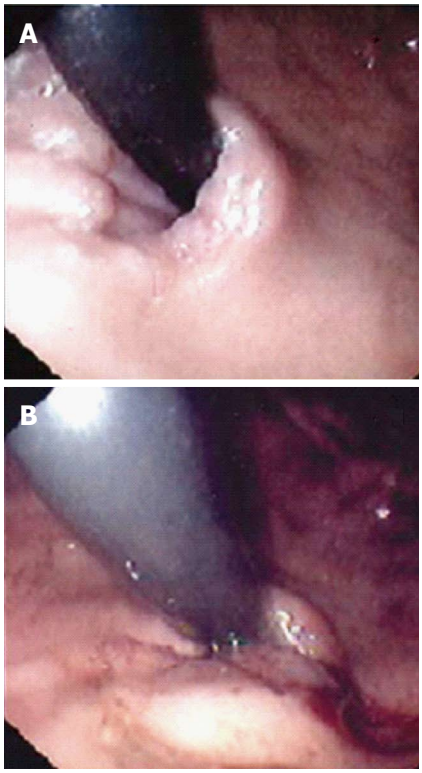

Figure 6 Endoscopic view (J manoeuvre) of a lax Gastro-Oesophageal junction in a child with major reflux before (A) and after (B) application of stitch with the EndoCinch®.

or below the Gastro-Oesophageal junction (GOJ). The main plication device be used with the authors' experience is the EndoCinch® (CR BARD Endoscopic technologies, Massachusetts, United States). This was initially developed by Swain *et al*[86] in London United Kingdom, in the mid-1980s, and was the first Federal Drug Agency (FDA) approved endoscopic sewing machine method for treating GORD[86].

The method involves placement of an overtube to facilitate repeat intubations that are required for the procedure. An endoscope with a capsule-shaped plication device (with a side hole) mounted at the tip is inserted to the level of the squamo-columnar junction

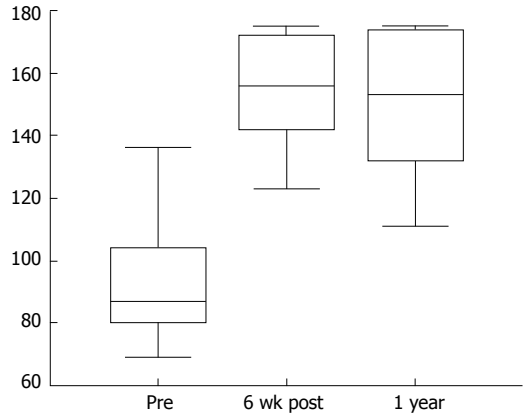

Figure 7 Significant improvement in the total QOLRAD scores (Quality of life in reflux and dyspepsia), 6 wk and 1 year after gastroplication with the Endocinch®.

through the overtube, where the side hole is brought into close contact with the wall to draw the mucosa into the capsule with the aid of air suction. A puncture needle with a non-absorbable suture attached (suture tag), is inserted into the biopsy channel and is then passed through. The suction pressure is released and the capsule is carefully rotated away from the stitch side. A suture tag is then set up in the endoscope again and a second set of sutures is placed following the same procedure at a position rotated between 30 and 60 degrees away from the first set. The two sutures form a plication using a knotting device that is inserted into the biopsy channel of a separate endoscope and the process is completed by plicating the tissue in the form of a pouch. The second and third plications are performed in either a linear or circumferential manner, or a combination of the two, depending on the available area within the GOJ and position preference[87].

The procedure can be carried out as a day case, with studies showing it to be relatively quick, non-invasive, effective and safe. Results have been shown it to be comparable to laparoscopic fundoplication in adults[88-90].

The authors have a preference of placing two plication suture lines circumferentially, 1.5 cm below the GOJ and one 0.5 cm below the GOJ, which we believe to be superior to other methods used in adults[88,91]. In a series of 17 children with a median age 13 years, with GORD refractory or dependent on proton pump inhibitors, all patients showed an improvement in symptom severity, frequency and reflux related quality of life scores[92]. Fourteen patients (88%) at 1 year and 9 patients (56%) at 3 years remained without a need for any anti-reflux medication. A sustained improvement in heartburn, regurgitation and vomiting was seen at 3 years. Only one complication of gastric bleeding was observed which resolved spontaneously[93]. The duration of action is conflicting in adults and is under on-going

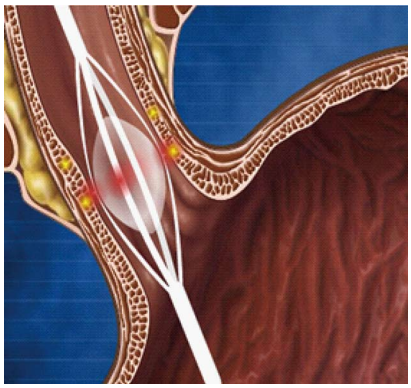

Figure 8 Use of a balloon to deliver radiofrequency energy *via* needle electrodes to the mucosa.

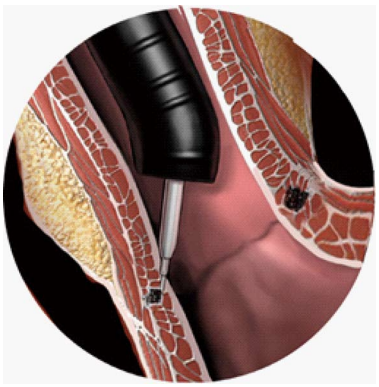

Figure 9 Injection of liquid polymer into the oesophageal mucosa. The Enteryx® procedure.

review[94-96]. However, there does appear to be superior efficacy in children and the reasons for this may be due to a relatively deeper suture depth in the thinner paediatric oesophagus[93].

Stricture formation through delivery of radio-frequency energy: Curon Medical designed the STRETTA® system (Figure 8) which gained FDA approval in 2000. The device employs a special balloon on a catheter with four needle electrodes. An upper GI endoscopy is undertaken first to identify the GOJ. A guide wire is then placed into the stomach, the endoscope is then removed and the STRETTA® catheter is then passed over, advancing the balloon to a position at the GOJ. The balloon is inflated and the electrodes are deployed to penetrate into the muscle layer. Radiofrequency energy is delivered through the electrodes to create thermal lesions radially at several levels in the lower oesophageal sphincter and gastric cardia[97]. As the lesions heal, it induces collagen tissue contraction, remodelling and modulation of the triggering threshold for transient LES relaxations[98].

Evidence for its benefit is promising, as shown in a recent meta-analysis including 1441 patients, although these results need to be interpreted with caution as there was significant heterogeneity between trials[99]. The largest randomised sham-control trial, to date, investigating 64 patients, revealed the radiofrequency group having significant improvement in heartburn symptoms (61% *vs* 33%) and GORD quality of life score (61% *vs* 30%) at 6 mo[100]. It is seldom associated with serious complications but there have been reports of delayed gastric emptying in a few[101].

There are only 2 reported case series in the paediatric setting. Islam *et al*[102] reported its first use in 6 teenagers (mean age 18, range 14-21) in those who had previous surgical reflux surgery. All had an improvement in their GORD symptom score with 5 out of 6 completely asymptomatic at 3 mo[102]. Liu *et al*[103] reported on 8 children aged 11-16, including 3 children with neurological impairment requiring a concomitant percutaneous gastrostomy feeding tube[103]. The follow-up period was up to 15 mo and 6 of the patients were considered to have a successful outcome, based on improvement of GORD symptoms and tolerability of feeding. Of the two failures, one required continued PPI use and the other a Nissen fundoplication.

Without larger published series in children to date, paediatric gastroenterologists are likely to be reserved in its use, particularly considering that it is unknown what the long-term effects of thermal injury to the GOJ in a child is likely to be.

Another novel endoscopic treatment, the ENTERYX procedure involves injecting a gastro-esophageal biopolymer into the lower oesophageal sphincter (Figure 9). The authors do not recommended its use in paediatric practice though. Besides concerns regarding long-term outcome of the ENTERYX injection, perforation of the oesophagus is a risk during administration of this treatment.

Assessment and excision of upper GI polyps: Over the last few years, investigation of number of polyposis syndromes has revealed the presence of upper GI polyps in addition to the more widely documented colorectal polyps. The most common polyposis syndrome, familial adenomatous polyposis (FAP) is an inherited autosomal dominant condition which results from mutations within the gene locus on chromosome 5[104]. In addition to causing the development of numerous colorectal polyps in FAP patients, it has also been found that multiple polyps may occur in the gastric antrum and duodenum[105-108]. Domizio *et al*[109], investigating a series of patients from St Mark's Hospital, demonstrated microscopic gastroduodenal pathology in 100/102 asymptomatic FAP patients. This included the presence of duodenal adenomas in 94 patients and gastric fundic gland polyps in 44 patients. Although the significance and natural history of gastric polyps in patients with polyposis syndromes has not been clearly described, it has been shown that patients with FAP have a higher risk of duodenal cancer and various methods of upper GI endoscopic assessment tools have been used

including standard endoscopy, endoscopy with a side-viewing scope and double-balloon enteroscopy[110,111].

In addition to FAP, other syndromes are known to predispose to upper GI polyps which can pose management challenges. It is known that children with Peutz-Jeghers (PJ) syndrome have a risk of polyps which can lead to harmful consequences like bleeding and obstruction. Children with PJ may often have to undergo laparotomies to manage these problems but increasingly less invasive, endoscopic management options are being used like balloon enteroscopy which can even be used to remove polyps in the proximal jejunum[112].

CONCLUSION

As experience grows in therapeutic interventions in the upper GI tract, treatment that was once considered pioneering is becoming relatively routine. Systems are now in place to develop training in this continually evolving speciality to allow expertise to develop. The current disparity between paediatric and adult endoscopy is likely to become narrower in the near future.

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REVIEW

Endoscopic management for congenital esophageal stenosis: A systematic review

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Abstract

Congenital esophageal stenosis (CES) is an extremely rare malformation, and standard treatment have not been completely established. By years of clinical research, evidence has been accumulated. We conducted systematic review to assess outcomes of the treatment for CES, especially the role of endoscopic modalities. A total of 144 literatures were screened and reviewed. CES was categorized in fibromuscular thickening, tracheobronchial remnants (TBR) and membranous web, and the frequency was 54%, 30% and 16%, respectively. Therapeutic option includes surgery and dilatation, and surgery tends to be reserved for ineffective dilatation. An essential point is that dilatation for TBR type of CES has low success rate and high rate of perforation. TBR can be distinguished by using endoscopic ultrasonography (EUS). Overall success rate of dilatation for CES with or without case selection by using EUS was 90% and 29%, respectively. Overall rate of perforation with or without case selection was 7% and 24%, respectively. By case selection using EUS, high success rate with low rate of perforation could be achieved. In conclusion, endoscopic dilatation has been established as a primary therapy for CES except TBR type. Repetitive dilatation with gradual step-up might be one of safe ways to minimize the risk of perforation.

Key words: Esophageal stenosis; Esophageal atresia; Tracheoesophageal fistula; Esophageal perforation; Dilatation; Endosonography; Deglutition disorders; Esophagoscopes; Esophageal ring; Plummer-Vinson syndrome

Core tip: Congenital esophageal stenosis (CES) is a rare malformation consisting of 3 types; fibromuscular thickening, tracheobronchial remnants (TBR) and membranous web. Endoscopic dilatation has been established as a primary therapy for CES except TBR type. Endoscopic ultrasonography is useful to distinguish TBR from other types of CES. Repetitive dilatation with gradual step-up is recommended to minimize the risk of perforation.

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INTRODUCTION

Congenital esophageal stenosis (CES) is an extremely rare malformation, and diagnostic criteria and standard treatment have not been completely established. By years of clinical research, evidence for the management of CES has been accumulated. In the management of CES, surgery and endoscopic modalities play a key role. Endoscopic management could be an effective and less-invasive, however, the risk of therapies and therapeutic margin should be considered. The aims of this systematic review were to identify all published studies of endoscopic management of CES and to assess outcomes in terms of relief of the stricture and complication rates. Frequency and characters of 3 categories of CES, and relationship with associated anomalies were also reviewed.

RESEARCH

A Definition of CES was based on the description by Nihoul-Fékété[1]; "an intrinsic stenosis of the esophagus, present although not necessarily symptomatic at birth, which is caused by congenital malformation of esophageal wall architecture".

Systematic review of English-language articles reporting CES was conducted by searching the PubMed database, in July 2014. Search terms "congenital" AND "esophageal stenosis" AND "endosc*", and MeSH term"Esophageal Stenosis" AND the term "congenital" were used. The references of each of the included studies were then screened for any additionally relevant articles. Studies were selected according to the following inclusion/exclusion criteria: the only inclusion criteria was diagnosis of CES, defined as intrinsic stenosis of the esophagus. Esophageal stricture due to compression by cardiac/vascular malformations or intrathoracic tumor was excluded, if it is "congenital". Secondary esophageal stenosis due to gastro-esophageal reflux, postoperative anastomotic stricture of esophageal atresia (EA) with/without tracheal fistula, leiomyoma and dermatological diseases including epidermolysis bullosa, dyskeratosis congenita, Rothmund Thomson syndrome and Goltz syndrome were also excluded. Review articles and mere letters were excluded. There were no exclusions based on patient numbers or length of follow-up. Accordingly, a total of 570 studies were identified by the initial searches, of which 144 studies satisfied the selection criteria (Figure 1). All the studies included were case reports or retrospective observational studies.

INCIDENCE

Investigators have commented on the rarity of CES, but the true incidence is still unknown. Bluestone *et al*[2] treated 24 cases of CES and approximately 200 cases of trachea-esophageal fistula in the single institution during the same 15 years, and estimated that the incidence of CES was one per 25000 births using that the incidence of tracheoesophageal fistula (TEF) was one per 2500 births[2]. Nihoul-Fékété *et al*[1] found 20 cases of CES and 484 cases of EA in the single institution during the same 25 years (1960-1984). According to this data, incidence of CES was lower than 1/20 of that of EA. Therefore, 1/25000-50000 live births is thought to be the incident rate of CES. These data are reliable and basically correct, but the frequency data should be revised based on the data at least in the 2000s.

CLASSIFICATION

The classification of CES has been confusing mainly because of its infrequency. Histological classification has been difficult because surgical specimens cannot be obtained if the only bougie can improves the symptom. Furthermore, it has also been difficult to differentiate CES from other non-congenital esophageal stricture such as achalasia, peptic esophageal stenosis due to gastroesophageal reflux and herpetic esophageal stenosis[3,4].

Various classification of CES had been proposed to date. Ohkawa *et al*[5] (1975) reported 5 entities of CES including tracheobronchial remnants, fibromuscular thickening, esophageal epithelioma, short esophagus and achalasia. Sneed *et al*[6] (1979) considered that there are congenital fibromuscular thickening (FMT), tracheobronchial remnants (TBR) and membranous web (MW) in the category of CES. Nihoul-Fékété (1989) clearly define CES and categorized the cases based on these 3 entities[1]. This categorization based on this sophisticated study has been broadly accepted to date. Ramesh *et al*[7] (2001) categorized CES into 3 groups; isolated segmental type, isolated diaphragm type and combined type. Isolated segmental type corresponds FMT and TBR, isolated diaphragm type corresponds MW and combined type corresponds segmental stenosis distal EA/TEF or MW. Although this classification involves the etiological consideration of CES, it is too complicated to use in clinical practice.

Frequency of 3 categories of CES were assessed by using the 3 observational studies including pediatric CES cases with detailed categorization (Table 1)[1,8,9]. Accordingly, overall frequency of FMT, TBR and MW were 53.8%, 29.9% and 16.2%, respectively. Locations of stenosis in each categories were assessed by using 52 case reports including 64 patients (Figure 2). Trends were as follows; MW mainly in the upper or middle third of the esophagus[10-27], FMT mainly in the

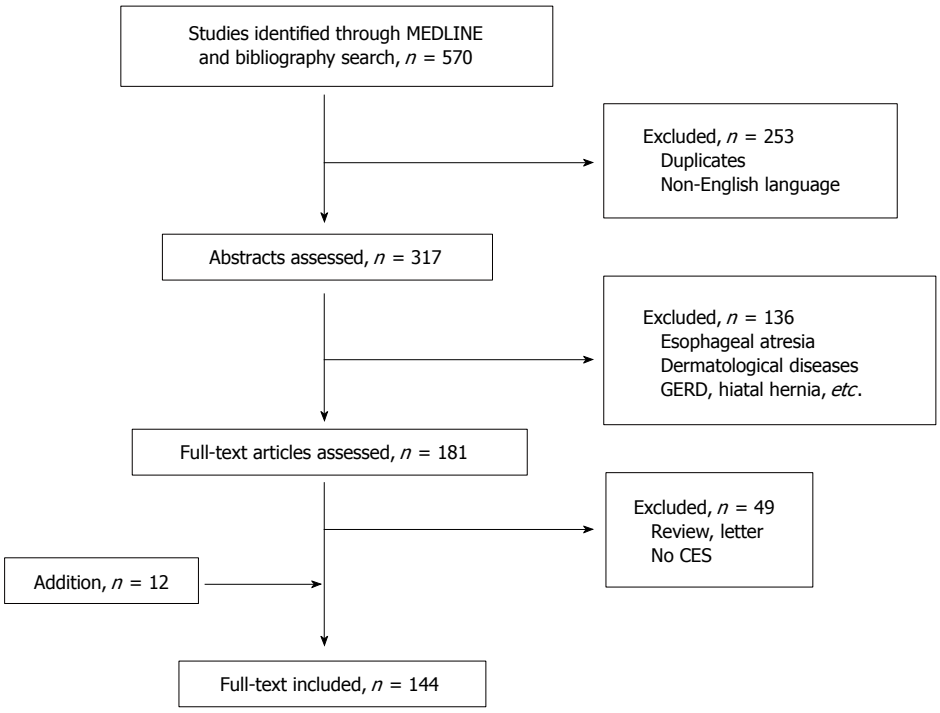

Figure 1 Flow chart of systematic search. CES: Congenital esophageal stenosis.

Table 1 Frequency of 3 categories of congenital esophageal stenosis

Ref.	FMT	TBR	MW	Total
Nihoul-Fékété *et asl*[1] (1987)	10 (50.0%)	4 (20.0%)	6 (30.0%)	20
Takamizawa *et al*[8] (2002)	13 (36.1%)	15 (41.7%)	8 (22.2%)[1]	36
Michaud *et al*[9] (2013)	40 (65.6%)	16 (26.2%)	5 (8.2%)	61
Total	63 (53.8%)	35 (29.9%)	19 (16.2%)	117

[1]Including cases of multiple web. FMT: Fibromuscular thickening; TBR: Tracheobronchial remnants; MW: Membranous web.

middle or lower third[28-39], and TBR mostly in the lower third[6,40-60].

Additionally, multiple web type of CES has been reported mainly in adults[61]. Only 1 pediatric case with multiple web has been reported[62].

ASSOCIATION WITH ESOPHAGEAL MALFORMATION

CES associated with esophageal atresia (EA) and/or tracheoesophageal fistula (TEF) is not so rare, and 44 cases have been reported as case(s) report to date[12,22,26,28,31,33,37,44,47,50,55,63-75]. To assess relationship and EA and/or TEF, 14 observational studies of pediatric cases were reviewed[1,2,8,9,76-85]. According to the 4 observational studies[76,80,81,84], overall incidence rate of CES among patients with EA and/or TEF was 9.6% (Table 2). All the CES located in the middle to lower third of the esophagus; 13.5% in middle third of the esophagus, and 86.5% in lower third of the esophagus. Pathological findings of CES associated

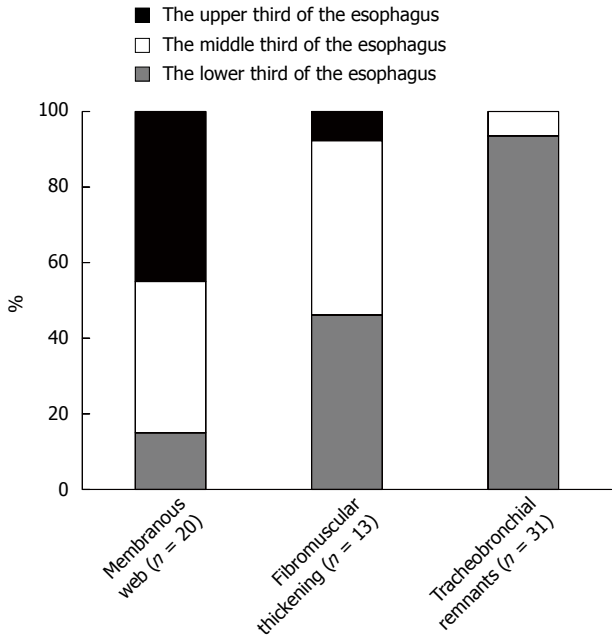

Figure 2 The locations of stenosis in each categories of congenital esophageal stenosis.

with TEF were not clear, because not all the cases had surgical specimens. In 15 cases (27% of CES cases), pathological assessment was performed; 10 cases (67%) had tracheobronchial remnant and 5 cases (33%) had fibromuscular stenosis. CES in TEF/EA is not a rare association, therefore, careful attention is required during the management of TEF/EA, especially in postoperative esophagogram.

According to the 10 observational studies[1,2,8,9,77-79,82,83,85],

Table 2 Incidence rate of congenital esophageal stenosis among patients with esophageal atresia and/or tracheoesophageal fistula

Ref.	Cases	Incidence rate	Location of CES	
			Middle	Lower
Holinger *et al*[76] (1963)	4/79	5.1%	0 (0%)	4 (100%)
Newman *et al*[80] (1997)	18/225	8.0%	NA	NA
Kawahara *et al*[81] (2001)	11/80	13.8%	2 (18%)	9 (82%)
Yoo *et al*[84] (2010)	22/187	11.8%	3 (14%)	19 (86%)
Total	55/571	9.6%	5 (13.5%)	32 (86.5%)

CES: Congenital esophageal stenosis.

overall incidence rate of EA and/or TEF among patients with CES was 24.8% (Table 3). Variation of the incident rate in each study may depend on study period, the role of institution and study design. Type of EA were not so different from original proportion; EA in 2.4%, EA+TEF in 92.7% and TEF in 4.9% of the cases. CES cases with complicated form of EA/TEF which cannot be classified were also reported[6,64].

Additionally, another esophageal malformation with CES, including esophageal duplication[22,50,86], diverticulum[18] and achalasia[11] were also reported.

ASSOCIATED ANOMALIES OTHER THAN ESOPHAGEAL MALFORMATION

Seven observational studies with detailed description about associated anomalies were reviewed[1,8,77-79,82,83]. These studies included a total of 199 cases of CES. The cases without any anomalies accounted for 55.3% of CES cases. Associated anomalies other than esophageal malformation were miscellaneous. Relatively frequent anomalies were as follows; congenital heart disease (4.5%), 21trisomy (4.0%), anorectal anomaly (2.0%), duodenal atresia (1.5%), tracheal malacia (1.5%), esophageal hiatal hernia (1.0%).

ADULT CASES

It is difficult to prove whether the adult cases with esophageal stenosis are truly "congenital". Actually, webs of the cervical esophagus have been commonly associated with Plummer-Vinson syndrome. In the largest series of adult CES cases, 62% of cases with upper esophageal webs had anemia, and all of them were female[87]. Khosla *et al*[88] also reported that among 117 patients with iron deficiency anemia, 6 cases (5.1%) had upper esophageal webs. Meanwhile, esophageal stenosis may also be found without the Plummer-Vinson syndrome. We found 24 case reports including 30 adult cases of CES with the categorization[10,11,13,15-18,20,21,40,41,59,89-99]. In these, 26 cases (86.7%) had MW type of CES[10,11,13,15-18,20,21,89-97,98,99]. In these, 16 cases had multiple webs[89-99], which was similar to ring of the trachea. Younes *et al*[61] treated 10 adult cases of multiple esophageal webs during 7 years, and stated that CES in adults is under-recognized cause for intermittent, long-standing dysphagia. Although extremely rare, TBR[40,41,59] and FMT[34] type of CES were also reported in adults.

FAMILY INCIDENCE

Occurrence of CES within a family was reported only in the 2 literatures; in father and son[94], and sisters[96]. They all were over middle age, suffered from dysphagia and/or food impaction for long duration, and had multiple esophageal webs (one of the sisters had no detail). In the former family, the son had male sibling who died 1 wk after birth because of an inability to swallow. In earlier reports, the nature of multiple esophageal webs has been speculated to be either congenital or acquired[89], and still remains unclear.

DIAGNOSIS

In diagnosis of CES, it is essential to exclude postnatally acquired stenoses (peptic, caustic, infectious, neoplastic), extrinsic compression, and achalasia[1]. Careful medical interview is of key importance. Both esophagogram and esophagoscopy is required to know location, range, form and degree of stenosis. To exclude peptic stenosis, pH monitoring may be useful. To exclude achalasia, measure of esophageal pressure is also informative.

Endoscopic ultrasonography (EUS) is brilliant way to classify the CES, especially distinguishing TBR from FMT[8,54,100,101]. By using this modality, the cartilage in the esophageal wall is visualized as low echoic area[54,100] or high echoic area[8,101]. Whether CES is classified as TBR or not is important information to determine the therapeutic strategy, because CES of TBR should be managed by surgery, not bougie due to high rate of perforation[55].

TREATMENT

Therapeutic option consists of dilatation and surgery. Although surgery tends to be reserved for ineffective dilatation, efficacy and risk of dilatation has been controversial. We, therefore, reviewed the literatures in which more than 5 cases of CES were treated by dilatation[1,8,9,79,81-83,85]. Studies were divided into two groups by whether EUS was used for case selection or not. EUS was to distinguish TBR type of CES. Accordingly, overall success rate of dilatation for CES with or without case selection was 89.7% and 28.9%, respectively (Table 4). Overall rate of perforation with or without case selection was 7.4% and 23.9%, respectively (Table 5). By using EUS, high success rate with low rate of perforation could be achieved. On the basis of this knowledge, flow chart of treatment is shown in Figure 3.

As a technique of dilatation, there are tapered

Table 3 Incidence rate of esophageal atresia and/or tracheoesophageal fistula among patients with congenital esophageal stenosis

Ref.	Cases	Incidence rate	EA	EA + TEF	TEF
Bluestone *et al*[2] (1969)	0/24	0.0%	0	0	0
Nishina *et al*[77] (1981)	4/81	4.9%	0	3	1
Dominguez *et al*[78] (1985)	5/34	14.7%	0	5	0
Nihoul-Fékété *et al*[1] (1987)	2/20	10.0%	0	1	1
Yeung *et al*[79] (1992)	6/8	75.0%	1	4	1
Vasudevan *et al*[82] (2002)	4/6	66.7%	1	2	1
Takamizawa *et al*[8] (2002)	13/36	36.1%	0	13	0
Amae *et al*[83] (2003)	4/14	28.6%	0	4	0
Romeo *et al*[85] (2011)	15/47	31.9%	0	15	0
Michaud *et al*[9] (2013)	29/61	47.5%	0	29	0
Total	82/331	24.8%	2 (2.4%)	76 (92.7%)	4 (4.9%)

EA: Esophageal atresia; TEF: Tracheoesophageal fistula.

Table 4 Success rate of dilatation for congenital esophageal stenosis with/without case selection by endoscopic ultrasonography

Ref.	Case selection by EUS		Modality
	+	-	
	Success rate		
Takamizawa *et al*[8] (2002)	16/21 (76.2%)	-	BD
Romeo *et al*[85] (2011)	45/47 (95.7%)	-	BD
Nihoul-Fékété *et al*[1] (1987)	-	7/14 (50.0%)	BD or TD
Yeung *et al*[79] (1992)	-	0/7 (0.0%)	BD or TD
Kawahara *et al*[81] (2001)	-	2/9 (22.2%)	BD
Vasudevan *et al*[82] (2002)	-	3/7 (42.9%)	TD
Amae *et al*[83] (2003)	-	3/11 (27.3%)	BD or TD
Michaud *et al*[9] (2013)	-	13/49 (26.5%)	BD or TD
Total	611/68 (89.7%)	28/97 (28.9%)	

BD: Balloon dilatator; TD: Tapered dilator; EUS: Endoscopic ultrasonography.

Table 5 Rate of perforation during dilatation of congenital esophageal stenosis

Ref.	Case selection by EUS		Modality
	+	-	
	Rate of perforation		
Takamizawa *et al*[8] (2002)	0/21 (0.0%)	-	BD
Romeo *et al*[85] (2011)	15/47 (10.6%)	-	BD
Nihoul-Fékété *et al*[1] (1987)	-	6/14 (42.9%)	BD or TD
Yeung *et al*[79] (1992)	-	1/7 (14.3%)	BD or TD
Newman *et al*[80] (1997)		3/18 (16.7%)	BD
Kawahara *et al*[81] (2001)	-	4/9 (44.4%)	BD
Amae *et al*[83] (2003)	-	1/11 (9.1%)	BD or TD
Fan *et al*[104] (2011)	-	1/8 (12.5%)	BD
Total	5/68 (7.4%)	16/67 (23.9%)	

BD: Balloon dilatator; TD: Tapered dilator; EUS: Endoscopic ultrasonography.

dilator and balloon dilatator, but there has been no comparison study of these. Some prefer balloon dilator because it enable expanding force to focus on the stenotic segment without shear stress, resulting in more effective and safer[8,102]. Appropriate diameter of dilatation for CES is still unknown. Kozarek *et al*[103] suggested that inflation of a single large-diameter dilator of less than 15 mm or an incremental dilation of more than 3 mm may be safe in simple esophageal strictures in adults. Fan *et al*[104] reported 9 procedures of balloon dilatation for CES including 1 esophageal perforation. Although there was no statistical significance, mean balloon diameter of the procedure with/without perforation was 12.1 mm and 15.0 mm, respectively. Mean dilation achieved with/without perforation was 5.4 mm and 8.4 mm, respectively. Not surprisingly, large dilatation with large increment might be a risk of perforation. Therefore, repetitive dilatation with gradual step-up might be one of safe ways to minimize the risk of perforation.

In cases of MW type of CES, efficacy of endoscopic dilatation with radial incision of the web has been reported. Instruments for incision include electrocoagulation[17,19,105], high-frequency-wave[27] and laser[23]. Nose *et al*[27] used balloon catheter for pulling up the web from the distal side during incision. Adverse events during dilatation with incision have not been reported.

LONG-TERM PROGNOSIS

It is well known that the association of Plummer-Vinson syndrome with carcinoma of the mouth, hypopharynx and upper esophagus. In the 58 adult cases of MW type of CES, 9 cases (15.5%) had carcinoma; buccal carcinoma in 6, esophageal carcinoma in 3[88]. Other than MW type, only one case has been reported, who had esophageal carcinoma associated with FMT type of CES; 65-year-old man who had suffered from dysphagia and vomiting since birth, but had not received any treatment because of mild symptom, underwent esophagectomy for worsening symptom. The resected specimen revealed squamous cell carcinoma in the region of fibromuscular stenosis[34]. The authors speculated that chronic mechanical stimulation by food trapped above the stenosis may have induced dysplasia of the mucosa. Special attention should be paid to status of the esophageal passage. Long-term functional prognosis after dilatation of pediatric CES has not been reported. Further studies are still needed.

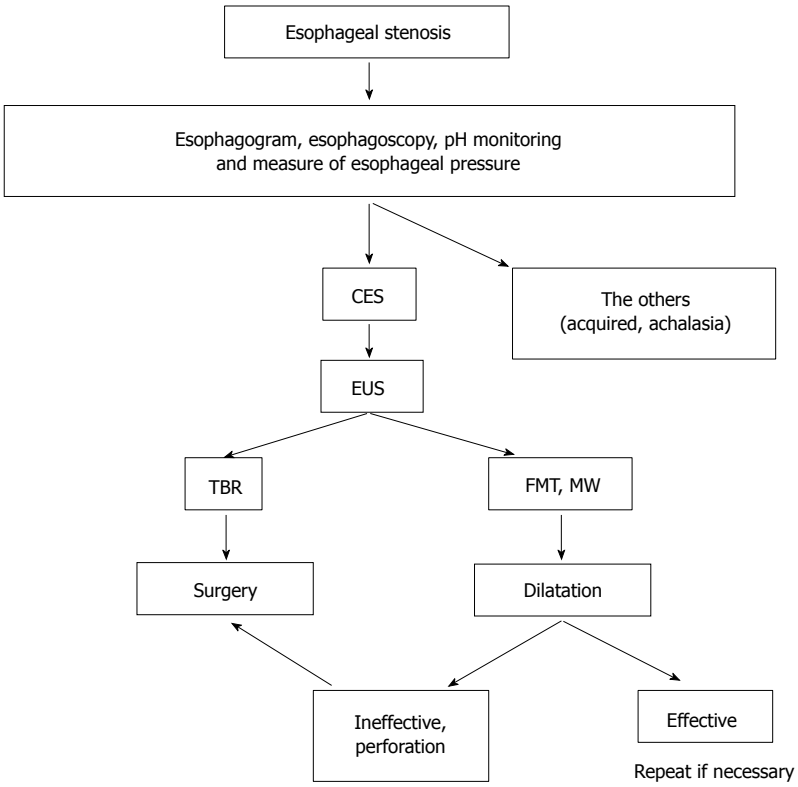

Figure 3 Flow chart of diagnosis and treatment for congenital esophageal stenosis.

CONCLUSION

Endoscopic dilatation has been established as a primary therapy for CES except TBR type. EUS is useful to distinguish TBR from other types of CES. Repetitive dilatation with gradual step-up is recommended to minimize the risk of perforation.

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REVIEW

Endoscopic treatment for gastrointestinal stromal tumor: Advantages and hurdles

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Abstract

One of the most prominent characteristics of gastrointestinal stromal tumors (GISTs) is their unpredictable and variable behavior. GISTs are not classified as "benign" or "malignant" but are rather stratified by their associated clinical risk of malignancy as determined by tumor size, location, and number of mitoses identified during surgical histology. The difficulty in assessing the malignant potential and prognoses of GISTs as well as the increasing incidence of "incidental GISTs" presents challenges to gastroenterologists. Recently, endoscopic enucleation has been actively performed as both a diagnostic and therapeutic intervention for GISTs. Endoscopic enucleation has several advantages, including keeping the stomach intact after the removal of GISTs, a relatively short hospital stay, a conscious sedation procedure, relatively low cost, and fewer human resources required compared with surgery. However, a low complete resection rate and the risk of perforation could reduce the overall advantages of this procedure. Endoscopic full-thickness resection appears to achieve a very high R0 resection rate. However, this technique absolutely requires a very skilled operator. Moreover, there is a risk of peritoneal seeding due to large active perforation. Laparoscopy endoscopy collaborations have been applied for more stable and pathologically acceptable management. These collaborative procedures have produced excellent outcomes. Many procedures have been developed and attempted because they were technically possible. However, we should first consider the theoretical basis for each technique. Until the efficacy and safety of sole endoscopic access are proved, the laparoscopy endoscopy collaborative procedure appears to be an appropriate method for minimally destructive GIST surgery.

Key words: Gastrointestinal stromal tumor; Endoscopy; Laparoscopy; Efficacy; Safety

Core tip: Several endoscopic approaches have recently been investigated for removing gastrointestinal stromal tumors. Endoscopic enucleation has several advantages. However, there is the possibility of peritoneal seeding when accidental perforation occurs. Furthermore,

the rate of R0 resection is not yet acceptable. While endoscopic full-thickness resection has a more solid theoretical basis than endoscopic enucleation in terms of R0 resection, the possibility of tumor cell shedding into the peritoneum would increase when capsule injury results from the procedure. Compared with endoscopy only procedures, laparoscopy endoscopy cooperative surgery and LAFTR provide a higher complete resection rate and a more stable process, which are accordant with the purpose of minimally destructive surgeries.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) constitute an unusual tumor type that is poorly understood by medical and surgical oncologists. GISTs are the most common mesenchymal tumor of the gastrointestinal tract and are believed to originate from the interstitial cells of Cajal regulating gastrointestinal motility. In the medical literature, GISTs have been confused with true smooth muscle tumors due to their similar features under light microscopy. Once a poorly recognized disease, GISTs have gained increasing interest following advances in diagnostics, both in terms of immunohistochemistry and the characteristic gain of functional mutations in either the *c-KIT* or *PDGFRa* genes, which have been identified as hallmarks of their pathogenesis[1-3]. The presence of c-KIT has been shown through its receptor in approximately 80% of GISTs[4], and 8% of GISTs have mutations in PDGFRa, which encodes a c-KIT-homologous receptor tyrosine kinase[1,2].

The range of clinical feature of GISTs ranges from symptomatic bleeding to incidental detection during a routine endoscopy[5]. In general, 10%-30% of GISTs are clinically malignant[6], but all GISTs are alleged to have some degree of malignant potential[5]. Despite size and location of GISTs are imperative factors facilitating an estimation of the risk of malignancy prior to operation[4,7], dependable preoperative examination for predicting malignancy are not readily available. Endoscopic ultrasonography is useful for obtaining some specimens[8], and the risk of GISTs can be stratified according to several factors[5,7]; for instance, micro-GISTs (no more than 1 cm) generally show benign behavior irrespective of the mitotic rate[9]. However, the difficulty in estimating the malignant potential and the increasing incidence of "incidental GISTs" are particularly challenging for gastroenterologists, who must make decisions regarding patient care and management of this disease; in the case of micro-GISTs, regular endoscopic follow up is generally accepted[10], but R0 resection is frequently considered in cases with larger tumors.

Endoscopic enucleation and related variations of this treatment have recently been introduced for managing GISTs, most often in incidentally detected cases. There are several advantages of endoscopic treatment, but it presents some risks as well. Endoscopic full-thickness resection (EFTR), laparoscopy endoscopy cooperative surgery (LECS), laparoscopy-assisted endoscopic full-thickness resection (LAEFR), and non-exposed wall-inversion surgery (NEWS) have been applied for more pathologically acceptable management. This article provides an overview of the theoretical basis and technical feasibility of gastric GIST treatment in terms of an endoscopic approach with or without laparoscopic collaboration, considering the imperative points of conventional surgical resection.

THEORETICAL BASIS

Incidental GIST

Endoscopic enucleation is typically performed for asymptomatic GISTs. Approximately 15%-30% of GISTs were incidentally discovered without presenting any symptoms[6,11,12]. In these studies, the incidental discovery of GISTs primarily occurred after surgical resection for other reasons or during postmortem examination. Several studies have noted the existence of subclinical microscopic gastric GISTs[13-16]. Microscopic gastric GISTs were discovered in 22.5% of consecutive autopsies conducted on patients aged no less than 50 years old[15]. Kawanowa *et al*[16] presented evidence that microscopic GISTs were observed in 35% of whole stomachs that were surgically resected due to gastric carcinoma. As upper gastrointestinal examination by endoscopy has been increased, the incidental recognition of subepithelial lesions has also substantially increased. According to one retrospective study, the prevalence of subepithelial gastric lesions was 0.36% during routine exanimation[17]. These studies show that GISTs are far more common than previously presumed. Considering this suggestion, a gastroenterologist may frequently encounter GISTs in normal clinical practice, and a practical guide should be established to avoid irregular management of incidentally detected GISTs.

Malignant potential

Importantly, all GISTs are thought to have some degree of malignant potential. Approximately 20%-25% of GISTs in the stomach demonstrate malignant behavior[4]. One of the most prominent features of GISTs is unpredictable and variable behavior. Large, presumably aggressive GISTs can progress in an indolent manner, whereas small, incidentally discovered GISTs can show malignant behavior. Thus, GISTs are not classified as "malignant" or "benign" but are rather stratified by the clinical

Table 1 Prognostication of gastrointestinal stromal tumor atdifferent sites by tumor size and mitotic rate based on follow-up studies of over 1700 gastrointestinal stromal tumors prior to imatinib

Tumor parameters			Percentage of patients with progressive disease during long-term follow-up and quantitative characterization of the risk for metastasis			
Group	Size	Mitotic rate	Gastric GISTs	Small intestinal GISTs	Duodenal GISTs	Rectal GISTs
1	≤ 2 cm				0 none	
2	> 2 ≤ 5 cm	≤ 5/50	1.9 (very low)	4.3 (low)	8.3 (low)	8.5 (low)
3a	> 5 ≤ 10 cm	HPFs	3.6 (low)	24 (moderate)	34 (high)[1]	57 (high)[1]
3b	> 10 cm		12 (moderate)	52 (high)		
4	≤ 2 cm		0[1]	50[1]	[2]	54 (high)
5	> 2 ≤ 5 cm	> 5/50	16 (moderate)	73 (high)	50 (high)	52 (high)
6a	> 5 ≤ 10 cm	HPFs	55 (high)	85 (high)	86 (high)[1]	71 (high)[1]
6b	> 10 cm		86 (high)	90 (high)		

[1]Small number of cases. Groups combined or prognostic prediction less certain; [2]No tumors encountered with these parameters. (Adopted from Miettinen *et al*[4]). HPF: High power field; 50 high: Power fields equal approximately 5 mm^2; GIST: Gastrointestinal stromal tumor.

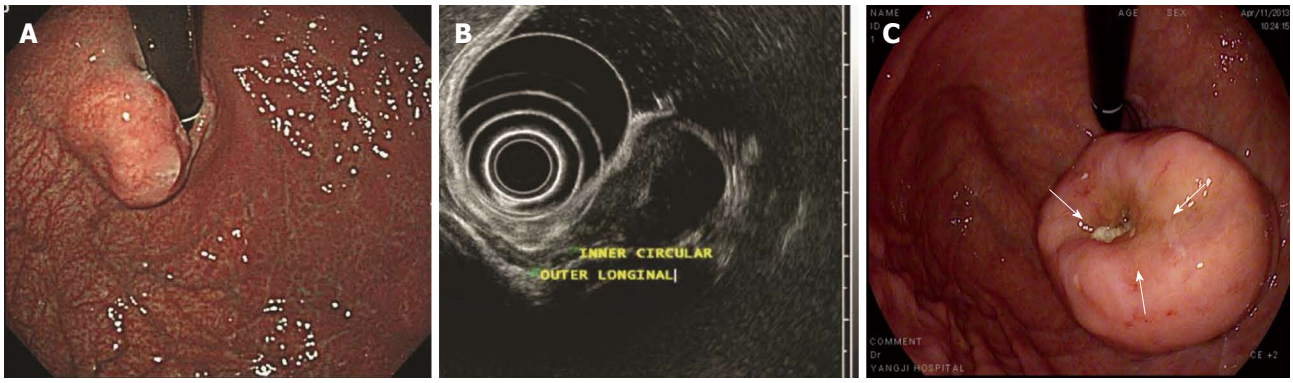

Figure 1 Features of gastrointestinal stromal tumors. A: An approximately 2-cm elevated lesion covered with nearly intact mucosa was observed at the cardia; B: EUS demonstrated a 21-mm, generally homogenous hypoechoic, well circumscribed pear-shaped lesion originating from the inner circular layer of the proper muscle layer. Inside the lesion, a hyperechoic septum-like structure was noticed; C: There was a small deep focal ulceration at the center of the gastrointestinal stromal tumor (GIST) (white arrows).

risk of malignancy depending on mitotic count, size, location (Table 1)[7]. A preoperative estimation of risk can be induced from size and location, but reliable criteria for surgery do not currently exist. Unlike gastric adenocarcinomas, regional lymph node metastasis of GIST is unusual; the prevalence has been reported to range from 1.1% to 3.4%[18-20]. Because it is difficult to predict the malignant behavior of GISTs, together with the rarity of lymph node metastasis, the theoretical basis for endoscopic removal can be reasonably supported if this method results in complete resection and does not cause peritoneal seeding.

Gross appearance and location in the gut wall

To estimate the feasibility of endoscopic procedures, it is important to understand the gross findings. GISTs range in size from a few mm to 35 cm, with a median size between 5 and 8 cm[11,21]. The targets of endoscopic enucleation and related procedures are small- to medium-sized gastric GISTs less than 5 cm in size. Small- to medium-sized GISTs typically form a well-delineated spherical or hemispherical mass, arising mostly from the proper muscle (PM) layer beneath the mucosa and pushing into the lumen to form a smooth-contoured elevation (Figure 1A and B).Focal mucosal ulceration is common in GISTs at all sites (Figure 1C) and is not related to tumor malignancy. GISTs are usually well circumscribed and surrounded by a pseudocapsule. The presence of a pseudocapsule contributes to the indication for complete resection in endoscopic enucleation.

When considering endoscopic enucleation, GISTs must be classified into several types according to their locations in the gastric wall (Figure 2). Type Ⅰ is a GIST that has a very narrow connection with the PM and protrudes into the luminal side, similar to polyps (Figure 2A). Type Ⅱ has a wider connection with the PM and protrudes into the luminal side at an obtuse angle (Figure 2B). Type Ⅲ is located in the middle of the gastric wall (Figure 2C). Type Ⅳ protrudes mainly into the serosal side of the gastric wall (Figure 2D). Of the four types, type Ⅰ is the best candidate for endoscopic enucleation due to its narrow connection with the PM layer, and it seems possible to remove type Ⅱ lesions by endoscopic enucleation. However, it is nearly impossible to achieve complete resection of type Ⅲ and type Ⅳ GISTs by endoscopic enucleation. Thus, EFTR, LECS, LAEFR, or NEWS should be considered for

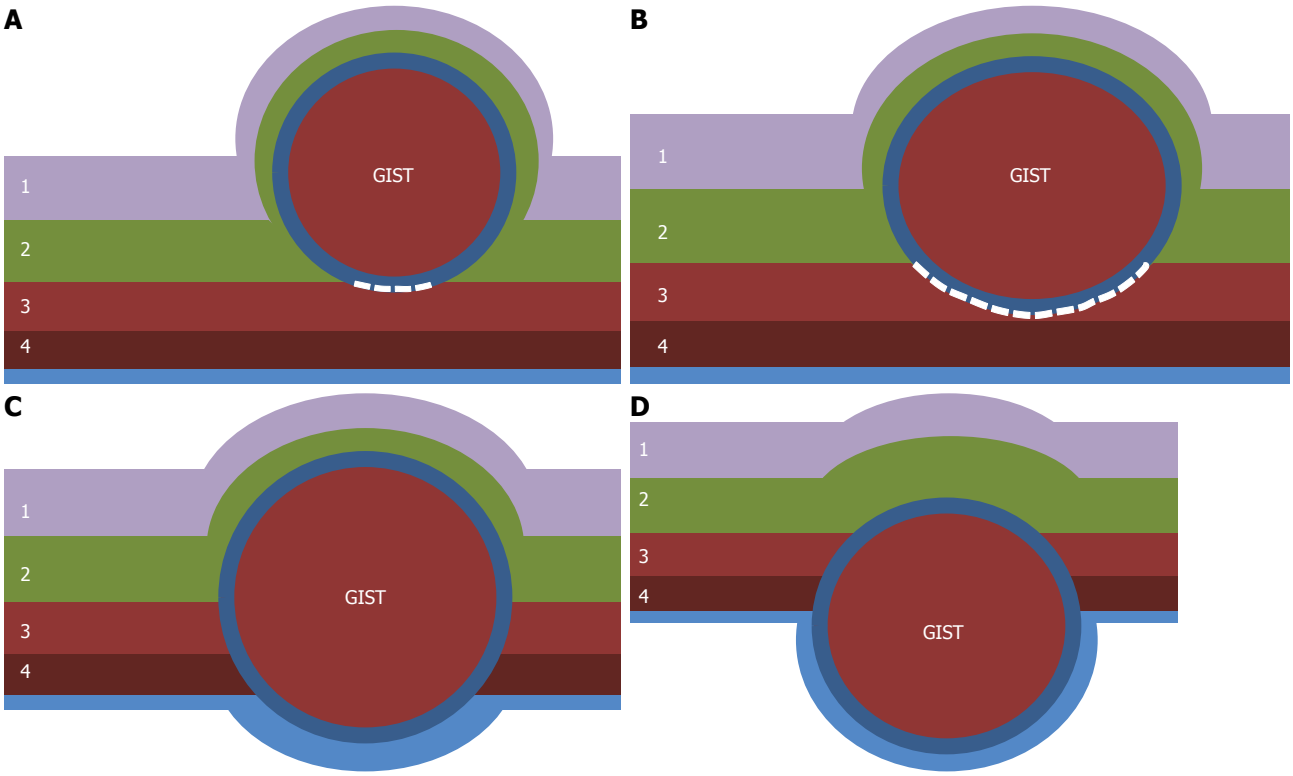

Figure 2 Classification of gastrointestinal stromal tumors according to the location in the gastric wall. A: Type Ⅰ is a gastrointestinal stromal tumor (GIST) that has a very narrow connection with the proper muscle layer and protrudes into the luminal side like a polyp; B: Type Ⅱ has a wider connection with the proper muscle layer and protrudes into the luminal side at an obtuse angle; C: Type Ⅲ is located in the middle of the gastric wall; D: Type Ⅳ protrudes mainly into the serosal side of the gastric wall. White dotted lines indicate the area dissected from the proper muscle layer. 1: Mucosa; 2: Submucosa; 3: Circular layer of proper muscle; 4: Longitudinal layer of proper muscle.

type Ⅲ and Ⅳ GISTs.

Surgical resection and follow-up program

Surgical removal is the primary treatment for a localized GIST in the majority of cases. Prior to evaluating the feasibility of therapeutic endoscopic procedures for GISTs, it is necessary to understand the surgical procedures and outcomes as a conventional standard strategy. The primary goal of surgery is complete tumor removal with clear resection margins. Avoiding pseudocapsule rupture is very important because intra-abdominal dissemination and a poor prognosis have been seriously associated with its occurrence[22]. It seems not necessary to perform routine lymphadenectomy due to rare nodal metastasis[23].

Depending on the location of the lesion, the type of surgery is determined. In cases of esophageal, small intestinal, and rectal GISTs, wide resections are the surgery of choice[24]. Gastric wedge resection is the most frequently performed procedure for gastric GISTs, and it is recommended as the treatment of choice; however, in some cases, tumor size and location may indicate extensive surgery, including a partial or total gastrectomy. Laparoscopic wedge resection, which is less invasive than the traditional technique, has been demonstrated to have comparable results in terms of efficacy, safety profile, and length of hospitalization[25-32]. Short- and long-term outcomes of laparoscopic wedge resection have been shown to be equivalent to the open surgical approach. Guidelines suggest that laparoscopic wedge resection can be used for tumors ≤ 5 cm[22]. Laparoscopic approaches to GIST management continue to expand and should adhere to standard oncological principles, including avoidance of direct grasping and tumor rupture, and an extraction bag is recommended when tumors are removed[31,33-37]. Although a microscopically positive margin was not found to be a significant adverse factor in some studies[23,38], one study did find it to be an adverse factor for survival[39].

The guidelines of the national comprehensive cancer network recommended abdominal and pelvic CT scan every 3-6 mo for 3-5 years and annually thereafter following completer resection[22]. Less frequent surveillance may be acceptable for small tumors (< 2 cm). Currently, Imatinib is approved both in the United States and the EU as an adjuvant therapy for GIST after surgical resection.

TECHNICAL FEASIBILITY OF THE ENDOSCOPIC APPROACH

Nearly all interventions have been performed for submucosal tumors originating from the PM layer without validating preoperative histological findings. Therefore, it is realistic to estimate the feasibility of an endoscopic approach for GIST by accessing data

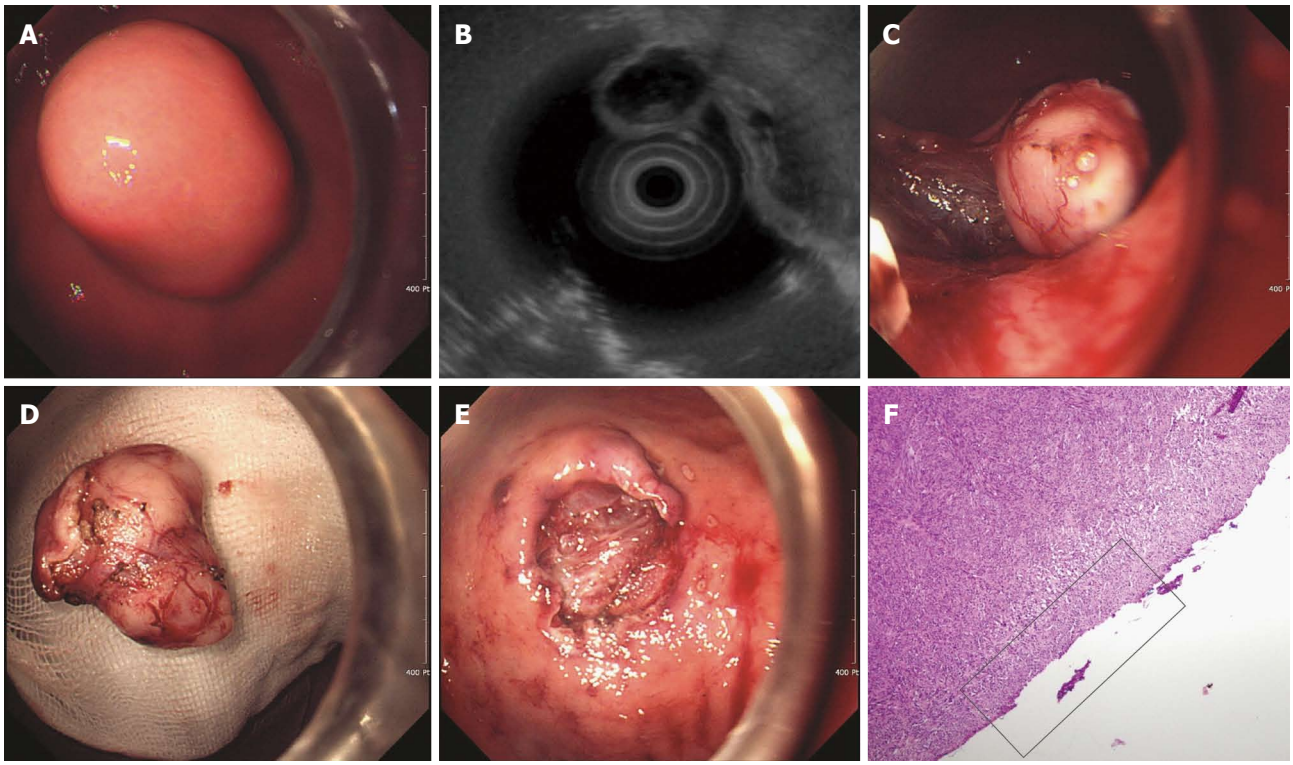

Figure 3 Endoscopic enucleation using the standard endoscopic submucosal dissection technique. A: An approximately 2.5-cm subepithelial tumor was identified at the greater curvature side of the upper body of the stomach; B: A 2.6-cm mixed echogenic tumor with a slightly irregular border arising from the proper muscle layer was noticed; C: Endoscopic enucleation using the endoscopic submucosal dissection technique was performed; D: *En bloc* resection was achieved; E: There was no perforation at the operation site; F: On pathologic examination, a vertical resection margin was apparently involved with tumor cells (red boxed area); R1 resection was confirmed. (Courtesy of Kyung Oh Kim, Gil hospital, Incheon, South Korea).

acquired from submucosal lesions originating from the PM layer.

ENDOSCOPIC ENUCLEATION

Submucosal endoscopic dissection

GISTs originating from the PM layer are not likely to be removed completely and safely using standard or modified endoscopic submucosal dissection (ESD). In such cases, deep submucosal dissection and PM layer resection should be performed. Moreover, the PM layer under the lesion must be carefully dissected (Figure 3). Thus, perforation risk is inevitably high. Furthermore, the margin seems to be minimal and easily involved in tumor cells (Figure 3F); there is also a potential risk of injury to the pseudocapsule. Several studies presented similar rates of successful *en bloc* resection (64%-94%) and perforation rates from 0% to 12% using ESD for GISTs originating from the PM layer (Table 2) (n = 11, 25, and 22)[40-42]. The imperative point, which should be noted, is that not all studies assessed pathologic evaluation, although they insisted on complete resection (n = 11 and 25)[40,41]. One recent study (n = 86) reported a 5.8% local recurrence rate after endoscopic enucleation of 86 GISTs, although all of the GISTs were completely removed endoscopically[43].

Endoscopic muscularis dissection

Liu *et al*[44] introduced another endoscopic technique, called endoscopic muscularis dissection (EMD), for tumors originating from the PM layer (n = 31, 14 esophageal and 17 gastric tumors)[44]. Of these tumors, 97% (30/31) were completely resected. The perforation rate was 13% (4/31)[44]. A longitudinal incision may have advantages in closing the mucosa with clips and promoting wound healing (Figure 4).

Endoscopic submucosal tunnel dissection

Endoscopic submucosal tunnel dissection (ESTD) is an innovative method that provides a solution for perforation, which frequently occurs during proper muscle dissection. The first case was reported by Inoue *et al*[45], submucosal endoscopic tumor resection for cardial and esophageal subepithelial tumors (n = 7)[45]. Submucosal tunnel dissection includes four major procedures (Figure 5): (1) creating a submucosal tunnel; (2) dissecting the tumor from the mucosa or submucosa; (3) dissecting the PM layer attached to the tumor; and (4) retrieving the specimen and closing the mucosal entry site with clips (n = 7, 12, and 85)[45-47]. The imperative advantage of ESTD is maintaining mucosal integrity during *en bloc* resection of subepithelial tumors (n = 143)[48]. ESTD may possibly decrease the risk of gastrointestinal tract leakage and subsequent infection[48]. Therefore, this technique may be a promising novel method for selected[46] GISTs arising from the PM layer at the cardia, particularly because endoscopic enucleation in this area can result

Table 2 Recent publications reporting endoscopic enucleation and endoscopic full-thickness resection for upper gastrointestinal tumors originating from the proper muscle layer

Ref.	*n*	Method	Mean operation time (min)	Mean tumor diameter (mm)	Complete resection rate (%)	Complications/recurrence
Wang *et al*[43] (2014)	86	Standard ESD	-	-	100	4 delayed bleedings 9 perforations 5 local recurrences
Ye *et al*[47] (2014)	85	ESTD	57	19	100	4 pneumothorax and subcutaneous emphysema 2 pneumothorax 2 subcutaneous emphysema
Feng *et al*[49] (2014)	48	EFTR	60	16	100	0
Li *et al*[48] (2012)	143	ESD (134), EFTR (6), ESTD (3)	45	18	94[1]	2 pneumothorax, 1 subcutaneous emphysema
Białek *et al*[42] (2012)	22	Standard ESD	-	-	68[1]	2 perforations
Liu *et al*[44] (2013)	31	EMD	77	22	97	4 perforations
Inoue *et al*[45] (2012)	7	SET	152	19	100	0
Gong *et al*[46] (2012)	12	ESTD	48	20	83	2 pneumothorax and subcutaneous emphysema
Zhou *et al*[52] (2011)	26	EFTR	105	28	100	0
Hwang *et al*[41] (2009)	25	ESD	-	29	64	3 perforations
Lee *et al*[40] (2006)	11	ESD	61	21	75	0

[1]Pathologically evaluated. EFTR: Endoscopic full-thickness resection; EMD: Endoscopic muscularis dissection; ESD: Endoscopic submucosal dissection; ESTD: Endoscopic submucosal tunnel dissection; SET: Submucosal endoscopic tumor resection.

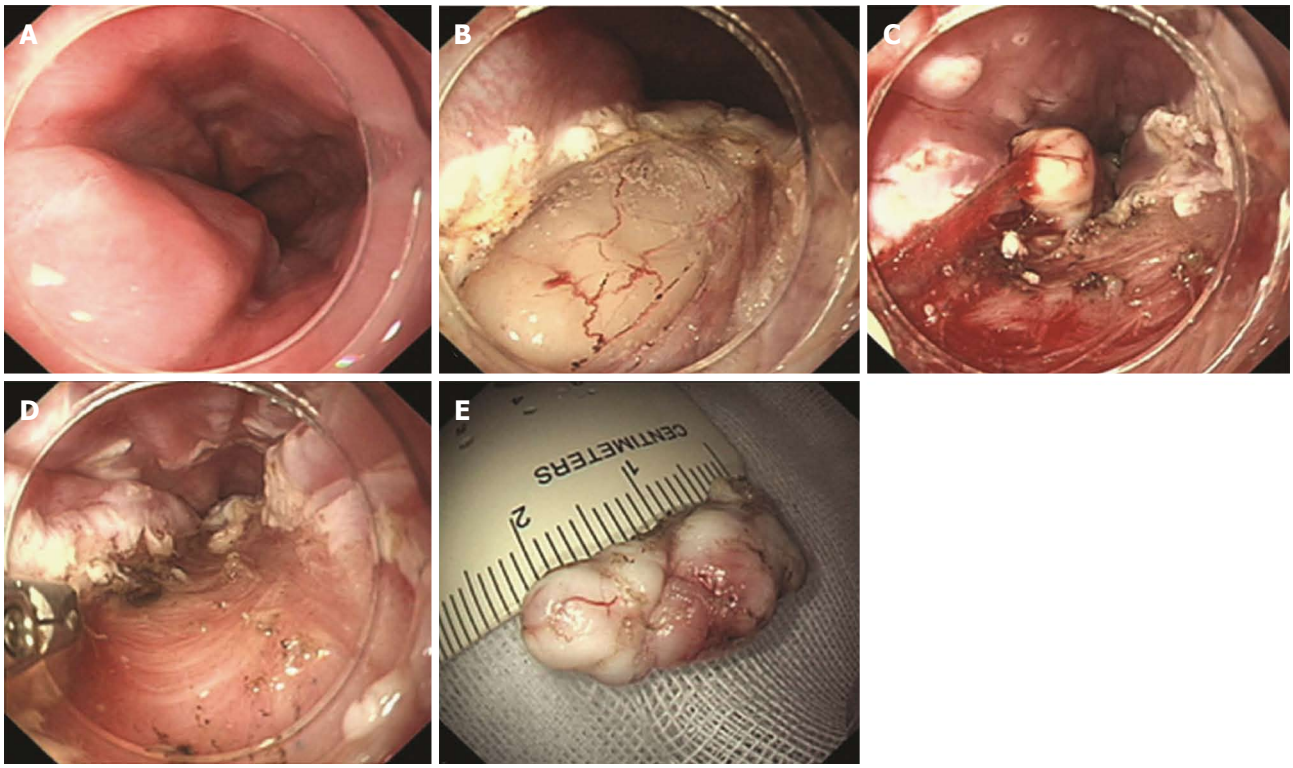

Figure 4 Endoscopic muscularis dissection of an esophageal subepithelial tumor originating from the proper muscle layers. A: Endoscopic view of the esophageal submucosal tumor; B: Exposure of the tumor using a longitudinal incision; C: Blunt dissection of the tumor as deep as the proper muscle layer with a transparent hood; D: Stopping bleeding after blunt dissection; E: The whole tumor was removed F: Linear clipping was performed to close the submucosal entry site (adopted from Liu *et al*[44]).

in pneumothorax and subcutaneous emphysema[46,47].

Advantages and drawbacks

Given the safety and efficacy of endoscopic enucleation, these emerging techniques can be preferable options for GISTs arising from the PM layer who are admitted to institutions with experienced operators. Endoscopic enucleation has several advantages, such as an intact stomach after GIST removal, a relatively short hospital stay, a conscious sedation procedure, relatively low

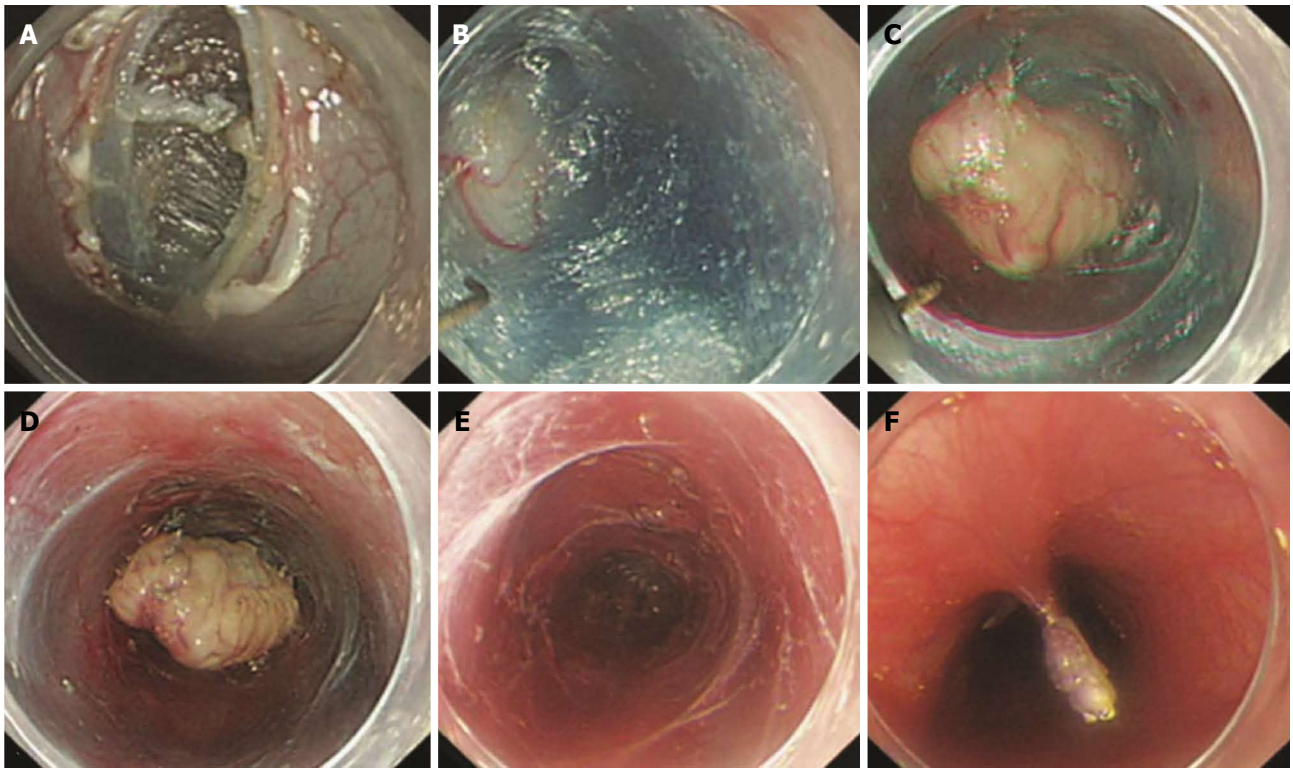

Figure 5 Endoscopic submucosal tunnel dissection procedure with longitudinal access. A: A 2-cm longitudinal mucosal incision was created, approximately 5 cm over the submucosal tumor; B: Submucosal dissection was performed, making a submucosal tunnel until the tumor was visible; C: Dissection was performed along the margin of the tumor; D: Dissection was completed; E: After removing the tumor, potential bleeding foci were coagulated; F: Closing the entry with clips (adopted from Gong *et al*[46]).

cost, and fewer human resources required compared with surgery.

However, it should be noted that several disadvantages also exist, which must be overcome to ensure the efficacy and safety of these advanced endoscopic techniques. First, there have been no data showing whether or not there was remnant GIST tissue at dissection sites when R1 resection was conducted; most studies have only validated *en bloc* resection[40,41,44,46,47,49]. The dissection surface was ablated by an electrical knife or snare, so there may not be remnant GIST cells, although R1 resection was achieved. Although this assertion seems logical, there have been no data proving this hypothesis. Moreover, one of the latest studies reported that a 5.8% local recurrence was observed even though complete endoscopic resection was achieved in all cases. To address this hypothesis, surgical resection of the dissected area should be obtained, and a careful pathological examination of the dissected surface must be conducted. Although several studies have shown that a microscopically positive margin was not a significant adverse factor[23,38], we should understand that these were surgical outcomes. In laparoscopic surgery, staples are used for the procedure, and the additional tissue from the resection line is essentially removed, indicating that R1 resection of GIST specimens during surgical procedures includes cases with R0 resection in a remnant stomach. In contrast, endoscopic enucleation does not involve this additionally removed area. There has also been disagreement regarding this result even in conventional surgical procedures[39]. Considering this information, R1 resection in endoscopic enucleation should be regarded as true R1 resection until appropriate studies demonstrate contrasting evidence. Currently, post-procedural management of R1 resection should be additional surgery, particularly for R1 resection of intermediate- to high-risk GISTs.

Second, because perforation is usually accompanied by pseudocapsule injury, the possibility of peritoneal seeding increases. Peritoneal seeding is accompanied by a high recurrence rate and can result in a poor prognosis. If PM layer dissection does not cause perforation, capsule injury may not be a serious problem; the tumor cells will shed into the lumen of the gut and will be destroyed. However, there is some likelihood of concomitant perforation and capsule rupture or injury during the procedure, particularly in cases where there is difficulty in conducting the procedure. In such situations, shedding of tumor cells into the peritoneal cavity is predicted. Currently, no comparative data with conventional surgical outcomes exist.

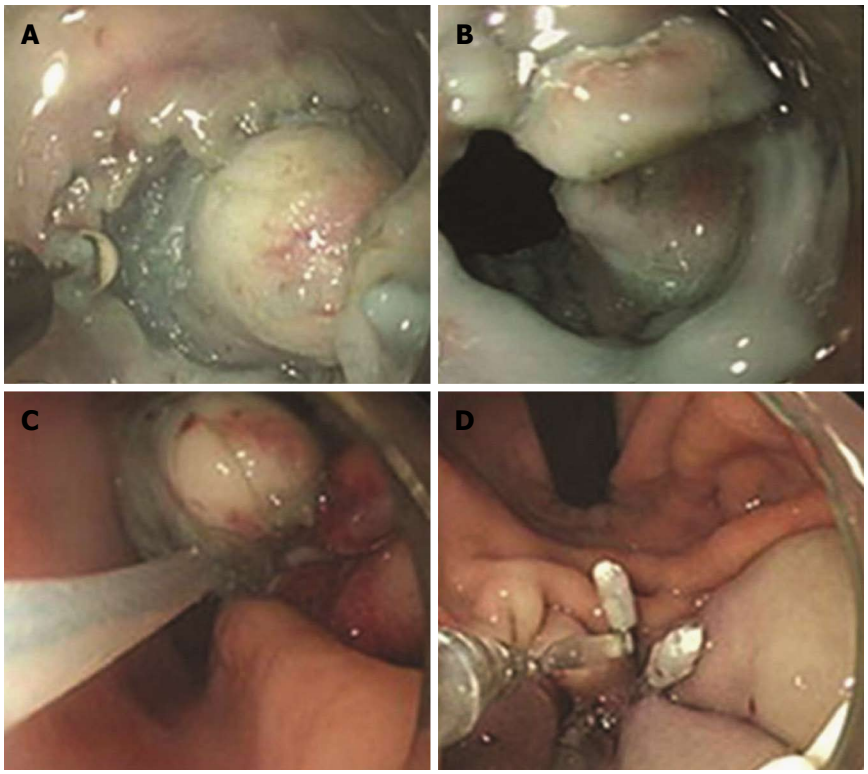

Figure 6 Procedure for endoscopic full-thickness resection of gastric subepithelial tumors originating from the proper muscle layer. A: A circumferential incision was made as deep as the proper muscle layer around the lesion with an IT knife; B: The tumor protruded into the peritoneal cavity after active perforation due to the incision into the serosal layer around the lesion; C: The tumor and surrounding tissue were pulled into the gastric cavity; D: The gastric wound was successfully closed with several metallic clips (adopted from Zhou *et al*[52]).

ENDOSCOPIC FULL-THICKNESS RESECTION WITHOUT LAPAROSCOPIC ASSISTANCE

The first case of EFTR using a snaring technique was reported in 2001[50]. Ikeda *et al*[51] recently presented EFTR by ESD in a swine stomach. This trial demonstrates an important step forward in endoscopic surgery, but it is currently not likely applicable in clinical settings. The risk of peritoneal infection and skeptical views of complete closure cause potentially major concerns in endoscopy-only procedures. Thus, EFTR should overcome the prevalent idea that perforation is a serious complication. However, Zhou *et al*[52] (n = 26) and Feng *et al*[49] (n = 48) succeeded in the use of EFTR for resecting gastric SMTs originating from the PM layer without laparoscopic assistance (Table 2). Their EFTR technique was based on standard ESD and consisted of four major procedures (Figure 6): (1) a circumferential incision as deep as the PM layer; (2) Creating active perforation by serosal layer incision; (3) removing a tumor and its surrounding PM and serosal layers by snare; and (4) closing active perforation site by several clips[49,52]. *En bloc* resection was achieved in all cases[49,52]. Furthermore, there were no serious complications[49,52]. According to these two studies, EFTR appears to be an ideal minimally destructive measure for gastric GISTs. One thing that should be noted is that EFTR essentially creates a large active perforation, which can result in the shedding of tumor cells into the peritoneum when the pseudocapsule is not intact. Thus, gentle maneuvering is required to maintain an intact pseudocapsule. The efficacy and safety of EFTR must be validated in multicenter studies to standardize this promising technique.

LAPAROSCOPIC ENDOSCOPIC COLLABORATIVE PROCEDURES

For the first time, a combination of gastrointestinal endoscopy and laparoscopy has been reported for removing esophageal subepithelial tumor by Izumi *et al*[53]. In this technique, a subepithelial tumor was pushed out by a balloon on an endoscope, and thoracoscopic enucleation was performed to remove the protruded tumor[53,54]. Hiki *et al*[55] (n = 7) reported the successful use of ESD for assisting local laparoscopic gastric resection to remove a GIST. In their technique, named LECS, laparoscopic multiple staplers were used for resection after approximately three-fourths cutline was completed by ESD. Tsujimoto *et al*[56] presented satisfactory surgical outcomes after LECS for gastric subepithelial tumor also (n = 20). Reducing the resected gastric wall volume is an important advantage of LECS compared with conventional laparoscopic wedge resection solely using

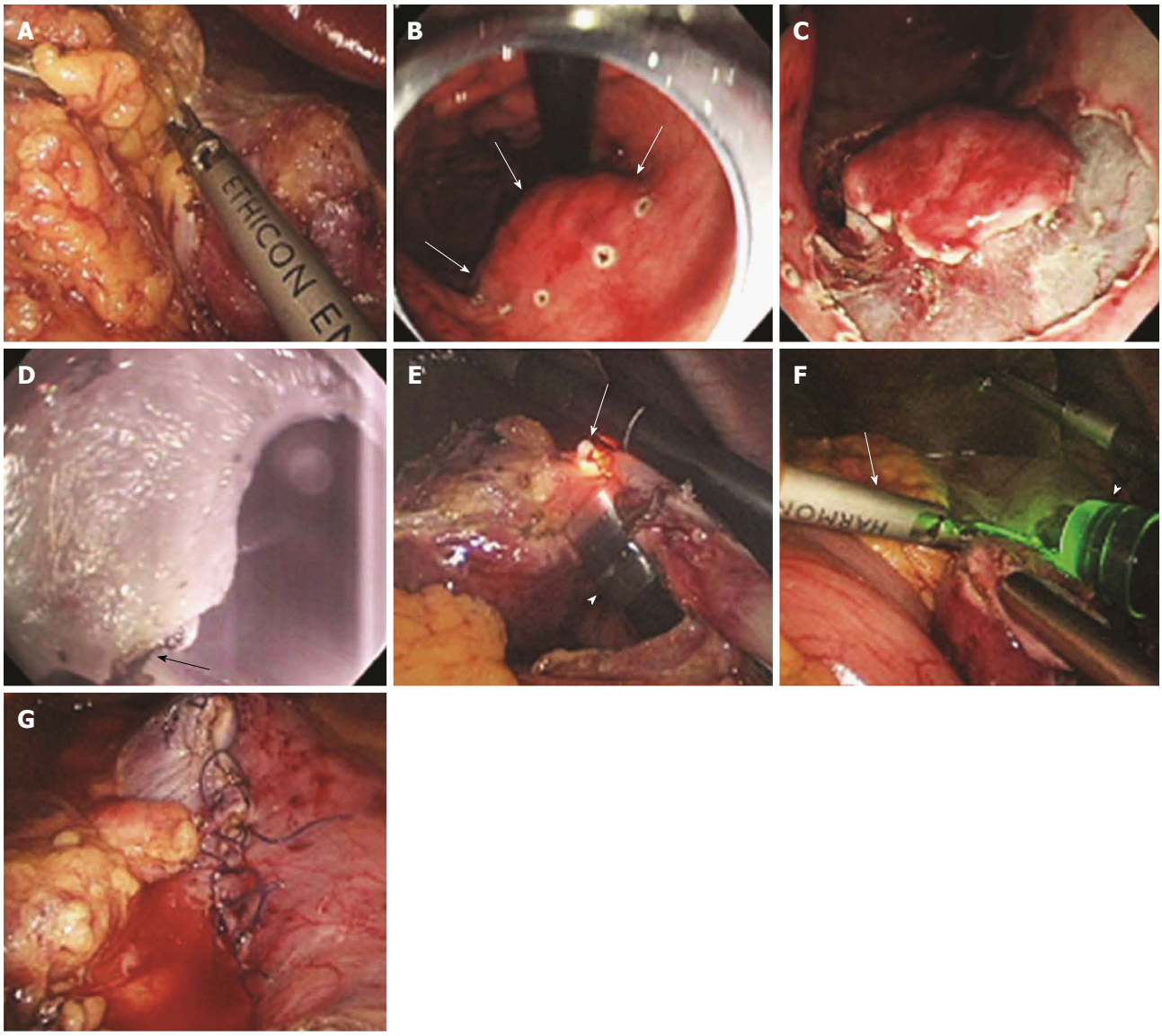

Figure 7 Procedure for laparoscopy-assisted endoscopic full-thickness resection. A: Laparoscopic view while the lesser omentum attached around the tumor site was dissected; B: Endoscopic view after marking around the gastric subepithelial tumor (white arrows) located on the lesser curvature side of the gastric body; C: Gastroscopic view after incision as deep as the submucosal layer around the lesion; D: Gastroscopic view of the full-thickness incision from inside the stomach using the IT knife (white arrow); E: Laparoscopic view of the full-thickness incision from inside the stomach using the IT knife (arrow, the tip of the IT knife; arrowhead, the gastroscope); F: Laparoscopic view of the remaining full-thickness incision from outside the stomach using a Harmonic ACE (arrow); G: Laparoscopic view after laparoscopic hand-sewn closure of the gastric-wall defect (adopted from Abe *et al*[58]).

a linear stapler[57].

LAEFR, *i.e.*, EFTR with laparoscopic assistance, is an effective treatment for selected patients with gastric subepithelial tumors (n = 4 and 25)[58,59]. There are four major steps in LAEFR (Figure 7): (1) deep submucosal incision using ESD[57]; (2) endoscopic seromuscular layer incision, three-fourths or two-thirds of the circumference; (3) laparoscopic seromuscular incision for remaining circumference; and (4) hand-sewn closure. The different point of LAEFR from LES is a hand-sewn closure without linear staples. LECS affords easier and more accurate resection, and the LAFTR results in minimal resection[57]. LECS and LAFER showed excellent outcomes. All reports have shown 100% complete resection rates and no complications (Table 3)[55,56,58,59]. The best indication for LECS and LAEFR may be intraluminal growing types of gastric GISTs originating from the PM layer. Such lesions cannot be well identified from the serosal side of the stomach; therefore, there is a high probability that conventional laparoscopic wedge resection will cause a larger-than-expected resection and bring about a gastric deformity or stenosis, or conversely, can produce a positive surgical margin[57]. LECS or LAEFR can avoid such problems. Full-thickness resection procedures are derived from ESD. Therefore, both can be applied regardless of tumor size, and a pathologically acceptable resection margin can be more easily accomplished[57-60].

NEWS is a newly suggested technique developed

Table 3 Publications reporting laparoscopic and endoscopic cooperative surgery, laparoscopy-assisted endoscopic full-thickness resection, and non-exposed wall-inversion surgery for submucosal tumors in the upper gastrointestinal tract

Ref.	*n*	Method	Mean operation time (min)	Mean tumor diameter (mm)	Complete resection rate (%)	Complications
Mitsui *et al*[61] (2014)	6	NEWS	306	34	100	0
Hoteya *et al*[59] (2013)	25	LAFER	156	32	100[1]	0
Tsujimoto *et al*[56] (2012)	20	LECS	157	38	100[1]	0
Hiki *et al*[66] (2011)	38	LECS			100	0
Abe *et al*[58] (2009)	4	LAEFR	201	30	100[1]	0
Hiki *et al*[55] (2008)	7	LECS	169	46	100	0

[1]Pathologically evaluated. LAEFR: Laparoscopy-assisted endoscopic full-thickness resection; LECS: Laparoscopic and endoscopic cooperative surgery; NEWS: Non-exposed wall-inversion surgery.

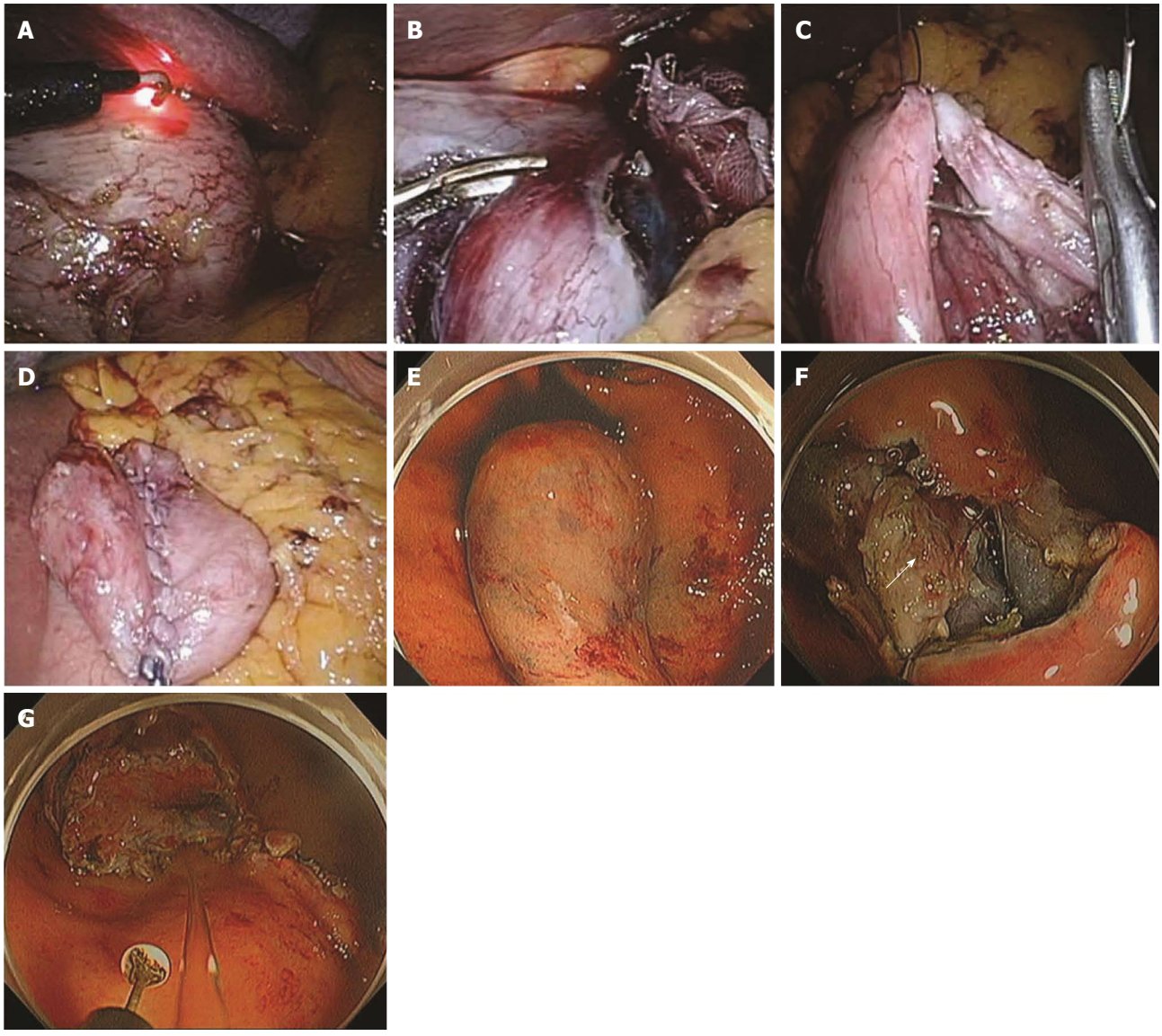

Figure 8 Procedure for non-exposed wall-inversion surgery. A: Laparoscopic markings on the serosal surface guided by light from the fiber-optic probe shining through the gastric endoscope; B: Circumferential seromuscular layer dissection outside the serosal markings; C: Seromuscular layer suture closure; D: Laparoscopic view of inversion of the dissected area; E: Endoscopic view of massive protrusion of the inverted tissue; F: Serosal surface (arrow) identified during mucosubmucosal layer dissection; G: Flipped tissue to be resected (adopted from Mitsui *et al*[61]).

to minimize the resected tissue volume as well as prevent peritoneal contamination (n = 6)[61]. There are 7 major steps in NEWS (Figure 8)[61,62]: (1) marking the mucosa around a lesion; (2) serosal marking using laparoscopy on the side opposite the mucosal markings; (3) injecting hyaluronate solution endoscopically into the submucosal layer; (4) laparoscopic circumferential seromuscular

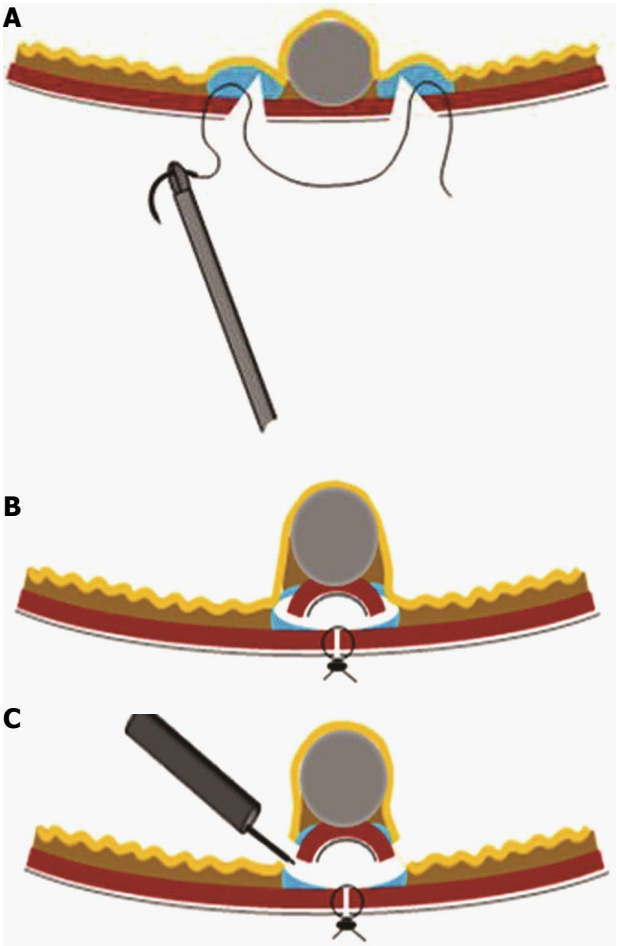

Figure 9 Scheme of the procedure for non-exposed wall-inversion surgery. A: Seromuscular layer suture after submucosal injection and seromuscular cutting; B: Divided seromuscular layer inversion after laparoscopic seromuscular closure; C: Mucosubmucosal layer dissection (adopted from Mitsui *et al*[61]).

layer incision; (5 suturing the seromuscular layer; (6) spontaneous inversion of the lesion; and (7) circumferential incision of the mucosubmucosal layer. Theoretically, this technique nearly perfectly prevents peritoneal contamination because seromuscular layer suture and closure is performed before mucosubmucosal layer cutting (Figure 9)[61]. However, this innovative technique contains a few downsides compared with LECS or LAEFR. Mitsui *et al*[61] reported 2 perforations in 6 cases: one laparoscopic mucosal injury during the seromuscular incision and musculoserosal tearing by ESD. Two cases out of 6 also converted due to poor recognition of the tumor margin[61]. Selecting appropriate lesions, type Ⅲ and type Ⅳ, and advancement of this technique would be necessary to apply NEWS in ordinary clinical fields.

IMATINIB AS AN ADJUVANT TREATMENT

Although a significant proportion of patients will be cured with surgery alone, approximately 40% will eventually have a relapse of disease, with the majority of these relapses occurring within the first 5 years. The ACOSOG Z9001 trial[63] compared 12 mo of imatinib treatment with a placebo and showed an estimated 1-year recurrence-free survival (RFS) of 98% in the Imatinib group compared with 83% in the placebo group (HR: 0.35). More recently, the Phase Ⅲ Scandinavian Sarcoma Group Trial[64] reported that patients affected by GISTs with a high risk of recurrence treated with adjuvant Imatinib for 36 mo had longer RFS (5-year RFS, 65.6% *vs* 47.9%; HR: 0.46) and improved overall survival (5-year survival, 92% *vs* 81.7%; HR: 0.45) compared with those receiving 12 mo of treatment. These trials provided Level 2 evidence, according to the latest edition of the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence, for the role of adjuvant imatinib in patients with resected GISTs. Together, the current evidence supports at least 3 years of adjuvant imatinib as a new standard for patients with resected, high-risk GISTs, although the optimal duration of therapy remains unknown[65]. In endoscopic enucleation, imatinib treatment appears to often be neglected, possibly for the following reasons. First, a lesion removed by endoscopic enucleation is typically small- to medium-sized. Second, most GISTs were incidentally detected in asymptomatic patients unlike gastric cancer cases, which are typically more serious and draw greater attention from doctors and surgeons. However, it is absolutely desirable for practitioners to follow the guidelines for adjuvant usage of imatinib, based on the risk level of the GISTs.

CONCLUSION

Unpredictable malignant potential and rare lymph node metastasis provided the theoretical basis for the concept of minimally destructive surgery for incidentally detected asymptomatic GISTs. Under this theoretical concept, technical advances have been made based on ESD-enabled surgeons performing endoscopic enucleation of GISTs. However, there is the possibility of simultaneous occurrence of perforation and pseudocapsule injury, which can cause peritoneal seeding. Furthermore, the rate of R0 resection is not yet acceptable, although one study reported a high R0 resection rate. Well-trained surgeons and a more secure endoscopic enucleation technique are needed to justify the implementation of this procedure. Moreover, long-term results of endoscopic enucleation will be necessary to confirm the true efficacy and safety because reports on the use of endoscopic enucleation are currently limited to case reports and small, retrospective, or pilot series. While EFTR has a much better theoretical basis than endoscopic enucleation in terms of R0 resection, the possibility of tumor cell shedding into the peritoneum would substantially increase when capsule injury results from the procedure. Moreover, a surgeon needs advanced

skills to close a large iatrogenic perforation. In contrast with procedures that employ only endoscopy, LECS and LAFTR provide safer procedures, a higher complete resection rate, and a more stable process. Although LECS and LAFTR require more resources, including more people, more devices, and even additional machines, LECS and LAFTR could represent more acceptable procedures in terms of conventional surgical purposes, because they result in complete resection and avoid peritoneal seeding.

Various endoscopic procedures have challenged conventional surgery with the aid of advances in modern medical technology. Many procedures were invented and attempted because they were technically possible. However, we should consider the aim of conventional surgery, which has accumulated vast data. Until the efficacy and safety of sole endoscopic access are demonstrated in multiple ways, LECS and LAFTR appear to be appropriate procedures for pursuing secure and effective surgical outcomes that conform to the concept of minimally destructive surgery.

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Techniques and efficacy of flexible endoscopic therapy of Zenker's diverticulum

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Abstract

Zenker's diverticulum (ZD) is an abnormal hypopharyngeal pouch often presenting with dysphagia. Treatment is often sought with invasive surgical management of the diverticulum being the only mode of definitive therapy. Primarily done by an open transcervical approach in the past, nowadays treatment is usually provided by otolaryngologists using a less invasive trans-oral technique with a rigid endoscope. When first described, this method grew into acceptance quickly due to its similar efficacy and vastly improved safety profile compared to the open transcervical approach. However, the main limitation with this approach is that it may not be suitable for all patients. Nonetheless, progress in the field of natural orifice endoscopic surgery over the last 10-20 years has led to the increase in utilization of the flexible endoscope in the treatment of ZD. Primarily performed by interventional gastroenterologists, this approach overcomes the prior limitation of its surgical counterpart and allows adequate visualization of the diverticulum independent of the patient's body habitus. Additionally, it may be performed without the use of general anesthesia and in an outpatient setting, thus further increasing the utility of this modality, especially in elderly patients with other comorbidities. Today, results in more than 600 patients have been described in various published case series using different techniques and devices demonstrating a high percentage of clinical symptom resolution with low rates of adverse events. In this article, we present our experience with flexible endoscopic therapy of Zenker's diverticulum and highlight the endoscopic technique, outcomes and adverse events related to this minimally invasive modality.

Key words: Zenker's diverticulum; Flexible endoscopy; Natural orifice endoscopic surgery; Per-oral endoscopy; Dysphagia; Cricopharyngeus myotomy; Cricopharyngeus septotomy

Core tip: Definitive therapy for Zenker's diverticulum (ZD) typically includes either diverticulectomy or myotomy/

septotomy of the cricopharyngeus muscle. Previously done as an open transcervical approach by surgeons, treatment has now evolved to include a minimally invasive trans-oral approach with flexible endoscopy performed by gastroenterologists. In this article we highlight our experience with flexible endoscopic therapy of ZD at our institution, describe commonly used flexible endoscopic techniques and devices, and assess efficacy and safety data related to this minimally invasive modality.

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INTRODUCTION

Zenker's diverticulum (ZD) is a pharyngeal outpouching caused by increased intraluminal pressure, in conjunction with an area of inherent weakness in the hypopharynx known as the Killian triangle. This area of vulnerability is formed in between two pharyngoesophageal muscles, the inferior pharyngeal constrictor and the cricopharyngeus. Since the original description of the condition by Ludlow[1] and then Zenker von Zeimssen[2]; the pathophysiology that leads to the ZD has been poorly understood. Currently, the mechanism that leads to increase in luminal pressures causing the ZD is thought to be due to poor upper esophageal sphincter (UES) compliance[3,4].

Characteristic symptoms for ZD include dysphagia, which is the presenting symptom in 80%-90% of patients. Additionally, patients may present with cough, dysphonia, malnutrition and weight loss. Occurrence is not usual in patients under the age of 40 years with incidence most prevalent in males in the seventh or eighth decade of life[5]. The diagnosis of ZD is based on clinical and radiographic findings, with dynamic barium esophagram being the confirmatory study[6]. Surgical intervention involving disruption of the cricopharyngeus by myotomy and/or diverticulectomy is the mainstay of treatment. The open trans-cervical approach that was originally described by Wheeler[7] has now evolved after a sentinel paper published by Dohlman and Mattson[8] to a less invasive trans-oral approach using a rigid endoscope. This technique currently performed by otolaryngologists, is the method of choice due to similar efficacy, reduced patient morbidity and overall shorter hospital stay compared to traditional open transcervical surgery[9].

Indeed, all patients who are diagnosed with ZD would ideally undergo endoscopic therapy as the benefits mentioned previously make this a more favorable choice for patients and clinicians. However, as with all surgical procedures there are several pre-interventional considerations. At the crux of these issues are the needs to visualize the diverticulum trans-orally. Several patient indicators including high body mass index and poor neck flexibility predispose the patient to higher risk of adverse events and procedural failure. As such, an open approach is still used in 15% to 68% of cases[5]. Nevertheless, within the past 20 years the trans-oral approach has progressed with the advent use of a flexible endoscope. Currently performed by interventional gastroenterologists/endoscopists, this method helps overcome the prior concerns of visual limitations while still providing a minimal invasive approach to this complex surgical condition. Several variations to this procedure have been explored and published in recent times, though, lacking comprehensive long-term analysis and comparative effectiveness of these various techniques. In this article we highlight our experience with flexible endoscopic therapy of ZD at our institution, describe commonly used flexible endoscopic techniques and devices, and assess efficacy and safety data related to this minimally invasive modality.

THE UNIVERSITY OF FLORIDA (UF) EXPERIENCE

Aims and outcomes

The aim of this study was to assess the efficacy and safety of patients undergoing flexible endoscopic treatment of ZD. Efficacy was defined by: (1) technical success of endoscopic therapy; and (2) improvement in dysphagia score. Safety was characterized by the lack of development of intra-procedural or post-procedural adverse events (AE).

Definitions

Technical success: Procedural technical success was defined as the ability to successfully perform flexible endoscopic cricopharyngeus myotomy.

Dysphagia score: A score range (0-4) was used to quantify dysphagia prior to and after endoscopic treatment[10].

Adverse events: Endoscopic adverse events were assessed based on previously established criteria by the American Society of Gastrointestinal Endoscopy (ASGE)[11].

Methods and techniques

This study was approved by the University of Florida Institutional Review Board (IRB). Our electronic endoscopy database was queried from January 2006 through June 2014 for patients who were referred to a single interventional endoscopist for flexible endoscopic treatment of ZD. Diagnosis of ZD was made with either barium esophagram, computed tomography or direct endoscopic visualization.

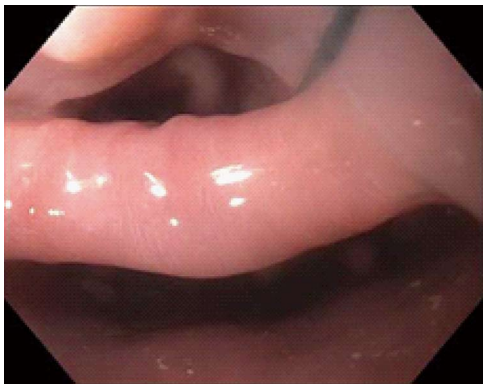

Figure 1 Endoscopic appearance of Zenker's diverticulum (esophageal lumen with guidewire is above the Zenker's diverticulum); note the cricopharyngeus septum separating the Zenker's diverticulum from the esophagus.

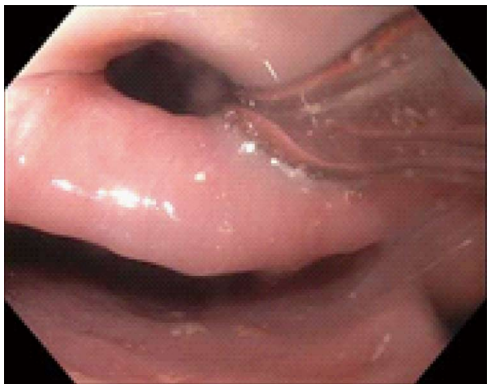

Figure 2 Nasogastric tube in true lumen of the esophagus.

General anesthesia was used per anesthesiologist recommendations and prophylactic antibiotics were typically not given. The procedure was begun after general endoscopic evaluation of the ZD (Figure 1), stomach and duodenum. A nasogastric or orogastric tube (Figure 2) was then placed over a guidewire for improving visualization of the diverticulum and protection of the anterior esophageal wall during myotomy. A needle knife was then used to perform the myotomy (Figure 3) exposing the transverse fibers of the cricopharyngeus. Following the procedure, all patients were then admitted overnight for observation and gradual advance of their diet.

Results

A total of 8 patients [50% male, mean age 72.4 years (range 58-88)] underwent technically successful flexible endoscopic myotomy of their ZD. One endoscopic treatment session was performed per patient and all patients noted improvement in their dysphagia symptoms after therapy. The mean pre-procedure dysphagia score was 2.6 (range 2-4) and post-procedure dysphagia score was 0.4 (range 0-2). There were no AE and mean follow-up time was 5.8 mo (range 0-17). Two patients with mild residual dysphagia did not wish to undergo a repeat procedure or other interventions.

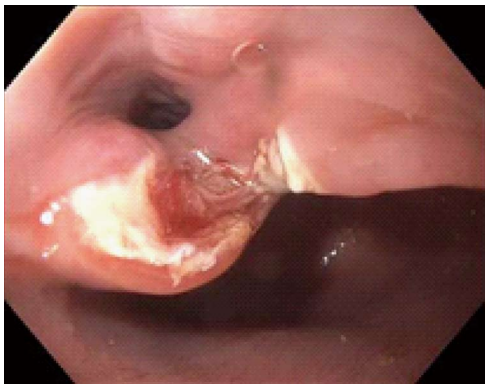

Figure 3 Cricopharyngeus myotomy.

TECHNICAL ASPECTS

Since landmark studies by Mulder[12] and Ishioka[13], the use of flexible endoscopy to treat ZD has come into many centers as an additional minimally invasive modality for management. Described by radiographic and manometric studies by Cook[3], pathogenesis of this abnormality seems to be related to poor UES compliance leading to increase swallowing pressures and in turn a Killian's dehiscence. As such, the mainstay of treatment has been ablation or division of the cricopharyngeus "septum" (cricopharyngeus myotomy or septotomy) and there have been many variations in the way this myotomy is performed. Additionally, most institutions have employed tools aiding to secure and expose the septum such as the diverticuloscope and clear cap assisted devices. Currently, 19 case series/analyses[10,12-29] have been published describing flexible endoscopic therapy in over 600 patients with ZD (Table 1).

Pre-operative assesment

Typically, symptomatic patients undergo barium esophagram and index upper endoscopy for diagnosis of ZD. One of the advantages of flexible endoscopic therapy for ZD is the ability to perform the procedure without general anesthesia in many cases. This allows patients who are not ideal candidates for endotracheal intubation to undergo either moderate sedation (conscious sedation/CS) or deep sedation/monitored anesthesia care (MAC). In published studies (Table 2) where mode of anesthesia was mentioned, greater than half of all patients underwent endoscopic procedures with either CS or MAC, without mention of intraoperative adverse events related to airway compromise. Nevertheless, some authors[26] still insist in using general anesthesia to protect the airway in case of bleeding at the UES and since the improved muscle relaxation provides greater safety assurance when manipulating the endoscope.

Table 1 Published cases for flexible endoscopic therapy of Zenker's diverticulum

Ref.	Total patients (n = 678)	Age (range)	Device for myotomy	Assist device	Pre-procedure dysphagia score	Post-procedure dysphagia score	Clinical symptom resolution rate	Adverse events	Recurrences	Followup (range)
Mulder *et al*[12]	20	Mean 82 (41-100)	FC	None	NA	NA	85%	0%	0	Mean 7 (1-18)
Ishioka *et al*[13]	42	Mean 68 (46-102)	NK	None	NA	NA	93%	5%	7	Mean 38 (12-96)
Hashiba *et al*[14]	47	(58-81)	NK	None	NA	0 or 1	96%	14.9%	0	(0-12)
Mulder *et al*[15]	125	Median 77 (41-100)	APC	None	NA	NA	100%	20%	NA	NA
Sakai *et al*[16]	10	(67-87)	NK	Cap	1.8	0	100%	0%	0	(2-12)
Evrard *et al*[17]	31	Median 78	NK	DS			93%	13%	9	Median 12.5
Costamagna *et al*[18]	28	Median 66 (47-86)	NK	Cap	NA	NA	43%	32%	4	Median 36 (9-60)
Costamagna *et al*[18]	11	Median 70 (63-84)	NK	DS	NA	NA	91%	0%	1	Median 6.5 (3-15)
Rabenstein *et al*[19]	41	Mean 73	APC	Cap	NA	NA	95%	19.5%	5	Mean 16
Christiaens *et al*[10]	21	Median 77.5 (52-89)	FC	Cap	1.5	0	100%	3%	2	Median 22.4
Volgelsang *et al*[20]	31	Median 69 (52-92)	NK	Cap	NA	NA	100%	23%	10	Mean 26
Manner *et al*[21]	8	Mean 66	APC	Cap	NA	NA	NA	37.5%	NA	NA
Tang *et al*[22]	6	Mean 71 (48-91)	NK	Endo Clips	NA	NA	100%	0%	0	NA
Al-Kadi *et al*[23]	18	Mean 80 (68-91)	NK	None	(2-4)	NA	87.5%	5.5%	NA	Mean 27.5
Case *et al*[24]	22	Median 85	NK	None	NA	NA	100%	32%	4	Mean 12.7
Repici *et al*[25]	32	Mean 74.8 (58-92)	HK	Cap	2.96	0.62	NA	6.25%	3	Mean 23.9 (12-48)
Hondo *et al*[26]	5	Median 69.6 (59-83)	HS	DS	2	0.20	NA	0%	0	Mean 1
Huberty *et al*[27]	150	Median 73 (42-94)	NK	DS	1.88	0.34	90.3%	2.2%	31	Median 43 (13-121)
Ramchandani *et al*[28]	3	Mean 79	SB-K	DS	NA	NA	100%	0%	0	NA
Manno *et al*[29]	19	Median 74 (46-84)	IT-K	DS	NA	NA	100%	0%	2	Median 27
Perbtani (current study)	8	72.4	NK	None	2.6	0.4	100%	0%	2	Mean 5.8 (1-17)

NK: Needle knife; IT-K: Insulated tip knife; SB-K: Stag beetle knife; HK: Hook knife; HS: Harmonic scalpel; FC: Forceps coagulation; APC: Argon plasma coagulation; DS: Diverticuloscope; NA: Not available.

Procedural technique

Prior to performing the procedure various steps are essential to ensure safety in performing the myotomy: (1) Placement of a nasogastric (NG) or orogastric (OG) tube is a common practice that has been introduced with two potential benefits: First, it allows enhanced visualization of the esophageal lumen and diverticulum, and secondly it protects the anterior esophageal wall from injury from instruments used during myotomy; (2) Accessories to improve visualization: Sakai *et al*[16] originally described the use of an assist or accessory device during ZD therapy to stabilize and visualize the septum. A transparent oblique-end hood was used at the tip of the endoscope that extended distally. This in turn served to prevent closure of the upper esophageal sphincter thus allowing for better visualization of the tissue bridge between the esophagus and the diverticulum. Similarly, clear mucosectomy caps[19] have been used with similar intentions. In 2003 Evrard *et al*[17] described the use of a soft diverticuloscope as an adjunct that served a similar function as the clear cap device. The diverticuloscope is placed as an overtube on the endoscope and contains two distal flaps that serve to straddle the septum and safeguard the anterior esophageal and posterior diverticular walls. At this point the instrument used to divide the septum is introduced either alongside or through a channel within the endoscope. In review of the published cases, only one study looked at outcomes between accessories. Costamagna *et al*[18] documented lower complication rates and procedural time with the diverticuloscope *vs* using a clear cap. However, it is worth noting that the diverticuloscope is only commercially available in Canada and Europe.

In performing the cricopharyngeus myotomy the optimal instrument for ablation remains debatable. Moreover, due to the lack of prospective comparative trials the device chosen is often dependent on prior training and preference of the endoscopist. The most commonly used device is the needle knife as is our

Table 2 Modes of sedation used *n* (%)

Sedation type	Patients (*n* = 678)
Conscious sedation	352 (52)
Monitored anesthesia care	60 (9)
General anesthesia	77 (11)
Not reported	189 (28)

practice, followed by argon plasma coagulation (APC) and forceps coagulation (Table 3). This is notably different amongst otolaryngologists, where either carbon dioxide laser or a stapler-assisted device is most frequently employed[30]. When using the needle knife the tip of the instrument is placed at the center of the septum where coagulation, blended or alternating current can be used[16,18,20]. The division through the septum occurs in craniocaudal motion, which exposes the transverse fibers of the cricopharyngeal muscle. The incision should not extend past the inferior portion of the diverticulum, as risk for perforation significantly increases. Length of the myotomy has been described safely up to 5-10 mm from the bottom of the ZD[16,26,27] with endoclips placed by some endoscopists[18] distally for prophylaxis against microperforations.

Emerging techniques: Recent advances in natural orifice translumenal endoscopic surgery (NOTES) have given rise to novel myotomy techniques including per oral endoscopic myotomy (POEM)[31]. Similarly, endoscopic submucosal dissection (ESD) techniques have recently been reported[32] to extend its application to aid in cricopharyngeal myotomies. In this small case series, a modified clear cap overtube was created to secure the diverticular wall while indigo carmine solution was injected into the septum. A submucosal bleb or lift was then created which served to increase exposure of the cricopharyngeal muscle fibers and theoretically enabling a safer and more complete myotomy. Although this variation of flexible endoscopic treatment of ZD is in it's infancy, this study highlights the continual innovative modifications being made to optimize clinical outcome, reduce recurrence rate and sidestep technical hurdles faced by its predecessor.

Post-operative care

In the post-operative period patients have been discharged as outpatients after as short as 6 h as long as there were no apparent adverse events[20]. However, in most cases, patients are hospitalized for 24-48 h with gradual progression of their diet 12 h post-operatively. Post-procedural radiologic studies remain institution dependent. The development of perforations is a concern but there is a low sensitivity for detection of microperforations using this method. Additionally, little correlation has been seen between radiographic findings and patient symptoms[6,33]. We endorse imaging only if there is a clinical suspicion for perforation.

Table 3 Devices used for cricopharyngeus myotomy *n* (%)

Device for myotomy	Patients (*n* = 678)
Needle knife	404 (59.6)
APC	174 (25.7)
Forceps coagulation	41 (6)
Hook knife	32 (4.7)
Insulated tip knife	19 (2.9)
Harmonic scalpel	5 (0.7)
Stag beetle knife	3 (0.4)

OUTCOMES

Multiple centers have reported their results of the flexible endoscopic approach to ZD therapy since it's original description in 1995. There have been 19 reported case series that have been published consisting of 670 patients (Table 1). However, due to the subjective manner in which procedural outcome is determined in these series, it is difficult to gauge true objective clinical success. Often, success is based on patient symptoms and not on objective data. Moreover, there are no guidelines or studies that suggest if endoscopic or radiologic surveillance would be beneficial. To improve upon this aspect some centers have instituted using a dysphagia score[10]. The scale ranges from 0-4 as follows: 0: no dysphagia; 1: dysphagia to solids; 2: dysphagia to semi solids; 3: dysphagia to liquids; 4: patient cannot swallow saliva. A score of this manner provides an objective measurement of outcome as is routinely used at our center and in this study as well. In studies where dysphagia score was used, the average pre- and post-treatment dysphagia score was 2.1 (range 1.8-4) and 0.26 (range 0-0.6) respectively. More routinely reported is the clinical resolution rate (CRR). This is commonly described as a symptom improvement either immediately or 2-4 wk post-procedurally. Of the available studies the reported CRR was over 90% (Table 1) and patients with persistent symptoms typically underwent either a repeat procedure or were referred to otolaryngologists for surgical management. Recurrence rate (RR) for symptoms was near 15% from the available data with an average follow-up time of 20 mo. However, follow-up period was not mentioned in nearly a quarter of the reports and is commonly seen as a shortcoming when reporting outcomes for this procedure.

ADVERSE EVENTS

Adverse events (AE) for the flexible endoscopic therapy of ZD have been well reported since first being described. However, due to the lack of standardization there remains heterogeneity of how accounted complications are reported and designated. In the 678 patients that have been reported to undergo the flexible endoscopic procedures, including our current study, 80 patients (11.8%) were reported to

Table 4 Published adverse events after flexible endoscopic therapy of Zenker's diverticulum *n* (%)

Adverse events	80/678 (11.8%)
Micro perforations	52/678 (7.7)
Cervical emphysema	1
Mediastinal emphysema	5
Subcutaneous emphysema	25
Unspecified	21
Macro perforations	4/678 (0.6)
Bleeding	9/678 (1.3)
Infection	12/678 (1.8)
Fever	10
Pneumonia	1
Neck abscess	1
Death	1/678 (0.1)
Adverse events, not otherwise specified	2/678 (0.3)

have AE (Table 4), the most common being micro-perforations, which encompasses greater than half of reported complications. These are described as the patient developing either: cervical, subcutaneous or mediastinal emphysema. Most of these documented by various radiographic studies, had inconsequential medical outcomes and were treated conservatively with or without antibiotics[34]. Macroscopic perforations, the more morbid AE, were only reported in 4 cases. These perforations were seen either during endoscopic visualization or by oral contrast extravasation and were typically managed with endoscopic clipping without any long-term sequelae being reported. Bleeding occurred in 6 of the reported cases, mostly intra-procedural and treated with epinephrine injection, endoclips or electrocautery. Prolonged post-procedural bleeding has only been recorded in 1 case[14] with hemostasis achieved with endoscopic injection of epinephrine. Fever was reported as the most common presentation of infections reported in published cases. Patients were usually treated with antibiotics if specific organ involvement was apparent or for fever lasting more than 24 h. If fever persisted and a focus of infection was not found, then appropriate testing to rule out perforation or mediastinitis is essential[35]. Patient mortality is infrequent, with only one case being reported[15] due to pulmonary embolism. At our institution, similar to previously published series from other centers, we did not encounter any procedural adverse events. However, as mentioned earlier, accurate reporting of AE is likely best achieved in prospective studies using objective predetermined criteria as suggested by the ASGE[11].

CONCLUSION

Flexible endoscopy therapy appears to be a minimally invasive option for the treatment of ZD with several studies showing favorable clinical outcomes and an adequate safety profile. Future efforts should include prospective trials with further standardization of technical aspects, comparison of endoscopic devices and accessories, and report of long-term clinical outcomes with this technique.

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MINIREVIEWS

Endosonography in the diagnosis and management of pancreatic cysts

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Abstract

Rapid advances in radiologic technology and increased cross-sectional imaging have led to a sharp rise in incidental discoveries of pancreatic cystic lesions. These cystic lesions include non-neoplastic cysts with no risk of malignancy, neoplastic non-mucinous serous cystadenomas with little or no risk of malignancy, as well as neoplastic mucinous cysts and solid pseudopapillary neoplasms both with varying risk of malignancy. Accurate diagnosis is imperative as management is guided by symptoms and risk of malignancy. Endoscopic ultrasound (EUS) allows high resolution evaluation of cyst morphology and precise guidance for fine needle aspiration (FNA) of cyst fluid for cytological, chemical and molecular analysis. Initially, clinical evaluation and radiologic imaging, preferably with magnetic resonance imaging of the pancreas and magnetic resonance cholangiopancreatography, are performed. In asymptomatic patients where diagnosis is unclear and malignant risk is indeterminate, EUS-FNA should be used to confirm the presence or absence of high-risk features, differentiate mucinous from non-mucinous lesions, and diagnose malignancy. After analyzing the cyst fluid for viscosity, cyst fluid carcinoembryonic antigen, amylase, and cyst wall cytology should be obtained. DNA analysis may add useful information in diagnosing mucinous cysts when the previous studies are indeterminate. New molecular biomarkers are being investigated to improve diagnostic capabilities and management decisions in these challenging cystic lesions. Current guidelines recommend surgical pancreatic resection as the standard of care for symptomatic cysts and those with high-risk features associated with malignancy. EUS-guided cyst ablation is a promising minimally invasive, relatively low-risk alternative to both surgery and surveillance.

Key words: Endoscopic ultrasound; Pancreatic cyst; Serous cystadenoma; Intraductal papillary mucinous neoplasms; Mucinous cystic neoplasm; Solid pseudopapillary neoplasms; diagnosis; Management; Ablation

Core tip: Endoscopic ultrasound with fine needle aspiration (EUS-FNA) is an important and safe diagnostic tool in pancreatic cystic lesions to help

diagnose malignancy, identify features concerning for malignancy, and differentiate mucinous from non-mucinous cysts. More recently EUS-guided pancreatic cyst ablation may offer a minimally invasive and safer alternative to surgical resection for carefully selected pancreatic cysts.

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INTRODUCTION

Endoscopic ultrasound with fine needle aspiration (EUS-FNA) has revolutionized diagnosis, and more recently treatment, of a variety of gastrointestinal conditions accurately and safely. This includes the seemingly ubiquitous pancreatic cystic lesion. The rapid advancement and widespread use of cross-sectional imaging has resulted in more incidentally discovered pancreatic cysts. Recent studies from the United states have estimated an overall prevalence of 2.5%[1]. Pancreatic cysts may be seen in as many as 14%-20% of magnetic resonance imaging (MRI) studies[2,3] and in 3% of computed tomography (CT) scans[4]. The prevalence of these incidental cystic lesions is directly correlated to increasing age[5]. Internationally, studies have shown steadily increasing rates of detection of pancreatic cysts over the years[6] and, specifically, intraductal papillary mucinous neoplasms (IPMN)[7]. In addition to increased frequency, the median size of these incidentally detected lesions has decreased by about half from 3 cm to 1.5 cm over 12 years in a Korean study[6] and from 4 cm to 2 cm over 5 years in a study from the United States[8].

This trend of increased discovery of pancreatic cysts is particularly important because specific types of pancreatic cystic lesions have varying potential for malignant transformation[9]. A study of a large national database estimated the overall prevalence of malignant cysts as 33 in 100000[1], and recent natural history studies have estimated 1.3%-3.3%[6,8]. Pancreatic cysts can generally be classified as non-neoplastic, neoplastic and necrosis of solid tumors. Non-neoplastic cysts have no malignant potential; these include pseudocysts, retention cysts, mucinous non-neoplastic cysts, lymphoepithelial cysts and benign epithelial cysts. Two-thirds of pancreatic cysts are cystic neoplasms (Table 1); these include mucinous cysts [mucinous cystic neoplasms (MCN) and intraductal papillary mucinous neoplasms (IPMN)], non-mucinous cysts [serous cystadenoma (SCA)] and solid pseudopapillary neoplasms (SPEN). Mucinous cysts and SPENs are considered premalignant or may harbor malignancy. There is further variability in malignant potential among the premalignant mucinous subtypes [MCN, branch duct (BD)-IPMN, main duct (MD)-IPMN and mixed/combined IPMN]. Non-mucinous SCAs have little to no malignant potential. Consequently, these different types of cystic lesions require a range of different management strategies, from monitoring to surgical resection, depending on the risk of malignant transformation[10,11]. Therefore, accurate diagnosis is of the utmost importance.

Initial diagnostic testing usually focuses on radiologic imaging. Following incidental identification of a pancreatic cyst, MRI of the pancreas with magnetic resonance cholangiopancreatography (MRCP) is recommended[12]. If MRI/MRCP cannot be performed, a pancreatic protocol multidetector (MD) CT should be obtained. MRI/MRCP is preferable as it is better able to evaluate septa, nodules, main pancreatic duct involvement, branch duct involvement, communication with the main pancreatic duct and cyst contents/debris; and is 79%-82% accurate in identifying mucinous cysts[13-16]. Both CT and MRI predict the presence of malignancy in pancreatic cysts with 73%-79% accuracy[17]. A recent retrospective study of resected pancreatic cysts noted MRI was 100% accurate for diagnosing mucinous and malignant cysts, although sample size was small (4-7 patients), while CT was 53%-56% accurate[18].

ROLE OF EUS IN DIAGNOSIS OF PANCREATIC CYSTS

Clinical evaluation, MDCT and MRI may be sufficient to make the diagnosis and guide management when certain pathognomonic and/or characteristic features are present[9-11,19]. While individual cyst types do have characteristic morphologic features, their actual appearance on imaging studies can be very similar[20,21]. Clinical and radiologic findings are often indeterminate, making diagnosis and estimating risk of malignancy difficult. A recent study examined the diagnostic utility of EUS and EUS-FNA beyond that of radiology. EUS with or without cyst fluid aspirate analysis [cytology, amylase and carcinoembryonic antigen (CEA)] was more sensitive (76%) than CT or MRI (48% and 34%) for differentiating neoplastic from non-neoplastic cysts[22]. While these results indicate EUS may be useful in identifying neoplastic cysts, the accuracy of radiologic imaging in this study was far lower than has been demonstrated by others. This study also only applies to resected cysts, which may bias in favor of EUS.

Following initial evaluation it is necessary to decide if a patient requires further diagnostic testing by EUS/EUS-FNA, radiologic surveillance or surgical resection. Patients with symptomatic pancreatic cysts (*e.g.,* pancreatitis) should be evaluated for surgery. In addition, the 2012 International Association of Pancreatology (IAP) guidelines for mucinous cysts

Table 1 Characteristics of common pancreatic cystic lesions

Characteristic	Pseudocyst	SCA	MCN	MD-IPMN[1]	BD-IPMN[1]	SPEN
Male:female	1:1	1:4	Nearly all female	2:1	2:1	1:4
Age (yr)	40-70	60-80	30-50	60-80	60-80	20-30
Location	Any	Any	Body, tail (90%)	Any (head and uncinate 50%)	Any (head and uncinate 50%)	Body, tail (60%)
Imaging features	Unilocular, thick or thin walled	Multilocular, lobulated. Typically microcystic appearance. Central scar	Unilocular, smooth and encapsulated. Septations and peripheral calcifications possible	Diffuse or focal main duct dilation. Fish-mouth papilla with visible mucus	Dilated side branches. Lobular with septations. "Bunch of grapes" appearance	Unilocular, encapsulated with solid and cystic structure. Hemorrhagic components
Communication with main duct	Variable	None	None	Yes	Yes	None
Cytology	Cyst contents	Cuboidal cells. Glycogen (+), PAS (+) and hemosiderin-laden macrophages	Columnar cells. Atypia varies. Mucin (+)	Columnar cells. Atypia varies. Mucin (+)	Columnar cells. Atypia varies. Mucin (+)	Branching papillae and fibrovascular stroma. Vimentin (+), chromogranin (-) and keratin (-)
Amylase (U/L)	> 250	< 250	< 250	> 250	> 250	N/A
CEA (ng/mL)	< 5	< 5	> 192	> 192	> 192	N/A
KRAS mutation	None	None	Yes	Yes	Yes	N/A
Malignant potential	None	Very rare	Yes (6%-27%)	Yes (40%-70%)	Yes (15%-20%)	Yes (2%-15%)
Morphological predictors of malignancy	None	None	> 6 cm, solid component, peripheral nodules or calcifications	Main duct ⩾ 8 mm, solid component, nodules	⩾ 3 cm, solid component, nodules, main duct ⩾ 1 cm, and suspicious/ malignant cytology	None

[1]Mixed IPMN have features of both MD and BD-IPMN. SCA: Serous cystadenoma; MCN: Mucinous cystic neoplasm; MD-IPMN: Main duct intraductal papillary mucinous neoplasm; BD-IPMN: Branch duct intraductal papillary mucinous neoplasm; SPEN: Solid pseudopapillary neoplasm; PAS: Periodic acid-Schiff stain; CEA: Carcinoembryonic antigen.

recommends that patients with these "high risk stigmata" for malignancy should undergo surgical evaluation: obstructive jaundice with a cyst located in the pancreatic head, a solid component with post-contrast enhancement, or a main pancreatic duct diameter ⩾ 10 mm[23]. Patients suspected of having SPENs should also be referred for surgery. Among asymptomatic patients with incidental cysts, a decision analysis study compared three management strategies: radiologic follow-up, surgery for all surgical candidates and an EUS-directed approach. The most cost-effective approach was to use EUS-FNA to guide the decision to manage the cystic lesion with radiologic follow-up or surgery[24].

The suggested approach to asymptomatic patients with incidentally discovered cysts is based on cyst size and the presence of features concerning for malignancy (solid component, mural nodule and main pancreatic duct ⩾ 1 cm) (Figure 1)[10]. Patients with cysts < 1 cm and no concerning features can be followed with radiologic imaging unless any change (*e.g.,* increased size) is detected, at which point EUS-FNA is warranted. In patients with cysts > 1 cm, further investigation by EUS-FNA would be advised to rule out the presence of concerning features and determine if the cyst is mucinous. In a recent retrospective study of resected cysts > 3 cm, EUS-FNA with cytology and cyst fluid analysis correctly identified mucinous and non-mucinous lesions in 88% of cases[18]. Even in patients with high risk features or imaging consistent with SPEN where surgery is indicated, evaluation by EUS-FNA and/or endoscopic retrograde pancreatography may be helpful in confirming risk of malignancy (or malignancy) prior to resection, particularly if the patient is a poor or reluctant surgical candidate. The same study of resected cysts > 3 cm found that 65% of these cysts were benign and that cytology, cyst fluid CEA and amylase had a negative predictive value of 94.1% for malignancy, which may allow conservative management in high-risk surgical candidates[18].

Among the mucinous lesions, MCN and IPMN can often be difficult to distinguish. In cases where these two types are lesions are suspected, the 2012 IAP guidelines recommend EUS in patients who present with pancreatitis or "worrisome features" (size ⩾ 3 cm, thick enhancing wall, non-enhancing nodule, main pancreatic duct diameter 5-9 mm, abrupt change in duct diameter with distal gland atrophy and lymphadenopathy)[23]. In these cases EUS should be used to confirm nodules, main duct involvement and cytological atypia with FNA. Surgery is indicated if any of these three features are confirmed. In cases where these features are absent, close surveillance of cysts > 2 cm by EUS and MRI is recommended. Alternatively, surgery may be considered in a young otherwise healthy person who would require prolonged monitoring. When initial EUS is inconclusive, cysts should be closely monitored with EUS and MRI[23].

EUS MORPHOLOGY

EUS is a minimally invasive procedure allowing high

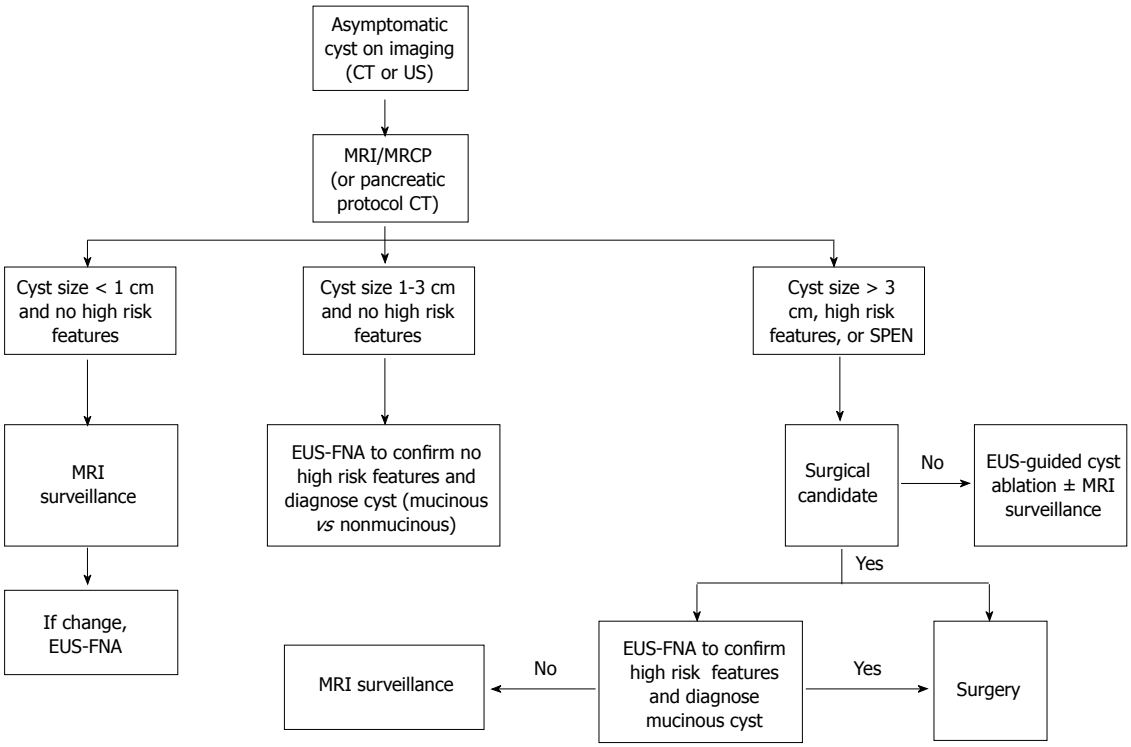

Figure 1 Approach using endoscopic ultrasound in the diagnosis of asymptomatic pancreatic cystic lesions. CT: Computed tomography; EUS: Endoscopic ultrasound; EUS-FNA: Endoscopic ultrasound-guided fine needle aspiration; MRCP: Magnetic resonance cholangiography; MRI: Magnetic resonance imaging; SPEN: Solid pseudopapillary neoplasm; US: Ultrasound.

Table 2 Endoscopic ultrasound features suggestive of mucinous or malignant cysts

EUS Feature	Type of cyst	Concerning for increased risk of malignancy
Size	-	> 3 cm
Shape	Smooth unilocular: pseudocyst or MCN	-
	Lobular, multilocular: SCA or BD-IPMN	
Number of cysts	Multiple: BD-IPMN	-
Calcifications	Central scar: pathognomonic for SCA	Peripheral calcification in MCN
	Peripheral calcification: pseudocyst, SPEN, MCN	
Cyst wall	Thick: pseudocyst, cystic neuroendocrine, MCN, SPEN	Thick
Septa	-	Thick
Nodule	-	Presence
Solid mass	-	Presence
Debris	Pseudocyst	-
Pancreatic duct diameter	Dilated > 5 mm: MD-IPMN or mixed IPMN	Dilated > 8-10 mm
Communication with pancreatic duct	IPMN, pseudocyst	-

EUS: Endoscopic ultrasound; MCN: Mucinous cystic neoplasm; SCA: Serous cystadenoma; BD-IPMN: Branch duct intraductal papillary mucinous neoplasm; MD-IPMN: Main duct intraductal papillary mucinous neoplasm; SPEN: Solid pseudopapillary neoplasm; IPMN: Intraductal papillary mucinous neoplasm.

resolution diagnostic evaluation of the pancreatic parenchyma and ductal system. A linear echoendoscope should be used to evaluate pancreatic cystic lesions as FNA may be performed. EUS is particularly valuable in assessing diagnostic features and potential predictors of malignancy, including size, shape (lobular *vs* smooth contour), number of cysts, calcifications, cyst wall structure (thick *vs* thin wall), septa, nodules, solid masses associated with the cyst, pancreatic duct diameter, communication with the pancreatic duct, and lymphadenopathy (Table 2, Figures 2A-G). In a study of 50 patients EUS was found to be comparable to MRI in its sensitivity for identifying septa (77.8%), mural nodules (58.3%), main duct dilation (85.7%) and communication with the pancreatic duct (88.9%)[17].

Nodules are an important predictor of malignancy, but may be difficult to distinguish from mucus. Mucus appears as a hypoechoic lesion relative to adjacent tissue with a smooth, hyperechoic rim (Figure 2H). On the other hand, nodules are iso- or hyperechoic compared to adjacent tissue without a hyperechoic rim or smooth edge (Figure 2I). During EUS, rotating the patient and trying to move the lesion with a FNA needle can also help to differentiate mucus from a

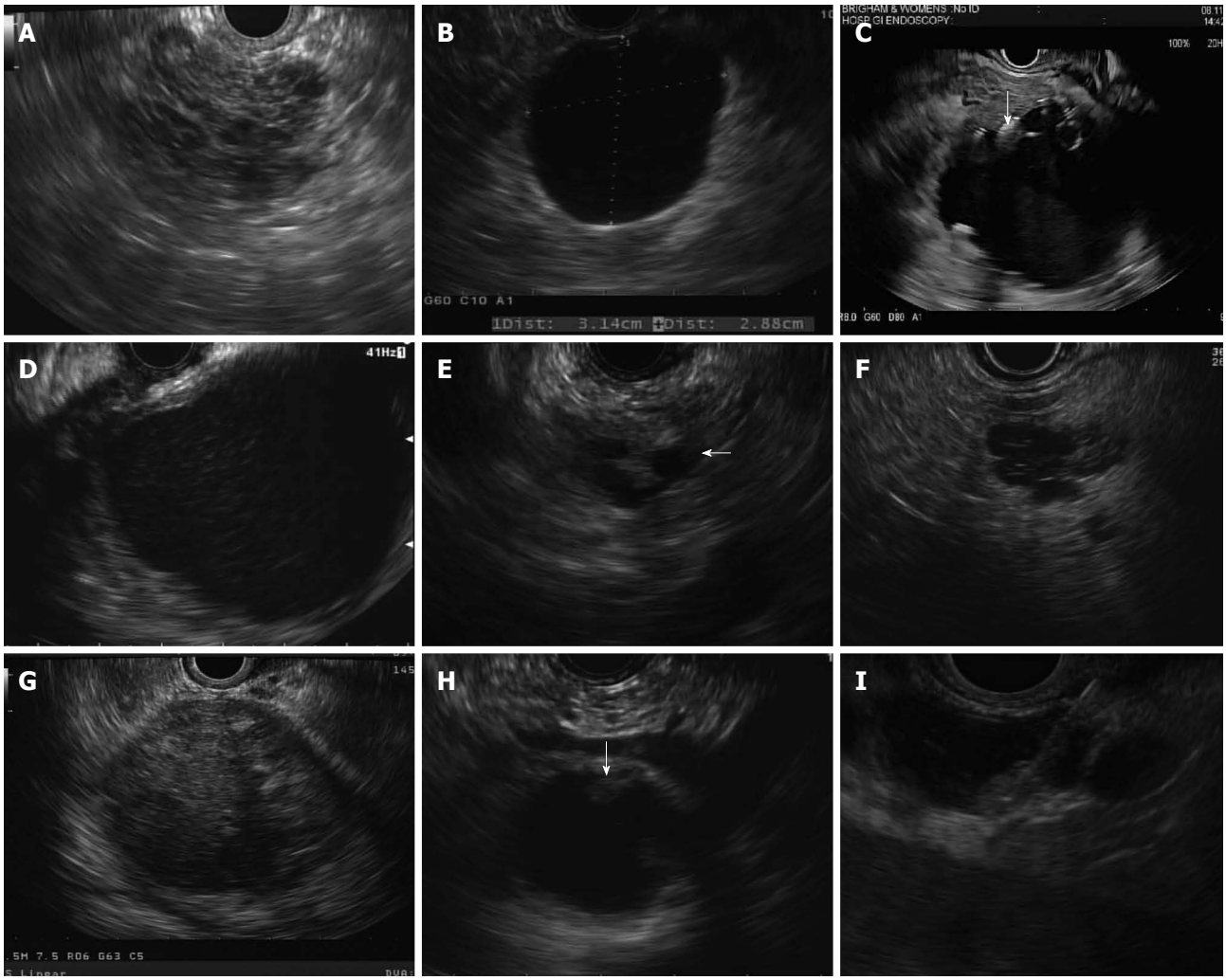

Figure 2 Endoscopic ultrasound imaging. A: A lobular microcystic lesion consistent with serous cystadenoma; B: A smooth, unilocular, thin walled cyst consistent with mucinous cystic neoplasm; C: A cyst with peripheral calcification (arrow) and debris layering at the bottom of the cyst consistent with pseudocyst; D: A thick walled cyst filled with debris representing walled-off pancreatic necrosis; E: A cyst communicating with a nondilated main pancreatic duct (arrow) representing branch duct intraductal papillary mucinous neoplasm; F: A multiseptated lobular cyst appearing like a "cluster of grapes" consistent with branch duct intraductal papillary mucinous neoplasm; G: A well-defined heterogeneous mass-like lesion with hyperechoic foci and small anechoic focus diagnosed as solid pseudopapillary neoplasm on cytology; H: A unilocular cyst with mucus (arrow) appearing hypoechoic relative to the adjacent pancreatic parenchyma with a smooth hyperechoic rim; I: Endoscopic ultrasound-guided fine needle aspiration of a nodule which appears isoechoic with pancreatic parenchyma without a hyperechoic rim within a dilated main pancreatic duct. Cytology showed adenocarcinoma.

nodule. A pathology-based study of MCN and BD-IPMN confirmed the modest diagnostic accuracy of EUS for a nodule (57%)[25]. However, after training endosonographers in the above EUS criteria for differentiating a nodule from mucus, accuracy improved to 79%. The sensitivity and specificity of EUS (75% and 83%) were superior to CT (24% and 100%) for nodules[25], and likely surpasses diagnostic yield of MRI as well when using these defined criteria. In addition, EUS is superior to CT and potentially MRI for detecting small pancreatic masses[26,27]. EUS demonstrated 98% sensitivity compared with 86% for MDCT for identifying pancreatic masses[26]. Data comparing EUS and MRI is limited with an older study supporting higher sensitivity for EUS. More studies are needed using the newer MRI machines.

A recent multicenter study from Korea examined 84 resected BD-IPMNs in order to evaluate EUS predictors of malignancy in BD-IPMNs[28]. An EUS scoring system (0-10) was developed in which points were assigned based on cyst size, mural nodules, pancreatic duct dilation, thick septa and the characteristic "patulous" papilla[28]. This scoring system was found to have an overall area under the curve of 0.944 with 75% sensitivity and 94% specificity for malignant BD-IPMN using an EUS score cutoff of $\geqslant$ 7. In their data, this EUS score was more specific than the 2012 IAP criteria (16%) and mural nodules alone (46%), but less sensitive (2012 IAP criteria 100% and mural nodules 94%).

Despite the utility of EUS imaging in diagnostic evaluation and estimating malignant potential of pancreatic cysts, EUS alone is not adequate for diagnosis of pancreatic cysts. A multicenter trial

Table 3 Endoscopic ultrasound-fine needle aspiration cyst fluid analysis

Cyst fluid marker	Type of cyst	Sensitivity	Specificity
CEA < 5 ng/mL	SCA, pseudocyst, neuroendocrine tumor	54%	94%
CEA >192 ng/mL	Mucinous cyst (MCN or IPMN)	73%	84%
CEA > 800 ng/mL	Mucinous cyst (MCN or IPMN)	98%	48%
Amylase < 250 U/L	Excludes pseudocyst	44%	98%
KRAS mutation + LOH	Malignant cyst	37%	96%
KRAS mutation	Mucinous cyst (MCN or IPMN)	54%	100%

CEA: Carcinoembryonic antigen; SCA: Serous cystadenoma; MCN: Mucinous cystic neoplasm; IPMN: Intraductal papillary mucinous neoplasm; LOH: Loss of heterozygosity.

of 341 patients found EUS morphology to be only 56% sensitive and 45% specific (51% accurate) in distinguishing mucinous from non-mucinous cysts[29]. Furthermore, EUS performance is highly operator dependent. Agreement among expert endosonographers (performed > 1000 pancreas EUS) was better than semi-experts (performed 50-200 pancreas EUS) in a Dutch study[30]. However, even among expert endosonographers, interobserver agreement was fair to moderate in distinguishing mucinous and non-mucinous cysts [intraclass correlation coefficient (ICC) = 0.43][30,31]. There was good agreement among experts for nodules (ICC 0.65); moderate for solid component (ICC = 0.52) and communication between cyst and main duct (ICC = 0.44); and fair for suspected malignancy (ICC = 0.27)[30]. An earlier study of 31 cases found only fair interobserver agreement (κ = 0.24) among 8 endosonographers at tertiary care referral centers for distinguishing neoplastic from non-neoplastic lesions by EUS, with accuracy ranging from 40%-93%[31].

EUS-FNA

Due to the limitations of imaging alone, diagnosing pancreatic cysts requires a combination of diagnostic imaging and cyst fluid analysis. Under EUS-guidance, FNA can safely obtain cyst fluid for cytologic and molecular analysis[32]. Cysts should be at least 1 cm in size to obtain sufficient fluid for analyses. The general technique of EUS-FNA of pancreatic cysts is similar to FNA of solid lesions with a few differences to minimize complications. Cyst fluid is usually aspirated with a single pass using a 22 or 25-gauge aspiration needle with the goal of completely collapsing the cyst. Occasionally 19-gauge aspiration needles can be advanced into larger cysts with thick fluid although these larger needles are difficult to use in the pancreatic head or uncinate process. A dose of prophylactic intravenous antibiotics (usually fluoroquinolone) is recommended followed by 3 d of oral antibiotic to prevent infection from cyst aspiration[33].

Before sending the cyst fluid for testing, visual inspection of the fluid may offer diagnostic clues. Fluid viscosity may be evaluated by the "string sign": a drop of fluid is placed between the thumb and first finger and slowly pulled apart. If the fluid stretches out at least 3.5 mm, this is consistent with a mucinous cyst[34]. SCAs typically have thin, serosanguinous or frankly bloody fluid while pseudocyst fluid appears cola-colored and fluid from lymphangiomas may look like milk.

Cyst fluid aspirates are often virtually acellular and consequently cytology has generally limited utility (< 50% sensitive) in diagnosing mucinous lesions[29,35,36]. Exceptions include cyst fluid cytology of cystic neuroendocrine tumors, SPENs, and lymphangiomas where diagnostic yield may be higher[37-41]. Specifically targeting the cyst wall during aspiration has been shown to increase the diagnostic yield of cytology for mucinous lesions by 29% compared to fluid cytology[42]. This is a simple technique whereupon after cyst fluid is aspirated and the cyst wall collapsed, the needle is advanced back and forth through the wall several times, and the tissue sent for cytology. A core biopsy needle may increase diagnostic yield from pancreatic cysts without increased complications. A study of 60 cysts biopsied using the 22 gauge Procore Echotip biopsy needle (Cook Medical, Ireland) reported a 65% sample adequacy rate and 100% concordance between biopsy diagnosis and surgical pathology (available in 28% of the patients) with only minor complications in 3.3% of patients[43]. Further studies are needed to compare fine needle biopsy with fine needle aspiration. In order to further improve diagnostic yield and accuracy, FNA should also target mural nodules and/or solid components when present.

Chemical analysis of cyst fluid usually measures carcinoembryonic antigen (CEA) and amylase concentrations (Table 3). Amylase below 250 U/L can rule out a pseudocyst with 98% specificity[44]. Usually, although not always, amylase is lower in SCA. Typically amylase levels are higher in IPMN than MCN although they can be similar as well. CEA is the main biomarker used to determine if a cyst is mucinous. CEA > 192 ng/mL is 73% sensitive, 84% specific, and 79% accurate for mucinous lesions from the classic study by Brugge *et al*[29]. The exact threshold used for diagnosing mucinous cysts remains debated with higher levels yielding greater specificity but lower sensitivity. For example, CEA > 800 ng/mL is 98% specific but only 48% sensitive for mucinous cysts, which means that cysts with elevated CEA are almost always mucinous while many mucinous cysts with CEA < 800 will be missed[44].

Conversely, low CEA < 5 ng/mL is 95% specific for SCA, pseudocyst, or neuroendocrine tumor[44]. Cyst fluid CEA is not predictive of malignancy[45]. It is important to note that currently available assays are validated for measuring serum, but not cyst fluid, CEA concentrations. Consequently, there is as much as 85% variation in mean cyst fluid CEA concentrations among the various assays[46].

Molecular analysis of aspirated cyst fluid for DNA mutations may help to distinguish mucinous from non-mucinous cyts. A study including 142 surgically resected cysts found that KRAS mutation was 54% sensitive and 100% specific for mucinous cysts[47]. Specifically, KRAS mutations were 67% sensitive for IPMNs but only 14% sensitive for MCN. Using a combination of CEA and KRAS improved sensitivity for mucinous lesions to 83% but specificity dropped to 85%[47]. On the other hand, a smaller study of 48 resected cysts reported that combining KRAS, CEA and cytology did not improve accuracy compared to CEA and cytology or KRAS alone[48]. Two or more loss of heterozygosity (LOH) mutations and DNA quantity > 40 ng/μL were each less than 11% sensitive for mucinous cysts. However, the presence of any molecular changes (KRAS, LOH or elevated DNA quantity) was over 90% specific for mucinous cysts. Consequently, the utility of DNA analysis may be limited to patients whose evaluation is indeterminate for a mucinous cyst.

The multicenter pathology-based PANDA study suggested that KRAS followed by LOH mutations could diagnose malignant cysts with 96% specificity and 37% sensitivity[49]. Our group evaluated the diagnostic accuracy for malignant cysts of the 2006 and 2012 IAP guidelines and commercially available DNA analyses (KRAS, LOH mutations, and DNA quantity) in 257 pancreatic cysts[50]. The 2012 guidelines were the most accurate for malignant cysts (90% specificity and 88% sensitivity). The addition of DNA mutation analysis contributed no significant improvement in diagnostic performance. To date, studies of commercial DNA analyses have not been able to clearly define their role in clinical practice[49-53].

Current cyst fluid analyses are unable to consistently differentiate specific cyst types or predict malignant potential[20,54]. Consequently, differentiating benign from pre-malignant cystic lesions remains challenging. Recent studies have found that the preoperative diagnostic accuracy for specific cyst type ranged from 47% to 68% compared to surgical pathology[55,56]; accuracy improved to 73% when cysts were categorized as benign, premalignant and malignant[56]. A retrospective study of 118 patients in a community setting suggested a higher accuracy for EUS (87%) in distinguishing benign, premalignant, and malignant cysts; however, this study is limited because 65% of patients were diagnosed mainly by CT radiologic surveillance with a median follow-up of only 337 d[57].

Therefore, in light of the limitations of current diagnostic tools, novel diagnostic biomarkers have received considerable interest[58]. GNAS mutations have been associated with IPMNs in resected tissue, cyst aspirates and pancreas fluid[59,60]. The combination of GNAS and KRAS mutations in aspirated cyst fluid has been shown to be specific and sensitive for IPMN[61]. Our own study (accepted for publication) on resected cysts found GNAS mutations to be significantly more prevalent in IPMNs (42%) than in SCAs (10%), adenocarcinomas (0%) and MCNs (0%). In addition, double mutations in KRAS and GNAS only occurred in IPMNs (P = 0.006). A recent study of genetic mutations in cyst fluid aspirated by EUS-FNA from 91 cysts found that GNAS mutations occurred in 39% of IPMNs and 22% of IPMNs with adenocarcinoma while KRAS mutations were present in 68% and 78%, respectively[61]. Notably, mutations in either GNAS or KRAS occurred in 83% of IPMNs, 89% of IPMNs with cancer and 6% of MCNs, and no mutations found in PNETs, SCAs and non-neoplastic cysts[61]. The combination of GNAS and KRAS was 98% specific and 84% sensitive for IPMN. Poor sensitivity for MCNs, as in other mutation studies, resulted in only 65% sensitivity for mucinous lesions overall. Neither gene was predictive of malignant potential within mucinous lesions.

MicroRNA (miRNA) are small noncoding RNA which may help diagnose a variety of malignancies and potentially pancreatic cystic lesions as well[62]. We evaluated miRNA in 69 pathology specimens of pancreatic cystic neoplasms, and identified several miRNA panels (4 miRNA in each) that differentiated SCAs from MCNs and IPMNs, and MCNs from BD-IPMNs (sensitivity 85%-100% and specificity 100%)[63]. These promising miRNA panels now need to be validated in EUS-FNA cyst fluid aspirates obtained during diagnostic evaluation. A recent study of the cyst fluid proteome demonstrated that proteomic profiling of mucin in cyst fluid (obtained by EUS-FNA) was 98% accurate for pre-malignant and malignant cysts[64]. A study of select proteins in 22 cyst fluid samples identified a 3 biomarker panel of protein glycoforms that was 91% accurate for mucinous cysts[65]. Metabolomic analysis has demonstrated that metabolites, glucose and kynurenine, were lower in mucinous cysts compared to non-mucinous cysts[66]. These molecular biomarkers may be able to provide improved diagnostic accuracy while requiring only small amounts of fluid, particularly as the number of small cysts identified by imaging continues to increase.

EUS-GUIDED THERAPY

For patients with pancreatic cystic neoplasms that are symptomatic, malignant, or have a high potential for malignant transformation, the current standard of care is surgery. Pancreatic surgical resections are major procedures associated with a high complication

rate (> 40%)[67,68] and long-term morbidity due to loss of pancreatic tissue (*i.e.,* diabetes and exocrine insufficiency). EUS-guided therapies may provide a minimally invasive alternative to surgery in poor or reluctant surgical candidates and a low-risk intervention in cases where conservative management is unsatisfactory because malignant potential is uncertain.

To date ethanol (80%-98%) and paclitaxel have been investigated as ablative agents in pancreatic cysts. Ethanol has effectively destroyed solid and cystic tumors in a number of organs, and elicits better response in pancreatic cysts than saline[69]. Ethanol lavage is believed to induce cell membrane breakdown, rapid protein degradation and vascular blockage[70,71]. Paclitaxel is a commonly used chemotherapeutic agent which stabilizes the microtubule polymer to inhibit its disassembly and consequently induce apoptosis. Its hydrophobic and viscous nature allows it to exert a long-lasting effect on the epithelial lining of the cyst while posing little risk of leakage[72].

Prospective studies evaluating EUS-guided pancreatic cyst ablation have shown cyst resolution (no visible residual cyst on cross-sectional imaging) in 33%-38% of patients using ethanol alone[69,73,74]. Injection of paclitaxel produced improved response with 60%-79% cyst resolution (< 5% of original size on CT follow-up)[75-77]. Long term follow-up of 9 patients who achieved resolution after ethanol lavage found that cyst resolution persisted in all patients over a median 26 mo follow-up (range 13-39 mo)[78]. In 22 patients undergoing EUS-guided ablation with ethanol and paclitaxel, 75% of patients demonstrated at least a 75% reduction in cyst volume (complete cyst resolution in 50% of patients) over a mean 27 mo follow-up (range 17-42 mo), and elimination of pre-operatively detected DNA mutations in LOH and KRAS in 36% of patients[79]. Although this may suggest that ablation leads to DNA changes that decrease risk of malignant progression, this has yet to be proven and new mutations were actually detected in 3 patients.

The technique of EUS-guided pancreatic cyst ablation uses a curvilinear-array echoendoscope. Following cyst puncture with a 22-guage needle, a syringe is used to completely aspirate cyst fluid, similar to when performing standard EUS-FNA of a pancreatic cyst. Complete evacuation of highly viscous fluid may not be possible, and saline injection (0.5-1.0 cc) may help thin the fluid to achieve this[80]. Without removing the needle, the cyst cavity is then injected with ethanol, equal in volume to the aspirated cyst fluid. For 5 min, the cyst cavity is repeatedly evacuated and injected. This involves 3-4 lavages over the 5 min when cyst fluid is thick, or 7-8 lavages if the fluid is thin. The ethanol is then completely removed. If used, paclitaxel is then injected into the cyst but not removed. At no point should the cyst be expanded beyond its original size. Care should be taken to ensure that the needle tip remains within the cyst during the whole procedure to avoid injury to the pancreatic parenchyma and leaks in the cyst wall[80-82].

Ideally, cysts considered amenable to ablation should be benign with no malignant features, 2-4 cm in diameter, uni/oligolocular, and demonstrate no connection with the pancreatic duct. Cysts consistent with MD-IPMN or features suggestive of malignancy should not undergo ablation. Patients with active pancreatitis, ascites, portal hypertension or coagulapathy are also excluded from cyst ablation.

Cyst ablation has been overall well tolerated although complication rates are higher than for EUS-FNA of pancreatic cysts. The most common acute complication is non-specific post-procedure abdominal pain (2%-20%)[69,73-77,79]. Pancreatitis rates range between 2%-10% with no reports of severe pancreatitis, while other less common adverse events include chemical peritonitis with ileus in 3%, gastric wall cyst in 3%, and intracystic bleeding in 2% of cases.

While promising, this procedure is still being studied as concerns about remnant premalignant epithelium, unclear effects on the natural history of cysts, and uncertainty over long term monitoring and outcomes remain[9,78,82].

CONCLUSION

The increasing number of incidentally discovered pancreatic cystic lesions, and their varying potential for malignant transformation, makes accurate diagnosis and choosing appropriate management strategies vitally important. Under current guidelines, EUS and EUS-FNA are critical components in the approach to evaluating and monitoring these lesions. EUS-FNA may provide additional information when the diagnosis is unclear, confirm the presence/absence of features associated with increased risk of malignancy, diagnose malignancy, and monitor for changes in the cysts. Even so, diagnosis remains challenging as current radiologic imaging modalities and EUS-FNA have proven to be limited in diagnostic accuracy. Promising research into new imaging, chemical and molecular biomarkers, as well as EUS-guided therapies may be able to improve diagnosis and management of pancreatic cystic lesions.

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Advanced endoscopic imaging to improve adenoma detection

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Abstract

Advanced endoscopic imaging is revolutionizing our way on how to diagnose and treat colorectal lesions. Within recent years a variety of modern endoscopic imaging techniques was introduced to improve adenoma detection rates. Those include high-definition imaging, dye-less chromoendoscopy techniques and novel, highly flexible endoscopes, some of them equipped with balloons or multiple lenses in order to improve adenoma detection rates. In this review we will focus on the newest developments in the field of colonoscopic imaging to improve adenoma detection rates. Described techniques include high-definition imaging, optical chromoendoscopy techniques, virtual chromoendoscopy techniques, the Third Eye Retroscope and other retroviewing devices, the G-EYE endoscope and the Full Spectrum Endoscopy-system.

Key words: Advanced endoscopic imaging; G-Eye; Full Spectrum Endoscopy-system; Chromoendoscopy; I-scan; Narrow band imaging; Fujinon Intelligent Color Enhancement; 3rd Eye; Polyps; Colorectal cancer

Core tip: Here we focus on the newest developments in the field of colonoscopic imaging to improve adenoma detection rates. Described techniques include high-definition imaging, optical chromoendoscopy techniques, virtual chromoendoscopy techniques, the Third Eye Retroscope and other retroviewing devices, the G-EYE endoscope and the Full Spectrum Endoscopy-system.

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INTRODUCTION

Colorectal cancer is the second most common cause for cancer related death in developed countries. The age-adjusted incidence of colorectal cancer is estimated 61.2 cases and 44.8 cases per 100000

populations among men and women, respectively[1]. Colonoscopy is considered the golden standard for screening of colorectal cancer and its precursor lesions, the colorectal adenomas. The main advantage of colonoscopy in comparison to non-endoscope based screening tests is that it also allows therapy or at least tissue acquisition of colorectal lesions to guide subsequent therapy.

Recently, Nishihara and coworkers examined the association of the use of colonoscopy with colorectal-cancer incidence and colorectal-cancer mortality among participants in the Nurses' Health Study and the Health Professionals Follow-up Study[2]. Overall, more than 88000 participants were followed over a period of 22 years. Within this time, 1815 incident colorectal cancers and 474 deaths from colorectal cancer were documented. Multivariate hazard ratios for colorectal cancer were 0.57 after polypectomy, 0.60 after negative sigmoidoscopy, and 0.44 after negative colonoscopy. In addition, negative colonoscopy was associated with a reduced incidence of proximal colon cancer. Moreover, a reduced mortality from proximal colon cancer was observed after screening colonoscopy but not after sigmoidoscopy. Accordingly, this long-term study confirmed the efficacy of screening colonoscopy to reduce colorectal cancer.

Very recently, Corley and coworkers evaluated the association between the adenoma detection rate and patients' risk of subsequent colorectal cancer (*i.e.,* interval cancer) and death[3]. Over 314000 colonoscopies performed by 136 endoscopists were included. The adenoma detection rates ranged from 7.4% to 52.5%. During the follow-up period, 712 interval cancers were diagnosed. The adenoma detection rate was inversely associated with the risks of interval colorectal cancer, advanced-stage interval cancer, and fatal interval cancer. Importantly, each 1% increase in the adenoma detection rate was associated with a 3% decrease in the risk of colorectal cancer.

Therefore, the above mentioned studies highlighted the importance of a precise colonoscopic examination to reduce colorectal cancer incidence. Within recent years, various new endoscopic imaging techniques have been introduced to assist endoscopists in performing accurate endoscopic examinations. In this review we will focus on the newest developments in the field of colonoscopic imaging including high-definition imaging, optical chromoendoscopy techniques, virtual chromoendoscopy techniques, the Third Eye Retroscope and other retroviewing devices, the G-EYE endoscope and the Full Spectrum Endoscopy (FUSE)-system.

ADVANCED ENDOSCOPIC IMAGING TECHNIQUES

High-definition imaging

Multiple studies have addressed the specific issue whether high-definition white-light imaging is superior to standard white-light endoscopy for diagnosis of colorectal adenomas. Results of those studies are sometimes conflicting. In addition, interpretation is often difficult as new endoscopes are not only equipped with newer chip technology allowing high-definition imaging, but also with wide-field optics and closer focus modes. Therefore, it is not possible to determine which of these individual factors led to altered adenoma detection. One recent meta-analysis compared the diagnostic yield of colonic polyps between high-definition colonoscopy and standard video endoscopy[4]. Five studies involving 4422 patients were included. The incremental yield of high definition colonoscopy for the detection of any polyp was 3.8% with a number needed to treat of 26. For the detection of adenomatous polyps the incremental yield was 3.5% with a number needed to treat of 28. There were no significant differences between high-definition and standard video endoscopy in the detection of high-risk adenomas. Nonetheless, the pooled weighted mean difference in small adenoma detection was significantly higher with high-definition colonoscopy. In a retrospective study including 2430 consecutive patients the adenoma detection rate was significantly higher among patients who underwent high-definition white-light endoscopy compared with standard white-light colonoscopies[5]. These data are in contrast to one recent trial including 426 individuals who underwent high-definition white-light endoscopy and 426 individuals who underwent conventional colonoscopy[6]. In this study, high-definition endoscopy did not increase the detection of individuals with polyps, adenomas, or high-risk adenoma features. High-definition did also not increase the detection of individuals with clinically insignificant colonic lesions.

Importantly, one recent study aimed to investigate whether detection rates of individual endoscopists increase within 1 year before and 1 year after the switch from standard to high-definition endoscopy[7]. In this study, the adenoma detection rates of endoscopists with a low detection rate (< 20%) increased significantly after switch from standard to high-definition endoscopy (P = 0.0076) while this effect was not measurable for high-adenoma detectors ($\geqslant$ 20%).

Optical chromoendoscopy

Optical chromoendoscopy uses optical filters within the light source of the endoscope to narrow the bandwidth of the light. The normal bandwidth consists of a red-green-blue image. The narrow band imaging (NBI; Olympus, Tokyo, Japan) narrows the red light. The resulting green-blue image improves imaging of the mucosal vascular and surface pattern morphology[8].

To date, four meta-analyses evaluated the impact of NBI for colon polyp detection as compared to white-light endoscopy. None of these could find convincing evidence that NBI is significantly better than white-

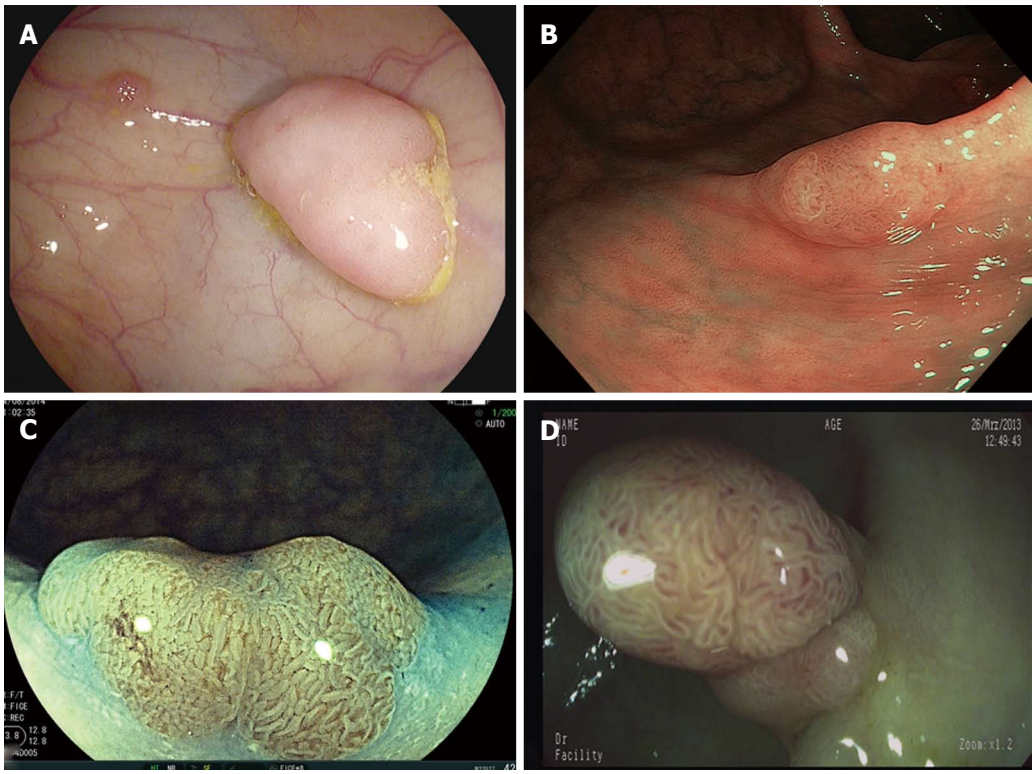

Figure 1 Colonic polyp imaged with high-definition white-light (A), narrow band imaging (B), Fujinon Intelligent Color Enhancement (C) and i-scan (D). Data on detection rates are inconsistent. Nevertheless, dye-less chromoendoscopy techniques allow for a detailed and adequate examination of the mucosal pit pattern and the mucosal vascular pattern morphology to predict polyp histology in real time.

light endoscopy for detection of colorectal polyps[9-12]. The most recent meta-analysis included 7 studies with a total of 2936 patients[12]. No statistically significant difference in the overall polyp or adenoma detection rate with the use of NBI or white-light endoscopy was detected. In addition, when the number of adenomas and polyps per patient was analyzed, no significant difference was found between NBI and white-light endoscopy.

One main disadvantage of the NBI system is the relatively dark image according to its principle of light filtering. While NBI has proven its efficacy for characterization of lesions in multiple studies its value for detection of lesions seems to be limited as the darker NBI image does mostly not allow a detailed view of the colonic structures.

Very recently, a new NBI system was launched (Olympus, Tokyo, Japan), now allowing an up to 4-times brighter image (Figure 1). The new system was already evaluated in a trial by Leung *et al*[13] which included 360 patients. Patients were randomized to undergo either NBI or high-definition white-light endoscopy. In this well designed study, both the adenoma and polyp detection rates were significantly higher in the NBI group as compared with the high-definition white-light group. No significant differences were observed in the adenoma miss rates between the two groups. Therefore, these early results suggest that the new NBI system is superior to conventional white-light endoscopy. The final results of multicenter studies addressing this issue are therefore highly anticipated.

Virtual chromoendoscopy

Virtual chromoendoscopy techniques rely on the principle of digital postprocessing and include Fujinon Intelligent Color Enhancement (FICE, Fujifilm, Tokyo, Japan), i-scan (Pentax, Tokyo, Japan) and the recently introduced SPIES system (Storz, Tuttlingen, Germany) (Figure 2). The technical details of the systems have been reviewed in detail elsewhere[14,15].

Similar to optical chromoendoscopy, results on the efficacy of virtual chromoendoscopy for improved adenoma detection are contrary with studies reporting on improved adenoma detection rates and others not. One early study by Arthur Hoffman included 220 patients which were randomized in a 1:1 ratio to undergo high-definition white-light endoscopy or i-scan[16]. Colonoscopy performed with i-scan detected significantly more patients with colorectal neoplasia (38%) as compared to standard white-light endoscopy (13%). These data were confirmed in a retrospective study by Testoni *et al*[17] reporting significantly more detected lesions with i-scan as compared to standard white-light endoscopy. Contrary, Hong *et al*[18] performed a prospective, randomized trial using a back-to-back colonoscopy design. Overall, 389 patients were randomized. The adenoma detection rates during the first withdrawal of high-definition white-light endoscopy and i-scan and the adenoma miss rates of each group were not statistically different between

Figure 2 RetroView devices allow for a 210 degree bending of the distal tip and are equipped with virtual chromoendoscopy techniques and large working channels to allow adequate characterization of colonic lesions and subsequent endoscopic therapy (Image with kind permission from Fujifilm).

the different groups. Based on the multivariate analysis, the application of i-scan was not associated with an improvement in adenoma detection and the prevention of missed polyps. While there are currently no data on the newly introduced SPIES-system, even the results of studies evaluating the FICE system produced inconsistent data. In this context, one study enrolled 359 patients and randomly assigned those to the white-light group followed by the FICE group and the FICE group followed by the white-light endoscopy group. There was no significant difference between FICE and white-light endoscopy in the adenoma detection rate[19]. Another study examined 135 consecutive patients by total colonoscopy and 128 patients were randomized to compare white-light colonoscopy and FICE[20]. Colonoscopy with FICE identified significantly more patients with small colorectal adenomas than conventional white-light colonoscopy.

Retroscope technology

In 2007, the Third Eye Retroscope (Avantis Medical Systems, Sunnyvale, United Ststes) was introduced[21]. The device consists of a fiber optic which is introduced through the working channel of a standard colonoscope until it extends beyond its other end. Afterwards, the Third Eye Retroscope turns around 180 degrees. The endoscopist has now two images on one monitor. One image is showing the standard colonoscopic view and one image is providing the retrograde view. Main advantage of the system is that it allows to visualize lesions located proximal (*i.e.,* behind) the colonic folds. Various studies have evaluated the Third Eye Retroscope. One multicenter study included eight different centers and a total of 249 patients[22]. 257 polyps were identified with the colonoscope alone while the Third Eye Retroscope detected significantly more additional polyps and adenomas. For lesions 6mm or larger and 10 mm or larger, the additional detection rates with the Third Eye Retroscope for adenomas was 25% and 33%, respectively. Every polyp that was detected with the Third Eye Retroscope was subsequently located with the colonoscope and removed. Another, open-labeled, prospective, multicenter study at nine sites evaluated the impact of the Third Eye Retroscope on adenoma detection rates during colonoscopy[23]. Overall, a 16% increase in the adenoma detection rate by using the Third Eye Retroscope was detected. For lesions 6mm or larger and 10 mm or larger, the overall additional detection rates with the Third Eye Retroscope for all adenomas were 24% and 19%, respectively. Meanwhile, the data have also been confirmed by other investigators demonstrating an improved adenoma detection rate with the Third Eye Retroscope by visualizing areas located proximal (*i.e.,* behind) colonic folds[24,25].

However, despite its efficacy, one potential limitation of the Third Eye Retroscope might be that the working channel is blocked. Accordingly, in order to perform endoscopic therapy of detected lesions, one have to withdraw the device first before advancing additional equipment necessary for polyp removal. In the attempt to offer a hybrid of a therapeutic scope which also allows relatively easy visualization of areas located behind the colonic folds, new "RetroView" devices were recently introduced. These devices (3490TFi, Pentax, Tokyo, Japan and 580RD, Fujifilm, Tokyo, Japan) are slim colonoscopes allowing retroflexion of the distal tip at 210 degrees (Figure 3) In addition, the endoscopes are equipped with latest virtual chromoendoscopy techniques (*i.e.,* i-scan; FICE) and working channels of 3.2mm thereby allowing characterization, demarcation and endoscopic therapy at once. Currently, no scientific evidence regarding the new retroviewing devices is available but multiple groups are already evaluating the potential beneficial effect of the technology.

The FUSE system

FUSE (EndoChoice, GA, United States) was recently introduced as a new platform (Figure 3). The FUSE-colonoscope consists of three imagers integrated into the distal tip of the endoscope and at the lateral sides thereby enabling a 330° angle of view of the colon. Images are displayed on three contiguous monitors. Very recently, Ian Gralnek *et al*[26] presented the results of a large international multicenter study comparing standard forward viewing endoscopy with the FUSE system. Patients underwent same-day, back-to-back tandem colonoscopy with a standard forward-viewing colonoscope and the full-spectrum colonoscope after a 1:1 randomization. Overall, 185 patients were included and randomly assigned to both groups. By per-lesion analysis, the adenoma miss rate was significantly lower in patients receiving FUSE than in those in the standard forward-viewing group (7% *vs* 41%). Therefore, the FUSE platform represents a new and promising technology to improve the efficacy of colorectal cancer screening and surveillance.

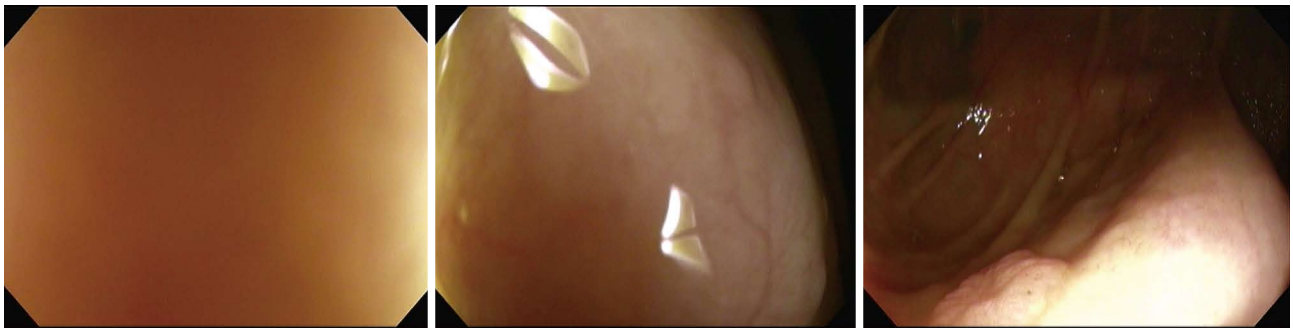

Figure 3 Full Spectrum Endoscopy-System allows 330° imaging on three contiguous monitors. Here, a small non-polypoid lesion located on the proximal part of the ileocecal valve is only visible on the right monitor. Those lesions can easily being missed as they are often located in the realm of the shades.

Figure 4 Newly introduced G-EYE endoscope is equipped with a balloon at the distal bending section of the endoscope. During withdrawal the balloon is inflated thereby stabilizing the endoscope for subsequent therapeutic maneuvers. In addition the balloon yields in a straightening of the colonic folds thereby potentially improving adenoma detection rates (Image with kind permission from Smart Medical).

G-EYE endoscope

Very recently, the G-EYE endoscope (Smart Medical, Ra'anana Israel) was launched. The G-EYE relies on a standard endoscope in which a permanently integrated balloon was incorporated at its distal bending section (Figure 4). The balloon is inflated in the cecum and the endoscope is withdrawn with the balloon inflated until the rectum is reached. The inflated balloon stabilizes the endoscope during the withdrawal phase and interventions and provides additional folds straightening in order to improve adenoma detection rates. Early data provided by Kiesslich and coworkers suggest that the adenoma detection rate with the G-EYE endoscope could be increased by at least 48% (personal communication). Final results of the ongoing multicenter studies are expected by the end of the year.

CONCLUSION

In the attempt to improve adenoma detection rates various advanced endoscopic imaging techniques have been introduced within the past 5 years. Scientific evidence is still missing for some of the new technologies. It is still not fully known whether pure high-definition white-light endoscopy improves adenoma detection rates. Therefore, prospective, randomized, multicenter studies addressing this issue are highly warranted. While there was no beneficial effect of the first NBI system, recent evidence suggests that the new NBI system is superior to conventional white-light endoscopy and could improve adenoma detection rates. Again, results of multicenter studies addressing this issue are highly anticipated. Study results on the potential of virtual chromoendoscopy techniques using digital postprocessing for improved adenoma detection in the colorectum are still inconsistent. Multiple, large and multicenter studies are currently addressing this issue and the results of those studies are anticipated latest within the next two years. New endoscope platforms now allow for a more detailed view of the luminal gastrointestinal tract. Early data demonstrate the impressive potential of those new platforms to improve early diagnosis of colorectal lesions without detriment to procedure time or procedure complications. Therefore, new endoscopic imaging techniques will assist the endoscopists to improve adenoma detection rates for better diagnosis and early therapy of colorectal lesions.

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MINIREVIEWS

New endoscopic imaging techniques in surveillance of inflammatory bowel disease

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Abstract

Endoscopy plays a crucial role in the management of inflammatory bowel disease (IBD). Advances imaging techniques allow visualization of mucosal details, tissue characteristics and cellular alteration. In particular chromoendoscopy, magnification endoscopy, confocal laser endomicroscopy and endocytoscopy seem to have the possibility to radically modify the approach to surveillance and decision making. Dye-based chromoendoscopy (DBC) and magnification chromoendoscopy improve detection of dysplasia, and evaluation of inflammatory activity and extension of ulcerative colitis and are thus considered the standard of care. Dye-less chromoendoscopy could probably replace conventional DBC for surveillance. Narrow band imaging and i-scan have shown to improve activity and extent assessment in comparison to white-light endoscopy. Confocal laser endomicroscopy (CLE) can detect more dysplastic lesions in surveillance colonoscopy and predict neoplastic and inflammatory changes with high accuracy compared to histology. This technology is best used in conjunction with chromoendoscopy, narrow-band imaging, or autofluorescence because of its minute scanning area. This combination is useful for appropriate tissue classification of mucosal lesions already detected by standard or optically enhanced endoscopy. The best combination for IBD surveillance appear to be chromoendoscopy for identification of areas of suspicion, with further examination with CLE to detect intraepithelial neoplasia. However cost, availability, and experience are still an issue.

Key words: Ulcerative colitis; Crohn's disease; Endoscopy; Surveillance; Colorectal cancer

Core tip: Modern endoscopic imaging techniques might change the approach to surveillance of patients with inflammatory bowel disease (IBD). They allow visualization of mucosal details, tissue characteristic and cellular changes. In particular chromoendoscopy,

magnification endoscopy, confocal laser endomicroscopy and endocytoscopy promise to radically modify surveillance and decision making in IBD, however their widespread availability and cost/effectiveness is an issue.

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INTRODUCTION

Endoscopy plays a basic role in the diagnosis, management, prognosis and surveillance of inflammatory bowel diseases (IBD). IBD is a chronic lifelong condition that requires careful medical management and follow-up because it can be associated with significant morbidity, need for hospitalization and surgery. Once IBD is suspected based on clinical signs, symptoms, laboratory markers and/or radiology studies, endoscopy with mucosal biopsies is the gold standard to confirm the diagnosis. After diagnosis, endoscopic examination is important to assess the disease extent and severity, to monitor disease activity, to provide endoscopic treatment and for surveillance of dysplasia and neoplasia[1,2]. Patients with longstanding IBD have an increased risk of colorectal cancer (CRC) compared to the general population and the CRC risk appears to be the same in Crohn's colitis and ulcerative colitis (UC)[3,4]. The exact mechanism behind this increased risk are unknown, although data suggest a profound role of chronic inflammation of the intestinal mucosa[5]. There are several meta-analysis evaluating the incidence of CRC in IBD patients. Eaden *et al*[6] reported an overall prevalence of CRC in UC patients of 3.7%, Ekbom found a standardized incidence ratio (SIR) of 5.7 (95%CI: 4.6-7.0)[7] while Bernstein *et al*[8] reported a SIR of 2.3 (95%CI: 2.0-2.6) in UC patients and 2.6 (95%CI: 1.69-4.12) in CD patients. There are many risks factors implicated in the development of CRC: the duration of the inflammatory disease, the extension of the disease, the degree of inflammation, the coexistence of primary sclerosing cholangitis (PSC), and family history of CRC. The association between duration of the disease and development of CRC is the rationale for endoscopic surveillance, that should begin after 7-8 years of initial symptoms complain. The extent of colitis is another important risk factor of CRC risk[9]. CRC risk is high in patients with extensive colitis, intermediate in left-colitis and low in proctitis. Risk assessment of CRC also critically relies on endoscopic appearance of the severity of disease activity: both endoscopic and histological inflammations were shown to be associated with increased risk. The presence of post-inflammatory polyps probably reflects a previous severe inflammation and is associated with an increased risk of CRC development. On these bases, is clear how surveillance endoscopy permits detection of dysplasia and early detection of CRC, leading to an improvement of prognosis[10]. Surveillance should be performed in everyone with UC or Crohn's colitis, except patients with proctitis or Crohn's colitis affecting only one segment of colon. Regarding optimal surveillance intervals there is not clear evidence yet but individualizing intervals based on risk stratification is basic. Patients with an high risk factors for development of CRC should perform a colonscopy every one year (extensive colitis with severe inflammation, diagnosis of PSC, stricture and dysplasia identified in the last five years, history of CRC in a first-degree relative with less than 50 years). Patients with intermediate risk factors should perform a colonscopy every 2-3 years (extensive colitis with mild or moderate inflammation, presence of post-inflammatory polyps, history of CRC in a first degree relative at 50 years and over). For patients with a low risk of CRC, guidelines advise to perform a colonscopy every 5 years[6,7].

CRC mostly develop in raised protruded lesions but it can also occur in flat lesions or in mucosa with normal feature too. In the recent past, raised neoplastic lesions arising within an area of inflammation have been termed dysplasia-associated lesions/masses (DALMs)[11,12]. These lesions may present low or high dysplasia, *in situ* and invasive cancer. Subsequently the term adenoma-like mass (ALM) has been introduced to describe polyps with dysplasia in an area of colitis, but endoscopically very similar to sporadic adenomas[13]. However, no clear endoscopic, histologic or immunohistochemical difference between DALMs, ALMs and sporadic adenomas has been described, although some endoscopic lesions are more common in UC than non-UC patients. Therefore the terms DALM and ALM are more recently dismissed. Actually, lesion's morphology is best described by the standardized terminology of the Paris classification[14] either in abbreviated (0-Ⅱa) or extensive form (*e.g,* flat, minimally elevated lesion), although some irregular or less defined lesions may not be easily categorized. A detailed endoscopic description of morphology, pit pattern, and grade of background mucosal inflammation is requested. Moreover, current terms to describe low and high-grade dysplasia are also low grade non-invasive neoplasia or high grade non-invasive neoplasia, respectively[15]. Surveillance endoscopy white standard light endoscopy and multiple random biopsies may miss a quantum of lesion. Previous literature data showed that in up to 50% of colitis-associated neoplasms, the lesions were not visible at endoscopy[16]. This problem have suggested to perform an high number of random biopsies, every 10 cm of colon in four quadrants, which is a time consuming and costly approach, either for endoscopists and pathologists[17]. Recently,

new emerging endoscopic imaging techniques have been introduced thus allowing a better visualization of mucosal and submucosal lesions[18]. This review will focus on these endoscopic modalities, highlighting their potential role in the surveillance of IBD.

MAGNIFICATION

Magnification endoscopy is performed by an endoscope with a variable lense, which allows to modify the magnification degree until 150-fold. Thanks to this feature is possible to have a detailed characterization of the mucosal surface and the pit pattern. It has been shown that magnification endoscopy combined with chromoendoscopy has the potential to improve targeting biopsy examination in patients with long-standing colitis and facilitate early detection of intraepithelial neoplasia and colorectal cancer[19].

CHROMOENDOSCOPY

Chromoendoscopy uses different staining techniques and endoscopic/optical or computer-based colour programs to enhance the mucosal detail and submucosal vascular pattern; this procedure improve detection of mucosal lesions and permit a more precise characterization. Currently, chromoendoscopy is distinguished in dye-based (DBC) and dye-less imaging techniques (DLC).

Dye agents uses in DBC can be grouped in three types: Contrast agents (Indigo carmine and Acetic acid), Absorptive agents (Toluidine blue, Lugol, Cresyl violet and Methylene blue) and Reactive staining agents (Congo red and Phenol red). These agents are frequently used through spraying or catheters. Chromoendoscopy in combination with high magnification, allows a better definition of spreading and degree of inflammation, if compared with standard white light colonoscopy, in particular in patient with IBD. In addition, these techniques highly improve early detection of intraepithelial CRC[20].

A randomized controlled trial has evaluated the chromoendoscopy for early detection of intraepithelial neoplasia and CRC in UC. A total of 165 patients with long-standing UC were randomized at a 1:1 ratio to undergo conventional colonoscopy or colonoscopy with chromoendoscopy using 0.1% of methylene blue. In the chromoendoscopy group, there was a significantly better correlation between the endoscopic assessment of degree (P = 0.0002) and extent (89% *vs* 52%; P < 0.0001) of colonic inflammation and the histopathologic findings compared, with the conventional colonoscopy group. In addition, significantly more intraepithelial neoplasia were detected in the chromoendoscopy group (32 *vs* 10; P = 0.003). Therefore DBC showed a more accurate diagnosis of extent and grade of inflammatory in UC compared with standard white-light endoscopy and, more importantly, improved early identification of intraepithelial dysplasia and CRC in patients with UC[21]. Some other trials and a meta-analysis evaluated pancolonic chromoendoscopy for detection of dysplasia in UC. Two of these have demonstrated that biopsies guided by dye spray revealed more dysplasia than random biopsies (P = 0.02 and P = 0.001, respectively)[22,23]. A meta-analysis showed a diagnostic odds ratio of 17.5 with a pooled sensitivity of 83.3% and a specificity of 91.3%. Therefore, chromoendoscopy appear to have an high sensitivity with an high diagnostic accuracy for detection of dysplasia[24]. High-magnification chromo-colonoscopy is also a tool for reliable assessment of disease extent in compared to conventional colonoscopy[25]. However, dye-based chromoendoscopy has some potential limitations, mainly its availability but especially the length of procedure. Moreover, dyes do not always coat all surface required and this procedure does not allow a detailed analysis of sub-epithelial capillary network, which is another important feature in the diagnosis of CRC.

DLC is grouped in optical chromoendoscopy and virtual chromoendoscopy. Optical chromoendoscopy include narrow band imaging (NBI; Olympus®). Virtual chromoendoscopy include I-scan (Pentax®) and Fujinon intelligent colour enhancement (FICE; Fujinon®). NBI uses an optical filters, applied on the light source of endoscope, which narrow the bandwidth of spectral transmittance. This methodology highly enhance the visualization of blood vessels pattern. I-scan and FICE, instead, use digital post-processing with computed spectral estimation to achieve a better tissue contrast[26]. The latter are not dependent on the presence of optical filters inside of the video endoscope. FICE and i-scan use endoscopic images and reconstruct virtual images in realtime by increasing the intensity of blue light to a maximum and by decreasing red light and green light to a minimum resulting in an improved contrast of the capillary patterns and enhancement of the mucosal surface. A nice study of Matsumoto *et al*[27] evaluated magnifying colonoscopy with NBI for the diagnosis of intraepithelial neoplasia in ulcerative colitis. In this trial it was showed that the tortuous pattern determined by NBI colonoscopy could be a clue for the diagnosis of dysplasia during surveillance for UC. Van den Broek *et al*[28] undertaken a randomized trial to compare NBI and high definition white-light colonoscopy (HDE). Twenty-five patients with UC underwent NBI or HDE in a random order with at least 3 wk of interval between the two endoscopies. The study showed that NBI does not improve the detection of neoplasia in patients with UC compared to HDE endoscopy. In addition, NBI was insufficient in differentiating neoplastic from non-neoplastic mucosa[28]. Subsequently, Van den Broek *et al*[29], have tested the efficacy of trimodal imaging for the surveillance of

neoplasia in fifty patients with longstanding UC. In the trial, each segment of colon was inspected twice, once with autofluorescence imaging (AFI) and once with standard white light endoscopy, in a randomized order. This study showed that AFI decreased the necessity of random biopsies improving the detection of neoplasia. In addition, NBI pit pattern analysis predicted the histologic findings with a moderate accuracy while AFI colour appeared useful in excluding the presence of neoplasia[29]. In another prospective, randomized study, NBI was compared with CE for the detection of intraepithelial lesions. NBI was less time consuming and equally effective compared to chromoendoscopy for identification of intraepithelial neoplasia (26.9 ± 9.9 min *vs* 15.7 ± 5.6 min, $P < 0.01$). NBI resulted in a significantly lower false-positive biopsy rate and a similar true-positive rate ($P = 0.001$). The percentage of missed intraepithelial neoplasia lesions was superior with NBI, although not reaching statistical significance. However, given the intraepithelial neoplasia miss rate, NBI should not be recommended as the gold standard endoscopic technique for surveillance in IBD[30]. Only one trial tested FICE in a IBD setting, the latter showed that FICE does not improve detection of ulcers and erosions due to Crohn's disease, but this data should be evaluated in larger prospective trials[31]. Finally a study tested the efficacy of high definition (HD) endoscopy compared to i-scan or chromoendoscopy with methylene blue (0.1%) in screening for colorectal cancer and it was found that both i-scan and chromoendoscopy identified more lesions compared to high definition endoscopy alone[12,32].

Given these evidences, ECCO consensus guidelines on endoscopy in IBD recommend pan-colonic methylene blue or indigo carmine chromoendoscopy during surveillance colonoscopy, with targeted biopsies of any visible lesion. When chromoendoscopy is not available multiple random biopsies should be performed.

CONFOCAL LASER ENDOMICROSCOPY

Confocal laser endomicroscopy (CLE) has been first introduced in 2004. It can be performed with two devices: one integrated into endoscope (e-CLE; Pentax®, Tokio, Japan), and one using a mini-probe through the scope (p-CLE; Cellvizio, Mauna Kea Technologies, Paris, France). Confocal laser microscopy consists of focusing a laser ray onto the mucosal surface and filtering the returned light by means of a small pinhole which rejects out of focus light. The illumination and detection systems are in the same focal plane and are termed confocal. After passing the pinhole, the fluorescent light is detected by a photo-detection, transforming the light signal into an electrical one, that is recorded by a computer. All detected signals from the illuminated spot are captured and measured. As the laser scans over the plane of interest, a whole image is obtained pixel-by-pixel and line-by-line, whereas the brightness of a resulting image pixel corresponds to the relative intensity of detected fluorescent light. The gray-scale image created is an optical section representing one focal plane within the examined specimen. Real-time confocal laser scanning microscopy-sequences (1 min-duration) are recorded and stored digitally for later evaluation. CLE evaluation and its high-quality images have shown high agreement with the histology[33-35]. A number of studies have investigated the usefulness of CLE in the diagnostic work-up of IBD, especially in ulcerative colitis. CLE has shown that could have a role in assessing the extension and the activity of disease. Moreover it could be useful in targeting biopsies and to improve the early detection of dysplasia. The most recurrent histologic modification in crypt architecture of UC are the crypt dilation, disorganized arrangement of crypts, dilatated spaces between crypts, destruction or fusion of crypts and crypt abscess. The microvascular modifications often consist of dilatation and swelling of branching vessels. Dysplasia is identified by darks cells with depletion of mucin and density reduction of goblet cell. The architectural pattern is often disorganized, epithelial thickness is variable with dark epithelial border and villiform structures. The blood vessels are enlarged with anomalous branching and weak orientation to basement membrane. The Miami classification system has been designed, with a worldwide consensus, for p-CLE images[36]. Due to the technical differences, p-CLE images are not comparable to e-CLE images and there is not a worldwide accepted classification f CLE images in UC, so this is a limitation of this technique[37]. Watanabe *et al*[38] and Li *et al*[39] reported on inflammation activity assessment by CLE. The inflammation activity assessment includes crypt architecture, cellular infiltration, and vessel architecture. These studies showed that images obtained with CLE techniques provided information that are similar to conventional histology, with a good differentiation between active and non-active UC during endoscopy examination. In a double-blind trial, CLE was shown to be superior to NBI[40]. In another study evaluating more than one hundred polyps, probe-based CLE showed a trend of higher sensitivity compared to NBI (86% *vs* 64%, $P = 0.08$), with similar accuracy (82% *vs* 79%, $P = 0.59$). The overall accuracy of using probe-based CLE together with NBI to predict polyp histology was greater than 94%[41]. In the management of patients with UC, an important diagnostic goal, is the detection of dysplasia/neoplasia, with a small number of biopsies, thus minimizing time and cost. In this contest Kiesslich *et al*[42] have shown that identification and diagnosis of dysplasia in UC could be maximized by using together pan-chromoendoscopy and targeted CLE, achieving high value of diagnostic accuracy (sensitivity 94%, specificity 98%). Subsequently this result has been confirmed also by Van den Broek *et al*[43]. A trial of longstanding ulcerative colitis, exploring

the efficacy of the combined application of CE and targeted p-CLE in diagnosing dysplasia, has underlined the high diagnostic accuracy of such procedures compared to standard histology (sensitivity 100%, specificity 90%, positive predictive value 83%, and negative predictive value 100%)[44]. Another recent study prospectively evaluated the clinical applicability and predictive power of endomicroscopy for the *in vivo* differentiation of dysplasia-associated lesional mass (DALM) or adenoma-like mass (ALM). This trial showed that the accuracy of endomicroscopy was 97% with an excellent agreement between endomicroscopy and histopathological diagnosis[45]. Neumann *et al*[46] have explored the clinical utility of CLE also in patients affected by Crohn's disease (CD), determining whether the disease activity can be graded by using CLE. The authors proposed a CLE score for assessing CD activity *in vivo*, with a potential utility of predicting the CD course and response to medical therapy. CLE application in IBD has been evaluated also under a prognostic view. A trial has shown that cell shedding and barrier loss detected by CLE are able to predict relapse of IBD and therefore has a potential role as diagnostic tool for the management. The sensitivity, specificity and accuracy for the CLE grading system to predict a flare were 62.5%, 91.2% and 79%, respectively[47]. A second paper confirmed the prognostic power of CLE in predicting the course for other relevant clinical end-points for patients affected by IBD, such as future hospitalization or surgery[48]. No data are available to compare p-CLE with e-CLE. pCLE has some advantages and disadvantages compared with eCLE. Advantages include the greater versatility of pCLE probes, which can be used in conjunction with virtually any endoscope (high-resolution endoscopes, NBI, cholangioscope, *etc.*), and acquisition at video frame rate of 12 frames/s, allowing *in vivo* imaging of capillary flow. Disadvantages include a slightly lower resolution (approximately1 μm compared with 0.7 μm for eCLE) and smaller field of view (240 μm *vs* 600 μm).This technology is best used in conjunction with chromoendoscopy, narrow-band imaging, or autofluorescence because of its minute scanning area. So it is useful only for appropriate classification of tissue at a mucosal site already detected by standard or optically enhanced endoscopy. The best combination in IBD surveillance appears to be chromoendoscopy for identification of areas of suspicion, and that examination with CLE to confirm intraepithelial neoplasia. However, confocal techniques are limited by high costs and need of contras media, such as intravenous Fluorescein. In addition, more prolonged time for the procedure is inevitable and the operator's expertise and learning curve is an issue. Larger studies on the combined use of such modalities are required to assess cost/effectiveness.

ENDOCYTOSCOPY

Endocytoscopy (EC; Olympus®) is a new imaging technique, enabling microscopic imaging of the mucosal layer of the gut at a magnification up to 1400-fold. Endocytoscopy is based on a contact light microscope which enables real-time visualization of cellular structures of the superficial epithelial layer in a plane parallel to the mucosal surface. Systems integrated into the distal tip of an endoscope (iEC) and probe-based (pEC) are available. Probe-based systems consist of handheld miniprobes, inserted through the accessory channel of a standard endoscope. The device provides ultra-high magnification imaging from an optical sampling site of about 0.5 mm in diameter. Endocytoscopy requires preparation of the mucosal layer with absorptive contrast agents like methylene blue or toluidine blue[13]. The technique seems to be useful and safe for the examination of gastrointestinal mucosal surfaces[49], and could recognize neoplasia in aberrant crypt foci and distinguish cancerous lesions from non-cancerous ones[50]. A trial has recently showed the value of EC for assessment of inflammatory disease activity and differentiation of single inflammatory cells in patients with IBD. In that study concordance between EC and histopathology for grading intestinal disease activity in CD was 100%[51].

CONCLUSION

The endoscopy is crucial for diagnosis, prognosis, and management of IBD. In addition, a critical role is that of surveillance of colorectal cancer and detection of dysplasia. In this context the colonoscopy is traditionally coupled with histology, with the need of multiple biopsies. This is suboptimal for dysplasia detection and time consuming for either endoscopists and pathologists. The utilization of chromoendoscopy, possibly combined with magnification, is actually considered the "gold standard", given the adequate diffusion of the methodology and the opportunity to perform targeted rather than random biopsies. In contrast, so far, the techniques of so called virtual or optical chromoendoscopy, although more operator friendly, have not proven to be comparable to chromoendoscopy with vital colorants. However, technology is on progress and several comparative trials underway. Finally, future development and diffusion of confocal endomicroscopy or endocytoscopy could prove further advantage including the need of less biopsies or avoid histology. However, possible medico-legal consequences should be taken into account, and cost/effectiveness, learning curve and length of procedure should be taken into account.

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Peroral endoscopic myotomy: Time to change our opinion regarding the treatment of achalasia?

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Abstract

Peroral endoscopic myotomy (POEM) is a new endoscopic treatment for achalasia. Compared to the classical surgical myotomy, POEM brings at least the advantage of minimal invasiveness. The data provided until now suggest that POEM offers excellent short-term symptom resolution, with improvement of dysphagia in more than 90% of treated patients, with encouraging manometric outcomes and low incidence of postprocedural gastro-esophageal reflux. The effectiveness of this novel therapy requires long-term follow-up and comparative studies with other treatment modalities for achalasia. This technique requires experts in interventional endoscopy, with a learning curve requiring more than 20 cases, including training on animal and cadaver models, and with a need for structured proctoring during the first cases. This review aims to summarize the data on the technique, outcomes, safety and learning curve of this new endoscopic treatment of achalasia.

Key words: Peroral endoscopic myotomy; Achalasia; Myotomy; Endoscopic treatment

Core tip: This review aims to highlight the importance of a new minimally invasive technique for the treatment of achalasia, compared to classical surgical treatment. Although discovered recently, this method has already imposed itself as a safe and very efficient therapy. The difficult issue in this topic is related to the specialist who performs it and the learning curve in such a rare pathology. The gastroenterologist has to be expert in interventional endoscopy and have special skills in surgery, an excellent knowledge in anatomy and the strength to manage the complications. Considering the low rate of adverse events and the efficacy, as a team already performing POEM, we believe that this is the therapy of the future for achalasia.

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INTRODUCTION

The loss of inhibitory innervation of the lower esophageal sphincter (LES) resulting in inadequate relaxation and higher baseline pressures of the LES defines achalasia. Another feature of achalasia is the absence of esophageal peristalsis, these pathogenic modifications explaining the clinical complaints such as regurgitation, dysphagia, retrosternal pain and weight loss. Achalasia has an incidence of 1/100000 per year, which places this disease in the area of rare pathologies. Otherwise, achalasia is the most frequent primary non malignant disease of the esophagus[1].

Although no treatment with curative intention has been identified, some palliative methods comprising medical, endoscopic and surgical methods have been proposed, all aiming to lower LES pressure. Medical treatment with nitrate and calcium antagonists has proved to have poor efficacy and significant side effects[2-4]. However, some of the medical methods such as smooth muscle relaxants are still used for chest pain relief in patients with vigorous achalasia. Of the endoscopic treatments, Botox injections and pneumatic dilatation (PD) have been traditionally used. Botox injections at the gastroesophageal junction (GEJ) are initially successful in over 90% of patients, but the effects only last for 6-9 mo. Botox injections are therefore generally reserved for elderly patients or poor surgical candidates[5]. Pneumatic dilatation is the nonsurgical technique with the highest success rate[6].

Surgical myotomy was originally reported by Heller in 1913 and consisted of 2 longitudinal incisions of approximately 8 cm on the anterior and posterior esophageal wall, the complete release of the LES being mandatory to achieve complete relief from achalasia symptoms. Later, bilateral myotomy was modified to a single myotomy. One of the limitations and failures of surgical myotomy is gastroesophageal reflux disease (GERD), which was reported in up to 30% of cases, resulting in an additional antireflux procedure, such as fundoplication.

A multicenter study recently published demonstrated no significant differences in clinical success between PD and laparoscopic Heller myotomy (LHM) with fundoplication at a 2 year follow-up[7]. Although these results are no longer available when it comes to a longer follow-up, the failure rate of PD remaining at 50%-60% promotes LHM as the treatment of choice in young patients and in those without special contraindications for surgery[6].

Considering these facts, a new endoscopic technique, the peroral endoscopic myotomy (POEM) that combines the surgical element of a controlled myotomy with the minimal invasiveness of endoscopic approach, imposes itself as a real alternative in the treatment of achalasia[8].

ENDOSCOPIC MYOTOMY

The endoscopy myotomy as a treatment option in achalasia was first described in 1980[9]. A limit of this first report was the use of direct incision of the mucosa, which was considered unsafe and unreliable, so it was abandoned. Later, the technique of endoscopic myotomy through a submucosal channel was described in an animal model[10,11]. Pauli was the first who described the crossing of gastroesophageal junction and esophageal cardiomyotomy[12]. Based on this experimental background, Inoue refined the technique for clinical application in humans, namely POEM[13,14].

During POEM, the muscle layer is intentionally dissected and divided through a submucosal tunnel. Mucosa works as a strong barrier to isolate gastrointestinal lumen from the mediastinum or peritoneum. If the mucosa is kept intact, neither peritonitis nor mediastinitis can occur. Complete endoscopic myotomy was first used in a clinical experience together with the development of the POEM.

POEM PROCEDURE

Indications, contraindications

It is generally recommended that teams beginning a POEM program should do it with approval from an institutional review board and after a learning curve completion. Age under 18, previous esophageal or mediastinal surgery and morbid obesity were previously considered exclusion criteria but are no longer valid today. Fungal infection or heavy esophageal loading with food are also considered contraindications but they can be eventually overcome. A real contraindication for POEM remains the inability to undergo general anesthesia[15] but there are some cases in which POEM has been performed without general anesthesia. POEM is considered to be a safe and effective alternative to the surgical approach in achalasia. The role of POEM in the treatment of other esophageal motor disorders such as diffuse esophageal spasm (DES), non-relaxing hypertensive LES and nutcracker esophagus is still under debate. Also, its role in treating patients with prior conventional therapies for achalasia, in the final stages of achalasia, in children, the elderly and in patients with significant comorbid diseases is still not clear. However, the first reports on this topic are optimistic regarding the benefit of POEM in these pathologies[8,16].

PREOPERATIVE INVESTIGATIONS

On admission to hospital, all patients diagnosed with achalasia complete a standardized validated symptom assessment form, according to the Eckardt classification. Based on the calculated score, the patients are included in different classes of severity. All patients undergo extensive preoperative investigations such as an esophagogastroscopy, barium swallow study and a pH study useful for the diagnosis of an asymptomatic reflux. In the diagnosis and classification

of achalasia, an essential tool is high resolution manometry.

According to the manometric measurements, achalasia is classified into 3 subtypes (Chicago classification)[17]: (1) type Ⅰ (classic achalasia) defined as mean integrated relaxation pressure (IRP) > 15 mmHg and when peristalsis has 100% failed; (2) type Ⅱ (achalasia with compression) as mean IRP > 15 mmHg, abnormal peristalsis, panesophageal pressurization with ≥ 20% of swallows; and (3) type Ⅲ as mean IRP > 15 mmHg, abnormal peristalsis, fragments of distal peristalsis or premature (spastic) contractions with ≥ 20% of swallows preserved.

A group of researchers[18] have elaborated a new endoscopic classification of achalasia based on three structures: multi-ring, crescent-like and diverticulum structure, named Ling classification. They divided achalasia into three types: type Ⅰ, smooth without multi-ring, crescent-like structure or diverticulum structure; type Ⅱ, with multi-ring or crescent-like structure, no diverticulum structure; and type Ⅲ, with diverticulum structure. Type Ⅱ and Ⅲ were also classified into three subtypes (Ⅱa, Ⅱb, Ⅱc; Ⅲ1, Ⅲr and Ⅲ1r). The authors concluded that patients classified as type Ⅰ and Ⅱa patients can be recommended for POEM. Patients included in class Ⅱb are at risk of mucosal damage so they might be considered for POEM, but cautiously. This classification needs further confirmation.

Preoperatively, all patients are recommended to have a liquid diet for at least one day before the procedure and some endoscopists perform an upper endoscopy the day before POEM to wash out the esophagus prior to the intervention. Patients may receive oral antimycotics preoperatively to treat any potential esophageal Candida overgrowth. A prophylactic dose of antibiotics was reported to be given before the procedure. Some authors reported the administration of dexamethasone at the start of the procedure to minimize mucosal edema, which will eventually make the closure of the mucosa more difficult, but this is not clearly stated[19].

TECHNICAL ASPECTS OF POEM

Set up and positioning

The procedure is usually done in the operating room under general anesthesia with endotracheal intubation. The gastroscope used for POEM is a standard one. Some authors use a large working channel endoscope with water jet function, but a slim diagnostic scope can be more suitable sometimes for crossing an extremely narrow GEJ. A transparent distal dissecting small cap or an oblique cap can be used at the tip of the endoscope. In order to avoid mucosal laceration at the mucosal incision site during POEM, an overtube might be placed for stabilization of the scope. Another important device to use during this procedure is the carbon dioxide (CO_2) insufflator, which helps to reduce the risk of complications related to air insufflation (pneumothorax, pneumoperitoneum, embolism and subcutaneous emphysema). The air supply button should expressly be closed during the procedure, even when the CO_2 insufflator is on. A thorough cleaning of the esophageal lumen is done before the beginning of the intervention. Sterile saline should be used during the creation of the submucosal channel given the potential mediastinal or peritoneal entry. Communication with the anesthesia team is essential as the patient may develop tension pneumoperitoneum and may require a decompression of the pneumoperitoneum with a Veress needle[19].

EQUIPMENT REQUIRED FOR POEM

Submucosal tunneling and myotomy are performed commonly using a triangle tip knife (TT knife) with three angulations which spreads the energy towards a wide circumferential range[19]. A high frequency electrosurgical energy generator is required that determines a spray coagulation during tissue dissection in a noncontact manner. It can be effectively used in combination with a special knife, *e.g.,* a TT knife, a hook knife, a water jet or hybrid knife for both submucosal dissection and myotomy[20]. Additionally, for the hemostasis of large bleeding vessels, a monopolar coagulating forceps might be useful during dissection[20].

POEM PROCEDURE

The following technical details of POEM are consistent with those from original reports[2,13,14,19].

General anesthesia

Most frequently, POEM is performed with the patient in a supine position, intubated, under general anesthesia. CO_2 insufflation avoids the risk of air-related complications. CO_2 insufflation does not eliminate the risk of gas entry in the mediastinum or abdomen. It does, however, greatly reduce it because CO_2 is rapidly reabsorbed. The air feeding button will remain closed during POEM. The upper abdomen will be checked from time to time during the whole procedure and if the abdomen is excessively distended, an abdominal wall puncture will be performed in order to prevent abdominal compartment syndrome.

Submucosal tunneling

Mucosal entry: Initially, the distal end of the dissection is marked with methylene blue when performing retroflexion in the stomach. Then, an esophageal mucosal lift is performed with a saline injection containing a small amount of methylene blue or indigo carmine on the right anterior side of the esophageal wall. This is followed by a longitudinal mucosectomy of 1-2 cm. It has to have a longitudinal orientation as transverse incisions are nearly impossible to close. Once the submucosal space is entered, the introduction

of the scope in the submucosa is facilitated by the use of a biliary stone extraction balloon. Then, a dissection fenestrated cap is placed on the tip of the scope for the progression in the submucosal space. A tunnel in the submucosa is created using a combination of spray coagulation, CO_2 insufflation and blunt dissection. The separation of the mucosa from the muscle layer is facilitated by repeated injections of the lifting solution. Researchers have tried to improve the technique of submucosal dissection by using a gel that has the capacity of auto-tunneling[20]. Further studies are needed to confirm the efficacy of this method. The submucosal tunnel should be extended beyond the GEJ for about 2 cm into the proximal stomach.

Identification of GEJ

It is important to correctly identify the GEJ for an adequate myotomy on the gastric side. There are some signs that can be helpful for finding the GEJ: length of insertion of the endoscope, the presence of palisading mucosal vessels, and the transitory increase and later decrease in the resistance of dissection when passing the LES. The increased thickness of the circular muscle bundles of the LES and the yellowish appearance of the submucosal cardial space are an important mark for GEJ. Finally, the discoloration of the cardial mucosa overlying the submucosal tunnel as seen upon retroflexion of the scope in the lumen of the stomach allows the estimation of the distance from the GEJ[19].

Circular muscle myotomy

The circular muscle bundle usually starts to be dissected two centimeters distal to the mucosal entry point in the submucosal tunnel. The progression of the dissection is important as both the mucosa and the longitudinal muscle layer should be preserved. The specialists observed that the standard length of myotomy should be more than 10 cm (12 cm on the esophageal side and 2 cm below the GEJ), with an average of 16 cm, but Inoue reported a myotomy length of up to 25 cm[19]. Given the high incidence of GER post-POEM, there is a tendency to decrease the length of the myotomy, except in cases of vigorous achalasia where a longer myotomy is needed. This tailored approach is facilitated by a new endoluminal imaging probe that measures the GEJ distensibility before and after the selective myotomy[21].

There are some groups of researchers that have compared the full thickness myotomy with a circular muscle myotomy. They concluded that full thickness myotomy improved the procedure time without a significant increase in the procedure-related adverse events or clinical reflux complications. Still, the dissection of the circular muscle layer is generally recommended[22].

Circular muscle dissection advances from proximal to distal and the plane of dissection should be maintained correctly. The confirmation of complete myotomy is immediately provided by the facile passage of the scope through the EGJ at the end of myotomy. When reaching the LES, the dissection of all muscle bundles responsible for achalasia should performed. No anti-reflux procedure is required after the POEM procedure because the external structures of LES are preserved. After completion of the myotomy, the complete relaxation of LES is endoscopically confirmed by the retroflex view of the cardia.

In cases of previous surgical failure, posterior myotomy is recommended to avoid the access to the scar site from the previous surgery.

Closure of mucosal entry

The stomach should be emptied of fluid and gas before closing the mucosa and an antibiotic (*e.g.,* gentamycin) should be spread into the submucosal tunnel[19]. The mucosal entry site, which is usually up to 3 cm long, is closed with endoscopic clips from the distal to proximal end with a distance of a maximum of 3 mm between clips. A few alternative closure methods have been described such as over-the-scope clips (OTSC)[23] and fibrin sealants in the case of perforation of the gastric cardia[24]. Another option described for mucosotomies that cannot be closed is a covered stent[25]. Lately, an endoscopic suturing device with a two layered closure of esophagotomy (OverStitch) has proved to be a good alternative to clips in difficult situations.

Postoperative care

Patients are kept *nil per os* the day after the procedure and they should receive an intravenous proton-pump inhibitor immediately after the end of procedure. The intravenous therapy can be subsequently changed to oral treatment once a *per os* diet is allowed. A gastrografin esophagram should be performed the next day to rule out a mucosal defect and to ensure adequate opening of the GEJ post myotomy. If there is no evidence of radiological complications, the patient can be discharged after 24 h of hospital stay, with recommendations of a liquid diet for one week. There is no consensus for a "second look" EGD within the next days following POEM as it often does not change the management of these patients[16]. As the experience in POEM grows, there are some authors that have reported the release of the patients from hospital on the same day after a normal postoperative contrast esophagography[26].

A 6 mo follow-up is performed after POEM. Patients should undergo follow-up manometry, pH study and esophagogastroscopy. The long-term follow-up consists of performing an upper endoscopy every 5 years in all achalasia patients, given the slightly increased risk for esophageal carcinoma[27].

RESULTS FROM THE DATA PUBLISHED UNTIL NOW-POEM FOR THE TREATMENT OF ACHALASIA

Effectiveness of POEM

The results obtained after treating achalasia can be assessed using clinical data and technical features. The decrease of Eckardt score under 3, the lowering of LES pressure by more than 50% and the improved aspect of barium esophagogram regarding the time of esophageal emptying can define an efficient therapy[28].

The first clinical study performed on a database of 17 patients was published by Inoue *et al*[13]. Blunt dissection combined with electrocautery were used to achieve the dissection of the circular muscle layer. The site of mucosal dissection was closed with endoclips and the procedure was completed in all patients. Regarding complications, pneumoperitoneum occurred in one patient, successfully treated using a needle to puncture the abdominal wall. No case of emphysema was reported postoperatively and no long-term complications occurred. The dysphagia symptom score was significantly reduced (from 10 to 1.3; $P = 0.0003$) and the resting LES pressure decreased from 52.4 to 19.8 ($P = 0.0001$) after POEM.

Since then, new studies have been conducted on the performance of POEM for achalasia, which have confirmed the high success rate of this technique[13,29-44] (Table 1).

The majority of studies published on this theme reported a successful therapy in more than 80% of patients, with significant reductions in the Eckardt score and LES pressure. There were a few studies assessing the efficacy of POEM only with a barium esophagogram, the majority using the decrease of pressure as an objective assessment of treatment. Still, there are new methods promising a high quality evaluation of POEM efficacy, such as EndoFLIP (Endolumenal Functional Lumen Imaging Probe), which provides a quantitative assessment of luminal patency and sphincter distension. EndoFLIP was tested for POEM procedure and surgical myotomy. A similar improvement in EGJ distensibility was demonstrated for both methods. The intraprocedural use of FLIP can be predictive of postoperative symptomatic outcomes, providing evidence that FLIP can be used as a calibration tool during therapeutic procedures for achalasia[45,46].

POEM compared to LHM

As a surgical approach in achalasia, including the relatively new experience with an endoscopic approach, has been used for a number of years, there are already some studies that have compared the efficacy, time of surgery and complications according to these two types of treatment. Teitelbaum *et al*[46] analyzed a group of 17 LHM *vs* a group of 12 POEM patients using timed barium esophagograms before and after the procedure. Both groups had improved column heights after treatment at 1, 2 and 5 min. There was no difference between the procedures in changes from baseline column height. Both operations resulted in a decreased esophageal width and less angulation between the esophageal body and esophagogastric junction. The authors concluded that POEM and LHM have similar anatomical and functional results in the short term. Ujiki *et al*[47] also compared POEM with LHM in 18 *vs* 21 patients and he observed that operative time, myotomy length and complication rates were equal. After treatment, pain differed significantly (POEM 3.9 ± 0.6 *vs* LHM 5.7 ± 0.4, $P = 0.02$ for the visual analog score) and analgesic use was also lower after endoscopic therapy (POEM 26.0 ± 13.7 mg *vs* LHM 90.0 ± 48.5 mg morphine, $P = 0.02$). Return to activities was significantly faster in the POEM group (2.2 ± 0.6 d *vs* 6.4 ± 1.0 d, $P = 0.03$). Postoperative dysphagia and Eckardt scores were not different in the two groups. Different results were reported regarding the pain and analgesia by Hungness *et al*[34]. They observed that pain scores were similar upon post-anesthesia care unit arrival and on postoperative day 1, but were higher at 2 h for POEM patients (3.5 *vs* 2, $P = 0.03$). The operative times were shorter for POEM (113 *vs* 125 min, $P < 0.05$) and estimated blood loss was less (≤ 10 mL in all cases *vs* 50 mL, $P < 0.001$). In terms of efficacy, POEM and LHM appeared to have similar perioperative outcomes. Two other American and European studies reported no differences between the two methods regarding the efficacy and safety[26,48].

POEM for refractory achalasia in the setting of prior interventions

Sharata *et al*[49] analyzed the outcomes of POEM in 12 patients (9 achalasia) in the setting of prior endoscopic interventions. POEM was successfully completed in all patients. The improvement of symptoms was achieved in all patients, based on the Eckardt score from 5 to 1 after POEM. There were no differences regarding perioperative outcomes when compared to POEM performed in patients without previous endoscopic intervention. A case of intramural bleeding was reported and one of dehiscence at the place of mucosotomy. The authors concluded that previous endoscopic therapies do not change the outcomes and complications with POEM. Another study compared 21 patients with failed pneumatic dilation with 30 patients without prior treatment, both groups treated subsequently with POEM. For patients with a failed pneumatic dilation, a significant improvement in the Eckardt score, LES pressure and barium esophagogram was observed after POEM. Regarding the operation time, the patients in the group of previously failed pneumatic dilations had a significantly longer procedure compared to patients without previous treatment of achalasia. The outcomes in terms of efficacy were similar in both groups[50].

Table 1 Efficacy of peroral endoscopic myotomy-data from literature (adapted after[27])

Ref.	*n*	Eckardt score (before/after)	LES pressure (before/after)	Efficacy	Time of follow-up (mo)	Patients with recurrent dysphagia
Inoue *et al*[13]	17	10/1.3	52.4/19	100%	5	0
von Renteln *et al*[30]	16	7.8/0.7	27.2/11.8	94%	3	1
Costamagna *et al*[31]	11	7.1/1.1	45.1/16.9	100%	3	0
Swanstrom *et al*[32]	18	6/0	45/16.8	94%	6	1
Ren *et al*[33]	119	-/<3	29.4/13.5	91.7%	10.4	-
Hungness *et al*[34]	18	7/1	19/9	89%	6	2
Inoue *et al*[35]	300	6.13/1.33	27.3/13.4	98%	12	5
Chiu *et al*[36]	16	5.5/0	43.6/29.8	100%	3	0
Lee *et al*[37]	13	6.4/0.4	30.3/15.3	100%	6.9	0
Minami *et al*[38]	28	6.7/0.7	71.2/21	100%	16	0
Verlaan *et al*[39]	10	8/1	20.5/6.8	-	16	-
Stavropoulos *et al*[40]	66	7.9/0.2	42.5/15.4	96%	13	2
Zhou *et al*[41]	205	Relief in 199/205	-	97%	8.5	3
Von Renteln *et al*[42]	70	6.9/1	27.6/8.9	82%	12	9
Teitelbaum *et al*[43]	41	7/1	22/9	92%	12	-

LES: Lower esophageal sphincter.

When analyzing the surgical Heller myotomy, the persistence of symptoms or the recurrence of them was reported in approximately 10%-20% of patients after 2 years of follow-up[7]. The team conducted by Zhou *et al*[51] published their experience in performing POEM after 11.9 years from primary HLM. The therapeutic efficacy was proved in 11/12 patients with a decrease of the Eckardt score under 3 and a significant improvement of LES pressure. Non-serious complications were reported: one case of mucosal perforation at GEJ managed endoscopically, one case of pneumoperitoneum that needed decompression with needle, and one patient requiring a chest tube for symptomatic pneumothorax.

Although the optimal therapy for these patients is not standardized yet, the authors suggested that POEM is feasible and has excellent results in terms of symptom relief.

Another report of 10 cases was published regarding the use of POEM after surgical myotomy for recurrence of symptoms. A significant decrease in LES pressure after rescue POEM was reported after a follow-up of three months, without complications. They concluded that short-term results of POEM after surgical myotomy were optimistic but long-term results are to be confirmed[52].

A very recent article studying the results of POEM after endoscopic and surgical treatment for achalasia was published. The authors reported excellent results in forty cases of POEM after prior endoscopic or surgical therapies. No differences were found with respect to the short-term outcomes and complications. The authors concluded that POEM is a reliable alternative to surgical techniques but longer follow-up will reveal the real results[53].

ADVERSE EVENTS IN POEM

The rate of serious adverse events of POEM, obtained from the data available until now, is low. The data we are discussing are based on information from the IPOEMS survey[16]. The most frequent complications reported until now are CO_2 retention, capnoperitoneum and mediastinal exposure[27].

Intraoperative adverse events

The risk of aspiration during intubation can be prevented by standard airway protection with a rapid induction time and frequent aspiration of mouth contents. Aspiration as a complication occurs very rarely (< 0.1%)[16]. As we already mentioned in the technique description, the use of CO_2 as the insufflation gas is extremely important. The occurrence of complications related to air or CO_2 insufflation can be prevented if the insufflations are used sparingly when creating the submucosal channel. In less than 10% of cases, a mucosal perforation or bleeding may occur. Regarding inadvertent perforations, as their occurrence is more frequent in full thickness myotomies during POEM, a more robust closure has to be executed[54]. If a lesion of the mucosa occurs during POEM, a tight closure of the breech should be performed using clips in order to prevent the intraluminal content reaching the mediastinum.

Bleeding can occur especially at the distal part of dissection. It is usually controlled with coagulation using the tip of the knife but it is important to have electrosurgical hemostatic forceps for larger bleeding vessels. Some authors reported the use of the endoscope, removed from the submucosal tunnel and advanced in the lumen for compression at the bleeding site.

Regarding the complications related to CO_2 insufflation, physiological effects were reported in some studies. Subcutaneous emphysema may occur in a significant manner in up to 15% of cases, but this is usually well tolerated. Capnothorax is rare (less than 5% of cases) and it is also well tolerated; however, if there are signs of hemodynamic instability, a needle for thoracostomy should be placed to prevent tension

pneumothorax. Capnoperitoneum occurs in up to 50% of the cases but it is clinically insignificant[28].

Postoperative adverse events

Mediastinitis was the most dangerous complication after POEM, due to an esophageal leak. The incidence of mucosal lesions that leads to leakage has been remarkably low (0.2%) and no severe consequences or deaths have been reported. The few cases reported with leaks were drained surgically, without complications[40,52].

Postoperative bleeding also has a low prevalence. The IPOEMS reported a rate of 1% for bleeding[16], with rates of 0.7%[55], 3%[26] and 7%[44] in three prospective series. The management of the bleeding complications was performed conservatively using transfusions as required and clinical observation, but there were some cases that required endoscopic re-intervention with hemostasis or Blakemore tamponade[33,56].

Cardiopulmonary complications are not frequent, although there was one case reported of aspiration pneumonia that required prolonged postoperative recovery[16].

Late adverse events

Incomplete myotomy and GERD are the main sources of treatment failure. The early studies reported a low prevalence of GERD based on symptoms but later studies indicated a higher prevalence of reflux disease, ranging between 20% and 46% after POEM, revealed by endoscopic findings (erosive esophagitis) or abnormal pH study[12-16,18,20-22,24]. The prevalence of GERD after POEM based on pH studies is similar to that reported in large prospective trials after a Heller myotomy with fundoplication[55,57,58].

POEM IN OTHER MOTOR ESOPHAGEAL DISEASES

There are some short reports in small groups of cases with hypertensive motility disorders of esophagus treated with POEM. The efficacy of POEM in patients with diffuse esophageal spasm[39,59-61], hypertensive LES[16,62], type Ⅲ spastic achalasia[1,13,14,16], nutcracker esophagus[38] and jackhammer esophagus[63] has been studied. It has been suggested that pain responds less well to POEM than dysphagia does[16]. An interesting remark is related to a low POEM efficacy in patients with diffuse esophageal spasm and type Ⅲ achalasia but the results observed in hypertensive LES and nutcracker esophagus were optimistic. Longer esophageal myotomy seems to be indicated in diffuse esophageal spasms that are characterized by long spastic segments in the distal esophagus. In the same respect, POEM may be more useful than LHM in motor esophageal disorders as the endoscopic approach allows the proximal extension in the body of the esophagus.

LEARNING CURVE IN PERFORMING POEM

POEM is a treatment for a rare disease, the low prevalence contributing to the difficulty of teaching. The procedure meets the principles of natural orifice transluminal endoscopic surgery (NOTES) and interventional endoscopy. It is a demanding procedure, implying potentially serious adverse effects that should be performed only in specialized centers by experts in interventional endoscopy or surgeons who are skilled in endoscopy. The procedure requires specific knowledge, judgment, technical skills and training, the ability to recognize anatomy and maintain orientation.

The team performing the procedure must be familiar with esophageal pathology, with peculiarities of EGJ, with the technique of submucosal dissection and with the management of the most frequent complications. A learning curve of approximately 20 cases has been proposed to accomplish the training period in POEM for an experienced endoscopist[61]. It has been proved that the length of the procedure and the incidence of inadvertent mucosotomies becomes constant after 20 cases[61].

Training in the laboratory on animal or cadaver models may facilitate the time for the acquisition of skills necessary to perform a POEM. Proctoring at first cases is also necessary. In a meta-analysis published recently, POEM operators pursued preclinical training before a human POEM in 10 of 16 centers analyzed. Most centers used live animal training with fewer centers using *ex vivo* models or cadavers. The extent of preclinical training varied widely (total hours spent on preclinical training ranged from 12 to 154 h). Proctoring was used in 9 of 16 centers in the first cases of a human POEM. The authors mentioned a number of proctored cases ranging between 1 and 7.

There are some studies published focusing on the learning curve of POEM. Kurian *et al*[61] analyzed the learning curve for their first 40 POEMs. The outcomes were assessed using the time of procedure and incidence of perforations. The learning curve seemed to reach a plateau at around 20 procedures. Another study observing the accidental mucosotomies and the number of clips required as a means for acquiring the ability of performing the POEM well demonstrated a learning curve of 7 procedures. The myotomy time was also acquired during these procedures but the tunneling time was not reached during this short practice[64]. Submucosal tunneling seems to be the most challenging part of POEM, with the longest learning curve, but in this study there were not enough patients to analyze the necessary number of procedures for a submucosal tunneling without adverse events.

POEM IN CHILDREN AND THE ELDERLY

A special concern regarding POEM was related to the feasibility of this procedure in patients with

age extremes. Successful therapy was reported in children aged 3 and also in the elderly, the highest age reported being 97. These results encourage us to believe that POEM is a feasible treatment option in different patients irrespective of age, if the patients are selected properly[41,46,65,66].

POEM IN PATIENTS WITH COMORBIDITIES

The majority of experts consider that POEM is not indicated in patients with a history of cirrhosis with portal hypertension, especially in the presence of varices. Severe coagulopathy could be a contraindication as well as prior interventions resulting in significant submucosal fibrosis, such as esophageal irradiation and ablation therapy. Pulmonary fibrosis with respiratory failure makes POEM difficult to recommend in patients with this type of pathology[16].

CONCLUSION

POEM appears to be a feasible endoscopic therapy for achalasia with excellent short-term clinical results and improvement in manometric outcomes. Compared to the classical gold standard approach (surgical myotomy), it is a minimally invasive procedure with good outcomes and a safe profile. On the other hand, POEM is a sophisticated and technically demanding procedure that should be performed only by experts in interventional endoscopy and developed in equipped technical centers with numerous cases of achalasia. Further prospective randomized trials are required to compare the effectiveness of POEM with other actual therapies and to establish its long-term outcomes for the management of achalasia.

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MINIREVIEWS

Examining the whole bowel, double balloon enteroscopy: Indications, diagnostic yield and complications

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Abstract

Double balloon enteroscopy (DBE) is an advanced type of endoscopic procedure which brings the advantage of reaching the whole small bowel using anterograde or the retrograde route. This procedure is both diagnostic and interventional for a variety of small intestinal diseases, such as vascular lesions, tumors, polyps and involvement of inflammatory bowel diseases. Main indication is the diagnosis and treatment of mid-gastrointestinal bleeding according to the recent published data all over the world. The complication rates seem to be higher than conventional procedures but growing experience is lowering them and improving the procedure to be safe and well tolerated. This review is about the technique, indications, diagnostic importance and complications of DBE according to the literature growing since 2001.

Key words: Endoscopy; Small bowel; Double balloon enteroscopy

Core tip: Double balloon enteroscopy (DBE) is a novel technique of great interest as the clinician gains the opportunity of examining the whole small bowel without any surgical intervention. Diagnostic and therapeutic ability of the procedure influences the importance and common use of DBE for patients with documented or suspected small bowel disease. This review summarizes the indications, diagnostic yield and complications of the procedure according to the worldwide knowledge since 2001.

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INTRODUCTION

Evolving fiber optic technology provided the opportunity of examining inner body compartments that can be reached through either a natural or an artificial orifice. Gastrointestinal (GI) endoscopy is one of the best

modalities to perform further investigations for the patients with digestive complaints. However before 1980s due to lack of technological improvements physicians had chance to examine only a short portion of the GI tract. Luckily only esophagogastroduodenoscopy and colonoscopy had the ability to diagnose and treat most of GI disturbances as we still experience in our daily practice that diseases associated with small bowel are comparably less to ones that involve upper GI and colon. The initial technique for small bowel endoscopy is push enteroscopy which was needed to be improved due to restricted capability of investigation depth. Single and double balloon enteroscopy (DBE) are now better procedures with improved visualization capability that gives physicians to examine the whole small bowel. By combining either upper or lower GI investigations now we have the opportunity to visualize the whole GI tract. These novel types of endoscopic procedures increase the effectiveness of diagnosis and minimally invasive treatments of small bowel and reduce the need for surgical interventions. This review aims to summarize indications, clinical importance and complications of DBE.

Figure 1 Double balloon system, the tip and overtube.

REVIEW

Technical information

DBE system consists of a high-resolution video endoscope, with a working length of 200 cm and a flexible overtube made of polyurethane. Latex balloons are attached at the tip of the endoscope and also on the overtube, and can be filled with air or emptied using a pressure controlled pump. The principle of the DBE technique is based on alternating pushing and pulling maneuvers, in order to place the small bowel segments onto the overtube step by step[1]. DBE can be performed *via* oral or anal route according to the clinical decision. Twelve hours of food and approximately 4 h of clear liquid fasting will be enough for the patient preparation of oral DBE. However standard colonoscopy preparation with restricted diet and laxatives will be needed for retrograde examination[2]. Peroperative sedation is necessary as the procedure duration is long and lower patient tolerance is expected to disturb the success of the procedure. Many options can be used for sedation but conventional conscious sedation with propofol is mainly used. Deep monitored sedation (with propofol, midazolam and/or fentanyl) can be preferred for oral examination with prolonged duration of the procedure[3]. Radiologic fluoroscopic assistance can be used according to the endoscopist's preference. The goal of the procedure is to examine the whole small bowel from duodenum to caecum or vice versa. However total enteroscopy can be performed in approximately 20% to 70% of the patients. Using both routes (oral and anal) complementary to each other by signing the furthest depth by tattooing or clip application, increases total enteroscopy rates. 230 cm beyond Treitz and 135 cm proximal to ileocecal valve can be considered as the average insertion depths for oral and anal route according to many different case series in the literature (Figure 1).

Indications of DBE

The indications of DBE mainly consist of similar pathologies of upper and lower GI system that are localized or suspected to be in the small intestine. As the procedure takes long time and is an advanced and hard intervention, it is mostly indicated after some initial investigations. The indications and some interventions due to diagnosis are summarized on Table 1.

Mid-GI bleeding

The most common indication (up to half of the procedures) for DBE is suspected or known mid-GI bleeding which refers to the blood loss from the distance between papilla Vateri and ileocecal valve. This can be either occult or obscure which may suggest an idea to choose the beginning route for the procedure, where melena encourages the oral route, the occurrence of hematochesia which cannot be defined by routine colonoscopy suggests retrograde examination for the initial management[4,5]. Video capsule endoscopy (VCE) is mostly the first choice to investigate occult mid-GI bleeding and after diagnosis of bleeding site or determining the need for additional intervention DBE is performed as a completing procedure[6]. DBE has up to 90% of diagnostic yield

Table 1 Indications and Interventions in double balloon enteroscopy

Indications	Therapeutic interventions
Mid-gastrointestinal bleeding	Endoscopic hemostatic therapies Injection sclerotherapy Argon plasma coagulation Endoscopic hemostatic clip application
Abnormal findings in other examinations	Diagnosis and therapy
Polyps of the small bowel (*e.g.*, polyposis syndromes)	Endoscopic polypectomy
Crohn's diseases	Diagnostic sampling
Diagnosis, complications	Balloon dilatation for strictures
Foreign body ingestion	Foreign body removal
Small bowel tumors	Diagnostic sampling Self-expanding stents for obstruction
Endoscopic retrograde cholangiography in surgically altered anatomy	Diagnosis Stone extraction Dilatation Stenting
Incomplete colonoscopy due to technical difficulty	Complete colonoscopy

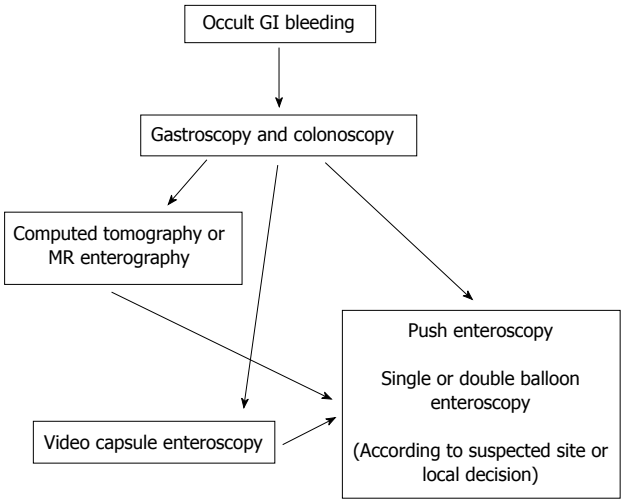

Figure 2 Algorithm for suspected occult gastrointestinal bleeding. Radiological imaging or video capsule endoscopy can be used for initial addressing the focus and enteroscopy (suitable route and modality) can be used for definitive diagnosis and therapeutic intervention. GI: Gastrointestinal; VCE: Video capsule endoscopy; MR: Magnetic resonance.

for mid GI bleeding which is comparable to VCE and significantly better than push enteroscopy as having the advantage of improved insertion depth[7]. As an alternative, push enteroscopy has been proven to have a diagnostic yield from 12% to 80% in investigating mid-GI bleeding, and higher rates are achieved when the bleeding is obscure (Figure 2).

Beyond diagnostic accuracy DBE brings the advantage of therapeutic interventions and ability to obtain tissue samples which is a great advantage when compared to VCE[8]. Clinician can perform endoscopic hemostatic techniques for bleeding sites at the time of diagnosis even documented initially with another

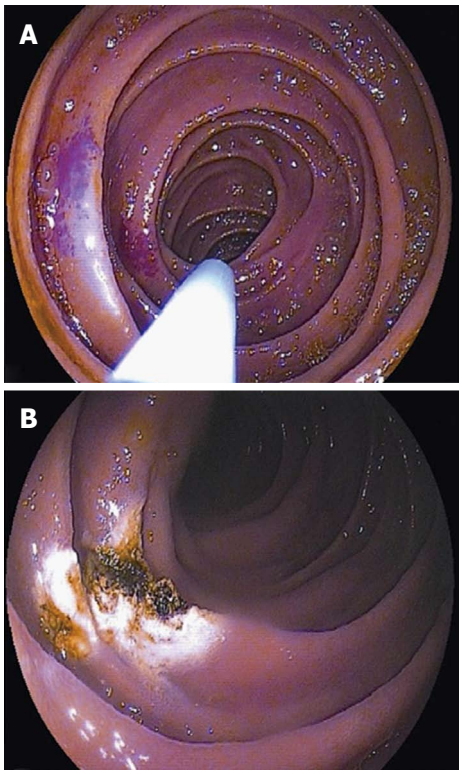

Figure 3 Double balloon enteroscopy. A: Endoscopic appearance of an angioectasia in mid jejunum; B: Eradication of angioectasia with Argon Plasma Coagulation application.

examination (*i.e.*, radiological, scintigraphic or angiographic) or not. Also lesions that cause bleeding (*i.e.*, angiodysplasia, polyps, small bowel tumors, foreign bodies...) diagnosed by using VCE can be reached with DBE for further tissue sampling or therapeutic interventions[9,10]. When the bleeding is severe and persistent or the probability of intervention is strong, DBE can take the first place instead of VCE (Figure 3).

Abnormal findings in other examinations

The interventional advantage offers DBE to be performed after abnormal findings of an initial diagnostic modality. Computed tomography (CT), magnetic resonance imaging (MRI) and VCE findings with suspected lesions can be confirmed and further applications can be performed with DBE. Also with suspected or known strictures of the small bowel, DBE comes further than VCE in order to avoid retention of the capsule and DBE becomes the initial approach for the patient[8].

Polyposis syndromes

The use of DBE in polyposis syndromes such as Familial Adenomatous Polyposis and Peutz Jeghers syndrome can be for screening and interventions for symptomatic patients (*i.e.*, bleeding or partial obstruction)[11]. Polyps larger than 15 mm are considered to bring tendency to intussusception and are recommended to be removed. VCE is mainly used for detecting the large polyps or for surveillance, but DBE is encouraged to be performed

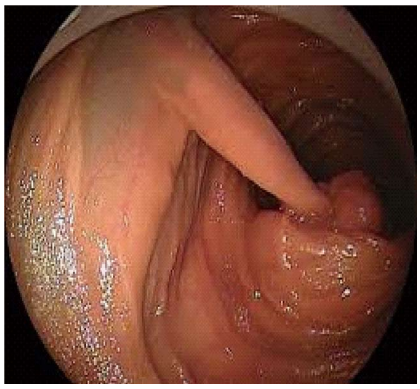

Figure 4 Jejunal polyp of Peutz-Jeghers syndrome.

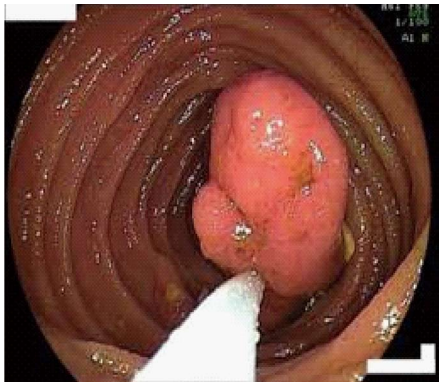

Figure 5 Polypectomy with double balloon enteroscopy.

for polypectomy instead of surgery. Patients with obstruction are treated with surgery and most of these patients that underwent surgery have intraabdominal adhesions. The risk of getting stuck and iatrogenic obstruction with capsule itself limits the use of CE in this setting and DBE becomes mainly the first choice for even surveillance of the small bowel. The opportunity for polypectomy and mechanical dilatation of the intestinal strictures are the other unique advantages of DBE against other diagnostic tools[12] (Figures 4 and 5).

Crohn's disease

DBE is not the first choice for the diagnosis of Crohn's disease (CD), but suspicion of the disease with only small bowel involvement and follow up of the strictures to confirm even inflammatory or fibrotic to modify the treatment of the patient would bring the need for using DBE in the diagnostic side of this disease. Also tissue sampling for suspected malignancy on CD and ability to dilate the strictures in the small bowel other implementations of DBE in CD[13]. Endoscopic confirmation of strictures to be inflammatory or fibrotic is of great importance to steer the treatment. Inflammatory strictures are suitable candidates for medical therapy where fibrotic strictures need mechanical interventions such as dilatation or surgery.

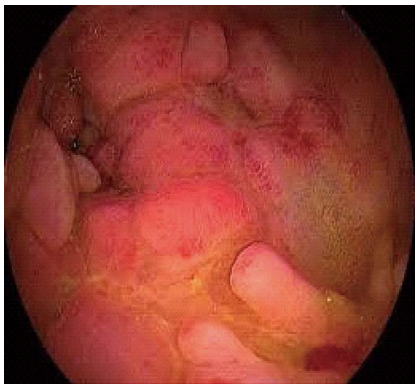

Figure 6 Jejunal stricture of Crohn's disease.

Endoscopic dilatation therapy is an option for short (< 3-4 cm), fibrotic strictures mainly due to scar tissues. The recurrence of strictures and need for repetitive dilatation or surgery is observed in a wide range and this information needs further investigations to be determined[14] (Figure 6).

Foreign body removal

Ligament of Treitz is one of the anatomical narrow points where the intestinal passage is relatively altered. However foreign bodies may pass this anatomical site and reach small bowel easily. The foreign bodies that are beyond the reach of gastroscopy and colonoscopy are candidates for DBE. Foreign bodies can be observed in pathologically narrowed intestinal sites such as tumors, strictures and large polyps. Even wireless capsules used for VCE can get stuck and need to be removed with DBE. Potentially harmful foreign bodies such as needles can be safely removed by using DBE with the help of overtube.

Small bowel tumors

Suspected small bowel lymphoma in Celiac disease and a solitary mass of small bowel documented in an initial diagnostic procedure can be the indication to perform DBE. As small bowel tumors can be seen nearly 5% of patients with mid GI bleeding, direct visualization of the lesion and histologic sampling before surgical intervention is crucial and DBE is the choice of initial procedure[15]. Also tattooing with DBE prior to surgery would be useful for surgeons to perform the most suitable surgical design (Figure 7).

Biliary interventions in surgically modified GI tract

DBE gives clinicians the chance to perform endoscopic retrograde cholangiopancreatography in patients with Bilroth Ⅱ and Roux-en-Y anastomosis who have altered anatomy due to surgery. This approach can be both diagnostic or interventional such as stone extraction, dilatation or biliary stenting. Also patients who underwent bariatric surgery and gastric bypass have a long descending small bowel loop that lead

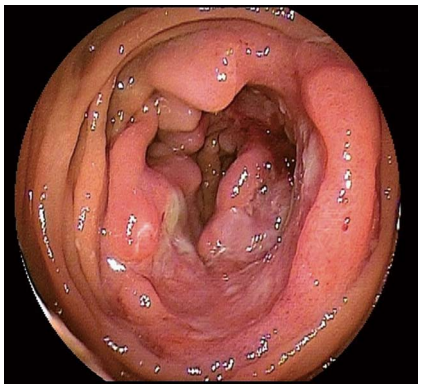

Figure 7 Ulcerating tumor located in mid jejunum.

to the afferent loop which can obtain access to the duodenum or the gastric remnant. DBE is used to pass this prolonged route in order to reach the biliary system.

DBE can also be used in patients who could not have complete ileocolonoscopy due to technical difficulties such as adhesions.

Complications

Procedure related complications differ according to the content of the examination. A procedure without therapeutic intervention brings low rates of complications. Due to prolonged procedure and air insufflation, abdominal pain can be observed in up to 20% patients. Acute pancreatitis with a rate of 0.3%-0.4% is the most common complication for oral route. It is supposed to be the result of increased pressure at the site of major papilla and ischemia of pancreas due to push and pull maneuvers. When therapeutic intervention is used complication rates increase up to 10% (perforation or bleeding following polypectomy or mucosal resection)[9,13,16]. Patients who had previous abdominal surgery and altered anatomy has greater risk of complications. Also prolonged sedation beyond from the procedure itself has the risk of respiratory depression and aspiration with a rate of 1%. Experience of the endoscopist, shorter time of procedure and inflating the balloons distal to Treitz ligament are the clues to reduce the rate of complications.

Contraindications of DBE

The contraindications for DBE are the same as conventional upper or lower GI endoscopic procedures. These are presence of shock, acute myocardial infarction, fulminant colitis, acute perforation and peritonitis. Intraabdominal adhesions increase the difficulty of the procedure and limit the depth of insertion but they are not counted as a contraindication.

Alternative techniques to examine the small bowel

VCE is a good alternative or an initial procedure to use as a diagnostic tool mainly investigating mid-GI bleeding. However the inability of intervention is the main drawback of VCE. Three meta-analyses in the literature of DBE *vs* VCE showed similar diagnostic yields in patients with obscure GI bleeding[17-19]. A retrospective study of 162 patients demonstrated an advantage of VCE where it is technically hard to reach with DBE and superiority of DBE in patients with Roux-en-Y loop anatomy and diverticula. Overall, the diagnostic yield for DBE *vs* VCE appears to be similar. VCE has the advantage of being noninvasive and is more likely to achieve complete small bowel enteroscopy. As VCE can be performed in outpatient setting without sedation it does not carry the additional risks of anesthesia.

In most clinical scenario the initial approach is VCE and after addressing the site of pathology DBE is used for sampling or therapeutic intervention. This sequential approach decreases the procedure duration and enhances interventional success.

Single balloon enteroscopy (SBE) is another alternative procedure for similar indications with similar capabilities. Limited number of trials that compare SBE and DBE have showed that they have similar diagnostic and therapeutic yield. However DBE seems to be more effective in performing complete enteroscopy[20-23].

Intraoperative enteroscopy (IOE) is an another alternative but after development of balloon enteroscopy techniques, IOE is not of initial choice as it is incomparably invasive.

CONCLUSION

DBE was first introduced by Yamamoto *et al*[1] In 2001. Evolving technologic advances and experience of the clinicians has made this particularly difficult procedure to be highly effective and safe for evaluation of the small bowel[24]. Growing experience more than a decade provided the chance to examine the whole intestinal system *via* oral or rectal route. DBE has reduced the need of surgery for small intestinal diseases. Despite its high diagnostic yield the complications of the procedure are reasonable and can be reduced with experience and basic precautions. Despite the easy use of VCE DBE will remain an important small intestinal examination as it has the ability of therapeutic intervention and tissue sampling. Cumulative experience of the endoscopist increase the success and insertion depth when reducing the complications and duration of the procedure. This knowledge suggest that DBE should be best performed in referral centers by educated endoscopists. Also use of carbon dioxide insufflation instead of ambient air increases insertion depth and patient tolerance during the procedure[25,26].

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MINIREVIEWS

Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of kidney lesions: A review

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Abstract

Traditionally, treatment of renal lesions is indicated based only on imaging features. Although controversy exists about tissue sampling from small renal masses, renal biopsy is indicated in some cases. In this review, we discuss the rationale for endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) and summarize the recent advances in this field, providing recommendations for the practicing clinician. The use of EUS-FNA appears to be a safe and feasible means of confirming or excluding malignancy. EUS allows assessment and biopsy of masses or lesions within both kidneys and related complications are rare. The main advantages of EUS-FNA are that it can be done as an outpatient procedure, with good results, minimal morbidity and a short hospital stay. Nevertheless, EUS-FNA of renal masses should be indicated only in selected cases, in which there is potential to decrease unnecessary treatment of small renal masses and to best select tumors for active surveillance and minimally invasive ablative therapies. Additionally, some renal lesions may be ineligible for EUS-guided biopsy because of anatomical limitations. EUS-FNA renal biopsy will probably be best applied to central anterior renal masses, while tumors on the posterior aspect of the kidney, percutaneous access will probably be superior.

Key words: Kidney; Renal; Endoscopic ultrasound; Cancer; Puncture

Core tip: Although controversy exists on the need of renal biopsy, endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) can be used in selected cases. In this review we discuss the rationale for EUS-FNA kidney and summarize the recent advances in this field, providing recommendations for the practicing clinician.

Lopes RI, Moura RN, Artifon E. Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of kidney lesions: A review. *World J Gastrointest Endosc* 2015; 7(3): 253-257 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i3/253.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i3.253

INTRODUCTION

Improvements on imaging technology and widespread use of imaging studies have not only increased the detection, but also allowed better characterization of incidental renal masses, which resulted in smaller lesions being depicted on such studies[1]. Up to 80% of renal cell carcinomas (RCC) are incidentally detected during radiological work-up, usually for non-urological indications. At time of nephrectomy, 70%-90% of solid renal lesions prove to be RCC[2,3], accounting for 2% of all cancers and being the leading kidney malignancy[2,4,5]. Therefore, an enhancing renal neoplasm on computed tomography (CT) or magnetic resonance imaging (MRI) has been considered by most urologists to be a sufficient indication for surgery because about 80% of such lesions prove to be RCC.

Some recent studies demonstrated that up to 30% of detected renal lesions are benign at surgery, depending on renal lesion size[6,7]. Furthermore, current management of small renal tumors involves from surveillance strategies to alternative minimally invasive and nephron-sparing options, such as laparoscopic/robotic partial nephrectomy, cryotherapy and radiofrequency ablation. In this scenario, pre-therapeutic guided biopsy might be helpful to avoid unnecessary surgery and to choose the most appropriate management strategy. In almost 30% of selected patients, a surgical procedure became non-mandatory after renal biopsy results were obtained[8]. Therefore, if a renal biopsy might impact treatment decisions, the use of core biopsy and fine needle aspiration (FNA) for better characterization of suspicious renal masses preoperatively should be considered.

In most patients, treatment of renal lesions is indicated based on imaging features alone. Although controversy exists about tissue sampling from small renal masses (tumors with less than 4 cm, since they have up to 30% chance of being benign), renal biopsy is indicated to: (1) characterize radiographically indeterminate lesions; (2) confirm malignancy in patients, who either are not surgical candidates or plan primary treatment with minimally invasive ablative therapy; and (3) rule out non-renal cell primary tumors (metastasis and lymphoma) or benign conditions (abscess), which may not require surgery[9-11].

Biopsy has also been used to confirm the diagnosis and the histological subtype of a renal primary lesion in patients with disseminated metastasis or unresectable retroperitoneal mass. In metastatic RCC, patients with clear cell subtype histology are most likely to benefit from adjuvant immunotherapy following cytoreductive nephrectomy. Additionally, new target therapies demonstrate variant response rates with distinctive RCC subtypes[2,8].

Tissue sampling of renal lesions is traditionally performed by using percutaneous sonographic or CT guidance. The use of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is infrequently performed for the evaluation for RCC and there are few reported studies addressing the safety and feasibility of this technique[2,8,11-14], as shown in Table 1.

The objective of this review is to: (1) outline the rationale for EUS-FNA kidney; (2) detail the procedural technique; (3) evaluate the clinical outcomes and limitations of the method; and (4) provide recommendations for the practicing clinician.

RATIONALE FOR EUS-FNA OF KIDNEY LESIONS

Since EUS initial report in the 1980s, it rapidly crawled from a pure imaging modality used mainly for diagnostic purposes, especially for lesions of digestive tract, to a more interventional and therapeutic application[15]. With the subsequent advent of FNA, this technique has became the gold-standard procedure for the assessment of benign and malignant diseases of the gastrointestinal tract and of adjacent organs[16,17]. EUS-FNA is highly accurate, sensitive and specific with estimates reaching 80%, 90% and 100%, respectively for cytological diagnosis[18-20].

As discussed above, percutaneous renal mass biopsy must not be performed for renal lesions less than 40 mm but it should be indicated for incompletely accurate renal imaging diagnosis after a full imaging evaluation. As well, EUS-FNA cannot currently be recommended as routine for cytologic diagnosis of renal masses, however, it might be useful in the aforementioned clinical situations when a renal biopsy should have an impact on clinical decision, especially for central and anterior renal masses. The advantages of a EUS-FNA in these cases is the potential to decrease unnecessary treatment of small renal masses and to best select renal tumors for active surveillance and minimally invasive ablative therapies[12,21]. EUS-FNA appears to be a safe and cost-effective way of confirming or excluding malignancy and may hinder the need for CT-guided exams[2].

PROCEDURAL TECHNIQUE

Anatomic approximation to both kidneys allows access for tissue sampling with the echoendoscope positioned in the upper gastrointestinal (GI) tract. Translating the probe within the duodenum or stomach, with the extension of 12.5 cm for 7.5 MHz probe, is sufficient to visualize both kidneys. The right kidney can be readily imaged by locating the transducer in the second portion of the duodenum (green area Figure 1) and rotating laterally, and the left kidney can be visualized when the transducer is facing posterolaterally into the body of the stomach (grey area Figure 1A)[12]. Color doppler ultrasound can verify the presence of major trespassing vascular structures, which should be identified and avoided during FNA.

Table 1 Reported endoscopic ultrasound-guided fine needle aspiration case series

Ref.	Design	Location	Mean size	Approach	No. of EUS-FNA	Technical success	Complications
Farrell *et al*[2]	Case report	Right kidney	9 cm	Duodenum 22 G needle 2 passes	1	100%	No
Eloubeidi *et al*[13]	Prospective study	N/A	N/A	N/A 22 G needle up to 5 passes	1	N/A	N/A
Artifon *et al*[12]	Case report	Left kidney	1.3 cm	Gastric body 22 G needle 3 passes	1	100%	No
DeWitt *et al*[11]	Case series	Right kidney (n = 5) Left kidney (n = 10)	3.2 cm (1.1-6 cm)	Duodenum for right kidney and gastric body for left kidney 22 G needle 2 - 4 passes	15	80% (12/15)	No
Lakhtakia *et al*[14]	Case report	Right kidney	1.5 cm	Duodenum 22 G needle N/A passes	1	100	Transient hematuria
Moura *et al*[8]	Case series	Right kidney (n = 4) Left kidney (n = 4) Bilateral (n = 1)	6 cm (1.3-16 cm)	Duodenum for right kidney and gastric body for left kidney 22 G needle 3 passes	10	90% (9/10)	No

EUS-FNA: Echoendoscopic ultrasonographic fine needle aspiration; N/A: Non available.

EUS-FNA is performed (Figure 1B) using curvilinear array echoendoscopes that are produced by three leading manufacturers: Olympus (Olympus Medical Systems Inc., Tokyo, Japan), Pentax (Pentax, Tokyo, Japan) and Fujinon (Fujifilm Corp., Tokyo, Japan). The working channel must be at least of 2.8 mm to accept the FNA needle and the echoendoscopes present at an elevator located on the side of the scope at the tip portion, that is able to make changes in the exit angle of the FNA needle to facilitate the targeting process[15].

Needles for renal EUS-FNA are currently available in 3 sizes (19, 22 and 25 gauge). Thinner needles are used to gather cytological specimens, while thicker needle are better applied for acquisition of a tissue specimen for histological examination, that can be more useful to reach the definitive diagnosis. The choice of the needle depends on the type and site of the lesion to be sampled. In all the studies listed in Table 1, the kidney was punctured using a 22-gauge needle. More data is probably needed to characterize the correct needle size depending to the type and location of the lesion.

Whenever possible, EUS-FNA should be done under deep sedation with the assistance of an anesthesiologist. The main advantages of EUS-FNA are that it can be done as an outpatient procedure, and it appears to be safe with good results, minimal morbidity and a short hospital stay, as demonstrated in Table 1.

PROCEDURAL LIMITATIONS

Some renal masses may be ineligible for EUS-guided biopsy because of anatomical limitations. EUS-FNA renal biopsy will probably be best applied to central anterior renal masses, while tumors on the posterior aspect of the kidney, percutaneous access will probably be superior. Among other reasons, these limitations are likely to restrict widespread application of EUS for this indication[11].

EUS-FNA related complications of kidney masses sampling are similar to those for aspiration of GI masses and include localized bleeding, infection, hematoma, hematuria, pneumothorax, and needle tract seeding[14]. The risk of complications associated with EUS-FNA spans from less than 1% to 6%. Tracheal suction (5%), vomiting (0.3%), aspiration (0.3%), esophageal perforation and death (less than 0.06%) are reported complications of EUS. In a relatively small group of patients, the frequency of bleeding as a result of fine-needle aspiration of the kidney was 0.5%, whereas that associated with fine-needle aspiration of GI lesions was 1.3%[2].

Since the EUS needle has to transverse fewer tissue layers, the risk of needle seeding may be lower, with few cases reported. Overall, the prospect of needle track seeding is minor and it should be balanced against the benefit of a tissue diagnosis[12]. In a retrospective review of patients submitted to pancreatic mass FNA, either by EUS-FNA or percutaneous access, the incidence of peritoneal carcinomatosis was lower in the EUS-FNA group, which might suggest a lower risk of needle seeding[22].

Higher accuracy rates are achieved with on-site cytopathology examination to assess specimen adequacy that, however, is not available in all centers and may increase the cost of the procedure[15].

EUS-FNA is not done in situations when it is unlikely to alter the management of a cancer. In addition to the usual contraindications for any endoscopic

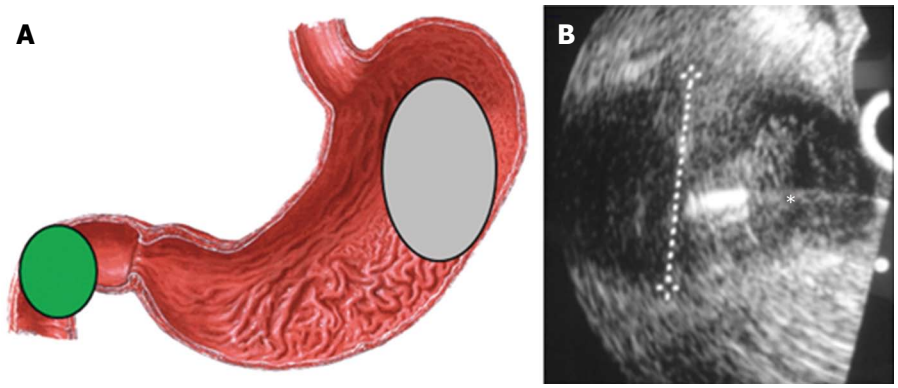

Figure 1 The right kidney image. A: Endoscopic ultrasound positioning and access for tissue sampling; B: Fine needle aspiration of a renal lesion. The asterix is over the needle to show the fine needle aspiration of the tumor.

procedure, including severe bleeding diathesis and thrombocytopenia, EUS-FNA is not advocated when good views of the lesion are not obtained or when a major vascular structure is present on the way to the target[15].

CONCLUSION

New techniques in EUS are emerging and will likely have a niche in aiding the diagnosis of undeterminate lesions. EUS allows visualization and sampling renal masses. This technique is evolving and will possibly have a role in diagnostic EUS in the future, as it appears to be a safe and feasible procedure with good results, minimal morbidity and a short hospital stay in the cases reported on the literature[2,8,11-13].

We recommend that EUS-FNA of renal masses should be indicated only in selected cases, in which the procedure may alter clinical management by avoiding unnecessary treatment and helping to select patients for active surveillance and minimally invasive ablative therapies. Further research should evaluate the benefits of preoperative renal biopsy use and randomization of percutaneous, laparoscopic and echoendoscopic approach should be compared.

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Head mass in chronic pancreatitis: Inflammatory or malignant

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Abstract

Chronic pancreatitis increases the risk of developing pancreatic cancer. This often presents as a mass lesion in the head of pancreas. Mass lesion in the head of pancreas can also occur secondary to an inflammatory lesion. Recognising this is crucial to avoid unnecessary surgery. This is sometimes difficult as there is an overlap in clinical presentation and conventional computed tomography (CT) abdomen findings in inflammatory and malignant mass. Advances in imaging technologies like endoscopic ultrasound in conjunction with techniques like fine needle aspiration, contrast enhancement and elastography as well as multidetector row CT, magnetic resonance imaging and positron emission tomography scanning have been shown to help in distinguishing inflammatory and malignant mass. Research is ongoing to develop molecular techniques to help characterise focal pancreatic mass lesions. This paper reviews the current status of imaging and molecular techniques in differentiating a benign mass lesion in chronic pancreatitis and from malignancy.

Key words: Chronic pancreatitis; Pseudotumour; Imaging; Endoscopic ultrasonography; Molecular tool

Core tip: Evaluating head mass in chronic pancreatitis is clinically challenging. Advances in pancreatic imaging including endoscopic ultrasonography and molecular tools have been reviewed.

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INTRODUCTION

The risk of developing pancreatic cancer in patients with chronic pancreatitis is about fifteen times higher than in the average population[1]. A meta analysis has shown that 5% of the patients with chronic pancreatitis develop pancreatic cancer over a 20 year period[2]. About 70% of these tumours are located in the head

region of pancreas[3]. Patients with chronic pancreatitis also tend to develop inflammatory lesions in the head of pancreas which appears like tumour mass and is referred to as pseudotumour[4]. Confirming the diagnosis preoperatively is crucial because confusion may lead to either major pancreatic resection for benign disease or rejection of surgery for a potentially curable lesion.

Clinical features and biochemical parameters that suggest malignant mass in head of pancreas are older age, persistent jaundice, worsening abdominal pain, gastric outlet obstruction, significant weight loss and elevated CA 19:9 greater than 300 U/mL[5]. Conventional Imaging techniques like Ultrasound abdomen, CT and MRI provide useful information that helps in differentiating benign from malignant mass in head of pancreas[6]. Unfortunately, due to an overlap in clinical, biochemical and conventional imaging parameters, it is sometimes difficult to differentiate an inflammatory mass from cancer in head of pancreas[6]. This is supported by the fact that most large series of pancreatic resections for carcinoma head of pancreas show that 5%-10% of cases of inflammatory mass masquerade as pancreatic carcinoma[7,8].

The advent of endoscopic ultrasound (EUS) has been a major development in assessment of pancreatic disease including mass lesions in the head of pancreas[9]. High frequency EUS probes in the stomach located close to the pancreas, provide detailed images with no intervening bowel gas[9]. In addition, fine needle aspiration (FNA) performed for obtaining tissue sample further helps in diagnosis. New EUS based techniques like Digital Image analysis, EUS Elastography and Contrast enhanced EUS have shown promise in better characterisation of pancreatic mass lesion. In this paper we review the role of EUS in assessing pancreatic head mass in chronic pancreatitis and also briefly look at other radiological and molecular tools available for evaluation of this entity.

ENDOSCOPIC ULTRASONOGRAPHY

Endoscopic ultrasonography has been found to be very useful in detecting small pancreatic mass lesions and has been shown to be better than other modalities for assessing vascular invasion and local spread[10,11]. EUS in association with other techniques like FNA or contrast enhancement has also been found to be useful in distinguishing benign from malignant pancreatic mass lesions. The data from studies evaluating the role of EUS in assessing pancreatic mass lesion has been summarised in Tables 1 and 2. Table 1 shows only studies which have included patients with background chronic pancreatitis. Most studies show that EUS alone is not capable of precisely differentiating between a pseudotumoral mass and carcinoma in the setting of chronic pancreatitis[12-14]. Presence of multilobularity, homogenous pattern, hyperechoic septa and Doppler signal within a lesion favour pseudotumour[12]. One of the limitations with EUS is the subjective nature of image assessment and performance which varies depending on experience. As the architectural changes are better detected by computer based methods than naked eye, it is possible that digital image analysis (DIA) obtained during EUS can remove the error of subjective assessment. Two studies with adequate number of subjects have shown that digital image analysis has sensitivity and specificity of above 90% in differentiating malignant and benign pancreatic mass lesion[15,16].

The limitations of conventional B mode EUS can be overcome by performing FNA which gives a tissue diagnosis. FNA is relatively safe as it does not traverse peritoneal cavity and avoids seeding of peritoneum. Unfortunately, FNA which has a sensitivity of above 90% in detecting pancreatic malignancy in pancreas with normal parenchyma, underperforms in the presence of chronic pancreatitis with sensitivity dropping to below 75%[12,17-19]. Vardarajulu and colleagues reported that in the 300 EUS FNA performed for pancreatic mass lesions, sensitivity was 91.3% in pancreas with normal parenchyma but only 73.9% when chronic pancreatitis was present[17]. Other studies have shown even poorer performance. In a study from Romania on 72 patients with Chronic Pancreatitis (17 had Pancreatic Carcinoma), EUS FNA had a sensitivity of only 50%[18]. Similarly, in another report from Germany on 13 patients with Chronic Pancreatitis and carcinoma, EUS FNA was able to detect carcinoma in only 7 of them[19]. Making more number of passes during FNA or repeating FNA may improve the yield[17,20].

Using molecular tools to detect mutation in tissue sample may be a useful adjunct to improve diagnostic yield[21-23]. Khalid *et al*[21], studied microsatellite markers and mutation in *K-ras* gene on EUS-FNA samples from patients with benign and malignant pancreatic masses. The mean fractional mutation rate was higher in pancreatic malignancy and use of molecular tool improved the diagnostic performance of FNA[21]. In another study from Czech Republic which included 101 subjects, mutations in *K-ras* and allelic loss in tumour suppressor genes were determined on EUS-FNA specimen[22]. Detection of mutation in *k-ras* gene, allelic loss of *p16* and *DPC4* gene improved the sensitivity of cancer detection to 100%[22]. A large prospective multicenter study which only looked at k-ras mutations in addition to cytopatholgy on FNA samples, found that assessing for *k-ras* mutation improved the diagnostic sensitivity for malignancy to 88% which was only marginally better than cytopathology alone (83%)[24]. However, absence of *K-ras* mutation was a strong indicator of benign lesion[24]. This study also highlights the importance of studying multiple markers rather than single one. Other studies have shown that absence of *k-ras* mutation in FNA samples from patients with chronic pancreatitis and mass lesion strongly suggest a benign lesion[24,25]. Data from the above studies suggest that molecular tests can play a significant role in diagnosing

Table 1 Endoscopic ultrasound in evaluating pancreatic mass lesions in patients with chronic pancreatitis

Ref.	Study subjects	Procedure	Outcome[1]
Fritscher-Ravens *et al*[19]	74 patients with focal pancreatic lesions and chronic pancreatitis	EUS FNA	Sn-54%
Vardarajulu *et al*[17]	75 patients with CP and focal pancreatic mass lesion	EUS FNA	Sn-73.9% Sp-100%
Iordache *et al*[18]	CP-55 CP and PC-17	EUS FNA	Sn-50% Sp-73.7%
Hocke *et al*[13]	86 patients with CP and pancreatic lesion	EUS CE-EUS	Sn-73.2% Sp-83.3% Sn-91.1% Sp-93.3%

[1]Differentiating malignant and non-malignant pancreatic lesion. Sn: Sensitivity; Sp: Specificity; CP: Chronic pancreatitis; PC: Pancreatic cancer; CE: Contrast enhanced; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration.

pancreatic cancer in FNA samples and one should assess for k-ras mutations along with loss of tumour suppressor genes to improve yield.

Recent advances in EUS based technology like EUS Elastography, Contrast Enhanced EUS and computer software in interpreting images have shown promise in better characterisation of pancreatic mass lesions[26-28]. EUS elastography measures tissue stiffness[26,29]. The stiffness in malignant tumour is different from benign lesion or normal tissue and this is represented as different colour regions on the conventional real time EUS images. Usually blue colour indicates hard tissue, red suggests soft tissue and green represents tissue with intermediate stiffness. To remove subjective error, tissue strain can be quantitatively measured by software to provide strain ratios which are different for benign and malignant lesions[29,30]. The results of earlier studies with EUS elastography were disappointing showing low sensitivity and specificity[31,32]. This was probably due to fibrous architecture in both tumour and chronic pancreatitis[31]. Subsequent studies after the introduction of quantitative assessment methods including measurement of strain ratio have shown better outcomes (sensitivity > 90%)[30,33-35]. In a study measuring strain ratio during EUS elastography, ratio was 1.68 for normal pancreas, 3.38 for inflammatory mass and a very high ratio of 18.12 for pancreatic adenocarcinoma[30].

Contrast enhanced (CE) EUS makes use of injected contrast to assess vascularity of lesion and low mechanical index technique enables this to be done in real time without problem of artefacts[36]. Arterial phase lasts for about 30 s and venous phase for the next 90 s[37]. Pancreatic tumours are hypovascular with delayed contrast uptake and usually lack venous structure[13,38,39]. A time intensity curve can be generated using image software and the peak characteristics can give a clue to the underlying diagnosis. Results from most studies using CE EUS have been encouraging with sensitivity and specificity greater than 90%[13,14,38,40,41]. Seicean *et al*[38] measured the contrast uptake ratio index during CE EUS and found it to be significantly lower in pancreatic cancer than in mass forming chronic pancreatitis. A cut-off ratio of 0.17 had good discriminatory value[38]. The contrast enhancement and elastography techniques can also be used in combination. In a study using combination of above techniques, the positive predictive value was 96.7% in evaluating pseudotumour of chronic pancreatitis and pancreatic cancer[41]. The results of elastography, CE EUS and digital image analysis are encouraging but are affected by equipment characteristics and type of contrast used. Development of consensus guidelines and uniformity in performing these procedures will make it easier to integrate their use in clinical practice.

OTHER IMAGING MODALITIES

Computed tomography

Computed tomography (CT) was considered to be the gold standard for pancreatic parenchymal imaging. Conventional CT however has difficulty in differentiating between inflammatory and neoplastic masses as well as detecting lesions < 2 cm in diameter as small tumours are sometimes isoattenuated to background pancreatic parenchyma. Recent developments including 64 slice multidetector row CT (MDCT) have shown promise in evaluating pancreatic mass lesion[42,43]. During triple phase pancreatic protocol CT, normal pancreas shows early washout (first phase) while there is delayed washout in chronic pancreatitis[44]. On the other hand pancreatic cancer shows an increasing pattern without washout[44]. This can be quantitatively assessed using time attenuation curve and Yamada *et al*[44] have shown this technique to have 90.4% accuracy in differentiating pancreatic cancer from chronic pancreatitis. Lu *et al*[45] evaluated 15 patients with pancreatic pseudotumor and 64 patients with pancreatic cancer and quantitative hemodynamic information obtained using time density curve was useful in distinguishing the two conditions.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has traditionally been considered less sensitive than CT scan for assessing pancreatic mass lesions. T1 weighted images have similar features in both chronic pancreatitis and pancreatic cancer but T2 weighted images show different signal intensity pattern in inflammatory and neoplastic tissue[46]. Assessment of pancreatic ductal structures can sometimes provide a clue as pancreatic cancers may lack pancreatic ductal structures while a pseudotumour may contain dilated side branches[47]. Recent advances in techniques and technology have been effective in distinguishing between inflammatory and malignant mass of pancreas[42,43,48,49]: (1) Diffusion weighted MRI: Huang *et al*[50] studied 37 patients

Table 2 Data from other studies on role of endoscopic ultrasound in evaluating pancreatic mass lesions

Ref.	Study subjects	Procedure	Outcome[1]
Ardengh *et al*[12]	69 patients with pancreatic head mass	EUS	Sn-63.63% Sp-75.86%
		EUS FNA	Sn-72.7% Sp-100%
Das *et al*[16]	Normal-22 CP-12 PC-22	EUS, Digital image analysis	Sn-93% Sp-92%
Zhu *et al*[15]	CP-262 PC-126	EUS, Digital image analysis	Sn-96.25% Sp-93.38%
Hirsche *et al*[32]	70 patients with focal pancreatic lesion	EUS Elastography	Sn-41% Sp-53%
Giovannini *et al*[33]	121 patients with pancreatic mass lesion	EUS	Sn-92.3% Sp-68.9%
		EUS Elastography	Sn-92.3% Sp-80%
Iglesias-Garcia *et al*[35]	78 patients with malignant pancreatic tumour 42 patients with inflammatory pancreatic mass	EUS Elastography	Sn-100% Sp-85.5%
Iglesias-Garcia *et al*[30]	86 patients with pancreatic mass (27 of them had inflammatory mass)	Quantitative EUS Elastography	Sn-100% Sp-92.9%
Seicean *et al*[38]	30 patients with pancreatic lesion (12 had pseudotumour)	CE harmonic-EUS	Sn-80% Sp-91.7%
Saftoui *et al*[41]	Focal pancreatic mass lesion (21 had pseudotumour)	CE + elastography during EUS	Sn-75.85 Sp-95.2%
Saftoui *et al*[34]	258 patients with focal pancreatic mass	Quantitative EUS Elastography	Sn-93.4% Sp-66%
Hocke *et al*[14]	Focal CP-39	EUS	Sn-61.5% Sp-73.7%
		EUS elastography	Sn-33.4% Sp-94.7%
	PC-19	CELMI-EUS	Sn-76.9% Sp-84.2%
		CEHMI-EUS	Sn-89.5% Sp-84.2%
Gheona *et al*[40]	PC-32 Pseudotumoural pancreatitis-19	Quantitative CE-EUS	Sn-93.7% Sp-89.4%

[1]Differentiating malignant and non-malignant pancreatic lesion. Sn: Sensitivity; Sp: Specificity; CP: Chronic pancreatitis; PC: Pancreatic cancer; CE: Contrast enhanced; CELMI: Contrast enhanced low mechanical index; CEHMI: Contrast enhanced high mechanical index; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration.

with pancreatic cancer and 14 patients with mass forming chronic pancreatitis using diffusion weighted MRI imaging with quantification techniques and showed that this technique can differentiate mass forming chronic pancreatitis from pancreatic cancer; (2) Gadolinium (Gd) enhanced 3D- Gradient echo: Kim *et al*[51] studied 22 patients with pancreatic mass (pancreatic cancer: 14; chronic pancreatitis: 8) using Gd enhanced 3D-GE and found that this technique differentiated pancreatic cancer from inflammatory mass with a sensitivity and specificity of 93% (13/14) and 75% (6/8), respectively; (3) Time signal intensity curve obtained during contrast enhanced MRI is another technique that helps in differentiating between malignant and inflammatory lesions[50]; and (4) Magnetic resonance spectroscopy: Focal pancreatitis has lower lipid content compared to cancer due to difference in fibrous tissue content in the two conditions. This can be detected by magnetic resonance spectroscopy and helps distinguish inflammatory mass from cancer[52].

Positron emission tomography

The sensitivity of FDG-positron emission tomography (PET) for differentiating pancreatic cancer from chronic pancreatitis is more than that of CT or MRI[53]. Singer and colleagues have shown that pancreatic cancer causes focal tracer enhancement while chronic pancreatitis causes diffuse enhancement[54]. This feature had 86.4% sensitivity and 78.9% specificity in distinguishing cancer from benign mass in their study on 41 patients. PET-CT detects unsuspected metastasis to liver, lung and bone which aids in discriminating between inflammatory mass and cancer. The sensitivity of PET is superior to CT in detecting lesions less than 2 cm in diameter, but CT scanning is superior to PET for diagnosing cancers larger than 4 cm in diameter because of lower metabolic rates in larger tumors[55].

Molecular techniques

Advances in molecular techniques and tools like microarray, nuclear magnetic resonance and mass

spectrometry have enabled detection of a large number of molecules rapidly. At cellular level genetic information gets transcribed into m RNA which gets translated into proteins and subsequently metabolised. Alteration of genes at cellular level in neoplastic cells leads to changes in protein and metabolites and this can be detected using "omics" technology[56-58]. Genomics aims at detecting genes, proteomics at detecting set of expressed proteins and metabolomics the metabolic profile. While molecular techniques can detect a large array of products, filtering out the specific markers useful for diagnosing different conditions remains a challenge. A proteomics based study from United States, aimed to identify the plasma protein profile in subjects with chronic pancreatitis, pancreatic cancer and non-pancreatic disease controls[59]. They identified more than 1300 proteins and found that a composite marker of TIMP1 and ICAM1 performed better than CA19-9 in differentiating pancreatic cancer from rest of the group. They also suggested that a protein called AZGP1 could serve as a biomarker for chronic pancreatitis[59]. Paulo *et al*[60] studied expressed proteins in chronic pancreatitis, pancreatic cancer and autoimmune pancreatitis and found a range of differentially expressed proteins in the three different groups. Using liquid chromatography with tandem mass spectrometry, they found that 29 proteins were exclusively expressed in chronic pancreatitis and 53 protein in pancreatic cancer[60]. These tests were conducted on tissue samples and hence can serve as an adjunct to histology but require validation in larger cohort.

Zhang *et al*[61] used NMR based metabolomics strategy to distinguish pancreatic cancer from chronic pancreatitis and healthy individuals and found the results promising. Patients with pancreatic cancer had a number of abnormalities in amino acid and lipid metabolism including elevated levels of N-acetyl glycoprotein and dimethylamine and reduced levels of citrate, alanine, glutamine. In another metabolomics based study done employing gas chromatography mass spectrometry on subjects with chronic pancreatitis, pancreatic cancer and healthy volunteers, Kobayashi and colleagues were able to develop a model which performed reasonably well in differentiating PC from CP. Other studies have shown, Ca 242, M2 pyruvate kinase, PBF-4, PNA binding glycoprotein, nTert, MMP-2, Synuclein-gamma, and neopterin to be useful biomarkers in differentiating pancreatic cancer from chronic pancreatitis[59,62,63]. A study from Germany has shown that micro RNA abundance measured in tissue and blood performs well in distinguishing chronic pancreatitis and pancreatic cancer[64]. Overall, molecular tools appear promising but are not yet ready for clinical application.

CONCLUSION

There have been a number of developments in imaging and molecular technologies to aid in differentiating benign from malignant mass lesion in patients with chronic pancreatitis. While some like EUS-FNA and advanced CT/MRI techniques are already in clinical use, technologies like CE EUS, EUS elastography and digital image analysis require development of standardised protocol, consensus and operator training facilities before they can be inducted into regular clinical usage. The molecular techniques are still in the early stage of development. Continued research and development is required to help in the correct diagnosis of this challenging condition.

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Collagenous gastritis: Review

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Abstract

Collagenous gastritis is a rare disease characterized by the subepithelial deposition of collagen bands thicker than 10 μm and the infiltration of inflammatory mononuclear cells in the lamina propria. Collagenous colitis and collagenous sprue have similar histological characteristics to collagenous gastritis and are thought to be part of the same disease entity. However, while collagenous colitis has become more common in the field of gastroenterology, presenting with clinical symptoms of chronic diarrhea in older patients, collagenous gastritis is rare. Since the disease was first reported in 1989, only 60 cases have been documented in the English literature. No safe and effective treatments have been identified from randomized, controlled trials. Therefore, better understanding of the disease and the reporting of more cases will help to establish diagnostic criteria and to develop therapeutic strategies. Therefore, here we review the clinical characteristics, endoscopic and histological findings, treatment, and clinical outcomes from case reports and case series published to date, and provide a summary of the latest information on the disease. This information will contribute to improved knowledge of collagenous gastritis so physicians can recognize and correctly diagnose the disease, and will help to develop a standard therapeutic strategy for future clinical trials.

Key words: Collagenous gastritis; Collagen deposition; Collagenous colitis; Nodularity

Core tip: The diagnosis of collagenous gastritis is based on the histological findings of collagen bands thicker than 10 μm in the subepithelial layer and infiltration of inflammatory mononuclear cells in the lamina propria. Similar histological changes are seen in the colon in collagenous colitis. While there are many cases of collagenous colitis published in the literature, there are only 60 reported cases of collagenous gastritis since the disease was first identified in 1989. The present review discusses the characteristics of this disease entity and summarizes the cases reported to date. Better knowledge and understanding of collagenous gastritis will help physicians to diagnose the disease, and the accumulation of future cases will help to develop a standard therapeutic strategy.

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INTRODUCTION

Collagenous gastroenteritides include collagenous gastritis, collagenous sprue, and collagenous colitis. This disease entity is relatively uncommon and believed to be rare. The diseases are characterized by marked subepithelial collagen deposition accompanying with mucosal inflammatory infiltrate[1-5]. The exact etiology and pathogenesis of this inflammatory disorder remains unclear and clinical presentations are related to the region of the gastrointestinal tract involved. While collagenous colitis is the most frequently found in this disease category[5,6], collagenous gastritis and collagenous sprue involving the proximal side of the gastrointestinal tract is rarer. Recently, it is reported that the overall annual incidence of collagenous colitis ranges from 1.1 to 5.2 cases per 100000 population and it is a relatively frequent cause of chronic diarrhea in elderly patients[7]. For collagenous gastritis, Colleti reported first case of 15-year-old girl who presented with recurrent abdominal pain and gastrointestinal bleeding in 1989[8]. On endoscopy, nodular changes were seen in the stomach. Subepithelial collagen deposits and inflammatory infiltration of the lamina propria were observed on histological examination. Despite treatment with histamine H2-receptor antagonists, sucralfate, and furazolidone, no clinical or pathological improvement was achieved[8]. Since 1989, only 60 cases of collagenous gastritis have been reported in the English literature[2-4,8-40]. Because of the small number of cases, no standard therapy has been established based on randomized, controlled clinical trials. However, based on case reports, two phenotypes of the disease (pediatric and adult) have been defined[21]. The presenting symptoms of the pediatric type are mainly upper gastrointestinal, including abdominal pain and anemia secondary to the stomach-specific inflammation and collagen deposition[10,21]. In contrast, the adult type is characterized by the simultaneous occurrence of collagenous colitis, which may be related to autoimmune processes and celiac disease[21]. The endoscopic findings of mucosal nodularity and the histological findings of inflammatory infiltration with thick collagen deposits are common in both adult and pediatric disease. However, the areas of the gastrointestinal tract involved are different, raising the possibility of a different etiology[1,3]. Because the pathophysiology of collagenous gastritis remains uncertain, no effective therapeutic strategies have been developed. Better knowledge and understanding of the disease will help physicians make a correct diagnosis at an early stage, and may help to establish rational treatment options. In this paper, we review the clinical and pathological characteristics of the 60 cases[2-4,8-40] reported to date.

LITERATURE ANALYSIS

A literature search was conducted using PubMed and Ovid, with the term "collagenous gastritis." The literatures written in English from relevant publications were selected. We summarized the available information on demographics, clinical symptoms, endoscopic and histological findings, treatment, and the clinical course.

CLINICAL CHARACTERS

Among the 60 reported cases of collagenous gastritis, there was a slight female predominance (35 females, 25 males). The ages ranged from 9 mo to 80 years[2-4,8-40].

Clinical symptoms included abdominal pain in 26 cases[3,4,8-10,12-15,17,18,20,26,30-33,38-40], anemia in 24[2,4,8,10,11,14,16,17,19,21,22,30,36,37,39,40], diarrhea in 18[13,17,21-29,35-37], nausea and vomiting in 7[3,15,17,31,32], body weight loss in 4[3,23,35], abdominal distention in 3[24,32,36], gastrointestinal bleeding in 3[8,17,36], and fatigue[4], retrosternal pain[11], dyspepsia[2], perforated ulcer[17], dysphagia[17], and constipation[38] in 1 case each. Lagorce-Pages *et al*[21] reported that clinical symptoms differ between pediatric and adult patients based on the severity of the disease and part of the gastrointestinal tract involved. Pediatric patients typically present in their early teens with anemia and abdominal pain related to involvement of the stomach[3,21,33,38]. The adult type is characterized by more diffuse involvement of the gastrointestinal tract and typically presents with a chronic watery diarrhea associated with collagenous colitis and collagenous sprue[36,37]. Adult collagenous gastritis is also associated with autoimmune diseases, such as Sjögren syndrome[36], lymphocytic gastritis, lymphocytic colitis, and ulcerative colitis[37]. Of the 11 patients who presented with abdominal pain and anemia, 8 were teenagers (72%)[4,8,10,14,17,30]. Of the 18 patients who presented with diarrhea, 15 were older than 20 years (83%)[17,21-27,35-37] (Table 1). Ten of the adult patients had collagenous duodenitis, which is extremely rare, and of these, 9 also had collagenous colitis[2,40]. Our literature search revealed no difference in the presence of *Helicobacter pylori* infection between pediatric (n = 6)[15,19,28,29] and adult patients (n = 4)[9,21,33]. The eradication of *H. pylori* did not produce any therapeutic benefit. The clinical characteristics of the 60 published cases supported the differences between pediatric-type and adult-type collagenous gastritis reported to date. In the pediatric form of the disease, inflammation is limited to the stomach and patients present with relatively severe upper gastrointestinal symptoms. The adult form of collagenous gastritis often involves other parts of the gastrointestinal tract, and might be the part the collagenous gastroenteritides disease entity. In

Table 1 Summary of 60 collagenous gastritis patients

Ref.	Age (yr)	Gender	Symptoms					Endoscopic Findings				*H. pylori*	Collagen band (μm)		Treatment	Follow-up biopsy duration (yr)	Histological changes	Clinical course
			Abdominal pain	Anemia	Diarrhea	Nausea, vomiting	Others	Nodularity	Erythema	Erosion, gastritis	Others		Stomach	Colon				
[10]	7	F	+	+	-	-	-	-	-	+	-	NA	Yes	None	Oral iron supplementation, Proton-pump inhibitor	0.5	Improvement of inflammation remaining of collagen band	Improve
[11]	9	F	-	+	-	-	Retrosternal pain	-	+	-	-	-	13-96	< 5	Proton-pump inhibitor, Sucralfate, Steroid	1.1	No reduction	No change
[12]	9	F	+	-	-	-	-	-	-	+	-	-	35	None	Oral iron supplementation	4	Decrease of chronic gastritis, Unchanged collagen bands	Clinical remission
[13]	9	F	+	-	-	-	-	+	-	-	-	-	Yes	Yes	Oral iron supplementation	NA	NA	Improve
[14]	9	F	+	+	-	-	-	-	-	-	NA	NA	Yes	NA	Mesalazine		NA	Remain
[15]	12	F	-	-	-	+	-	+	-	-	-	+	NA	None	Proton-pump inhibitor	1	Severe erosive gastritis	Remain
[15]	12	F	+	-	-	-	-	+	-	-	-	+	NA	None	Proton-pump inhibitor	6	Decrease of nodules	Improve
[15]	12	F	+	-	-	-	-	+	-	-	-	+	NA	NA	Proton-pump inhibitor	0.17	NA	Improve
[16]	12	F	-	+	-	-	-	+	-	-	-	-	Yes	None	Oral iron supplementation	NA		
[17]	13	F	-	+	-	-	-	+	-	-	-	-	76	NA	None	NA	NA	NA
[18]	14	F	+	-	-	-	-	+	-	-	-	-	75	None	Proton-pump inhibitor, Sucralfate, H2-receptor antagonist	12	Gradual progression	Remain
[17]	14	F	-	-	-	+	-	-	-	+	-	-	23	NA	Proton-pump inhibitor	NA	NA	Remain
[8]	15	F	+	+	-	-	Gastrointestinal bleeding	+	-	-	-	-	75	None	H2-receptor antagonist, sucralfate, furazolidone	2	No reduction	NA
[19]	15	F	-	+	-	-	-	+	-	-	-	+	NA	NA	Proton-pump inhibitors, Oral iron supplementation, Steroid	0.83	NA	Clinical remission
[17]	15	F	+	+	-	-	-	+	-	-	-	-	69	None	Steroid	3.4	Decrease of inflammation	Improve
[4]	16	F	+	+	-	-	-	+	-	-	-	-	NA	None	H2-receptor antagonist, Proton-pump inhibitor, Oral iron supplementation,	6	No reduction	Improvement of anemia

[20]	20	F	+	-	-	-	-	+	-	-	-	-	30-70	None	Proton-pump inhibitor	2	No change	NA
[21]	22	F	-	+	-	-	-	+	-	-	-	-	40-45	NA	None	NA	NA	NA
[40]	22	F	+	+	-	-	Gastrointestinal bleeding	+	-	+	Duodenitis	-	60-100	None	H2-receptor antagonist, Proton-pump inhibitor	1	No change	Improve
[22]	25	F	-	+	-	-	-	+	-	-	-	-	24	Yes	None	0.25	No change	NA
[23]	25	F	-	-	+	-	-	-	-	-	NA	NA	Yes	NA	None	NA	NA	NA
[23]	25	F	-	-	+	-	Body weight loss	-	-	-	NA	NA	Yes	Yes	NA	NA	NA	NA
[39]	25	F	+	+	-	-	-	+	-	-	NA	-	17	None	H2-receptor antagonist, Proton-pump inhibitor	4	No change	No change
[24]	35	F	-	-	+	-	Abdominal distention	+	-	-	-	-	20-30	None	Sulfasalazine	NA	NA	Remission of diarrhea
[4]	39	F	-	+	-	-	Fatigue	-	-	-	Normal	-	NA	Yes	Gluten-free diet	4	No reduction	Improve
[21]	40	F	-	-	+	-	-	-	-	-	Normal	-	40-41	None	Steroid, Sulfasalazine, Parenteral nutrition	2	Resolve of collagen band	NA
[21]	52	F	-	+	-	-	-	-	-	-	Normal	+	15-20	None	None	NA	NA	NA
[17]	52	F	+	-	+	-	-	-	-	+	-	-	78	None	Gluten-free diet	NA	NA	Improve
[25]	57	F	-	-	+	-	-	-	+	-	-	-	20-40	> 30	Steroid	1.5	No change	Responded to steroid
[17]	57	F	+	-	-	-	-	+	-	-	-	-	40	NA	Gluten-free diet	NA	NA	Improve
[22]	58	F	-	-	+	-	-	+	-	-	-	-	15.8	None	Steroid	1.5	Improvement of inflammation remaining of collagen band	NA
[17]	62	F	-	-	-	+	-	-	-	+	-	-	94	NA	None	NA	NA	NA
[2]	68	F	-	+	-	-	Dyspepsia	+	-	-	-	-	None	None	Oral iron supplementation, Proton-pump inhibitor	0.83	Improvement of inflammation increase of collagen band	Partial relief
[26]	74	F	+	-	+	-	-	-	+	-	-	-	Yes	Yes	Proton-pump inhibitor	0.08	No change	Improve
[27]	75	F	-	-	+	-	-	-	-	-	Normal	NA	30-60	10-30	NA	NA	NA	NA
[28]	0.75	M	-	-	+	-	-	-	-	+	-	+	50	17	Steroid, Total parenteral nutrition	14	Gradual progression	Improve with total parenteral nutrition
[29]	2	M	-	-	+	-	-	-	-	+	-	+	> 5	NA	Proton-pump inhibitors, Mesalazine, Steroid, Bismuth subsalicylate	NA	NA	Improve
[30]	9	M	+	+	-	-	-	+	-	-	-	-	30-150	None	Oral iron supplementation	2	NA	NA
[21]	11	M	-	+	-	-	-	+	-	-	-	-	50-69	None	None	8	Moderate decrease	NA

[10]	11	M	+	+	-	-	-	+	-	-	-	NA	> 10	NA	Proton-pump inhibitor, Oral iron supplementation	5	Improvement of inflammation resolve of collagen band	Improve
[13]	15	M	-	-	+	-	-	+	-	-	-	-	30	30	Proton-pump inhibitor, Steroid, Mesalazine	NA	NA	Clinical remission
[17]	19	M	+	+	-	-	Perforation of ulcer	+	-	-	-	-	40	NA	Sucralfate	0.25	Improvement of inflammation decrease of collagen band	Improve
[38]	19	M	+	-	-	-	Constipation	+	-	-	-	NA	15	None	None	0.5	Progression	Improve
[31]	20	M	+	-	-	+	-	+	-	-	-	-	15-43	20-30	H2-receptor antagonist, Oral iron supplementation	4	Progression	No change
[32]	25	M	+	-	-	+	Abdominal distention	+	-	-	-	-	> 10	None	Proton-pump inhibitor	NA	NA	Improve
[33]	25	M	+	-	-	-	-	-	-	-	Normal	+	Yes	NA	None	NA	NA	NA
[17]	34	M	+	+	-	-	Gastrointestinal bleeding	+	-	-	-	-	78	NA	None	9.9	Gradual progression	NA
[33]	35	M	-	-	-	-	-	+	-	-	-	-	50	None	None	14	Increase	Increase
[21]	36	M	NA	NA	NA	NA	NA	-	-	-	NA	-	15-20	NA	None	NA	NA	NA
[35]	37	M	-	-	+	-	Body weight loss	+	-	-	-	-	120	None	Steroid, Azathioprine, Parenteral nutrition	1.67	No change	Improve
[36]	42	M	-	+	+	-	Abdominal distention, Rectal bleeding	-	+	-	-	NA	26-10	None	Gluten-free diet	0.25	No change	Improve
[9]	47	M	+	-	-	-	-	-	-	-	Normal	+	70	None	Proton-pump inhibitor	NA	NA	Improve
[17]	56	M	-	-	-	+	-	+	-	-	-	-	87	None	Steroid, Gluten-free diet	NA	NA	Improve
[3]	56	M	+	-	-	+	Body weight loss	-	-	+	-	NA	Yes	NA	NA	NA	NA	NA
[37]	57	M	-	+	+	-	-	-	+	-	-	NA	13-45	None	Steroid, Mesalazine	NA	NA	Improve
[17]	59	M	-	-	-	-	Dysphagia	-	-	-	Normal	-	54	NA	None	NA	NA	NA
[17]	68	M	-	-	+	-	-	-	-	+	-	-	20	NA	Steroid, Gluten-free diet	0.75	Gradual progression	Remain
[23]	72	M	-	-	+	-	Body weight loss	-	-	-	NA	NA	Yes	Yes	Steroid	NA	NA	Improve
[21]	77	M	-	-	-	-	-	-	-	+	-	+	20-28	NA	None	NA	NA	NA
[17]	80	M	-	+	+	-	-	+	-	-	-	-	47	None	Steroid	NA	NA	NA

NA: Not available.

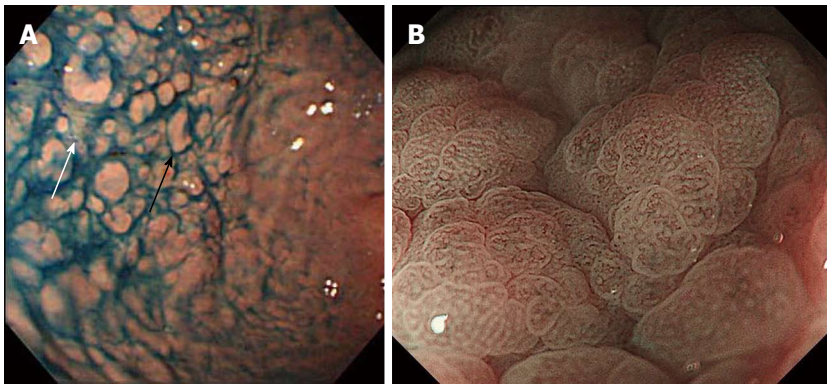

Figure 1 Endoscopic findings of collagenous gastritis. A: Nodular lesions (black arrow) in the greater curvature of the gastric body. Depressive mucosal lesions are seen in between nodular lesions (white arrow)[34]; B: Magnifying endoscopic image with narrow band imaging. Amorphous or absent surface pit pattern and abnormal capillary vessel patterns are seen in the depressed mucosal area[41].

adults, the presenting symptoms vary depending on the severity of the inflammation and the areas of the gastrointestinal tract involved.

ENDOSCOPIC FINDINGS

Nodularity of the gastric corpus is the characteristic endoscopic finding in collagenous gastritis. However, it is not seen in all cases. Our literature review found that 32 of the 60 patients showed endoscopic nodularity, with no difference in frequency between pediatric (n = 17)[4,8,10,13,15-19,21,29,30,38] and adult (n = 16)[2,17,20-22,24,31,32,34,35,39,40] cases (Table 1). The other endoscopic findings included mucosal erythema, erosions, and exudates. Normal gastric mucosa was found in 7 patients. The mucosal nodules were irregular in size and were located diffusely throughout the gastric body and antrum. The size and number depended on the severity of the inflammation (Figure 1A)[34]. Interestingly, in collagenous gastritis, it is not the mucosal thickening that causes the typical nodular appearance, but the depressed mucosa surrounding the nodules. This suggests that uneven inflammation causes glandular atrophy and collagen deposition in the depressed mucosa. Therefore, the nodular lesions show fewer inflammatory infiltrates and atrophic changes. In contrast, collagenous colitis shows a relatively even distribution of inflammation and atrophic changes, resulting in the homogeneous mucosal changes seen on the endoscopy of the colon. These findings have been supported by the recent results of narrow band imaging (NBI) studies and histological analysis. Kobayashi *et al*[41] used NBI with magnifying colonoscopy to examine the gastric mucosa in collagenous gastritis patients. The mucosal surface of the nodular lesions showed no marked changes and no abnormal capillary vessels were observed. However, as expected, the depressed mucosa surrounding these nodules showed an amorphous or absent surface structure and abnormal capillary vessels, including blind endings and irregular caliber changes (Figure 1B). This indicates that the depressed mucosal pattern is the result of inflammation with atrophic changes and collagen deposition, whereas the nodular lesions are the remaining undamaged mucosa[34].

PATHOLOGICAL FINDINGS

The pathological findings of collagenous gastritis are characterized by the infiltration of chronic inflammatory cells in the subepithelial layer, especially in the lamina propria, and the deposition of collagen bands thicker than 10 μm[13,37]. The inflammatory cells include lymphocytes, plasma cells, and eosinophils. Inflammation causes atrophic changes in the mucosal glands and leads to the depressed mucosal pattern found on endoscopy (Figure 2A)[34]. The pathological changes are less marked in the nodular mucosal lesions (Figure 2B)[34]. Therefore, a heterogeneous inflammatory pattern causes the nodular lesions in the stomach. These pathological findings suggest that several mucosal biopsies are needed for correct diagnosis, and careful mapping is required for the follow-up of mucosal inflammation and the thickness of collagen deposits. Our review found that most of the cases with information on the thickness of collagen deposits had bands thicker than 10 μm, with a range between 10 and 100 μm[11,20,30,40]. This supports the evidence for the heterogeneity of collagen deposition. The thickness of the collagen deposits may increase with disease duration; however, it may also be influenced by the location of the biopsy rather than the severity of the disease[16,17,19,21,37]. Total of 11[4,11,13,22,23,25-28] patients showed collagen deposition in colon and 7 (63%)[4,22,23,25-27] were older than 20 years old. These adult patients with coexisting collagenous colitis, showed diffuse and continuous collagen deposits in the colon but heterogeneous changes in the stomach[4]. This finding supports the hypothesis that the adult type of collagenous gastritis is part of the collagenous gastroenteritides, which tend to present with more severe symptoms related to involvement of the colon[4]. In addition, as 4 patients among 11 who showed collagenous colitis were young patients

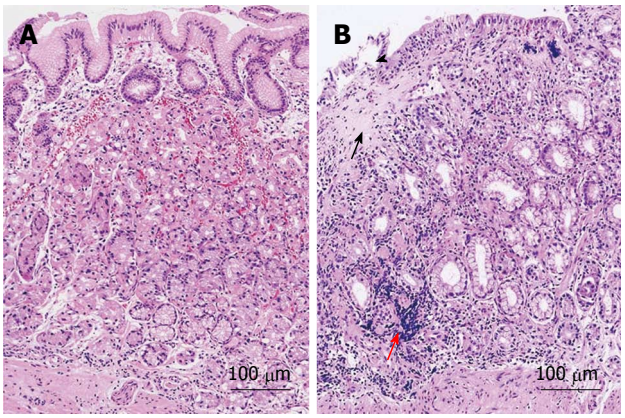

Figure 2 Histological findings of collagenous gastritis. A: Nodular mucosal lesion did not show marked inflammatory infiltration and collagen deposition; B: Depressive mucosal lesion showed a thick collagen deposition (black arrow) and inflammatory infiltrates (red arrow). The glandular atrophy and epithelial damage is marked (black arrowhead)[34].

(36%)[11,13,28], it is suggested that the disease type might not only be related to the age, but the etiology reflecting the tract involved.

Collagen deposition can be clearly visualized with Masson Trichrome staining. Collagen samples have been typed in a few patients[4,18,20,21,25], with types Ⅲ and Ⅵ identified. Some samples were positive for tenascin, a marker of cell proliferation and migration[4,42]. Type Ⅲ collagen is released from subepithelial fibroblasts to repair damage caused by inflammation. Therefore, the collagen synthesis in collagenous gastritis is not a primary pathology but a reparative response[4]. The study focusing on the collagen tissue type may contribute to clarify the etiology and help to differentially diagnose adult and pediatric types. The pathological findings reported in the published cases support the evidence that the endoscopic finding of nodularity is the result of heterogeneous inflammation and the destruction of mucosal glands and the surrounding mucosa (Table 2). However, the reason for the uneven inflammation in the stomach, in contrast to the relatively homogeneous inflammation in the colon, remains unclear.

THERAPY

Because of the small number of patients and the unknown etiology, there is no established standard therapy for collagenous gastritis. Anti-secretary agents including proton-pump inhibitors[2,4,9-11,13,15,17-20,26,29,32,39,40], and H2-receptor antagonists[4,8,18,39,40], steroids[11,13,17,19,21-23,25,28,29,35,37], iron supplementation[2,4,10,12,13,16,19,30], and hypoallergenic diets[4,17,36] have been tried with limited success (Table 1). Other treatment modalities, such as sucralfate[8,11,17,18], mesalazine[13,14,29,37], bismuth subsalicylate[29], furazolidone[8], sulfasalazine[21,24], azathioprine[35], and parenteral nutrition[21,28,35] have also been tested. A few patients have shown improvement of the clinical symptoms but no randomized, controlled trials have been performed. Further cases are needed to establish a standard therapeutic strategy. However, potential therapeutic approaches are complicated by the possibility that the pediatric and adult forms of the disease may have different etiologies. Furthermore, it remains unclear whether the pediatric type transforms to the adult type over time.

Table 2 Difference of mucosal pattern

Nodular mucosa	Depressive mucosa
No significant inflammation	Infiltration of inflammatory cells
Irregular distribution	Atrophic glands
Irregular size	Collagen band
Normal mucosal surface pattern	Amorphous or absent surface structure
	Abnormal capillary vessels

FOLLOW UP

The course and prognosis of collagenous gastritis remain unclear. The case reports include 30 patients who had undergone follow-up (Table 1). The median follow-up period was 2 years (0.08-14) and the clinical course and the response to therapy was evaluated. Kamimura *et al*[34] reported that in a patient followed for 14 years, the nodular appearance on endoscopy became more conspicuous and extended throughout the stomach. Histology showed that the thickness of collagen deposits increased over the 14 years. As discussed above, the heterogeneity of inflammation affects the thickness of the collagen deposits. Therefore, it is difficult to conclude that the collagen bands did become thicker. However, Billiemaz *et al*[28] reported similar endoscopic and histological findings of gradual disease progression during long-term follow-up. Conversely, Winslow *et al*[18] found no changes in the nodular appearance on endoscopy during the 12 year follow-up of one patient. Over the same 12 year period, biopsies showed patchy, chronic active gastritis with gradual progression in disease severity, although the collagen deposits did not appear to become more diffusely distributed or thicker over time. Lagorce-Pages *et al*[21] reported on 2 patients who showed complete absence of collagen deposits (40-year-old female) or a moderate decrease (11-year-old male) in the thickness of subepithelial collagen deposits on biopsy obtained 2 and 8 years after the initial diagnosis, respectively. The patient who recovered had been treated with steroid, salazopyrin, and parenteral alimentation. Hijaz *et al*[10] also reported on a patient who showed improvement of inflammation and an absence of collagen deposits 5 years after the initial diagnosis. This patient was treated with oral iron supplementation and proton-pump inhibitors[10]. Leung *et al*[17] reported a case of a 19-year-old male

Table 3 Differences of adult and pediatric type of collagenous gastritis

	Pediatric type	Adult type
Etiology	Unknown	Systematic disease, Autoimmune disease, drug induced
Gastrointestinal tract involved	Stomach	Stomach, colon, duodenum
Symptoms	Abdominal pain, anemia	Diarrhea
Endoscopy	Heterogeneous, Nodular pattern,	Homogeneous
Histology	Heterogeneous inflammatory infiltration, collagen band	Homogeneous inflammation

who showed improvement of inflammation and a decrease in the thickness of collagen deposits 3 mo after treatment with sucralfate[17]. On the other hand, Vakiani *et al*[22] and Rustagi *et al*[2] reported on patients who showed improvement of inflammation but unchanged or thicker collagen deposits after treatment with steroids and budesonide for 1.5 years, and oral iron supplementation and a proton-pump inhibitor for 0.83 years. These reports suggest that the inflammation can be managed by treatment. However, in most cases, the collagen deposits remain unchanged or become thicker as a result of continued inflammation. There was no evidence of the transformation of the pediatric-type disease to adult-type among the case reports.

DISCUSSION

Collagenous gastritis is a rare clinicopathological entity with only 60 cases reported to date[2-4,8-40] (Table 1). Although a primary vascular abnormality causing increased vascular permeability and collagen deposition has been proposed, the etiology of the disease is poorly understood[10]. The symptoms vary depending on the area of gastrointestinal tract involved, and in young patients, abdominal pain and anemia occur secondary to stomach-specific infiltration. Multiple areas are involved in adult patients, who often show chronic diarrhea because of coexisting collagenous colitis[3,5,6,21]. Characteristic differences are summarized in Table 3 and our review supports this hypothesis. Of the 11 patients who presented with abdominal pain and anemia, 8 were teenagers (72%)[4,8,10,14,17,30]. Conversely, of the 18 patients who presented with diarrhea, 83% (15 patients) were adults[17,21-27,35-37]. This suggests that adult-type collagenous gastritis is part of the collagenous gastroenteritides disease entity. The endoscopic findings include relative nodular changes in the mucosa, due to the chronic inflammatory infiltration, mucosal atrophy, and the deposition of bands of collagen. Compared with the diffuse and continuous deposition seen in collagenous colitis, the changes in collagenous gastritis are heterogeneous. The reason for this heterogeneity remains unclear, but it might be related to the etiology of gastritis. In addition, as 4 among 11 patients who had collagenous colitis were young patients[11,13,28], it is suggested that the disease type might not only be related to the age, but the etiology reflecting the tract involved.

Compared with collagenous gastritis, more patients are diagnosed with collagenous colitis. In these patients, adult-type collagenous gastritis may coexist. Therefore, upper endoscopy is recommended. In addition, multiple mucosal biopsies are needed because of the heterogeneous inflammatory pattern. Some areas of the stomach may show normal mucosa and our review identified 7 patients with endoscopically normal mucosa. Currently, transition from pediatric-type to adult-type disease is thought to be rare. However, more cases are needed to better understand this disease entity and to establish a standard therapeutic strategy.

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MINIREVIEWS

Endoscopic treatment of difficult extrahepatic bile duct stones, EPBD or EST: An anatomic view

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Abstract

Large bile duct stone (> 10 mm) or multiple stones (≥ 3) are challenging for endoscopists. Endoscopic sphincterotomy (EST) is a routine therapeutic endoscopic retrograde cholangiopancreatography (ERCP) procedure usually used. It is safe and effective, but severe perforation or massive bleeding are the main causes of mortality. Because of the permanent destroy of Oddi sphincter, the use of EST is still controversial. Endoscopic papillary balloon dilation (EPBD) gives another way to open the sphincter. Less incidence of bleeding, perforation and partly preserving the Oddi sphincter's function are the main advantages. But high incidence of post-ERCP pancreatitis becomes a predominant problem. According to the anatomical feature of Oddi sphincter, limited EST + EPBD seems a more reasonable procedure. Compared to the former two procedures, it makes the stone extraction process much easier with lower incidences of short-term and long-term complications.

Key words: Endoscopic retrograde cholangiopancreatography; Common bile duct stone; Endoscopic sphincterotomy; Endoscopic papillary balloon dilation

Core tip: This review describes endoscopic sphincterotomy (EST), endoscopic papillary balloon dilation (EPBD) and limited EST + EPBD in the treatment of difficult bile duct stones. We analyze the advantages and disadvantages of these procedures from a unique anatomic view. Limited EST + EPBD may be the most reasonable procedure with the highest successful rate and the lowest incidence of complications.

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INTRODUCTION

Endoscopic sphincterotomy (EST) which was developed from the 70's of last century has been widely used in

therapeutic endoscopic retrograde cholangiopancreatography (ERCP) for a few decades. It is a safe and effective method for the treatment of extrahepatic bile duct stones. Although the short-term complications are decreased with the development of technique and equipment, massive bleeding and perforation are still the main causes for patients' death. As an operation which destroys the Oddi sphincter permanently, the use of EST is controversial. The long-term complications, such as intestinal content reflux, biliary tract inflammation and stone recurrence, are the grounds of argument for those who object the use of EST. In 1982, Staritz treated common bile duct stones by endoscopic papillary balloon dilation (EPBD) successfully. Since then, many authors published reports on the benefits of EPBD and their outcome were almost comparable to EST. Compared with EST, EPBD was easier to operate and of less incidence of bleeding and perforation. Most of all, it might preserve the function of the Oddi sphincter. But soon the high incidence of post ERCP pancreatitis (PEP) reported by DiSario *et al*[1] and his colleagues after a series of multicenter studies questioned the value of this technique. Their results showed that 15%-20% patients developed PEP after EPBD and 2 patients died of severe pancreatitis and EPBD was the only reason for PEP. Incomplete dilation of the papilla, intramucosal bleeding and local edema were thought to be the main causes. Due to the high risk of PEP, most of the endoscopists in North America abandoned this method. But EPBD was still used in Europe and East Asia. Recently some authors report that with large balloon ($\geqslant$ 10 mm) and long term (3 to 5 min) could prominently decreased the incidence of PEP after EPBD compared to the traditional small balloon and short term (< 1 min) procedure. More recent reports recommend the combination of limited EST + EPBD and it seems to be a more reasonable technique.

A WIDE OPENING IS CRUCIAL FOR A SUCCESSFUL STONE EXTRACTION

The treatment of a large bile duct stone (> 10 mm) or multiple stones sometimes appears to be a difficult experience for endoscopists. How to get the opening as wide as possible is the key factor for a successful treatment. To understand the difference between these 3 techniques, some further understanding should be made on the anatomy of the Oddi sphincter. It is a very complicated muscle structure which is composed of sphincter choledochus, sphincter pancreaticus, sphincter ampullae and some longitudinal bundles. In most human beings, the muscle fibers around the orifice of the papilla and the one passing through the duodenum wall are dense and thick. They are the main barrier for stone extraction like two dense rings in the papilla (Figure 1).

It is usually defined that the tunnel starts from the distal portion of the bile duct to the orifice of the papilla as the stone extraction tunnel (SET). Based upon the anatomy described above, we divide the tunnel into two segments: the distal bile duct and the intra-mural portion of the Oddi sphincter constitute the proximal segment, which contains the proximal ring, and the intra-duodenal portion of the papilla forms the distal segment which contains the distal ring around the orifice (Figure 1). EST, EPBD and limited EST + EPBD have different effects on that tunnel. Traditional EST cuts almost the entire distal segment from the orifice up close to the duodenal wall. EPBD dilates the total SET. Limited EST opens the distal portion of the intraluminal papilla and at the same time EPBD dilates the rest portion. Analyzing based on our "2-ring" theory, EST opens the distal ring, shortens SET while does nothing on the proximal ring. EPBD dilates the entire SET including 2 rings but keep the whole structure intact. Limited EST + EPBD cut the distal ring to shorten SET and dilate the proximal ring as well. So the combination procedure may be better to access a wide opening of SET from the anatomical view.

Poincloux *et al*[2] studied 64 cases of limited EST + EPBD for difficult bile duct stones retrospectively. The successful rate in the first attempt was 95.3% without the use of mechanical lithotripsy (ML). Stefanidis *et al*[3] did a prospective study on EST + EPBD and EST + ML for the treatment of large stones (> 12 mm). There was no difference between the two groups of the successful rate in the first attempt (97.7% *vs* 91.1%, $P > 0.05$). It was concluded that EST + EPBD decreased the frequency of ML usage. Another RCT study[4] shows that there's no difference on the successful rate between limited EST+EPBD and EST group. However, the frequency of ML usage is much lower in the former group (28.8% *vs* 46.2%, $P = 0.028$) and the difference becomes more prominent when the diameter of the stones are beyond 15 mm (58.1% *vs* 90.9%, $P = 0.002$).

Reviewing the recent 5-year reports on simple EPBD in treating difficult bile duct stones, the successful rate in the first attempt was 65.8%-92.7% and ML was frequently used[5-8], which indicates the effects are not as good as EST and EST + EPBD.

MORE PATENT THE PANCREATIC OUTFLOW, LESS POST-ERCP PANCREATITIS

Although most of post-ERCP pancreatitis (PEP) cases are mild, it is a common early complication after ERCP intervention. Studies on early EPBD treatment showed a higher incidence of PEP when compared with EST, especially for the severe PEP. Obstruction of the outflow of pancreas aroused by intra-mucosa bleeding and/or local edema after EPBD is assumed to be the main cause. But some authors think that the procedures before EPBD, such as difficult cannulation, guidewire runing into the pancreatic duct repeatedly, opacification of the pancreatic duct or even ML are the

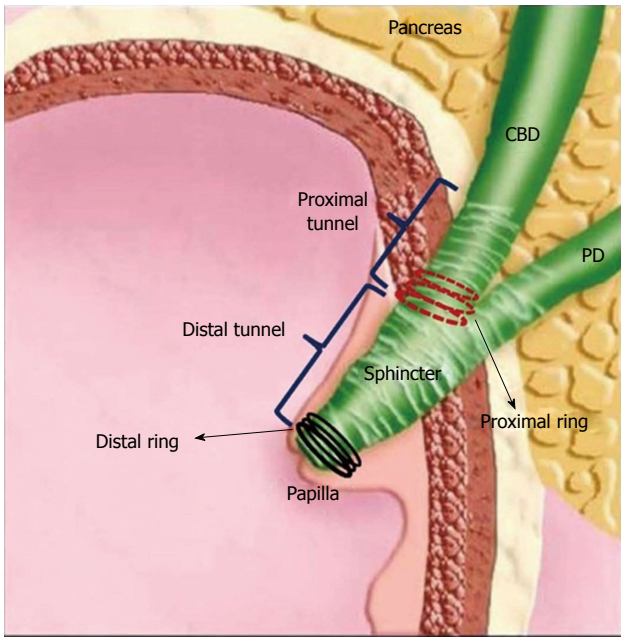

Figure 1 The anatomy of Oddi sphincter and stone extraction tunnel.

key factors for PEP. To prove this hypothesis, Seo *et al*[9] designed an interesting study. Fifty-six antegrade balloon dilation of the papilla through the PTCD method were done for the treatment of common bile duct stones. Two hundred and eight cases of EPBD of the same period were put into the control group. Except for 4 cases of hyperamylasemia, there was no pancreatitis in the experimental group, but the PEP and hyperamylasemia rate was 6.7% (including 1 severe type) and 29.8% respectively in control group. But this hypothesis can't explain why there is a lower incidence of PEP in the EST group when the similar pre-EPBD procedures exists. Reviewing some early reports on EPBD, we can find that the incidence of PEP was as high as 15%-20%. Most of these studies utilized short-term (< 1 min) dilation of the Oddi sphincter with small diameter balloons. Incomplete dilations brought difficulties in stone extraction and resulted in high incidence of ML usage. The subsequent intra-mucosa bleeding and/or local edema around the pancreatic orifice became the main cause of pancreatic outflow obstruction and thus PEP. Comparing to the incomplete short-term dilation with small balloons, EST shortens SET and makes a wider opening which facilitates stone extraction. Therefore, it leads to less edema and eventually a lower incidence of PEP.

Recently, there has been a great development in the EPBD therapy. Long term (3-5 min) dilation with large balloon (12-20 mm) is replacing the old method. Complete dilation results in a total paralysis of the sphincter. It not only makes the extraction easier, but also guarantees a patent bilio-pancreatic outflow for a period of time. Limited EST with long-term large balloon dilation is more widely accepted now, especially in East Asia. This operation is recommended for that it not only opens the distal ring to shorten SET, but also dilates the proximal ring. The bilio-pancreatic outflow is more patent than that made by EST because EST has done nothing to the proximal ring. Although it is called "limited", the cutting edge can usually reach or even exceed the pancreatic orifice. So the subsequent balloon stress maybe only focused on the proximal ring, which may alleviate the extent of edema around the pancreatic orifice.

The recent reports on large balloon and long-term EPBD with or without EST indicate that the incidence of PEP is 5% and there's no significant difference when compares to EST. Park *et al*[10] published a multicenter retrospective studying which EPBD with or without limited EST were used to treat 964 cases of large (> 10 mm) common bile duct stones. Their result confirms that the incidence of PEP has an inverse correlation to the diameter of the balloon. We don't agree that "the bigger, the better" can be the principle for choosing a balloon caliber. The common consensus is that the adequate diameter of a balloon should at least be equal to that of the biggest stone. Furthermore, EPBD is not recommended for the patients without bile duct dilation and those with distal bile duct stricture[10].

LESS CUTTING, LESS BLEEDING AND LESS PERFORATION

The incidence of bleeding after EST is about 0.8%-2%. Radiologic intervention or surgery may be necessary when massive bleeding occurs. Cirrhosis, coagulopathy and anti-coagulant taking are the contraindications for EST. The early purpose of replacing EST with EPBD is to avoid bleeding and perforation. In Japan, Takahara *et al*[11] reported a 37-case group of bile duct stone patients who were undertaking hemodialysis. Only 2 (5.4%) patients developed bleeding after EPBD. When reviewing the recent Meta-analysis comparing EST and EPBD, it is showed that EST has a higher incidence of bleeding.

According to the anatomy of vessel distribution around Oddi sphincter, the small vessels are usually located at the roof of the papilla just close to the duodenal wall. The territory from 11 o'clock to 1 o' clock direction is recommended for a safe EST. In order to get a large outlet for stone extraction, total EST is recommended to extend the incision up close to the duodenal wall, as a result bleeding cannot be totally avoided. Limited EST only cut the distal ring and leave the proximal portion intact to keep a distance from these vessels, so bleeding is rare. Park's *et al*[10] study demonstrated this hypothesis. They found that complete EST or limited EST is the independent factor that influences the incidence of post-operative bleeding (OR 6.22, $P < 0.001$).

Although the incidence of bleeding after EPBD or limited EST + EPBD is low, the result is unacceptable. Excessive cutting, distal bile duct stricture or inadequate use of a large balloon are the main factors for tearing the mucosa of the lower bile duct apart.

Because the location of the bleeding vessels is very high as described, the uncut structure after EPBD or limited EST + EPBD prevent the endoscopists from visualizing the bleeding point directly under the scope. And finally, there may be multiple bleeding exists when the mucosa is torn apart. These factors make the diagnosis and treatment much challenging. Recurrent hemorrhage is common after radiologic intervention or even surgery. Fully covered metal stent maybe useful in this situation.

IS ODDI SPHINCTER WORTH PROTECTING IN CHOLEDOCHOLITHIASIS?

Besides the advantages for less bleeding and less perforation, preserving the function of Oddi sphincter is another goal of EPBD. According to Kojima's[12] excellent manometry study on patients' sphincter before and after EPBD, he concluded that 70% of the sphincter function was preserved after EPBD.

Changes of bile composition and bacterial infection are well-known causes for bile duct stone formation. But little is known in present about the role of biliary dynamics. We believe that it takes great part in the pathogenesis of choledocholithiasis or even cholecystolithiasis.

The normal functions of Oddi sphincter are: (1) to provide a patent pathway for bile excretion; and (2) to prevent bowel reflux. Either disorder in these 2 aspects may result in stone formation. If the etiology is due to an inadequate patency, EST maybe the correct choice; while if bowel reflux is the main problem, such as the para-papilla diverticulum, it may be more reasonable to do EPBD. Some further evidence-based studies was needed on these interesting topics. But above all, development in atraumatic and repeatable diagnostic methods to evaluate the status of Oddi sphincter was looking forward.

CONCLUSION

In summary, EST + EPBD is a reasonable procedure for difficult bile duct stones. It makes a wide opening of the Oddi sphincter to ensure a high success rate of stone extraction with lower incidence of PEP, bleeding and perforation. The long-term results need further researches on the dynamics study of the biliary tract, especially the Oddi sphincter.

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ORIGINAL ARTICLE

Retrospective Study

Rotational assisted endoscopic retrograde cholangiopancreatography in patients with reconstructive gastrointestinal surgical anatomy

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Author contributions: All authors helped equally in: Substantial contributions to the conception or design of the work including the acquisition, analysis, and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval: The study was reviewed and approved by the Duke University Health System (DUHS) Institutional Review Board (IRB).

Informed consent: The study is a retrospective review. Only general demographic information in regards to the patients was obtained. No informed consent was obtained from involved persons. A waiver of consent was filled and approved by DUHS IRB.

Conflict-of-interest: All authors declare that there is no conflict of interest.

Data sharing: No additional data are available.

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Abstract

AIM: To evaluate the success rates of performing therapy utilizing a rotational assisted enteroscopy device in endoscopic retrograde cholangiopancreatography (ERCP) in surgically altered anatomy patients.

METHODS: Between June 1, 2009 and November 8, 2012, we performed 42 ERCPs with the use of rotational enteroscopy for patients with altered anatomy (39 with gastric bypass Roux-en-Y, 2 with Billroth Ⅱ gastrectomy, and 1 with hepaticojejunostomy associated with liver transplant). The indications for ERCP were: choledocholithiasis: 13 of 42 (30.9%), biliary obstruction suggested on imaging: 20 of 42 (47.6%), suspected sphincter of Oddi dysfunction: 4 of 42 (9.5%), abnormal liver enzymes: 1 of 42 (2.4%), ascending cholangitis: 2 of 42 (4.8%), and bile leak: 2 of 42 (4.8%). All procedures were completed with the Olympus SIF-Q180 enteroscope and the Endo-Ease Discovery SB overtube produced by Spirus Medical.

RESULTS: Successful visualization of the major ampulla was accomplished in 32 of 42 procedures (76.2%). Cannulation of the bile duct was successful in 26 of 32 procedures reaching the major ampulla (81.3%). Successful therapeutic intervention was completed in 24 of 26 procedures in which the bile

duct was cannulated (92.3%). The overall intention to treat success rate was 64.3%. In terms of cannulation success, the intention to treat success rate was 61.5%. Ten out of forty two patients (23.8%) required admission to the hospital after procedure for abdominal pain and nausea, and 3 of those 10 patients (7.1%) had a diagnosis of post-ERCP pancreatitis. The average hospital stay was 3 d.

CONCLUSION: It is reasonable to consider an attempt at rotational assisted ERCP prior to a surgical intervention to alleviate biliary complications in patients with altered surgical anatomy.

Key words: Gastric bypass; Gastrostomy; Cholangiopancreatography; Endoscopic retrograde; Double-Balloon enteroscopy; Ampulla of vater; Sphincterotomy; Endoscopic; Pancreatitis; Retrospective studies

Core tip: This manuscript shows a single tertiary care center experience in a large number of patients with surgically altered anatomy by evaluating the success rates of reaching the major ampulla, cannulating the bile duct, and subsequently performing therapy utilizing a rotational assisted enteroscopy device in an endoscopic retrograde cholangiopancreatography. This study will also determine the associated morbidity, mortality, and length of hospitalization associated with the procedures. Given our institutions success rates and minimal complication profile, specialized centers could consider this approach in this rapidly growing population. This will be instrumental in the development of new therapeutic options for patients suffering from this condition.

Zouhairi ME, Watson JB, Desai SV, Swartz DK, Castillo-Roth A, Haque M, Jowell PS, Branch MS, Burbridge RA. Rotational assisted endoscopic retrograde cholangiopancreatography in patients with reconstructive gastrointestinal surgical anatomy. *World J Gastrointest Endosc* 2015; 7(3): 278-282 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i3/278.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i3.278

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) remains the gold standard in both diagnosis and therapeutic management of pancreato-biliary diseases. However, patients with surgically altered anatomy present a unique endoscopic challenge. In patients with normal anatomy, rate of successful cannulation and sphincterotomy by expert endoscopists is greater than ninety percent[1]. In patients who have had reconstructive gastrointestinal surgery, reaching the ampulla and subsequently performing therapy during ERCP has been reported in a multicenter study to be 63%[2]. Additionally, as the obesity epidemic has widened in the United States, patients with altered anatomy due to bariatric surgery are increasingly presenting with the need for evaluation for pancreato-biliary disease[3].

Multiple methods have been described to gain access to the biliary tract in post surgical patients, which is particularly challenging because the standard duodenoscope cannot reach the ampulla due to increased distance of the Roux limb. Methods to gain biliary access with a standard duodenoscope, such as a surgically created gastrostomy have been previously described[4-6]. Non-surgical endoscopic methods using different types of enteroscopy techniques have also been described. These endoscopic techniques include double-balloon, single-balloon, and rotational assisted-ERCP (RA-ERCP)[7-9].

The goal of this retrospective study is to review a single tertiary care center experience in RA-ERCP in patients with reconstructive gastrointestinal surgery. Outcomes measured include the success rates of reaching the major ampulla, cannulating the bile duct, and subsequently performing a complete ERCP. Additionally, the associated morbidity, mortality, and length of hospitalization associated with RA-ERCP were measured.

MATERIALS AND METHODS

Study and patients

An IRB approved retrospective review of all patients undergoing rotational assisted ERCP was performed.

Between June 1, 2009 and November 8, 2012, a total of 42 RA-ERCPs were attempted for patients with altered anatomy. Thirty-three of these patients underwent Roux-en-Y gastric bypass, 2 underwent Billroth Ⅱ gastrectomy, and 1 underwent hepaticojejunostomy associated with liver transplant. A total of 6 patients had repeat procedures.

Procedures

Sedation for the procedures were either moderate sedation (9 patients) or general anesthesia (33 patients) with the positioning of all patients in the prone position. An attending advanced endoscopist performed all procedures with the assistance of the advanced endoscopy fellow. A total of 4 attending physicians with experience in rotational assisted ERCP performed the procedures.

All RA-ERCPs were performed using an Olympus SIF-Q180 enteroscope and the Endo-Ease Discovery SB overtube manufactured by Spirus Medical.

Patients were not randomized, as the procedure was chosen based on availability and physician discretion. Procedural time for RA-ERCP was determined from the onset of the "time-out" patient verification to the time

Table 1 Patient characteristics

No. of patients	36
No. of ERCPs	42
Age	49.3
Sex	M = 2, F = 34
BMI	36.3
Roux-en-Y surgery patients	33
Billroth Ⅱ surgery patients	2
Hepaticojejunostomy associated with liver transplant	1

M: Male; F: Female; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 2 Indications for endoscopic retrograde cholangiopancreatography

Suspected gallstones/choledocholithiasis	13
Sphincter of Oddi dysfunction Ⅰ / Ⅱ	1/3
Biliary obstruction on imaging	20
Ascending cholangitis	2
Biliary obstruction with negative imaging	1
Bile leak	2

the patient arrived in the recovery bay.

Statistical analysis

The statistical methods of this study were reviewed by Majed El Zouhairi, MD and Rebecca Burbridge, MD from Duke University Medical Center.

RESULTS

Rotational enteroscopy was performed in forty-two separate procedures, in thirty-six patients with altered anatomy. Thirty-four patients were women (94.4%) and the mean age was 49.3 (range 29-75) (Table 1). The indications for ERCP were: biliary obstruction suggested on imaging 20 of 42 (47.6%), choledocholithiasis 13 of 42 (30.9%), suspected sphincter of Oddi dysfunction 4 of 42 (9.5%), ascending cholangitis 2 of 42 (4.8%), bile leak 2 of 42 (4.8%), and abnormal liver enzymes 1 of 42 (2.4%) (Table 2). The ability to reach and visualize the major ampulla was successful in 32 of 42 procedures (76.2%) (Figure 1). Attempted cannulation of the bile duct was performed in 29 out of the 32 procedures which successfully reached the major ampulla, with a subsequent bile duct cannulation rate of 89.7% (Figure 2). No attempt was made to cannulate the bile duct in three patients because procedures were only intended to remove previously placed stents. The reason for failed cannulation in the three patients in whom we were not able to cannulate the bile duct despite reaching the ampulla was an ampullary polyp (1 patient) and biliary stricture (2 patients). Successful therapeutic intervention including, but not limited to, sphincterotomy, stone removal, bile duct/pancreatic duct stent placement, balloon sweeping, and brushing was completed in 24 of 26 procedures

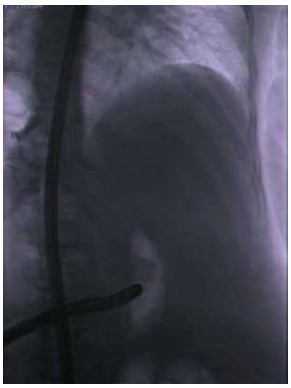

Figure 1 Scout film with the positioning of the scope.

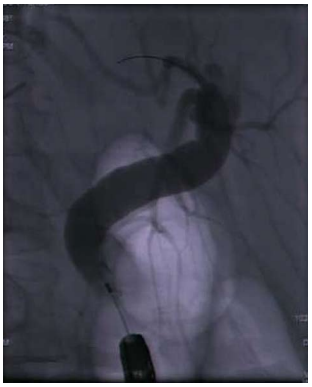

Figure 2 Cholangiogram.

in which the bile duct was cannulated (92.3%) (Figure 3). Of the total 42 cases, there were 15 failed cases, and 27 successful procedures, therefore the overall intention to treat success rate was 64.3%. In terms of cannulation success, 24 of 39 attempts at cannulation were successful, with an intention to treat success rate of 61.5%.

Ten patients out of 42 procedures (23.8%) required hospital admission for abdominal pain and nausea following the procedure. Three of those 10 patients (7.1%) had a diagnosis of post-ERCP pancreatitis. The average hospital stay was 3 d (Table 3). There were no overtube related complications.

DISCUSSION

Surgically altered anatomy has become increasingly more common in the United States, particularly due to bariatric surgery. Reaching the ampulla in patients with surgically altered anatomy remains challenging even for skilled endoscopists despite advances in deep small bowel enteroscopy. Currently, the standard of care for pancreato-biliary disease in these patients often involves surgical assistance to help access the major ampulla. Success rates with single-balloon[10-13] and double-balloon enteroscopy systems[2,14-19] have been reported to range from 60% to 88%[2]. In limited studies, RA-ERCP has been shown to be a promising

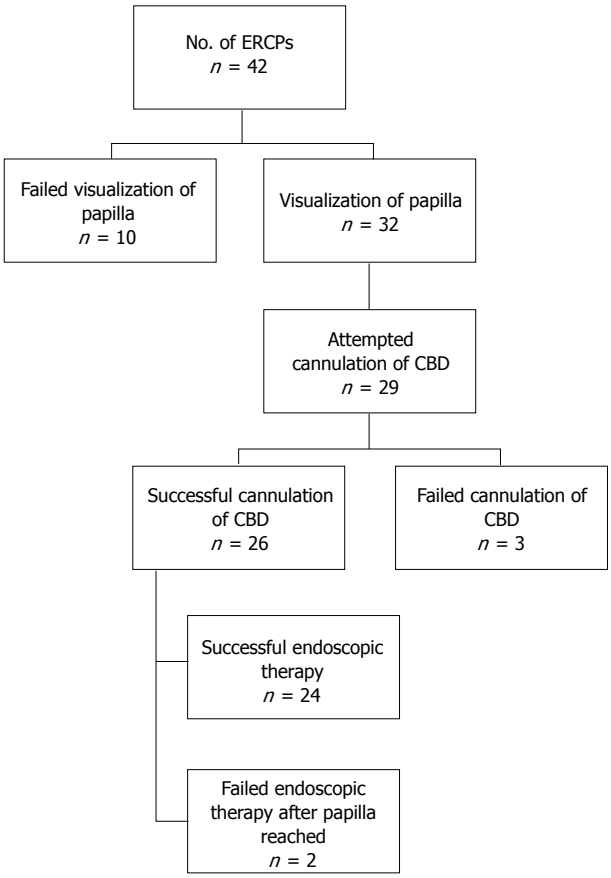

Figure 3 Outcomes. ERCP: Endoscopic retrograde cholangiopancreatography.

technique for pancreato-biliary access in post surgical patients. Hegde *et al*[7] reported that RA-ERCP allowed successful cannulation in 2 patients after double-balloon assisted ERCP had failed, but that it was more time-consuming. Al-Lehibi *et al*[8], also noted that RA-ERCP was successful in 5 of 6 cases. A recent prospective study reported in 2012 by Wagh *et al*[9] on 13 patients showed that cannulation of the desired duct and endoscopic therapy using RA-ERCP in patients with surgically altered anatomy was successful in 90% of the procedures if the papilla/duct-enterostomy was reached.

A recent multi-center retrospective study published in January 2013 by Shah *et al*[2] compared ERCP success in 129 patients with surgically altered anatomy utilizing single-balloon (SBE), double-balloon (DBE), or rotational overtube enteroscopy. Fifty-seven RA-ERCP cases were performed with an intention to treat success rate of 63%, defined as successful planned therapeutic intervention. They concluded that therapeutic success in long-limb surgical bypass was similar irregardless of the endoscopic method used.

Our study is the largest single-center experience evaluating RA-ERCP in patients with reconstructed gastrointestinal anatomy. We noted RA-ERCP procedural success rate in visualizing the ampulla of 76.2%, cannulating the bile duct in procedures reaching the major ampulla of 81.3%, and successfully completing

Table 3 Complications

Adverse events	10
No. of admission	10
Length of hospital stay after admission (d)	3

therapeutic interventions after cannulating the major ampulla of 92.3% with an overall intention to treat success rate of 61.5%. This seems consistent with the rate published by Shah *et al*[2], and would suggest that RA-ERCP is on par with other non-surgical endoscopic techniques.

Limitations of this study include the lack of direct comparison with other deep enteroscopy techniques. A second limitation is that all procedures were performed in a tertiary-care center which may not be generalizable to smaller gastroenterology practices which serve a local community. Additionally, the strength of one specific endoscopic technique for non-ERCP enteroscopy has not been consistently demonstrated. The concept that experience may play an important role in success is supported by data from the non-ERCP enteroscopy literature. For example the efficacy of double balloon compared to rotation assisted enteroscopy is still debatable and experience in either modality may be more important than the type of enteroscopy modality chosen[20-22].

Given our institution's success rates and minimal complication profile, we believe it is reasonable to consider an attempt at rotational assisted ERCP prior to a surgical intervention to evaluate pancreato-biliary diseases in patients with altered surgical anatomy. Our data, as well as other smaller studies, have confirmed the safety and relative efficacy of this approach. In determining the method of endoscopic approach to ERCP in post surgical patients, relative experience with other enteroscopy modalities such as DBE or SBE should also be considered.

COMMENTS

Background

Endoscopic retrograde cholangiopancreatography (ERCP) has been a mainstay in the diagnosis and management of pancreato-biliary diseases. With the use of a standard duodenoscope, success rates are greater than ninety percent in patients with normal gastrointestinal anatomy. However, reaching the ampulla and subsequently performing therapy during ERCP is difficult in patients with surgically altered anatomy. Utilizing a rotational enteroscopy device to assist in reaching the ampulla in this population may increase the chances of being able to successfully complete the procedure.

Research frontiers

There have been only a few small number of studies examining the use of RA-ERCP in approaching biliary complications in patients with Roux-en-Y gastric bypass surgery.

Innovations and breakthroughs

This manuscript shows a single tertiary care center experience in a large number of patients with surgically altered anatomy by evaluating the success rates of reaching the major ampulla, cannulating the bile duct, and subsequently performing therapy utilizing a rotational assisted enteroscopy device in order to complete an ERCP. This study will also determine the associated morbidity, mortality, and length of hospitalization associated with the procedures.

Applications

Surgically altered anatomy has become increasingly more common in the United States, particularly due to bariatric surgery. Currently, the standard of care for pancreatico-biliary complications in these patients often involves surgical assistance to help access the major ampulla. Given our institutions success rates and minimal complication profile, the authors believe it is reasonable to consider an attempt at rotational assisted ERCP prior to a surgical intervention to alleviate biliary complications in patients with altered surgical anatomy.

Terminology

ERCP; rotational assisted-ERCP (RA-ERCP); single-balloon enteroscopy (SBE); double-balloon enteroscopy (DBE).

Peer-review

This paper is interesting.

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SYSTEMATIC REVIEWS

Endoscopic ultrasound-guided biliary intervention in patients with surgically altered anatomy

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Abstract

AIM: To evaluate the efficacy of endoscopic ultrasound guided biliary drainage (EUS-BD) in patients with surgically altered anatomies.

METHODS: We performed a search of the MEDLINE database for studies published between 2001 to July 2014 reporting on EUS-BD in patients with surgically altered anatomy using the terms "EUS drainage" and "altered anatomy". All relevant articles were accessed in full text. A manual search of the reference lists of relevant retrieved articles was also performed. Only full-text English papers were included. Data regarding age, gender, diagnosis, method of EUS-BD and intervention, type of altered anatomy, technical success, clinical success, and complications were extracted and collected. Anatomic alterations were categorized as: group 1, Billroth Ⅰ; group 2, Billroth Ⅱ; group 4, Roux-en-Y with gastric bypass; and group 3, all other types.

RESULTS: Twenty three articles identified in the literature search, three reports were from the same group with different numbers of cases. In total, 101 cases of EUS-BD in patients with altered anatomy were identified. Twenty-seven cases had no information and were excluded. Seventy four cases were included for analysis. Data of EUS-BD in patients categorized as group 1, 2 and 4 were limited with 2, 3 and 6 cases with EUS-BD done respectively. Thirty four cases with EUS-BD were reported in group 3. The pooled technical success, clinical success, and complication rates of all reports with available data were 89.18%, 91.07% and 17.5%, respectively. The results are similar to the reported outcomes of EUS-BD in general, however, with limited data of EUS-BD in patients with altered anatomy rendered it difficult to draw a firm conclusion.

CONCLUSION: EUS-BD may be an option for patients with altered anatomy after a failed endoscopic-retrograde-cholangiography in centers with expertise in EUS-BD procedures in a research setting.

Key words: Endoscopic ultrasound-guided anterograde approach; Endoscopic ultrasound-guided biliary drainage; Endoscopic ultrasound-guided choledochoduodenostomy; Endoscopic ultrasound-guided hepaticogastrostomy; Endoscopic ultrasound-rendezvous technique; Surgically altered anatomy; Overtube-assisted enteroscopy-endoscopic retrograde cholangiopancreatography

Core tip: Endoscopic retrograde cholangiopancreatography (ERCP) in patients with surgically altered anatomy is challenging, with a failure rate as high as 26%. Data of endoscopic ultrasound-guided biliary drainage (EUS-BD) in patients with altered anatomy from the literature show a similar efficacy to that of EUS-BD in general. EUS-BD may be selected as an alternative for patients with altered anatomy who failed overtube-assisted enteroscopy-ERCP in centers where the expertise in EUS-BD is available. However, the EUS-BD approach should be performed in a research setting based on the current stage of EUS-BD techniques.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) has been widely accepted as a standard procedure with a high success rate for the management of biliary disorders[1]. However, conventional ERCP in patients with surgically altered anatomy is technically difficult, and is accompanied by a relatively high rate of complications. In large case series, technical failures varied from 13% to 67%, and the rate of perforation was as high as 18%, with a mortality rate of 3%[2,3]. ERCP with overtube-assisted enteroscopy (OAE-ERCP), with a balloon or spiral overtube, achieved a success rate of approximately 74% and a 3.4% complication rate in patients with surgically altered anatomies[4]. Percutaneous transhepatic biliary drainage (PTBD) is a well-established technique that is usually selected as an alternative in patients with failed ERCP. However, despite the high clinical success rate, the PTBD approach is associated with 0.5%-15% morbidity and 0%-4.9% mortality rates[5].

Endoscopic ultrasound-guided biliary drainage (EUS-BD) was first reported in 2001 by Giovannini *et al*[6]. Subsequently, many groups reported the utilization of EUS-BD with various approaches as an alternative biliary drainage for failed ERCPs, with an average success rate varying from 77% to 94% and complication rate of 19%-27%[7]. This method may be an option for patients with altered anatomy for whom OAE-ERCP is difficult, as reflected by a high failure rate (26%)[4]. However, the role of EUS-BD in patients with altered anatomy and failed ERCP is not well defined, and the suitability of this as an alternative drainage procedure is unclear. This review analyzes the clinical efficacy, complications, clinical implication, and limitations of EUS-BD in patients with surgically altered anatomy from data available in the literature.

MATERIALS AND METHODS

A PubMed search of the MEDLINE database was conducted for articles published between 2001 and July 2014 using the terms "EUS drainage" and "altered anatomy". A manual search of the reference lists of relevant retrieved articles was also performed. Only full-text English papers were included. The computerized endoscopic data at our center were also searched for additional cases of EUS-BD in altered anatomy conducted after our published data[8]. Data regarding age, gender, diagnosis, method of EUS-BD and intervention, type of altered anatomy, technical success, clinical success, and complications were collected.

Classification of EUS-BD techniques

The three main techniques of EUS-guided procedures for biliary drainage that were included were: anterograde EUS-BD, transluminal drainage, and the rendezvous method[7,9,10]. Anterograde EUS-BD involves intervention *via* an anterograde route across the ampulla or anastomosis. Transluminal drainage encompasses transesophageal, transgastric (hepaticogastrostomy), transduodenal (choledochoduodenostomy, EUS-CDS), or transjejunal approaches. The rendezvous method involves EUS-guided placement of a guide-wire across the ampulla or anastomosis that is exchanged with a standard duodenoscope or enteroscope to perform the intervention.

Classification of surgically altered anatomy

Anatomic alterations were categorized as: group 1, Billroth Ⅰ; group 2, Billroth Ⅱ; group 3, Roux-en-Y with pancreaticoduodenectomy (with or without a modified Child procedure), pylorus-preserving pancreaticoduodenectomy, hepaticojejunostomy, choledochojejunostomy, and total or partial gastrectomy, distal gastrectomy without specific anastomosis mentioned, and hepatic and bile duct resection; and group 4, Roux-en-Y with gastric bypass (RY-GB).

Statistical analysis

The descriptive data of age was analyzed by using Minitab 15® and no other statistical analysis was done since this study was a descriptive review.

RESULTS

EUS-BD IN patients with surgically altered anatomy

Of the 23 articles identified in the literature search, three reports were from the same group with different numbers of cases[11-13]. As no details regarding individual cases were available from these three reports, the cases with the same type of surgically

Table 1 Demographics of endoscopic ultrasound-guided biliary drainage patients with altered anatomy[8,11,14,18-32] (*n* = 74)

Characteristic	Value
Age, yr (*n* = 36)	64.14 ± 15.08
Sex, female/male (*n* = 36)	22/14
Diagnosis (*n* = 38)	
Bile duct stone	14
Benign stricture	10
Malignant stricture	11
Gastric cancer	2
Occluded stent	1
Outcome of EUS-BD, *n* (%)	
Clinical success	51 (91.1)
Complications	7 (17.5)
Technical success	66 (89.2)
EUS-BD technique with technical success, *n*	
Anterograde	28
Hepaticogastrostomy	18
Hepaticojejunostomy	2
Hepaticoesophagostomy	1
Rendezvous	3
Unavailable	14

EUS-BD: Endoscopic ultrasound-guided biliary drainage.

altered anatomy and the same diagnosis were treated as one case. In total, 101 cases of EUS-BD in patients with altered anatomy were identified. Only one report was a case series[14], all other reports were case reports or reports of EUS-BD that included normal and altered anatomy patients. Twenty-seven cases had no information and were excluded[12,15-17], leaving 74 patients with altered anatomy who underwent EUS-BD[8,11,14,18-32]. Available demographic and procedural information of these cases is presented in Table 1. Of the 40 cases reporting complications, there were incidences of mild pancreatitis (*n* = 2), mild abdominal pain (*n* = 1), hematoma (*n* = 1), cholangitis (*n* = 1), minor bleeding (*n* = 1), and surgical repositioning of a stent in the peritoneum (*n* = 1), with no mortalities.

EUS-BD in altered anatomy subtypes

The classification of altered anatomy types is listed in Table 2. In group 1, one case of EUS-BD with common bile duct (CBD) stones was reported[25], and EUS-BD was performed in one patient with distal CBD stricture at our center. Both had successful clinical outcomes. There were three cases with EUS-BD in group 2: two cases with malignant stricture and one case with a CBD stone, in whom the EUS-BD failed[11,32].

Within group 3, Roux-en-Y was performed with hepaticojejunostomy (*n* = 10), choledochojejunostomy (*n* = 1), total gastrectomy (*n* = 5), subtotal gastrectomy (*n* = 2), Whipple's operation (*n* = 6), distal gastrectomy (*n* = 2), pylorus-preserving pancreaticoduodenectomy (*n* = 5), pancreaticoduodenectomy with a modified Child procedure (*n* = 2), and hepatic and bile duct resection (*n* = 1)[8,11,14,18-32]. The diagnoses in group 3 included bile duct stones (*n* = 9), benign stricture (*n* = 9), malignant stricture (*n* = 9), occluded metallic stents placed by percutaneous route (*n* = 1), or were unspecified (*n* = 6). The success rates were in the range reported for EUS-BD in general. However, the missing data in a large proportion of patients in this group rendered it difficult to draw a firm conclusion.

Table 2 Results of endoscopic ultrasound-guided biliary drainage in altered anatomy subgroups

Group	Subtype	No. of cases	Technical success	Clinical success	Complications
1	Billroth Ⅰ	2	2	2	0
2	Billroth Ⅱ	3	2	2	0
3	Roux-en-Y	34	33 (97.0%)	23 (92.0%)	5
4	Roux-en-Y gastric bypass	6	6	5	1

Twenty-seven cases with unspecified type and no details available were excluded.

Six cases within group 4 received EUS-BD with RY-GB[33]. These patients all had CBD stones, and stone clearance was achieved with EUS-BD in five of these, with a failure in one with a hematoma.

In 27 cases that were excluded from analysis due to insufficient information[12,15-17], the overall technical success rate (including patients with altered anatomy) varied from 67.2% to 94.0%, the clinical success rate varied from 63.2% to 97.0%, and the complication rate varied from 12.0% to 23.2%.

DISCUSSION

EUS-BD vs PTBD

PTBD is a traditional alternative for patients with a failed ERCP, though it is associated with a risk of complication and significant morbidity[5]. One of the major drawbacks of PTBD is external bile loss, which leads to a decreased total bile pool. Theoretically, maintenance of enterohepatic bile circulation is important for host defense function. Kamiya *et al*[33] reported that bile replacement by oral intake of the externally diverted bile helped restore gut barrier function in patients with bile duct obstruction, but internal drainage is still more physiologic than external drainage. Moreover, the burden to the patients or family members caring for the catheter is considerable, and individuals who bathe twice daily may be disturbed by the inability to do so, thus decreasing their quality of life. In one retrospective study that compared 22 EUS-BD patients with 51 PTBD patients, the procedures showed a similar clinical success, but EUS-BD was associated with fewer adverse events and was less costly in the long term[34]. However, PTBD in their study had a 100% success rate, which was significantly higher than the 86.4% with EUS-BD. Another retrospective study compared 25 cases with EUS-BD with 26 cases with PTBD, and showed that EUS-BD was superior to PTBD in terms of success and complication rates[35]. In contrast, a prospective study showed a similar efficacy between EUS-BD performed

in 13 patients and PTBD in 12 patients[36]. Taken together, these data suggest that EUS-BD is a suitable alternative in patients with failed ERCP, and it may be an option in the centers where EUS-BD is available.

Role of EUS-BD in altered anatomy patients

The available data suggest that EUS-BD is as effective in patients with altered anatomy as in general patients. EUS-BD is still in a state of development, with proper procedural techniques under refinement. Furthermore, EUS-BD for patients with altered anatomy and failed ERCP should be assessed in a research setting to properly define its role. A standardized treatment algorithm for selection of EUS-BD techniques based on the clinical context may improve the outcome[26].

In patients with a Billroth Ⅰ operation, the straight anatomy of the stomach and duodenum cause the tip of a standard duodenoscope to come too close to the papilla, making it difficult to position the ERCP catheter along the axis of the bile duct, leading to a failed procedure in some patients[37]. In patients with Billroth Ⅱ anatomy, OAE-ERCP has an endoscopic success rate of 96% and a successful ERCP rate of 90%[4]. ERCP is the most difficult in patients with RY-GB, and OAE-ERCP has an endoscopic success rate of only 80% and successful ERCP rate of only 70%[4]. In post RY-GB patients with failed OAE-ERCP, laparoscopy-assisted ERCP may be an alternative, as the results in four publications[38-41] demonstrated a high success rate of 90%-100%. However, these studies were limited by the number of patients, longer procedure time, the need for a laparoscopic doctor, and a much higher cost of treatment. The data supporting the role of EUS-BD in groups 1, 2 and 4 were very limited, and need further evaluation.

EUS-BD may be a suitable alternative in patients with failed OAE-ERCP with altered anatomy classified as group 3. In patients with benign stricture, the accepted treatment includes extended multiple plastic stents or metallic stent placement[42-44]. Short-term outcome of EUS-BD for a small number of these patients was promising, though no long-term data is available[8,11,14,18,21,27,31]. Anterograde balloon dilation has been reported in very few cases, with a successful short-term outcome[8,14,21], and transgastric placement of multiple plastic stents across the anastomotic stricture was feasible in select patients. One patient in our report had a good long-term result after three years[8]. Because of the repeated nature of the procedures in this group for the assessment of stricture patency or insertion of an additional stent, EUS-BD with anterograde or rendezvous techniques may be initially selected as a bridging procedure in the patients with endoscopic access of the papilla or biliary anastomotic site, but failed ERCP cannulation. At present, EUS-BD in patients with benign stricture and failed OAE-ERPC access to the papilla or biliary anastomosis is challenging. In patients with malignant strictures, the same approach is applicable, but transluminal drainage is preferred, as repeated procedures may be easier using a standard endoscope. In patients with bile duct stones associated with altered anatomy and OAE-ERCP access to the papilla or biliary anastomosis with failed ERCP cannulation, EUS-BD with anterograde or rendezvous procedures may be preferred for stone removal[4,45]. EUS-BD with anterograde stone removal using balloon dilation with the stones pushed across the ampulla or anastomosis was reported in 11 patients with one failure[8,14,22], and may be an option in select patients with failed OAE-ERCP access to the papilla or biliary anastomosis. Placement of a transgastric nasobiliary drainage tube or a plastic stent to maintain access for subsequent repeated procedures was also an option[8,14]. The details of the procedure should be customized based on clinical setting.

EUS-BD as an initial modality

OAE-ERCP is increasingly used in patients with altered anatomy with more supporting data compared with EUS-BD[4,8,11,14,18-32,45], though no comparative studies are available. In patients with benign strictures, standard ERCP (for patients with Billroth Ⅰ or Ⅱ anatomy, Whipple's operation,) or OAE-ERCP is more suitable because of the likelihood for repeated procedures for additional stent placement or stent exchange. In patients with malignant strictures, EUS-BD may be an alternative to PTBD in centers with appropriate expertise when OAE-ERCP is not available, however, this should be done in a research setting. For patients with bile duct stones, OAE-ERCP may be suitable as the options for treatment of the stones are more readily available, and EUS-BD should be reserved for patients in whom this procedure fails.

Limitations of EUS-BD

As it is difficult to pass the linear EUS endoscope into the afferent limb[46], EUS-CDS is not the appropriate option for patients with altered anatomies. The EUS-BD drainage access is limited to the left biliary system, and requires the presence of a dilated ductal system. Manipulation of the guide-wire to cross a stricture or papilla may be difficult, and the guide-wire can be sheared[47,48]. As only limited data for anterograde EUS-BD were available[48], the success rate may be lower with a lower complication rate compared with other techniques[7]. EUS-hepaticogastrostomy is limited by the lack of adherence between the stomach and the liver, which may increase the risk of stent dislocation and lead to bile leak. The risk of bleeding from the liver may also increase[48]. The main limitation of the rendezvous method is the requirement of an endoscopically accessible papilla or anastomosis, which is always troublesome in cases of surgically altered anatomy. In addition, the rendezvous procedure requires exchanging the echoendoscope for a duodenoscope, during which guide-wire access can be lost[48].

The majority of the data concerning EUS-BD is reported by experts, and may not translate to clinical practice. For example, in a national study in Spain involving community endoscopists, EUS-BD had a lower success rate (67.2%) and a complication rate of 23.2%[15]. Moreover, there is no well-designed EUS-training system and training using swine models, or computer-based simulators are expensive and not accessible by all trainees[47]. This may hinder the establishment of skills in therapeutic EUS.

FUTURE DEVELOPMENTS

Most of EUS-BDs were performed with conventional fine-needle aspiration needles. The new 19-gauge blunt tip (Echo-HD; Cook Medical, Bloomington, IN, United States) may reduce catching at the needle tip during to-and-fro manipulation of a guide-wire that may reduce shearing. Needle-knife dilation was reported to increase the risk of complications in EUS-BD[49]. The tip of the needle knife may not align with the axis of the guide-wire, thus a 6 Fr catheter with diathermic ring (Endoflex, Voerde, Germany) was used in some centers[47]. A prototype compression coil and twin-headed needle may simplify the EUS-BD procedure, and shows promise for use in EUS-CDS in a study in canines[50]. The development of a forward-viewing echoendoscope allows simultaneous visualization of the endoscopic and EUS operating fields, while the perpendicular access and lack of angulation at the exit of the working channel allow for easy introduction of a 19-gauge needle and passing of the stent without indentation[51]. Although the forward-viewing echoendoscope showed a high success rate for EUS-CDS in a prospective case series[52], further studies are needed to confirm its advantage in EUS-BD. Multiple exchanges over the wire during EUS-BD may increase the risk of leakage, increase the procedure time, and increase the chance to lose guide-wire access[47]. Non-exchange systems have been evaluated in experimental animal studies[53,54], and may minimize the aforementioned drawbacks of the current EUS-BD technique when the devices are available in the future.

CONCLUSION

EUS-guided biliary intervention is technically feasible and the available data indicate a high success rate in patients with surgically altered anatomies. Although the complication rate may be higher than for OAE-ERCP in patients with altered anatomy (17.5% *vs* 3.4%[4]), EUS-BD may be a rescue option in patients for whom OAE-ERCP has failed when conducted within centers with appropriate expertise and in a research setting. A standardized algorithm for using different EUS-BD techniques, refinement of these methods, and the development of new devices may improve the efficacy of EUS-BD and minimize the complication rate. The role of forward-viewing echoendoscope and comparison with the current standard EUS endoscope remain to be assessed.

COMMENTS

Background

Surgically altered anatomy is a consequence of an operation for treatment of a specific disease. This precludes a normal access to the bile duct opening by a standard duodenoscope in many cases and an over-tube assisted endoscopy (OAE) is usually needed to access the bile duct. However, OAE has a failure rate as high as 26%. Endoscopic ultrasound guided biliary drainage (EUS-BD), a recently developed technique, showed a high success rate. The efficacy of EUS-BD in altered anatomy is not well defined.

Research frontiers

To the best of our knowledge, no review of EUS-BD in surgically altered anatomy has been previously published. The objective of this study was to review systematically the efficacy of EUS-BD in altered anatomy.

Innovations and breakthroughs

EUS-BD in the setting of surgically altered anatomy has an efficacy similar to EUS-BD in general, nonetheless, the available data were limited and further studies to evaluate the role of EUS-BD in altered anatomy are needed.

Applications

EUS-BD may be an option for patient with surgically altered anatomy with a failed OAE therapeutic intervention but this should be done in centers with the expertise in EUS-BD in a research setting.

Terminology

EUS-BD is a technique using an endoscope with ultrasound technology to visualize a bile duct. A needle puncture of the bile duct was done under ultrasound guidance then intervention was done using various kinds of endoscopic accessories. OAE is a technique of endoscopy that utilizing an over-tube with a balloon at the tip or an over-tube with a spiral configuration to facilitate the insertion of an enteroscope.

Peer-review

This study was well investigated and will give us important information especially in clinical gastroenterology.

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CASE REPORT

Esophageal papilloma: Flexible endoscopic ablation by radiofrequency

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Abstract

Squamous papilloma of the esophagus is a rare benign lesion of the esophagus. Radiofrequency ablation is an established endoscopic technique for the eradication of Barrett esophagus. No cases of endoscopic ablation of esophageal papilloma by radiofrequency ablation (RFA) have been reported. We report a case of esophageal papilloma successfully treated with a single session of radiofrequency ablation. Endoscopic ablation of the lesion was achieved by radiofrequency using a new catheter inserted through the working channel of endoscope. The esophageal ablated tissue was removed by a specifically designed cup. Complete ablation was confirmed at 3 mo by endoscopy with biopsies. This case supports feasibility and safety of as a new potential indication for Barrx™ RFA in patients with esophageal papilloma.

Key words: Esophageal papilloma; Endoscopic ablation; Radiofrequency; Minimally invasive; Natural orifice transluminal endoscopic surgery

Core tip: This paper reports for the first time a flexible endoscopic treatment of esophageal papilloma by a new radiofrequency system that goes into the working channel of the endoscope. This allows the endoscopist to see what he is doing along the procedure and to complete the procedure in few minutes. The procedure was performed without particular difficulties and did not required elevated skills.

del Genio G, del Genio F, Schettino P, Limongelli P, Tolone S, Brusciano L, Avellino M, Vitiello C, Docimo G, Pezzullo

A, Docimo L. Esophageal papilloma: Flexible endoscopic ablation by radiofrequency. *World J Gastrointest Endosc* 2015; 7(3): 290-294 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i3/290.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i3.290

INTRODUCTION

Esophageal benign lesion is often a major concern due to need of an effective and low risk procedure combined to unmodified physiology[1]. Radiofrequency ablation (RFA) is an established endoscopic technique for the eradication of Barrett esophagus, which has been investigated in a variety of study designs and settings[2-6].

RFA is associated with an acceptable safety profile, high rates of complete eradication of dysplasia and intestinal metaplasia, durability of effect, and a significant relative risk reduction for neoplastic progression, thus it is considered a standard of care for patients with high-grade dysplasia[7].

Squamous papilloma (SP) of the esophagus is a rare benign lesion of the esophagus. The prevalence ranges from 0.01% to 0.45%[8]. SP of the esophagus is usually asymptomatic and rarely causes dysphagia. Esophageal squamous papillomatosis is typically reported as a wart-like and fleshy-pink single lesion, most commonly in the middle or distal esophagus; the typical endoscopic appearance is a single, round sessile lesion[9]. The underlying etiology is unclear, but chronic reflux disease, mucosal trauma, and human papillomavirus (HPV) infection have been implicated, although most lesions are found in absence of HPV[10]. The malignant potential of the lesion is unknown, and no guidelines exist regarding follow-up of these lesions[11]. Some authors have recently reported the possibility of an endoscopic removal[12,13]. To the best of our knowledge, no cases of endoscopic ablation of esophageal papilloma by RFA has been reported. We report a case of esophageal papilloma successfully treated with a single session of RFA.

CASE REPORT

This case was conducted according to the Declaration of Helsinki and approved by the local institutional review board. In February 2014, a 52-year-old white asymptomatic woman was referred to our unit in the preoperative assessment of intragastric baloon placement for obesity. Upper gastrointestinal endoscopy (UGIE) revealed the presence of a single whitish wart-like area of about 0.5 cm in diameter which was located 37 cm from the incisors, above the Z-line (Figure 1). Narrow band imaging (NBI) confirmed the presence of an unstained area. Histologic examination showed the presence of micropapilloma of the esophagus surrounded by cilindric epithelium with congestion and flogosis (Figure 2). In April 2014 a session of RFA (Barrx™, Covidien, CA, United States) on the dysmorphic esophageal area was performed. Total length of the procedure was 10 min. No complications occurred during the procedure. Postoperative course was uneventful.

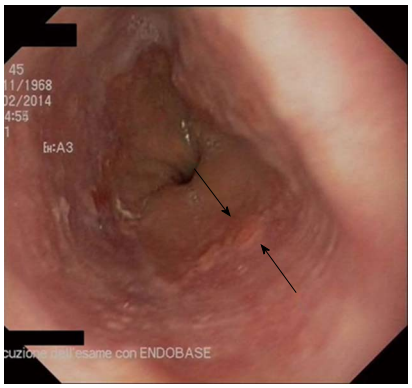

Figure 1 Endoscopic view of esophageal papilloma.

Endoscopic technique

The patient was positioned in the left lateral decubitus position under monitoring of vital signs. Intravenous sedation was administered. An UGIE allowed identification of the esophageal papilloma. The total length of the area was calculated. Esophageal lumen was pre-treated with N-acetycysteine 1% (Mucomyst™). A new designed catheter (Channel RFA Endoscopic Catheter, Barrx™, Covidien) was inserted through the working channel of a standard flexible gastroscope (Figure 3). The electric pad of the catheter was placed under direct visualization so that the entire suspected area was covered. Radiofrequency was applied at 300 W and 12 J/cm^2. The wound along the ablation zone was cleaned from debris using Barrx™ RFA Cleaning cup mounted on distal end of endoscope. The ablation was repeated using the same procedure (Figure 4). The patient was discharged the same day. An UGIE was repeated after one months, showing a whitish area suggestive of scarring at the site of ablation without macroscopical evidence of residual papilloma. A second UGIE with biopsies, at 3 mo, excluded the presence of recurrent disease.

DISCUSSION

RFA has been recently reported to be more effective and less costly than photodynamic therapy in the treatment of Barrett's related dysplasia[14]. On the other hand, an important advantage of RFA lays on simplicity and safety of the procedure suggesting the treatment can be effective with potential lower complications rates than more invasive techniques such as endoscopic resection. In this case an asymptomatic patient was discovered to have an esophageal papilloma in course of preoperative EGDS

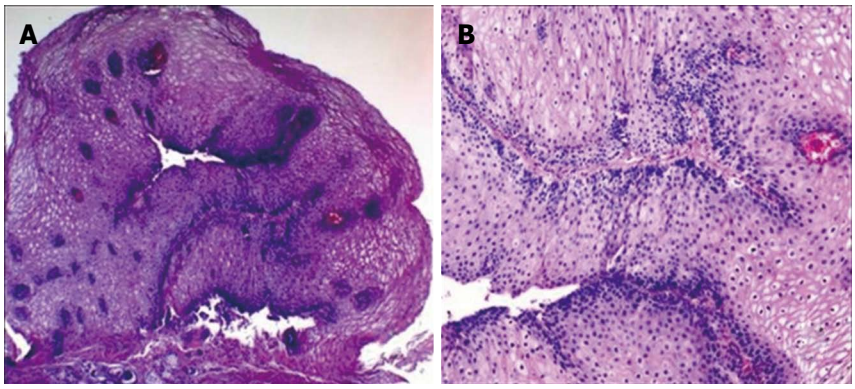

Figure 2 Esophageal biopsy showing papillary projections lined with acanthotic squamous epithelium (A: HE 4 ×; B: HE 10 ×).

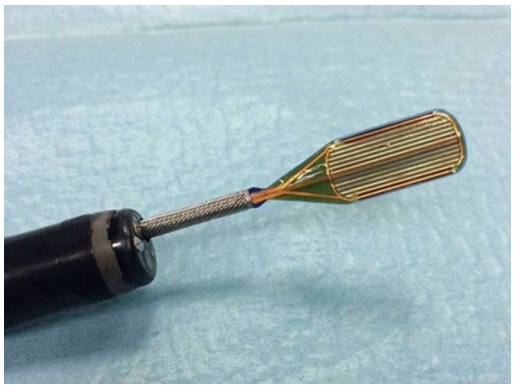

Figure 3 Radiofrequency catheter inserted into standard flexible gastroscope operative channel (Barrx™, Covidien).

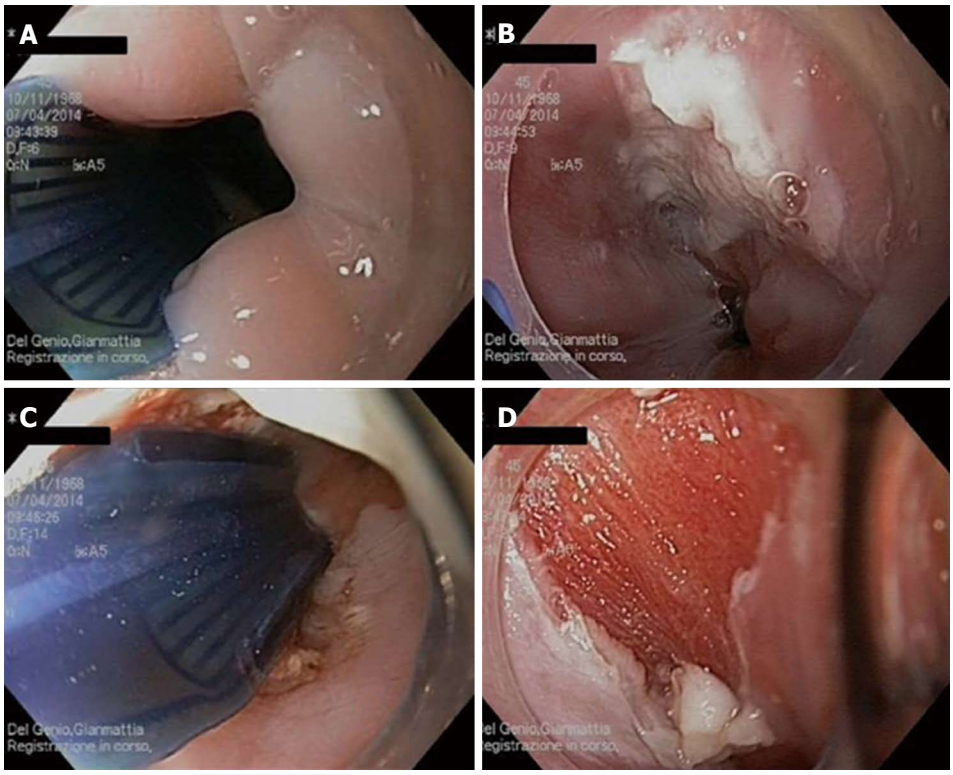

Figure 4 Radiofrequency pad is placed over the lesion under direct visualization (A); Ablation area after the first application of energy (B); Second application of the pad to include all the area of esophageal papilloma (C); Esophageal wound cleaned from debris by cleaning cup (D).

before bariatric treatment.

In this case, the efficacy was reached by a single session of RFA, with a minimal discomfort for the patient and a relatively low impact on the endoscopic center. Our initial experience supports the feasibility and safety of a new potential indication for Barrx™ RFA in patients with esophageal papilloma. Further cases and a longer follow up will be needed to drive a definitive conclusion.

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"Considerate la vostra semenza: Fatti non foste a viver come bruti, ma per seguir virtute e canoscenza." (Consider well the seed that gave you birth: you were not made to live as brutes, but to follow virtue and knowledge). Ulysses in The Divine Comedy. Dante Alighieri, Canto XXVI, 1308-21.

COMMENTS

Case characteristics

A 52-year-old female with esophageal papilloma.

Clinical diagnosis

The tumor was diagnosed during routine gastroscopy for preoperative assessment before placing intragastric baloon.

Differential diagnosis

Esophageal high grade dysplasia, metaplasia, early adenocarcimona or squamous cell carcinoma.

Laboratory diagnosis

All blood test were within normal limits.

Imaging diagnosis

Upper endoscopy showed the lesion, byopsies were taken.

Pathological diagnosis

Histologic examination showed the presence of micropapilloma of the esophagus surrounded by cilindric epithelium with congestion and flogosis.

Treatment

Single treatment of endoscopic ablation by radiofrequency.

Related reports

Endoscopic curative treatment is becoming more popular. This is the first report of squamous esophageal papilome treated by a new catheter radiofrequency technology.

Term explanation

RFA: Radiofrequency ablation is a relatively new technique generally used to treat Barrett's esophagus related high grade dysplasia. This technology uses bipolar energy associated to impedance to automatically controll the energy output.

Experiences and lessons

The new technical possibility allows a less invasive approach with a reduced risks of potentially serious complication and a faster return to normal life.

Peer-review

The manuscript is very well.

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Contents

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REVIEW

MINIREVIEWS

Contents

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REVIEW

Gastrointestinal bleeding from Dieulafoy's lesion: Clinical presentation, endoscopic findings, and endoscopic therapy

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Abstract

Although relatively uncommon, Dieulafoy's lesion is an important cause of acute gastrointestinal bleeding due to the frequent difficulty in its diagnosis; its tendency to cause severe, life-threatening, recurrent gastrointestinal bleeding; and its amenability to life-saving endoscopic therapy. Unlike normal vessels of the gastrointestinal tract which become progressively smaller in caliber peripherally, Dieulafoy's lesions maintain a large caliber despite their peripheral, submucosal, location within gastrointestinal wall. Dieulafoy's lesions typically present with severe, active, gastrointestinal bleeding, without prior symptoms; often cause hemodynamic instability and often require transfusion of multiple units of packed erythrocytes. About 75% of lesions are located in the stomach, with a marked proclivity of lesions within 6 cm of the gastroesophageal junction along the gastric lesser curve, but lesions can also occur in the duodenum and esophagus. Lesions in the jejunoileum or colorectum have been increasingly reported. Endoscopy is the first diagnostic test, but has only a 70% diagnostic yield because the lesions are frequently small and inconspicuous. Lesions typically appear at endoscopy as pigmented protuberances from exposed vessel stumps, with minimal surrounding erosion and no ulceration (visible vessel sans ulcer). Endoscopic therapy, including clips, sclerotherapy, argon plasma coagulation, thermocoagulation, or electrocoagulation, is the recommended initial therapy, with primary hemostasis achieved in nearly 90% of cases. Dual endoscopic therapy of epinephrine injection followed by ablative or mechanical therapy appears to be effective. Although banding is reportedly highly successful, it entails a small risk of gastrointestinal perforation from banding deep mural tissue. Therapeutic alternatives after failed endoscopic therapy include repeat endoscopic therapy, angiography, or surgical wedge resection. The mortality has declined from about 30% during the 1970's to 9%-13% currently with the advent of aggressive endoscopic therapy.

Key words: Dieulafoy's lesion; Gastrointestinal bleeding

Core tip: Dieulafoy's lesion is an important cause of acute gastrointestinal bleeding. Dieulafoy's lesions maintain an abnormally large caliber despite their

peripheral, submucosal, location. Dieulafoy's lesions typically present with severe, active, gastrointestinal bleeding. About 75% of lesions are located in the stomach, most commonly close to the gastroesophageal junction, but lesions can occur in duodenum and esophagus. Endoscopy is the first diagnostic test (70% diagnostic yield). Lesions typically appear at endoscopy as pigmented protuberances from exposed vessel stumps, with minimal surrounding erosions. Endoscopic therapy, including clips, sclerotherapy, argon plasma coagulation, thermocoagulation, or electrocoagulation, is the recommended initial therapy, with primary hemostasis achieved in nearly 90% of cases. Mortality of bleeding from this lesion is 9%-13%.

Nojkov B, Cappell MS. Gastrointestinal bleeding from Dieulafoy's lesion: Clinical presentation, endoscopic findings, and endoscopic therapy. *World J Gastrointest Endosc* 2015; 7(4): 295-307 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i4/295.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i4.295

INTRODUCTION

Although relatively uncommon, Dieulafoy's lesion represents an important etiology of acute gastrointestinal (GI) bleeding because of its propensity to cause massive, life-threatening, and recurrent bleeding; and its amenability to life-saving endoscopic therapy. It most commonly causes upper GI bleeding[1], but can also cause middle GI bleeding (defined as bleeding localized between the ampulla of Vater and the cecum[2])[3], and rarely cause lower GI bleeding[4], depending upon the location of the lesion. Numerous, recent, small, retrospective studies have analyzed the efficacy and safety of individual endoscopic therapies for this lesion, but these studies generally lack a comprehensive review of the literature. This work comprehensively reviews the pathophysiology, epidemiology, clinical presentation, endoscopic diagnosis, and endoscopic therapy of Dieulafoy's lesions, with an emphasis on recent studies of endoscopic therapy.

BRIEF HISTORY

Although first reported by Gallard[5] in 1884, Dieulafoy's lesion was more precisely described 14 years later by the French surgeon, Georges Dieulafoy[6]. He reported fatal GI hemorrhage in three, asymptomatic, young, male patients caused by large, actively bleeding, blood vessels within the stomach associated with small ulcers, which he called "exulceratio simplex", as he erroneously believed these lesions were early peptic ulcers. Since then, a multitude of cases of Dieulafoy's lesions have been reported throughout the world[7,8]. The lesion nomenclature has been variable, including the following alternative names: caliber-persistent artery, gastric arteriosclerosis, cirsoid aneurysm, and submucosal arterial malformation[9]. However, the most commonly accepted name is Dieulafoy's lesion, even though the term caliber-persistent artery has the virtue of aptly summarizing its pathophysiology. The term gastric arteriosclerosis is to be avoided because the pathophysiology does not involve arteriosclerosis or atherosclerosis. Likewise, the term cirsoid aneurysm should be avoided because the pathophysiology does not involve an aneurysm.

PATHOPHYSIOLOGY

The lesion is defined anatomically as a dilated, aberrant, submucosal artery that erodes overlying GI mucosa in the absence of an underlying ulcer, aneurysm, or intrinsic mural abnormality[10]. Unlike the normal arterial tree, which like branches of a tree, progressively narrows when approaching distal branches, Dieulafoy's lesion maintains constant arterial caliber, of approximately 1-3 mm, despite its very distal, submucosal location within the GI wall[7]. This caliber is up to ten-fold larger than the normal maximal caliber of such submucosal vessels. The aberrant artery can protrude through a small mucosal defect, become susceptible to even minor mechanical trauma (*e.g.*, passage of food bolus in stomach or solid stool in colon), and eventually erode into the lumen to cause severe acute GI bleeding. Each arterial pulsation transmits mechanical pressure that may traumatize the fragile, thin layer of mucosa overlying the vessel. Alternatively, enhanced blood flow through the enlarged artery may cause hypoperfusion, ischemia, and erosion of overlying mucosa from shunting and redistribution of blood perfusion[11]. This hypothesized "vascular steal" phenomenon resembles that which produces a pale mucosal halo that sometimes surrounds angiodysplasia[12]. Chronic age-related mucosal wear and tear and atrophy may explain the tendency for this bleeding to generally present in older age[8].

About 70% of lesions occur in the stomach[8,9]. The proximal stomach, in particular within 6 cm from the gastroesophageal junction and along the lesser gastric curve, is the most common gastric location, accounting for about 75% of all gastric lesions (Table 1)[13,14]. This proclivity is attributed to the blood supply to this area coming directly from the arterial chain running along the lesser gastric curve because the usual submucosal, arterial anastomotic gastric plexus is absent in this area[15]. Other common lesion locations include duodenum (15% prevalence)[7,9], distal stomach (12% prevalence)[8], and esophagus (8% prevalence)[16]. However, recent publications, consisting mostly of case reports or limited case series, also report Dieulafoy's lesions of the jejunum[3,17], ileum[17-21], cecum[22], appendix[23], colon[24,25], rectum[26], and anal canal[27] which present with lower GI bleeding. Figure 1 summarizes the approximate distribution of bleeding Dieulafoy's lesions within the GI tract. Also,

Table 1 Clinico-epidemiologic characteristics of Dieulafoy lesion

Anatomy
Dilated, aberrant, submucosal artery eroding overlying gastrointestinal mucosa in absence of either underlying ulcer or local aneurysm
Location
70% of ulcers in stomach
In stomach most commonly located within 6 cm of gastroesophageal junction along lesser curve
Can occur moderately commonly in esophagus or duodenum, occasionally in jejunum or ileum, and rarely in colon
Epidemiology
Generally presents clinically in older age, but can occur at any age
Male:female ratio = 2:1
No known epidemiologic risk factors or clinically associated diseases
Clinical presentation
Typically presents with overt GI bleeding, often with hematemesis or melena, or both
Bleeding typically severe
No prodromal symptoms
Typically bleeding is painless
Frequent presentation with signs or laboratory tests of hemodynamic instability, including: tachycardia, hypotension, orthostasis, and acute prerenal azotemia
Frequently requires transfusion of multiple units of packed erythrocytes
Frequent recurrent bleeding if undetected or not treated at initial endoscopy

GI: Gastrointestinal.

extra-gastrointestinal locations of Dieulafoy-like lesions can present with acute non-gastrointestinal bleeding, such as bronchial Dieulafoy's lesion presenting with hemoptysis[28].

It is unknown if this lesion is inherited or acquired[29]. It has not been associated with genetic mutations. The generally older age of patients with Dieulafoy's lesion might suggest an acquired defect. Contrariwise, the propensity of these lesions to be located within 6 cm of the gastroesophageal junction might reflect a congenital defect. While the pediatric literature suggests that the tortuous, dilated artery with a variable course length may represent a congenital anomaly[30], scant data supports familial predisposition in adults[7].

EPIDEMIOLOGY

Dieulafoy's lesion is responsible for approximately 1.5% of acute upper GI bleeding[14,31], and is responsible for approximately 3.5% of jejunoileal GI bleeding[17]. For example, in a recent, retrospective, multicenter, study of 284 patients with suspected overt or occult small intestinal bleeding who underwent 317 double-balloon and 78 single-balloon enteroscopies, 10 patients (3.5%) had Dieulafoy's lesion in the jejunum or ileum as the bleeding etiology[17]. Most of the small bowel lesions were located in the jejunum. Colonic Dieulafoy's lesion is presumably rare; less than 30 cases have been reported since three patients with colonic Dieulafoy's lesion were first reported in 1985[24,32,33].

Epidemiologic characteristics of patients with Dieulafoy's lesions have been described. The lesion

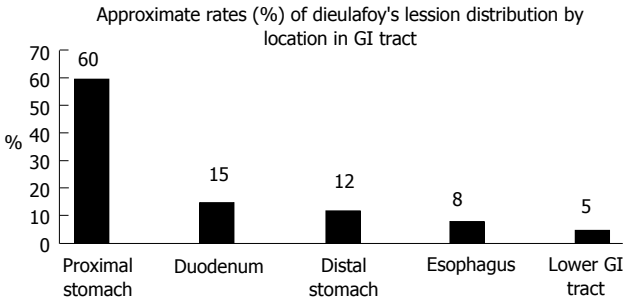

Figure 1 Segmental distribution of Dieulafoy's lesion within the gastrointestinal tract in patients presenting with acute gastrointestinal bleeding. GI: Gastrointestinal.

is reportedly more common in males than females, with a sex ratio of 2:1[8,20,34]. It can occur at any age[7,8], although older series reported a predisposition towards advanced age, with most cases presenting in the sixth or seventh decades[14,35]. Affected patients often have non-gastrointestinal comorbidities such as cardiovascular disease, hypertension, diabetes, and chronic renal insufficiency. Also, affected patients are often administered non-steroidal anti-inflammatory drugs (NSAIDs) or anticoagulants most likely because these drugs promote bleeding from underlying Dieulafoy's lesions which results in clinical detection[10,36]. No causal link has, however, been found between Dieulafoy's lesions and use of NSAIDs, alcohol or tobacco; or the presence of peptic ulcer disease or *Helicobacter pylori* infection[10,15,36-38].

CLINICAL PRESENTATION

Patients are typically asymptomatic before presenting with acute, profuse GI bleeding, which can manifest as hematemesis, melena, or hematochezia[39,40]. Approximately half of patients present with both hematemesis and melena[9]. For example, in a review of 177 cases, 51% presented with hematemesis and melena, 28% of patients presented with hematemesis, and 18% presented with melena alone[40]. Patients with colonic Dieulafoy's lesions typically present with profuse bright red blood per rectum. The bleeding is typically severe, attributed to the arterial nature of the bleeding and the enlarged arterial vessel (Table 1). Patients rarely present with chronic, occult, GI bleeding. Signs of hemodynamic instability such as tachycardia, hypotension, and orthostasis, or laboratory abnormalities of acute prerenal azotemia frequently occur because of the severity and acuity of the GI bleeding[41,42]. For example, 10 (50%) of 20 Mexican patients presented with signs of hemodynamic instability[40]. The mean hemoglobin on admission for bleeding is about 9 g/dL[43]. The bleeding is frequently recurrent, with recurrence < 72 h after initial presentation if it is left untreated at the initial endoscopy[7]. Recurrent bleeding is often extremely severe, which emphasizes the importance of accurate diagnosis and appropriate therapy at the initial

Table 2 Diagnosis of Dieulafoy's lesion

EGD
Small, relatively inconspicuous pigmented protuberance with minimal surrounding erosion and no ulceration
Lesion often actively bleeding or oozing at EGD
Gastric lesions most commonly within 6 cm of GE junction along lesser curve
Initial EGD may be nondiagnostic in up to 30% of cases due to relatively small lesion size
Avoid endoscopic biopsies of lesion
Colonoscopy or enteroscopy
May be useful to diagnose colonic or jejunoileal lesions, respectively, if EGD was negative in setting of severe, acute GI bleeding
Angiography
May be helpful in setting of rectal bleeding after negative EGD and colonoscopy

EGD: Esophagogastroduodenoscopy; GI: Gastrointestinal.

endoscopy. Other GI symptoms, especially abdominal pain, are uncommon and their presence suggests alternative diagnoses such as peptic ulcer disease or complications from the bleeding such as mesenteric ischemia from hemorrhagic shock[14].

The clinical presentation of patients with jejunoileal lesions is similar to that of patients with upper GI Dieulafoy's lesions[17]. Among 10 patients diagnosed with small-intestinal Dieulafoy's lesions, all presented with overt bleeding and all had severe, transfusion-dependent, anemia[17]. Eight of the ten Dieulafoy's lesions were actively bleeding at enteroscopy. Most patients were elderly (mean age = 69.7 years), but the disease occurred at younger ages as well (youngest patient = 35 years old).

Dieulafoy's lesion is also an important cause of obscure GI bleeding because it frequently bleeds intermittently, it occasionally involves unusual GI bleeding sites that are relatively inaccessible to conventional endoscopy, such as the jejunum or ileum; and the lesions are frequently relatively small, subtle, and inconspicuous despite repetitive use of standard diagnostic techniques[44]. Conversely, alternative diseases can sometimes mimic a Dieulafoy's lesion in the setting of acute GI bleeding. For example, two recent reports from Japan describe patients whose initial clinical presentation and endoscopic findings suggested gastric Dieulafoy's lesions, but who were subsequently diagnosed with GI stromal tumors[45,46].

Dieulafoy's lesions are apparently not associated with other GI vascular lesions, such as angiodysplasia or hemangiomas. Although syndromes with multiple vascular lesions occur with angiodysplasia (in hereditary hemorrhagic telangiectasia), syndromes with multiple or disseminated Dieulafoy's lesions have not been reported, One patient, however, had two GI Dieulafoy's lesions[47]. Unlike the genetic mutations associated with hereditary hemorrhagic telangiectasia[48], no genetic mutations have been associated with Dieulafoy's lesions. Hereditary hemorrhagic telangiectasia is occasionally associated with high-output cardiac failure[49], or individual organ (*e.g.*, liver) failure[50], from extensive shunting of blood. However, Dieulafoy's lesion is not associated with high-output cardiac failure or individual end-organ failure because it produces minimal individual organ or systemic vascular shunting due to its relatively moderate size and single lesion status.

DIAGNOSIS

Esophagogastroduodenoscopy (EGD) is usually the first diagnostic test performed for acute, upper, GI bleeding. Dieulafoy's lesion is, therefore, usually diagnosed by EGD, which reveals a pigmented protuberance from the vessel stump, with minimal surrounding erosion and no ulceration (visible vessel sans ulcer; Figures 2A, 3A and 4A). The pigmented protuberance has a variable color, including reddish, purple, blue, or greyish-white. The protuberance is usually relatively inconspicuous at EGD; it is approximately 10-15 mm wide and about 5-10 mm high (Table 2). Approximately 50%-60% of identified upper GI Dieulafoy's lesion are actively bleeding at the initial EGD, typically with spurting or oozing of blood from a miniscule (1-5 mm in diameter) point source on the GI mucosa[40,42]. For example, in a study of 29 patients, 66% had oozing, and 28% had spurting bleeding at endoscopy[51]. Spurting bleeding is often micro-pulsatile reflecting the underlying arterial breach. Other patients typically have a fresh adherent clot or visible (non-actively bleeding) Dieulafoy's lesion at the initial endoscopy. Dieulafoy's lesion should be strongly considered, when a lesion is located in proximal stomach and/or has a small mucosal defect connected by a narrow attachment point to an adherent clot[9]. Dieulafoy's lesion may not be detected when covered by an adherent clot, and the lesion may be exposed by washing away an adherent clot with moderate endoscopic perfusion. The authors do not recommend guillotining an adherent clot covering a Dieulafoy's lesion because of the risk of inducing severe hemorrhage.

Dieulafoy's lesion should be endoscopically distinguished from other clinical entities with a similar clinical presentation and endoscopic appearance, including: arteriovenous malformations, hereditary hemorrhagic teleangiectasia (Osler-Weber-Rendu syndrome), or vascular neoplasms. Additionally, when located close to the gastroesophageal junction, the lesion has to be distinguished from a Mallory-Weiss tear, in which the bleeding originates from a superficial mucosal tear instead of a superficial protruding blood vessel. A history of vomiting before hematemesis may suggest a Mallory-Weiss tear. However, given their frequently similar anatomical location, endoscopic misdiagnoses of Dieulafoy's lesions as Mallory-Weiss tears have been reported[7]. It is important to differentiate a colonic Dieulafoy's lesion from an adenomatous colonic polyp to prevent massive hemorrhage from performing "polypectomy" of a Dieulafoy's lesion[52].

Initial EGD is diagnostic in only about 70% of cases

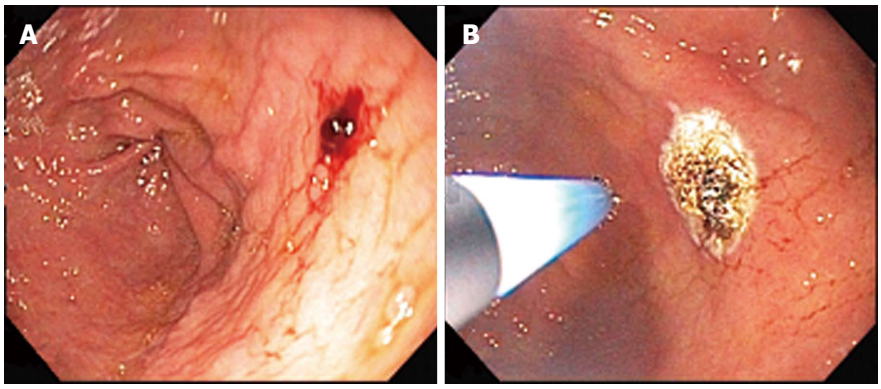

Figure 2 An 86-year-old woman who had undergone two esophagogastroduodenoscopies in the prior 2 years for 2 episodes of acute upper gastrointestinal bleeding that had not revealed any upper gastrointestinal lesions, presented with acute onset of melena and an acute hemoglobin level decline from 11.0 g/dL to 8.6 g/dL. Esophagogastroduodenoscopy revealed an actively oozing, darkly red, 6-8 mm wide, raised, lesion without surrounding erosions or ulceration that was actively oozing along the greater curvature of the gastric body (A), findings characteristic of a Dieulafoy lesion. The lesion was successfully cauterized using 50 watts of argon plasma coagulation at 1 L/min (note probe hovering over cauterized lesion in (B) with cessation of active oozing. The patient was discharged four days later with no evidence of recurrent bleeding during the hospitalization and no further gastrointestinal bleeding during 4 mo of follow-up.

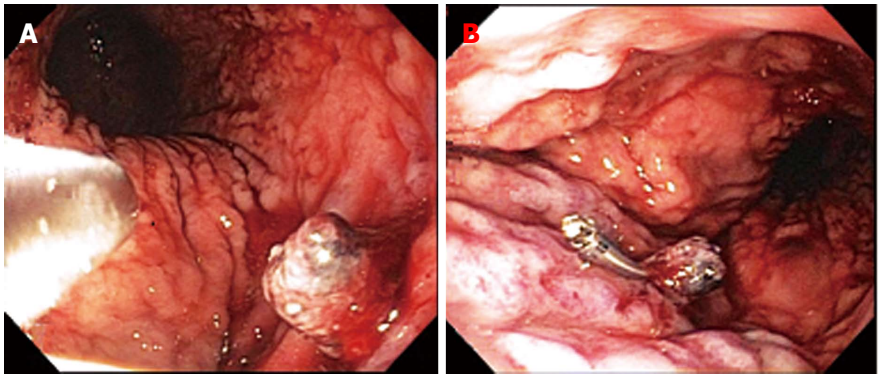

Figure 3 An 88-year-old woman with prior bleeding duodenal ulcer 40 years earlier, and actively administered aspirin, presented with acute onset of hematemesis and melena, with an acute decline in the hemoglobin level from 11.2 g/dL to 9.2 g/dL. Esophagogastroduodenoscopy revealed an actively oozing, darkly red, 8-10 mm wide, raised, lesion without surrounding erosions or ulceration that was actively oozing in the gastric cardia (A), findings characteristic of a Dieulafoy lesion. The lesion was first injected with 7 mL of epinephrine (1:10000 solution), followed by successful placement of a single hemoclip around the protruding vessel (B), with cessation of active oozing. The patient was discharged three days later with no evidence of recurrent bleeding during the hospitalization.

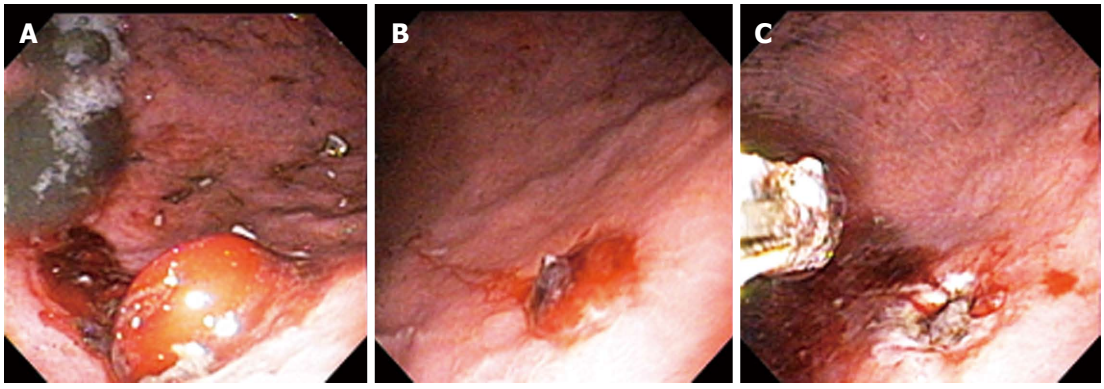

Figure 4 An 81-year-old woman presented with nausea, coffee-ground emesis, and dizziness. She underwent urgent esophagogastroduodenoscopy (EGD), despite a normal initial hemoglobin level of 13.0 g/dL, because of the hematemesis. EGD revealed a small blood clot, overlying a lesion without surrounding ulceration, located in proximal gastric body, which was slowly oozing red blood (A). After detachment of the blood clot with irrigation, a raised, darkly red, blood vessel was visualized consistent with a Dieulafoy lesion (B). The lesion was treated with 4 mL of 1:10000 solution of epinephrine and thermocoagulated *via* heater probe 5 pulses of 30 Joules/pulse without post-procedural bleeding (C). Patient remained stable after the EGD with no further bleeding and she was discharged 3 d later.

due to relatively small lesion size; intermittently active bleeding; lesion location between folds; or lesion location underneath gastric contents, an adherent blood clot, or a pool of blood from massive bleeding[53]. For

example, in a retrospective study of 177 patients with Dieulafoy's lesions causing acute GI bleeding, repeat endoscopic evaluation was needed in 33% of cases, due to nondiagnostic initial examinations[37]. Indeed, about 6% of patients require three or more endoscopies to establish the diagnosis[8]. This diagnostic yield at EGD is significantly lower than that of about 95% for other lesions causing upper GI bleeding[54]. Gastric insufflation may expose a Dieulafoy's lesion previously buried between gastric rugae. Careful aspiration of the gastric lake may demonstrate an underlying Dieulafoy's lesion. Cautious removal of an adherent clot may reveal an underlying Dieulafoy's lesion. Lesion identification may require careful gastric retroflexion due to its predilection to be near the gastroesophageal junction. As with EGD, repeat enteroscopic examinations, after initially nondiagnostic enteroscopy, are frequently required to diagnose jejunoileal lesions. In one study 40% of cases required a second or even a third enteroscopy to establish the diagnosis[17].

Several small reports suggest that, supplemental methods such as endoscopic ultrasound or bleeding provocation with intravenous heparin, may help increase the diagnostic yield of Dieulafoy's lesions at endoscopy[55,56]. Typical endosonographic features include an abnormally large (2-3 mm wide) caliber, pulsatile, high-flow, submucosal artery, usually located along the lesser gastric curve near the gastroesophageal junction. Endosonography has been used to confirm endoscopic hemostasis of a bleeding Dieulafoy's lesion by demonstrating absent blood flow after therapy[55]. However, combining endoscopy with such costly, advanced technology is currently not recommended for routine clinical practice due to insufficient data concerning efficacy. Endoscopic biopsies of suspected Dieulafoy's lesion are generally contraindicated because of the risk of inducing severe bleeding by biopsying the exposed artery and the lack of pathologic diagnosis from endoscopic biopsies.

Colonoscopy is usually indicated following a negative EGD for acute GI bleeding. Multiple individual cases of bleeding Dieulafoy's lesion diagnosed at colonoscopy have been reported during the past 30 years. However, the diagnostic yield of colonoscopy for this entity is unknown[24-27,56-61].

Enteroscopy is often indicated for acute GI bleeding after nondiagnostic EGD and colonoscopy. It enables viewing of the small bowel up to about 150 cm beyond the pylorus, to identify distal duodenal or proximal jejunal lesions. There is limited data on the diagnostic yield of enteroscopy for acute bleeding from small bowel Dieulafoy's lesions[3,17-21]. Single-balloon and double-balloon enteroscopies permit intubation of more distal small intestine, thereby permitting detection of more distal Dieulafoy's lesions.

Several Dieulafoy's lesions have been diagnosed by capsule endoscopy[34,62]. While noninvasive, capsule endoscopy lacks therapeutic capabilities, and a positive test still requires a subsequent invasive therapeutic modality. Still, capsule endoscopy may be diagnostically helpful for Dieulafoy's lesion causing obscure GI bleeding, especially from the distal small intestine[62].

If endoscopy is nondiagnostic, angiography may help establish the diagnosis in the setting of acute bleeding, especially for lower GI Dieulafoy's lesions, because detailed colonoscopic examination of mucosa may be difficult to achieve due to overlying blood or the performance of colonoscopy on an unprepared colon because of severe, acute bleeding (Table 2)[10,35,37]. No angiographic pattern is specific for Dieulafoy's lesions, but features such as visualization of a non-tapering (caliber-persisting), ectatic (tortuous), artery at the bleeding site may suggest this entity[7,63,64]. Often, however, only extravasation is visualized at an eroded site of an otherwise normal appearing artery[65]. Angiography may also suggest an underlying Dieulafoy's lesion when extravasation of contrast is visualized from a point source in the proximal stomach. Angiodysplasia, another point source of bleeding, may be distinguished from Dieulafoy's lesion by its characteristic angiographic features, such as an early filling vein, that are inconsistent with Dieulafoy's lesion[8,66]. In one study, angiography was diagnostic in 11 of 14 patients with Dieulafoy's lesions who underwent nondiagnostic endoscopic examinations[37].

Technetium 99-m-labeled erythrocytes scanning is reportedly useful to locate a bleeding Dieulafoy's lesion after nondiagnostic endoscopies[67,68]. This test may permit diagnosis at lower rates of active GI bleeding, because the threshold to detect blood extravasation is less than half that required for angiography[69].

TREATMENT

As for any severe, acute, GI bleeding, pre-endoscopic therapy for a recently bleeding Dieulafoy's lesion focuses on volume resuscitation to prevent systemic hypotension and consequent end-organ damage to heart, brain, or kidneys from hypoperfusion. Multiple, reliable, large-bore, intravenous lines are inserted. Volume resuscitation is initially performed with crystalline solution, with normal saline or Ringer's lactate, but transfusion of packed erythrocytes is often required, after typing and crossing of blood, as guided by the tempo of the GI bleeding and serial hematocrit determinations. Patients with Dieulafoy's lesions often require transfusion of three or more units of packed erythrocytes due to the severity of the bleeding[9]. Electrolyte abnormalities are assessed and appropriately corrected. Treatment to reverse a severe coagulopathy is important before endoscopy, particularly when endoscopic therapy is contemplated.

Hemostatic therapy is important because of the bleeding severity from Dieulafoy's lesion, the propensity for bleeding to recur without therapy, especially within 72 h after an initial bleed, and the high mortality if it is left untreated. Minimally invasive therapies are derived from their respective diagnostic tests, including

Table 3 Therapy for Dieulafoy's lesion

Pre-endoscopic therapy
Secure IV access using multiple, large bore catheters
Volume resuscitation initially using crystalloid followed by transfusions of packed erythrocytes as dictated by serial hematocrit determinations and tempo of bleeding
Endoscopic therapies
Mechanical therapies
Hemoclips
Band ligation
Injection therapies
Epinephrine injection
Absolute alcohol
Ablative therapies
Heater probe
Electrocoagulation: Bicap, gold probe, *etc.*,
APC (argon plasma coagulation)
Combination therapies
Usually epinephrine injection therapy followed by:
Heater probe
Hemoclip
Or APC
Interventional angiography
Embolization
Pledgelets
Metal coils
Balloon occlusion
Surgery
Mostly salvage therapy after failure of other interventional therapies

APC: Argon plasma coagulation.

therapeutic endoscopy immediately after diagnostic endoscopy, and therapeutic angiography immediately after diagnostic angiography (Table 3). While no consensus recommendations on treatment exist, there has been increased use of endoscopic therapy and therapeutic angiography, with decreasing use of surgery during the last few decades[10,70]. As Dieulafoy's lesions are relatively uncommon, most data on treatment modalities consist of small, retrospective, case-series, or individual case-reports[7,8,10].

Therapeutic endoscopy is the primary treatment modality for acute GI bleeding. It can achieve initial hemostasis in about 90% of accessible lesions with a < 10% rate of rebleeding during the next 7 d[36,71-73]. Therapeutic endoscopy for recently bleeding peptic ulcers depends upon the Forrest criteria, with endoscopic therapy recommended only for lesions that are actively bleeding or oozing, that have a visible vessel, or perhaps have an adherent clot[74]. Endoscopic therapy is not recommended for peptic ulcers that have a flat, pigmented spot or have a clean, homogeneous, flat base. Contrariwise, therapeutic endoscopy is recommended for virtually all Dieulafoy's lesions, whether actively bleeding, oozing, or without any stigmata of recent bleeding. The difference in therapeutic strategies reflects the natural history of Dieulafoy's lesion as compared to peptic ulcers. Peptic ulcers with a flat pigmented spot have a low risk of rebleeding of about 8%-10% without endoscopic therapy and peptic ulcers with a clean, homogeneous, flat, base have only about a 3% risk of rebleeding without endoscopy therapy[74]. This low risk of rebleeding with these two types of peptic ulcers does not justify incurring the approximately 1% or more risk of major, life-threatening, complications from endoscopic therapy including, gastrointestinal perforation, massive bleeding, pulmonary aspiration, and cardiovascular complications[74]. In contrast, the risk of continued bleeding or rebleeding within 72 h from an untreated Dieulafoy's lesion is very high. This high risk of rebleeding justifies undertaking the risks of therapeutic endoscopy to prevent further bleeding from Dieulafoy's lesion.

Although initially developed for EGD for upper GI Dieulafoy's lesions, endoscopic therapy is now performed using the same techniques and devices during colonoscopy for colonic Dieulafoy's lesions[22-25], and during single or double balloon enteroscopy for jejunoileal lesions[17]. The current modalities of endoscopic therapies include injection, ablation, and mechanical therapy. Injection therapy most commonly involves local injection of epinephrine, sclerosing agents (sclerotherapy), or cyanoacrylate. Epinephrine therapy promotes hemostasis *via* vasospasm and tamponade/mechanical pressure from interstitial injection that leads to stasis of blood and thrombus formation. Relative contraindications to epinephrine therapy may include severe tachycardia, cardiac arrhythmias such as atrial flutter, unstable vital signs from severe, uncorrected hypovolemia, and recent myocardial infarction or unstable angina. Sclerotherapy promotes vascular inflammation and thrombosis from local irritation, whereas cyanoacrylate promotes gluing to plug a bleeding artery. Ablation modalities include thermocoagulation, electrocoagulation, and argon plasma coagulation (APC). Photocoagulation using the yittrium aluminum garnet laser to ablate tissue has been discontinued due to an unacceptably high risk of gastrointestinal perforation. Ablation modalities can stem bleeding by destroying and devitalizing tissue. Thermocoagulation and electrocoagulation involve point contact with the lesion with apposition of the probe against the bleeding vessel. Contrariwise, APC involves hovering the probe over the lesion without lesion contact[74]. Mechanical therapy, including band ligation or endoscopic clips, can arrest bleeding by mechanically closing off the bleeding vessel. Mechanical therapy likely requires greater endoscopic skill and experience than injection or ablative therapies because correct placement of the band or clip directly around the lesion is critical for successfully strangulating the vessel within Dieulafoy's lesion.

These therapies are generally effective for most Dieulafoy's lesions, when used individually or in combination[17,35,38,71-75]. Successful cases of hemostasis of bleeding Dieulafoy lesions using various modalities of endoscopic therapy are illustrated in Figures 2-4. Available data suggest that mechanical hemostasis may be more effective than other endoscopic modalities in

Table 4 Efficacy of endoscopic mechanical monotherapies for bleeding Dieulafoy's lesions

Endoscopic procedure (No. of patients)	Lesion location	Type of study	Follow-up	Outcome	Ref.
Hemoclips					
EGD (34)	Stomach/duodenum	Prospective	54 mo	initial hemostasis 32/34 pts (94%), 3 pts (9%) rebled	[75]
EGD (18)	Stomach	Retrospective	36 mo	1 (5%) rebled	[77]
EGD (16)	Stomach/duodenum	Prospective, randomized	1 wk	1 (6%) rebled	[78]
Mostly EGD (14)	Mostly stomach/duodenum	Retrospective	Hospitalization	No rebleeding	[36]
EGD (8)	Stomach	Retrospective	19 mo	1 (12%) rebled	[73]
Colonoscopy (1)	Rectum				
EGD (6)	Stomach/duodenum	Retrospective	47 mo	1 (17%) rebled, unclear if single/combination therapy	[79]
Colonoscopy (3)	Rectum	Retrospective	5 mo	No rebleeding	[80]
Double balloon enteroscopy (3)	Jejunum	Retrospective, multicenter	14.5 mo	1 (33%) rebled 69 d after hemoclip	[17]
Single balloon enteroscopy (2)	Ileum	Retrospective	2 mo	No rebleeding	[18]
Colonoscopy (1)	Colon	Case report	6 mo	No rebleeding	[33]
Band ligation					
EGD (24)	Stomach 23 Jejunum 1	Retrospective	18 mo	1 (4%) hemostasis failure, 1 (4%) rebled (jejunum)	[81]
EGD (13)	Stomach Esophagus	Prospective	24 wk	No rebleeding	[82]
EGD (13)	Stomach/duodenum	Retrospective	30 d	No rebleeding	[83]
EGD (10)	Stomach	Prospective	30 d	No rebleeding	[76]
EGD (7)	Stomach	Retrospective	8 mo	No rebleeding	[84]
EGD (3)	Upper GI	Retrospective	19 mo	No rebleeding	[73]
"Mostly" EGD (2)	Stomach	Retrospective	Hospitalization	No rebleeding	[75]
EGD (1)	Stomach	Retrospective	2 d	No rebleeding	[35]
Colonoscopy (4)	Rectum	Retrospective	2-5 d	2 (50%) rebled	[85]
Colonoscopy (3)	Rectum	Retrospective	5 mo	No rebleeding	[80]

Pts: Patients; EGD: Esophagogastroduodenoscopy; GI: Gastrointestinal.

patients with GI bleeding from Dieulafoy's lesion[73,76]. A review of the published literature on application of endoscopic hemoclips in 106 patients and on application of band ligation in 80 patients as monotherapies for bleeding Dieulafoy lesions reveals that both techniques are almost uniformly effective to achieve initial hemostasis and both techniques have low re-bleeding rates, generally $\leqslant$ 10% (Table 4)[17,18,33,36,73,75-85]. They are particularly effective in the hands of expert endoscopists with extensive experience with these techniques. However, endoscopic band ligation may be less desirable than clips because it can cause perforation from banding too deep tissue. This is a particular concern in GI segments with thin walls such as gastric fundus, small bowel, or right colon. Also bleeding may occur from an ulcer after the band falls off[86,87].

A literature review of endoscopic injection encompassing 68 cases of epinephrine injection and 13 cases of sclerotherapy (12 with injection of absolute ethanol and 1 with injection of ethanolamine) appears to show a somewhat lower rate of achieving hemostasis for injection therapy than mechanical therapy (Table 5)[35,36,40,72,73,78,88,89]. However, this therapy may be particularly useful for initially treating massive bleeding. This therapy is technically easier than mechanical therapy and can be performed rather quickly. Also, injection therapy, especially with epinephrine, may slow down massive bleeding so that the lesion can be more readily visualized to apply mechanical therapy.

A literature review of endoscopic ablation therapies for Dieulafoy's lesion encompassing 40 cases, including 18 cases with thermocoagulation, 7 cases of APC, and 15 cases of electrocoagulation shows a high rate of initial hemostasis (Table 6)[17,35,36,40,72,77,82]. However, the data on efficacy for this therapy is less reliable than that for the mechanical or injection therapies because the individual studies on ablative therapies are all retrospective and relatively small and the total number of studied patients is only 40.

Combined endoscopic mechanical hemostasis with injection or ablation therapeutic endoscopy are highly effective therapeutic modalities (Table 7)[17,35,36,40,59,71,72,79,88-90]. Although combined endoscopic treatment modalities are recommended as more effective in the setting of non-variceal acute upper GI bleeding, there is contradictory evidence on such practice when it comes to Dieulafoy's lesions; some studies found no added benefit from endoscopic dual therapy *vs* monotherapy[10,36]. The overall risk of short-term (< 72 h) recurrent bleeding after endoscopically-achieved initial hemostasis is about 10%[10,37,61]. Dieulafoy's lesions treated with single-modality endoscopic therapy may be more likely to rebleed compared to lesions treated with dual endoscopic therapy[51,72].

Other potential risk factors for rebleeding after endoscopic therapy include administration of NSAIDs, administration of anticoagulants, and Dieulafoy's lesions with actively spurting blood at the time of initial

Table 5 Efficacy of endoscopic injection monotherapy for bleeding Dieulafoy's lesions

Endoscopic procedure (No. of patients)	Lesion location	Type of study	Follow-up	Outcome	Ref.
Epinephrine injection					
EGD (16)	Stomach/duodenum	Prospective	1 wk	2 (12%) hemostasis failure, 5 (31%) rebled	[78]
EGD (11)	Stomach	Retrospective	22 mo	3 (27%) hemostasis failure, 4 (36%) rebled	[73]
Colonoscopy (1)	Rectum				
EGD (11)	Stomach/duodenum	Retrospective	18 mo	3 (27%) hemostasis failure, 2 (18%) rebled	[88]
"Mostly" EGD (8)	Mostly stomach/duodenum	Retrospective	Hospitalization	No rebleeding	[36]
EGD (8)	Stomach	Prospective	30 d	6 (75%) rebled	[76]
EGD (6)	Stomach	Retrospective	60 d	2 (33%) hemostasis failure	[40]
EGD (3)	Stomach/duodenum	Retrospective	14 mo	No rebleeding	[35]
Colonoscopy (1)	cecum (1)				
EGD (3)	Stomach	Retrospective	32 mo	2 (66%) rebled	[72]
Absolute ethanol injection					
EGD (12)	Stomach/duodenum	Retrospective	69 mo	1 (8%) hemostasis failure, no rebleeding	[89]
Ethanolamine injection					
EGD (1)	Stomach	Retrospective	8 mo	Rebled	[72]

EGD: Esophagogastroduodenoscopy.

Table 6 Effectiveness of endoscopic ablation monotherapies for bleeding Dieulafoy's lesions

Endoscopic procedure (No. of patients)	Lesion location	Type of study	Follow-up	Outcome	Ref.
Heater probe coagulation					
EGD (6)	Stomach/duodenum	Retrospective	14 mo (2/3 of pts)	No rebleeding	[35]
EGD (6)	Stomach	Retrospective	36 mo	2 (33%) rebled	[77]
Mostly EGD (5)	Mostly stomach/duodenum	Retrospective	Hospitalization	No rebleeding	[36]
EGD (1)	Stomach	Retrospective	40 mo	No rebleeding	[72]
Argon plasma coagulation					
Double balloon enteroscopy (3)	Jejunum-2, Ileum-1	Retrospective /multicenter	14 mo	1 (33%) rebled	[17]
EGD (3)	Stomach	Retrospective	2 mo	No rebleeding	[40]
EGD (1)	Likely upper GI	Retrospective	Hospitalization	No rebleeding	[36]
Multipolar electrocoagulation					
EGD (14)	Stomach	Retrospective	24 mo	1 (7%) hemostasis failure, 1 rebled	[82]
EGD (1)	Likely upper GI	Retrospective	Hospitalization	Rebled	[36]

EGD: Esophagogastroduodenoscopy.

endoscopy[42,51]. The data in Tables 4-7[17,18,33,35,36,40,59,71-73,75-85,88-90] on initial hemostasis and re-bleeding rates with single-modality and combination-modalities endoscopic therapy for both upper and lower Dieulafoy's lesions should be interpreted cautiously; most reported studies are retrospective, have relatively small sample-size, and generally lack controls to exclude potential confounding variables.

Recurrent bleeding after attempted endoscopic hemostasis can be treated by repeat endoscopic hemostasis, angiographic embolization, or surgical wedge resection. Subtotal gastrectomy is unnecessary if the lesion has been properly localized preoperatively or intraoperatively. Successful hemostasis with angiographic embolization has been reported in scattered case reports[65,91], but requires specialized angiographic expertise. Embolization of a too large and too central vessel feeding the Dieulafoy lesion can occasionally cause GI ischemia leading to GI perforation[92].

The mortality of GI bleeding from Dieulafoy's lesions prior to the era of flexible diagnostic endoscopy was up to 80%, due to the frequent need for emergency surgery for severe, refractory GI bleeding, but declined to about 30% with the advent of flexible diagnostic endoscopy in the 1970's, and has declined to about 9%-13% currently with the advent of therapeutic endoscopy[93].

FUTURE TRENDS

Although the anatomic basis of Dieulafoy's lesion and the pathophysiology of bleeding from this lesion is fairly well understood, the etiology of lesion formation is poorly understood. Why does the lesion most commonly occur within 6 cm below the gastroesophageal junction along the lesser curve? Is this a developmental defect during organogenesis? Do genetic mutations play any role? Is there a familial predisposition to this lesion? Hopefully, the molecular mechanisms and developmental origin of this lesion will be elucidated. Such an understanding might provide a mechanism to

Table 7 Effectiveness of various combination endoscopic therapies for bleeding Dieulafoy's lesions

Endoscopic therapies (No. of patients)	Endoscopy: lesion location	Type of study	Mean length of follow-up	Study outcome	Ref.
Epinephrine and polidocanol (27)	EGD: stomach/duodenum	Retrospective	28 mo	5 (18%) rebled	[71]
Epi and heater probe (28)	EGD: stomach/duodenum	Retrospective	14 mo (2/3 of patients)	2 (7%) rebled	[35]
Epi and heater probe (10)	EGD: stomach/duodenum	Retrospective	18 mo	No rebleeding	[88]
Epi and heater probe (9)	"Mostly" EGD; Mostly stomach/duodenum	Retrospective	Hospitalization	1 (11%) rebled	[36]
Epi and heater probe (8)	EGD: stomach/duodenum	Retrospective	32 mo	No rebleeding	[72]
Epi and heater probe (6)	EGD	Retrospective	2 mo	No rebleeding	[40]
Epi and heater probe (2)	Colonoscopy	Retrospective	1 and 7 mo	No rebleeding	[59]
Epi and hemoclip and ethanol injection (21)	EGD: stomach/duodenum	Retrospective	47 mo	1 (4%) rebled	[79]
Epi and hemoclip (19)	EGD: Stomach	Retrospective	47 mo	1 (5%) rebled	[79]
Epi and hemoclip (16)	"Mostly" EGD: mostly stomach/duodenum	Retrospective	During hospitalization	1 (6%) rebled	[36]
Epi and hemoclip (3)	EGD: Stomach	Retrospective	2 mo	No rebleeding	[40]
Epi and multipolar electrocoagulation (5)	"Mostly" EGD: Mostly stomach/duodenum	Retrospective	During hospitalization	1 (20%) rebled	[36]
Epi and banding (1)	EGD: stomach	Retrospective	During hospitalization	No rebleeding	[36]
Epi and ethanol (52)	EGD: Stomach/ duodenum	Retrospective	69 mo	Approximately 9% hemostasis failure, 10 (20%) rebled	[89]
Epi and ethanol (11)	EGD: stomach duodenum	Retrospective	47 mo	1 rebled	[79]
Epi and ethanolamine (5)	EGD: stomach/duodenum	Retrospective	32 mo	2 (40%) rebled	[72]
Injection therapy and clip (2)	Double balloon enteroscopy: jejunum	Retrospective, multicenter	14 mo	No rebleeding	[17]
Injection therapy and APC (1)	Double balloon enteroscopy: jejunum	Retrospective, multicenter	14 mo	Rebled after 9 d	[17]
Injection and heater probe and clips (1)	Colonoscopy: colon	Case report	NA	No rebleeding	[90]

Epi: Epinephrine; APC: Argon plasma coagulation; NA: Not available.

prevent lesion formation.

Currently the ideal endoscopic therapy for recently bleeding Dieulafoy's lesion is uncertain. Large, prospective, head-to-head clinical trials are needed of different endoscopic modalities are needed but these are difficult to perform and complete due to the relative rarity of this lesion. It is reasonable, therefore for gastroenterologists to adopt particular techniques based on personal and local experience and technologies available within their endoscopy suite. Use of a spray to stem bleeding is an exciting technology because of ease of use but is experimental and unproven[94].

Therapeutic angiography is likely to become a more viable alternative to endoscopic therapy, with greater experience with this technology for this indication, but it is likely to remain a second option after failed endoscopic therapy due to the easy availability of therapeutic endoscopy at the same session when performing the initial diagnostic endoscopy and the very high success rate of therapeutic endoscopy. It is expected that endoscopic therapy will evolve with even better techniques for lesion ablation or mechanical occlusion of vascular lesions, such as the development of clinically applicable endoscopic micro-suturing devices[95].

Although endoscopic ultrasound may potentially prove very useful in identifying whether a vessel in a Dieulafoy's lesion has active flow through it, widespread adoption of this technique awaits lowering the cost of this technology, greater availability of endosonographers, and demonstration of its clinical benefits through clinical trials. CT angiography may assume a greater diagnostic role after nondiagnostic endoscopy in the face of severe, active bleeding, but its role is likely to remain limited due to a lack of therapeutic capabilities.

Currently, single-balloon and double-balloon enteroscopy are generally limited to tertiary hospitals, but should become more available in the future with lowering of costs. This may offer a new technology for diagnosing and treating small bowel Dieulafoy's lesions that are otherwise difficult to reach and treat. Capsule endoscopy may become more helpful in diagnosing jejunoileal lesions with development of capsules with active propulsion, better camera resolution, and longer-lasting and more powerful batteries, but its role will likely remain limited for bleeding from jejunoileal Dieulafoy's lesions because of a lack of therapeutic capabilities[96].

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REVIEW

Biomarkers in bile-complementing advanced endoscopic imaging in the diagnosis of indeterminate biliary strictures

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Abstract

Biliary strictures present a diagnostic challenge and a conundrum, particularly when an initial work up including abdominal imaging and endoscopic retrograde cholangiopancreatography based sampling are non-diagnostic. Advances in endoscopic imaging have helped us diagnose these strictures better. However, even with modern technology, some strictures remain a diagnostic challenge. The proximity of bile fluid to the bile duct epithelia makes it an attractive option to investigate for bio-markers, which might be representative of the functions/abnormal changes taking place in the biliary system. A number of biomarkers in bile have been discovered recently in approaching biliary strictures with their potential future diagnostic utility, further supported by the immunohistochemical analysis of the resected tissue specimens. Novel biliary biomarkers especially carcinoembryonic cell adhesion molecule 6 and neutrophil gelatinase-associated lipocalin seem promising in differentiating malignant from benign biliary strictures. Recent developments in lipidomic profiling of bile are also very promising. Biliary biomarkers appear to complement endoscopic imaging in diagnosing malignant etiologies of biliary stricture. Future studies addressing these biomarkers need to be incorporated to the current endoscopic techniques to determine the best approach in determining the etiology of biliary strictures.

Key words: Bile; Pancreato-biliary malignancies; Biomarkers; Cholangiocarcinoma; Pancreatic cancers; Biliary strictures

Core tip: Pancreato-biliary malignancies remain a diagnostic challenge despite advances in endoscopy and imaging. Serum carbohydrate antigen 19-9 which is the most commonly used tumor marker has not been able to complement the endoscopic techniques effectively. Bile fluid is a better representative of the pancreato-biliary malignancies and various tumor markers in bile have been described recently with advances in proteomics. Carcinoembryonic cell adhesion molecule 6, neutrophil gelatinase-associated lipocalin and other novel biliary markers seem promising with high sensitivities and specificities, little affected by the presence of inflammation or the degree of biliary obstruction. These are potential future tumor markers

that can complement endoscopic techniques in diagnosing malignant biliary strictures.

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INTRODUCTION

Pancreato-biliary malignancies are often difficult to diagnose with the current diagnostics, and many are detected in their advanced stages with poor prognosis[1,2]. Endoscopic retrograde cholangiopancreatography (ERCP) with brushings is often the routine choice for the endoscopists to diagnose these malignancies, but is limited by its low to moderate sensitivities[3,4]. Also, the desmoplastic nature of cholangiocarcinoma (CCA) can make the histological diagnosis more complicated[5]. Fluoroscence *in situ* hybridization polysomy to increase the sensitivity of diagnosis has also not yielded very significant differences[6,7]. Imaging techniques like endoscopic ultrasound with needle aspirations have certain limitations. Though they offer better sensitivities for pancreatic malignancies[8], they have been found to increase the risk of peritoneal metastasis in hilar CCA and cannot be justified for routine use, particularly in hilar CCA[9]. Advanced endoscopic-imaging options such as use of cholangioscopes require expertise in the field and not much data is available on their use[10]. Peroral cholangioscopy can provide direct visualization of the bile ducts, and targeted biopsies obtained through spyglass cholangioscopy (single operator cholangioscopy) might help diagnose malignant lesions especially cholangiocarcinoma better than the conventional ERCP brushing/biopsy techniques[11,12]. But they are available only in a few centers, and more randomised trials comparing the effectiveness of spyglass biopsies with the routine ERCP brush cytology or forceps biopsies are necessary to justify their advantages in routine use. Clinical and/or radiological methods thus have not been successful in the early detection of the biliary tract malignancies. Surgery is the only cure for pancreato-biliary malignancies, and early detection of these lesions is necessary. With the limitations of the above diagnostics, several tumor markers have been analyzed to complement the endoscopic techniques. The relative rarity of these biliary tract neoplasms has been a hindrance for the progression in biomarker detection, though there have been recent advances in the techniques of biomarker analysis, especially the proteomics.

One of the most commonly employed diagnostic/prognostic markers in pancreato-biliary malignancies is serum carbohydrate antigen 19-9 (CA 19-9), which is also not without limitations. Firstly, in about 10% of the patients with a negative Lewis antigen, the test would prove futile[13]. Also there have been reports on the limitation of serum CA 19-9 with its values getting affected by the presence of biliary obstruction, which can be a confounding factor in differentiation of benign and malignant lesions[14,15]. Though it can be a reasonably good prognostic marker, its diagnostic utility is not very convincing. Hence the search for new markers continues.

Biliary biomarkers

Serum has been more easily the choice for many studies in identifying biomarkers, as it is easier to obtain unlike bile which requires ERCP. The proximity of bile to the bile duct epithelia makes it a harbor of various substances, which might be representative of the functions/abnormal changes taking place in the biliary system. Bile can be obtained during the routine diagnostic or therapeutic ERCPs performed in patients with indeterminate biliary strictures without imparting any additional risks apart from the baseline risks of the procedure. Novel methods have also been used for obtaining bile (BIDA-Bile Intraductal Aspiration)[16]. Here, the biliary catheter is connected to a central suction line through a specimen trap, and obtaining bile can be quick and simple. In one of the recent studies, it was found that a large proportion of the proteins detected in bile were cellular ("secreted'" from the surrounding biliary system), stressing the importance of bile fluid analysis[17]. The fact that after bile centrifugation, the supernatant analysis and not the cell debris (sediments) reveals the presence of these tumor markers could explain that it is mostly the secreted substances in bile that are analyzed[17]. Hence, paucity of shed cells in bile should not affect the bile analysis. The results of many of the recent studies identifying novel bile biomarkers have been encouraging with their potential future diagnostic utility, further supported by the immunohistochemical analysis of the resected tissue specimens. Table 1 summarizes the various bile bio-markers that have been studied in biliary strictures.

Is there a new role for the traditional tumor markers?

Serum CA 19-9 and carcinoembryonic antigen (CEA) are the tumor markers routinely used in the diagnosis and prognosis of pancreato-biliary malignancies[18-20]. The utility of these glycoprotein tumor markers in bile has been studied too, and their diagnostic performance has not been consistent. In a large study involving 100 patients, reasonably high sensitivity of 84% and a specificity of 64% was obtained with biliary CEA (levels > 20 ng/mL), but there was a considerable overlap between the malignant and benign lesions. Moreover, in the multivariate analysis biliary CEA levels were not predictive of malignancy[21]. The low to moderate specificities for these markers suggest that

they are increased in benign/inflammatory conditions too. Multiple studies have shown that biliary CA 19-9 and CEA did not add much to the diagnostic accuracy when compared to the serum levels, as they had high false positive results[22-25]. Further supporting this view, in an older study[26], a reasonably high specificity of 84% with CEA was obtained, when benign biliary diseases due to stones were excluded from the study. In another recent study of biliary strictures[27], CA19-9 levels in bile had a sensitivity of 74%, but a poor specificity of 34%, even after eliminating patients with cholangitis.

CA 125, a marker for ovarian cancer was found to be the most specific marker in bile for CCA (specificity-76%, sensitivity-59%) in a study, which could complement endoscopic methods either alone or in combination with CEA (specificity-88%) for diagnosing malignancy[22]. Summarizing, the available studies of these tumor markers in bile are limited. However these appear to have limited diagnostic utility.

Proteomics

The changes that occur at protein level when a normal cell undergoes malignant transformation form the basis of proteomics[28]. The analytical techniques in proteomics, which are used in quantifying the proteins, are the liquid chromatography-mass spectrometry and nuclear magnetic resonance spectroscopy, apart from Western blot (Immuno blot) and ELISA. Bile serves as the direct media, which carries proteins from the local environment (liver, biliary tract and pancreas). This makes it a very valuable source of novel proteins for identifying biomarkers suggestive of biliary tract malignancy. But, one of the limitations of bile is its complex constitution with various components, and proteins accounting for a mere 7% of the total dry weight; and differential fractionation (centrifugation) could be used to reduce the complexity, concentrating the protein component as a preparatory for mass spectrometry[17]. Delipidation and desalination of bile to remove the abundant phospholipids and bile salts have also been proposed[29]. Protein biomarkers might be suggestive of the possible mechanisms of carcinogenesis, as they are reflective of the changes taking place in DNA, but more importantly in clinical context, might play a major role in improving the prognosis through early detection. Alterations of tissue proteins can occur during the early stages of carcinogenesis, and hence proteomics could detect cancers early[30].

Bile can be a host of various proteins, especially those secreted from the hepatocytes/biliary epithelia and the enzymes from the distally located pancreas. Presence of various classes of proteins such as the transport proteins (haptoglobulin, ceruloplasmin, albumin, and globulin), immune proteins (complements, immunoglobulins), and other liver and pancreatic

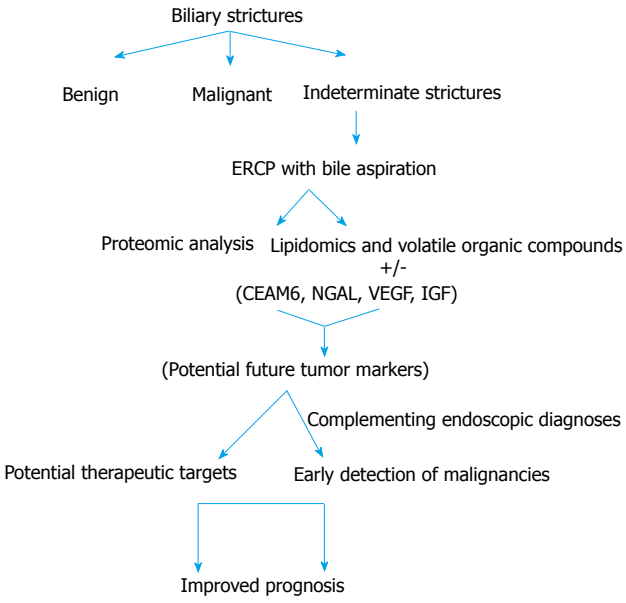

Figure 1 Approach to biliary strictures through bile biomarkers. ERCP: Endoscopic retrograde cholangiopancreatography; CEAM6: Carcinoembryonic cell adhesion molecule 6; NGAL: Neutrophil gelatinase-associated lipocalin; VEGF: Vascular endothelial growth factor; IGF: Insulin like growth factor.

enzymes (GGT, Adenosine deaminase, pancreatic lipase, carboxypeptidase) are expected to contribute to a large proportion of the proteins in bile[31]. Hence to identify the low abundance proteins that might play a role in tumorigenesis, albumin and immunoglobulins, were removed prior to separating the peptides with electrophoresis and subsequent analysis by mass spectrometry in a study[32]. Also, the presence of normally occurring proteins in elevated levels could be pathologic, suggestive of increased apoptosis/protein catabolism occurring in malignant conditions[33]. In this study, a model for identification of CCA was based on the differential levels of normally occurring proteins in bile. Hence it is not always the tumor-associated proteins that give clue regarding the possibility of malignancies.

Potential bio-markers

Novel biliary proteins that appear promising with supporting evidences from tissue immunochemistry are carcinoembryonic cell adhesion molecule 6 (CEAM6) and Neutrophil gelatinase-associated lipocalin (NGAL), though available literatures on their biliary levels are not many. Lipocalins are glycoproteins found to be associated with various inflammatory conditions and malignancies[34-36]. Table 1 describes the characteristics of the potential tumor markers in bile. Figure 1 shows the approach to the biliary strictures through bile biomarkers.

NGAL: The presence of NGAL in bile was first reported in a patient with CCA[31]. Two recent studies have found significantly elevated biliary levels of NGAL in pancreato-biliary malignancies[37,38]. In the most recent

Table 1 Potential biomarkers in bile

Bile biomarkers	Cut off value	Identification of CCA/pancreatic cancer	Sensitivity	Specificity	Comments
VEGF[57]	0.5 ng/mL	Pancreatic cancer (*vs* benign)	93.3%	72.7%	VEGF level in bile in CCA was not elevated. Another study[58] demonstrated increased serum VEGF in CCA-possible basolateral secretion of VEGF in bile duct epithelia in CCA?
	0.5 ng/mL	Pancreatic cancer (*vs* CCA)	93.3%	88.9%	
IGF[58]	NA	CCA	NA	NA	ROC (area under the curve = 1); Serum IGF levels were similar among CCA, pancreatic cancer and benign groups
CEAM6[50]	67.9 ng/mL	Malignant (CCA + pancreatic cancer)	93%	83%	Biliary levels were not critically affected by bile duct obstruction; Serum CEAM6 levels were not significantly different between the malignant and benign groups
CEAM6 + Serum CA 19-9	67.9 ng/mL, 157 kU/L		97%	83%	
NGAL[37]	459 ng/mL	Malignant (CCA + pancreatic cancer)	77.3%	72.2%	In both the studies, serum NGAL levels were not significantly different between benign and malignant groups; biliary levels were independent of serum bilirubin levels. Especially elevated in early well differentiated carcinomas in tissue immunohistochemistry-possible future application in PSC to R/O early malignant lesions/dysplasias
NGAL + Serum CA 19-9	459 ng/mL, 30.1 U/mL		91%	66.7%	
NGAL[38]	570 ng/mL	Malignant (CCA + Pancreatic cancer + GB carcinoma + metastasis)	94%	55%	
NGAL + Serum CA 19-9	3000 ng /mL, 125 U/L		85%	82%	
HSP[67]					
HSP 27	2.52 ng/mL	CCA	90%	90%	Serum levels of these markers were not significantly different between CCA and benign strictures
HSP 70	5.67 ng/mL		80%	80%	
HSP 27 + HSP 70	10.2 ng/mL		90%	100%	
Galectin Ligands					
Mac 2-BP[76]	853 ng/mL	All malignant strictures	69%	67%	Serum levels were not elevated in malignancies
Fibronectin[77]	40 ng/μmol	CCA	57%	79%	-
MCM 5[82]	1000 (cells)	CCA + Pancreatic cancer	66%	94%	MCM 5 levels in bile were significantly more sensitive than brush cytology (66% *vs* 20%; $P = 0.004$)
Pancreatic Elastase/ Amylase[83]	0.065	CCA	82%	89%	mRNA of PE 3B was also up-regulated in CCA tissues
Lipids[84]					
ON-PC	6020.1 nmol/L	CCA	85.7%	80.3%	-
S-PC	12 nmol/L	CCA	83.3%	77.8%	
ON-PC + S-PC	6032.2 nmol/L	CCA	100%	83.3%	
VOCs					
(TMA, acetone, isoprene, dimethyl sulfide, and acetaldehyde)[86]	Logarithmic model	Pancreatic cancer	83.3%	81.9%	-
(Acrylonitrile, methyl hexane and benzene)[87]	Logarithmic model	CCA in the setting of PSC	90.5%	72.7%	Biliary levels of VOCs in CCA (in the setting of PSC) were significantly lower than (benign) PSC

CCA: Cholangiocarcinoma; VEGF: Vascular endothelial growth factor; IGF: Insulin like growth factor; CEAM6: Carcinoembryonic cell adhesion molecule 6; NGAL: Neutrophil gelatinase-associated lipocalin; HSP: Heat shock proteins; PSC: Primary sclerosing cholangitis; MCM: Minichromosome maintenance proteins; VOC: Volatile organic compounds.

study, the sensitivities and specificities of NGAL in diagnosing malignant biliary strictures were 77% and 72% respectively when the cut off was taken as 459 ng/mL[37]. A higher sensitivity of 94% was achieved in the other study with the cutoff of 570 ng/mL, albeit with decreased specificity (55%)[38]. Addition of serum CA 19-9 to biliary NGAL had varying impacts on the sensitivities and specificities in both studies, but led to better results than obtained with biliary NGAL levels alone. Further encouraging was biliary NGAL's low correlation to serum bilirubin levels in both the studies, indicating that NGAL's elevation might be independent of the level of biliary obstruction. Significant NGAL elevation (tissue immunohistochemistry) in early dysplastic pancreatic lesions (including pancreatic intraepithelial neoplasia-1) in addition to well-differentiated adenocarcinoma was observed in a study[39]. Most studies report biliary/tissue NGAL rather than serum NGAL to be more representative of pancreato-biliary malignancies[37-40]. Prospective studies comparing both serum and biliary NGAL levels are much needed.

The role of NGAL in cancer progression, metastasis and potential therapy deserves mention[41,42]. Targeted silencing of *NGAL* gene in human CCA cell lines significantly decreased the *in vitro* cellular migration and invasion, suggestive of its role in cancer metastasis, and its potential for targeted anti-cancer therapy[41]. On the contrary, another study reported that NGAL as a potential suppressor of invasion and angiogenesis by suppressing vascular endothelial growth factor (VEGF) production in pancreatic cells[42]. Also in this study, tissue NGAL was expressed only by the well-

differentiated cells and not by the poorly differentiated pancreatic adenocarcinoma cells. This suggests the possible diagnostic role of NGAL in early pancreato-biliary malignancies, such as in the setting of primary sclerosing cholangitis which is a risk factor for the development of CCA[43-45]. Also as most of these patients undergo repeated ERCP stenting for biliary drainage, obtaining bile would not be a major issue too. Future studies on bile levels of NGAL in primary sclerosing cholangitis (PSC) patients with suspicious strictures would be valuable and interesting.

CEAM6: Other biliary biomarker, which seems very promising with high diagnostic sensitivities and specificities, is CEAM6. It is a cell adhesion molecule belonging to the immunoglobulin super family, which plays an important role in cell adhesion, invasion and metastasis[46]. Increased tissue expression of CEAM6 on immunohistochemical analysis of tissues in 82/89 patients with pancreatic adenocarcinoma was reported initially[47]. In this study, it was also found that negative expression of CEAM6 was significantly associated with absent lymph node metastasis and increased postoperative survival. The same group had earlier demonstrated an increase in caspase mediated apoptotic response and inhibited *in vivo* metastatic potential of pancreatic adenocarcinoma cells with *CEAM6* gene silencing. Thus this could be a possible therapeutic target for pancreatic adenocarcinoma[48]. Infact in a preclinical animal study, Strickland *et al*[49] targeted CEAM6 expressing pancreatic tumor cells using anti-CEAM6 monoclonal antibody, and observed marked inhibition of tumor growth. Its role in cancer progression, invasion and metastasis remains obvious.

Biliary CEAM6 levels were found to be elevated in malignant biliary lesions from a recent proteomic analysis of bile involving 41 patients, and the results appear promising[50]. With a cut off value of 67.9 ng/mL, the sensitivity and specificity of CEAM6 in diagnosing malignant strictures was 93% and 83% respectively, with area under the curve (AUC) of 0.92. The results were also not critically affected by biliary obstruction according to the authors when the correlation between the markers and bilirubin levels was analyzed. Addition of serum CA 19-9 further improved the diagnostic sensitivity, specificity and accuracy (sensitivity-97%, specificity-83%, AUC-0.96). The same group showed that CEAM6 was rather secreted into bile directly as it was found in the soluble form (supernatant) and not as a sediment along with the cellular debris, proving the role of bile analysis in identifying the marker.

VEGF: VEGF plays an important role in angiogenesis in cancer by stimulating the vascular endothelial proliferation, increasing vascular permeability and vasodilatation[51]. Expression of VEGF in pancreatic and cholangiocarcinoma has been described[52-54]. The role of VEGF in pancreatic cancers is especially significant as they are being used in clinical trials as therapeutic targets[55,56]. We recently analyzed the VEGF levels in bile from patients with biliary strictures; and with a cut off value of 0.5 ng/mL, we distinguished pancreatic cancer from CCA with a sensitivity of 93.3% and a specificity of 88.9%[57]. Using the same cut off value, pancreatic cancer could be differentiated from benign lesions with a sensitivity of 93.3% and a specificity of 72.7%. We also confirmed the pancreatic specificity of biliary VEGF through immunohistochemical analysis of the resected pancreatic specimens. An earlier study found increased levels of VEGF in serum of patients with CCA when compared to other groups, but the levels in bile did not differ significantly among the benign and malignant groups[58]. The insignificant levels of VEGF in bile in CCA patients could be linked to the baso-lateral secretion of VEGF from the bile duct epithelium, and not into the lumen. But in the Italian study, the levels of biliary VEGF were normal in the patients with pancreatic cancer, which contrasts with our observations. When compared to 84%, only 30% in the Italian study had histological confirmation. Future studies need to target the above mentioned issues.

Insulin like growth factor: In the same study as above, they also found biliary insulin like growth factor (IGF) to be diagnostic of extra-hepatic CCA, with the AUC = 1, when benign conditions or pancreatic cancer were taken as the control[58]. The levels of biliary IGF were also not correlating with the degree of cholestasis. IGF has been found to be associated with many cancers such as endometrial and other gynecological malignancies, lung cancers, and various other cancers including pancreatic cancers[59-62]. In a recently published study, silencing IGF 1 receptors in human pancreatic ductal adenocarcinoma cell lines inhibited pancreatic cell growth and metastasis by blocking many key signaling pathways[63]. IGF-1R antagonists have already entered clinical trials in patients with metastatic pancreatic cancer[64,65]. More studies on biliary levels of IGF to enhance its diagnostic significance in pancreato biliary malignancies are needed.

Heat shock proteins: Heat shock proteins (HSP) play an important role in protein folding and are anti-apoptotic and favors tumorigenesis[66]. A recent study showed that by combining the biliary values of HSP27 and HSP70, the sensitivity and specificity of diagnosing CCA was 90% and 100%, respectively[67]. However there was no significant increase of these proteins in serum of the patients with CCA when compared to benign lesions, though immunohistochemistry showed increased expression of these proteins in CCA and biliary intraepithelial neoplastic cells[67]. Plasma antibodies against HSP 70 were very recently described as one of the potential markers of CCA[68]. Expression of HSP 27 and HSP 70 has been found to modulate the

response of pancreatic cells to chemotherapy and hence might be potential prognostic markers as well[69,70]. In a very recent study where CCA cell lines from 78 patients with intrahepatic CCA were treated with a combination of HSP 90 inhibitor and a PTEN related pathway inhibitor *in vitro*, antiproliferative and proapoptotic effects were observed in the cell lines, demonstrating their potential therapeutic use[71]. In another study HSPD1, a heat shock protein was overexpressed in bile in patients with CCA[72]. Here in this study, other markers such as SSP411 (spermatogenesis associated protein) and PGAM-1 (phosphoglycerate mutase) in bile were also significantly elevated in CCA. Its sensitivity and specificity for detecting CCA were 90% and 83% respectively in that study. The role of these proteins, although studied remains unclear because of low specificity.

Galectin ligands: Galectins mediate cell to cell, cell to matrix interactions, apoptosis and angiogenesis; Fibronectin, Mac 2-binding protein (Mac 2-BP) and laminin are some of the ligands[73-75]. Koopmann *et al*[76] found that biliary Mac 2-BP could differentiate benign and malignant biliary tract lesions with a sensitivity and specificity of 69% and 67% respectively, that was comparable to serum CA 19-9. Similarly fibronectin, another ligand for galectin, was found to be a biliary diagnostic marker for CCA with a sensitivity of 57% and a specificity of 79%, but it was also elevated in biliary inflammation[77]. Future studies to validate these observations are necessary.

Minichromosome maintenance proteins: These are involved in DNA replication and have been found to be associated with the carcinogenesis[78-81]. The role of minichromosome maintenance proteins (MCM) 2 and MCM 5 proteins was studied through immunohistochemistry prospectively on 102 consecutive patients undergoing ERCP for biliary strictures[82]. In this study, the levels of MCM 5 in bile were also determined by automated immunoflurometric assay and compared with brush cytology. An additional 45% of cases of pancreato-biliary malignancies were detected through MCM 5 analysis in bile. With a cutoff greater than 1000, the sensitivity and specificity were 66% and 94% respectively, with a good accuracy (AUC 0.8).

Elastase/amylase: Increased levels of pancreatic elastase and decreased amylase levels in bile were detected in patients with CCA compared to benign strictures in a study[83]. The elastase-amylase ratio could detect CCA with a sensitivity and specificity of 82% and 89% respectively, with AUC-0.877. They also detected increased pancreatic elastase 3B mRNA in the CCA tissues.

Lipidomic profiling: In a pilot study, we showed that lipidomic profiling of bile could help differentiating benign and malignant biliary strictures[84]. Oxidative stress in the setting of malignancy results in the expression of oxidized phospholipids on the cancer cells, which are recognized by the host defenses leading to apoptosis of cancer cells[85]. The oxidized phospholipids were analyzed using a specialized liquid chromatography electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS) assay. Two phosphatidylcholines {ON-PC [1-palmitoyl-2-(9-oxononanoyl)-sn -glycero-3-phosphatidylcholine], S-PC (1-palmitoyl-2-succinoyl-sn -glycero-3-phosphatidylcholine)} were elevated in CCA, with ON-PC being the most diagnostic with a sensitivity and specificity of 86% and 80% respectively (AUC-0.86). The combination of the two yielded even better results with a sensitivity of 100%, specificity of 83% and area under the curve of 0.91. The development of global lipidomics of bile could make this more interesting in the development of specific biomarkers for the diagnosis of CCA.

Volatile organic compounds: Our group has also shown, from our preliminary observation, that volatile organic compounds in bile in the headspaces (gas above the sample) may be useful for early diagnosis of CCA in the setting of PSC and in distinguishing malignant from benign strictures[86,87].

About 5 mL of bile collected at the time of ERCP is centrifuged for 8 min at 150 g and 4 ℃ and the sample heated to 40 ℃ to allow the volatile organic compounds (VOCs) in the headspace to equilibrate with the samples. Twenty milliliters of headspace gas was removed and analyzed with a selected ion flow tube mass spectrometry instrument. In a prospective cross sectional study, we showed that the concentrations of 6 compounds (acetaldehyde, acetone, benzene, carbon disulfide, pentane, and trimethylamine) were increased in patients with pancreatic cancer compared with controls ($P < 0.05$)[86]. In another study, we demonstrated that out of 22 analytes tested, a VOC signature consisting of acrylonitrile, methyl hexane and benzene, had a sensitivity and specificity of 90.5% and 72.7% respectively, with a significantly lower level in CCA in the setting of PSC, after accounting for all confounding variables[87]. By using receiver-operating characteristic curve analysis, we developed a model for the prediction and diagnosis of cholangio-pancreatic cancer based on the levels of signature VOC's in these two settings[86,87]. This might need validation from our ongoing prospective study and results reproducible from other centers. The extension of this to develop biomarkers based on the concept of exhaled breath VOC print, which could be detected by a simple test, is intriguing as a potential non-invasive diagnostic marker for pancreato-biliary cancer.

To compare the biomarkers in bile and to identify the differentially expressed proteins between intra and extra hepatic CCA would be valuable, and might provide insight on their origin and pathogenesis. In a recent meta analysis, Wiggers and coworkers identified certain markers including VEGF-A, epidermal growth

factor receptor, c-erbB-2 (HER-2/neu) through tissue immunohistochemistry that were significantly differing between the intra and extra hepatic CCA[88]. Based on the tumor markers, treatment strategies might also differ between the two. Future comparative studies on bile markers (Intrahepatic *vs* Extrahepatic CCA) would be worthful.

CONCLUSION

Novel biliary biomarkers especially CEAM6 and NGAL seem promising in differentiating malignant from benign biliary strictures. Also in malignant strictures, they appear to be elevated in bile rather than serum, which is interesting and must be, evaluated in future studies. Biliary VEGF, IGF, MCM's, lipidomic profiles and VOC's are new biomarkers in bile that might become available to clinicians in the near future when facing a challenging patient with biliary strictures. Analyses of biomarkers in bile have yielded encouraging results with supporting evidences from tissue immunohistochemistry in most of the studies. In addition, with their potential therapeutic implications, targeting the malignant cells/receptors with the antibodies/inhibitors remains plausible, and more future studies on establishing their therapeutic role are also necessary. Thus, biliary biomarkers complement endoscopic imaging in diagnosing malignant etiologies of biliary stricture. Future studies addressing these biomarkers need to incorporate endoscopic techniques to determine the best approach in determining the etiology of biliary strictures.

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REVIEW

Endoscopic ultrasound in the evaluation of pancreatic neoplasms-solid and cystic: A review

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Abstract

Pancreatic neoplasms have a wide range of pathology, from pancreatic adenocarcinoma to cystic mucinous neoplasms. Endoscopic ultrasound (EUS) with or without fine needle aspiration (FNA) is a helpful diagnostic tool in the work-up of pancreatic neoplasms. Its utility in pancreatic malignancy is well known. Over the last two decades EUS-FNA has become a procedure of choice for diagnosis of pancreatic adenocarcinoma. EUS-FNA is highly sensitive and specific for solid lesions, with sensitivities as high as 80%-95% for pancreatic masses and specificity as high as 75%-100%. Multiple aspects of the procedure have been studied to optimize the rate of diagnosis with EUS-FNA including cytopathologist involvement, needle size, suctioning and experience of endoscopist. Onsite pathology is one of the most important elements in increasing diagnostic yield rate in EUS-FNA. EUS-FNA is valuable in diagnosing rare and atypical pancreatic neoplasms including neuroendocrine, lymphoma and metastatic disease. As more and more patients undergo cross sectional imaging, cystic lesions of the pancreas are becoming a more common occurrence and EUS-FNA of these lesions can be helpful for differentiation. This review covers the technical aspects of optimizing pancreatic neoplasm diagnosis rate, highlight rare pancreatic neoplasms and role of EUS-FNA, and also outline the important factors in diagnosis of cystic lesions by EUS-FNA.

Key words: Endoscopic ultrasound-fine needle aspiration; Pancreatic neoplasms; Pancreatic cysts; Review; Pancreatic adenocarcinoma

Core tip: Endoscopic ultrasound-fine needle aspiration (EUS-FNA) is a common, reliable way of obtaining tissue from within the abdominal cavity. This review details the current evidence of optimizing EUS-FNA results for pancreatic lesions, specifically adenocarcinoma. EUS and cytology from rare pancreatic lesions are highlighted to demonstrate the wide variety of pancreatic lesions and the importance of cytopathology. Also covered are cystic lesions and the ability of EUS-FNA to differentiate cysts based on EUS appearance and aspiration analysis

including new DNA analysis and measurement of k-ras mutation.

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INTRODUCTION

Pancreatic neoplasms have a wide range of pathology, from pancreatic adenocarcinoma to cystic mucinous neoplasms. Endoscopic ultrasound (EUS) with or without fine needle aspiration (FNA) is a helpful diagnostic tool in the work-up of pancreatic neoplasms. Its utility in pancreatic malignancy is well known. Over the last two decades it has become the procedure of choice for tissue diagnosis and staging of pancreatic adenocarcinoma. In this review the utility of EUS in the diagnosis of pancreatic adenocarcinoma and technical aspects of the procedure that can increase rates of pathology diagnosis will be discussed. Examples of rare and atypical lesions and the role of EUS-FNA will be highlighted. Also reviewed are the advances in differentiation and diagnosis of pancreatic cysts, including new tests (DNA analysis, k-ras measurement) that may play a role in the future discriminating cystic lesions. The current evidence, limitations, and complications of EUS-FNA in the evaluation of both solid and cystic pancreatic neoplasms will be reviewed.

PANCREATIC ADENOCARCINOMA

Pancreatic adenocarcinoma remains a rising and leading cause of cancer death in the United States. The five year survival is less than 5%[1,2], which stems from the fact that more than 80% of pancreatic adenocarcinomas present as advanced disease at time of diagnosis[2]. Often the diagnosis and stage can be clearly established with cross sectional imaging and patients can be taken for definitive surgical management. However, when there is lack of clarity in the diagnosis or stage of the disease, EUS-FNA can play an important role. Additionally, it is useful when neoadjuvant therapy is planning to be used and tissue diagnosis is needed. EUS alone is a valuable tool for staging pancreatic lesions. Figure 1 demonstrates an endoscopic ultrasound image (Figure 1A) and typical cytology of a pancreatic adenocarcinoma (Figure 1B and C). EUS has been shown to be superior to other imaging [computed tomography (CT) or abdominal US] in pancreatic tumor detection, specifically in tumors < 3 cm[3]. Earlier studies showed that EUS may be superior to CT in staging and determining surgical resectability. However with the advances in CT imaging, whether EUS still holds advantage in this setting appears to be less clear[4]. It is likely that these two modalities are complimentary in the staging of pancreatic adenocarcinoma.

EUS-FNA was first described in the early 1990's and since then it has become the standard of care in diagnosis of pancreatic masses[5]. Much of the data regarding EUS-FNA is in regards to diagnosing pancreatic adenocarcinoma. EUS-FNA is highly sensitive and specific for solid lesions, with sensitivities as high as 80%-95% for pancreatic masses and specificity as high as 75%-100%[6-8]. More recently a meta-analysis of 41 studies of EUS-FNA found a pooled sensitivity of 87%[9]; additionally, a recent systemic review of ten high-quality studies showed a pooled sensitivity and specificity of 94% and 95%, respectively[10]. When compared to CT-guided biopsy and endoscopic retrograde cholangiopancreatography (ERCP) with brush cytology, EUS-FNA has a distinct advantage. ERCP brush cytology sensitivity is quite low ranging from 30% to 85%[11]. CT-guided biopsy is a more invasive procedure than EUS-FNA and has a lower diagnostic yield. CT guided biopsy also carries the risk of peritoneal seeding, with one retrospective study showing rates as high as 16.3% compared to 2.2% with EUS-FNA[12]. Currently more centers are performing EUS-FNA so there may be a wide range of diagnostic yield in pancreatic masses, but the general trend over the last 10 years is towards higher sensitivity and specificity for pancreatic masses[9].

OPTIMIZING EUS-FNA OF PANCREATIC MASSES

Much of the research in EUS-FNA has focused on optimizing diagnostic yield for pancreatic masses. Multiple aspects of the procedure have been studied including cytopathologist involvement, needle size, providing suctioning and experience of endoscopist. The current data regarding optimization of EUS-FNA results will be reviewed below.

Studies have shown that the total number of EUS-FNA performed within a facility have been linked to higher diagnostic yield. Additionally, the availability of rapid on-site cytopathology evaluation (ROSE) evaluation also significantly increased diagnostic yield of EUS-FNA[13,14]. ROSE has become much more common in practice. All studies to date have shown that ROSE improves diagnostic yield for EUS-FNA and reduces the need for more passes and duration of the procedure[15-17]. An EUS-FNA study of 182 patients showed that with ROSE there was a significantly lower number of inadequate samples (1% *vs* 12.6%) and a much higher diagnostic sensitivity (96.2% *vs* 78.2%)[18].

Cytopathologist availability may be difficult and costly; many institutions do not have a cytopathologist readily available to come to endoscopy suites. Two studies have shown that having cytopathologist

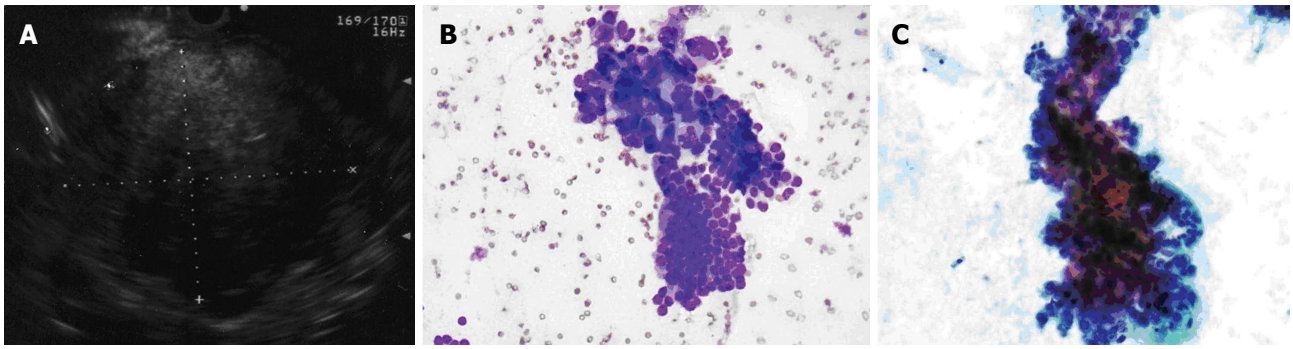

Figure 1 Pancreatic adenocarcinoma. A: Endoscopic ultrasound image demonstrating a large pancreatic adenocarcinoma; B: Pancreatic adenocarcinoma. A crowded group of large, pleomorphic ductal cells with irregular hyperchromatic nuclei and prominent anisocytosis. These contrast well with an orderly sheet of benign ductal epithelial cells with round, uniform nuclei (bottom) (Diff-QuikTM stain, × 100); C: Similar in appearance malignant cells in a Papanicolaou-stained preparation (× 400).

available *via* telepathology for rapid review is as effective as when they are present in the room[19,20]. Further studies are looking at the impact of individual cytopathologists and cytology technicians on diagnostic yield. Recently it was shown that providing specific training to cytology technicians can dramatically impact their personal ability to confirm accuracy and diagnosis[21].

The use of optimal equipment for EUS-FNA, including optimal needle size, has been studied extensively. Most commonly 22 or 25 gauge needles are used in EUS-FNA of pancreatic masses. There have been three randomized control studies looking at 22 gauge *vs* 25 gauge needles. The overall trend of these studies was a slightly more favorable yield with the 25 gauge needle, however none showed a statistically significant difference[22-24].

Beyond choosing the appropriate needle size, different aspects of obtaining cytology including suctioning and stylet use have been studied. The role of suctioning in EUS-FNA has been studied with two randomized control trials showing no difference in diagnostic yield. One study did show higher cellularity with suctioning, however this did not lead to an increase in diagnostic accuracy[25,26]. Most experts agree that suction does not increase diagnostic yield, and in fact likely increases the amount of blood in specimens[27]. Use of stylet has also shown no benefit in improving diagnostic yield, with studies showing that it also increases the amount of blood thus leading to poorer samples[28,29].

There is a definite learning curve in performing EUS-FNA for pancreatic masses. As endoscopists perform more EUS-FNA, sensitivity rises[30]. The current ASGE guidelines recommend 25 supervised EUS-FNA for the diagnosis of pancreatic adenocarcinoma, however literature supports more experience. It has been shown that rates of complications and number of passes needed also decrease with more experience. This study looked specifically at the performance of one endoscopist over the course of the first 300 EUS-FNAs, showing improved performance when comparing the last 100 procedures performed to the first 100[31].

NON-ADENOCARCINOMA MASSES

Pancreatic adenocarcinoma is the most common pancreatic mass lesion, however approximately 10%-15% masses are due to other lesions including cystic neoplasms and neuroendocrine tumors[32]. Thus, getting an accurate diagnosis is important to devise an appropriate management plan. Recently, primary non-adenocarcinoma of the pancreas was found in 25% of EUS-FNA of pancreatic masses[33]. Neuroendocrine tumors comprised 37.5% of the primary non-adenocarcinomas of the pancreas while mucinous neoplasms with mixed cystic/solid components made up 25%. In this study, masses in the tail of the pancreas were more commonly primary non-adenocarcinoma of the pancreas, and these masses were less likely to have vascular invasion or malignant lymphadenopathy when compared to adenocarcinoma[33]. Primary non-adenocarcinoma of the pancreas is often difficult to differentiate from adenocarcinoma with EUS alone. Cytopathology becomes more useful in these cases. The differential diagnosis for pancreatic masses should include not only adenocarcinoma but also neuroendocrine tumors, lymphoma, and metastatic disease.

NEUROENDOCRINE TUMORS

Neuroendocrine tumors of the pancreas are most commonly sporadic but some arise in context of inherited genetic syndromes, including multiple endocrine neoplasia type 1 and 2. Pancreatic neuroendocrine tumors are non-functional 40%-91% of time; the most common functioning tumors are insulinomas followed by glucagonomas, gastrinomas (Zollinger-Ellison syndrome) and somatostatinomas[34]. Some studies have shown that EUS-FNA is effective for obtaining preoperative determination of Ki-67 expression, which is an important prognostic factor for grading pancreatic endocrine tumors[35]. EUS-FNA is highly accurate for neuroendocrine tumors with sensitivity above 90%;

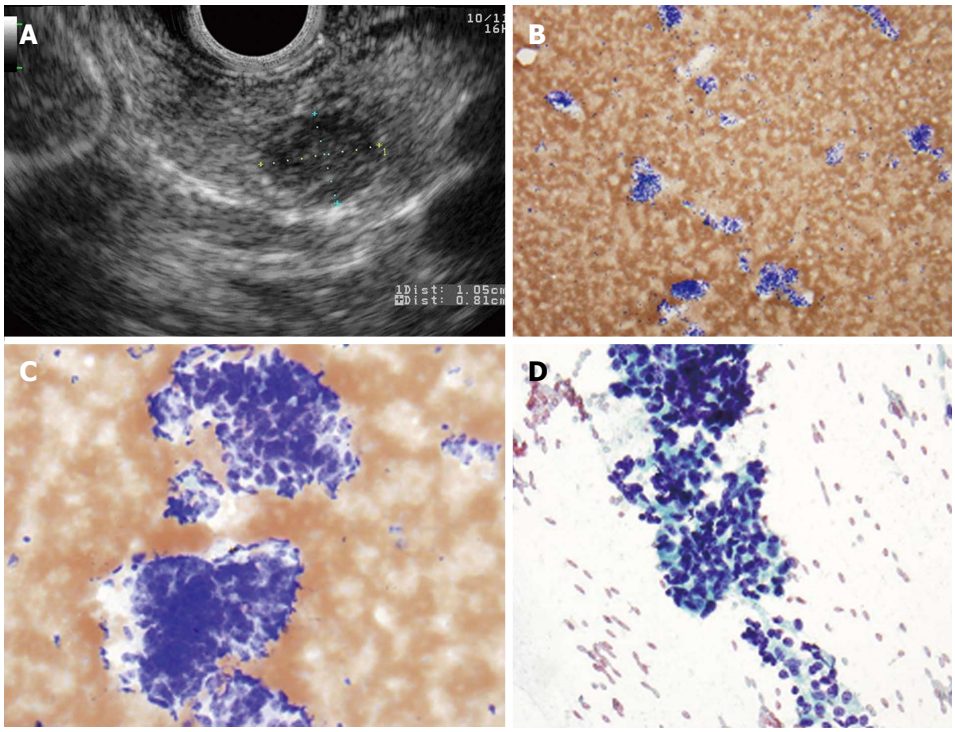

Figure 2 Pancreatic neuroendocrine neoplasm. A: Endoscopic ultrasound image showing a 9 mm × 10 mm neuroendocrine tumor (insulinoma); B: Low-power view shows a cellular aspirate composed of clusters of uniform cells (Diff-QuikTM stain, × 100); C: High power view shows uniform cells with high N:C ratios and coarse chromatin (Diff-QuikTM stain, × 400); D: Papanicolaou stain highlights coarse, evenly distributed chromatin (× 400).

thus it is helpful for making a diagnosis[35,36]. Typical EUS imaging of a neuroendocrine tumor and cytologic appearance of the tumor cells are presented in Figure 2.

LYMPHOMA

Primary pancreatic lymphoma is rare, comprising only 0.5% of all pancreatic masses[37]. In one study of EUS-FNA, lymphoma made up to 8% of the non-adenocarcinoma masses[33]. Most pancreatic lymphomas are non-Hodgkin lymphomas. Making an accurate diagnosis of lymphoma is important as treatment is generally chemotherapy and/or radiation as opposed to adenocarcinoma which is most often managed by surgery[37]. EUS-FNA has become more commonly used in the diagnosis of pancreatic lymphoma. Pancreatic lymphomas are less likely to present with jaundice. The addition of flow cytometry has greatly improved lymphoma diagnosis compared to cytology alone[38]. Figure 3 represents cytology from pancreatic follicular lymphoma showing a cellular aspirate composed of relatively monotonous in appearance lymphocytes with mild atypia.

PANCREATIC GASTROINTESTINAL STROMAL TUMOR

Primary extra-gastrointestinal stromal tumor arising in the pancreas is exceedingly rare. There have been 21 cases reported in the English literature in the last 10 years. The diagnosis of gastrointestinal stromal tumor (GIST) is based on histological, immunohistochemical, and molecular features. Microscopically the tumor usually consists of spindle and/or epithelioid cells typically arranged in fascicles or nests. GIST can often have the appearance of neuroendocrine tumors on EUS (Figure 4) thus an addition of EUS-FNA is highly valuable for differentiating these tumor types[39]. Figure 5 represents cytology from a primary pancreatic GIST tumor. Immunoistochemical positivity of CD117 confirms the diagnosis of GIST (Figure 6).

METASTATIC DISEASE

Metastatic disease to the pancreas is uncommon. The most common metastatic disease found with EUS-FNA includes renal cell carcinoma, melanoma and small cell lung cancer with renal cell carcinoma being the most common[33,40,41]. Other tumors metastatic to pancreas include papillary serous carcinoma (Figure 7), breast cancer, and rarely, sarcoma. EUS-FNA may be helpful in making these rare diagnoses.

NON-DIAGNOSTIC SAMPLES

Despite pancreatic adenocarcinoma being the most common mass of the pancreas, the above examples highlight the broad differential that exists with a pancreatic mass. It also highlights the importance of tissue diagnosis especially when diagnosis is not clear. While EUS-FNA remains the procedure of choice for

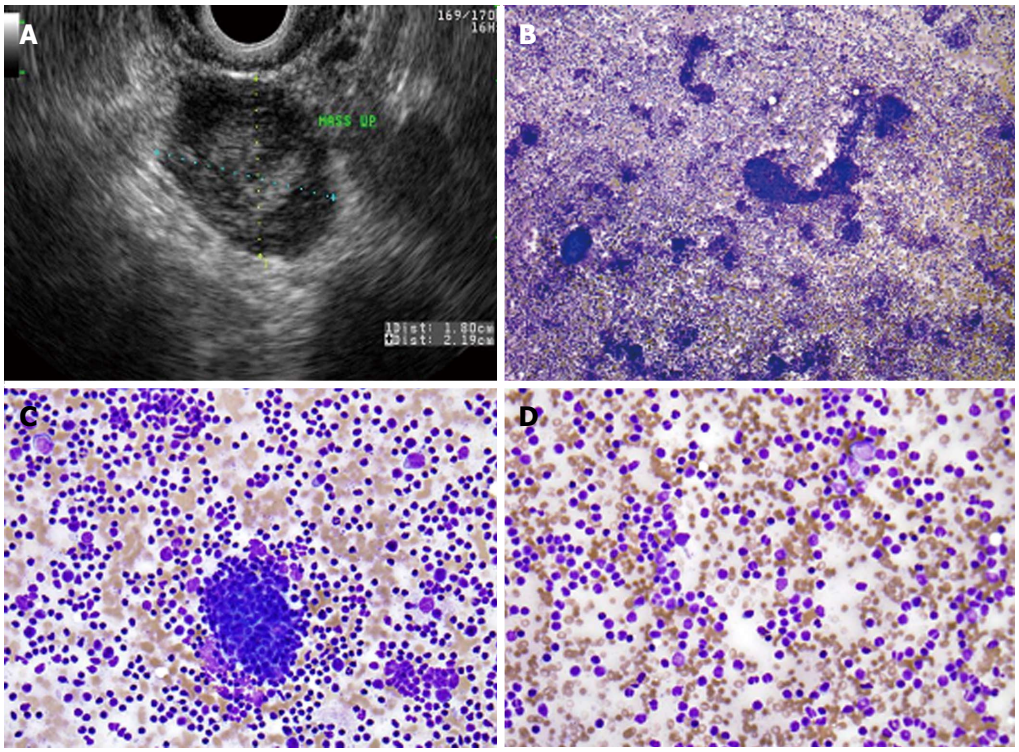

Figure 3 Primary pancreatic lymphoma. A: Endoscopic ultrasound demonstrating a 1.8 cm × 2.2 cm lymphoma in the uncinate process of the pancreas; B: Low-power view showing a very cellular aspirate composed of discohesive lymphoid cells (Diff-QuikTM stain, × 100); C: High-power view showing an admixture of mature lymphocytes of various sizes with no more than a minimal atypia; lymphoid aggregates resembling a germinal center are also present (bottom); D: Small mature lymphocytes with cleaved and irregular nuclei raising suspicion for a mature B-cell lymhoma. (Diff-QuikTM stain, × 400).

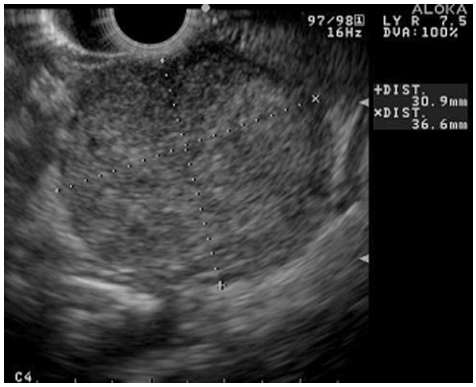

Figure 4 Endoscopic ultrasound image of large, 3.5 cm × 4.4 cm, round, hypoechoic, heterogenous mass lesion arising from the tail of the pancreas.

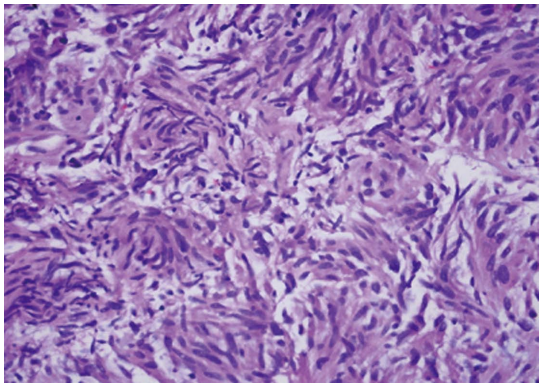

Figure 5 Cytology from a primary pancreatic gastrointestinal stromal tumor.

obtaining tissue from pancreas lesions, non-diagnostic samples are not uncommon. Determining what to do when FNA is non-diagnostic is difficult. Multiple studies have shown the benefit of repeat EUS-FNA with high diagnostic yield rates of 61% to 84%[42-44]. Given this data, many authors recommend repeat EUS-FNA when providers are faced with a non-diagnostic sample.

PANCREATIC NEOPLASMS-CYSTIC LESIONS

EUS-FNA plays a vital role in the examination of pancreatic cystic lesions. Pancreatic cysts are quite common with incidental cysts being reported in range of 2.6%-13.6% depending on imaging modality used[45,46]. In one autopsy study cysts occurred in 24.3% of patients[47]. The true incidence of neoplastic pancreatic cysts is difficult to determine. Deciding which pancreatic cysts require EUS-FNA for evaluation is one of the first steps in management. With advances and ease of EUS-FNA, it would be tempting for endoscopists to perform FNA on all lesions referred to them; however there are certain attributes on imaging which may help to avoid FNA altogether. Magnetic resonance imaging (MRI) and CT are valuable in assessing cystic size and determining if cystic lesions have worrisome findings

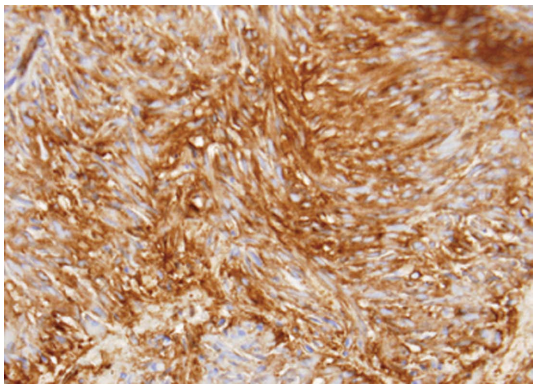

Figure 6 Pancreatic gastrointestinal stromal tumor, cytology demonstrates a spindle cell neoplasm with moderate nuclear pleomorphism which stains strongly positive for CD117 and negative for desmin, consistent with a gastrointestinal stromal tumor arising from the pancreas. (Courtesy of Rashmi Agni, University of Wisconsin Department of Pathology and Laboratory Medicine).

such as connection with the pancreatic main duct. MRI has a distinct advantage over CT in visualizing fluid, particularly in T2 weighted series[46]. EUS alone has a particular advantage over other imaging modalities for evaluation of cysts due to the close proximity of lesions. EUS is particularly good at examining cyst morphology including size location, internal structural features, wall thickness, the presence of calcifications and ductal communication.

Generally cystic lesions are divided into two categories: neoplastic cystic tumors and non-neoplastic cystic tumors. Neoplastic cystic tumors include mucinous cystic neoplasm (MCN), intraductal papillary-mucinous neoplasm (IPMN), and serous cystic neoplasm (SCN). Morphologic features are different for each cyst type.

SCNs, often called microcystic adenoma or glycogen-rich cystadenoma, are generally considered benign lesions as they have been associated with only a few cases of malignant conversion. On imaging, SCNs often have a honeycomb appearance. A central stellate scar is pathognomonic for SCN. There tend to be thin internal septa that are hypervascular on Doppler. Around 10% of SCNs are unilocular without an obvious microcystic component[48,49].

MCNs are found almost exclusively in the distal pancreas. They tend to occur in middle-aged women and generally considered to have a low malignant potential[50]. MCNs are characterized by two distinct histologic components: an inner epithelial layer composed of tall mucin-secreting cells, and a densely cellular ovarian-type stroma[50]. On imaging, MCNs are multiloculated cysts with a visible cystic wall. Peripheral calcification (egg shell calcification) can be seen in 10%-25% of MCNs and help to differentiate them from SCN. It is not always possible to determine lesions to be MCN on imaging alone thus FNA can be helpful. Due to malignant potential, most MCNs are removed surgically. Lesions less than 4 cm have low malignant potential, and in elderly patients who are not strong surgical candidates, these lesions can be observed[50]. Differentiating MCN from mucinous cystadenocarcinoma (Figure 8) by imaging alone is difficult; cytology and fluid analysis are both helpful in differentiating the two.

IPMNs were first recognized in 1982 and since then these cysts are commonly seen incidentally on cross sectional imaging. IPMN can appear as a cyst or a cluster of cysts in the uncinate process (Figure 9). IPMNs are generally defined as intraductal epithelial neoplasms of mucin-producing cells of the main duct or side branches[51]. Main duct IPMNs can cause dilation of the pancreatic duct up often > 5 cm; and have higher malignant potential thus are generally managed surgically[52]. Main duct IPMNs can create the classic "fish mouth papilla" due to the presence of mucin within the main duct (Figure 10).

Despite the advances of EUS in visualizing cystic lesions, EUS alone is often not enough in determining if malignancy is present. The addition of cystic fluid analysis further helps differentiate cysts. Currently, measurement of amylase and carcino-embryonic antigen (CEA) are the most routinely used in clinical practice. Amylase is often used in differentiating cystic neoplasms from pseudocysts, with amylase < 250 U/L being highly specific for SCN and MCNS (98%). In a review of 12 studies, the median values of amylase in pseudocysts, SCN, MCN and mucinous cystadenocarcinoma were 11000, 250, 8000 and 150 IU/L, respectively[53].

Multiple tumor markers have been studied to help differentiate mucinous neoplasms from non-mucinous neoplasms. These markers include CEA, CA 19-9, CA 72-4 and CA-125; ultimately CEA was determined to be the most useful in this setting[53]. A cut off of 192 ng/mL for CEA was first demonstrated by Brugge *et al*[54] as providing the greatest area under the curve (0.79) for differentiating mucinous *vs* nonmucinous cystic lesions. Additionally, a CEA > 800 ng/mL has been shown to be 79% accurate for mucinous lesions (MCN or mucinous cystadenocarcinoma)[53]. Higher CEA levels are more often associated with malignant lesions. Cyst fluid cytology can also be helpful in determining if there is an underlying mucinous cystadenocarcinoma although sensitivity is not high (sensitivity of 48% for malignant cystic lesions)[53]. Brugge *et al*[54] showed the sensitivity of cytology for MCN to be as low as 34.5% with a specificity of 83%. Figure 11A and B represents cytology from a mucinous neoplasm; mucinous cystic neoplasm and intraductal papillary mucinous neoplasm are indistinguishable cytologically. Most centers combine amylase and CEA measurements and fluid cytology to establish the diagnosis of mucinous cystic neoplasm.

Recently DNA analysis and k-ras mutation have also been shown to be useful to determine pancreatic cyst type and the presence of malignancy. In the PANDA

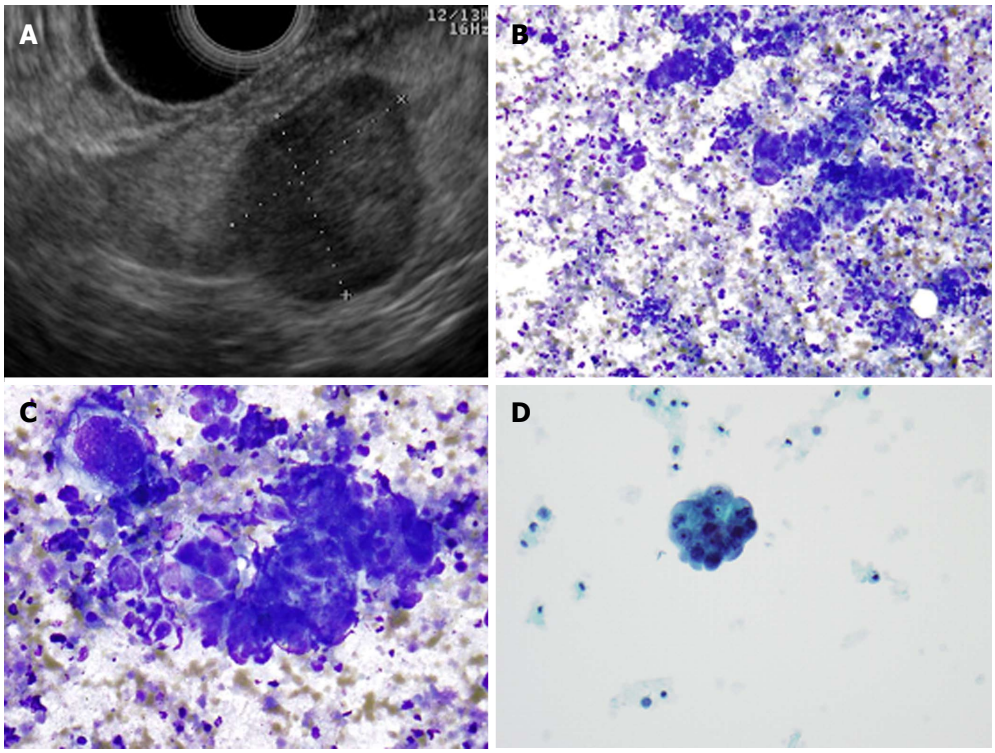

Figure 7 Metastatic high-grade serous carcinoma of the ovary. A: Endoscopic ultrasound image of a metastatic high-grade serous carcinoma of the ovary; B: Low-power view showing a cellular aspirate with a necrotic background (Diff-QuikTM stain, × 100); C: High-power view showing groups of malignant cells with large nuclei and prominent nucleoli. These cells are difficult to distinguish from a primary pancreatic ductal adenocarcinoma; however, necrotic background is not common in a primary tumor (Diff-QuikTM stain, × 400); D: Papanicolaou stain showing a cannon ball shaped group of malignant cells with large, round nuclei and prominent nucleoli, characteristic of serous ovarian carcinoma (× 400).

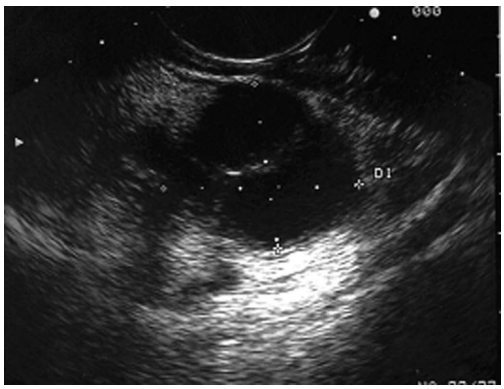

Figure 8 Endoscopic ultrasound image demonstrating a cystadenocarcinoma.

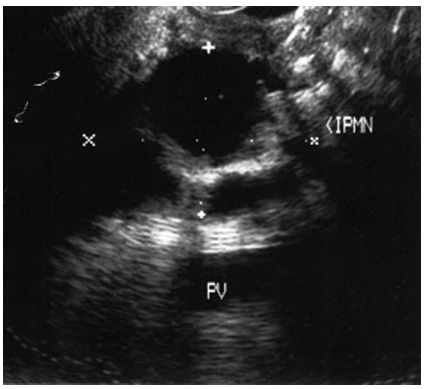

Figure 9 Endoscopic ultrasound image demonstrating an intraductal papillary-mucinous neoplasm.

study, using the criteria of a high amplitude k-ras mutation followed by allelic loss showed a maximum specificity of 96% for malignancy. Additionally, this study was able to demonstrate that all malignant cysts that were negative by conventional cytologic evaluation could be diagnosed as malignant by using DNA analysis[55]. Recently two studies have used microRNAs (miRNA) with good success differentiating pancreatic cysts[56,57] with one study showing a panel of miRNA being able to distinguish MCN from SCN, branch duct-IPMN, main duct-IPMN, and adenocarcinoma with a sensitivity and specificity of 100%.

COMPLICATIONS

One of the biggest concerns when considering aspiration of a cystic lesion is the introduction of infection. Although rare, multiple aspirations increase this risk. The current guidelines recommend one aspiration for cysts to minimize this risk, followed by 48 h of antibiotic therapy[58]. Another complication when aspirating cysts is intracystic hemorrhage, also rare, endoscopists should be aware of this complication. Most patients with intracystic hemorrhage can still be managed on an outpatient basis with antibiotics[59].

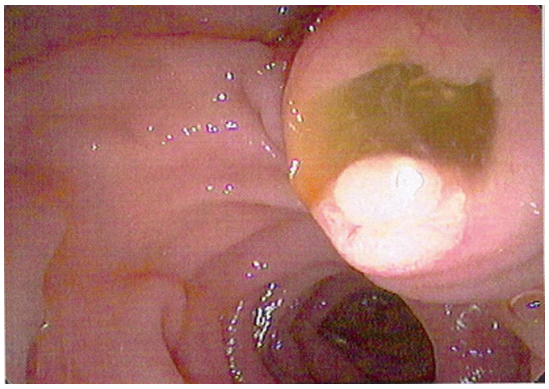

Figure 10 Endoscopic view of "fish mouth papilla" due to the presence of mucin within the main duct.

The overall rate of complication with EUS alone or EUS-FNA is quite low. Complications other than infection and bleeding include perforation and the unique risk of pancreatitis. Perforation with EUS is rather rare. In a survey study, cervical esophageal perforation occurred in only 16 of 43852 reported upper EUS procedures at a frequency of 0.03%. Most of these patients were elderly, and most of the EUS procedures were done by trainees or personal with limited experience (less than 1 year)[60]. Experts agree that EUS is associated with a similar rate of perforations compared with standard endoscopy[58].

Pancreatitis is a unique complication associated with EUS-FNA for aspiration of both masses and cysts. Reported rates of pancreatitis associated with pancreatic EUS-FNA range from 0% to 2%[58]. In one study where two cases of pancreatitis were reported, both were mild and both patients had a recent history of pancreatitis. Authors concluded a history of recent pancreatitis could be potential risk factor for procedure-induced pancreatitis[61].

CONCLUSIONS

EUS-FNA is a safe and effective procedure for the evaluation of solid and cystic lesions of the pancreas. Ways to optimize diagnostic yield for pancreatic masses continue to be investigated; overall the availability of ROSE seems to have the biggest impact on results. Optimal needle size appears to be 22 or 25 gauge, while suctioning and stylet do not have a positive impact on performance. EUS-FNA is helpful in differentiating adenocarcinoma from other more rare lesions including neuroendocrine tumors, lymphoma and metastatic lesions, and whenever diagnostic uncertainty exists; EUS-FNA should be pursued. In the evaluation of cystic lesions, EUS-FNA is a safe and effective way of classifying lesions. Measurement of cystic fluid CEA, amylase and cytology remain valuable in routine aspiration. Studies on DNA markers show promise in optimizing the detection of cystic malignancies, although currently routine use of DNA markers is not recommended. Whether it is evaluating a solid or cystic pancreatic lesion, EUS-FNA plays a pivotal role, as technology improves this role will continue to grow.

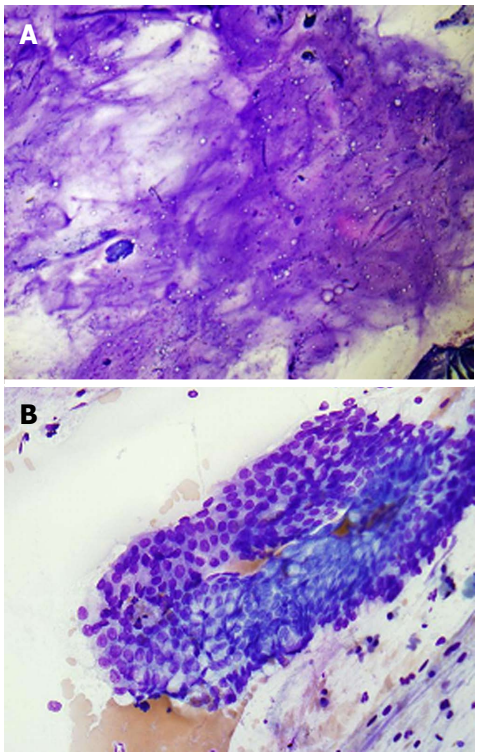

Figure 11 Pancreatic mucinous neoplasm. A: Low-power view of pancreatic mucinous neoplasm showing copious thick, colloid-like mucin (Diff-QuikTM stain, × 100); B: High-power view of pancreatic mucinous neoplasm showing sheets of only mildly atypical columnar cells containing intracytoplasmic mucin; these cells are very difficult to distinguish from benign gastric or duodenal epithelium (Diff-QuikTM stain, × 400).

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REVIEW

Quality monitoring in colonoscopy: Time to act

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Abstract

Colonoscopy is the gold standard test for colorectal cancer screening. The primary advantage of colonoscopy as opposed to other screening modalities is the ability to provide therapy by removal of precancerous lesions at the time of detection. However, colonoscopy may miss clinically important neoplastic polyps. The value of colonoscopy in reducing incidence of colorectal cancer is dependent on many factors including, the patient, provider, and facility level. A high quality examination includes adequate bowel preparation, optimal colonoscopy technique, meticulous inspection during withdrawal, identification of subtle flat lesions, and complete polypectomy. Considerable variation among institutions and endoscopists has been reported in the literature. In attempt to diminish this disparity, various approaches have been advocated to improve the quality of colonoscopy. The overall impact of these interventions is not yet well defined. Implementing optimal education and training and subsequently analyzing the impact of these endeavors in improvement of quality will be essential to augment the utility of colonoscopy for the prevention of colorectal cancer.

Key words: Colonoscopy; Quality improvement; Cecal intubation rate; Adenoma detection rate

Core tip: Quality is a measure of actual performance compared to the defined standard as outlined by the medical community. Important quality measures in colonoscopy include informed consent, adequate bowel preparation, cecal intubation, withdrawal time, adenoma detection rate, appropriate screening and surveillance follow-up recommendations, and adverse events. The above quality measures could affect patient outcomes and therefore should be implemented and monitored regularly.

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INTRODUCTION

In 1998, the Institute of Medicine identified significant variations in practice, safety, and lack of accountability in healthcare, thereby highlighting the necessity of quality assurance[1]. Endoscopy is an important

modality in the diagnosis and management of digestive diseases. High quality endoscopy ensures that a patient receives an appropriately indicated procedure that is properly and effectively delivered with minimal risk. This satisfies the three parameters of quality outlined by the institute of medicine: safety, practice consistent with medical knowledge, and customization[2].

More than 14 million colonoscopies were performed in the United States in 2002, making it one of the most common procedures performed[3]. Colonoscopy is largely safe, effective, and well tolerated by patients with a major indication for colonoscopy of colorectal cancer screening and surveillance[4]. Colonoscopy is the only cancer-screening test that can both provide diagnosis and therapy as the adenoma-carcinoma sequence renders most colorectal cancer preventable by the identification and removal of adenomatous polyps[5].

The outcomes of health care are intimately linked to its quality. Many studies have shown that the quality of colonoscopy is directly linked to interval cancer, likely the result of missed lesions[6-8]. A high quality colonoscopy requires involvement of three different factors in order for the exam to be adequate: the patient (bowel preparation), the structure (facility, equipment), and the provider (competence). Each component is critically important to ensure that a malignancy or adenoma is detected. The efficacy to reduce colon cancer requires adequate visualization of the entire colon, diligence in examining the mucosa, and patient compliance. Based on the available literature and expert consensus, a joint task force of the American College of Gastroenterology (ACG) and the American Society for Gastrointestinal Endoscopy (ASGE) has proposed several quality measures to establish competence[9].

MEASURES OF QUALITY IN COLONOSCOPY

Pre-procedure

Prior to examination, potential risk factors that may increase complications should be identified. This includes use of antithrombotic therapy or significant medical comorbidities (heart disease, lung disease, renal failure). The American Society of Anesthesiology (ASA) classification is the most commonly employed system to identify patients at higher risk of developing endoscopy (and sedation) related complications. Those with a higher ASA class (Ⅲ or above) should be performed in a hospital as opposed to outpatient setting with consideration for anesthesia support.

Informed consent with discussion of risks, benefits, and alternatives should be discussed and documented. The risk of missed lesions may also be addressed, as no examination in medicine is infallible[10]. Tandem colonoscopy has demonstrated miss rates up to 27% for lesions ≤ 5 mm. Even for adenomas ≥ 1 cm, the miss rate has been calculated to be as high as 6%[11].

Quality of bowel preparation

Complete examination of the colon is feasible only with an adequate bowel preparation[12]. Inadequate bowel cleansing is associated with increased healthcare expenditure between 12% to 22% given altered recommendations for earlier follow-up[13]. Education on the importance of sufficient bowel cleansing should be addressed[14,15]. Patients with a lower socioeconomic status (and decreased health literacy)[16], history of constipation[17], diabetes[18], those on chronic narcotics, or prior history of inadequate bowel preparation have an increased probability for poor bowel preparation and should be recognized early. These patients should have modifications to their regimen such as following a low residue diet[19], and/or extended (two day) bowel preparation. Split-dose preparation yields improvement in bowel quality and should be universally applied to all patients[20].

Documentation of the bowel preparation is fundamental to the overall quality of the procedure[10]. The effectiveness of the bowel cleansing can be described with qualitative terms ranging from poor to excellent. An adequate preparation is defined by the ability to detect lesions ≥ 5 mm[21]. However, this format is not validated and subject to operator bias. Integration of a validated scale such as the Boston Bowel Preparation Scale[22] may reduce bias and aid in consistent and objective documentation.

Cecal intubation rate

Depth of maximal insertion should be documented in the text with support of endoscopic photographs. Cecal intubation with complete inspection of the cecal caput is imperative given the fact that many interval cancers occur in the proximal colon[23,24]. Two major landmarks confirm visualization of the cecum: the appendiceal orifice and ileocecal valve. A careful inspection of the cecal floor behind the ileocecal valve is very important. Current guidelines expect cecal intubation in ≥ 90% of cases overall and in ≥ 95% of screening colonoscopies[9]. In a large population based study, colonoscopy performed at an office or private setting in contrast to a hospital or academic institution was the strongest predictor for an incomplete examination[25].

Adenoma detection rate

Adenoma detection rate (ADR) is perhaps the most important quality metric of colonoscopy. It is defined as the percentage of colonoscopies in which at least one adenoma was identified and removed per colonoscopy. The prevalence of adenomas varies by age and gender. According to current recommended guidelines on quality indicators, among healthy asymptomatic patients undergoing screening colonoscopy, adenomas should be detected in ≥ 25% of men and ≥ 15% of women[9,26,27]. A landmark study by Kaminski *et al*[6]

Table 1 Colonoscopy screening and surveillance guidelines

Finding	Advised interval
No polyps/adenomas	10 yr
Single first degree relative with cancer (or adenomas) ⩾ 60 yr	10 yr (begin age 40)
Two or more first degree relatives with cancer (or adenomas) or one first degree relative diagnosed ⩽ 60 yr	5 yr (begin age 40)
Few (1-2), small tubular adenomas (< 1 cm)	5 yr
Advanced adenomatous lesions (> 1 cm or villous histology or high grade dysplasia) or > 3 adenomas	3 yr
Numerous (> 10) adenomas	Individualized approximately < 3 yr
HNPCC	1-2 yr (begin age 20-25)
Sessile adenomas > 2 cm, removed piecemeal	2-6 mo
Post cancer resection surveillance	Clear colon, then 1 yr, then 3 yr, then 5 yr

Joint guidelines from the American Cancer Society, the United States Multi-Society Task Force on Colorectal Cancer, and the American College of radiology. HNPCC: Hereditary nonpolyposis colorectal cancer.

validated that ADR is an independent predictor of the risk of interval cancer if ADR is less than 20%. Missed lesions have been hypothesized to be a principal contributor for interval cancer after colonoscopy[7], again highlighting the necessity of monitoring the ADR among individuals and the institutions.

The current benchmarks for ADR may be setting the standard too low. Multiple studies have shown much higher rates of adenoma detection[28-30] with significant variation among individual endoscopists. The endoscopist performing the procedure may have a stronger correlation with ADR more than previously identified traits such a patient's age or gender[31].

Unfortunately, despite the obvious strengths of this metric, it has some limitations. It is time intensive to calculate this measure because it requires manual integration of the endoscopy and pathology reports. ADR cannot be calculated in real-time as pathology findings are not available at the time of endoscopy. Hence, PDR has been advocated in some studies to be a surrogate for ADR[30,32]. The proposed benchmarks for PDR are 40% for men and 30% for women[33]. This method is certainly more convenient; however given high prevalence of hyperplastic polyps in the recto-sigmoid area and non-neoplastic polypectomy, there is risk for gaming the system by falsely inflating one's PDR.

The primary goal of screening and surveillance colonoscopy is detection and removal of all neoplastic colon polyps. However, ADR fails to distinguish endoscopists who identify more than one adenoma. Because every adenoma has risk of malignancy, endoscopists who are able to identify more adenomas per colonoscopy may be providing greater protection for colorectal cancer. Hence, novel scoring systems such as ADR-Plus[34] or mean adenoma per procedure (MAP)[35] have been proposed to provide greater discriminating ability among endoscopists. These models do provide more detail compared to ADR, however they carry the same burden of calculation, without clear benefit on outcomes.

Withdrawal time

Withdrawal time is the time at which the cecum is reached to when the colonoscope is withdrawn from the anus. The majority of detailed inspection of the colonic mucosa occurs during this phase. A landmark study by Barclay has demonstrated that there is increased detection of significant neoplastic lesions if the withdrawal time exceeds six minutes[36]. As a result, the United States Multi-Society Task Force on colorectal cancer recommends that withdrawal, excluding time for biopsy and polypectomy, should average between six to ten minutes[9]. Although this quality measure has been validated in some respects, it has significant limitations. For instance, an inefficient endoscopist may spend much longer than 6 min on withdrawal without complete visualization of the mucosa missing critical area between the haustral folds. A comprehensive examination includes careful examination of mucosa proximal to folds and flexures, better colonic distension, and washing of debris from the colon[37]. Ideally, rather than a quantitative requirement, focus should instead be on clear and effective visualization.

Screening and surveillance intervals

Screening and surveillance interval guidelines after colonoscopy have been published by the United States Multi-Society Task Force and are summarized in Table 1[38]. Compliance (with documentation) with these guidelines is an important quality measure. Adherence to guidelines is emphasized to decrease overuse of colonoscopy, which leads to increased exposure to potential procedural harm and drains resources that could be more effectively used. The efficiency and cost-effectiveness of colorectal cancer screening by colonoscopy is dependent upon the ability of the endoscopist to confidently follow established guidelines. For reasons unclear, studies have shown that postpolypectomy surveillance colonoscopy is frequently performed at shorter intervals[39]. Nonetheless, there are instances when repeat colonoscopy recommendations require an individualized approach based on clinical judgment that may differ than conventional guidelines; procedures performed at shorter or longer intervals than advised should be supported by written documentation. The variation discussed above underscores the need for

Table 2 Healthcare quality improvement projects[46]

Plan-Do-Study-Act (P-D-S-A)
Employs cycles of planning (P), small scale pilot testing (D), analysis of test results and lessons learned (S), followed by incorporation and maintenance of new processes into practice (A)
Useful when resources and time are limited and rapid stepwise improvement is desired
Lean method
Seeks to increase efficiency and reduce waste by excluding all processes, steps, or inputs that fail to contribute value to the end product
Useful when existing practices are deemed to be inefficient and cumbersome, with bottlenecks and excessive rework
Employs collaborative team input and process revision through value stream mapping
Six Sigma method
Intensively data driven approach to minimizing variation and thereby reducing defects or errors to improve quality
Use a cyclic approach referred to as the Define-Measure-Analyze-Improve-Control method
Employs more rigorous analytical tools and process control charting under the guidance of local experts
Especially appropriate for repetitive high frequency processes

quality monitoring of this aspect of colonoscopy.

Adverse events

Risk of complication is inherent to any procedure but endoscopists should be competent and proficient in their skills in order to maximize benefit while minimizing potential harm. Once a complication occurs however, it is important to document and monitor trends to ensure quality control. If rates exceed the established guidelines for an endoscopist or institution, investigation should be pursued to assess patient risk factors and procedure complexity to amend this situation.

Postpolypectomy bleeding is the common complication of a colonoscopy[40]. Typically, the risk of bleeding increases with increasing size of polyps, especially those located in the proximal colon. While the overall risk for postpolypectomy bleeding is around 1%[41,42], for polyps larger than 2 cm, bleeding rates are as high as 10%[40]. Bleeding can occur immediately or within 14 d of the procedure. Most bleeding stops spontaneously, however some patients require endoscopic evaluation. Therapy includes injection, cautery, or clipping. Data thus far is conflicting regarding the role of use of clips prophylactically[43,44].

Perforation is the most serious complication. The incidence of perforation due to colonoscopy is variable in the literature ranging between 1 in 500 to less than 1 in 1000[45]; about 5% of colonoscopic perforations are fatal[41,42]. During a diagnostic procedure, perforation can occur due to mechanical rupture with insertion primarily though the sigmoid colon, or may be secondary to barotrauma causing a rent in the cecum. Perforation can also occur with attempts to traverse a stricture. The greatest risk of perforation occurs with large polypectomies in the proximal colon where the walls are thinner.

THE PROCESS OF QUALITY IMPROVEMENT

Quality improvement refers to monitoring the performance, making continuous refinements, and then further assessing the outcomes of the interventions taken. As mentioned previously, there is marked variation in quality in colonoscopy. As a result, continuous quality improvement is essential to the success of colonoscopy.

Continuous tracking of performance for high volume procedures can be challenging. Monitoring quality metrics is time intensive and costly because it often requires data collection from multiple sources. Automated data collection *via* modern electronic endoscopic databases assist with this process, yet some deficiencies still exist. This includes integration of pathology findings to determine ADR, an important quality metric. Infrequent and delayed occurrences such as adverse events are also difficult to capture. Episodic audits of sequential procedures on a monthly, quarterly, or annual basis are one option to accruing representative data samples[46].

Methods used in quality improvement projects are outlined in Table 2. The essential elements include collecting information about standards, assembling data about current practices, identifying gaps in performance, executing a performance strategy, followed by reassessment, and further testing.

FUTURE AREAS FOR IMPROVEMENT

There are several patient-related, procedural-related, and endoscopist performance-related factors that account for inconsistency. In an editorial by Douglas Rex, he tabulated multiple questions to improve detection during colonoscopy[47]. Review of this editorial provides important hypotheses that warrant further investigation to improve quality.

Patient related improvements include health literacy on the benefits of colorectal cancer screening. Increasing awareness leads to increased attendance for screening examinations[48]. Better compliance with bowel cleansing will have innumerable benefits as poor bowel preparation prolongs procedure time, reduces detection of polyps, and increases likelihood of an incomplete procedure[14,49]. Education on quality markers will encourage patients to seek high quality

endoscopists.

One procedural related method that may improve the quality of colonoscopy includes the use of the water method. Rather than the use of air insufflation, which causes sharp angulations, water infusion results in the straightening of the sigmoid colon and other angulations easing insertion. Studies have shown aid with technically difficult colonoscopies[50], decreased pain, and lower requirements for sedation[51]. Future prospective studies are needed to assess the true value of water immersion. Another technique proposed is use of a cap-fitted colonoscopy. A cap may ease insertion by creating a distance between the instrument tip and colonic mucosa, thus facilitating navigation through angulation[52]. Data has shown shorter intubation times as well as avoidance of a failed or incomplete procedure with use of this method[53]. Cap-fitted colonoscopy may also assist with detection of lesions between the haustral folds though studies have had conflicting results in regards to overall adenoma detection[54-56].

Technology to aid with adenoma detection includes chromoendoscopy and the Third Eye Retroscope (Avantis Medical, Sunnyvale, California, United States). Chromoendoscopy has been advocated for use in order to identify subtle flat lesions[57]. Chromoendoscopy includes use of a colored dye that is sprayed into the colon or electronic light variation such as narrow band imaging (Olympus America, Center Valley, Pennsylvania, United States). Studies thus far have shown marginal benefit with only an improvement in the detection of diminutive lesions[58-60]. The Third Eye Retroscope is passed down the colonoscope channel and provides a continuous retrospective view on a second monitor[61]. A randomized control trial showed improved adenoma detection however with a longer withdrawal time[62]. This technology also requires accessing the accessory (and suction) channel making it a bit tedious in practice. One recent development is known as the full spectrum endoscopy (FUSE; EndoChoice, GA, United States). While a standard forward viewing colonoscope visualizes 170° of the colon, the FUSE instead has a more comprehensive view with the capability to capture 330° of the mucosa. This is accomplished by the addition of imagers on the sides of the tip of the scope to provide three images on adjacent monitors. The result is a lower miss rate of adenomas (7% *vs* 41%; $P < 0.00001$)[63]. Thus far, these technologies are not yet supported for incorporation into routine care. They may however, have a role for patients with increased risk for malignancy and/or endoscopists with low adenoma detection rates.

The quality of the examination by the proficient endoscopist is a significant predictor of adenoma detection therefore should be the focus of quality improvement efforts[64]. Internal audits are necessary to identify weaknesses in the practice. For instance, several studies have found that physician fatigue has an impact on adenoma detection with less adenomas found during afternoon procedures[65]. This phenomenon improves if endoscopists work in shorter shifts such as half-day blocks[66]. Direct observation and feedback has had variable results on outcomes[67]. In a study by Imperiali *et al*[68], less experienced endoscopists had more time dedicated to endoscopy with intermittent supervision, and their skills were regularly audited. Completion rates improved, variability between endoscopist polyp detection decreased, but no change in overall adenoma detection was observed[68].

A controversial issue is the endoscopic training of nongastroenterologists. The suggested threshold number for competence in colonoscopy is 200 procedures[69]. However, this quota may be misleading, as most trainees require many more procedures than dictated to achieve competence. Studies have shown an increase in interval cancer among nongastroenterologists[70]. This issue should be resolved through a collaboration of gastroenterology and nongastroenterology training programs to define uniformity to grant involvement in endoscopy.

In accordance with the changing paradigm of healthcare, rather than the fee-for-service model which rewards volume, a pay-for-performance reimbursement method will become the primary financial incentive with a focus more on value[71]. Within this model, satisfying national quality metrics may have a role in compensation as well. Several national endoscopic benchmarking programs are now in effect around the world. For instance, the GI Quality Improvement Consortium is a non-profit collaboration between the ASGE and ACG. This program facilitates data submission to various institutions, including the Physicians Consortium for Performance Improvement[46].

CONCLUSION

Quality measurement and improvement are essential components of a colonoscopy program. Quality is a multifactorial and dynamic process that requires regular monitoring to ensure adherence to national standards. Although several challenges exist, development and implementation of educational tools and improved endoscopic technology are imperative to enhance the benefits of colonoscopy, thereby reducing the incidence and mortality attributed to colon cancer.

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REVIEW

Review of the diagnosis and management of gastrointestinal bezoars

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Abstract

The formation of a bezoar is a relatively infrequent disorder that affects the gastrointestinal system. Bezoars are mainly classified into four types depending on the material constituting the indigestible mass of the bezoar: phytobezoars, trichobezoars, pharmacobezoars, and lactobezoars. Gastric bezoars often cause ulcerative lesions in the stomach and subsequent bleeding, whereas small intestinal bezoars present with small bowel obstruction and ileus. A number of articles have emphasized the usefulness of Coca-Cola® administration for the dissolution of phytobezoars. However, persimmon phytobezoars may be resistant to such dissolution treatment because of their harder consistency compared to other types of phytobezoars. Better understanding of the etiology and epidemiology of each type of bezoar will facilitate prompt diagnosis and management. Here we provide an overview of the prevalence, classification, predisposing factors, and manifestations of bezoars. Diagnosis and management strategies are also discussed, reviewing mainly our own case series. Recent progress in basic research regarding persimmon phytobezoars is also briefly reviewed.

Key words: Bezoars; Gastrointestinal endoscopy; Persimmon phytobezoar; Trichobezoar; Endoscopic removal; Gastric ulcer; Ileus

Core tip: Among the gastrointestinal bezoars, phytobezoars, which consist of indigestible plant materials, are the most common. An administration of Coca-Cola®

is believed to be the primary choice for phytobezoar treatment because it is safe, inexpensive, and effective. However, persimmon phytobezoars (diospyrobezoars) are often resistant to Coca-Cola® dissolution and may require different treatment. Endoscopic fragmentation or surgical removal should be applied in urgent cases, such as those manifesting gastrointestinal bleeding and/or ileus, and in patients with refractory bezoars.

Iwamuro M, Okada H, Matsueda K, Inaba T, Kusumoto C, Imagawa A, Yamamoto K. Review of the diagnosis and management of gastrointestinal bezoars. *World J Gastrointest Endosc* 2015; 7(4): 336-345 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i4/336.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i4.336

INTRODUCTION

A bezoar is an indigestible conglomeration trapped in the gastrointestinal tract. This indigestible mass can be formed by a variety of materials that were intentionally or accidentally ingested. Representative substances forming bezoars include plant materials such as fibers, skins and seeds of vegetables and fruits (*i.e.*, phytobezoars), ingested hair (*i.e.*, trichobezoars), medications (*i.e.*, pharmacobezoars), and milk protein in milk-fed infants (*i.e.*, lactobezoars)[1]. Bezoars can be formed and found in any part of the gastrointestinal tract, but the stomach is the most common. Once the diagnosis of bezoar is made, the bezoar is generally dissolved or removed because it can cause gastric outlet obstruction, ileus, ulcerations due to pressure necrosis, and subsequent gastrointestinal bleeding. Here we review relevant clinical studies, case reports and basic research findings, using mainly our recent studies[2-4], for a better understanding of the etiology and epidemiology of this disease entity.

PREVALENCE

Bezoars of the gastrointestinal tract are a relatively rare disease entity, with a variable incidence among studies[5]. In 1978, Kadian *et al*[6] reported that they found six cases of gastric bezoars in a four-year period during which time 1400 gastroscopies were done (0.43% of the gastroscopies). In 1987, Ahn *et al*[7] reported a similar incidence of 0.43% (14/3247 esophagogastroduodenoscopy examinations) over a seven-year period. More recently, Mihai *et al*[8] noted that there were 49 cases of gastric bezoars over a period of 20 years (0.068% of all endoscopies).

Although the majority of bezoars are found in the stomach, bezoars sometimes move from the stomach into the small intestine, or they can be primarily formed in the small intestine. Such small intestinal bezoars occasionally cause small bowel obstruction and ileus. Yakan *et al*[9] reviewed 432 cases of small bowel obstruction treated within 10 years; of these, 14 (3.2%) cases were caused by phytobezoars. In a meta-analysis by Ghosheh *et al*[10] reviewing 19 reported studies published from 1994 to 2005, laparoscopy was attempted in 1061 patients presenting with acute small bowel obstruction, and bezoars represented the 5th most common cause, accounting for 0.8%[11].

Overall, bezoars can be found in the stomach in less than 0.5% of individuals undergoing esophagogastroduodenoscopy examinations and in the small intestine in 0.4%-4.8% of all cases presenting with intestinal obstruction[9-13]. However, the prevalence of bezoars likely varies among ethnic groups and geographic locations, since the occurrence rate of phytobezoar, the most common type of bezoar, is mostly reflected by food cultures. For example, multiple cases of persimmon phytobezoar (diospyrobezoar) have been reported in regions where the residents frequently consume fresh persimmon fruits and dried persimmons, such as South Korea, Japan, Israel, Spain, Turkey, and Southeastern United States[3,14-19].

BEZOAR CLASSIFICATION

Phytobezoar

Among the four types of bezoars, phytobezoars are the most common[20]. Celery, pumpkins, grape skins, prunes, raisins and, in particular, persimmons are representative causatives of phytobezoars[14]. Some of these foods contain high amount of cellulose, hemicellulose, lignin, and tannins (leucoanthocyanins and catechins), and these nondigestible food materials are the main components of phytobezoars[1,21,22]. Persimmon phytobezoars, *i.e.*, diospyrobezoars, are formed after a frequent consumption of persimmons (Figure 1). The skin of unripe persimmons contains high concentrations of the persimmon tannin. Upon reaction with stomach acid, persimmon tannin is believed to polymerize and form a conglomerate in which cellulose, hemicelluloses, and various proteins are accumulated[20,23]. For example, Holloway *et al*[21] investigated the plant fiber content in a gastric phytobezoar by using the acid and neutral detergent method. The gastric phytobezoar was composed of approx, 11% cellulose, 5% hemicellulose, and 2% lignin. In a thin-layer chromatography analysis, phytobezoar tissue contained only polymerized tannins, without tannin monomers. Maki *et al*[24] succeeded in generating an artificial mass *in vitro* that mimicked a phytobezoar by using persimmon skin pieces, hydrochloric acid, and high-molecular-weight organic polymers. In light of the basic research findings, we speculate that persimmon tannin plays a vital role in the formation of phytobezoars acting as cementing agents that hold undigestible plant fibers together. However, the precise mechanism of the emergence of a phytobezoar is still unknown.

Trichobezoar

A trichobezoar is a hair ball trapped in the gastroin-

testinal tract, mainly in the stomach. Trichobezoar is a rare condition, nearly always diagnosed in young females[25-30]. Psychiatric comorbidities that involve strong urges to pull out one's own hair (trichotillomania) and eat it (trichophagia) are observed in these patients. Due to its enzyme-resistant properties and smooth, slippery surface, human hair cannot be digested and it can be stagnant in the gastrointestinal system. Consequently, eaten hairs retain and accumulate between the gastric mucosal folds and finally lead to the formation of a hair ball together with food and mucus[25]. In some cases, the hair ball extends from the stomach into the small intestines and colon. This condition is named Rapunzel syndrome, which was first described by Vaughan *et al*[31] in 1968[32].

Pharmacobezoar

Pharmacobezoars are an uncommon complication caused by conglomerations of medications or medication vehicles in the gastrointestinal tract. Bulk-forming laxatives, *e.g.*, perdium and psyllium, and guar gum appear to contribute to the formation of pharmacobezoars because of their hygroscopic properties and bulk-forming nature[1,33-37]. Extended-release drug products are other candidate causatives for bezoars[38-40]. The development of time-release technology enabled drug tablets/capsules to be slowly dissolved and gradually release active ingredients of the medication. Extended-release drugs, *e.g.*, nifedipine and verapamil, are coated with cellulose acetate, a synthetic chemical compound derived from the plant substance cellulose. Cellulose acetate may aggregate and lead to bezoar formation in the gastrointestinal tract. Enteric coatings, which use a polymer barrier to stabilize drug tablets at the highly acidic pH found in the stomach, are dissolved at a less acidic pH in the small intestine. Because of the insolubility of the carrying vehicle of enteric-coated medications, *e.g.*, aspirin, they can also be responsible for bezoar formation[39].

Lactobezoar

A lactobezoar is an undigested mass composed of milk and mucus components[41]. In clear contrast to the other types of bezoars, virtually all patients affected with a lactobezoar are milk-fed infants. The pathogenesis is likely multifactorial and includes both exogenous risk factors (*i.e.*, the composition of synthetic milk, medications lowering gastric motility and secretion, and methodologies of feeding) and endogenous risk factors (*i.e.*, dehydration, premature birth, and the subsequent insufficient activity and capacity of the digestive tract)[42-44]. Heinz-Erian *et al*[42] reviewed 96 published cases since the first report in 1959 and noted that most cases were published in the period 1975-1985, whereas only 26 cases have been reported since 1986. The reasons for the infrequency of lactobezoar cases in recent years have not been revealed, but the improvement of synthetic milk composition and advances in premature infant management have probably affected the prevalence.

Other types of bezoar

Varieties of substances other than those responsible for the aforementioned four types of bezoars (*i.e.*, plant materials, hair, medications, and artificial milk) have been reported as a source of bezoars. Such bizarre materials include plastic[45], metals[46], parasitic worms (ascaris)[47], and even toilet paper[48]. Theoretically, all indigestible food materials and foreign bodies can cause a mass formation together with mucus and semi-digested foodstuffs.

STRUCTURE OF PERSIMMON PHYTOBEZOAR

Compared with other phytobezoars, persimmon phytobezoars are more difficult to dissolve or break up into small pieces due to their hard consistency. In addition, persimmon phytobezoars usually have a black or darkish-brown color (Figure 1). We recently investigated persimmon phytobezoar fragments by microscopy, transmission electron microscopy, energy dispersive X-ray spectroscopy, and infrared spectroscopy and revealed the unique structure and components that cause the characteristic hard consistency and dark color[2]. In this section, we briefly introduce our analysis regarding the microstructure of persimmon phytobezoar fragments.

First, the bezoar fragments were analyzed by scanning electron microscopy (SEM). The SEM analysis revealed a high-density, continuous layer approx. 20- to 50-μm thick that formed the exterior of the phytobezoar. Close-up observation revealed that aggregated microgranules constituted the exterior surface. These microgranules were stuck together and created an almost seamless structure with a few slits. In contrast, the density of the inner part of the persimmon phytobezoar was low. The inner part consisted of sheet-like structures with curved or wavy shapes. The wiggly arrangement of the sheet-like structures resulted in unoccupied areas existed between the sheets. These microscopic features indicate that the persimmon phytobezoar's resistance to mechanical and chemical forces was rendered by almost seamless, dense layers of the exterior surface.

Secondly, to investigate the chemical components that constitute the surface structure and the inner part of the persimmon phytobezoar, we performed an infrared spectroscopy analysis. The surface layer and the inner part of the persimmon phytobezoar were manually segmented with a surgical knife. Both parts were air-dried and analyzed by infrared spectroscopy. The spectra obtained from the surface and the inner parts of the persimmon phytobezoar were quite similar to that of persimmon juice. The persimmon juice was extracted from green, unripe persimmon

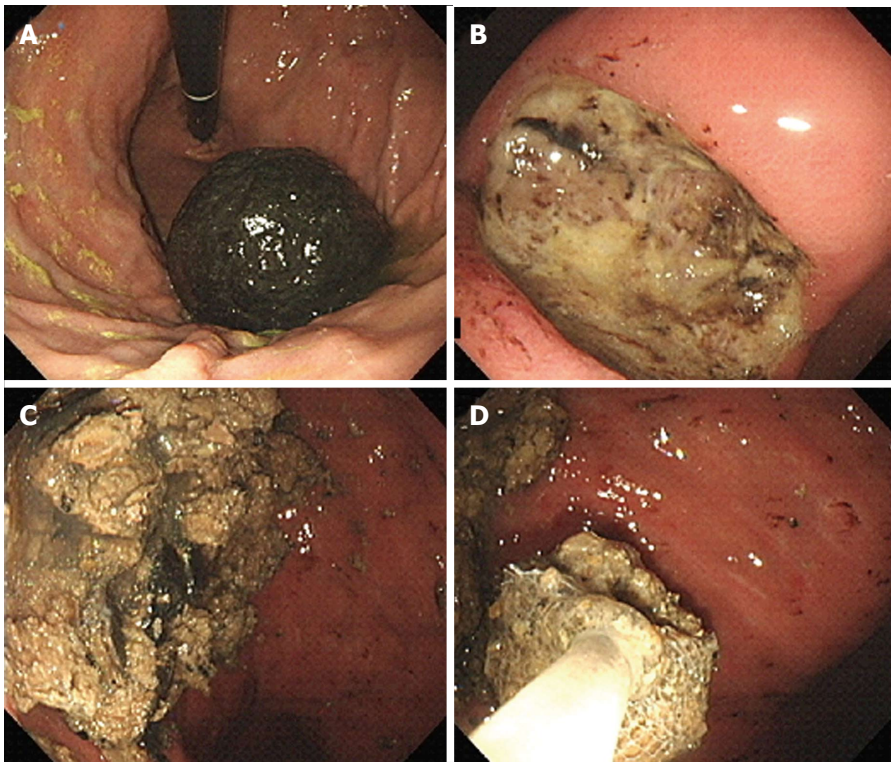

Figure 1 Endoscopic images of a persimmon phytobezoar. A: A large, black bezoar is seen in the gastric fundus; B: A peptic ulcer is also observed in the gastric angle; C: Fragmentation of the bezoar was performed by endoscopy forceps and polypectomy snares; D: The fragments were removed by a retrieval net device and used in the subsequent *in vitro* analysis.

fruits that contained plenty of tannin. This juice can be commercially purchased in Japan as a natural dyestuff and as a coating material for fabric, paper, and wood. The striking resemblance of spectra between the persimmon juice and the phytobezoar fragments indicates that a quite high concentration of persimmon tannin exists in a phytobezoar. It also suggests the importance of persimmon tannin in the pathogenesis of phytobezoars.

Thirdly, to compare the elemental composition of the surface and the inner part of the phytobezoar, we used S4800 scanning electron microscopy and energy dispersive X-ray spectroscopy (EDX) (EDAX Genesis APEX2 system, Ametek, Paoli, PA). The net intensity of each element was measured at five different points on the surface and the inner part, respectively. We analyzed the spectrum of the EDX results using Genesys software (Ametek). The amount of each element was quantified by the standardless EDAX ZAF quantification method. As a result, higher amounts of sulphur and iron were detected in the surface layer compared to the inner part (Table 1). We speculate that the iron deposition and resulting compound, iron(Ⅲ) tannate, are responsible for the black color of the persimmon phytobezoar surface. In our study, yttrium, aluminum, and osmium were detected in the persimmon phytobezoar, in addition to the major elements such as carbon, oxygen, sodium and sulfur. Generally, edible plants have yttrium at a concentration of 20-100 ppm[49]. The seeds of woody plants have high amounts, up to 700 ppm. Aluminum is also contained in foods and food additives. Osmium was probably contaminated during the process of sample preparation for the SEM analysis, because it was used as a fixing agent.

A limitation associated with our study is that the phytobezoar examined was obtained from a single patient. Since the structure of phytobezoars presumably varies among patients, an analysis of the ultrastructure would ideally include phytobezoars extracted from several different patients. Another subject of great interest is the structure and components of other types of bezoars (*i.e.*, trichobezoars, pharmacobezoars, and lactobezoars). Although the formation of bezoars is a relatively infrequent disorder, further *in vitro* investigations could provide findings that contribute to the management of phytobezoars.

PATIENT SUSCEPTIBILITY

Bezoars are believed to form as a complication of delayed gastric emptying. Predisposed risk factors include prior gastric surgery such as partial gastrectomy, vagotomy and pyloroplasty, peptic ulcer disease, chronic gastritis, Crohn's disease, carcinoma of the gastrointestinal tract, dehydration and hypothyroidism[46,50]. These conditions lead to reduced gastric acidity, gastric stasis, loss of pyloric function, and/or pyloric stenosis. Elderly individuals and diabetic patients with neuropathy or myotonic dystrophy have

Table 1 Net intensity of elements determined by energy-dispersive X-ray spectroscopy in a persimmon phytobezoar

	Surface layer	Inner part	*P* value
C	52.91 ± 13.88	62.30 ± 15.77	0.35
O	22.42 ± 5.95	43.71 ± 14.56	< 0.05
Na	12.77 ± 5.09	21.24 ± 6.26	< 0.05
Al	9.98 ± 2.55	13.01 ± 2.64	0.1
Y	160.62 ± 29.73	209.37 ± 38.48	0.06
S	16.96 ± 3.22	5.27 ± 1.95	< 0.01
Fe	9.88 ± 1.69	2.02 ± 1.17	< 0.01
Os	45.02 ± 3.96	60.35 ± 6.26	< 0.01

For comparisons, statistical analyses were performed by *t* tests. C: Carbon; O: Oxygen; Na: Sodium; Al: Aluminum; Y: Yttrium; S: Sulfur; Fe: Iron; Os: Osmium.

impaired gastric motility[1,12,51,52].

In our previous study, we reviewed 19 Japanese patients with gastrointestinal bezoars and presented their clinical characteristics[3]. To date, we have collected an additional 12 cases. A summary of the 31 cases (13 males and 18 females) is shown in Table 2. In accord with previous studies, the histories of our patient series included diabetes mellitus (*n* = 3, 9.7%) and surgery of the gastrointestinal tract (*n* = 11, 35.5%). Notably, except for the 10-year-old patient with a trichobezoar, all patients were 61 years of age or older. Consequently, the potential development of bezoars in elderly individuals and patients with underlying disease that causes poor gastric motility should be borne in mind by clinicians.

Table 2 Clinical characteristics of bezoar patients

	n (%)
Total	31
Female	18 (58.1)
Median age (yr, range)	74 (10-93)
Past histories	
Diabetes mellitus	3 (9.7)
Surgery of gastrointestinal tract	11 (35.5)
Symptoms	
Pain	11 (35.5)
Bloody or tarry stool	5 (16.1)
Abdominal fullness	5 (16.1)
Discomfort	5 (16.1)
Anemia	4 (12.9)
Difficulty of swallowing	3 (9.7)
Hematemesis	3 (9.7)
Nausea	3 (9.7)
Anorexia	1 (3.2)
Faint	1 (3.2)
None	3 (9.7)
Bezoar location	
Stomach	29 (93.5)
Small intestine	2 (6.5)
Diagnosis modality	
Esophagogastroduodenoscopy	23 (74.2)
Computed tomography	8 (25.8)
Complications of bezoar	
Gastric ulcer	20[1] (64.5)
Ileus	3[1] (9.7)
Reflux esophagitis	1 (3.2)
Acute gastric mucosal lesions	1 (3.2)
Duodenal ulcer	1 (3.2)
None	6 (19.4)

[1]One patient presented with both gastric ulcer and ileus.

MANIFESTATIONS AND DIAGNOSIS

Bezoars can be asymptomatic or present with a variety of gastrointestinal symptoms. In our series of 31 patients with gastrointestinal bezoars, pain (*n* = 11), bloody or tarry stool (*n* = 5), abdominal fullness (*n* = 5), discomfort (*n* = 5), anemia (*n* = 4), difficulty swallowing (*n* = 3), hematemesis (*n* = 3), nausea (*n* = 3), anorexia (*n* = 1), and fainting (*n* = 1) were observed as initial presentations (Table 2). In contrast, bezoars were coincidentally found in asymptomatic patients (*n* = 5) by esophagogastroduodenoscopy or computed tomography (CT) scans performed during a health check-up or follow-up of other diseases. Symptoms related to gastrointestinal bleeding such as hematemesis, bloody or tarry stool, anemia, and fainting are the result of the development of ulceration in the gastric mucosa due to pressure necrosis induced by the bezoar[1]. As shown in Table 2, gastric ulcers were observed in 20 of the 31 patients (64.5%) by esophagogastroduodenoscopy. Lee *et al*[53] also documented a high rate of gastric ulcers as a complication of bezoars (41.2%, 7/17 cases). Obstruction of the gastrointestinal tract is another vital manifestation caused by bezoars, particularly by small intestinal bezoars.

Endoscopic examinations play the most important role in the detection of gastric bezoars, as well as in the treatment of this disease. A phytobezoar is typically observed in the gastric fundus as a single mass, but it can be multiple. The color is diverse depending on the materials constituting the phytobezoar, ranging from beige, tan, ocher, yellow green, to black[3]. As described above, the black color of persimmon phytobezoar's surface is probably imparted by iron(III) tannate (Figure 1A)[2].

CT scanning is useful to detect both gastric and small intestinal bezoars. Phytobezoars are visualized by CT scan as an ovoid or round occupational mass in the gastrointestinal tract with air bubbles retained inside and a mottled appearance[54,55]. A CT scan is particularly valuable in patients requiring the surgical removal of small intestinal bezoars, not only because it demonstrates the obstructed site of the intestines; it also enables the visualization of multiple bezoars[19].

TREATMENT OF BEZOARS

Overview

The currently available treatment options for a gastric phytobezoar include dissolution of the bezoar by Coca-Cola®, removal by endoscopic devices, laparotomy, and laparoscopic surgery. It should be noted that persimmon phytobezoars are often resistant to chemical dissolution

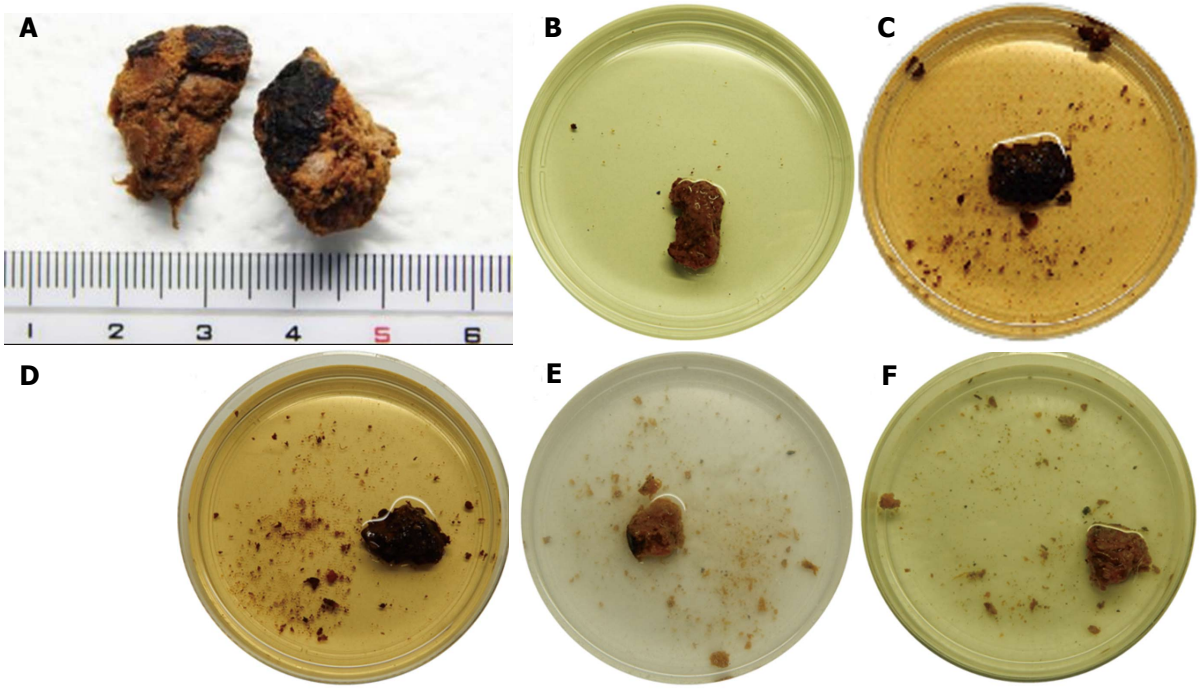

Figure 2 Photographs of the *in vitro* experiment. A: Endoscopically extracted fragments of the gastric bezoar were used; B: Representative photographs of the bezoar fragments incubated at 37 ℃ with gentle swirling for 12 h with double-distilled water; C: Bezoar fragments after incubation with Coca-Cola®; D: Bezoar fragments after incubation with Coca-Cola Zero®; E: Bezoar fragments after incubation with a digestive enzymes supplement including cellulase; F: Bezoar fragments after incubation with papain. The bezoar fragments were clearly more softened and more fragmented after 12-h incubation with Coca-Cola® or Coca-Cola Zero® than with the other agents.

because of their hard consistency, and they are thus usually removed endoscopically or surgically[53,55].

Intestinal bezoars are generally removed by a surgical procedure, since patients with this type of bezoar often present with intestinal obstruction and ileus.

Coca-Cola

The first successful treatment achieved with Coca-Cola® lavage was reported in 2002 by Ladas *et al*[56]. In a recent review by Ladas *et al*[56], they summarized 24 publications including 46 patients and noted that Coca-Cola® administration resulted in phytobezoar resolution in 91.3% of the cases, either as a sole treatment or in combination with an endoscopic procedure[20]. The protocol for Coca-Cola® administration has varied among authors[53]. Ladas *et al*[56] performed gastric lavage *via* nasogastric tubes with 3000 mL of Coca-Cola® administered over 12 h. Hayashi *et al*[57] reported that the peroral intake of 500-1000 mL/d of Coca-Cola® for 3 wk resulted in a decrease in size and softened structure of the phytobezoar. Mihai *et al*[8] described 12 patients treated with 4800 mL of Coca-Cola® ingestion over 12 h (100 mL every 15 min); complete dissolution of the bezoar was observed in 5 patients (42%), and fragmentation of the bezoar was found in 5 patients (42%). In the latest review, Ladas *et al*[20] recommended gastric lavage with 3000 mL of Coca-Cola® for 12 h, or drinking 3000 mL of Coca-Cola® over 12 h. The adequate dose and timing of Coca-Cola® administration should be investigated, because no standard protocol for bezoar treatment has been established to date.

In our recent paper, we investigated persimmon phytobezoar dissolubility by Coca-Cola® *in vitro*[4]. A gastric persimmon phytobezoar was fragmented by endoscopy forceps and polypectomy snares (Figure 1C) and extracted with a retrieval net device (Figures 1D and 2A). A fragment and hydrochloric acid-potassium chloride buffer (pH 2.0) was put into each of several tubes. Double-distilled water, Coca-Cola®, Coca-Cola Zero®, a digestive enzyme supplement containing cellulase, or papain supplement was added to the tube. After a 12-h incubation, the contents of the tubes were gently decanted into 100-mm polystyrene dishes, and photographs of these dishes were taken. Representative images of each group at post-incubation are shown in Figures 2B-2F. The particles of broken bezoar were fewest in the control (Figure 2B).

By contrast, more particles of the broken bezoar were observed after incubation with Coca-Cola® (Figure 2C) or Coca-Cola Zero® (Figure 2D), even compared to cellulase (Figure 2E) or papain (Figure 2F). Next, the undissolved bezoar fragments were extracted, and their weights were measured after 30 min of air-drying and compared the values with the weight at pre-incubation. The phytolytic activities of the solvents are summarized in Figure 3. Bezoar fragments showed significantly better dissolubility in Coca-Cola Zero® (16.1% ± 0.4%) than in water (7.0% ± 5.3%) ($P < 0.05$, t test). The dissolubility in Coca-Cola® (18.5% ± 5.8%) was also higher than that in cellulase (10.1

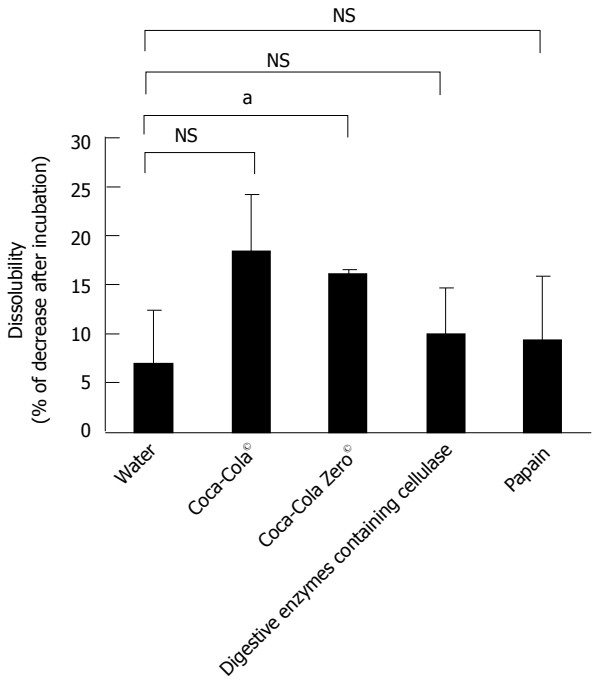

Figure 3 The dissolubility of bezoar fragments. The mean dissolubility of bezoar fragments was highest by Coca-Cola®, but the difference between Coca-Cola® and water was not significant (P = 0.06) due to the relatively large standard deviation. NS: Not significant. $^{a}P < 0.05$.

± 4.5%), papain (9.5% ± 6.5%), and water, though the difference between Coca-Cola® and water was not significant (P = 0.06) due to the relatively large standard deviation. Overall, our study obtained the first evidence of the comparative benefits of Coca-Cola® beverages. In addition, Coca-Cola® and Coca-Cola Zero® showed equal phytolytic activities *in vitro*.

Although the mechanism has not been fully elucidated, it has been speculated that some ingredients in Coca-Cola® play a key role in bezoar dissolution. Such hypotheses include enhanced bezoar digestion by the mucolytic effect of sodium bicarbonate and/or by the acidifying effect of carbonic acid and phosphoric acid. Destruction of the bezoar may also be assisted by the carbon dioxide bubbles, which penetrate into the bezoar through the microscopic pores on its surface[5,20,56,58,59]. Diet Coke®, Coca-Cola Light®, and Coca-Cola Zero® all contain these ingredients. Since the clinical success of bezoar dissolution by Diet Coke®, Coca-Cola Light®, and Coca-Cola Zero® was documented in previous reports, several authors have speculated that these sugar-free beverages have the same effect of bezoar dissolution as the regular version of Coca-Cola®[5,60]. Although our study was conducted using the phytobezoar obtained from a single patient, the results confirmed this speculation, revealing almost equal bezoar dissolubility between Coca-Cola® and Coca-Cola Zero®. A future study should determine whether or not other carbonated beverages such as Pepsi-Cola® and carbonated water have the same lytic action against phytobezoars.

Despite the number of reports describing a successful treatment outcome of phytobezoars, however, persimmon phytobezoars may not be dissolved by Coca-Cola® beverages alone because of their hard consistency. For example, Lee *et al*[53] reported that complete dissolution by Coca-Cola® administration was observed in 4/6 patients (66.7%) with non-persimmon phytobezoars, whereas Coca-Cola® was completely ineffective in all 11 patients with persimmon phytobezoars (0%) in whom this method was attempted. For such phytobezoars that are resistant to chemical dissolution, endoscopic fragmentation and removal in combination with or without Coca-Cola® dissolution is generally effective[55].

Papain

Papain, an enzyme extracted from the Carica papaya plant, has been used as an alternative enzymatic therapy for bezoars. Generally, papain rapidly hydrolyzes a variety of proteins based on the proteolytic activity. Several authors have described bezoar dissolution by the oral administration of Adolph's Meat Tenderizer or gastric lavage with the tenderizing agent[61]. However, papain is no longer included in Adolph's Meat Tenderizer, because the manufacturer changed the chief ingredient from papain to bromelain, which is another proteolytic enzyme contained in pineapples. Papain is currently used in other products for tenderizing meat, in clarifying beer, and in biochemical research involving the analysis of proteins. Papain is thus still commercially available, but physicians should keep in mind that adverse events such as gastric ulceration and esophageal perforation following papain therapy have been documented[62,63].

In our previous study, papain powders were extracted from a capsule of dietary supplement, but the bezoar dissolubility in papain was not significantly higher than that in water (Figures 2 and 3)[4]. The insufficient dissolubility of bezoars in papain is contradictory to the previous successful clinical outcomes. We speculate that this might be due to the small dose size of the active enzymes in a dietary supplement capsule. An excess doses of papain supplement may be effective for the dissolution of bezoars, but it is impractical in a clinical setting because the maximum dose of papain for safe ingestion have not been elucidated.

Cellulase

Cellulase has been widely used for phytobezoar treatment, since vegetables and fruits contain large amounts of cellulose. The enhancement of phytobezoar digestion by cellulase may originate in its degradation activity against cellulose by cleaving the glycosidic bond. A successful outcome of bezoar treatment with tablet-form gastroenterase (containing pepsin, pancreatic enzyme concentrate, cellulase, and dehydrocholic acid) was described in the 1970s[64,65]. However, these tablets have been discontinued. Additionally, in many countries, cellulase is not readily available for ingestion as a commercial product, or even as a medication under prescription[60]. For example,

in the United States, cellulase is only available as a dietary supplement in combination with other digestive enzymes. In our previous study, however, one capsule of cellulase supplement was not effective for the lysis of bezoar fragments (Figures 2 and 3)[4].

Endoscopic removal

Endoscopic fragmentation has often been applied for gastric bezoars. Various types of endoscopy devices including biopsy forceps, alligator forceps, a polypectomy snare, a basket catheter, an argon plasma coagulation device and an electrohydraulic lithotripsy device have been used for fragmentation[3]. Kurt *et al*[66] recently reported the first patient with a gastric bezoar successfully treated with a bezoaratom, an oval polyfilament snare device specifically designed for the treatment of bezoars. Endoscopic spraying or the endoscopic injection of Coca-Cola® into bezoars probably assists fragmentation *via* lytic activity for gastrointestinal bezoars[20,67]. It should be noted that persimmon phytobezoars may require multiple sessions of endoscopic treatment to be completely broken down because of the hard consistency[3].

Trichobezoars are resistant to enzymatic degradation and pharmacotherapy. Endoscopic fragmentation is generally ineffective due to the high density of the hair conglomerate. In a review of the 40 reported trichobezoar cases, endoscopic removal was successful in only two of the cases; the other cases required laparotomy or laparoscopic surgery[35]. In our experience, however, we achieved fragmentation of trichobezoar in one patient by using an electrosurgical knife[3]. Electrosurgical knives developed for endoscopic submucosal dissection may thus be useful for treating trichobezoars.

Surgical removal

Surgical removal is inevitable for cases presenting with ileus or patients with refractory bezoars. Bezoars were traditionally managed by open surgical retrieval (laparotomy). Recent papers emphasized the importance of a minimally invasive surgical approach by laparoscopy in the management of gastrointestinal bezoars[54,68-70]. Intraoperative endoscopic removal has also been reported[71].

Other treatment strategies

In some patients, the administration of prokinetic agents was reportedly effective in resolving the gastric bezoar[3]. As described above, a reduction in the evacuation of indigestible foods due to insufficient gastric motor activity can lead to bezoar formation. Prokinetic agents such as itopride, mosapride, and metoclopramide may improve gastric emptying and facilitate the break-down of a bezoar by enhancing contractions of the gastrointestinal tract and increasing their frequency, if the bezoar is soft enough to be digested with gastrointestinal peristalsis.

Spontaneous disappearance of a bezoar under the absence of specific treatment was also observed in some patients[3,6]. The etiology of the bezoars and the mechanisms underlying how the bezoars were digested in these patients remain to be determined. However, careful follow-up without any specific treatment is a possible option in the management of bezoar patients, if they are in stable condition[6].

CONCLUSION

We reviewed the prevalence, classification, structure, predisposing factors, manifestations, diagnosis, and treatment strategies of gastrointestinal bezoars. Endoscopy and CT play key roles in the detection and management of bezoars. The administration of Coca-Cola® is currently the primary choice for phytobezoar treatment because it is safe, inexpensive, and effective. Endoscopic fragmentation or surgical removal should be applied in urgent cases, such as those manifesting gastrointestinal bleeding and/or ileus, and patients with refractory bezoars.

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REVIEW

Endoscopic diagnosis and management of type I neuroendocrine tumors

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Abstract

Type I gastric neuroendocrine tumors (TI-GNETs) are related to chronic atrophic gastritis with hypergastrinemia and enterochromaffin-like cell hyperplasia. The incidence of TI-GNETs has significantly increased, with the great majority being TI-GNETs. TI-GNETs present as small (< 10 mm) and multiple lesions endoscopically and are generally limited to the mucosa or submucosa. Narrow band imaging and high resolution magnification endoscopy may be helpful for the endoscopic diagnosis of TI-GNETs. TI-GNETs are usually histologically classified by World Health Organization criteria as G1 tumors. Therefore, TI-GNETs tend to display nearly benign behavior with a low risk of progression or metastasis. Several treatment options are currently available for these tumors, including surgical resection, endoscopic resection, and endoscopic surveillance. However, debate persists about the best management technique for TI-GNETs.

Key words: Gastric neuroendocrine tumor; Narrow band imaging; Magnifying endoscopy; Endoscopic submucosal dissection; Endoscopic surveillance

Core tip: The incidence of type I gastric neuroendocrine tumors (TI-GNETs) has significantly increased, TI-GNETs are the most frequently diagnosed of all GNETs, accounting for about 70%-80%. Endoscopically, TI-GNETs are present as small (< 10 mm), polypoid lesions or, more frequently, as smooth, rounded submucosal lesions. Especially, narrow band imaging and high resolution magnification endoscopy may be helpful for the endoscopic diagnosis of TI-GNETs. TI-GNETs tend to display a nearly benign behavior and a low risk of progression or metastasis in spite of submucosal invasion. Therefore, endoscopic submucosal dissection is a feasible technique for the removal of TI-GNETs.

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INTRODUCTION

Neuroendocrine tumors (NETs), originally termed

Table 1 Characteristics of gastric neuroendocrine tumors

Characteristic	Type Ⅰ GNETs	Type Ⅱ GNETs	Type Ⅲ GNETs
Proportion of all GNETs	70%-80%	5%-10%	10%-15%
Associated disease	Chronic atrophic gastritis	MEN type 1/ZES	None
Gender	Women > men	Women = men	Women < men
Tumor number	⩾ 1	⩾ 1	1
Tumor size	< 10 mm	< 10 mm	Often > 20 mm
Tumor location	Fundus or corpus	Fundus or corpus	Any region
Histology	Well differentiated	Well differentiated	From well to poorly differentiated
Invasion depth	Mucosa or submucosa	Mucosa or submucosa	Any depth
Serum gastrin level	High	High	Normal
Gastric pH	Low	High	Normal
Metastasis risk	2%-5%	10%-20%	> 50%
Tumor-related death	0	< 10%	25%-30%
Prognosis	Excellent	Good	Poor

GNET: Gastric neuroendocrine tumor; MEN: Multiple endocrine neoplasia; ZES: Zollinger-Ellison syndrome.

carcinoid tumors, arise from neuroendocrine cells of the diffuse neuroendocrine system[1]. NETs are rare neoplasms; however, the incidence of gastrointestinal NETs (GNET) is gradually increasing with all NETs[2,3], while the ratio of GNETs to all GI NETs has increased according to the latest reports[4-9]. This increase in the incidence of GNETs reflects the true increase (that the incidence of GNET is increasing); however, this also might be related to improvements in diagnostic technology including endoscopy and increased GNET awareness. Because of the increasing incidence and prevalence, GNETs represent a substantial clinical problem.

GNETs are classified into three distinct subgroups: types Ⅰ to Ⅲ[10]. Table 1 shows the clinical characteristics of these three types[11-19]. Type Ⅰ GNETs (TI-GNETs) arise in patients with chronic atrophic gastritis (CAG), including autoimmune gastritis (AIG; *i.e.*, type-A gastritis) and *Helicobacter pylori (H. pylori)*-associated atrophic gastritis. Most TI-GNETs are small (< 10 mm), multiple, located within the gastric fundus or corpus, and limited to the mucosa or submucosa. TI-GNETs comprise the great majority (70%-80%) of GNETs. TI-GNETs are generally considered benign, with low metastasis rates and a 100% long-term survival rate.

Type Ⅱ GNETs, which account for 5%-6% of all GNETs, are associated with the gastrin-secreting neoplasms in multiple endocrine neoplasia-Zollinger-Ellison syndrome (MEN-ZES). Therefore, hyperacidity-induced peptic ulceration is often seen in patients with type Ⅱ GNETs. Type Ⅱ GNETs are also small, multiple, and considered benign. However, the survival rate of patients with type Ⅱ GNETs is lower than that of patients with type Ⅰ because of the course of the gastrinoma[20].

On the contrary, type Ⅲ GNETs are sporadic tumors whose development is unrelated to gastrin conditions. Type Ⅲ NETs are often single and large, have a diameter around 20 mm, and comprise approximately 10%-15% of all GNETs. These GNETs behave more aggressively and are usually metastatic and spread to the regional lymph nodes or liver.

This review focuses on TI-GNET pathogenesis, endoscopic diagnosis, and management.

TI-GNET PATHOGENESIS

TI-GNETs are associated with CAG, which leads to hypergastrinemia and enterochromaffin-like (ECL) cell hyperplasia. The loss of fundic glands seen in CAG results in a lack of acid production (achlorhydria). In response to achlorhydria, antral G-cells undergo hyperplasia and secrete more gastrin, resulting in hypergastrinemia. Gastrin stimulates gastric epithelial cell proliferation and acts as a trophic factor for ECL cells and leads to ECL cell hyperplasia. Therefore, hypergastrinemia results in the progression to TI-GNET development.

In either AIG- or *H. pylori*-associated gastritis, under the CAG condition, a lack of gastric acid production results in hypergastrinemia and leads to TI-GNET progression. In the AIG, anti-parietal cell antibody acts on gastric parietal cells, leading to acid secretion disorder and resulting in more gastrin secretion by antral G-cells. The role of *H. pylori* in TI-GNET development is unclear. However, it is well known that *H. pylori* infection induces hypergastrinemia[21,22]. *H. pylori* induces gastric mucosal atrophy, resulting in low acid output[23]. The negative feedback loop created by this low acid output causes hypergastrinemia. One possible mechanism is that antibodies against *H. pylori* may act like those against parietal cells[24-26]. Furthermore, *H. pylori* lipopolysaccharide stimulates DNA synthesis in ECL cells, suggesting that it may contribute to ECL cell hyperplasia[27]. Some reports have suggested that *H. pylori* infection might be a risk factor for TI-GNET in humans due to hypergastrinemia[28,29]. However, a minority of patients with CAG had TI-GNETs; therefore, it has been proposed that other cofactors (*i.e.*, Reg[30], mcl-1[31], *MEN-1* gene mutation[32]) might play a role in TI-GNET development.

Proton pump inhibitors (PPI) create hypergastrinemia secondary to gastric hypoacidity. Therefore, PPI treatment causes ECL hyperplasia in rats[33,34]. In humans, there are some case reports of GNETs that developed after long-term PPI treatment[35-38], and one revealed disappearance of the tumors after PPI treatment discontinuation[38]. However, the number of reports about GNETs compared to those on PPI users remains very small, and it is generally accepted that continual PPI use is not associated with GNET development in

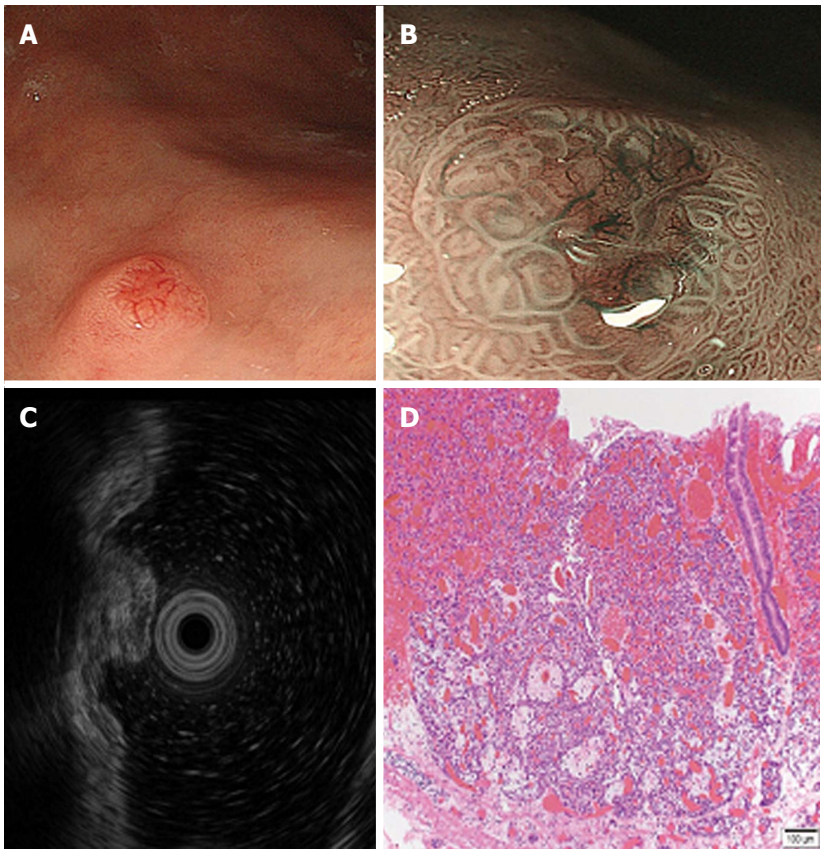

Figure 1 Type Ⅰ gastric neuroendocrine tumor. A: Conventional endoscopic image taken under white light. A hemispherical reddish polyp with a central depression is visible; B: Magnifying endoscopic image taken with a narrow band imaging system. Gastric pit-like structures present on the tumor's surface, except for the central depression. In the central depression, the pit-like structure was not present, whereas dilated blackish-brown subepithelial vessels with cork-screw capillaries are visible; C: Endoscopic ultrasound showing a hypoechoic intramural structure in the second layer of the tumor; D: Histological appearance. Magnification (40 ×) of a hematoxylin-and-eosin–stained section of the tumor revealing a gastric neuroendocrine tumor limited to the mucosa.

humans.

TI-GNET DIAGNOSIS

Clinical features

Most patients with TI-GNETs have no specific symptoms related to "carcinoid syndrome"[39,40] such as flushing, tachycardia, and diarrhea. However, those with TI-GNET have nonspecific symptoms (nausea, abdominal pain, dyspepsia)[41] or pernicious anemia complicated by AIG. Therefore, TI-GNETs are detected incidentally during esophagogastroduodenoscopy.

TI-GNETs are more prevalent in women[14,16], a finding that is attributed to the fact that AIG occurs more commonly in females[42]. AIG is also substantially more common in patients with other autoimmune-related diseases (type 1 diabetes mellitus[43], autoimmune thyroiditis[44], and primary biliary cirrhosis[45]) than in the healthy population. Therefore, the existence of TI-GNETs should be also appropriately investigated in patients with those diseases. Moreover, under the condition of CAG, the stomach becomes unable to produce sufficient amounts of pepsinogen and pepsin due to gastric chief cell injury. Therefore, patients with CAG show the low pepsinogen Ⅰ level and pepsinogen Ⅰ/Ⅱ ratio on serological testing[46], while the measurement of pepsinogen Ⅰ level and pepsinogen Ⅰ/Ⅱ ratio might be helpful for distinguishing TI-GNETs from the other two GNET types.

Serum chromogranin A (CgA) levels are increased in patients with TI-GNETs[39]. However, an elevated serum CgA level is not specific to GNETs. Therefore, measuring CgA is not recommended as a routine screening but rather as a surveillance marker for monitoring GNET progression.

Endoscopy

TI-GNETs are often small (< 10 mm), multiple, and found in the gastric corpus or fundus. Endoscopically, TI-GNETs present as polypoid lesions or, more frequently, as smooth and rounded submucosal lesions[47] and may appear yellow or red in color. A depression can sometimes be seen at the center of the tumor. The use of high-resolution magnifying endoscopy (ME) and narrow band imaging (NBI) might be helpful for the endoscopic diagnosis of GNETs[48]. The ME with NBI approach provides very clear images of the fine superficial structure and microvasculature of the gastric mucosa. Endoscopic TI-GNET images are shown in Figure 1. Endoscopy with white light revealed

Table 2 Histological grading of gastrointestinal neuroendocrine neoplasms

ENETS grading	Mitotic index (× 10 HPF)	Ki-67 proliferation index (%)	WHO classification 2010
G1	< 2	≤ 2	NET G1 (carcinoid)
G2	2-20	3-20	NET G2
G3	> 20	> 20	NEC G3; large-cell or small-cell type

ENETS: European neuroendocrine tumor society; HPF: High power field; NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma.

a hemispherical reddish polyp with or without a central depression (Figure 1A). Most of the GNET surface is covered with normal mucosa; therefore, gastric pits can be visualized in ME using the NBI system. However, in the area of the central depression, gastric glands vanish, so the gastric pits cannot be visualized. The tumor grows expansively beneath the epithelium; therefore, abnormally dilated subepithelial vessels with blackish-brown or cyan corkscrew-shaped capillaries are visible (Figure 1B). This finding reflects the fact that the tumor grew beneath the epithelium without a gland structure. Differential diagnoses include gastric lymphoma and metastatic lesions (breast cancer, lung cancer, and melanoma), which also present as protruding tumors covered with non-tumorous mucosa.

Endoscopic ultrasonography (EUS) is useful for judging GNET invasion depth[49]. On EUS, GNETs are commonly seen in the second (deeper mucosa) or third (submucosa) echo layer and have a hypoechoic intramural structure (Figure 1C). The tumors generally have a hypoechoic structure with uniform echotexture. The tumor margins are typically well defined and smooth, and the overall shape is round and oval. A 20 MHz frequency ultrasound probe is generally useful for the evaluation of small GNETs; however, lesions > 20 mm may require the use of a lower frequency (12 MHz) probe[50].

Additionally, as documented above, the greater portions of these tumors are covered with normal mucosa; therefore, the collection of adequate endoscopic biopsy specimens in the deeper cut is required for diagnosis. Sampling biopsy should be taken of not only the TI-GNET lesion but also each antrum and corpus/fundus to assess for the presence of atrophic gastritis and hyperplastic/dysplastic proliferation of ECL cells as TI-GNET precursors[51].

Histology

TI-GNETs are composed of small uniform cells in nests and infiltrating strands with a ribbon-like, tubular, or acinar pattern (Figure 1D). According to the European Neuroendocrine Tumor Society (ENETS) consensus proposal in 2006, NETs are classified by counting mitosis and Ki67 index (Table 2)[52]. Based on this grading method, in 2010, the World Health Organization (WHO) classification[53], histological classification of NETs is based on proliferation and differentiation: G1 NET, G2 NET, neuroendocrine carcinoma (NEC), mixed adenoneuroendocrine carcinoma, and hyperplastic and pre-neoplastic lesions. A G3 tumor classified by ENETS criteria would correspond to NEC on WHO criteria. Histologically, most TI-GNETs are G1 NETs.

Other imaging

Computed tomography or magnetic resonance imaging can provide useful information about local spread and distal metastasis to aid with tumor staging. The role of fludeoxyglucose positron emission tomography is unclear in the assessment of TI-GNETs[54]. Findings of somatostatin receptor scintigraphy, also known as an octreoscan, are often negative in TI-GNETs[55] because this method cannot usually identify small GI-NETs.

TI-GNET MANAGEMENT

The clinical management and treatment of TI-GNETs depends on tumor size and the presence of risk factors such as muscular wall infiltration, increased proliferation, and/or metastasis. Simple surveillance or endoscopic resection (ER) is generally recommended for TI-GNETs < 10 mm that have not invaded the muscularis propria or otherwise metastasized. The treatment of TI-GNETs 10-20 mm that are limited to the submucosa is controversial: ENETS guidelines recommend ER, whereas National Comprehensive Cancer Network (NCCN) guidelines[56] recommend both ER and endoscopic surveillance. Patients with TI-GNETs measuring > 20 mm, or those that have invaded beyond the submucosa, or have multiple lesions that are unsuitable for ER generally require surgical resection.

Endoscopic resection

Hitherto, endoscopic mucosal resection (EMR) has been recommended and is performed, as it is the most useful method of mucosal resection for local TI-GNETs. However, TI-GNETs frequently invade the submucosa; therefore, they are difficult to remove completely, even when small, using snare polypectomy or conventional EMR. In contrast, endoscopic submucosal dissection (ESD) is a feasible technique for the removal of tumors such as TI-GNETs within the submucosal layer. Recent reports have shown that the complete resection rate of GNETs using ESD was superior to that using EMR[57,58].

Surgical resection

Surgical resection is generally recommended for TI-GNETs > 20 mm in diameter or those that have invaded beyond the submucosa[52,56]. Moreover, surgery should also be performed in the presence of lymph nodal, distant disease spread, or poorly differentiated neoplasms[51]. For surgical therapy, local resection and/or antrectomy to reduce gastrin levels should

be chosen. Antrectomy removes G-cell–mediated hypergastrinemia; however, it might not effectively prevent recurrence and/or metastasis[59]. This suggests that TI-GNETs can grow autonomously independent of gastrin and beyond the gastrin responsive growing point. In the case of TI-GNET recurrence or persistence after local resection and antrectomy, total gastrectomy would be needed.

Medical management

Somatostatin analogs (SSAs) act on G-cells to inhibit gastrin secretion and play a role in reducing ECL cell hyperplasia. SSA treatment effectively reduces TI-GNET number and size[60-62]. However, its use cannot be recommended due to its short-term effects (*i.e.*, the tumor recurs after its cessation)[63] and its relatively high cost. Recently, natazepide (YF476), a peripheral gastrin (CCK-B) receptor antagonist, has been reported to suppress gastric acid output and ECL cell proliferation and reduce TI-GNET size and number[64]. However, there is no study on the long-term administration or large studies on CCK-B receptor antagonist treatment for TI-GNETs.

TI-GNET PROGNOSIS AND FOLLOW-UP STRATEGY

Patients with TI-GNETs generally have an excellent prognosis; in fact, disease-specific survival approaches 100%[39,40,59,60,65-74]. Tumor size and depth predict lymph node metastasis for GNETs[75], and presence of metastasis was the only factor that influenced long-term prognosis of patients with GNETs[40]. Moreover, histological tumor grading is well correlated with patient survival[68]. Therefore, the assessment of tumor metastasis, size, depth, and histological grade may predict patient prognosis. In fact, metastatic TI-GNETs are related to tumor size ⩾ 1 cm, an elevated Ki-67 index, and high serum gastrin levels[76]. On the other hand, TI-GNET recurrence rates are relatively high; however, recurrent lesions are small, indolent, and unrelated to prognosis[39,72].

Post-treatment ENETS guidelines propose that endoscopic surveillance be provided every 12 mo for patients with recurrent TI-GNET and every 24 mo for patients without recurrence[51]. NCCN guidelines recommend that patients with small (< 20 mm) TI-GNETs who did not require ER or treatment be evaluated using patient history and a physical examination every 6-12 mo[56]. The guidelines also recommend that follow-up endoscopy be performed every 6-12 mo for the first 3 years and annually thereafter if no evidence of recurrence or progression is seen[56]. However, an optimal follow-up schedule as a clinical standard has yet to be established.

CONCLUSION

The incidence of NETs has increased significantly, and the vast majority of NETs are TI-GNETs. TI-GNETs present as small (< 10 mm) and multiple lesions that are generally limited to the mucosa or submucosa. TI-GNETs tend to display a nearly benign behavior and a low risk of progression or metastasis. Several treatment options are currently available for TI-GNETs; however, their optimal management has not yet been established. Further studies on TI-GNETs are needed to develop new promising management strategies for patients with TI-GNETs.

In routine clinical practice, the careful observation of the gastric mucosa in CAG and the knowledge of the endoscopic characteristic of TI-GNETs would be required for detection of TI-GNETs. When it exists, it would be important to choose appropriate treatment after the assessment of the size, invasion, metastasis and histological grading of the tumors.

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REVIEW

Endoscopic ultrasound guided drainage of pancreatic fluid collections: Assessment of the procedure, technical details and review of the literature

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Abstract

Endoscopic ultrasound (EUS) guided drainage of pancreatic fluid collections (PFC) has become increasingly popular and become first line management option in many centers. Use of therapeutic echoendoscopes has greatly increased the applicability of EUS guided transmural drainage. Drainage is indicated in symptomatic PFCs, PFC related infection, bleed, luminal obstruction, fistulization and biliary obstruction. EUS guided transmural drainage of PFCs is preferred in patients with non bulging lesions, portal hypertension, bleeding tendency and in those whom conventional drainage has failed. In the present decade significant progress has been made in minimally invasive endoscopic techniques. There are newer stent designs, access devices and techniques for more efficient drainage of PFCs. In this review, we discuss the EUS guided drainage of PFCs in acute pancreatitis.

Key words: Acute pancreatitis; Pancreatic fluid collections; Endoscopic ultrasound-guided drainage

Core tip: Endoscopic ultrasound guided drainage has become first line option in the management of pancreatic fluid collections in acute pancreatitis. There are many new stent designs and techniques available that has made the procedure and its outcome more impressive. In this manuscript we present a concise review on this topic.

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INTRODUCTION

Acute pancreatitis (AP) is sometimes accompanied by

Table 1 Classification of pancreatic fluid collections as per revised Atlanta classification

Acute pancreatitis
Interstitial edematous pancreatitis
Necrotizing pancreatitis (pancreatic necrosis and/or peripancreatic necrosis)
Sterile necrosis
Infected necrosis
Fluid collections during acute pancreatitis
< 4 wk after onset of acute pancreatitis
Acute peripancreatic fluid collection
ANC
⩾ 4 wk after onset of acute pancreatitis
Pancreatic pseudocyst
WOPN

ANC: Acute necrotic collection; WOPN: Walled-off pancreatic necrosis.

local complications in the form of fluid collections and necrosis. The local complications seen with AP include acute pancreatic fluid collections (PFCs), pancreatic pseudocysts, acute necrotic collections (ANCs), and walled off pancreatic necrosis (WOPN). The nature and sites of PFCs are diverse as are the management options. The recent revision of Atlanta classification has reclassified these fluid collections[1]. Acute PFCs develop in the early phase of interstitial edematous AP, and they lack a wall and are confined by the fascial planes (Table 1). They are generally not complicated and usually resolve without intervention[2]. PFCs that persist for longer than 4 wk usually develop a defined wall and are described as pancreatic pseudocysts. Pseudocysts are less commonly seen with AP; they are more common with chronic pancreatitis. ANC refers to those developing in cases of necrotizing pancreatitis. When the ANCs persist for more than 4 wk they develop into WOPN. ANC and WOPN have variable amount of necrosis and the chances of infection and complications are higher. PFCs are also seen with post-operative complications and abdominal trauma[3-6]. In this review, we will confine the discussion to AP related PFC.

There have been a lot of controversies in identifying PFCs that require intervention. The recent data indicate drainage in PFCs that are symptomatic. Other indications include PFC related infection, bleed, luminal obstruction, fistulization, and biliary obstruction[7-11]. Size alone is not a criterion for drainage of PFCs, but those larger than 6 cm are usually symptomatic. The methods of drainage include, percutaneous radiologic, endoscopic and surgical. Each of these modalities has advantages and disadvantages. A recent retrospective study comparing the two nonsurgical techniques; percutaneous radiologic *vs* endoscopic drainage (conventional transluminal drainage by forward-viewing endoscopy or endoscopic ultrasound-guided drainage) in PFC showed no significant difference between technical success rates[12]. However, percutaneous drainage was associated with a higher re-intervention rate, longer hospital stay, and increased number of subsequent abdominal imaging studies[12]. The authors concluded that, overall endoscopic drainage should be the preferred method. Another recent prospective randomized controlled trial regarding surgical drainage *vs* endoscopic ultrasound (EUS)-guided drainage for symptomatic PFCs revealed that both groups were comparable in treatment success, complications, or re-interventions. But the duration of hospitalization was less, the physical and mental health scores were better, and the total mean costs were lower for the EUS group[13]. There was also no recurrence in PFCs following endoscopic drainage, thereby showing that surgical drainage is not superior in outcome. The authors concluded that, In view of less invasiveness, lower costs, lower re-interventions, and lower morbidity endoscopic drainage should be considered as the first-line method in the management of PFCs.

Endoscopic drainage is performed by transmural route or endoscopic retrograde cholangiopancreatography (ERCP) guided transpapillary route. Transmural drainage is done for PFCs close to the lumen and can be performed by conventional method (using duodenoscope) or under EUS guidance[14,15]. The specific advantages of EUS guided intervention are: (1) EUS can confirm the presence of PFCs and distinguish it from cystic neoplasms, true cysts, gall bladder and other lymphovascular structures[16]; (2) EUS can identify the presence of solid necrotic material inside the collection. Extensive necrotic debris warrant more aggressive debridement; (3) EUS can identify the presence of any intervening vessels or organs that can be damaged at the time of puncture of PFC[17,18]; and (4) EUS is of extreme importance in localizing "non-bulging" PFCs and determining the correct site of approach into these lesions. Non-bulging PFC are present in 40% of cases[19,20]. Clinical success occurs in 70% to 87%, and complications in 11% to 34% of patients undergoing EUS drainage[7,21,22]. Improvement in techniques, availability of new accessories, stent designs and development of exchange free access devices have increased the safety and efficacy of EUS guided PFC drainage. Disadvantages of EUS drainage include the complications in the form of bleed, secondary infection, luminal perforation and stent migration. Multiloculated collections may fail to resolve completely with conventional EUS draining techniques. Lesions not close to luminal wall may not be accessible to EUS drainage.

Prerequisites for EUS drainage

The PFCs are considered for endoscopic drainage when they are symptomatic, demonstrate a well-formed wall and are located in an endoscopically accessible location (within 1 cm of the luminal wall)[7-11]. Computed tomography (CT) or magnetic resonance imaging is performed before drainage. They help in delineation of the anatomy and PFC. With expertise PFCs that have failed drainage by other methods and those in unusual locations are also considered for drainage[7,16,23]. Many experts recommend assessment of the main pancreatic duct at the time of PFC drainage with ERCP as uniden-

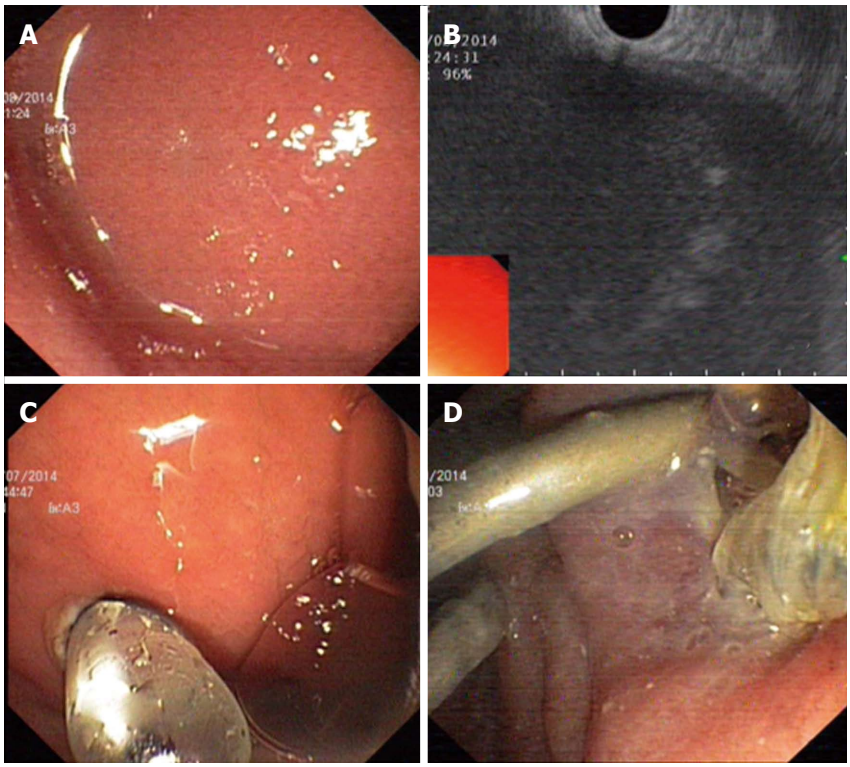

Figure 1 Endoscopic view of intragastric bulge due to pancreatic fluid collections (A), endosonographic view of pancreatic fluid collections (B), Dilation of fistula with Controlled radial expansion (CRE™) catheter balloon (C), Placement of double pigtail plastic stents through the fistula (D).

tified pancreatic duct stricture or leak may result in failure of resolution or recurrence of PFC[16,24,25].

TECHNIQUE OF EUS GUIDED DRAINAGE OF PFC

EUS guided PFC drainage is performed under conscious sedation in the left lateral position or under general anesthesia (Figures 1 and 2). Most endoscopists prefer fluoroscopy suite for procedure, since in some cases the radiologic view can be helpful either for insertion of the stent or for completing the drainage with cyst irrigation and/or additional stent placement. After identification of cyst in relation to luminal wall, evaluate the cyst with the linear array echoendoscope (with a channel size of at least 3 mm to allow placement of 10 French stents) looking for a site with optimal contact with the gastric or duodenal wall, assess with doppler to eliminate interposition of large vessels, evaluate distance of PFC to the gut wall, presence of solid debris inside the cyst, evidence of portal hypertension, communication of the cyst with the pancreatic duct and presence of coexistent biliary disease (such as common bile duct stones)[25]. After this, identify an adequate point to puncture; where there are no intervening blood vessels and the distance between the gut lumen and the PFC is less than one centimeter. Thereafter a 19 G needle (Wilson-Cook, Winston-Salem, NC, United States) is introduced through the working channel of the endoscope and pseudocyst is punctured under real-time guidance, it is preferable to have a fixed and straightened position of echoendoscope. After removing the needle stylet, aspirate at least ten cc of pseudocyst contents for Grams stain, culture and analysis for determination of amylase, carcino embryonic antigen levels, and other tests as per the clinical indication.

Afterwards, introduce a guide-wire (Jagwire, Boston Scientific Corp, Natick, MA, United States) through the needle under real-time ultrasonographic and fluoroscopic guidance. Without losing the endoscope position we remove the needle, leaving the guide-wire in place, and a 6 F cystotome is passed over guide-wire to puncture bowel wall and cyst wall, this establishes a fistula. Some authors have used tapered cannula or needle knife. This fistula track is further dilated with either a 6 or 8 mm biliary balloon dilatation catheter (Hurricane Rx, Boston Scientific Corp, Cork, Ireland) over the wire or 12-15 mm CRE balloon (Boston Scientific Corp, Cork, Ireland) under endoscopic or EUS view[20]. After obliteration of waist, the balloon is deflated and a lot of pseudocyst contents usually drains into the stomach and it must be aspirated. Once there is a clear vision of the fistula, a double pigtail stent (Solus, Cook Medical, Limerick, Ireland) are inserted over the wire and placed through the fistula, connecting the pseudocyst and the gastric lumen or appropriately sized self-expandable metal stents (SEMS) are placed depending on cyst contents. In order to insert more stents, we have to re cannulate the fistula and again insert the guide wire into the cyst to be able to introduce a second stent or a nasocystic catheter. We repeat this maneuver as many times as the number of

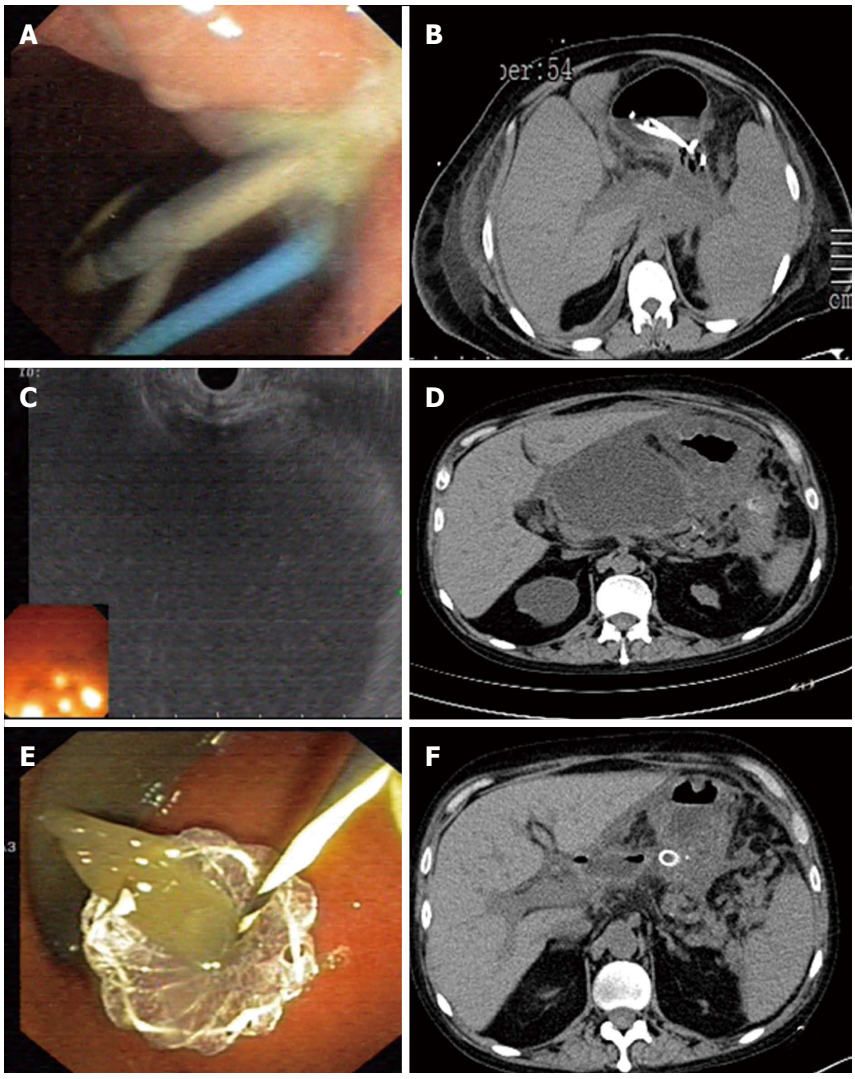

Figure 2 Placement of double pigtail plastic stent and nasocystic drain (A), computed tomography view of pancreatic fluid collections after insertion of stent and nasocystic drain (B), endosonographic view of pancreatic fluid collections before drainage (C), computed tomography view of pancreatic fluid collections before drainage (D), Placement of NAGI stent into pancreatic fluid collections (E), computed tomography view after placement of NAGI stent (F).

stents we want to place.

Normally 2 to 3 stents, 10 F diameter and 5 cm long are placed into the PFC. The patient resumes oral feeding several hours after the exploration and is discharged 48-72 h later if there are no procedure-related complications. Patients needs follow up on four weekly basis with cross sectional imaging. All the stents can be removed after confirmation of the resolution of collection and after ensuring the integrity of pancreatic duct[23]. We routinely remove stent at three months and SEMS at 8 wk. New accessories include modified access needles (19 G needle, Grosse, Daldorf, Germany, loaded with a modified 7- or 10-Fr stent and a Teflon pusher catheter, Wilson-Cook)[25,26], exchange free access design, NAVIX (Xlumena Inc., Mountain View, CA, United States)[27,28] and Giovannini Needle Wire Oasis a needle wire device (Cook Endoscopy, Winston-Salem, NC, United States)[29]. Some authors recommend placement of a nasocystic catheter in the presence of solid debris inside the cyst that allows nasocystic lavage[30].

REVIEW OF LITERATURE

There are reports of PFC drainage through stomach that date back to early 1990s (Table 2). Grimm *et al*[31] successfully created a fistula between the stomach and a cyst with a linear echoendoscope. Binmoeller *et al*[21] in 1995 had reported a series (n = 27) of EUS guided drainage of pancreatic pseudocysts with a success rate of 78%. Over years the technique and accessories evolved and with the advent of the therapeutic linear echoendoscope with larger working channels of 3.7 or 3.8 mm, successful drainage with placement of multiple large-bore stents without changing the scope became feasible. In 2001, Giovannini *et al*[32] reported 88.5% success rate (n = 35) in patients undergoing the drainage of pseudocyst or pancreatic abscess. One patient had pneumo-peritoneum that resolved with conservative care and four had failure

Table 2 Summary of technical success, clinical success and complications with endoscopic ultrasound-guided drainage of pancreatic fluid collection

Ref. (number of cases)	Type of study	Technical Success (%)	Clinical Success (%)	Complications (%)	Complications
Grimm *et al*[31], 1992 (1)	Retrospective	100	100	0	Nil
Binmoeller *et al*[21], 1995 (27)	Retrospective	93	78	7	Bleeding (*n* = 2)
Giovannini *et al*[32], 2001 (35)	Prospective	100	89	3	Pneumoperitoneum (*n* = 1)
Azar *et al*[33], 2006 (23)	Retrospective	91	82	4	Pneumoperitoneum (*n* = 1)
Antillon *et al*[19], 2006 (33)	Prospective	94	87	15	Bleeding (*n* = 4), pneumoperitoneum (*n* = 1)
Krüger *et al*[34], 2006 (35)	Prospective	94	88	0	Nil
Kahaleh *et al*[35], 2006 (46)	Prospective	100	93.5	20	Superinfection (*n* = 4), bleeding (*n* = 2), pneumoperitoneum (*n* = 2) stent migration (*n* = 1)
Hookey *et al*[22], 2006 (32)	Retrospective	96	93	9	Pneumoperitoneum (*n* = 2), bleeding (*n* = 1)
Lopes *et al*[36], 2007 (51)	Retrospective	94	84	4	Pneumoperitoneum (*n* = 1), migration (*n* = 1)
Varadarajulu *et al*[37], 2007(21)	Prospective	100	95	0	None
Barthet *et al*[38], 2008 (28)	Prospective	100	89	18	Superinfection (*n* = 5)
Varadarajulu *et al*[39], 2008 (24)	Randomized controlled trial	100	96	0	Nil
Park *et al*[40], 2009 (31)	Randomized controlled trial	94	89	7	Minor bleeding (*n* = 1), stent migration (*n* = 1)
Zheng *et al*[41], 2011 (21)	Retrospective	90.5	90.5	19	Stent blockade (*n* = 2), Infection (*n* = 2)
Varadarajulu *et al*[42], 2011 (148)	Prospective	100	98	5	Infection (*n* = 4), perforation (*n* = 2), bleeding (*n* = 1), stent migration (*n* = 1)
Bakker *et al*[43], 2012 (10)	Randomized controlled trial	90	80	20	Pancreatic fistula (*n* = 1), death from multiorgan failure (*n* = 1)
Seewald *et al*[44], 2012 (80)	Retrospective	97	84	26	Bleeding (*n* = 12), perforation (*n* = 7), portal air embolism (*n* = 1), ogilvie syndrome (*n* = 1)
Fabbri *et al*[45], 2012 (22)	Prospective	100	77	14	Superinfection (*n* = 1), superinfection and stent migration (*n* = 1), failed stent removal (*n* = 1)
Itoi *et al*[46], 2012 (15)	Retrospective	100	100	7	Stent migration (*n* = 1)
Berzosa *et al*[47], 2012 (7)	Retrospective	100	100	0	None
Penn *et al*[48], 2012 (20)	Prospective	100	85	15	Superinfection (*n* = 2), pancreatitis (*n* = 1)
Mangiavillano *et al*[49], 2012 (21)	Prospective	85.7	81	4.8	Bleeding (*n* = 1)
Weilert *et al*[27], 2012 (18)	Prospective	100	77.8	5.6	Tract dehiscence (*n* = 1)
Gornals *et al*[28], 2012 (9)	Prospective	89	89	11.1	Tension pneumothorax (*n* = 1)
Puri *et al*[50], 2012 (40)	Prospective	100	97	5	Pneumoperitoneum n-1, infection (*n* = 1)
Siddiqui *et al*[51], 2013 (87)	Retrospective	99	79	18	Stent occlusion (*n* = 16)
Lin *et al*[52], 2014 (93)	Retrospective	95	95	12	Secondary infection (*n* = 11)

Table modified from the tables described by Fabri *et al*[8] and Singhal *et al*[25].

requiring surgery[32]. None of the patients developed bleed. In 2006, Azar *et al*[33] using a therapeutic linear echoendoscope described a new technique of introducing a 19-gauge needle and guide-wire into the PFC followed by creation of a fistula with a cystoenterostome. Maximum upto four stents were placed through the tract after balloon dilation. They reported successful drainage (*n* = 23) of pancreatic pseudocysts in 91.3% patients with only a single case of significant pneumo-peritoneum. Another study by Krüger *et al*[34] described EUS-guided drainage with placement of 8.5 Fr stents (*n* = 34). The procedure was successful in 88%. There was recurrence (12%) over next 2 years, and cyst resolution of pseudocyst was increased in 30% with cyst irrigation. Hookey *et al*[22] described EUS-guided drainage of PFC (*n* = 116) which included acute pseudocysts, necrosis, and abscess. They noted 29/32 (90.6%) success. Of these patients, 20 had non bulging lesions. 4 (12.5%) patients had recurrence and 3 (9.4%) had complications[22].

In 2006, Kahaleh *et al*[35] reported a prospective comparative study of non EUS guided *vs* EUS guided drainage. 53/99 patients underwent non EUS guided, and rest EUS guided drainage. Those with visible bulge and no portal hypertension were included in the former group. The outcomes at 6 mo (84% *vs* 91%) and overall complications (18% *vs* 19%) were comparable in the two groups. They reported that the choice between these two techniques, therefore, depends on individual patient characteristics and availability of skilled EUS intervention. They recommended EUS guided drainage for non-bulging collections and those at risk for bleeding[35]. Another study by Varadarajulu *et al*[39] in 2008 compared EUS and conventional transmural drainage of pancreatic pseudocysts. Only 5/15 patients had successful drainage with the conventional method, and all of them had complete drainage on cross over to EUS. Major procedure related bleed was seen in 2 patients in the conventional drainage group. The authors concluded that EUS

guided drainage should be the first option.

In a prospective randomized controlled trial by Park *et al*[40], patients with pancreatic pseudocysts (*n* = 60) were randomly allotted to conventional drainage (*n* = 29) and EUS guided drainage groups (*n* = 31). In an intention-to-treat analysis, the technical success of the procedure was more for EUS guided drainage (94%) than for conventional drainage (72%, *P* = 0.039). With the failure of conventional drainage (n = 8), crossover to EUS guided drainage was made, which was successful in all. Complications in both groups were comparable (7% *vs* 10%, *P* = 0.67). Long term clinical success on per protocol analysis was comparable in both groups (89% *vs* 86%, *P* = 0.69). The authors concluded that EUS guided drainage, and conventional transmural drainage can both be considered first-line methods, but with non bulging cysts the former should be preferred.

In another study by Varadarajulu *et al*[42] (*n* = 148) to evaluate complications in patients undergoing EUS-guided PFC drainage, authors reported low rates of complications; perforation (*n* = 2) bleeding (*n* = 1) infection (*n* = 4) and stent migration (*n* = 1). Both cases of perforation occurred in pseudocysts in uncinate process. Most of the patients could be managed conservatively, 2 with perforation and 2 with infection required surgery. They concluded that most of the complications during EUS drainage can be managed successfully, and EUS guided drainage should be the first option in places with expertise.

Seewald *et al*[44] in a retrospective analysis of 80 patients with symptomatic PFC (mean diameter: 11.7 cm, range 3-20 cm; pseudocysts: 24/80, abscess: 20/80, infected WOPN: 36/80) observed clinical success in 83% initial for PFC drainage. The long-term clinical success over 21 mo followup was 72.5%. There was recurrence in 9 patients due to failure of endoscopic treatment of pancreatic duct abnormalities. They concluded that EUS drainage is safe and effective. They emphasized that EUS guidance is important for reduced bleeding related complications, and surgical or endoscopic treatment of pancreatic ductal lesion is extremely important for complete resolution of PFCs.

We had studied the role of combined EUS-guided drainage (with placement of double pigtail stents) and nasocystic drainage in a series of 40 patients who had non bulging pancreatic pseudocysts, 32 had no evidence of infection and 8 had infection. All 32 patients without infection and 7 out of 8 patients with infection had complete drainage. One patient had to undergo surgery due to bleeding in the pseudocyst[50]. Siddiqui *et al*[51] reported drainage of pseudocysts with viscous solid debris by combination of stents and nasocystic tubes (*n* = 63) *vs* stents alone (*n* = 24). They found three times higher short-term success rate for combined group with both stents and nasocystic tube (*P* = 0.03). After 1 year of follow up, they found that with nasocystic drain there was higher occurrence of complete resolution (79% *vs* 58%, *P* = 0.59), lower occurrence of stent occlusion (13% *vs* 33%, *P* = 0.03)[51]. Authors recommended combining both nasocystic drain and transmural stents in EUS guided drainage of pseudocysts with viscous debris-laden fluid.

Lin *et al*[52] in a retrospective study to define the number of stents required for successful drainage of PFCs evaluated 93 patients [acute pseudocyst (*n* = 67), chronic pseudocyst (*n* = 9), and WOPN (*n* = 17)]. There was no difference in the outcome based on the type of collection. Clinical success for single-stent drainage was 93.9% (46/49) *vs* 97.4% (37/38) for multiple stent drainage (*P* = 0.799). The occurrence of secondary infection for single-stent drainage was 18.4% (9/49) *vs* 5.3% (2/38) for multiple-stent drainage (*P* = 0.134). Secondary infection for stent diameter less than or equal to 8.5 F was 3.4% (1/29). It was 17.2% (10/58) for stent diameter larger than or equal to 10 F (*P* = 0.138). The authors concluded that during EUS-guided transmural drainage of PFCs, single-stent transmural drainage of PFCs is sufficient, and the number of stents or its size does not seem to influence clinical success or occurrence of secondary infection. In a similar study Bang *et al*[53] retrospectively studied 122 patients; 45 (36.9%) had 10Fr stents of which 30 patients (66.7%) had more than one stent, 77 (63.1%) patients had 7 Fr stents of which 56 (72.7%) had more than one stent. The overall treatment success was 94.3%**.** On multiple logistic regression analysis, the stent size (OR = 1.54; 95%CI: 0.23-10.4) and number of stents inserted (OR = 1.15; 95%CI: 0.25-5.25) were not associated with the number of interventions required for treatment success. Authors concluded that the number of interventions required and stent characteristics in patients undergoing endoscopic transmural drainage of uncomplicated pancreatic pseudocysts does not influence the clinical outcome[53].

Panamonta *et al*[54] reported a meta-analysis of (2 randomized-controlled trials and two prospective studies, 229 patients) comparing conventional transmural drainage and EUS guided drainage They found that the technical success rate was significantly higher for EUS group than for conventional drainage group (RR = 12.38, 95%CI: 1.39-110.22). A crossover to EUS drainage with failure of conventional drainage of non-bulging lesions (*n* = 18) was successful in all 16 cases. All patients with portal hypertension and bleeding tendency underwent EUS guided drainage to avoid severe complications. The authors found that the outcome of EUS drainage was comparable to conventional drainage in terms of short-term success (RR = 1.03, 95%CI: 0.95-1.11), long-term success (RR = 0.98, 95%CI: 0.76-1.25) and occurrence of complications (RR = 0.98, 95%CI: 0.52-1.86). They concluded that, either EUS drainage or conventional drainage are equally good for bulging pseudocysts and EUS guided drainage should be preferred for those with non-bulging pseudocysts, portal hypertension, or

coagulopathy.

The promising results of these studies on EUS drainage has increased the application of EUS guided PFC drainage world over. Yusuf *et al*[55] reported the results of a web-based survey of United States and International members of the American Society for Gastrointestinal Endoscopy. Of the 266 replies they received 198 performed pseudocyst drainage. A baseline CT scan was performed by 95% of responders. Endoscopic ultrasound was used before drainage by 70% of United States endoscopists and 59% of International endoscopists and EUS guided drainage was used by 56% and 43% of endoscopists respectively. The most common access route was transgastric (65%), and 1 to 5 stents were placed for drain.

USE OF COVERED SELF-EXPANDING METAL STENTS

Most of the studies reported the use of plastic double pigtail stents of varying size and nasocystic drains[35,56]. There are a few studies that have reported the use of metal stents for drainage of PFC. They are wide bore stents and tend to stabilize the pseudocyst wall at the site of insertion by applying radial expansive force. Talreja *et al*[57] reported drainage of PFC (n = 18) with covered self-expandable metal stents (covered SEMS; VIABIL; Conmed, Utica, NY, United States). Seventeen patients had a successful response, and 14 achieved complete resolution of their fluid collection (median number of sessions, n = 1, range 1-4). There were only a few complications in the form of superinfection (5), bleeding (2), and inner migration (1). There was no group with plastic stents for comparing the results.

Fabbri *et al*[45] reported 22 patients with infected PFC (mean size, 13.2 cm) of which 20 underwent EUS guided transmural drainage with covered SEMS. Early complications (superinfection, n = 1 and stent migration, n = 1) were seen in 2 patients. In the remaining 18 patients, stents could be removed easily in 17 patients (after a median of 26 d). In one patient stent had to be removed surgically due to inflammatory tissue in growth. Resolution of PFC was achieved in 17 patients (mean follow-up of 610 d) with only one symptomatic recurrence. Penn *et al*[48] reported use of combining double pigtail stent with covered SEMS (n = 20) to prevent migration of the latter. Partial migration occurred in 2 patients and the double pigtail prevented complete migration of covered SEMS. Initial success was reported in 17/20patients (1 patient had complete migration), with recurrence of PFC in three patients after stent removal. Weilert *et al*[27] in another study of 18 patients reported a success rate of 14 (78%) with the use of fully covered SEMS and only 1 patient required repeat stent placement. There are no randomized controlled trials that have shown the superiority of these stents over plastic stents.

NEW DEVELOPMENTS IN ACCESS DEVICES STENTS AND TECHNIQUES

One limitation of EUS guided drainage in many settings is dependence on fluroscopy and anesthesia. Schneider *et al*[58] evaluated the short and long-term outcomes of PFC drainage with endoscopic ultrasound guidance without fluoroscopy or anesthesia support**.** They studied 80 consecutive patients with symptomatic fluid collections ($\leqslant$ 6 cm in size and located < 2 cm from the gastrointestinal wall). PFCs were approached through gastric or duodenal wall, and those with estimated > 40% debris were excluded unless the features of sepsis. EUS was performed under conscious sedation with midazolam (2.5-10 mg) and fentanyl (100-300 μg). Procedural success was achieved in 74/80 (93%) with re-interventions in 16/74 (22%) cases and complications in only 11% (2 severe bleeding, 4 free perforations, 1 stent-related pressure ulcer, 1 minor bleed, 1 stent migration).

NAVIX access device is a multifunction, exchange-free system. It has a 3.5 mm switch blade to provide easy access across through the luminal wall. It has an 8 mm anchor balloon to maintain the catheter position in the pseudocyst, a 10-mm dilating balloon, and 2 guide-wire ports[27]. It was described for successful placement of fully covered SEMS (n = 18 patients) for drainage of PFC[27]. Gornals *et al*[28] used NAVIX system and reported a shorter median procedure duration (22 min; range, 10-30) compared to exchange devices (40 min; range, 25-55)[25,28].

Anchoring covered SEMSs have been recently introduced for improved drainage of PFCs. Itoi *et al*[46] first reported the use of Xlumena Mountain view CA (AXIOS) stent; a lumen-apposing fully covered, 10-mm diameter, nitinol, braided stent. The cyst wall and luminal wall are held together by anchoring flanges. This study involved 15 patients with symptomatic pancreatic pseudocysts who underwent 12 transgastric and three transduodenal pseudocyst drainage procedures. They showed that the AXIOS stents were successful in all cases with just one case of migration into stomach without any complications (median follow-up time of 11.4 mo). NAGI stent, a novel covered self-expanding metallic stent (Taewoong-Medical Co, Seoul, South Korea, with a 10 mm diameter in the center and 20 mm ends, for an endoscopic cystogastric anastomosis) prevents stent migration and ensures safe and effective of PFCs. It can be deployed in a single step procedure and a larger fistula diameter in the endoscopic cystogastric anastomosis. Téllez-Ávila *et al*[59] reported the use of NAGI stent in successful drainage of PFC and reported complete resolution of the PFC at 6 mo follow up. In another study AXIOS stent was compared with plastic double pigtail stents and found similar technical and clinical success rates[28]. But with multiple plastic stents, they noted increased number of adverse events, use of increased

number of stents and increased mean procedure duration. One patient however developed a tension pneumothorax secondary to trans-esophageal AXIOS placement. AXIOS stent placement in esophagus is technically challenging due to its large size. These new stents provide stent stability, minimize the risk of migration due to the anchoring effect, and maintain the larger SEMS lumen which helps in easy passage of echoendoscope into the cavity of PFC.

The different studies described so far followed single transluminal gateway drainage using transmural stenting (single or multiple plastic stents or SEMSs). It is usually successful in complete resolution of unilocular or uncomplicated PFCs. In the presence of multilocular or huge infected PFCs, particularly WOPN, a new approach by multiple transluminal gateway drainage has been described[60,61]. In this technique, the caudal part of the WOPN is first drained initially with two 7Fr stents. For WOPN between 6-12 cm only one transluminal tract and those between 12 and 15 cm atleast 2 transmural tract and those more than 15 cm multiple tracts (3-6) are made. An 18 Fr nasogastric tube is placed in cranial part of collection to help irrigation[62]. Combination of transluminal and percutaneous drainage techniques can help in accessing all the subcavities in certain cases. Patients who fail to respond clinically to these drainage methods require endoscopic necrosectomy or surgery. Dhingra *et al*[63] has recently described percutaneous endoscopic necrosectomy (PEN) in patients with infected pancreatic necrosis who had failed to percutaneous catheter drainage. In their study 14 of 15 patients improved (mean of 5 sessions) after single or multiport PEN, with only minor side effects in two patients (self-limiting bleeding and pancreatic fistula in 1 patient each) and death in one patient.

CONCLUSION

The use of EUS in drainage of pancreatic fluid collections has increased over the last few years. Many new techniques and stent designs have increased the applicability of this method. Compared to conventional transmural drainage there are some clear advantages for EUS-guided drainage over as in accessing non-bulging cysts and in patients with portal hypertension and bleeding tendency. Covered SEMS and anchoring covered SEMS are shown to drain PFCs successfully. Prospective randomized trials are required to establish the exact role of covered SEMS as compared to the plastic stents. Further experience will enable us to utilize EUS guided techniques for more successful drainage of PFCs with fewer complications.

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MINIREVIEWS

Palliative percutaneous endoscopic gastrostomy placement for gastrointestinal cancer: Roles, goals, and complications

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Abstract

Percutaneous endoscopic gastrostomy tube placement is an invaluable tool in clinical practice that has an important role in the palliative care of patients with gastrointestinal cancer. While there is no extensive data regarding the use of this procedure in patients with gastrointestinal malignancy, inferences can be made from the available information derived from studies of similar or mixed populations. Percutaneous endoscopic gastrostomy tubes can be used to provide enteral nutrition for terminal malignancies of the upper gastrointestinal tract as well as for decompression of malignant obstructions. The rates of successful placement for cancer patients with either of these indications are high, similar to those in mixed populations. There is no conclusive evidence that the procedure will help patients reach nutritional goals for those needing alimental supplementation. However, it is effective at relieving symptoms caused by malignant obstruction. A high American Society of Anesthesiologist physical status score and an advanced tumor stage have been shown to be independent predictors of poor outcomes following placement in cancer patients. This suggests the potential for similar outcomes in the palliative care of patients with advanced stage gastrointestinal cancer who may be in relatively poor physiologic condition. However, this potential should not preclude its use in patients with terminal gastrointestinal cancer considering the high rate of successful tube placement, the possible benefits and the ultimate goal of comfort in palliative care.

Key words: Percutaneous endoscopic gastrostomy tube; Palliative care; gastrointestinal cancer; Nutritional supplementation; Gastrointestinal decompression

Core tip: Percutaneous endoscopic gastrostomy tube placement may be used in the palliative care of patients with gastrointestinal cancer for supplemental nutrition or to decompress distal obstructions. There is a high rate of successful placement in cancer patients. It has been shown to relieve symptoms of malignant obstruction and has the potential to help patients reach nutritional goals. While poor physiologic condition and advanced tumor stage have been associated with a higher risk of worse outcomes, this should not preclude its use in these patients considering the high rate of successful placement, potential benefits and the goal of comfort in palliative care.

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INTRODUCTION

The use of gastrostomy tubes to gain enteral access has been implemented since the late 19th century. The Witzel or Stamm techniques, either open or laparoscopic, have been the standard of care for surgical gastrostomy through the 1970s[1]. In 1980, Gauderer *et al*[2] first described the percutaneous endoscopic gastrostomy (PEG) method for enteral access in children with swallowing disorders[2]. Since that time, the use of PEG has been extended broadly to patients with dysphagia, either physiologic or obstructive, for the provision of enteral nutrition. PEG tube placement can be performed quickly at the bedside and requires only local anesthesia and minimal sedation resulting in substantial time and cost savings compared to surgical gastrostomy[3]. Additionally, it has been successfully used to decompress the stomach and/or proximal gastrointestinal tract in the setting of malignant obstructions distal to the pylorus[4]. PEG placement has become an important and frequent procedure performed by surgeons and gastroenterologists. In a review 20 years following its initial description there were estimated to be greater than 216000 PEG procedures performed annually in the United States[5].

This endoscopic procedure has also been utilized with a palliative intent as a means to provide enteral nutrition or relieve intestinal obstructions. The World Health Organization characterizes "palliative care" as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness[6]". More concisely, "palliative care" provides "care alleviating symptoms without curing the underlying disease"[7]. It was a surgeon, Balfour Mount, who originally coined the term "palliative care" in 1975[8]. Since that time, as the elderly population and the prominence of chronic disease have increased, the need for palliative care has increased in kind[9]. Palliative medicine is an essential component to the care of patients with gastrointestinal cancer, encompassing any malignancy from the mouth to the anus, and PEG tube placement is an invaluable tool in the field. In the palliative care of patients with terminal gastrointestinal cancer, PEG may be used either as a method to provide enteral nutrition in patients with an obstructing upper gastrointestinal cancer or as a means to decompress the upper gastrointestinal tract in patients with malignant bowel obstructions.

The purpose of this review is to better understand roles (uses) and goals (outcomes) of palliative PEG tube placement in patients with gastrointestinal cancer. Unfortunately, the use of this type of palliative PEG for patients with terminal gastrointestinal cancer has not been extensively studied. There are no clear guidelines regarding the role of PEG placement in the palliative care of these patients. However, an understanding of the use, broad outcomes and complication incidence of PEGs placed in all cancer patients for nutritional support or bowel decompression may provide insight into its roles and goals in the palliative care of patients with gastrointestinal cancer. While the need to decompress a gastrointestinal obstruction is a clear indication for intervention, PEG tube placement for nutritional purposes in the setting of palliative care raises multiple ethical issues. This review will focus on better understanding the risks and benefits of the procedure in these situations in order to properly guide the patient towards an informed decision.

ROLES

Enteral nutrition

The most common indication for PEG tube placement is provision of enteral nutrition for patients with neurologic disorders, head/neck cancer and trauma[10,11]. With respect to gastrointestinal cancer, PEG tube placement in patients with obstructing oropharyngeal, esophageal or stomach cancer is designed to provide enteral nutrition. In a recent retrospective review of all patients within a cancer institution who underwent PEG, roughly half of the patients had head/neck cancer; 22% of the patients had a different gastrointestinal cancer. The most common indication for PEG was nutritional supplementation[12]. Similarly, another retrospective study of all cancer patients found that 73% of the patients received a PEG tube for enteral access and nutritional supplementation while the remaining 27% had it placed for bowel decompression[13].

Decompressive PEG

Malignant bowel obstruction is an important consideration in patients with gastrointestinal cancer. It is particularly relevant to palliative care as its occurrence often serves as a harbinger of worsening disease or recurrence[14]. Though the rates of obstruction vary in the literature, the incidence of malignant obstruction for colorectal cancer has been reported to be between 10% and 28.4%[15]. In the setting of metastatic disease its identification is particularly ominous and often signals the need for end-stage palliation[16].

Obstruction of the gastrointestinal tract by a malignancy leads to a complex pathophysiologic process that involves aggregation of bowel gas and secretions, impaired motility, decreased absorption and inflammation[17]. The result is malnutrition and debilitating nausea, vomiting and abdominal pain. PEG tube placement is a method to decompress the stomach and proximal bowel to alleviate these symptoms[18].

For patients ineligible for definitive surgical treatment, other management strategies for malignant bowel obstruction include medical therapy, nasogastric tube decompression, stent placement in colorectal cancer and surgical resection. Medical treatment is targeted both at resolution of obstruction and symptom management. In addition to their antiemetic effect, a Cochrane review showed that corticosteroids have the potential to aide in the resolution of intestinal obstruction[19]. The medical armamentarium also includes other antiemetics, anti-cholinergics, somatostatin analogues and opiates, all of which may be of limited benefit[16,20,21]. The initial management of malignant obstruction usually involves nasogastric tube decompression. However, long-term use of nasogastric tubes is not feasible considering patient discomfort and the potential erosion of the nasal pathways[14,17]. For patients with colorectal cancer, stents have been used to relieve obstruction. A systematic review of self-expanding metal stents found a median clinical success rate of 92% however complication rates of stent migration and re-obstruction were both > 10%[22]. Given the mixed success and complication rates of these strategies, the role of decompressive PEG tube placement should be considered.

In a retrospective review of all PEG tubes placed at a medical center, 6% were performed for decompressing a malignant obstruction[16]. When limited to cancer patients excluding those with head/neck and thoracic malignancies, Keung *et al*[13] found that 27% of PEGs were performed for gastric decompression/management of obstructive symptoms. This procedure has the ability to both alleviate obstructive symptoms and permit patients to participate in the culturally important act of eating, albeit non-nutritive, that can dramatically improve the quality of life of patients undergoing palliative care. The success and complication rates of both decompressive PEG and those placed for nutritional supplementation in patients with gastrointestinal malignancy is considered below.

GOALS

Outcomes

In patients with head and neck cancer, PEGs placed for enteral alimentation is well studied and has clearly been shown to improve both nutritional status and quality of life[12,23-25]. Similarly, the use of decompressive PEG in patients with malignant bowel obstruction secondary to advanced gynecologic cancer has been shown to effectively ameliorate obstructive symptoms[18,26,27]. While the use of PEG in these scenarios has been well studied, there has been relatively little data regarding the outcomes of PEG in patients with primary gastrointestinal malignancy outside of the oropharynx. As mentioned above, several recent studies have looked at PEG placement in all cancer patients who may benefit from PEG as a palliative measure either for nutritional support or decompressing malignant obstructions[12].

There is a high rate of success for PEG placement in patients with cancer. Three retrospective studies analyzing PEG in cancer patients reported success rates > 95%[13,28,29]. One of these studies found a 98.9% success rate despite 51.9% of their patients having had prior abdominal surgery[13]. The success rate for PEG placement in cancer patients is similar to that of the overall population. This suggests that cancer is not necessarily a physiologic or technical limitation. For cancer patients who had successful PEG placement, studies have found varied median survival times. A 2013 retrospective study of 218 cancer patients who underwent PEG found a median survival time of 10.2 mo (8 d-5.7 years); the 30-d mortality rate was 13%[12]. This is comparable to a 14% 30-d mortality rate reported by Zera *et al*[28] in a similar patient population[28]. Interestingly, a study that excluded patients with head/neck and thoracic cancer found a slightly higher 30-d mortality rate of 18.5%[13]. It is important to note that Keung *et al*[13] additionally assessed the achievement of nutritional goals following PEG. Among all cancer patients (those who received PEG for nutritional support and those who received decompressive PEG) 73.5% were able to tolerate some degree of tube feeding following the procedure. However, among those who had the procedure for nutritional support and received total parental nutrition (TPN) prior, only about half became independent of TPN following the PEG[13].

Several smaller retrospective studies have looked at the outcomes of decompressive PEG placement for malignant obstruction alone and have reported similar outcomes[16,26,27,30-35]. The largest and most recent of which, performed by Kawata *et al*[30] in 2013 with 76 patients, reported a success rate of 93%, obstructive symptom relief in 95% and a median survival of 63 d (range of 8-444 d). Notably, 96% of patients in the study who required nasogastric decompression prior to the procedure no longer required it following PEG placement[30]. These data suggest that patients with malignant obstruction secondary to a GI malignancy would benefit from a PEG with a high probability of success and obstructive symptom relief.

Complications

PEG complications are differentiated as major and minor. While minor complications include pain, formation of granulation tissue, cellulitis, *etc.*, major complications are more immediately life-threatening such as pneumonia, peritonitis, perforation, and deep venous thrombosis/pulmonary embolism (DVT/PE)[12,36-40]. In mixed patient populations, the incidence of major PEG complications has been reported at 1%-3% to as high as 9%; the incidence of minor complications is more widely varied ranging from 16% to 50%[41,42]. A large systematic review of patients with head/neck cancer found a 7.4% incidence of major complications and a 28.9% incidence of minor complications[37].

Table 1 American Society of Anesthesiologists Physical Status Classification

Class	Description
1	Patient is a completely health fit patient
2	Patient has mild systemic disease
3	Patient has severe systemic disease that is not incapacitating
4	Patient has incapacitating disease that is a constant threat to life
5	A moribund patient who is not expected to live 24 h with or without surgery

E. Emergency surgery, E is placed after the Roman numeral.

In all cancer patients, many who receive PEG for palliative reasons, several studies have assessed the incidence of complications and their predictors[12,13,28]. Richards et al. studied the incidence of PEG complications in all cancer patients, 22% had gastrointestinal cancer, and found a major and minor complication incidence of 8.7% and 37%, respectively; 30-d mortality was 13% while overall mortality was 72%[12]. Only the overall mortality was inconsistent with mixed populations as would be expected in cancer patients[42]. The only significant predictor of major complications on multivariate analysis was an American Society of Anesthesiologist (ASA) score of 4/4E/5E (HR = 4.9, p = 0.0394); packed red blood cell transfusion was nearly significant (HR = 4.6, *P* = 0.0543). Table 1 describes the ASA physical status classification[43]. With respect to 30-d mortality, an ASA score 4/4E/5E (HR = 4.66, *P* = 0.0292), advanced tumor stage (HR = 8.22, *P* = 0.0362) and elevated WBC count (HR = 1.17, *P* = 0.0060) were found to be independent predictors. Interestingly, the indication of decompressing a malignant obstruction was an independent predictor of overall mortality (HR = 1.74, *P* = 0.031)[12]. As may be expected, this data suggests that patients in worse physiologic condition (*e.g.*, higher ASA scores) or with more terminal stages of cancer (*e.g.*, advanced tumor stage), such as patients receiving a PEG for palliative reasons, would potentially have a higher incidence of major complications and 30-d mortality.

Several studies have also evaluated complication rates for only decompressive PEGs in cancer patients. In the recent study performed by Kawata *et al*[30] assessing palliative PEG in patients with malignant bowel obstruction deemed ineligible for surgical intervention, 15 of 71 patients (21%) experienced complications, only one of which would be considered a major complication[30]. This incidence of complications is consistent with previous studies that evaluated decompressive PEGs[16,26,27,31-35]. In these studies only 1 case of PEG-related death was reported, secondary to peritonitis[27]. These complication incidences for decompressive PEG with malignant obstruction are comparable with mixed populations. Therefore, while this indication may be a predictor of worse outcomes, likely a reflection of the terminal status of the illness, the procedure itself does not seem to put the patient with malignant bowel obstruction at undue risk.

CONCLUSION

PEG tube placement may be used in the palliative care of patients with terminal gastrointestinal cancer either as a means to provide enteral nutrition in cases of proximal obstruction or to decompress the upper gastrointestinal tract in cases of distal bowel obstruction. The evidence suggests that PEG can be performed in these patients with a high level of success[12]. With respect to goal achievement, it is not clear that terminal cancer patients receiving PEG for enteral alimentation will meet their nutritional goals and become independent of TPN. Additionally, considering the goal of palliative care is to provide comfort, it is unclear if PEG placement for nutritional supplementation is consistent with this objective. While nutritional supplementation may help ameliorate suffering involved with starvation and comfort family members faced with this difficult situation, PEG placement for this purpose does not ensure achievement of nutritional goals, may lead to further patient discomfort and could unduly prolong suffering. The decision to place a PEG tube for nutritional supplementation in patients with terminal gastrointestinal cancer involves careful discussion of the potential risks and benefits in addition to understanding the patient's wishes. Patients receiving PEG for decompression of a malignant obstruction, however, clearly have improvement of their obstructive symptoms. Given both the association of major complications with high ASA scores and the association of 30-d mortality with both high ASA scores and advanced tumor stage, it would not be surprising if palliative patients with advanced stage gastrointestinal cancer, who may be in relatively poor physiologic condition, would have a higher incidence of these bad outcomes. However, these poor outcome rates would need to be viewed through the lens of the palliative care ethos whereby the ultimate goal is patient comfort. Undoubtedly, more objective data is needed to determine evidence-based guidelines for palliative PEG placement in patients with gastrointestinal cancer.

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MINIREVIEWS

Multiband mucosectomy for advanced dysplastic lesions in the upper digestive tract

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Abstract

Endoscopic resection (ER) is at present an accepted treatment for superficial gastrointestinal neoplasia. ER provides similar efficacy to surgery; however, it is minimally invasive and less expensive. Endoscopic mucosal resection (EMR) is superior to biopsy for diagnosing advanced dysplasia and can change the diagnostic grade and the management. Several EMR techniques have been described that are alternatively used dependent upon the endoscopist personal experience, the anatomic conditions and the endoscopic appearance of the lesion to be resected. The literature suggests that EMR offers comparable outcomes to surgery for selected indications. EMR techniques using a cap fitted endoscope and EMR using a ligation device [multiband mucosectomy (MBM)] are the most frequently use. MBM technique does not require submucosal injection as with the endoscopic resection-cap technique, multiple resections can be performed with the same snare, pre-looping the endoscopic resection-snare in the ridge of the cap is not necessary, MBM does not require withdrawal of the endoscope between resections and up to six consecutive resections can be performed. This reduces the time and cost required for the procedure, while also reducing patient discomfort. Despite the increasing popularity of MBM, data on the safety and efficacy of this technique in upper gastrointestinal lesions with advanced dysplasia, defined as those lesions that have high-grade dysplasia or early cancer, is limited.

Key words: Endoscopic mucosal resection; Barrett's esophagus; Esophageal cancer; Early gastric cancer; Stepwise radical endoscopic resection; Multiband mucosectomy; Endoscopic submucosal dissection

Core tip: Early detection of upper gastrointestinal lesions with advanced dysplasia is especially important in the management of the patients. These changes may indicate an increased risk of cancer or may detect cancer at an earlier stage, when it can be more effectively treated. Multiband mucosectomy (MBM) is an easy endoscopic mucosal resection technique allowing a definitive histologic diagnosis and potentially being curative. The available evidence suggests that MBM for these conditions, has an initial success rate comparable

to surgical treatment, but with fewer complications.

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INTRODUCTION

Most commonly, the treatment of high-grade dysplasia (HGD) and mucosal cancer has been surgical. However, it does carry procedure-related morbidity and mortality[1-4]. In addition, a notable proportion of these patients have significant comorbidities, which medically preclude them from undergoing surgery. These high rates of morbidity and mortality have filed attention in other types of less invasive treatment. Endoscopic mucosal resection (EMR) is an endoscopic therapeutic proposal in which the dysplastic epithelium is removed, thus making it possible for a definitive histologic diagnosis and treatment[5-9]. EMR is possible due to the existence of a loose adhesion between the submucosa and the muscular layer in the gastrointestinal tract's wall because of a different embryologic origin. This anatomic characteristic allows, for example, the saline injection between the two layers, thus transforming a flat or depressed lesion into an elevated one. This permits the safe resection of mucosal lesions without causing damage of the deeper muscle layer, and reduces the risk of perforation. EMR has been used not only for Barrett's esophagus with HGD but also for early cancer in which the risk of hematogenous dissemination or lymph node involvement is low[10-12]. EMR is effective and safe for total resection of superficial lesions. Furthermore, EMR does not compromise subsequent ablative therapy. Ablative techniques do not supply specimen for histopathologic evaluation and are mainly use as an adjunct therapy to EMR[13]. Several different EMR techniques have been described[14]: (1) strip biopsy; (2) endoscopic double snare polypectomy; (3) EMR using a transparent cap fitted endoscope; and (4) EMR using a ligation device [multiband mucosectomy (MBM)]. EMR is a technique that requires skill, both to resect lesions in a safe and effective manner and to manage complications. EMR should only be carried out by experienced endoscopists in advanced therapeutic endoscopy. Despite the increasing popularity of MBM, limited data on the safety and efficacy of this technique in lesions with advanced dysplasia (LAD), are available.

This article reviews the current evidence and gaps in knowledge in the understanding of management of LAD of the upper gastrointestinal tract with MBM. "Advanced dysplasia" was defined as those lesions that have HGD or early cancer (EC).

MBM DEVICE

MBM (Duette; Cook Medical) uses a modified variceal band ligator that includes a transparent cap with 6 bands and a handle that allows the passage of a snare through the accessory channel (Figure 1). The target mucosa is sucked into the cap and a pseudopolyp is created. The pseudopolyp can then be removed (Figure 2). MBM has several advantages: (1) no lifting is need because the esophageal muscle layer will immediately retract when captured within a band; (2) several resections can be performed by repetitive suck-band-snare sequences; (3) pre-looping the endoscopic resection-snare in the ridge of the cap is not required; (4) MBM does not need withdrawal of the endoscope between resections, and sequential 6 bands resections can be carried out; (5) MBM yields tissue specimen for hystology and staging[7]; (6) MBM is minimally invasive and carries lower morbidity and mortality compared to surgical treatment; and (7) surgery can be performed if advanced neoplasia is confirmed on histologic evaluation of the MBM specimen. By contrast, MBM has some disadvantages: (1) MBM demands advanced endoscopic skills; (2) larger lesions can only be resected by piecemeal technique which might preclude complete histological evaluation; and (3) there are no randomized trials directly comparing MBM with surgery.

MBM TECHNIQUE

MBM is generally performed with the patient under unconscious sedation with titrated intravenous propofol. After, the endoscope is introduced without the ligator and the lesion for resection is recognized. The lesion is outlined by using argon plasma coagulation. Marks are placed 2-5 mm outside the margins of the lesion (Figure 3). Then, the endoscope is withdrawn and the ligator assembled on the endoscope. The wires are placed in line with the working channel to provide the best endoscopic view (Figure 4). The endoscope is then reintroduced with the ligator, the dysplastic mucosa is sucked into the cap, and a rubber band is deployed. The rubber band forms a pseudopolyp which is then immediately resected by using pure coagulating current (Figure 5). It does not matter whether the snare is placed above or below the band. In most of the cases, however, the snare will lie below the rubber band. The second ligation is performed by suctioning the adjacent mucosa with a small overlap to ensure that no dysplastic mucosa remnant remains[15-18]. After each resection, the specimen is pushed into the stomach by using the tip of the snare's catheter. Resected specimens are retrieved from the stomach with a polypectomy snare or retrieval net. If cancer diagnosis is made, the histological report should include these characteristics: tumor infiltration depth, tumor differentiation grade, existence of lymphatic or vascular infiltration and the radicality of

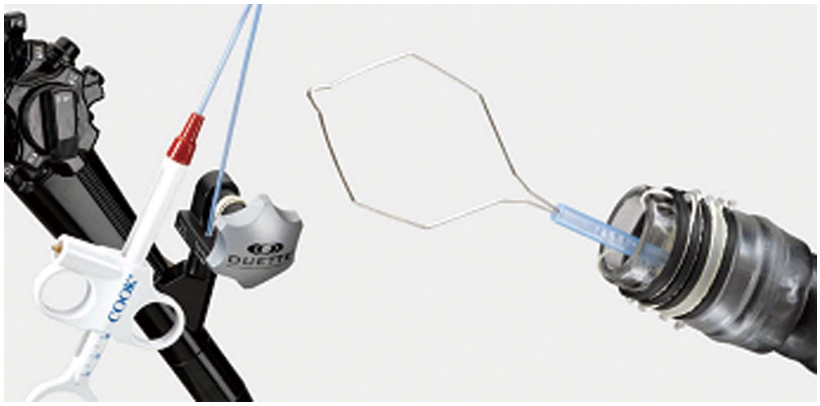

Figure 1 Multiband device (Duette). A variceal ligation device is used to suck the lesion into the ligation cap, allowing it to be captured with a rubber band and resected with a hexagonal snare (Courtesy of Cook®).

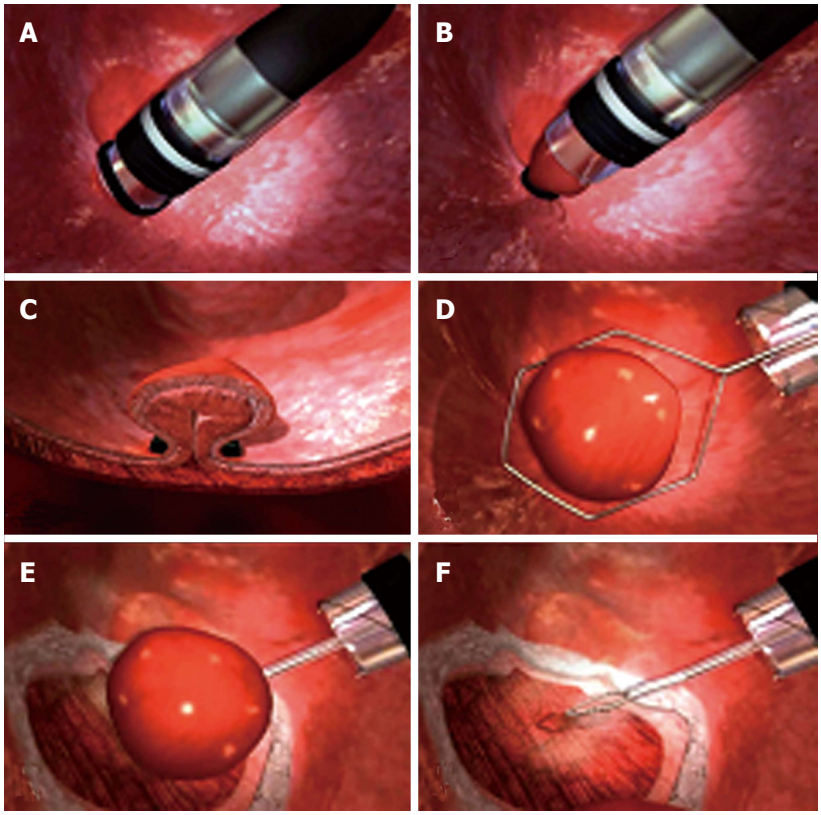

Figure 2 Multiband mucosectomy technical sequence (A to F) (Courtesy of Cook®). A-C: Pseudopolyp that is created by suctioning the mucosa into the ligation cap and releasing a rubber band; D-F: Pseudopolyp resection by hexagonal snare.

the lateral margins. After MBM, patients are put on a proton pump inhibitor and sucralfate suspension. A pureed diet is recommended. In patients without comorbidities, MBM can be performed on an outpatient basis. However, we prefer that patients are discharged after 24 h of observation. Primary endoscopic follow-up is performed 4 wk later on an outpatient basis.

INDICATIONS FOR MULTIBAND MUCOSECTOMY

The most common indication for EMR in the upper gastrointestinal tract is the staging and treatment of early neoplasia in Barrett's esophagus (BE). MBM has been applied not only to mucosal lesions with HGD but also to early cancer in which the risk of lymph node involvement or hematogenous dissemination is low enough to justify a relatively conservative approach compared with surgery[15-31].

Nondysplastic BE

At present, there are no randomized controlled trials reviewing the role of endoscopic treatment compared with surveillance alone in nondyspastic BE. Probably, the number needed to treat to prevent one cancer is high and the risk of endoscopic treatment outweighs the benefits of this procedure**.** Thus, the current American Gastroenterological Association (AGA) guidelines do not recomend endoscopic eradication therapy (EET) in patients with nondysplastic BE[32].

Low-grade dysplasia in BE

The natural history of low-grade dysplasia (LGD) in BE is unclear with variability in the rates of development to esophageal adenocarcinoma (EAC), poor interobserver concordance, unclear risk stratification, and lack of

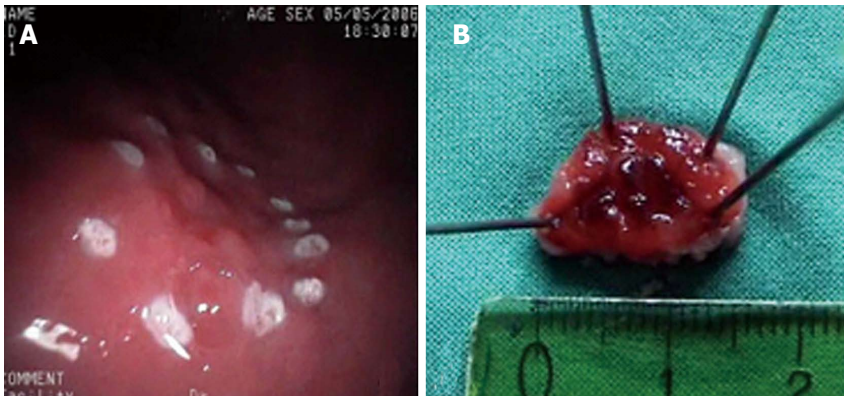

Figure 3 Early gastric cancer treated with multiband mucosectomy. A: Argon plasma coagulation marks are placed 2-5 mm outside the margins of the lesion; B: Specimen resected (15 mm).

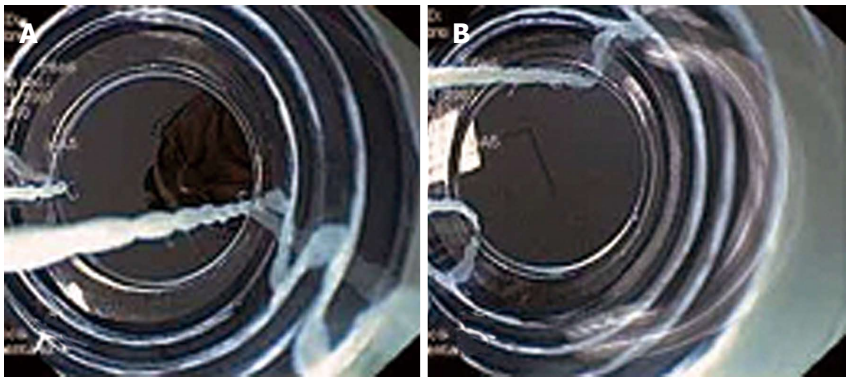

Figure 4 Best endoscopic views. A: Wires positioned incorrectly; B: Wires positioned correctly (in line with the working cannel).

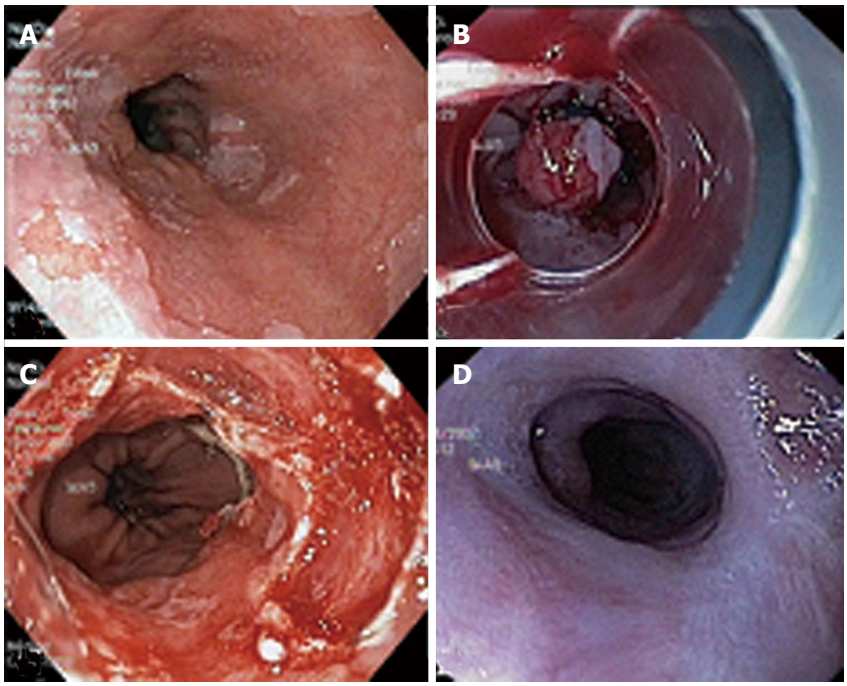

Figure 5 Stepwise radical multiband endoscopic resection of Barrett's esophagus with high-grade dysplasia (A to D). A: A 3-cm long Barrett's mucosa; B: Rubber band applied for resection; C: Circumferential resection; D: Complete neosquamous re-epithelization.

established benefit of eradication[33-35]. Therefore, systematic EET of patients with LGD is not currently advised. Now, AGA guidelines suggest the use of RFA as an alternative for the treatment of verified LGD but, this decision should be individualize with agreement between the patient and the physician[32].

HGD or early adenocarcinoma in BE

At the present, AGA guidelines recommend EET in the management of patients with HGD[32]. Current evidence suggests that EMR of HGD and early cancer EC has similar success rates as surgical treatment[6,36]. The indications for EMR in the setting of Barrett's neoplasia include the following: flat mucosal lesions, tumor size between 20-30 mm, and good to moderate differentiation on histology[6]. Furthermore, EMR has better diagnostic reproducibility compared to mucosal biopsies alone, suggesting a possible role in BE

surveillance[37].

Esophageal squamous cell carcinoma

Usually, EMR is indicated for superficial well- or moderately differentiated squamous cell carcinoma without venous or lymphatic involvement that is limited to the lamina propria[38].

Early gastric cancer

Candidates for MBM must meet the following criteria: well- or moderately differentiated adenocarcinoma, confined to the mucosa, < 20 mm for elevated lesions, < 10 mm for flat or depressed lesions, with no evidence of ulceration, lymphatic or venous involvement[39].

MULTIBAND MUCOSECTOMY AS STAGING PROCEDURE

Accurate T-staging is critical in making therapeutic decisions in patients with dysplastic Barrett's esophagus. The distinction between different categories of dysplastic lesions can be difficult since it depends in part upon the size, location, depth, and number of biopsies. The Seattle biopsy protocol is recommended for mapping Barrett's esophagus with HGD[40]. Targeted biopsies are acquired from all visible abnormalities and random four-quadrant biopsies are taken every 1 cm starting from the top of the gastric folds up to the most proximal extent of the BE (squamocolumnar junction). Another concern with the diagnosis of dysplastic lesions is the interobserver reliability among pathologists. Therefore, it is recommended that a second, experienced pathologist should confirm the diagnosis of HGD. Studies comparing routine biopsies of visible lesions with EMR report a 30% to 48% rate in change in diagnosis after obtaining an EMR[26,28]. Furthermore, in a study comparing preoperative EMR with histologic examination on esophagectomy specimens, there was perfect agreement between the two[41]. We consider MBM may represent not only a reasonable treatment option but also the final step of the diagnostic work-up for patients with dysplastic lesions[37]. Assessment of the depth of infiltration and estimation of local nodal metastasis can be achieved by endoscopic resection of these areas within a lesion which look suspicious[42,43]. Among patients diagnosed with dysplastic lesions, other imaging techniques could be taken into account to evaluate tumor infiltration depth, local lymph node status and metastatic spread. Endoscopic ultrasonography (EUS) and computerized tomography (CT) scan are the most widely used techniques. Although the role of EUS has been established in the accurate T and N staging of invasive EAC, recent studies have shown only a modest accuracy in delineating T-staging in patients with HGD and intramucosal EAC[44-47]. Recent studies report that the overall accuracy of EUS in establishing T-stage (depth of invasion), using EMR/surgical pathology as the gold standard, was 65%-72%. Based on this information, EUS has a limited role in the evaluation of patients with early neoplasia[44,48]. Other techniques, such as magnetic resonance imaging and positron emission tomography scanning, do not have a role in the evaluation of patients with these lesions.

MULTIBAND MUCOSECTOMY AS THERAPEUTIC PROCEDURE

The first objective of endoscopic therapy is to prevent the development of invasive EAC by treating the dysplastic lesion. The available evidence suggests that endoscopic resection (ER) for these conditions has an initial success rate comparable to surgical treatment, but with fewer complications[6,8,26,28,36]. The rate of complete remission ranges from 59% to 99% in different studies[6,8,26,28,36,49,50]. Higher degrees of success are seen in patients with lower risk lesions. In a systematic review, complete eradication of HGD or EC was achieved in 95% of patients, and complete eradication of all Barrett's mucosa was achieved in 89%[51]. ER is best performed on patients with small (< 20 mm diameter), solitary, flat type lesion that is limited to the mucosa. Histopathologic differentiation is less important, since the great majority of these early lesions will be classified as HGD or well differentiated cancers[7]. However, patients who develop dysplasia are at higher risk of recurrence of neoplasia and metachronous lesions from the remaining segment of BE, which occurs in up to 30% of patients undergoing EET[6,8,28,36,52-54]. Factors associated with recurrence in BE are larger diameter, long segment, piecemeal resection, lack of adjunctive ablative therapy, presence of multifocal neoplasia, an elapsed time of more than 10 mo prior to achieving complete remission and the presence of residual dysplasia[8,36]. In most patients, recurrences can be successfully treated endoscopically[54]. Recurrence is a possible limitation after EMR. Patients therefore require regular follow up with endoscopy (every three months during the first year and annually thereafter) and treatment of any residual Barrett's mucosa. Endoscopic ablative therapy with radiofrequency ablation or photodynamic therapy allows treatment of the whole Barrett's segment in a few sessions. Complete ER of the whole Barrett's segment may also be used as endoscopic treatment [stepwise radical endoscopic resection (SRER)][21-23,49] (Figure 5). Most experts believe that EMR resection of the entire Barrett segment can be performed in patients with Barrett segment length of less than or equal to 5 cm. This technique has several advantages over ablative therapy: it allows complete removal of the whole mucosa at risk for malignant progression and provides tissue samples for histological diagnosis. Furthermore, the feasibility and safety of ER of the entire Barrett's segment has been demonstrated on several series[21-23,49]. However, the role of the stepwise

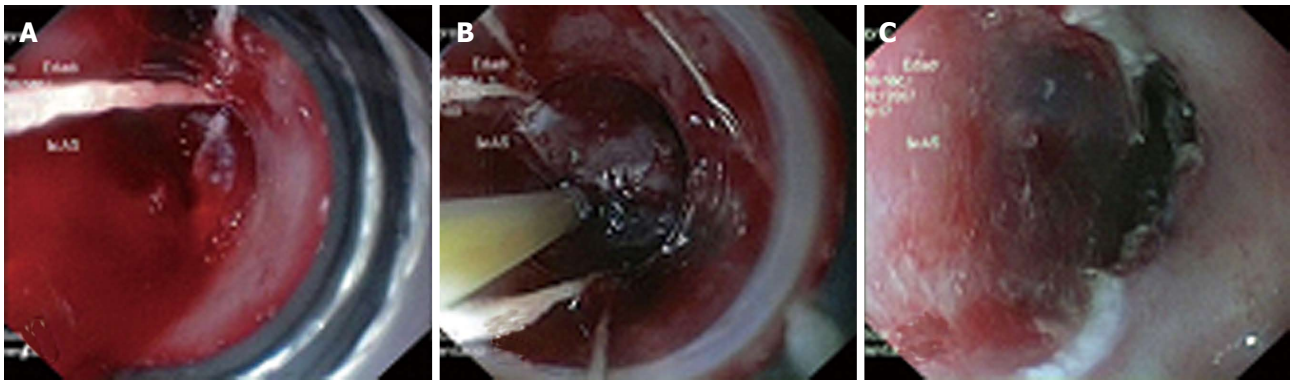

Figure 6 Active bleeding post-multiband mucosectomy in Barrett's esophagus, effectively treated by adrenaline injection (A to C). A: Active pumping bleeding; B: Adrenaline injection by needle; C: Cessation of bleeding.

radical endoscopic resection technique seems restricted to selected patients in the treatment of HGD or EC in Barrett's esophagus. Although the SRER technique is equally effective and has several advantages over ablative treatment, it is related to a much higher rate of strictures than ER plus RFA. Currently, it is advised for complete eradication of intestinal metaplasia, that patients with HGD and early esophageal adenocarcinoma(EAC) undergo EMR of a visible lesion followed by RFA to the remaining Barrett segment, or to use the SRER procedure only for patients with more extensive lesions in BE up to 5 cm[30].

MULTIBAND MUCOSECTOMY COMPLICATIONS

The three major EMR-complications include: (1) bleeding; (2) perforation; and (3) strictures[20,29,55-58]. Bleeding is apparent in 0% to 46% of cases and can be managed with endoscopic treatment**.** Immediate bleeding can be considered as a complication if there are clinical signs. Perforation has been described in less than 5%. The risk is higher in piecemeal resection. Strictures have been described in 2% to 88% of patients undergoing EMR for dysplastic Barrett's esophagus. The size/length of the mucosal defect and the circumferential involvement by the BE predicts stenosis formation. Stenosis are more frequent if the BE involves more than 75% of the esophageal circumference. Stenosis can be successfully treated with endoscopic dilation**.** Chest pain occurs in about 30% of patients undergoing EMR.

Several studies demonstrated that the MBM is safe and effective[15,17,18,29] (Table 1). In these studies, acute complications were observed in 3% and no perforations occurred[15,17,26]. MBM does not appear to be associated with more complications than endoscopic resection-cap, despite lack of submucosal lifting. Perforations occur in approximately 1% of the endoscopic resections performed with the widely used cap technique in Barrett's esophagus[59,60], compared to MBM where the probability of perforation seems to be very low, with perforation rates reported in the range of 0% to 1.2%[16-31]. Most acute bleedings with MBM resolve spontaneously or can effectively be treated by adrenaline injection or coagulation techniques (Figure 6). Several studies have reported stenosis rates of 26%-70% after radical resection with MBM of the whole Barrett's segment[16,23,25,26]. A larger study evidenced stricture requiring dilatation in 48% of the patients who underwent the MBM procedure as part of the (stepwise) radical resection protocol. Stenosis rates increase with the extent of the resected area in the esophagus, especially if the resection is more than 3 cm in length and comprises more than 75% of the circumference[61]. Suitable data comparing stenosis rate with MBM and cap technique, is not available.

MULTIBAND MUCOSECTOMY *VS* CAP-ASSISTED EMR

Multiband mucosectomy and cap-assisted EMR are new minimally invasive therapies alternatives for LAD. A randomized controlled trial comparing these two techniques demonstrated that there is no difference in the thickness of the specimen and submucosal resection; however, the multiband mucosectomy had a shorter procedure time and produced smaller EMR specimens. The clinical relevance of these findings may be questioned, since there was no significant difference in the depth of resection between the two techniques[18]. In addition, costs for disposables were significantly lower for MBM procedures. Rates of complete endoscopic resection were similar for MBM (91% of delineated focal lesions, 86% of delineated areas in Barrett's esophagus, and 100% of the escape treatments) and the cap technique (88% success rate for complete endoscopic resection)[60]. Both techniques are very effective in this respect[18,60,62,63]. MBM can fail if there is significant fibrosis which impeded suctioning of the mucosa into the cap and subsequent rubber band ligation[17]. Similarly, both techniques seem equally safe and the lack of submucosal lifting with MBM does not increase the risk of perforation compared with that of the cap technique. A disadvantage for MBM may be decreased visibility due to

Table 1 Results of multiband mucosectomy procedures from different studies

Ref.	Number and procedures	Complete eradication	Recurrence rate	Complications	Follow-up (mo)
Soehendra *et al*[16]	10 MBM	90%	N/A	Stricture (SRER 70%)	N/A
Ell *et al*[62]	100 MBM (%N/A) Cap	99%	11%	0%	33
Peters *et al*[31]	40 MBM	N/A	N/A	Bleeding (6%)	N/A
Chennat *et al*[26]	49 MBM (4%) Cap FH	65%	2.50%	Stricture (SRER 36.7%)	23
Espinel *et al*[15]	8 MBM	100%	0%	Stricture (SRER 25%)	32
Moss *et al*[28]	75 MBM (%N/A) Cap	94%	0%	Stricture (SRER 8%)	31
Pouw *et al*[27]	169 MBM (%N/A) Cap FH	95.30%	1.80%	Bleeding (1.8%) Perforation (2.4%) Stricture (SRER 50%)	32
Brahmania *et al*[63]	22 MBM	82%	18%	Stricture (SRER 13%)	24
Pouw *et al*[18]	42 MBM	100%	N/A	Perforation (2%)	N/A
Alvarez Herrero *et al*[17]	243 MBM	91%	0%	Bleeding (3%) Stricture (SRER 48%)	3
Van Vilsteren *et al*[30]	25 MBM (48%) Cap FH	100%	4%	Perforation (4%) Stricture (SRER 88%)	25
Gerke *et al*[29]	41 MBM (76%) Cap	78%	9%	Perforation (4.9%) Stricture (SRER 44%)	25
Tomizawa *et al*[56]	681 MBM (18%) Cap	N/A	N/A	Bleeding (1.2%) Stricture (1%)	63

MBM: Multiband mucosectomy; Cap: Cap technique; FH: Free hand technique; N/A: No data available; SRER: Stepwise radical endoscopic resection.

the effect of the black rubber bands. Therefore, it is desirable to have previously correctly delineated the target area by placement of markers, in order to maximize complete endoscopic resection. The learning curve for MBM is shorter compared with that of cap-assisted EMR, because it combines the techniques of variceal band ligation and polypectomy.

MULTIBAND MUCOSECTOMY *VS* ENDOSCOPIC SUBMUCOSAL DISSECTION

Endoscopic submucosal dissection (ESD) was initially introduced for the endoscopic treatment of early gastric cancer in Japan[64,65]. It was developed for the *en-bloc* resection of large lesions and enables precise histological assessment of specimens. The comparison between ESD and EMR in the treatment of early esophageal carcinoma is debatable. EMR and ESD have been suggested as alternatives to esophagectomy in the treatment of these lesions, without lymph node metastasis. A meta-analysis has compared the efficacy and safety of EMR and ESD for the treatment of early esophageal carcinoma[66]. Five retrospective trials were identified and a total of 710 patients and 795 lesions were included. The results confirmed substantial advantages of ESD over EMR for early esophageal carcinoma regarding en bloc resection rate, histologically complete resection rate and local recurrence even for small lesions, without increasing the complication rate. A previous meta-analysis by Cao *et al*[67] compared clinical outcomes of ESD with EMR in the treatment of tumors of the gastrointestinal tract, and they found that ESD showed better en bloc and curative resection rates and local recurrence, but was more time-consuming and had higher rates of bleeding and perforation complications.

A recent review on the safety and efficacy of MBM compared with ESD for the treatment of early neoplasia in Barrett's or neoplasias at the esophagogastric junction (EGJ), showed that the recurrence rate was slightly higher in the EMR group (2.8%) compared with the ESD group (0.3%), but the difference did not reach statistical significance (P = 0.06)[68]. All recurrences in the EMR group were managed by additional endoscopic resections. Complete eradication rate in the EMR group was 95.5%. Curative resection rate in the ESD group was 75.5%. The risk of delayed bleeding and perforation rates in both groups was similar (EMR group 1.2%; ESD group 2.1%, P = 0.26). The perforation rate in the EMR group (1.2%) was similar to that in the ESD group (1.5%), and the difference was not statistically significant. The stricture rate was similar in both groups when comparing resection of the neoplastic lesion alone. Stricture rates increased rapidly in the SRER group when the complete Barrett's mucosa was resected. The procedure time was less time-consuming in the EMR group (mean time: 36.7 min, 95%CI: 34.5-38.9) compared with the ESD group (mean time: 83.3 min, 95%CI: 57.4-109.2). The authors concluded that the MBM technique appears as effective as ESD when comparing important outcome parameters on the eradication of early Barrett's or EGJ neoplasia. There

are no differences in the outcome when comparing strictures, bleedings and perforation rates for both EMR and ESD in experienced hands. The MBM technique has considerable advantages in being both easier to master and less time-consuming.

MULTIBAND MUCOSECTOMY AND EARLY GASTRIC CANCER

The endoscopic treatment of early gastric cancer (EGC) with mucosectomy has increasingly proven to be an effective modality for local treatment, especially if the tumor is limited to the mucosa, of a size no greater than 2 cm, with neither histologic ulceration nor lymphatic vessel invasion and a cancer-negative resection line. Mucosectomy has also demonstrated to be useful in the resection of precancerous lesions such as adenomas[69-71]. European experience in EMR for early gastric cancer is still relatively low, since early stomach cancer is diagnosed at a much lower rate in Europe than in Japan and generally, operable patients are referred to surgery for radical resection. With EMR, complete resection rates have been reported in 74%-97% and survival rates between 95%-100%[14,72]. The most frequent complication is bleeding (1%-20%)[73] and recurrence rates were observed to be between 2%-13%[74]. EMR appears to have a better post-procedure quality of life compared with surgical gastrectomy[75]. Data on the use of MBM in the management of patients with EGC is small. Our experience is very limited but, highly positive, in selected patients[15]. Three patients diagnosed by biopsy of EGC (type Ⅱa) and 1 patient with HGD were treated by MBM (Figure 3). The length of lesions ranged between 10 mm and 20 mm. MBM was accomplished in 1 session in each patient. The histological analysis of MBM specimens confirmed mucinous adenocarcinoma with submucosal infiltration (1 patient who was referred for surgery), EGC (2 patients), and HGD (1 patient). Minor bleeding without clinical consequences occurred in 1 patient and was controlled by local adrenaline injection. Endoscopic surveillance was recommended for all our patients and *Helicobacter pylori* was eradicated. Regular follow-up did not detect any recurrent lesions. MBM in EGC may have also diagnostic and therapeutic implications. Further studies are needed in this field to determine the clinical impact of this therapeutic approach.

CONCLUSION

MBM is an exciting EMR technique that provides heightened levels of diagnostic accuracy and minimally invasive therapy for the management of upper gastrointestinal tract lesions with advanced dysplasia. This minimally invasive technique is safe and effective for complete resection of superficial lesions with high-grade dyspasia or early cancer.

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Advances in the endoscopic management of pancreatic collections

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Abstract

Treatment of pancreatic collections has experienced great progress in recent years with the emergence of alternative minimally invasive techniques comparing to the classic surgical treatment. Such techniques have been shown to improve outcomes of morbidity *vs* surgical treatment. The recent emergence of endoscopic drainage is noteworthy. The advent of endoscopic ultrasonography has been crucial for treatment of these specific lesions. They can be characterized, their relationships with neighboring structures can be evaluated and the drainage guided by this technique has been clearly improved compared with the conventional endoscopic drainage. Computed tomography is the technique of choice to characterize the recently published new classification of pancreatic collections. For this reason, the radiologist's role establishing and classifying in a rigorously manner the collections according to the new nomenclature is essential to making therapeutic decisions. Ideal scenario for comprehensive treatment of these collections would be those centers with endoscopic ultrasound and interventional radiology expertise together with hepatobiliopancreatic surgery. This review describes the different types of pancreatic collections: acute peripancreatic fluid collection, pancreatic pseudocysts, acute necrotic collection and walled-off necrosis; the indications and the contraindications for endoscopic drainage, the drainage technique and their outcomes. The integrated management of pancreatic collections according to their type and evolution time is discussed.

Key words: Pancreatic collection; Endosonography; Drainage; Pancreatic duct; Endoscopic retrograde cholangiopancreatografic

Core tip: The interventional endoscopic ultrasonography (EUS) development has become in recent years as the first therapeutic alternative for the management of pancreatic collections. The great advantage of EUS is the possibility to in see in real-time image with ultrasound guidance all the material previously introduced into the working channel. The new classification of Atlanta 2012 defines two different evolved pancreatic collections (⩾ 4 wk) such as pseudocysts and necrotic encapsulated collections. If both types of collections are symptomatic, they would be subsidiaries of treatment. Given their morphological differences, the technique is similar but the stents used and the results generated differ.

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INTRODUCTION

Acute pancreatitis (AP) is a potentially life-threatening disease with a wide spectrum of severity, representing an acute inflammation of the pancreas that may be triggered by a variety of etiologies. After the initial etiologic insult, the activation of pancreatic enzymes occurs in the gland itself, triggering a process of the pancreas self-digestion accompanied by inflammation. This phenomenon leads a repairing and healing process or, less commonly, a systemic inflammatory response that can cause disease in other systems (circulatory, respiratory or renal) promoting the development of organ failure and even death of patient[1]. AP prevalence is increasing, leading to a significant consumption of medical resources[2].

In Atlanta symposium in 1992 a global consensus and a classification system universally applicable for AP was discussed[3]. However, some of these definitions have proved somewhat confusing, and the better understanding of the pathophysiology of organ failure and the development of pancreatic necrosis and the better progress in diagnostics imaging methods have forced a revision of the original classification of Atlanta[4].

An important and illuminating compilation of the terminology of local complications of AP has been established. Four types of collections based on content and time evolution have been defined. These collections are called acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and encapsulated necrosis or walled-off necrosis. This new classification represents a breakthrough and facilitates therapeutic decisions in these patients.

The aim of this review is to perform an update of endoscopic management of each of these collections, evaluating the endoscopic treatment role in their comprehensive management.

CLASSIFICATION OF ATLANTA 2012

According to the new classification of Atlanta 2012, pancreatic collections can be classified depending to their content, purely liquid or with associate necrosis, and its evolution time, greater or less than 4 wk. Therefore, four types of pancreatic collections can be found.

Acute peripancreatic fluid collection (Figure 1A): is developed in the first phase of AP and characterized by flowing purely liquid homogeneous collections on CT, with no wall defined. It is confined to normal retroperitoneal fascial planes and can be multiple. Most of these collections resolve spontaneously in the first weeks after the AP. In addition to its spontaneous resolution usually it remain sterile[5].

Pancreatic pseudocysts (Figure 1C): it develops when acute pancreatic fluid collection persists more than 4 wk. A well-defined wall is usually generated and they rename pancreatic pseudocyst, presenting high liquid content in amylase and other pancreatic enzymes. The pancreatic pseudocyst is considered to be formed by obstruction or disruption of the main duct or secondary branches, which facilitates its chronicity. The development of pancreatic pseudocyst in the setting of AP on healthy pancreas is rare, most frequently it develops within chronic pancreatitis. In a recent prospective observational study that included 302 patients with AP, acute peripancreatic fluid collection was developed in 129 (42.7%). Among them, pancreatic pseudocyst was developed only in 19 (14.7%). In 90 patients (69.8%) there was spontaneous resolution of acute peripancreatic fluid collection and the other 20 patients (15.5%) failed to complete the follow-up. Regarding to the 19 patients with pancreatic pseudocyst, spontaneous resolution occurred during follow-up in 5 patients (26.3%), a decrease in size in 11 (57.9%) and finally in another patient the monitoring could not be completed. Two patients developed infection with pancreatic pseudocyst requiring percutaneous treatment in one case, and endoscopic drainage on the other[6]. Thus, the percentage of pseudocysts requiring treatment is small.

Acute necrotic collection (ANC) (Figure 1B): it is developed during the first 4 wk of AP evolution and it can contain varying amounts of fluid and necrotic tissue. It may be difficult to distinguish from acute peripancreatic fluid collection during the first week of evolution, but then the distinction between the two is clearer. Like pancreatic pseudocyst, acute necrotic collection may be associated with disruption or obstruction of the pancreatic duct.

Walled-off necrosis (WON) (Figure 1D): consisting of a variable number of necrotic tissue encapsulated within a reactive tissue wall, derived from acute necrotic collection encapsulation past 4 wk. A well-defined wall around the collection can be observed in the imaging, whose complete formation typically occurs within 4 wk of AP origin. The percentage of spontaneous resolution of acute necrotic collections and encapsulated necrosis is unknown, so the knowledge of the natural history of all pancreatic collections is not complete[7].

The presence of necrosis in a pancreatic collection is considered an important prognostic marker, the mortality in patients with necrotizing pancreatitis can reach 15% and even 30% in patients with infected necrosis. This infection typically occurs from the second week after the onset of pancreatitis, but can occur at any time during the clinical course[8]. Through

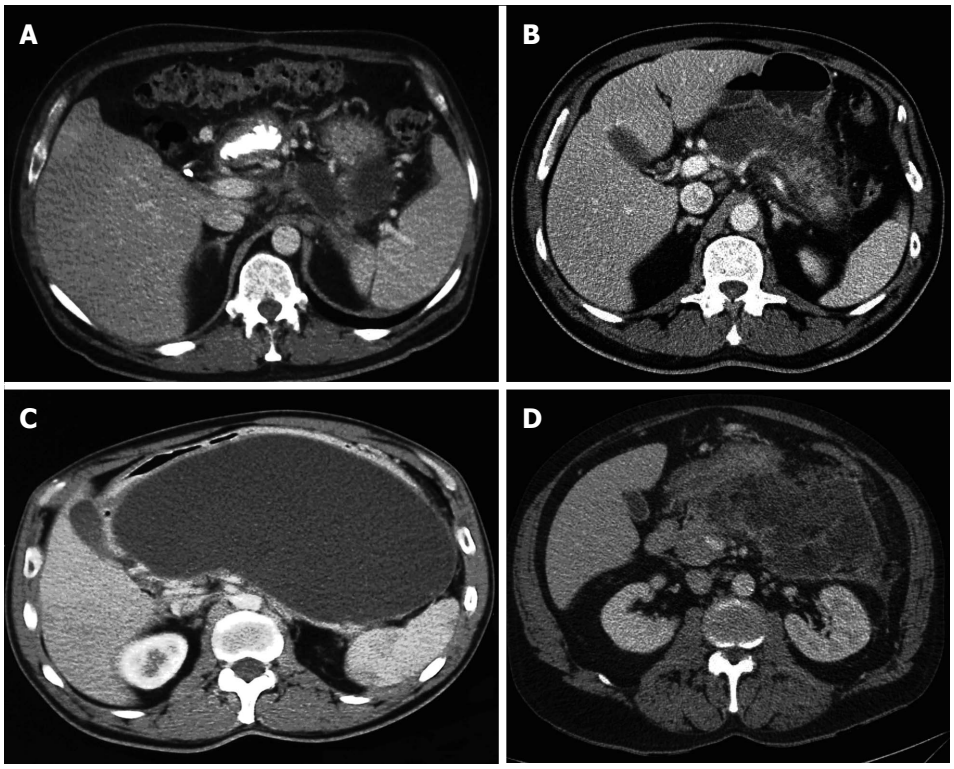

Figure 1 Acute peripancreatic fluid collection (A), acute necrotic collection (B), pancreatic pseudocyst (C), and walled-of necrosis (D).

Gram staining or culture from material aspirated by percutaneous or endoscopic puncture, the infection can be tested, but also the presence of gas within the acute necrotic collection or encapsulated necrosis by computed tomography can be a good infection diagnostic indicator.

INDICATIONS AND CONTRAINDICATIONS FOR ENDOSCOPIC DRAINAGE OF PANCREATIC COLLECTIONS

Pancreatic pseudocysts and WON are considered the most often treated collections, having the characteristics and evolution time required for such treatment.

The transmural approach is the most commonly used. Conducting a transpapillary or combined approach will depend on the collection size, its relationship with the pancreatic duct, its location, and underlying disease.

Usually, pigtail stents are used for pseudocysts drainage while for WON covered self-expandable metallic stents are more commonly employed, associated to an inner coaxial pig-tail stent. Futhermore, the use of flushing nasocystic catheter in WON has been reported in several studies with good results[9,10].

To perform an endoscopic treatment of pancreatic collections is accepted in those cases of symptomatic collections, complicated collections with infections and those producing obstructive symptoms in neighboring viscera, such as stomach, duodenum or bile duct obstruction. It is also accepted the prophylactic treatment in collections which produce vascular compression[11].

Endoscopic drainage is contraindicated in unencapsulated collections, those away from gastroduodenal tract (> 1 cm) and collections with vascular pseudoaneurysm, which should be treated by interventional radiology prior to endoscopic drainage. The presence of neovascularization by portal hypertension is considered a relative contraindication[12].

RESULT OF ENDOSCOPIC DRAINAGE OF PANCREATIC COLLECTIONS

The therapeutic success of endoscopic drainage of pancreatic collections differ in the case of a pseudocyst or an encapsulated necrotic collection.

Conventional endoscopy has been deprecated for drainage of pancreatic collections, being overtaken by the therapeutic endoscopic ultrasonography (EUS) being reflected in numerous studies[13]. The use of EUS allows a better study of collections and may change management in 5%-9% of cases, either by making an alternative diagnosis or by checking the resolution of pancreatic pseudocyst (Figure 2)[14]. Endoscopic drainage of pancreatic pseudocysts is simpler and more resolutive than WON drainage[15].

In a recent study involving 117 patients with pancreatic pseudocyst drained endoscopically, pancreatic pseudocyst resolution was achieved in 98.3% of

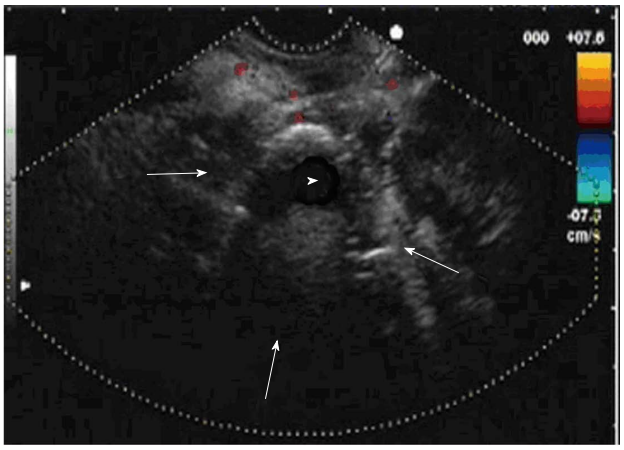

Figure 2 Endoscopic ultrasonography image of walled-off necrosis collection. The limits of the walled-off necrosis are signalled by the arrows. The necrotic content is marked with arrowhead.

cases. In 87.2% of patients the pancreatic pseudocyst was resolved with only an endoscopic procedure, with no significant differences in treatment success depending on the size (7 or 10 F) or number of stents placed (Figure 3A, B and C)[16].

The recurrence of pancreatic pseudocyst after endoscopic drainage is less than 1%, with series with 0% recurrence at two years when ductal pathology associated is treated by transpapillary stent and transmural stents are maintained indefinitely if there is a ductal disconnection syndrome[17].

By contrast, the result of endoscopic drainage of WON is less effective, demonstrating in different series treatment success rates significantly lower[18]. Therapeutic success described in a multicenter Japanese study (JENIPaN) including 57 patients with WON treated with endoscopic necrosectomy was 75% with a median of 5 endoscopic sessions per patient[19]. In 14 patients in whom endoscopic treatment was ineffective, 8 received other percutaneous or surgical treatment, while 6 patients died during the treatment period without achieving WON resolution. In another similar study from Germany involving 93 patients the WON resolution was achieved in 80% of patients[20]. The median of endoscopic sessions to successfully complete the endoscopic treatment in these patients is between 3 and 6 in the different studies.

In a recently published meta-analysis study that included the results of 12 studies with 481 patients presenting infected necrosis treated only with conservative measures, including percutaneous or endoscopic drainage, treatment success was achieved without any necrosectomy in 59% of patients[21].

Currently, it is very difficult to predict which are the WON collections that can be efficiently and safely managed without necrosectomy. In cases of large and anfractuous collections with a large amount of necrosis, necrosectomy is usually required, either by means of retroperitoneal or endoscopic access. Necrosectomy is usually performed when the initial endoscopic drainage has not been effective. Several studies have shown that the therapeutic success of endoscopic treatment depends largely on the amount of necrosis[22,23].

In this regard, a new lumen-apposing metallic stent (AXIOS®, Xlumena, Mountain View, Ca) has been designed recently for draining pancreatic collections proving good effectiveness in different studies. These stents are completely covered and offer a maximum size of 15 mm so endoscopic necrosectomy is allowed in repeated sessions without the need for replacement of the stents[24].

Assessment of pancreatic ductal pathology in all patients with pancreatic pseudocyst or WON is vital, as if the transmural resolution of the collection is not accompanied by a correct diagnosis and treatment of the underlying ductal pathology, the risk of recurrence is high[25]. In this sense, ductal disruption or stenosis should be ruled out. Currently, the least invasive technique for assessing the integrity of the pancreatic duct is secretin enhanced pancreatic MRI. Ductal evaluation by means of ERCP is another recommended option prior to removing the transmural stents. Varadarajulu *et al*[17] described the presence of ductal disruption in 10 patients and ductal disconnection syndrome in 4 from 18 patients with pancreatic pseudocyst treated endoscopically[17].

Furthermore ERCP is an endoscopic technique which provides the possibility of transpapillary drainage by placing duct stents in addition to a transmural drainage or as monotherapy, mainly in pseudocysts located in the head or body of the pancreas. This approach is considered less traumatic than the transmural. It is accepted that in patients with underlying chronic pancreatitis with pancreatic pseudocyst under 6 cm communicated with the pancreatic duct, a transpapillary drain as monotherapy can be performed[26].

COMPLICATIONS OF ENDOSCOPIC DRAINAGE OF PANCREATIC COLLECTIONS

Endoscopic drainage of pancreatic collections is not free of complications. The most frequent are bleeding, perforation, post-procedure infection and migration of the stents.

A prospective study aimed to determine the frequency of these complications included 148 patients with pancreatic collections of mean diameter 92.3 mm drained by EUS[27]. These collections were classified as pancreatic pseudocyst in 72 (48.6%), abscess in 38 (25.7%) and necrosis in 38 patients (25.7%). There was a transgastric fistula perforation in two patients (1.3%) with pancreatic pseudocyst located at the level of the uncinate process. These perforations were not suspected during the procedure, which in both cases was uneventful. In pseudocysts localised at uncinate process level drained transduodenally no perforation occurred. The authors attributed this drilling to a lack

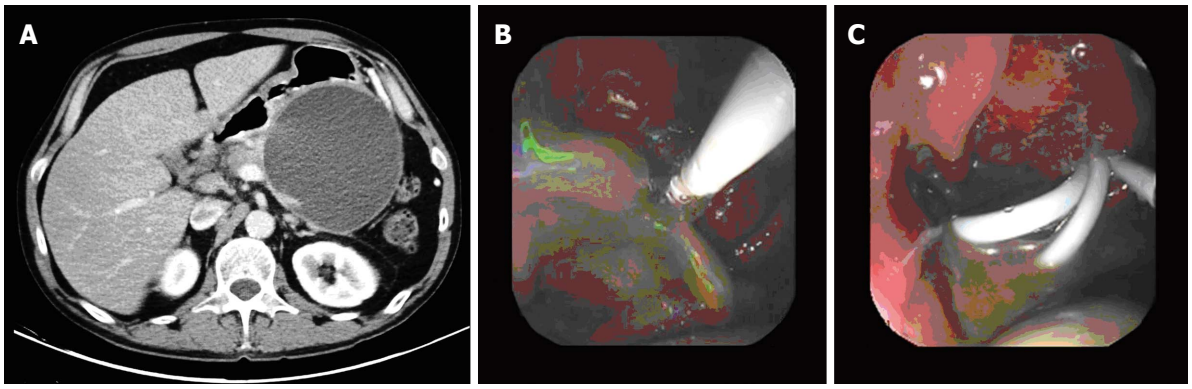

Figure 3 Pancreatic pseudocyst (A), endoscopic dilation of transmural tract (B), and three double-pigtail plastic stents placed (C).

of adhesion of pancreatic pseudocyst to the stomach wall despite being at a distance less than 1 cm. It is postulated that after decompression of pancreatic pseudocysts by the stents, it is separated from the stomach due to be originated in uncinate process and stents were housed in the retroperitoneum. Therefore it is recommended to avoid transgastric drainage of pancreatic pseudocyst localized at uncinate process. Other authors have reported perforations related with the use of electrocautery during drainage procedure[28]. For this reason it is recommended to avoid the use of electrocautery during the creation and expansion of the fistula, making a gradual mechanical dilation. The vast majority of these perforations can be managed by conservative measures with antibiotic treatment and nasogastric suction. The need for surgery in these cases is exceptional[29].

The rate of bleeding after endoscopic drainage has decreased dramatically with EUS. In a prospective randomized study comparing drainage of pancreatic pseudocyst by EUS and conventional endoscopy, severe bleeding occurred in two patients (13.3%) drained by conventional endoscopy. One of them died and no cases of bleeding were observed in the group of patients drained with EUS[30]. The intracystic hemorrhage is inaccessible to endoscopic treatment methods, most of them stop spontaneously or by intracystic washing with serum and diluted epinephrine, sometimes requiring treatment by interventional radiology or surgery. The haemorrhage in the fistula tract is more easily treated by endoscopic methods such as sclerosis or hemoclips placement.

Stent migration is another complication associated with endoscopic drainage of pancreatic collections. Its incidence ranges from less than 1% and 2%[27]. External migration requires only a repetition in the procedure. By contrast, internal migration of stent represents a serious complication and a therapeutic challenge. It is advisable to remove it as early as possible to avoid the fistula closure previously created (Figure 4).

Another complication of endoscopic drainage of pancreatic collections is the infection after endoscopic manipulation, so it is very important the proper drainage. In the series published by Varadarajulu *et al*[27], infection occurred in 4 patients (2.7%) which was resolved by new endoscopic drainage in two patients and by surgery in the other two[27].

Finally, another potentially fatal complication related to endoscopic necrosectomy is air embolism. It has been described in different multicenter series. In the GEPARD study from Germany that included 93 patients, endoscopic necrosectomy was performed and air embolism occurred in two patients[20]. In JENIPaN study from Japan, there was also an air embolism in a series of 57 patients with endoscopic necrosectomy[19]. Although its usefulness has not been proven, it is now recommended the CO_2 distension during necrosectomy to avoid this complication.

Overall, the complication rate is significantly lower with endoscopic drainage of pancreatic pseudocyst drainage compared with WON drainage[31].

In a recent study, Varadarajulu *et al*[17] compared the results of endoscopic drainage of pancreatic pseudocysts by endoscopic *vs* surgical cystogastrostomy with 20 patients in each group observing no complications related to endoscopic treatment[17]. Moreover, in the series of patients undergoing endoscopic necrosectomy previously mentioned, the complication rate was much higher. Thus, in the GEPARD study complications occurred in 26% of patients, with a mortality rate of 7.5% and in the JENIPaN study the complication rate was 33% with an overall mortality of 11%[19,20].

The transpapillary drainage has a complication rate of 16%, especially post-ERCP pancreatitis and infectious complications[32].

INTEGRATED AND MULTIDISCIPLINARY MANAGEMENT OF PANCREATIC COLLECTIONS AND IMPORTANCE OF THEIR CHARACTERIZATION

Endoscopic treatment of pancreatic collections is an alternative therapy that offers a high success rate with a reasonably low morbidity and mortality compared with other available options. For this reason it is

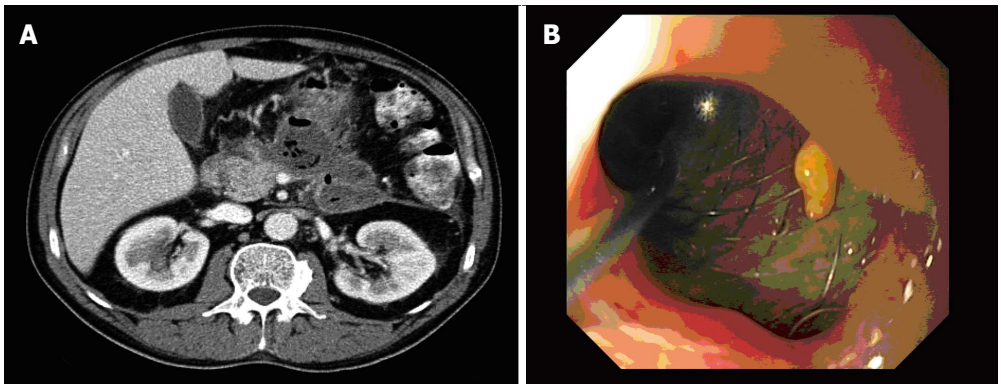

Figure 4 Walled-of necrosis with air content suspicious of fistulization or infection (A) and internal migration of stent (B).

becoming the first-line treatment in many centers. This may vary depending on the experience and resources available so the optimal management of these patients will be in those centers with interventional endoscopist but also interventional radiologist and surgeons specifically devoted to pancreatic surgery. However, endoscopic treatment is not the only therapeutic option in this scenario and is not always the best approach, which will depend on the type of collection and the chronology[33]. Several factors will influence the choice of the initial approach for treatment of pancreatic collections, such as duration of the collection, anatomical factors, previous surgeries, clinical status and integrity of the pancreatic duct.

In the pancreatic pseudocyst treatment, the endoscopic drainage is clearly superior to other therapeutic options, and currently is the therapeutic method of choice[18].

In a recent randomized study, Varadarajulu *et al*[17] compared the endoscopic drainage of pancreatic pseudocysts *vs* surgical drainage and they did not find significant differences regarding treatment success (95% *vs* 100%), complications (0% *vs* 10%), reoperation rate (5% *vs* 5%) or pancreatic pseudocyst recurrence (0% *vs* 5%). However, the median hospital stay (2 *vs* 6) and hospital costs were significantly lower in the endoscopic treatment group[17].

Endoscopic drainage offers advantages over percutaneous or surgical alternatives because it does not require an open incision or placement of an external drainage catheter thereby preventing the onset of complications such as incisional hernia, or fistulae, which can occur in up to 27% of cases[33].

The initial approach of choice in WON collections is less clear because the results are significantly worse with any of the methods used, and sometimes a combination of different techniques is necessary. Traditionally, open surgical necrosectomy has been the treatment of choice in patients with symptomatic or infected pancreatic necrosis. In the past decade minimally invasive therapeutic alternatives have been developed in an attempt to improve the high morbidity (34%-95%) and mortality (11%-39%) of traditional surgical treatment[34].

Currently, it is used the endoscopic transmural approach, percutaneous or a combination of both. It has been also developed less invasive surgical techniques such as video-assisted necrosectomy transretroperitoneal and laparoscopic necrosectomy.

Until recently, there were not enough evidences to confirm that the results obtained with minimally invasive techniques were superior to classical surgery. In 2010, a Dutch multicenter randomized prospective study is published comparing the results obtained by open surgical necrosectomy *vs* a minimally invasive approach. This approach consisted on percutaneous or endoscopic drainage followed by a second similar drain if there was no improvement produced after 72 h or on video-assisted necrosectomy transretroperitoneal alternatively[35].

In this study, 45 patients with infected pancreatic necrosis were included in the surgical group and 43 in the minimally invasive approach group. Percutaneous drainage was initially performed in 40 patients and endoscopic drainage in one patient. 35% of patients in the minimally invasive approach did not require any necrosectomy. The group of surgical necrosectomy presented a percentage significantly higher of severe complications (69% *vs* 40%, $P = 0.006$), there was no difference in mortality rate (16% *vs* 19%, $P = 0.7$) and at six months of follow up the patients who undergone surgical necrosectomy had a higher incidence of incisional hernias (24% *vs* 7%, $P = 0.03$), diabetes mellitus of recent onset (38% *vs* 16%, $P = 0.02$) and need for pancreatic enzyme replacement therapy (33% *vs* 7%, $P = 0.002$). These results were later confirmed in a meta-analysis including 215 patients with infected necrosis treated with minimally invasive approach and 121 treated with surgical necrosectomy[36].

Two years later the Dutch group published a second study that randomly compared the results of minimal invasive surgical necrosectomy (video assisted transretroperitoneal necrosectomy or laparoscopic necrosectomy) *vs* endoscopic transgastric necrosectomy including 10 patients with infected necrosis in each group[37]. The proinflammatory response determined

by IL-6 was significantly lower after endoscopic necrosectomy compared with surgical necrosectomy (P = 0.004). This aspect is relevant because of organ failure in these patients is due to persistent proinflammatory response[38]. In fact, the incidence multiple organ failure after endoscopic treatment was significantly lower (0% *vs* 50%, P = 0.03) while the incidence of pancreatic fistula (10% *vs* 70%, P = 0.02) and the need of pancreatic enzymes (0% *vs* 50%, P = 0.04) were significantly higher after surgical treatment. Median necrosectomy procedures required were significantly higher in the laparoscopic group (3 *vs* 1, P = 0.007).

One of the most determining factors in deciding the initial approach is the time evolution time of the pancreatic collection. Here, reclassification of Atlanta has a crucial importance for the endoscopic treatment, since only endoscopic treatment is recommended in those patients with pancreatic pseudocyst or encapsulated necrosis, *i.e.*, in patients with pancreatic collections of more than 4 wk given the risk of complication, inherent in such treatment in earlier stages[4]. However, it is postulated that patients with pancreatic collections presenting clinical deterioration may undergo endoscopic drainage with relative safety from the third week. Probably management of those patients with progressive clinical deterioration requiring invasive treatment before the third week, should begin by percutaneous retroperitoneal drainage with possibility of subsequently adding video-assisted transretroperitoneal necrosectomy or transgastric endoscopic necrosectomy if there is no clinical improvement. Importantly, maximum delay in necrosectomy (> 4 wk) in patients with infected pancreatic necrosis improves treatment outcomes, if necessary, always using less invasive techniques[39]. This concept was demonstrated in a prospective randomized study comparing early surgical necrosectomy (within the first 48-72 h of admission) *vs* late necrosectomy with conservative management (past 12 d after admission). It was verified that the mortality in the early surgery group reached 56% compared to 27% of the group managed more conservatively with delayed surgery (OR = 3.4). Most of these deaths were due to multiple organ failure and cardiogenic shock[38].

In conclusion, in recent years there have been significant advances in the endoscopic management of pancreatic collections. On the one hand, there are clearer recommendations concerning the most appropriate time to propose an endoscopic treatment of a pancreatic pseudocyst or WON collection. The new classification of Atlanta indicates that endoscopic treatment should wait at least for three or four weeks if imaging tests show maturity of the walls of pancreatic collection. Endoscopic drainage is currently considered as the first treatment of choice for treatment of pancreatic pseudocyst. Furthermore it has been shown that the minimally invasive treatment of the WON offers significant advantages over surgical necrosectomy. In coming years new studies to clarify whether the initial endoscopic approach is better than percutaneous for management of WON and which is the best combination of treatments available for drainage as an alternative rescue.

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MINIREVIEWS

Future directions of duodenal endoscopic submucosal dissection

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Abstract

Endoscopic therapies for lesions of the duodenum are technically more difficult than those for lesions of the other parts of the gastrointestinal tract due to the anatomical features of the duodenum, and the incidence rate of complications such as perforation and bleeding is also higher. These aforementioned trends were especially noticeable for the case of duodenal endoscopic submucosal dissection (ESD). The indication for ESD of duodenal tumors should be determined by assessment of the histopathology, macroscopic morphology, and diameter of the tumors. The three types of candidate lesions for endoscopic therapy are adenoma, carcinoma, and neuroendocrine tumors. For applying endoscopic therapies to duodenal lesions, accurate preoperative histopathological diagnosis is necessary. The most important technical issue in duodenal ESD is the submucosal dissection process. In duodenal ESD, a short needle-type knife is suitable for the mucosal incision and submucosal dissection processes, and the Small-caliber-tip Transparent hood is an important tool. After endoscopic therapies, the wound should be closed by clipping in order to prevent complications such as secondary hemorrhage and delayed perforation. At present, the criteria for selection between ESD and EMR vary among institutions. The indications for ESD should be carefully considered. Duodenal ESD should have limitations, such as the need for its being performed by experts with abundant experience in performing the procedure.

Key words: Duodenal tumor; Endoscopic submucosal dissection; Cancer; Adenoma; Neuroendocrine tumor; Technical know-how; Complication; Endoscopic mucosal resection

Core tip: Endoscopic therapies for duodenal lesions are technically more difficult than those for lesions of the other parts of the gastrointestinal tract due to the anatomical features of the duodenum, and the incidence rate of complications such as perforation is also higher. These aforementioned trends were especially noticeable for the case of duodenal endoscopic submucosal dissection (ESD). Thus, the indications for ESD should be carefully considered. For applying endoscopic therapies to duodenal lesions, accurate preoperative histopathological diagnosis is necessary. At present, duodenal ESD should have limitations, such as the need for its being performed by experts with abundant

experience in performing the procedure.

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INTRODUCTION

Endoscopic submucosal dissection (ESD) is widely recognized as an effective treatment strategy for early gastric cancer[1,2]. In recent years, the indications for ESD have been expanded to include lesions of the esophagus and the large intestine[3-5]. Although there are several reports of ESD performed for non-ampullary duodenal tumors[6-8], the indication of ESD for the treatment of these tumors remains controversial, because the procedure is technically difficult and associated with a high incidence rate of complications[1]. While ESD may be indicated for non-ampullary duodenal tumors, including adenomas, carcinomas, and neuroendocrine tumors (NET), there is the need to determine whether ESD or endoscopic mucosal resection (EMR) might be optimal. At present, the criteria for selection between ESD and EMR vary among institutions.

In order to determine whether ESD is indicated for duodenal tumors, examination of the site, size, and macroscopic and histological morphology of the tumors is necessary. Development of guidelines for ESD of duodenal lesions (duodenal ESD) is awaited.

DIFFICULTY IN DUODENAL ESD

The duodenum is curved in the shape of a letter C and divided into four portions. The first portion is covered by the peritoneum and is mobile, whereas the second and third portions are dorsally fixed by the peritoneum and located in the retroperitoneum. These portions are immobile. The duodenal wall is thin, which consists of the mucosal, submucosal, proper muscle, and subserosal layers, starting from the lumen inward. At the outermost layer, the anterior aspect of the duodenal wall (peritoneal cavity aspect) is covered by serosa (peritoneum), while the posterior aspect is connected with the retroperitoneum. There are numerous mucosal folds on the internal surface of the duodenum, except in the first portion. The surface of the folds carries many villi which function to absorb nutrients, *etc*. In the duodenal lumen from the second portion downward, a number of circular folds (Kerckring's folds) composed of the mucosa and submucosa are arranged perpendicular to the long axis. Duodenal glands (Brunner's glands), which produce alkaline fluid rich in mucus, are distributed in the submucosa.

In endoscopic therapies for lesions of the duodenum, the maneuverability of the endoscope is poor due to the anatomical features. Moreover, because of the presence of the folds and Brunner's glands, it is more difficult to achieve sufficient bulging by local injection into the submucosa, as compared with the case in other parts of the gastrointestinal tract, and the duration of bulge of the submucosa is also short. Furthermore, because the duodenal wall is thin, the incidence rate of complications such as bleeding and perforation is high. Especially, duodenal ESD is technically difficult, often takes long time to perform, and is associated with a high risk of perforation[6]. Thus, it would seem that duodenal ESD should be performed by operators skilled in safe and reliable techniques for ESD of at least lesions of the stomach, esophagus, and large intestine.

SELECTION OF ENDOSCOPIC THERAPIES FOR LESIONS IN THE DUODENUM

The indication for ESD of duodenal tumors should be determined by assessment of the histopathology, macroscopic morphology, and diameter of the tumors. The three types of candidate lesions for endoscopic therapy are adenoma, carcinoma, and NET.

In the case of duodenal tumors, unlike tumors of the stomach and the large intestine, it is often difficult to differentiate between benign and malignant tumors on the basis of the macroscopic endoscopic findings alone. Thus, histopathological diagnosis is basically essential. However, the high risk of development of fibrosis in the submucosa occurring after biopsy reportedly makes endoscopic therapy difficult[9]. While magnifying endoscopy with narrow-band imaging has frequently been reported to be useful for qualitative diagnosis of early esophageal[10,11], gastric[12,13], and colorectal cancers[14], it is also useful for qualitative diagnosis of superficial non-ampullary duodenal epithelial tumors[15]. For depressed-type lesions, because fibrosis is likely to occur after biopsy, optical biopsy using magnifying endoscopy with narrow-band imaging has been reported to be more effective than tissue biopsy[16].

Endoscopic therapies for duodenal adenomas

Duodenal adenomas have the potential for malignant transformation[17,18]. Especially, those that are 2 cm or more in diameter and adenomas showing high-grade dysplasia on histopathology show a high likelihood of becoming malignant[19-21], and resection is preferable for such lesions. On the other hand, there is a report that low-grade adenomas measuring less than 1 cm in diameter remained low-grade lesions even at 2 years after the first diagnosis[22]. EMR of duodenal tumors has been reported to be safe and useful and to be associated with a favorable long-term prognosis[23-29].

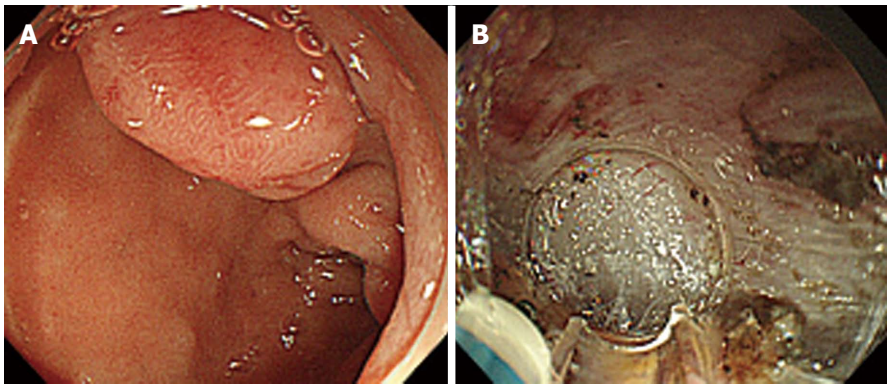

Figure 1 Endoscopic submucosal dissection of a neuroendocrine tumors in the superior duodenal bulb. A: A protruded-type tumor 0.9 cm × 0.9 cm in size was identified; B: We performed a submucosal dissection. The tip of a knife is perpendicularly oriented to the dissection surface.

In addition, piecemeal resection of adenomas is acceptable. Thus, EMR seems to be preferable for the treatment of duodenal tumors. However, a study showed that the preoperative pathological diagnosis was adenoma in 3 of 4 cancer patients who underwent EMR[30], and accurate preoperative diagnosis is necessary. At our institution, endoscopic therapy is not selected for patients with low-grade adenomas measuring less than 1 cm in diameter; instead, such patients are followed up with regular endoscopy. We select endoscopic therapies for adenomas that are at least 1 cm in diameter or show a tendency to grow, those that are histopathologically diagnosed as low-grade adenoma, but appear red and are macroscopically suspected as cancer, *etc.*

Endoscopic therapies for duodenal cancer

In a study of 128 lesions of early duodenal cancer for which surgery or endoscopic polypectomy was performed, it was reported that none of the cases of intramucosal carcinoma showed lymph node metastasis[31]. Thus, endoscopic therapies should be considered for well-differentiated noninvasive carcinomas not showing submucosal invasion. The complete remission rate after EMR for duodenal tumors ranges from 63% to 97%[24-39]. Lesions measuring 2 cm or more in diameter are likely to require piecemeal resection[23,29], and the persistence and recurrence rates are higher after piecemeal resection than after *en bloc* resection[16,29]. Complete (R0) resection is more frequently achieved by ESD than by EMR[16,30]. Furthermore, *en bloc* resection enables accurate histopathological assessment of deep and lateral surgical margins[33]. Thus, it seems preferable to perform EMR for lesions that can be resected *en bloc* by EMR and to perform ESD for lesions in which EMR is expected to result in piecemeal resection.

Endoscopic therapies for duodenal NET

The common sites of NET are the ileum, appendix, and rectum[34], and NET originating from the duodenum accounts for less than 5% of NET[35-38]. While according to one previously reported retrospective study, no recurrence was observed after local excision in any patients with tumors measuring less than 2 cm in diameter[39], another report indicated that lymph node metastasis was observed in 13% of patients with tumors measuring less than 1 cm in diameter[40]. No consensus has been reached on the association between tumor diameter and the likelihood of lymph node metastasis. Burke *et al*[41] reported the following three risk factors as being predictive of metastasis: tumor invasion to the muscle layer, tumor diameter 2 cm or more, and the presence of mitotic figures[41]. Zyromski *et al*[39] also reported that in cases of tumors measuring less than 2 cm in diameter, no metastasis was observed, regardless of the depth of invasion, recommending endoscopic therapies for tumors measuring less than 1 cm in diameter, and open transduodenal local excision for those measuring 1 to 2 cm in diameter[39]. There are reports that endoscopic resection is safe, minimally invasive, and effective for patients with tumors measuring less than 1 cm in diameter that are not identified by EUS as invading the muscle layer[42]. Although EMR may be well applicable in tumors measuring less than 1 cm in diameter invading the superficial layers of the submucosa, especially lesions with polypoid morphology, ESD may be useful for lesions that are difficult to resect *en bloc* by EMR. However, when the lower margin of a tumor lesion is widely attached to the muscle layer, ESD is associated with an extremely high risk of perforation, and the histopathological diagnosis of the deep surgical margin is also slightly uncertain; thus, surgical treatment should be considered for such cases[7].

TECHNICAL KNOW-HOW OF METHODS OF DUODENAL ESD

The most important technical issue in duodenal ESD is the submucosal dissection process, and it is common to encounter difficulties during submucosal dissection, such as when the tip of a knife is perpendicularly oriented to the dissection surface (Figure 1). In

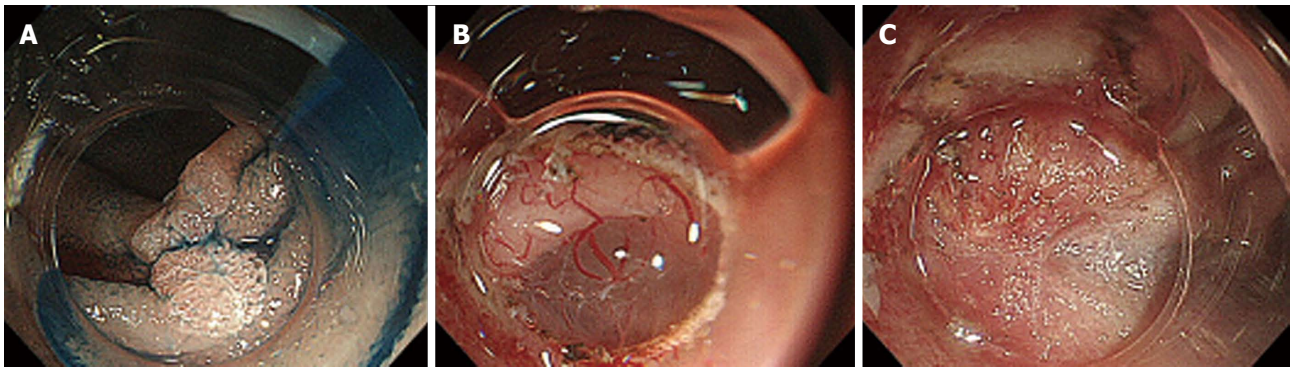

Figure 2 Endoscopic submucosal dissection of an adenoma in the descending part of the duodenum. A: A depressed type tumor 1.2 cm × 1.2 cm in size was identified; B: After incising the oral side of the lesion, we slightly detached it to form a mucosal flap; C: A severe submucosal fibrosis was found.

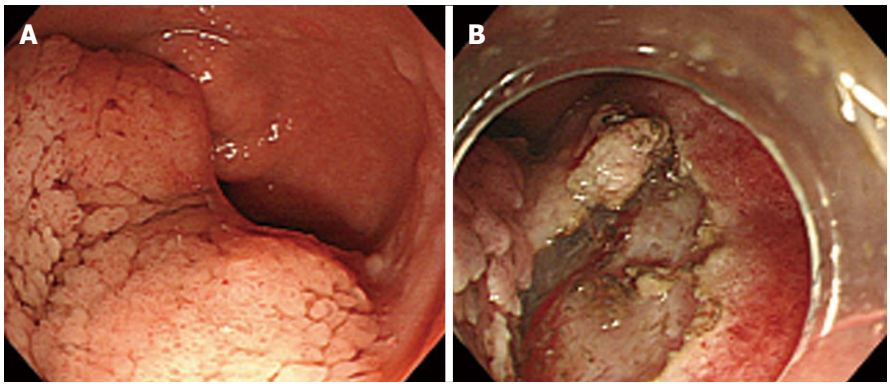

Figure 3 Endoscopic submucosal dissection of an adenoma in the anterior duodenal bulb. A: A flat-elevated type tumor 6.0 cm × 5.0 cm in size was identified; B: We performed submucosal dissection using the ST hood.

duodenal ESD, a short needle-type knife is suitable for the mucosal incision and submucosal dissection processes. The authors use the Dual knife (Olympus, Tokyo, Japan). Moreover, for the submucosal dissection process, the Small-caliber-tip Transparent (ST) hood (Fujifilm, Tokyo, Japan) is an important tool[6]. One of the important aspects of the procedure is to ensure a space for the ST hood to be placed directly under a lesion by incising the oral side of the lesion and slightly detaching it to form a mucosal flap in the early stage (Figure 2). This is the key for the success of the procedure. When a lesion is detached from the anterior wall, the tip of a knife is likely to be perpendicularly oriented to the dissection surface. Under such a situation, the authors make direct visualization of the submucosa easy using the ST hood and apply electrical current while keeping the knife slightly pressed on the lesion (Figure 3) or while the tissue to be detached is hooked and pulled toward the scope by the Hook knife (Olympus, Tokyo, Japan). When the submucosa is detached, it is important to leave as much submucosa on the dissection surface as possible in order not to expose the surface of the muscle layer. Moreover, because there is also a possibility of perforation due to an attachment of the knife such as ST hood, it seems preferable to slightly press the attachment on the dissection surface. The tips for ESD of lesions in the second portion of the duodenum are to push and pull the endoscope and control the intraduodenal air volume. In the third portion of the duodenum, the maneuverability of a scope is poor, and it is essential to check the maneuverability before the operation. If the maneuverability is poor, double-balloon enteroscopy may be useful[43].

Control of bleeding during the procedure is a key to the success of duodenal ESD. It is important to recognize the blood vessels and coagulate them before cutting. Hemostatic forceps should be slightly pulled away from the muscle layer before coagulation to prevent electrical injury of the thin muscle layer[43]. In addition, bipolar coagulation forceps are effective to prevent and restrain hemorrhage.

Because of the high incidence rate of complications caused by duodenal ESD, we have used carbon dioxide insufflation during the ESD. Carbon dioxide insufflation has been reported to be useful for early esophageal[44] and gastric ESD[45]. In addition, a system for ensuring backup by the surgical department may be essential when the procedure is performed. At our institution, in an effort to provide safer treatment, duodenal ESD has been performed under general anesthesia in the operating room since 2010.

Meanwhile, there are also difficult situations encountered during EMR of duodenal lesions. In EMR of lesions in the first portion of the duodenum, the pyloric ring may pose an obstacle to snaring. Moreover, because a lesion relatively often extends over several folds in the second portion, where the space between the folds is small, it may be difficult to ensure snaring in EMR lesions in the second portion of the duodenum.

AFTER DUODENAL ESD

At our institution, intravenous injection of a proton pump inhibitor is started on the day of the ESD, and intravenous cephem antibiotics are administered for approximately 3 d. A blood test is performed on the day after the ESD. If complications such as perforation do not occur, a rice gruel diet is started approximately 3 d after the ESD. Yamamoto suggests taking the fasting period a few days longer in duodenal ESD than other ESDs[43]. During the hospitalization, endoscopy is not performed to check for the formation of ulcers after ESD. If no complications occur, the patients are usually discharged within one week after the operation.

COMPLICATION OF DUODENAL ESD

The most common complication of endoscopic therapies for duodenal lesions is bleeding, which, in general, occurs within 24 h after the operation. The frequency of bleeding after EMR of adenomas ranges from 4% to 33%[23-28]. The frequency of bleeding after ESD ranges from 6.7% to 22.2%[6,30]. The incidence rate of perforation complicating duodenal ESD ranges from 21% to 35.7%[6,46,47], which is extremely high as compared to that of perforation complicating gastric ESD, which ranges from 1.2% to 3.6%[48-50]. Moreover, attention should be paid not only to intraoperative perforation, but also delayed perforation due to exposure to bile or pancreatic juice[6]. As compared to that in patients undergoing EMR, the incidence rate of perforation is significantly higher in those undergoing ESD, and the duration of postoperative hospital stay is also significantly longer[30]. If patients complain of abdominal pain or fever after procedure, they should be checked for their abdominal tenderness and free air in the abdomen by computerized tomography. Thus, the wound should be closed by clipping in order to prevent complications such as secondary hemorrhage and delayed perforation[46,51]. However, in some patients with lesions located in the first portion of the duodenum, closure of the wound by clipping may be difficult, and there is a report of patients in whom perforation occurred after closure of the wound by clipping[52]. In such patients, coverage of the wound with polyglycolic acid sheets (Neoveil; Gunze Ltd., Kyoto, Japan) and fibrin glue (Bolheal; Kaketsuden, Kumamoto, Japan) as a substitute to closure of wound by clipping may be effective for the prevention of delayed perforation[52].

SURGERY FOR NON-AMPULLARY DUODENAL TUMORS

At present, the frequency of complications of duodenal ESD is high, even in institutions with experts in endoscopic therapies. Unlike gastric ESD, it is more difficult to popularize the use of duodenal ESD around the world. Therefore, ESD for duodenal lesions should be performed at limited institutions with abundant experience in performing the procedure. There is also a report that surgery is preferable for lesions exceeding 20 mm in major axis[16]. It is necessary to always keep in mind surgery as one of the treatment options, and endoscopic therapies should not be insisted upon.

Recently, there have been an increasing number of institutions where endoscopists and surgeons cooperatively perform Laparoscopy and Endoscopy Cooperative Surgery (LECS). In a study conducted on 22 patients undergoing LECS for duodenal tumors, the mean tumor diameter was 13.3 mm; the mean diameter of the resected specimens was 28.9 mm; the mean operative time was 133 min; and the duration of postoperative hospital stay was 15.1 d. Complications were observed in 5 patients, 3 (13.6%) of whom had asymptomatic minor leakage. All patients recovered with conservative therapy, and no serious complications were encountered in this study[53].

LONG-TERM PROGNOSIS

In regard to the long-term prognosis, according to one study with a mean follow-up period of 10 mo, no recurrence was observed in any of the 16 patients treated by duodenal ESD, while recurrence was observed in one of the 31 patients undergoing duodenal EMR[30]. Another study also reported that no recurrence was observed with a mean follow-up period of 48 mo in any of the 37 patients treated by ESD for duodenal tumors measuring 20 mm in diameter[54]. Further accumulation of cases may be needed to clarify the long-term prognosis.

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MINIREVIEWS

Optimal management of biopsy-proven low-grade gastric dysplasia

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Abstract

Gastric adenocarcinoma generally culminates *via* the inflammation-metaplasia-dysplasia-carcinoma sequence progression. The prevalence of gastric adenomas shows marked geographic variation. Recently, the rate of diagnosis of low-grade dysplasia (LGD) has increased due to increased use of upper endoscopy. Many investigators have reported that gastric high-grade dysplasia has high potential for malignancy and should be removed; however, the treatment for gastric LGD remains controversial. Although the risk of LGD progression to invasive carcinoma has been reported to be inconsistent, progression has been observed during follow-up. Additionally, the rate of upgraded diagnosis in biopsy-proven LGD is high. Therefore, endoscopic resection (ER) may be useful in the treatment and diagnosis of LGD, especially if lesions are found to have risk factors for upgraded histology after ER, such as large size, surface erythema or depressed morphology. Fatal complications in endoscopic submucosal dissection (ESD) are extremely low and its therapeutic and diagnostic outcomes are excellent. Therefore, ESD should be applied preferentially instead of endoscopic mucosal resection.

Key words: Intraepithelial neoplasia; Low-grade dysplasia; Adenoma; Endoscopic resection; Endoscopic submucosal dissection

Core tip: According to the guideline, endoscopic resection or follow-up is recommended for noninvasive category 3 low-grade dysplasias (LGDs), while category 4 lesions such as high-grade dysplasia, non-invasive carcinoma and intramucosal carcinoma should be removed by local resection. However, as LGD has a relatively high underdiagnosis rate and rarely contains submucosal cancer, a follow-up strategy might result in the opportunity for endoscopic therapy being missed. Furthermore, repeated endoscopic examinations with biopsies might impose a psychological and financial burden on the patient. Based on its efficacy and safety, the use of endoscopic submucosal dissection as a primary procedure for LGD should be considered.

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INTRODUCTION

Gastric cancer (GC) is the fourth-most common cancer and the second-leading cause of cancer-related deaths worldwide, and is especially prevalent in Asia-Pacific countries, including South Korea[1]. In general, gastric adenocarcinoma culminates *via* the inflammation-metaplasia-dysplasia-carcinoma sequence progression, which is described as the Correa cascade of multi-step gastric carcinogenesis[2]. Gastric atrophy and intestinal metaplasia are lesions that confer a high risk for the development of gastric adenocarcinoma, and gastric epithelial dysplasia (GED) is considered the penultimate stage of gastric carcinogenesis[3,4]. Understanding the clinicopathological characteristics of GC is important for prevention. Along with the increasing number of endoscopies performed, the detection of precancerous lesions has increased in clinical practice[5].

The prevalence of gastric adenomas shows marked geographic variation. The reported prevalence is approximately 0.5%-3.75% in western countries and approximately 9%-20% in Asian countries where the prevalence of GC is high[6-8]. Some precancerous lesions progress to adenocarcinoma, whereas others remain unchanged for an extended period of time[9,10]. Furthermore, irrespective of used classification, several studies have demonstrated inter-observer variation in the histological assessment of GED[11-13]. Therefore, it is difficult to establish coincident international guidelines for the management of such lesions.

This review discusses the current optimal strategies for managing gastric low-grade dysplasia (LGD). In preparation for this review, we searched for epidemiological studies, clinical studies, meta-analyses and published guidelines related to GED in the Medline and PubMed databases. The search was performed using index words related to LGD ("gastric epithelial dysplasia" or "low grade dysplasia" or "gastric adenoma" or "gastric dysplasia") and treatment ("endoscopic resection" or "endoscopic submucosal dissection").

DEFINITION

Dysplasia is defined as an unequivocally neoplastic but non-invasive lesion, distinguished from regenerative changes[14]. Used initially to define inflammatory bowel diseases, the term is currently applied throughout the gastrointestinal tract and other organs. Grundmann[15] first used the term gastric dysplasia, and the World Health Organization (WHO) defined dysplasia as cellular atypia, abnormal differentiation and disorganized architecture[4,6]. Conventionally, dysplasia was a term used to describe flat or depressed lesions, whereas adenoma described raised circumscribed lesions that were either sessile or pedunculated. Therefore, a WHO committee defined adenoma as a circumscribed benign neoplasm composed of tubular and/or villous structures lined by dysplastic epithelium. On the other hand, Lewin[16] defined adenoma as a circumscribed lesion unassociated with underlying inflammation whether pedunculated, sessile, flat or depressed; and dysplasia was defined as a benign neoplastic lesion associated with underlying inflammation. However, most clinicians use these terms widely without distinction between adenoma and dysplasia in clinical practice.

Although the biological potential of GED as a precancerous lesion is clear, the classification of these lesions has been controversial in the diagnostic approach. For example, Japanese studies have referred to these lesions as borderline (Group 3 or 4), while the terms gastric adenoma or dysplasia have been used widely in Western countries (Table 1)[12,17]. Because dysplasia implies carcinoma in Japan, pathologists are reluctant to use the term gastric adenoma with LGD[18]. Furthermore, intraepithelial gastric neoplasias are classified into adenoma or carcinoma with low and high-grade cytological atypia[19]. Therefore, the term adenoma with low-grade atypia has been substituted for dysplasia in Japan. From the Japanese viewpoint, gastric adenoma with LGD diagnosed using western criteria include typical adenomas of the small intestinal type and tubular structures, and are thus diagnosed as carcinoma without invasion in Japan[18]. The Vienna classification for GED was proposed as a consensus between western and Asian countries (Table 1)[11,20]. In this classification, dysplastic lesions without invasion of the lamina propria are placed as category 3 or 4 according to the degree of cytologic atypia or architectural complexity[9,11]. Category 3 is a non-invasive low-grade neoplasia, also known as low-grade adenoma/dysplasia. Currently, the WHO recommends the terminology of non-invasive low-grade and high-grade intraepithelial neoplasia and defines carcinoma as invasion into the lamina propria or beyond[21].

NATURAL HISTORY

Although several studies have addressed the risk of carcinoma in GED[22-24], its natural course remains unclear. A large cohort study from the Netherlands suggested that the risk of progression to cancer within 10 years was 3.9% in individuals with LGD[25]. The differences among previous studies regarding the natural course of LGD are due primarily to the differences in diagnostic criteria including the classification and grading (Table 1). Additional reasons for these differences include sampling error in forceps biopsy, discrepancies between forceps biopsy and endoscopic resection (ER), and variations in the rate of malignant transformation. As mentioned earlier, noninvasive intramucosal neoplastic lesions with high-grade cellular and architectural atypia are termed intramucosal carcinoma in Japan, whereas the same lesions are diagnosed as high-grade dysplasia (HGD) by most pathologists in western countries[26]. Under these definitions, lesions diagnosed as gastric adenomas in

Table 1 Common reporting classifications of gastric epithelial neoplasia

Vienna classification[11,20]	WHO[21]	JGCA[19]
Negative for neoplasia/dysplasia		Group 1; Normal tissue or non-neoplastic lesion
Indefinite for neoplasia/dysplasia		Group 2; Material for which diagnosis of neoplastic or non-neoplastic lesion is difficult
Noninvasive neoplasia, low grade (low-grade adenoma/dysplasia)	Low-grade intraepithelial neoplasia	Group 3; Adenoma
Noninvasive neoplasia, high grade	High-grade intraepithelial neoplasia	
High grade adenoma/dysplasia		Group 4; Neoplastic lesion that is suspected to be carcinoma
Noninvasive carcinoma		Group 5; Carcinoma
Suspicious of invasive carcinoma		
Invasive carcinoma	Carcinoma	

WHO: World Health Organization; JGCA: Japanese Gastric Cancer Association.

Japan rarely progress to cancer[18]. Yamada *et al*[27] reported follow-up data for 48 gastric adenomas (38 LGD and 10 HGD) with a median of 4.7 years. During the follow-up period, 37 (97%) LGD lesions showed no histological change, while the remaining lesions progressed to HGD. However, this description of an indolent natural course may have been influenced by selection bias and the use of different LGD classifications in Japan. LGD lesions with invasive carcinoma were more likely to be excluded at the time of the first biopsy. Additionally, a substantial number of patients were excluded since they underwent ER or surgery due to a larger lesion or greater malignant potential. Therefore, half of the patients (19/38) in the study had lesions < 0.5 cm, with most lesions (76.3%, 29/38) measuring < 1 cm. This selection bias may influence a favorable LGD prognosis[28]. In contrast, Rugge *et al*[29] performed a prospective long-term follow-up study to evaluate the clinicopathological behavior of GED. A total of 118 gastric non-invasive neoplasias, including 90 LGDs, were followed for a mean of 52 mo. Among 90 LGDs, 48 (53.3%) were no longer detectable and 28 (31.1%) were unchanged; however, 14 (15.5%) LGDs evolved into HGD and GC.

To date, few studies have determined the predictors for malignant transformation of GEDs[30-32]. Gastric inflammation is a well-known risk factor for gastric carcinoma[33,34]. Correa[2] postulated that chronic gastritis may lead to intestinal metaplasia and atrophy, and that these lesions should be considered a GC risk factor as they are frequently found to be closely related to cancer. In a study that evaluated the endoscopic, pathological and immunophenotypic differences in LGD and HGD lesions according to the revised Vienna classification, Jung *et al*[32] determined that the size, color change and ulceration of the lesion, as well as gastritis score of the surrounding mucosa and positive expression of MUC6, were risk factors for malignant transformation. Because of the use of different diagnostic criteria and ethical reason, it is difficult to confirm a consistent natural history of LGD at present. Recent observational studies have indicated that the cancer progression risk of LGD is relatively low[27,29]. Nonetheless, it is possible that LGD can progress to invasive carcinoma[24,29,35]. Therefore, further studies are needed to understand the natural course of LGD to determine the most effective management option for follow-up treatment.

DISCREPANCIES BETWEEN BIOPSY AND ER

The endoscopic forceps biopsy (EFB) is crucial for grading pre-neoplastic gastric lesions and determining an appropriate treatment strategy. Because EFB specimens are not representative of the entire lesion, significant histologic discrepancies have been found between diagnoses based on EFB and subsequent ER (Figure 1). Recent advances in technology such as image-enhanced endoscopy with narrow-band imaging have led to improvements in the diagnostic accuracy of gastric lesions. However, the discrepancy between pre-endoscopic and post-ER diagnoses remains a concern[36]. Several studies have indicated that pretreatment EFB is inadequate for obtaining a correct diagnosis. We retrospectively reviewed 285 lesions that were initially diagnosed as LGD by EFB[37]. After ER, 46 LGDs (16.1%) showed an upgraded histology: 22 HGD (7.7%) and 24 differentiated adenocarcinoma (8.4%)[37]. In another study from South Korea, Kim *et al*[38] reported that the histologic discrepancy rate was 18.7% (51/273) in LGDs detected using forceps biopsy. Among 51 upgraded lesions, 24 lesions (8.8%) were upgraded to a diagnosis of adenocarcinoma.

Discrepancies in EFB and ER diagnoses contribute to the suboptimal treatment of biopsy-proven LGDs. Therefore, it is essential to identify the risk factors affecting these discrepancies for the proper management of LGD. We found that a lesion size ⩾ 2 cm, surface erythema and a depressed-type lesion were significant predictors of upgraded LGDs. Several studies have reported similar results regarding the endoscopic risk factors for histologic discrepancies in patients with LGD (Figure 2). Kim *et al*[38] reported that lesion size and the presence of spontaneous bleeding were significant factors predicting an upgraded histology after ER; in contrast, the presence of whitish discoloration was a significant negative factor. In a different retrospective

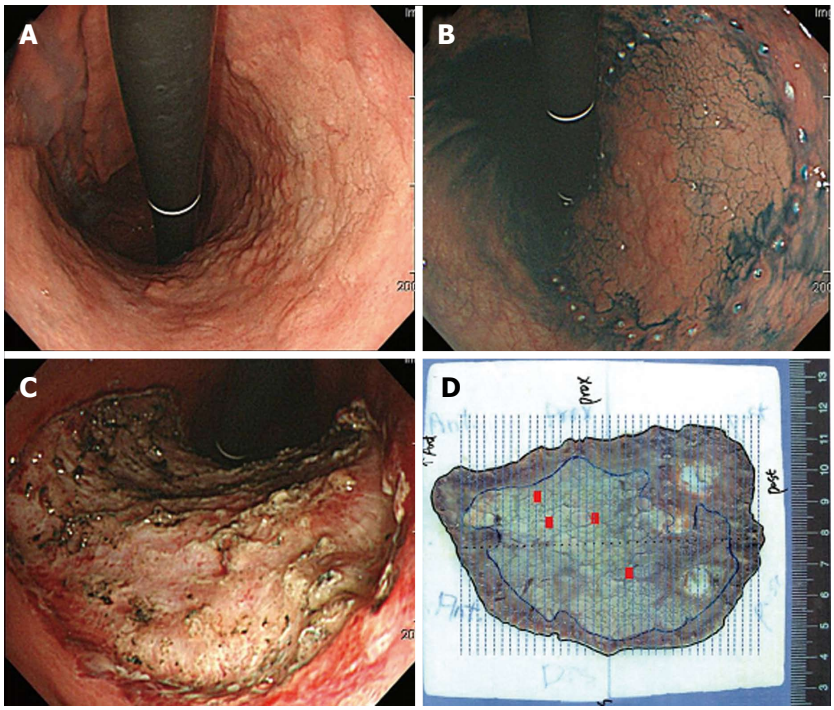

Figure 1 A lesion with a histologic upgraded from extended low-grade dysplasia to adenocarcinoma following endoscopic submucosal dissection. A: White light endoscopy reveals a large elevated mucosal lesion with nodularity in the lesser curvature side of the body. This lesion was diagnosed as LGD by the endoscopic forceps biopsy; B: This lesion is removed by ESD; C: A large mucosal defect is noted over the gastric body after ESD; D: Mapping of the resected specimen. The tumor size is 75 mm, focal cancer lesions (red bar) mixed with LGD are evident. The lateral and vertical margins are free from tumor. LGD: Low-grade dysplasia; ESD: Endoscopic submucosal dissection.

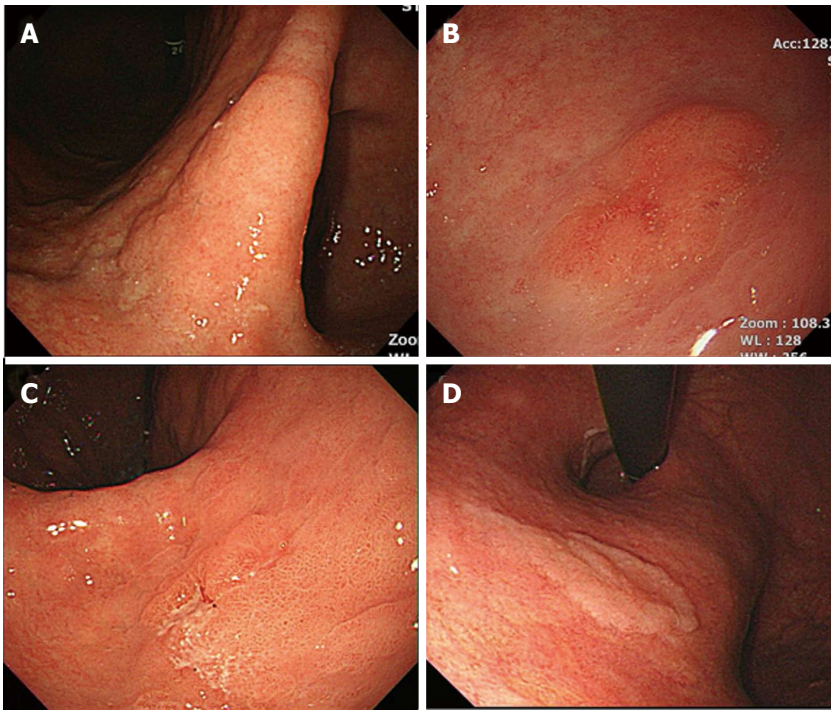

Figure 2 Endoscopic images of biopsy-proven low-grade dysplasia. A-C: lesion size > 2 cm (A), surface erythema (B), and depressed appearance (C) are endoscopic risk factors for an upgraded histology after endoscopic resection; D: In contrast, the presence of whitish discoloration was a negative factor.

study, Cho *et al*[28] demonstrated that a lesion size ⩾ 1 cm, depressed morphology, and erythema were significantly associated with HGD and carcinoma. In a study from Japan[39], a lesion size > 2 cm and depressed appearance were significant independent factors suggesting cancer. To summarize, lesions of larger size and morphology with surface erythema and depression in biopsy-proven LGDs were predictive of an upgraded histology after ER. Therefore, when selecting treatment methods for these lesions, the collection method of the suspected malignant foci should be taken into consideration. ER should be considered for diagnostic and therapeutic purposes in lesions with these risk factors.

MANAGEMENT

In developing a therapeutic plan for LGD management, it is important to identify LGDs that have histological and classical risk factors for GC progression. In South Korea, ERs-including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)-are performed widely for the treatment of gastric adenoma, in which early GC and gastric adenoma

are prevalent. According to the revised Vienna classification, ER or follow-up is recommended for noninvasive category 3 LGD lesions, while category 4 lesions such as HGD, non-invasive carcinoma and intramucosal carcinoma should be removed by endoscopic or surgical resection[20]. Some investigators have suggested regular endoscopic surveillance with repetitive biopsy, while others have proposed ER for accurate diagnosis and treatment of LGDs. As mentioned earlier, various factors account for these discrepancies, including differences in diagnostic criteria, inconsistent results among studies of the natural course in LGD, and histologic discrepancies in EFB and ER.

Recent advances in endoscopic techniques have enabled the removal and histological diagnosis of most intra-mucosal lesions regardless of size, shape and location in the stomach[40]. However, performing resections in all patients with LGDs with relatively low malignant potential may lead to significant increases in cost, procedure time, risk of complication, and requirement for advanced technical skills. Although EMR is an easily and rapidly applicable method for therapeutic and diagnostic modalities, it has some limitations. Conventional EMR techniques are unreliable for lesion > 2 cm in diameter due to high rates of positive lateral and/or deep resection margins[41,42]. Even in lesions < 2 cm, the complete resection rate with EMR was 33%-76%[43,44]. Lesion factors, such as tumor size and location, contribute to the difficulty of en bloc resection. To overcome these problems, the development of ESD has allowed complete resection regardless of tumor size and location. In a meta-analysis[45], ESD was significantly more effective than EMR for en bloc resection, complete resection, curative resection and local recurrence. Whereas intra-operative bleeding, perforation risk, and operation time were significantly greater for ESD, overall bleeding risk and all-cause mortality did not differ significantly between ESD and EMR. One meta-analysis[46] showed that procedure-related bleeding (OR = 2.2, 95%CI: 1.58-30.7) and perforation rates (OR = 4.09, 95%CI: 2.47-6.80) during ESD were much higher compared with those for EMR. However, these were not statistically significant in another meta-analysis including 12 studies[45]. Both studies[45,46] showed that ESD was more time-consuming.

Several studies have evaluated endoscopic techniques as a treatment for LGD. Kim *et al*[47] compared the therapeutic outcomes of ESD and EMR in histologically confirmed LGD cases. The en bloc resection rate was significantly lower in the EMR groups (31.1%) compared with the ESD group (75.0%) (P < 0.001). However, no significant difference was observed in the prevalence of remnant lesion or recurrence rate (P = 0.911). On the other hand, Choi *et al*[48] reported a 96.1% complete resection rate using ESD, and the local recurrence rate was 1.4% in patients with biopsy-proven LGD. In this study, no patient had perforation and four (1.4%) patients had significant post-ESD bleeding that was treatable by endoscopic intervention. A multicenter study by the Osaka University ESD study group[49] analyzed a total of 468 subjects with GED. The results showed that the complete en bloc resection rate was 97%, and the incidences of post-ESD bleeding, perforation and serious complication were 5.5%, 4.7% and 0.43%, respectively. Miyamoto *et al*[50] reported that tumor size and location of the lesion are important factors that affect the success rate of en bloc resection. Because not all lesions can be resected en bloc for technical difficulty, another treatment option such as ablation therapy should be considered for the treatment of LGDs[51].

As LGD has a relatively high underdiagnosis rate and rarely contains submucosal cancer, a follow-up strategy might result in the opportunity for endoscopic therapy being missed[49]. Furthermore, repeated endoscopic examinations with biopsies might impose a psychological and financial burden on the patient. Based on its efficacy and safety, the use of ESD as a primary procedure for LGD should be considered.

CONCLUSION

The increased use of upper endoscopy has resulted in increased diagnosis of gastric adenoma. Although many investigators have suggested that gastric HGD should be removed due to its high potential for malignancy[20], the treatment of gastric LGD remains controversial. Although previous studies have reported inconsistent results regarding the risk of LGD progression to invasive carcinoma, such progression can occur during follow-up. Additionally, the rate of upgraded diagnosis in biopsy-proven LGDs is high. Considering these results, the use of ER might enhance treatment and diagnosis, especially of lesions with risk factors such as large size, surface erythema or depressed morphology. Furthermore, the incidence of fatal complications of ESD has been extremely low, with excellent therapeutic and diagnostic outcomes. Therefore, ESD should be applied in preference to EMR.

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ORIGINAL ARTICLE

Retrospective Study

Re-bleeding events in patients with obscure gastrointestinal bleeding after negative capsule endoscopy

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Author contributions: Magalhães-Costa P, Bispo M and Chagas C designed the research; Magalhães-Costa P performed the research; Magalhães-Costa P analyzed the data; Magalhães-Costa P wrote the paper; Bispo M, Santos S, Couto G, Matos L and Chagas C critically revised the manuscript.

Ethics approval: This study was reviewed and approved by the Centro Hospitalar de Lisboa Ocidental Institutional Review Board.

Informed consent: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest: None reported (all authors). All authors declare not having received any fee for serving as a speaker nor had received any research funding nor is an employee nor owns stocks and/or shares nor own any patent related to the article content.

Data sharing: Technical appendix, statistical code, and dataset avaliable from the corresponding author at pmagalhaescosta@gmail.com. Participants gave informed consent for data sharing.

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Abstract

AIM: To investigate long-term re-bleeding events after a negative capsule endoscopy in patients with obscure gastrointestinal bleeding (OGIB) and the risk factors associated with the procedure.

METHODS: Patients referred to Hospital Egas Moniz (Lisboa, Portugal) between January 2006 and October 2012 with OGIB and a negative capsule endoscopy were retrospectively analyzed. The following study variables were included: demographic data, comorbidities, bleeding-related drug use, hemoglobin level, indication for capsule endoscopy, post procedure details, work-up and follow-up. Re-bleeding rates and associated factors were assessed using a Cox proportional hazard analysis. The Kaplan-Meier method was used to estimate the cumulative incidence of re-bleeding at 1, 3 and 5 years, and the differences between factors were evaluated.

RESULTS: The study population consisted of 640 patients referred for OGIB investigation. Wireless capsule endoscopy was deemed negative in 113 patients (17.7%). A total of 64.6% of the population was female, and the median age was 69 years. The median follow-up was forty-eight months (interquartile range 24-60). Re-bleeding occurred in 27.4% of the cases. The median time to re-bleeding was fifteen months (interquartile range 2-33). In 22.6% (n = 7) of the population, small-bowel angiodysplasia was identified as the culprit lesion. A univariate analysis showed that age > 65 years old, chronic kidney disease, aortic stenosis, anticoagulant use and overt OGIB were risk factors for re-bleeding; however, on a multivariate analysis, there were no risk factors for re-bleeding. The cumulative risk of re-bleeding at 1, 3 and 5 years of follow-up was 12.9%, 25.6% and 31.5%, respectively.

Patients who presented with overt OGIB tended to re-bleed sooner (median time for re-bleeding: 8.5 mo *vs* 22 mo).

CONCLUSION: Patients with OGIB despite a negative capsule endoscopy have a significant re-bleeding risk; therefore, these patients require an extended follow-up strategy.

Key words: Capsule endoscopy; Gastrointestinal hemorrhage; Anemia; Angiodysplasia; Risk factors

Core tip: This study describes a large cohort of patients with obscure gastrointestinal bleeding in whom the first capsule endoscopy was negative. Re-bleeding events, risk factors and causes were analyzed. A significant risk of re-bleeding was observed; however, independent predictors for re-bleeding were not identified. Re-bleeding due to small-bowel angiodysplasia was a frequent occurrence; therefore, these patients require an extended follow-up strategy, perhaps involving repeated endoscopic procedures if re-bleeding occurs.

Magalhães-Costa P, Bispo M, Santos S, Couto G, Matos L, Chagas C. Re-bleeding events in patients with obscure gastrointestinal bleeding after negative capsule endoscopy. *World J Gastrointest Endosc* 2015; 7(4): 403-410 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i4/403.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i4.403

INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) represents approximately 5% of all gastrointestinal bleeding cases and, in most cases, the culprit lesion located in the small-bowel[1]. OGIB is defined as bleeding from the gastrointestinal tract that persists or recurs without an obvious source, as assessed by esophagogastroduodenoscopy (EGD), colonoscopy and radiologic evaluation of the small-bowel[1]. OGIB is classified as either occult or overt; occult OGIB is characterized by iron deficiency anemia (IDA) with or without a positive fecal occult blood test[1,2], and overt OGIB is characterized by clinically perceptible bleeding that recurs or persists despite negative initial endoscopic (EGD and colonoscopy) and radiologic evaluations. Wireless capsule endoscopy (WCE) is a cost-effective investigation in patients with OGIB[3]. In one study, after a WCE evaluation, there was a significant reduction in hospitalizations, additional investigations and units of blood transfused compared to before WCE[4]. Currently, OGIB is the main indication for a capsule endoscopy study. A myriad of studies have analyzed and compared the diagnostic yield (*vs* other techniques)[5-7] and clinical impact of a positive WCE study on patient outcome[8]. Still, a negative WCE study remains a clinical challenge, and little is known about the long-term follow-up of such patients. Therefore, many questions persist about the "protective effect" of a negative WCE study on future re-bleeding events. To date, there are some conflicting data about the re-bleeding rates and predictive factors linked to a re-bleeding event, and in addition, the median follow-up period varies substantially among studies[9-15]. The aim of this study is to assess the long-term outcome (especially re-bleeding events) after a negative WCE study in patients referred for OGIB investigation and risk factors associated with a re-bleeding event.

MATERIALS AND METHODS

We present a retrospective, observational cohort, single center study. Clinical data were obtained from medical records of all patients referred to our tertiary referral hospital - Endoscopy Unit (Hospital Egas Moniz, Centro Hospitalar Lisboa Ocidental, Lisboa) - to undergo a WCE for OGIB investigation between January 2006 and October 2012. All of the patients presented with overt or occult gastrointestinal bleeding according to guidelines[1]. All patients had at least one negative EGD and ileo-colonoscopy before referral for WCE. After signing a written informed consent, every patient underwent a WCE with a PillCam SB (R) (M2A, from January 2006) or SB2© (since June 2007) capsule endoscopy system (Given Imaging, Yoqneam, Israel) according to the standard protocols[16]. All the procedures were performed in an outpatient setting. Since January 2008, a small-bowel purgative preparation with a 2-L polyethylene glycol solution before WCE was introduced in our protocol. Simethicone was also used on a routine basis before all procedures. Two hours after taking the capsule, patients received a clear liquid diet and, two hours later, a light meal, as recommended in the standard protocol. Eight hours after WCE, the patients returned to the Endoscopy Unit, the data recorder was removed, and images were downloaded. The recordings were independently reviewed by four experienced gastroenterologists (Chagas C, Couto G, Santos S, Bispo M) at 8-10 frames per second using the Rapid® Reader. When possible, the colon was also observed. The WCE findings were classified into three types based on the Saurin classification[17,18] as follows: lesions considered to have a high potential for bleeding (P2); lesions with uncertain bleeding potential (P1); and lesions with no bleeding potential (P0). Positive WCE studies were defined as examinations that identified one or more P1 or P2 lesions, whereas those that identified only P0 or no abnormal lesions were regarded as negative WCE studies. Exclusion criteria were as follows: concomitant or not non-gastrointestinal blood loss (hematuria, hemoptyses and gynecological blood loss), incomplete exams (not

Table 1 Clinical characteristics of patients with obscure gastrointestinal bleeding and a negative capsule endoscopy (*n* = 113)

	% (*n*)
Age	
≤ 65 years old	37.2 (42)
> 65 years old	62.8 (71)
Gender	
Female	64.6 (73)
Male	35.4 (40)
Comorbidities	
Chronic kidney disease	12.4 (14)
Aortic stenosis	6.3 (7)
Prior angiodysplasia	3.5 (4)
Medication	
None relevant	54 (61)
Single anti-platelet agent	16.8 (19)
Anticoagulant	7.1 (8)
NSAID	7.1 (8)
Double anti-platelet agent	5.3 (6)
SSRI	3.5 (4)
Occult OGIB	69 (78)
Iron deficiency anemia	63 (71)
Overt OGIB	31 (35)
Melena	19.5 (22)
Hematochezia	11.5 (13)
[Hb] prior to WCE (median; IQR; g/L)	86 (70-100)
Transfusional needs prior to WCE (RBC units; median; IQR)	1 (1-2)
Technical Issues	
Gastric Transit Time (min; median; IQR)	18 (11-37)
Small-bowel Transit Time (min; median; IQR)	253 (216-323)
WCE per Examiner (%)	
Person A	42.5 (*n* = 48)
Person B	38.9 (*n* = 44)
Person C	9.7 (*n* = 11)
Person D	8.9 (*n* = 10)

NSAID: Non-steroidal anti-inflammatory drugs; SSRI: Selective serotonin reuptake inhibitor; OGIB: Obscure gastrointestinal bleeding; [Hb]: Serum hemoglobin; WCE: Wireless capsule endoscopy; IQR: Interquartile range; RBC: Red blood cells.

reaching the ileocecal valve), poor preparation (as dictated by the examiner) and less than twelve months of follow-up. Negative WCE cases were selected and analyzed. A re-bleeding event was defined as occult re-bleeding [a decrease in 20 g/L of [Hb] - (serum hemoglobin) from the patient baseline] or overt re-bleeding (melena, hematochezia). Cases of re-bleeding due to non-small-bowel pathology (*e.g.*, peptic ulcer disease, erosive esophagitis/gastritis/duodenitis, gastroesophageal varices, colorectal carcinoma, *etc.*) detected during follow-up were excluded from further analysis. The median follow-up for all patients strictly monitored for re-bleeding was forty-eight months (interquartile range 24-60). Study variables included the following: demographic data (patient age and gender), comorbidities (chronic kidney disease, aortic stenosis, prior diagnosis of angiodysplasia), relevant medication [use of anticoagulant, antiplatelet agent/s, nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs)], hemoglobin level prior to WCE, indication for WCE (occult or overt - melena/hematochezia OGIB), time from OGIB detection to WCE procedure, post procedure details and follow-up [type of treatment for bleeding, hospital admissions (especially for anemia and/or recurrent gastrointestinal bleeding), blood transfusions, need for iron supplementation, additional endoscopies and surgery, re-bleeding causes (if determined) and patient status at the end of follow-up (on-going investigation or treated successfully)].

Statistical analysis

The Statistical Package for Social Science (version 20.0; SPSS Inc., Chicago, IL, United States) was used for all statistical analysis. Continuous variables are expressed as the mean ± SD or median (interquartile range) as appropriate. Qualitative and quantitative differences between subgroups were analyzed using the χ^2 test or Fisher's exact test for categorical parameters and Student's *t* test or Mann-Whitney test for continuous parameters as appropriate. Univariate and multivariate analyses by Cox proportional hazards regression model was performed to identify factors associated with re-bleeding. After the univariate analysis, variables with a $P < 0.05$ were entered in the multivariate analysis. Effect sizes are expressed as hazard ratios (HRs) and 95%CIs. The Kaplan-Meier method was used to estimate the cumulative incidence of re-bleeding at 1, 3 and 5- years of follow-up, and differences between factors were evaluated using the log-rank test. All statistical tests were 2 sided. Statistical significance was set at $P < 0.05$.

RESULTS

Patient characteristics

During the follow-up period, 640 patients were referred for OGIB investigation. In 113 exams (17.7%), the WCE could not find the culprit lesion and was deemed negative (P0 lesions or no abnormal findings). A summary of baseline characteristics is displayed in Table 1. Among the studied population, 73 patients were female (64.6%), with a median age of 69 years old (interquartile range 56-79); 62.8% (*n* = 71) of the patients were > 65 years old. Forty-five patients (39.8%) were taking bleeding-related drugs (single anti-platelet agent: *n* = 19 (16.8%); anticoagulant: *n* = 8 (7.1%); double anti-platelet agent: *n* = 6 (5.3%); non-steroidal anti-inflammatory (NSAIDs): *n* = 8 (7.1%); SSRI: *n* = 4 (3.5%). Thirty-five out of 113 (31%) presented with overt obscure bleeding (overt OGIB) - melena (*n* = 22; 19.5%) and hematochezia (*n* = 13; 11.5%).

Follow-up

The median follow-up was forty-eight months (interquartile range 24-60). After the exclusion of re-bleeding cases due to non-small-bowel pathology, re-bleeding from the small-bowel (or unknown origin) occurred in thirty-one out of 113 negative WCE studies (27.4%). The median time from index negative WCE

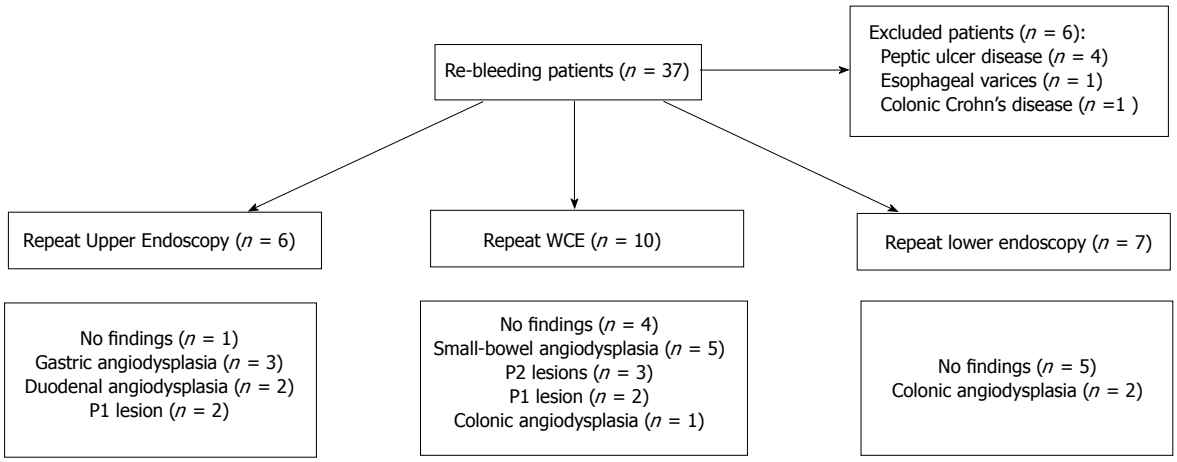

Figure 1 Endoscopic investigations after re-bleeding. WCE: Wireless capsule endoscopy.

Table 2 Characteristics of patients with a negative capsule endoscopy

Variable	All	Non re-bleeders	Re-bleeders	*P*
Age (years old)	67 ± 15	65 ± 15	72 ± 11	0.007
Gender (M/F)	40/73	27/55	13/18	0.386
OGIB presentation (*n*)				
Occult	79	61	18	0.067
Overt	34	21	13	
[Hb] (median)	86	86	79	0.143
Anticoagulant use (*n*)	11	4	7	0.009
Small-bowel Transit time (median)	253	253.5	251.5	0.650

Values are presented in mean ± SD unless stated otherwise. M/F: Male/female; OGIB: Obscure gastrointestinal bleeding; [Hb]: Serum hemoglobin.

to the re-bleeding episode was 15 mo (interquartile range 2-33). Figure 1 provides data regarding endoscopic investigations in patients who re-bled and the associated causes. Among the re-bleeding cases, 29 (94%), were submitted to at least one additional endoscopic procedure. In ten re-bleeding cases (32%), the culprit lesion was/remains unknown; in thirteen cases (42%) an angiodysplasia (small-bowel *n* = 7, colon *n* = 3, stomach *n* = 3) was identified on a subsequent study. Half of the repeated WCE visualized a previously unrecognized small-bowel angiodysplasia. Of those who re-bled from a small-bowel angiodysplasia (*n* = 7), three (all P2 lesions; 43%) were submitted to argon-plasma thermocoagulation (APC) *via* deep enteroscopy (one patient received one APC session, one received two APC sessions and the other patient had to be submitted to five APC sessions), with complete resolution of the gastrointestinal bleeding. Among the total re-bleeding population, five patients (16%) received specific medical therapy (proton pump inhibitor and/or NSAIDs or anticoagulant withdrawal), three patients (9.7%) received non-specific medical therapy (iron supplementation or blood transfusions), and twenty patients (64.5%) did not receive any type of treatment.

Overall, at the end of the follow-up period, twenty-four patients with re-bleeding (77.4%) were considered successfully treated [*i.e.*, despite the re-bleeding event they were asymptomatic, did not require a blood transfusion or iron supplementation and had a normal (Hb) level]. Seven patients (22.6%) remain under close follow-up (requiring regular iron supplementation, blood transfusions).

Risk factor analysis and risk of re-bleeding

A comparison of baseline characteristics between re-bleeders *vs* non re-bleeders is summarized in Table 2. The results of univariate and multivariate analyses regarding factors associated with re-bleeding in patients with a negative WCE are summarized in Table 3. According to a univariate analysis, age > 65 years old, chronic kidney disease, aortic stenosis, anticoagulant use and overt OGIB were detected as factors associated with a significant risk of re-bleeding after a negative WCE. After subjecting the previous variables to a multivariate analysis using a Cox proportional hazards regression model, none of the previously identified factors were able to independently predict future re-bleeding events.

The overall cumulative risk of re-bleeding at 1, 3 and 5-year of follow-up was 12.9%, 25.6% and 31.5%, respectively (Figure 2). To perform a comprehensive analysis, a subgroup comparison between those who initially presented with occult OGIB vs overt OGIB is summarized in Table 4. The overt group tended to re-bleed sooner than the occult group (median time until re-bleeding event: 8.5 mo *vs* 22 mo; *P* = 0.257); however, re-bleeding rates between these two groups were not significantly different (Figure 3; *P* = 0.099).

DISCUSSION

Capsule endoscopy revolutionized the world of gastrointestinal endoscopy, mainly OGIB, by allowing the gastroenterologist to identify the possible cause of OGIB and enhance a directional or specific treatment.

Table 3 Univariate and Multivariate analysis *via* Cox proportional hazard regression model: Re-bleeding risk factors in patients with obscure gastrointestinal bleeding and a negative capsule endoscopy

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*	HR	95%CI	*P*
Female	1.408	0.676-2.929	0.361			
Age > 65 years old	3.599	1.364-9.501	0.010	2.591	0.951-7.060	0.063
Chronic kidney disease	3.498	1.265-9.671	0.016	2.252	0.749-6.770	0.148
Aortic stenosis	4.159	1.412-12.247	0.010	1.548	0.352-6.811	0.563
Prior angiodysplasia	3.637	0.851-15.457	0.081			
Bleeding-related drugs	1.586	0.761-3.304	0.219			
Anticoagulant use	3.903	1.542-9.875	0.004	2.699	0.705-10.330	0.147
Overt OGIB	2.104	1.011-4.380	0.047	1.986	0.933-4.231	0.075
[Hb] < 80 g/L	1.857	0.868-3.970	0.111			
Transfusional (RBC) needs prior to WCE	1.122	0.919-1.370	0.257			

Values are presented in mean ± SD unless stated otherwise. HR: Hazard ratio; OGIB: Obscure gastrointestinal bleeding; [Hb]: Serum hemoglobin; RBC: Red blood cells; WCE: Wireless capsule endoscopy.

Capsule endoscopy is a safe and effective technology in the evaluation of small-bowel pathology[1]. Whether a positive or negative WCE study impacts patient outcome remains ill defined. Two recent studies failed to demonstrate that a higher diagnostic yield is related to an improved outcome in patients with OGIB[19,20]. Moreover, on a recent nationwide study by Min *et al*[8], the authors concluded that WCE did not have a significant impact on the long-term outcome of patients with OGIB. Some studies analyzed the long-term outcome defining the occurrence of a re-bleeding event as a primary outcome[9-12,14,15,21]. In the paramount study of Lai *et al*[9], patients with a negative WCE study (n = 18) displayed a low re-bleeding rate (5.6%) when followed for twelve months (median). Another study by Macdonald *et al*[10] that analyzed 49 patients with OGIB (median follow-up = 17 mo) demonstrated a higher re-bleeding rate in this subgroup (negative WCE) of patients (11%) and, when assessing risk factors associated with re-bleeding, identified anticoagulant use as the only independent predictor. Therefore, these first two studies claimed a low re-bleeding probability in patients whose first WCE study was negative, thus advising an expectant approach. Thereafter, it has been postulated that a negative WCE result predicts a favorable prognosis in patients with OGIB and a low risk of re-bleeding. Later, a study by Park *et al*[12] with 51 patients followed for thirty-two months demonstrated a re-bleeding rate of 35.7% in WCE negative patients. Hence, the authors recommended a close follow-up of these patients for at least 2 years. Moreover, two of the most recent studies[14,19] report re-bleeding rates of 23% and 33%, respectively. Additionally, it has been demonstrated that there are no significant difference in the cumulative re-bleeding rates between patients with positive *vs* negative WCE findings[8,12,14].

In the present study, we focused on and followed 113 patients referred for OGIB investigation with a negative WCE. Similar to previous recent retrospective cohort studies[12,14], we demonstrated high re-bleeding rates (27.4%) in this group of patients when followed for longer periods (> 12 mo). Studies that reported lower re-bleeding rates had shorter follow-up periods[9,10,15,22]. To optimize the definition of the risk, we set the minimum follow-up period at 12 mo, and we obtained a median follow-up period of 48 mo (4 years). In approximately 1/3 of the re-bleeders, the culprit lesion remained unknown (*i.e.*, persistently negative endoscopic studies), and when identified, angiodysplasia was the most frequent lesion (42%), mainly small-bowel angiodysplasia (53.8% of all the missed angiodysplasia), which is in line with a previous report[23]. One explanation for these findings might be that some angiodysplasias were missed in the first WCE (although some lesions may have developed after the index WCE). In addition, the natural history of such vascular lesions remains unclear, and their dynamic nature makes them hard to demonstrate consistently. Additionally, it is important to note that knowing that there is a positive correlation between diagnostic yield and small-bowel transit time (SBTT), especially in OGIB[24], as presented in Table 4, SBTT did not differ between re-bleeders and non-re-bleeders; therefore, it is unlikely that re-bleeders had a higher rate of important missed lesions than non-re-bleeders.

In Western countries, angiodysplasia seems to be more frequent than in Asia, and this might be another explanation for the lower re-bleeding rates observed across some of the Asian studies, where small-bowel ulcers dominate the OGIB etiology[8,22]. In patients with recurrent OGIB or IDA who had a negative WCE, a repeat WCE revealed the presence of angiodysplasia in up to 29% of patients (75% of all findings) and led to changes in patient management in two small studies[25,26], which is in line with our data.

Similarly to previous studies[14,15] our median time until re-bleeding was 15 mo, which strengthens the importance of closely following these patients in the first 2 years after index WCE and seemingly over the 3rd year, as our interquartile range for re-bleeding was between 2 and 33 mo. Although the results were not statistically significant (Figure 3; Log-Rank test =

Table 4 Comparison between patients presenting with occult/overt obscure gastrointestinal bleeding

Variable	Occult OGIB	Overt OGIB	*P*
Age (years old)	66	68	0.448
Sex (M/F)	24/54	16/19	0.141
[Hb] (median)	8.9	7.9	0.015
Anticoagulant use (*n*)	8	3	1.000
Time from OGIB to WCE (d; median)	31	29	0.653
Follow-up period (mo; median)	48	42	0.450
Rebleeding cumulative events (at 12 mo) (*n*)	9% (7)	21% (7)	0.133
Rebleeding cumulative events (at 36 mo) (*n*)	20% (13)	39% (11)	
Rebleeding cumulative events (at 60 mo) (*n*)	29% (16)	39% (11)	
Rebleeding cumulative events (at 84 mo) (*n*)	34% (17)	49% (12)	
Rebleeding cumulative events (total) (*n*)	17	12	
Time to rebleeding event (mo; IQR)	22 (6-33)	8.5 (0.5-27)	0.257

Values are presented in mean ± SD unless stated otherwise. OGIB: Obscure gastrointestinal bleeding; M/F: Male/female; [Hb]: Serum hemoglobin; IQR: Interquartile range.

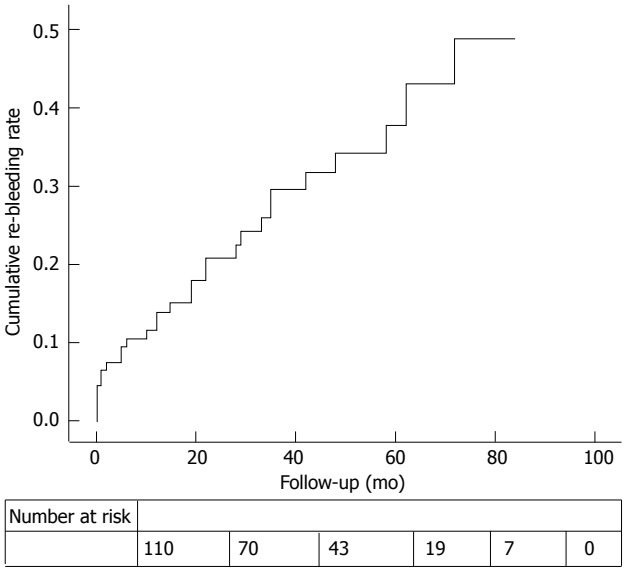

Figure 2 Kaplan-Meier curve showing cumulative re-bleeding rates in the study population.

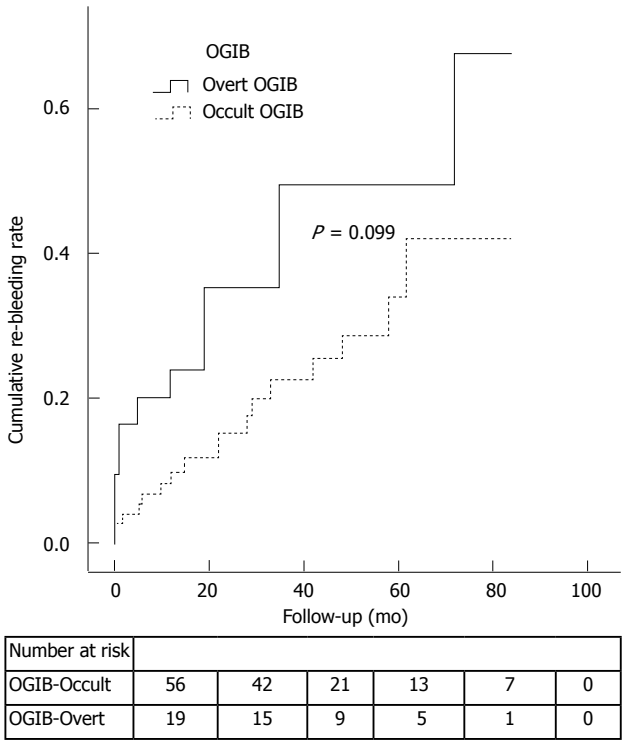

Figure 3 Kaplan-Meier curve showing cumulative rebleeding rates after a negative capsule endoscopy according to initial obscure gastrointestinal bleeding presentation (Log-Rank = 0.099). OGIB: Obscure gastrointestinal bleeding.

0.099), when the subgroups of patients presenting with occult and overt OGIB were analyzed separately, we observed that patients who presented with overt OGIB, in contrast with the occult group, tended to re-bleed sooner (median time until re-bleeding = 8.5 mo *vs* 22 mo).

Previous studies pinpointed anticoagulant intake[10,14] as an independent risk factor for re-bleeding, regardless of WCE results. Others[15] identified younger age (< 65 years old) and the onset of bleeding as independent risk factors for re-bleeding after a negative WCE. Consistent with another recent study[23], our results showed that in a univariate analysis, patients who re-bled were older (HR = 3.599; 95%CI: 1.364-9.501; *P* = 0.010). One explanation is that the prevalence of angiodysplasia (the most frequent re-bleeding lesion in most studies) is known to be higher in older individuals[1], making them a group prone to re-bleeding. It is also known that the incidence of small-bowel vascular lesions (mainly angiodysplasia) in patients with chronic kidney disease is high[27-29], thus making them more likely to re-bleed, as shown in an univariate analysis (HR = 3.498; 95%CI: 1.265-9.671; *P* = 0.016). In our study, as demonstrated previously[14], taking anticoagulants is an important risk factor for re-bleeding (HR = 3.903; 95%CI: 1.542-9.875; *P* = 0.004). Another interesting finding was that even though patients who presented with an overt OGIB tended to re-bleed more than those who presented with occult OGIB (HR = 2.104; 95%CI: 1.011-4.380; *P* = 0.047), a statistically significant difference could

not be found between the groups (Figure 3). Patients with aortic stenosis may have a higher prevalence of angiodysplasia (condition also known as Heyde Syndrome) through the gastrointestinal tract[30,31]. In patients with aortic stenosis, the tendency to harbor angiodysplasia in the gut may pose an elevated risk of re-bleeding events. In this study, there was a trend towards more re-bleeding events in these patients (HR = 4.159; 95%CI: 1.412-12.247; *P* = 0.010). However, when all of these factors were pooled on a multivariate analysis, their statistical significance became null.

Our study limitations were the following: (1) the data were collected from a single tertiary referral hospital and the study had a retrospective design; (2) some of the patients included are followed at other institutions; thus, some follow-up data are missing; and (3) we focused only on patients referred for OGIB with a negative WCE. A comparison of re-bleeding rates with positive WCE cases would have been interesting; however, in a recent study[8], it was demonstrated that re-bleeding rates between positive and negative WCE cases were not significantly different. A leverage point of our study was the very long-term post procedure follow-up period and the relatively large number of patients included.

In conclusion, patients with OGIB with a negative WCE have a significant re-bleeding risk (27.4%), and a follow-up strategy is recommended. In this study, predictive factors for re-bleeding events could not be found using a multivariate analysis; however, a tendency was demonstrated (older age, chronic kidney disease, aortic stenosis, anticoagulants use and overt OGIB), and in future series, a tailored approach/surveillance may be required. Prospective observational studies addressing this topic with long-term follow-up are urgently needed.

COMMENTS

Background

Obscure gastrointestinal bleeding (OGIB) is defined as occult or overt gastrointestinal bleeding of unknown origin that persists or recurs after initial negative endoscopic evaluation (esophagogastroduodenoscopy and colonoscopy). OGIB represents approximately 5% of all gastrointestinal bleeding cases, and the culprit lesion is located in the small-bowel in most instances. Angiodysplasias of the small-bowel account for 30% to 40% of OGIB. Wireless capsule endoscopy (WCE) is a safe and well-accepted technology that enables visualization of the small-bowel.

Research frontiers

A negative (WCE) study remains a clinical challenge, and little is known about the long-term follow-up of such patients. The "protective effect" of a negative WCE study on future re-bleeding events remains controversial. To date, there are some conflicting data about the re-bleeding rates and predictive factors linked to a re-bleeding event, and in addition, median follow-up period varies among studies.

Innovations and breakthroughs

In a retrospective analysis, the authors evaluated the long-term re-bleeding events after a negative WCE in patients referred for OGIB. In a concrete and relatively large cohort from a tertiary center in Europe with long-term follow-up (48 mo), it was found that patients with OGIB, despite a negative WCE, have a significant re-bleeding rate (27.4%). Small-bowel angiodysplasia was the most frequent re-bleeding related lesion (22.6%). The median time from index negative WCE to the re-bleeding episode was fifteen months. After a multivariate analysis, there were no independent predictors for re-bleeding.

Applications

This study suggests that patients with OGIB and a first negative WCE should have an extended follow-up. Although independent predictors for re-bleeding were not found, physicians should recognize some important risk factors for re-bleeding (older age, chronic kidney disease, aortic stenosis, anticoagulants use and overt OGIB) and consider further endoscopic investigations if re-bleeding occurs.

Terminology

OGIB is defined as bleeding from the gastrointestinal tract that persists or recurs without an obvious source being discovered by esophagogastroduodenoscopy, colonoscopy and radiologic evaluation of the small-bowel. Small-bowel capsule endoscopy uses a wireless miniature (pill sized) encapsulated video camera designed to visualize the entire small-bowel.

Peer-review

In a retrospective analysis the authors evaluated the long-term re-bleeding events after a negative wireless capsule endoscopy in patients referred for obscure gastrointestinal bleeding. They found that patients with obscure gastrointestinal bleeding, despite a negative capsule endoscopy, during a 48 mo mo follow-up period have a significant re-bleeding rate (27.4%). They concluded that there are no reliable risk factors that can predict a future re-bleeding event in these patients. The topic is interesting and suitable for publication.

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ORIGINAL ARTICLE

Prospective Study

N-butyl-2-cyanoacrylate, iso-amyl-2-cyanoacrylate and hypertonic glucose with 72% chromated glycerin in gastric varices

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Data sharing: The technical appendix, statistical code, and dataset are available from the corresponding author at saratropical@yahoo.com. The participants gave informed consent for the data sharing.

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Abstract

AIM: To compare n-butyl-2-cyanoacrylate, iso-amyl-2-cyanoacrylate and a mixture of 72% chromated glycerin with hypertonic glucose solution in management of gastric varices.

METHODS: Ninety patients with gastric varices presented to Endoscopy Unit of Ain Shams University Hospital were included. They were randomly allocated into three groups; each group included 30 patients treated with intravariceal sclerosant injections in biweekly sessions till complete obturation of gastric varices; Group I (n-butyl-2-cyanoacrylate; Histoacryl®), Group II (iso-amyl-2-cyanoacrylate; Amcrylate®) and Group III (mixture of 72% chromated glycerin; Scleremo® with glucose solution 25%). All the procedures were performed electively without active bleeding. Recruited patients were followed up for 3 mo.

RESULTS: 26% of Scleremo group had bleeding during puncture *vs* 3.3% in each of the other two groups with significant difference, ($P < 0.05$). None of Scleremo group had needle obstruction *vs* 13.3% in each of the other two groups with no significant difference, ($P > 0.05$). Rebleeding occurred in 13.3% of Histoacryl and Amcrylate groups *vs* 0% in Scleremo group with no significant difference. The in hospital mortality was 6.6% in both Histoacryl and Amcrylate groups, while it was 0% in Scleremo group with no significant difference. In the first and second sessions, the amount of Scleremo needed for obturation was significantly high, while the

amount of Histoacryl was significantly low. Scleremo was the less costly of the two treatments.

CONCLUSION: All used sclerosant substances showed efficacy and success in management of gastric varices with no significant differences except in total amount, cost and bleeding during puncture.

Key words: Gastric varices; N-butyl-2-cyanoacrylate; Iso-amyl-2-cyanoacrylate; Hypertonic glucose solution; 72% chromated glycerin

Core tip: We compared n-butyl-2-cyanoacrylate (Histoacryl®), iso-amyl-2-cyanoacrylate (Amcrylate®) and a mixture of 72% chromated glycerin (Scleremo®) with hypertonic glucose solution (25%) in management of gastric varices. The study included 90 patients who were randomly allocated into three groups, and each group included 30 patients treated with sclerosant injections in biweekly sessions till complete obturation: Group Ⅰ (Histoacryl®), Group Ⅱ (Amcrylate®) and Group Ⅲ (Scleremo® with Glucose 25%). Patients were followed up for 3 mo. We concluded that all used sclerosants showed efficacy and success in management of gastric varices, without significant differences, except in total amount, cost and bleeding during puncture.

Elwakil R, Montasser MF, Abdelhakam SM, Ibrahim WA. N-butyl-2-cyanoacrylate, iso-amyl-2-cyanoacrylate and hypertonic glucose with 72% chromated glycerin in gastric varices. *World J Gastrointest Endosc* 2015; 7(4): 411-416 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i4/411.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i4.411

INTRODUCTION

Varices occur in approximately 50% of cirrhotic patients[1,2]. Gastric varices (GV) are less common than esophageal varices (EV), with a prevalence of approximately 20% in patients with portal hypertension[3], and about 15%-25% of GV bleed during the patient's lifetime[4,5].

The management of GV has not been well studied as that of EV. Both the evaluation and treatment of GV are still controversial[6,7].

Cyanoacrylates are synthetic glues that rapidly polymerize on contact with water or blood[8]. Injection therapy with cyanoacrylates is now considered to be the first-line endoscopic intervention for bleeding GV and for the secondary prevention of gastric variceal bleeding[9].

N-butyl-2-cyanoacrylate (Histoacryl®; Germany) has been used extensively in endoscopic therapy for the last 10 years. Another N-butyl-2-cyanoacrylate (Glubran®; Italy) was recently approved for endoscopic use in Europe[10].

Scleremo, a compound of 72% chromated glycerin, is a polyalcohol that is often considered to be a sclerosant chemical irritant, as it causes cell surface protein denaturation leading to thrombo-fibrosis[11]. The compound is commonly used in Europe, but it has not been approved by the FDA for use in the United States[12].

This work aimed at comparing n-butyl-2-cyanoacrylate (Histoacryl®), iso-amyl-2-cyanoacrylate (Amcrylate®) and a mixture of 72% chromated glycerin (Scleremo®) with a hypertonic glucose solution (25%) in the management of GV in Egyptian patients.

MATERIALS AND METHODS

Patients and methods

This prospective randomized study was conducted on ninety patients who presented with GV at the Endoscopy Unit of Ain Shams University Hospital. Patients with non-variceal causes of upper gastrointestinal bleeding and those with severe co-morbidities were excluded.

The patients were randomly allocated into three groups. Each group included 30 patients who were treated with sclerosant injections in biweekly sessions until the complete obturation of the GV was achieved, with follow-up of 3 mo: (1) Group Ⅰ (Histoacryl® Group); (2) Group Ⅱ (Amcrylate® Group); and (3) Group Ⅲ (Scleremo® with Glucose 25% Group).

The three groups were matched for age, gender, cause of liver cirrhosis (viral hepatitis B or C), Child score and endoscopic findings (including the number, grade of the EV and the size of GV).

All of the included patients underwent: (1) a complete clinical evaluation; (2) laboratory investigations: CBC, liver profile, viral markers (HBs Ag, HB core Ab, HCV Ab) using the ELISA technique; (3) child classification according to the modified Child Pugh's criteria[13]; (4) abdominal ultrasonography for liver and spleen size, portal vein diameter and ascites; (5) upper gastrointestinal endoscopy using the Pentax video endoscope EG 3440. The EV were classified according to their size at the gastroesophageal junction into 4 grades according to Westaby *et al*[14]; The GV were classified into either gastro-EV or isolated GV according to Sarin *et al*[15]; and (6) therapeutic interventions: The intravariceal injection technique was performed according to Soehendra *et al*[16].

The Histoacryl® was diluted as 0.5 mL histoacryl: 0.8 mL lipidol as a contrast agent to dilute the adhesive material to fill the entire varix and to prevent rapid hardening and the obstruction of the needle. The mixture was injected slowly to minimize the risk of embolization and was followed by the injection of 2 mL of distilled water. The first ml of water was injected to force the material into the varix, and the second ml was injected during the withdrawal of the needle to prevent its obstruction[8].

The Amcrylate® was injected slowly followed by injection of 2 mL distilled water without mixing with any other substances[17].

The Scleremo® was mixed with glucose 25% in a ratio of 1:1. The mixture was injected very slowly and with the waiting for moments inside the variceal lumen after injection to give enough time for the sclerosing material to be in contact with the vessel wall. There was no need for an injection of distilled water[11].

Informed consent was obtained from all of the included patients, and the study protocol was approved by the ethical guidelines committee.

All of the procedures were performed electively, without active bleeding. The patients who had bleeding that occurred immediately or after the procedure were treated with additional injections.

The primary end point of this study was the obturation of the GV. The secondary endpoint was the occurrence of bleeding, whether from the puncture site during or immediately after the injection or delayed bleeding (in-hospital or after discharge) and mortality.

Statistical analysis

The statistical review of the study was performed by a biomedical statistician.

The quantitative variables are presented as the mean and the SD. An unpaired (*t*) test was used for the comparisons.

The qualitative variables are presented as numbers and percentages. The χ^2 test was used for the comparisons.

A value of $P < 0.05$ was considered to be statistically significant (S), $P < 0.01$ was considered to be highly significant (HS), and $P > 0.05$ was considered to be non-significant (NS).

RESULTS

This study included 90 Egyptian patients with chronic liver disease. There were 58 males (64.4%, mean age: 50.88 ± 9.08 years) and 32 females (35.6%, mean age: 49.28 ± 8.11 years). A total of 74 patients (82.2%) had hepatitis C virus (HCV), 12 patients (13.3%) had hepatitis B virus (HBV), and 4 patients (4.4%) had both HCV and HBV. According to the Child-Pugh classification, 18 patients (20%) were class A, 36 patients (40%) were class B, and 36 patients (40%) were class C.

The recruited patients were randomly allocated into three groups that were matched for age, gender, cause of chronic liver disease, Child score and endoscopic findings. Each group included 30 patients who were treated with sclerosant injections in biweekly sessions until the complete obturation of GV was achieved. The groups consisted of Group Ⅰ (the Histoacryl® Group), Group Ⅱ (the Amcrylate® Group) and Group Ⅲ (the Scleremo® with glucose 25% Group).

There were non-significant ($P > 0.05$) differences among the 3 groups regarding previous bleeding or previous sclerotherapy for EVs (93.3%, 66.6% and 93.3%, for Groups Ⅰ, Ⅱ, and Ⅲ, respectively) as shown in Table 1.

Table 1 Previous bleeding and previous sclerotherapy for esophageal varices in the 3 groups *n* (%)

		Histoacryl	Amcrylate	Scleremo with glucose	χ^2	*P* value
Previous bleeding	None	2 (6.6)	10 (33.3)	2 (6.6)	11.6	> 0.05 (NS)
	Once	20 (66.6)	8 (26.6)	20 (66.6)		
	Twice	2 (6.6)	8 (26.6)	4 (13.3)		
	3 times	2 (6.6)	0 (0)	0 (0)		
	4 times	4 (13.3)	4 (13.3)	4 (13.3)		
Previous sclerotherapy for EV	None	2 (6.6)	10 (33.3)	2 (6.6)	16.5	> 0.05 (NS)
	Once	6 (20)	6 (20)	0 (0)		
	Twice	6 (20)	0 (0)	4 (13.3)		
	3 times	2 (6.6)	6 (20)	8 (26.6)		
	4 times	14 (46.6)	6 (20)	16 (53.3)		

EV: Esophageal varices; NS: Non-significant.

The endoscopic findings for the 3 studied groups are shown in Table 2. There were non-significant differences among the 3 groups for the location, the size of the GV and associated EV ($P > 0.05$).

Table 3 shows the non-significant differences among the 3 groups regarding the rate of the obturation of the GV ($P > 0.05$). In the first month, the rate of the obturation was 66.6%, 53.3% and 46.6%; in the second month, the rate of the obturation was 86.6%, 80% and 73.3% and in the third month, the rate of the obturation was 93.3%, 93.3% and 100% in the Histoacryl, Amcrylate and Scleremo groups, respectively.

Regarding the number of sessions needed for the obturation of the GV; in the Histoacryl group, 33.3% of the patients needed one session and 66.6% needed two sessions. In the Amcrylate group, 26.6% of the patients needed one session, 70% needed two sessions and 3.3% needed three sessions. In the Scleremo group, 20% of the patients needed one session, 66.6% needed two sessions and 13.3% needed three sessions.

The amount of the sclerosant used per session is shown in Table 4. In the first and second sessions, a significantly high amount of Scleremo was used compared with the Amcrylate and Histoacryl ($P < 0.05$). In the third session, there was insignificant differences among the amounts of the 3 sclerosant materials used ($P > 0.05$).

Regarding problems with the endoscopy, eight patients (26.6%) in the Scleremo group had bleeding of their GV during the puncture compared with one patient (3.3%) in each of the other two groups, with a significant difference ($P < 0.05$). None of the patients in the Scleremo group had needle obstructions during the injections compared with four patients (13.3%) in each of the other two groups, with non-significant differences ($P > 0.05$).

Table 2 Endoscopic findings among the 3 studied groups *n* (%)

		Histoacryl	Amcrylate	Scleremo with glucose	χ^2	*P* value
Site of GV	Fundal	24 (80)	22 (73.3)	18 (60)	1.514	> 0.05
	Cardiac	6 (20)	8 (26.6)	12 (40)		(NS)
Size of GV	L	10 (33.3)	12 (40)	8 (26.6)	2.68	> 0.05
	M	12 (40)	16 (53.3)	14 (46.6)		(NS)
	S	8 (26.6)	2 (6.6)	8 (26.6)		
Associated EV	No EV	2 (6.6)	6 (20)	0 (0)	7.85	> 0.05
	Grade II EV	10 (33.3)	4 (13.3)	6 (20)		(NS)
	Grade III EV	14 (46.6)	16 (53.3)	18 (60)		
	Grade IV EV	4 (13.3)	4 (13.3)	6 (20)		

GV: Gastric varices; EV: Esophageal varices; L: Large tortuous varices; M: Medium nodular varices; S: Small straight varices; NS: Non-significant.

Table 3 Outcomes of gastric varices for rates of obturation and number of sessions *n* (%)

		Histoacryl	Amcrylate	Scleremo with glucose	χ^2	*P* value
Obturation of varices	1st month	20 (66.6)	16 (53.3)	14 (46.6)	1.4	> 0.05
	2nd month	26 (86.6)	24 (80)	22 (73.3)		(NS)
	3rd month	28 (93.3)	28 (93.3)	30 (100)		
No. of sessions	One	10 (33.3)	8 (26.6)	6 (20)	2.5	> 0.05
	Two	20 (66.6)	21 (70)	20 (66.6)		(NS)
	Three	0 (0)	1 (3.3)	4 (13.3)		

GV: Gastric varices; NS: Non-significant.

Bleeding in the Scleremo group during the puncture was controlled by injecting more of the sclerosing mixture and leaving the needle in the puncture site for few minutes to allow time for the blood to clot and occlusion of the puncture to occur. In 2 of the cases in the Scleremo group (Child C) this maneuver failed to stop the bleeding, and an injection of Histoacryl was used to control the bleeding.

Rebleeding (within 5 d of the injection) occurred in 4 cases (13.3%) in both the Histoacryl and the Amcrylate groups, while no cases (0%) of rebleeding were recorded in the Scleremo group, with a non-significant difference ($P > 0.05$).

Two of the patients (6.6%) in each of the Histoacryl and Amcrylate groups died in the hospital 2 d after the injection (due to hepatic comas), while the mortality rate in the Scleremo group was 0%, with a non-significant difference ($P > 0.05$).

There were insignificant ($P > 0.05$) differences among the 3 groups in complications in the form of chest pain (6.6%, 6.6% and 13.3%) in the Histoacryl, Amcrylate and Scleremo groups, respectively, transient dysphagia (13.3%) in the Amcrylate group only, low grade fever in the Histoacryl group only (6.6%); and ulceration in both the Histoacryl and Amcrylate groups only (13.3% *vs* 6.6%).

Regarding the total cost of the sclerosant materials used in the current study, Scleremo was the least costly compared with the Histoacryl and Amcrylate, as shown in Table 5.

Table 4 Total amount of sclerosant used per session

	Histoacryl	Amcrylate	Scleremo with glucose	*P* value
1st session	42 cc	80 cc	126 cc	< 0.05 (S)
2nd session	20 cc	28 cc	74 cc	< 0.05 (S)
3rd session	0	2 cc	10 cc	> 0.05 (NS)

S: Significant; NS: Non-significant.

Table 5 Amount of sclerosants and their cost

	Histoacryl	Amcrylate	Scleremo with glucose
Amount of one ampoule	0.5 cc	0.5 cc	5.0 cc
Total used amount	62 cc	110 cc	210 cc
No. of all injected ampoules	124	220	42
Cost of one ampoule	88 EGP (14.6 USD)	44 EGP (7.3 USD)	15 EGP (2.5 USD)
Cost of all injected ampoules	10912 EGP (1809 USD)	9680 EGP (1605 USD)	630 EGP (104.5 USD)

EGP: Egyptian Pound; USD: United States Dollar.

DISCUSSION

In contrast to the treatment of EV, the endoscopic treatment of GV is still controversial[18]. Treatment options for GV that have been studied in prospective trials include injections of cyanoacrylate-based tissue adhesives, alcohol, sclerosants, and band ligation[3,4,19-21]. The results from this limited number of small studies had varying success rates and were uncontrolled, making it difficult to draw definitive conclusions about their efficacy or the superiority of one therapy over another[22].

The purpose of this prospective randomized study was to compare the efficacy of n-butyl-2-cyanoacrylate (Histoacryl)®, iso-amyl-2-cyanoacrylate (Amcrylate)® and a mixture of 72% chromated glycerin (Scleremo)® with a hypertonic glucose solution (25%) in the management of GV in Egyptian patients.

The present work shows the obturation of varices in all of the groups, with no significant differences ($P > 0.05$) after three months of follow-up. We observed that the obturation of the GV occurred sooner and with fewer sessions in both the Histoacryl and Amcrylate groups than in the Scleremo group. Similarly, it has been previously reported that glue injections had achieved variceal eradication in approximately 75% of patients (range: 50%-100%)[3].

In comparison with the other types of sclerosants that were used in previous studies, obliteration was achieved in only 32% of the sodium tetradecyl sulphate group and 81% of the hypertonic (50%) glucose water group ($P < 0.05$) in the study of Chang *et al*[7].

The Scleremo (72% chromated glycerin) was useful

primarily in the sclerosis of small vessels. Its principal advantage is that it rarely causes extravasation necrosis; its viscosity also allows maximum surface contact time and avoids the risk of an oily base causing the formation of an embolus. The main problems with Scleremo are that it is difficult to work with because it is extremely viscous, that it can be quite painful on injection, and that the chromate moiety is highly allergic[12].

To our knowledge, there is no previous Egyptian study that addresses the efficacy of Scleremo in the management of GV. In the current study, Scleremo with glucose 25% was characterized as being more economical, with a clean and smooth endoscopic field of vision and fewer side effects. However, bleeding from the puncture site, specific dealing during the injection, its high amount and number of sessions required and a delay in the obturation of the varices were its disadvantages.

El-Wakil[11] investigated the efficacy of Scleremo in the management of bleeding EV and demonstrated that the rate of the eradication of EV in the Scleremo group was 75% in comparison with 60% in the Ethanolamine Oleate group.

In the present study, none of the patients in the Scleremo group had needle obstruction during the injection in comparison with four patients (13.3%) in each of the other two groups, with a non-significant difference ($P > 0.05$). Chang *et al*[7] reported the frequent obstruction of the injection needle when using Histoacryl during the treatment of active gastric variceal bleeding, although it achieved a nearly 100% success rate for the initial hemostasis.

In the current study, rebleeding occurred in 4 cases (13.3%) in both the Histoacryl and Amcrylate groups, while no cases (0%) were recorded in the Scleremo group, with an insignificant difference. Previous studies of glue injections for GV have shown a rebleeding rate ranging from 23%-50%[3,21].

In the current study, the mortality rate was (6.6%) in both the Histoacryl and the Amcrylate group compared with 0% in the Scleremo group, with a non-significant difference.

El-Wakil[11] reported that the mortality rate was 5% in the Ethanoleamine Oleate group, while no fatalities were reported in the Scleremo group during the management of bleeding EV.

Kind *et al*[23] treated 174 cirrhotic patients who had actively bleeding GV with cyanoacrylate and then by weekly sessions until their varices were eradicated. The hemostasis, early rebleeding and hospital mortality rates after the cyanoacrylate treatment were 97.1%, 15.5% and 19.5%, respectively. In approximately 75% of the patients, the GV were successfully obliterated.

In the present work, all of the groups reported some minor complications, with non-significant differences among them, in the form of chest pain (6.6%, 6.6% and 13.3%) for the Histoacryl, Amcrylate and Scleremo groups, respectively, transient dysphagia in the Amcrylate group only (13.3%), low grade fever in the Histoacryl group only (6.6%) and ulceration in both the Histoacryl and Amcrylate groups only (13.3% *vs* 6.6%).

It has been previously reported by Ljubicic *et al*[24] that fever, retrosternal discomfort and dysphagia frequently occur with Histoacryl injections and usually resolve within 48 h.

In the study of El-Wakil[11], the Scleremo showed fewer complications than Ethanoleamine Oleate in the form of chest pain (15% *vs* 40%), transient dysphagia (15% *vs* 40%) and low grade fever (5% *vs* 20%). A large post-sclerotherapy ulcer occurred in (10%) of patients in the Ethanolamine Oleate group, while no ulcers were reported in the Scleremo group.

All of the sclerosant substances that we used (Histoacryl, Amcrylate and Scleremo with glucose 25%) showed both efficacy and success in the management of GV, with no significant differences among them except in the total amount required, their cost and incidences of bleeding during the puncture; however, they did vary in their superiority in some aspects.

ACKNOWLEDGMENTS

The authors gratefully acknowledge all of their colleagues for their contributions.

COMMENTS

Background

The endoscopic treatment of gastric varices (GV) is still a matter of debate. Treatment options for GV that have been studied in prospective trials include the injection of cyanoacrylate-based tissue adhesives, alcohol and sclerosants. The results from this limited number of small studies had varying success rates and were uncontrolled, making it difficult to draw definitive conclusions about their efficacy or the superiority of one therapy over another.

Research frontiers

Cyanoacrylates are synthetic glues that rapidly polymerize on contact with water or blood. Scleremo, a compound of 72% chromated glycerin, is a polyalcohol that is considered to be a chemical irritant sclerosant that causes cell surface protein denaturation leading to thrombo-fibrosis. The authors compared n-butyl-2-cyanoacrylate (Histoacryl®), iso-amyl-2-cyanoacrylate (Amcrylate®) and a mixture of 72% chromated glycerin (Scleremo®) with hypertonic glucose solution (25%) in the management of GV. All of the sclerosants showed efficacy and success in the management of GV; they differ in the total amount required, cost and the occurrence of bleeding during the puncture.

Innovations and breakthroughs

This is the first Egyptian study that addresses the efficacy of Scleremo® in the management of GV; it is characterized as being economical and clean, with a smooth endoscopic field of vision and few side effects.

Applications

This study may represent a future strategy for the use of a mixture of 72% chromated glycerin (Scleremo®) with a hypertonic glucose solution (25%) in the management of GV.

Terminology

Variceal obturation employs the injection of sclerosant substances leading to the plugging and thrombosis of the varices and an immediate cast of the vessel, followed by the consequent sloughing of the cast after 1-2 wk.

Peer-review

This is a well-researched and well-written article that will be of interest to the readers and will add to the literature on the management of this condition. The endoscopic treatment of GV is still a matter of debate, and controversy exists

on their evaluation and possible pharmacologic and endoscopic treatment. Additionally, Scleremo appears to be the least costly alternative.

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META-ANALYSIS

Impact of formal training in endoscopic submucosal dissection for early gastrointestinal cancer: A systematic review and a meta-analysis

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Author contributions: All authors contributed to this work.
Conflict-of-interest: All authors declare non conflict-of-interest.
Data sharing: No additional data are available.

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Abstract

AIM: To summarize the clinical impact of a formal training for the effectiveness and safety of endoscopic submucosal dissection for gastrointestinal cancer.

METHODS: We searched databases including PubMed, EMBASE and the Cochrane Library and Science citation Index updated to August 2014 to include eligible articles. In the Meta-analysis, the main outcome measurements were *en bloc* resection rate, local recurrence rate (R0) and the incidence of procedure-related complications (perforation, bleeding).

RESULTS: *En bloc* resection was high for both, dissecting stomach tumors with an overall percentage of 93.2% (95%CI: 90.5-95.8) and dissecting colorectal tumors with an overall percentage of 89.4% (95%CI: 85.1-93.7). Although the number of studies reporting R0 resection (the dissected specimen was revealed free of tumor in both vertical and lateral margins) was small, the overall estimates for R0 resection were 81.4% (95%CI: 72-90.8) for stomach and 85.9% (95%CI: 77.5-95.5) for colorectal tumors, respectively. The analysis showed that the percentage of immediate perforation and bleeding were very low; 4.96 (95%CI: 3.6-6.3) and 1.4% (95%CI: 0.8-1.9) for colorectal tumors and 3.1% (95%CI: 2.0-4.1) and 4.8% (95%CI: 2.8-6.7) for stomach tumors, respectively.

CONCLUSION: In order to obtain the same rate of success of the analyzed studies it is a necessity to create training centers in the western countries during the "several years" of gastroenterology residence first only to teach EGC diagnose and second only to train endoscopic submucosal dissection.

Key words: Endoscopic submucosal dissection; Training

Core tip: Endoscopic submucosal dissection (ESD) has gained widespread use in Asia because of a well-

documented higher *en bloc* and curative resection rates for early neoplastic gastrointestinal lesions. Unfortunately, ESD has not been yet widespread in the West due to remain the very flat learning curve and lack of training resources. In Asia, ESD skills are acquired in the time-honored mentor/apprentice model over a period of few years. Although, there is a great heterogeneity in the medical literature reports about training and learning curve of ESD. In this meta analysis we had analyzed the results from these training centers reports. Because technical maturation often requires measurable standard to achieve.

Tanimoto MA, Guerrero ML, Morita Y, Aguirre-Valadez J, Gomez E, Moctezuma-Velazquez C, Estradas-Trujillo JA, Valdovinos MA, Uscanga LF, Fujita R. Impact of formal training in endoscopic submucosal dissection for early gastrointestinal cancer: A systematic review and a meta-analysis. *World J Gastrointest Endosc* 2015; 7(4): 417-428 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i4/417.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i4.417

INTRODUCTION

There are few training centers around the world in which an endoscopy fellow can be trained in the ESD technique. There is probably only a formal ESD training program in Asian countries (Japan, South Korea and China). As ESD is a highly technical and demanding minimal invasive procedure, endoscopists require training before performing the procedure. The operator must possess a good understanding of all aspects of ESD: full knowledge of early GI lesions, the endoscopes, EUS, ESD knives, electro surgical unit parameters, injection agents, sedation, complications and other aspects.

In Asian countries like Japan, South Korea and China, gastrointestinal intraepithelial neoplasm is more prevalent than in Western countries. Accordingly, most medical institutions in Japan provide training (in a stepwise manner): initially, endoscopists participate as an assistant, starting with ESD in the gastric antrum or the rectum with a supervisor, then in the proximal stomach, the colon or the esophagus. In contrast, in Western countries, cases of early gastrointestinal lesions are less diagnosed, resulting in a slow introduction of the ESD technique. Efforts are currently underway to change this situation. Possible solutions to improve training and experience are the use of animal models and the establishment of training centers. Further, deficiencies in training and experience can now be more rapidly overcome as a result of new technologies. As described above, new advances have led to devices that are easy to handle, making it simpler for beginners to perform ESD. Devices with scissors and forceps, like the Clutch Cutter or other covered devices, are easier to use, leading to fewer complications (*e.g*., perforation), although the procedure time is longer than those with non-covered devices. The other new approach in ESD, the use of mesna (2-mercaptoethanesulfonate sodium), may also make submucosal dissection safer and faster.

MATERIALS AND METHODS

Data sources and searches

We searched databases including PubMed, EMBASE and the Cochrane Library and Science citation Index updated to August 2014 to identify related articles in English language that review Endoscopic submucosal dissection training[1-121]. All bibliographies were indentified in the reference lists and were analyzed separately by two experts in ESD during the selection process. The initial searching Medical Subject Headings *(MeSH)* used were "Endoscopic submucosal dissection", afterwards "Endoscopic submucosal dissection training" and finally the articles that does not analyze the operation time, *en bloc* resection rate, local recurrence rate and the incidence of procedure-related complications were excluded (Figure 1A).

Study selection

The inclusion and exclusion criteria are shown in Table 1.

Data extraction and quality assessment

Data were extracted with a predefined MeSH criteria by one investigator and confirmed by the others according to a data extraction form. The following data were collected: year of publication, first author, country, number of participants, site of the lesions and lesions in each group, tumor size and endpoints (*en bloc* resection rate, local recurrence rate, and complications). The definitions of the endpoints were: (1) site of resection; (2) *en bloc* -removal in one piece without fragmentation; (3) local recurrencte rate - during the follow-up an histological diagnosis of tumor at the resected site; (4) operation time - from marking to complete resection; and (5) rate of complications - related bleeding or perforation incidence.

Statistical analysis

Meta-analysis: The statistical review of the study was performed by a biomedical statician of the Infectology department from the National Institute of Medical Sciences and Nutrition S.Z. (Mexico). The DerSimonian/Laird random effects model was used due to expected heterogeneity among studies. Statistical heterogeneity was assessed using the Higgins I^2 test. For the Higgins test, I^2 < 25% indicates low heterogeneity, 25%-50% moderate and > 50% severe heterogeneity. Preplanned analyses included analyses limited to studies including resection of stomach tumors and colorectal tumors using endoscopic submucosal dissection. Data quality assurance and data analysis were conducted using Stata™ 12.0

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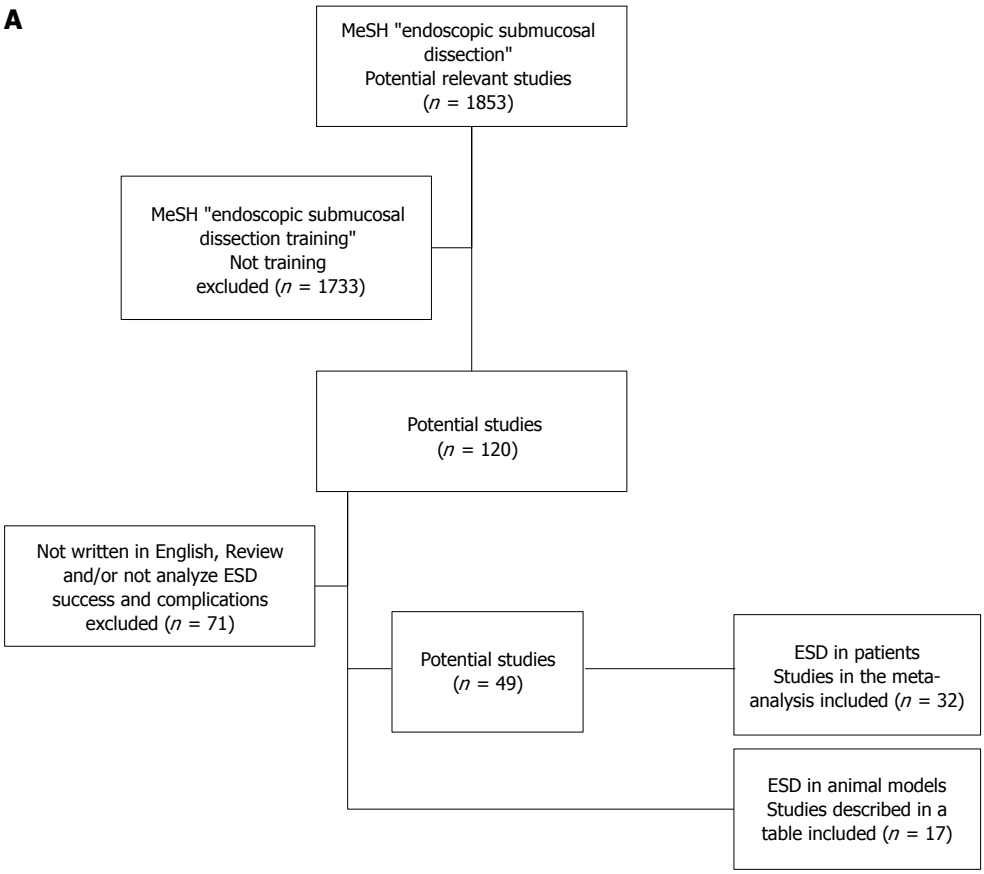

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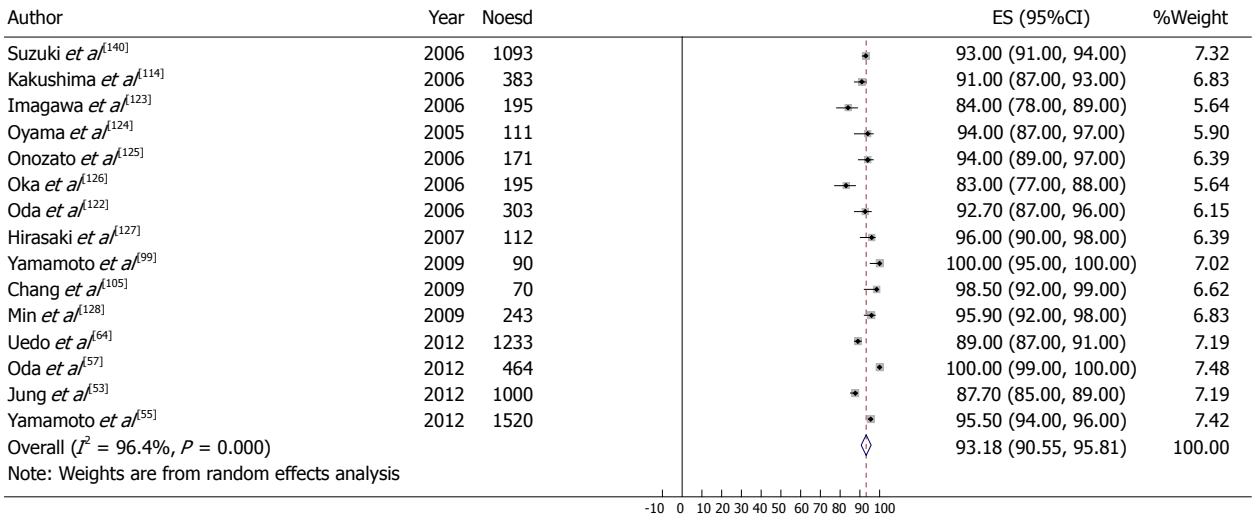
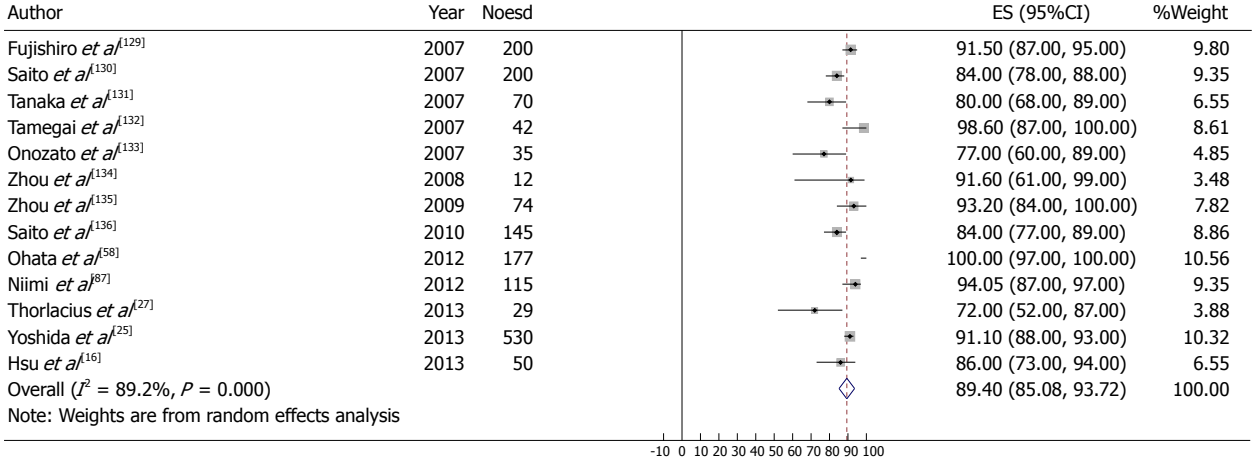


Author	Year	Noesd	ES (95%CI)	%Weight
Suzuki *et al*[140]	2006	1093	93.00 (91.00, 94.00)	7.32
Kakushima *et al*[114]	2006	383	91.00 (87.00, 93.00)	6.83
Imagawa *et al*[123]	2006	195	84.00 (78.00, 89.00)	5.64
Oyama *et al*[124]	2005	111	94.00 (87.00, 97.00)	5.90
Onozato *et al*[125]	2006	171	94.00 (89.00, 97.00)	6.39
Oka *et al*[126]	2006	195	83.00 (77.00, 88.00)	5.64
Oda *et al*[122]	2006	303	92.70 (87.00, 96.00)	6.15
Hirasaki *et al*[127]	2007	112	96.00 (90.00, 98.00)	6.39
Yamamoto *et al*[99]	2009	90	100.00 (95.00, 100.00)	7.02
Chang *et al*[105]	2009	70	98.50 (92.00, 99.00)	6.62
Min *et al*[128]	2009	243	95.90 (92.00, 98.00)	6.83
Uedo *et al*[64]	2012	1233	89.00 (87.00, 91.00)	7.19
Oda *et al*[57]	2012	464	100.00 (99.00, 100.00)	7.48
Jung *et al*[53]	2012	1000	87.70 (85.00, 89.00)	7.19
Yamamoto *et al*[55]	2012	1520	95.50 (94.00, 96.00)	7.42
Overall (I^2 = 96.4%, P = 0.000)			93.18 (90.55, 95.81)	100.00
Note: Weights are from random effects analysis				

C

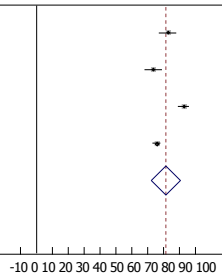


Author	Year	Noesd	ES (95%CI)	%Weight
Fujishiro *et al*[129]	2007	200	91.50 (87.00, 95.00)	9.80
Saito *et al*[130]	2007	200	84.00 (78.00, 88.00)	9.35
Tanaka *et al*[131]	2007	70	80.00 (68.00, 89.00)	6.55
Tamegai *et al*[132]	2007	42	98.60 (87.00, 100.00)	8.61
Onozato *et al*[133]	2007	35	77.00 (60.00, 89.00)	4.85
Zhou *et al*[134]	2008	12	91.60 (61.00, 99.00)	3.48
Zhou *et al*[135]	2009	74	93.20 (84.00, 100.00)	7.82
Saito *et al*[136]	2010	145	84.00 (77.00, 89.00)	8.86
Ohata *et al*[58]	2012	177	100.00 (97.00, 100.00)	10.56
Niimi *et al*[87]	2012	115	94.05 (87.00, 97.00)	9.35
Thorlacius *et al*[27]	2013	29	72.00 (52.00, 87.00)	3.88
Yoshida *et al*[25]	2013	530	91.10 (88.00, 93.00)	10.32
Hsu *et al*[16]	2013	50	86.00 (73.00, 94.00)	6.55
Overall (I^2 = 89.2%, P = 0.000)			89.40 (85.08, 93.72)	100.00
Note: Weights are from random effects analysis				

D

Author	Year	Noesd	ES (95%CI)	%Weight
Oka *et al*[126]	2006	195	83.00 (77.00, 88.00)	24.25
Oda *et al*[122]	2006	303	73.60 (68.00, 79.00)	24.25
Min *et al*[128]	2009	243	93.00 (89.00, 96.00)	25.52
Uedo *et al*[64]	2012	1233	76.00 (73.00, 78.00)	25.97
Overall (I^2 = 95.6%, P = 0.000)			81.45 (72.08, 90.83)	100.00

Note: Weights are from random effects analysis



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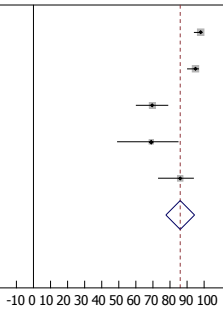
Author	Year	Noesd	ES (95%CI)	%Weight
Saito *et al*[136]	2010	145	98.00 (94.00, 99.00)	25.24
Ohata *et al*[58]	2012	177	94.95 (90.00, 97.00)	24.73
Niimi *et al*[87]	2012	115	69.55 (60.00, 79.00)	19.53
Thorlacius *et al*[27]	2013	29	69.00 (49.00, 85.00)	11.98
Hsu *et al*[16]	2013	50	86.00 (73.00, 94.00)	18.53
Overall (I^2 = 90.9%, P = 0.000)			85.99 (77.48, 94.50)	100.00

Note: Weights are from random effects analysis



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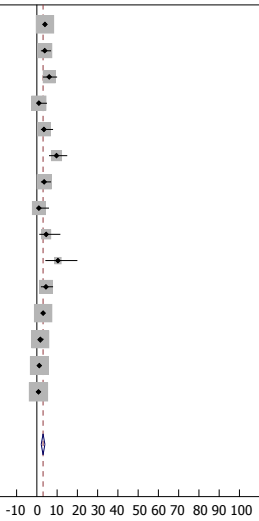
Author	Year	Noesd	ES (95%CI)	%Weight
Suzuki *et al*[140]	2006	1093	4.00 (3.00, 5.00)	9.99
Kakushima *et al*[114]	2006	383	3.90 (2.00, 7.00)	6.61
Imagawa *et al*[123]	2006	195	6.10 (3.00, 10.00)	4.76
Oyama *et al*[124]	2005	111	1.00 (0.02, 5.00)	6.63
Onozato *et al*[125]	2006	171	3.50 (2.00, 8.00)	5.61
Oka *et al*[126]	2006	195	9.70 (6.00, 15.00)	3.47
Oda *et al*[122]	2006	303	3.60 (2.00, 7.00)	6.61
Hirasaki *et al*[127]	2007	112	1.00 (0.02, 6.00)	5.63
Yamamoto *et al*[99]	2009	90	4.60 (1.20, 11.60)	2.82
Chang *et al*[105]	2009	70	10.40 (4.20, 20.00)	1.43
Min *et al*[128]	2009	243	4.50 (2.00, 8.00)	5.61
Uedo *et al*[64]	2012	1233	3.10 (2.00, 4.00)	9.99
Oda *et al*[57]	2012	464	1.74 (0.70, 3.30)	9.36
Jung *et al*[53]	2012	1000	1.20 (0.60, 2.10)	10.44
Yamamoto *et al*[55]	2012	1520	0.80 (0.60, 0.90)	11.05
Overall (I^2 = 86.9%, P = 0.000)			3.06 (2.05, 4.07)	100.00

Note: Weights are from random effects analysis



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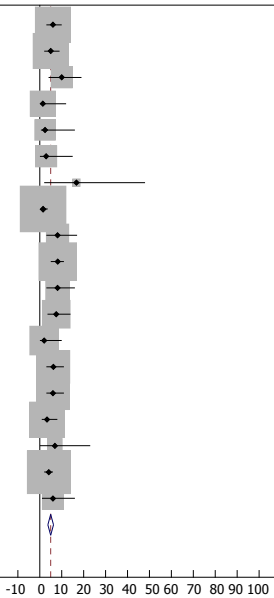
Author	Year	Noesd	ES (95%CI)	%Weight
Fujishiro *et al*[129]	2007	200	6.00 (3.00, 10.00)	7.47
Saito *et al*[130]	2007	200	5.00 (2.00, 9.00)	7.47
Tanaka *et al*[131]	2007	70	10.00 (4.00, 19.00)	2.73
Tamegai *et al*[132]	2007	42	1.40 (0.06, 12.00)	3.88
Hurlstone *et al*[137]	2007	42	2.40 (0.50, 16.00)	2.59
Onozato *et al*[133]	2007	35	2.90 (0.07, 15.00)	2.75
Zhou *et al*[134]	2008	12	16.70 (2.00, 48.00)	0.35
Toyonaga *et al*[80]	2010	468	1.50 (0.80, 3.60)	12.57
Zhou *et al*[135]	2009	74	8.10 (3.00, 17.00)	3.05
Isomoto *et al*[138]	2009	292	8.20 (5.00, 11.00)	8.57
Zhou *et al*[135]	2009	74	8.10 (3.00, 16.00)	3.42
Yoshida *et al*[95]	2010	119	7.50 (3.50, 14.00)	4.66
Takeuchi *et al*[139]	2010	50	2.00 (0.05, 10.00)	5.00
Saito *et al*[136]	2010	145	6.20 (3.00, 11.00)	6.51
Ohata *et al*[58]	2012	177	6.00 (3.00, 11.00)	6.51
Niimi *et al*[87]	2012	115	3.30 (0.90, 8.00)	7.37
Thorlacius *et al*[27]	2013	29	6.90 (0.08, 23.00)	1.31
Yoshida *et al*[25]	2013	530	4.10 (2.00, 6.00)	11.07
Hsu *et al*[16]	2013	50	6.00 (1.00, 16.00)	2.73
Overall (I^2 = 46.9%, P = 0.013)			4.96 (3.58, 6.33)	100.00

Note: Weights are from random effects analysis



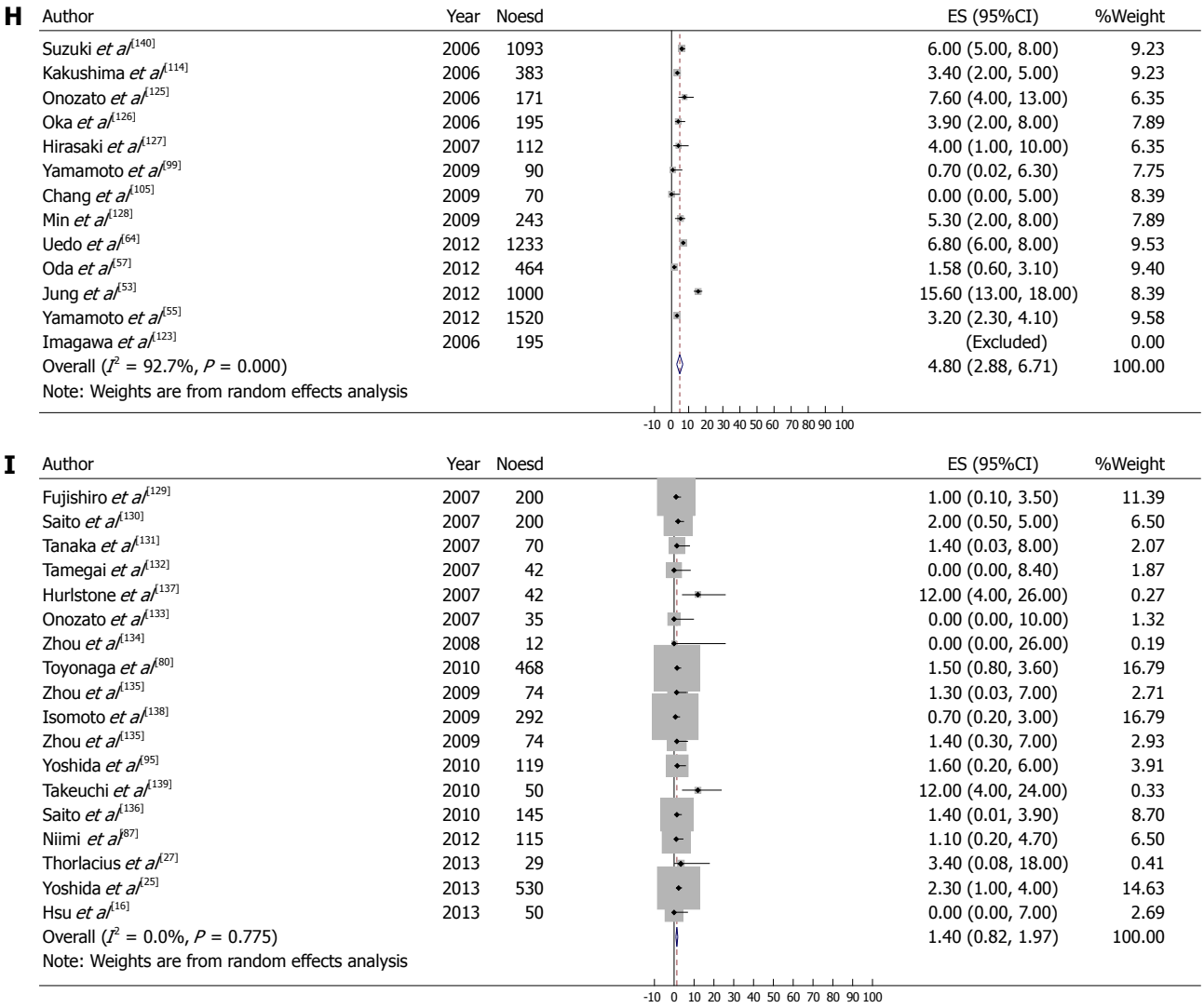


Figure 1 Flow diagram of trial selection and *en-bloc* resection percentage %. A: Flow diagram of trial selection; B: Stomach ESD: *En-bloc* resection percentage %; C: Colorectal ESD: *En-bloc* resection percentage %; D: Stomach ESD: Local recurrence (R0) rate %; E: Colorectal ESD: Local recurrence (R0) rate %; F: Stomach ESD: Perforation rate %; G: Colorectal ESD: Perforation rate %; H: Stomach ESD: Bleeding rate %; I: Colorectal ESD: Bleeding rate %. MeSH: Medical Subject Heading; ESD: Endoscopic submucosal dissection.

(Statistics/Data analysis Special Edition; Statacorp, College Station, Texas, United States). All statistical test in the analysis were two-sided and were conducted with α = 0.05 (95%CI).

RESULTS

Study selection

A total of 1853 were retrieved with the MeSH "endoscopic submucosal dissection" to estimate the potential studies for the meta-analysis. Afterwards, we refine the search including the word training with the MeSH "endoscopic submucosal dissection training" and 1733 were excluded. In the remaining 120 potential studies 71 were excluded because of the exclusion criteria in Table 1[1-12,14-16,18-28,30-33,35-40,42-50,52-62,64-82,95-114].

From the 49 remaining studies 32 were included in the meta-analysis. All of these 32 studies were in human patients respective case/control studies, not randomized controlled trials.

En bloc resection rate (Figures 1B and C)

The present analysis shows that the percentage of *en bloc* resection was high for both, dissecting stomach tumors with an overall percentage of 93.2% (95%CI: 90.5-95.8) and dissecting colorectal tumors with an overall percentage of 89.4% (95%CI: 85.1-93.7).

Local recurrence rate (Figures 1D and E)

Although the number of studies reporting R0 resection (the dissected specimen was revealed free of tumor in both vertical and lateral margins) was small, the overall estimates for R0 resection were 81.4% (95%CI: 72-90.8) and 85.9% (95%CI: 77.5-95.5) for stomach and colorectal tumors, respectively.

Procedure-related complications

Data for procedure-related complications were

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
ESD in patients	Case report
Report ESD success *en bloc* resection rate, local recurrence rate	Comment
(R0) and the incidence of procedure-related complications	Review
(perforation, bleeding)	Letters to editor
Written in English	Insufficient data
	Guidelines

ESD: Endoscopic submucosal dissection.

reported in all of the studies included in the meta-analysis. The analysis showed that the percentage of immediate perforation and bleeding were very low.

Perforation rate (Figures 1F and G)

The perforation rate was 3.1% (95%CI: 2.0-4.1) for stomach tumors and 4.96 (95%CI: 3.6-6.3) for colorectal tumors. In most studies, late perforation and bleeding was not reported and thus not included in the current analysis.

Bleeding rate (Figures 1H and I)

The bleeding rate was 4.8% (95%CI: 2.8-6.7) for stomach tumors and 1.4% (95%CI: 0.8-1.9) for colorectal tumors.

Finally, the last 17 studies were in animal models and even though they were not included in the meta-analysis, we resume them in a table that contains: author, year, type of animal model, number of patients, organ and main conclusion (Table 2)[13,17,29,34,41,51,63,83,94,96,115-121].

DISCUSSION

To our knowledge, this systematic review and meta-analysis is the first to analyze the impact of a formal training in ESD for early gastrointestinal cancer. Probably there are ESD formal training centers only in the Asian countries (Japan, China and South Korea). For the above reason almost 100% of the analyzed studies were from Asia. All the studies included in our analysis were done in a formal ESD training setting although most of them does not include the number of trainees and/or a comparison between preceptees *vs* experts and thus not included in the current analysis. The present study shows that the percentage of *en bloc* resection was high for both, dissecting stomach and colorectal tumors. Even with a small number of studies reporting R0 resection (the dissected specimen was revealed free of tumor in both vertical and lateral margins), the overall estimates for R0 resection were 81.4% (95%CI: 72-90.8) and 85.9% (95%CI: 77.5-95.5) for stomach and colorectal tumors respectively. The analysis also showed that the percentage of immediate perforation and bleeding were very low. ESD was developed in Japan in the year 1999 to preserve intact gastrointestinal function and for *en bloc* resection of lesions larger than 2 cm. ESD also has made it possible to resects early gastrointestinal tumors even with large submucosal fibrosis or ulcerative scars in an *en bloc* fashion and it has gradually gained acceptance as a standard treatment for these tumors. The ESD era began with pioneers trained in Japan on South Korea (2003-now) and in China (2006-now) rapidly gaining expertise and acceptance. Hotta *et al*[77] reported that 80 procedures must be carried out to acquire skill at ESD. In order to acquire this skill all the procedures even in animal models must be carried out under supervision of ESD experts and with availability of all the equipment and high trained team. Because this is not just a fact of endoscopic skills but of knowledge, technology and team work. This procedure should never be trained in an experimental ("not supervised by an ESD expert") fashion with animal models just focusing on the dissection technique without firstly make a good analysis of the borders and deepness of the early gastrointestinal cancer (EGC) lesion invasion under an expert supervision. Probably the lack of research, diagnose and case series of early gastrointestinal cancer lesions in the Western countries are due to a lack of formal training centers firstly with certified EGC experts and afterwards ESD experts. In order to obtain the same rate of success of the analyzed studies it is a necessity to create training centers in the western countries during the "several years" of gastroenterology residence first only to teach EGC diagnose and second only to train ESD. In the same manner that the medical techniques should never anticipate the clinic, nor the endoscopic skills, nor the technology or both could substitute tutorial training by an expert.

Although, there is a great heterogeneity in the medical literature reports about training and learning curve of ESD. In this meta analysis we had analyzed the results only from the formal training centers reports. The results presented in the literature that can be included in our meta analysis to clarify the training efficacy concerning the procedure length, completeness and complications such as *En bloc* resection rate, Local recurrence rate, Procedure-related complications, Perforation and Bleeding rate were included. But unfortunately, we can only assume that the procedure was done in a formal training center, such as the one in which some of the authors had been trained. Even when there are very detailed description of the learning curve specially in the Japanese and European reports there is a great heterogeneity of the numeric information presented and thus cannot be included in a meta analysis. There is not uniform information if the procedure was done by a trainee with/without supervision. Also, the analyzed issues in each report has great heterogeneity

Table 2 Endoscopic submucosal dissection studies in animal models

Ref.	Year	Model	*n*	Organ	Main conclusion
González *et al*[17]	2013	Porcine	30	Stomach	A sequential ESD training program of a unique endoscopist contributed to learning ESD for its subsequent application in humans, yielding good results in efficacy and safety
Takizawa *et al*[13]	2013	Porcine	30	Colon	Large mucosal target sites in the rectum and distal colon could be safely removed *en bloc* by means of a hybrid technique, SEMR, with blunt submucosal balloon dissection
Moss *et al*[115]	2012	Porcine	10	Colon	HK-ESD with SG submucosal injection is superior to CSI-EMR for *en bloc* excision of 50 mm diameter lesions. The technique is rapidly learn
Gostout *et al*[41]	2012	Porcine	16	Rectum and colon	Large mucosal target sites in the rectum and distal colon can be safely removed *en bloc* by means of a hybrid technique, ie, submucosal endoscopy with mucosal resection, combining elements of ESD with our SEMF method
Kumano *et al*[117]	2012	Porcine	24	Esophagus	PCH permits more reliable ESD of the esophagus without complications than do SH and HS
Balogh *et al*[51]	2012	Porcine	15	Esophagus	Training in live pig models could help endoscopists to overcome the learning curve and minimize the risk of complications before starting the procedure in humans Reduction in the resection time and low risk of complications, especially bleeding, could be achieved by the application of a flush knife
Tanaka *et al*[63]	2012	Porcine *ex vivo*	10	stomach	*Ex vivo* training model was helpful to endoscopists with experience in gastric ESD in acquiring the basic skills for performing esophageal ESD
Parra-Blanco *et al*[29]	2011	Porcine	18	Stomach	A Clip-band traction technique is feasible, safe, effective, and relatively inexpensive gastric ESD
Von Renteln *et al*[118]	2011	Porcine	12	Stomach	Submucosal mesna injection did not affect ESD procedure times but was associated with a trend toward a lower incidence of intraprocedural bleeding
Tanimoto *et al*[94]	2011	Canine	10	Esophagus	ECE-ESD training is feasible in canine models for postgraduate endoscopy fellows
Hon *et al*[96]	2010	Porcine	10	Colon	Technical proficiency improved by repetition. This setup may be a promising training model for endoscopists working in areas with a low incidence of early gastric cancer
Von Renteln *et al*[119]	2010	Porcine	12	Stomach	The flexible Maryland dissector was demonstrated to be efficient, safe, and feasible for facilitating gastric ESD
Parra-Blanco *et al*[34]	2010	Porcine	30	Esophagus stomach	Training in animal models could help endoscopists overcome the learning curve before starting ESD in humans
Moss *et al*[116]	2010	Porcine	10	Colon	CSI-EMR with submucosal injection of succinylated gelatin is safe and superior to conventional EMR.With experience, total procedure duration is comparable
Von Delius *et al*[120]	2008	Porcine	10	Stomach	PMT-ESD is feasible and safe. With the use of PA-ES, mucosal pieces of various sizes can be resected *en bloc* in gastric locations that are difficult to access by flexible endoscopy alone
Yamasaki *et al*[121]	2006	Porcine	2	Stomach	ESD by submucosal injection of viscous SCMC solution appeared to be an easy, safe, and technically efficient method for dissection of gastric lesions
Neuhaus *et al*[83]	2006	Porcine	17	Stomach	The R-scope (double channel endoscope) facilitated ESD of large gastric areas. Procedure is technically demanding and time-consuming, with a high risk of perforation may be related to an insufficient volume of solution being injected submucosally

HK: Hybrid knife; ESD: Endoscopic submucosal dissection; CSI-EMR: Circumferential submucosal incision endoscopic mucosal resection; SEMF: Mucosal safety valve flap; HS: Hypertonic saline solution; PCH: Photocrosslinkable chitosan hydrogel; SFC: Submucosal fluid cushion; SH: Sodium hyaluronate; ECE: *En bloc* circumferential esophageal; PA-ES: Percutaneously assisted endoscopic surgery; PMT-ESD: PEG-minitrocar ESD; SCMC: Sodium carboxymethylcellulose.

(animal model, human, periods of time, *etc.*) and the results are presented for example in ranges but not in mean ± SD. Because technical maturation often requires measurable standard to achieve. As this procedure become more standardized in the Western countries we can also be able to make more precise comparisons between training centers and learning curve. There are no shortcuts and probably we have to find out the way to establish training centers with the same training scheme as the Asian countries if we are expecting to have similar rates of success, but as always time will say.

COMMENTS

Background

Endoscopic submucosal dissection (ESD) was originally developed to preserve intact gastrointestinal function after *en bloc* resection of early GI cancer lesions larger than 2 cm.

Research frontiers

This systematic review and meta-analysis is the first to analyze the impact of a formal training in ESD for early gastrointestinal cancer.

Innovations and breakthroughs

Authors designed the meta-analysis to systematically evaluate the ESD formal training impact in the early gastrointestinal cancer regarding *en bloc* resection rate, local recurrence rate and procedure-related complications rate.

Applications

The conclusions of this meta-analysis can help the endoscopists to select the right tool to treat early gastrointestinal cancer lesions.

Terminology

ESD is a newly developed technique in which submucosal dissection is carried out using an electrocautery knife to acquire a single-piece specimen, it is developed for *en bloc* removal of large (> 2 cm) GI tract lesions.

Peer-review

This paper is intereting and valuable because technical maturation often requires measurable standard to achieve.

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CASE REPORT

Bowel perforation due to break and distal passage of the safety ring of an adjustable intra-gastric balloon: A potentially life threatening situation

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Laeeque A Qureshi, King Abdullah Medical City, Makkah 24246, Saudi Arabia
Author contributions: Al-Zubaidi AM placed and removed the balloon, the MRP who responsible for case and wrote the case report; Alghamdi HU did the laparotomy; Alzobydi AH participated in the laparotomy; Dhiloon IA done the case; Qureshi LA was peer reviewer.
Ethics approval: The case approved by the Hospital Board Ethical Committee.
Informed consent: Informed consent was taken from the patient.
Conflict-of-interest: The authors have no commercial associations that might be a conflict of interest in relation to this article.

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Abstract

A 45-year-old man of Middle Eastern origin, morbid obese, with a body mass index of 39 had an intra-gastric balloon, filled with 500 mL of saline/methylene blue and intended as definite therapy, inserted some 8 wk previously. He was admitted to the emergency department with abdominal cramps. An ultrasound of the abdomen was performed in ER which confirmed the balloon to be in place without any abnormality. He was discharged home on symptomatic medication. Patient remains symptomatic therefore he reported back to ER 2 d later. Computed tomography scan was performed this time for further evaluation which revealed a metallic ring present in the small bowel while the intra-gastric balloon was in its proper position. There was no clinical or radiological sign of intestinal obstruction. Patient was hospitalized for observation and conservative management. The following night, patient experienced sudden and severe abdominal pain, therefore an X-ray of the abdomen in erect position was done, which showed free air under the right dome of diaphragm. Patient was transferred to O.R for emergency laparotomy. There were two small perforations identified at the site of the metallic ring entrapment. The ring was removed and the perforations were repaired. Due to increasing prevalence of obesity and advances in modalities for its management, physicians should be aware of treatment options, their benefits, complications and clinical presentation of the known complications. Physicians need to be updated to approach these complications within time, to avoid life-threatening situations caused by these appliances.

Key words: Spatz adjustable balloon; Intragastric balloon; Morbid obesity; Safety ring; Perforation

Core tip: Because the rare reported unexpected complications that the balloon safety ring which designed to prevent its complication it was by it self the cause of

serious complication. The u/s confirmation of balloon position was miss leading so radiographic images was essential when there is suspicious.

Al-Zubaidi AM, Alghamdi HU, Alzobydi AH, Dhiloon IA, Qureshi LA. Bowel perforation due to break and distal passage of the safety ring of an adjustable intra-gastric balloon: A potentially life threatening situation. *World J Gastrointest Endosc* 2015; 7(4): 429-432 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i4/429.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i4.429

INTRODUCTION

Obesity is a major health problem, and is challenging the modern world. Its distribution is insidious throughout the world. Because it is a major risk factor for many potential life-threatening conditions, different invasive and non-invasive therapeutic techniques are being used to help the individuals suffering from obesity return to a healthy life.

Among these modalities, intra-gastric balloons are gaining popularity because of their efficacy, safety, and technical ease, as shown by some studies[1,2]. Moreover, it has been recommended as a weight reduction adjuvant before bariatric surgery, and before all kinds of planned surgery in morbidly obese persons; to reduce life-threatening co-morbidities and reduction of surgical risk[3,4].

Most of the reported serious complications with the newer generation of balloons take place 6 mo after placement of the balloon[5]. Here, we are reporting a case of small bowel perforation, secondary to break down and migration of the safety ring of an adjustable intra-gastric balloon (Spatz) that happened 8 wk after its insertion.

CASE REPORT

A 45-year-old man was brought to the emergency department with a history of abdominal cramps, on and off, for a few days, associated with anorexia and nausea. Patient had a history of saline filled adjustable intra-gastric balloon placement for the management of obesity 8 wk ago. Initial investigations including an ultrasound abdomen were unremarkable for any complication or pathology. Symptomatic treatment trial was unsuccessful and patient remained symptomatic, therefore, he reported back to ER.

He was in mild distress this time, but stable hemodynamically. Although his abdomen was soft and bowel sounds were active, a new onset mild generalized abdominal tenderness was noticed on clinical examination, therefore an abdominal computed tomography (CT) scan was planned which later reported the presence of a metallic ring (foreign body) in the small bowel without any sign of perforation or obstruction, while the adjustable balloon was in place (Figure 1).

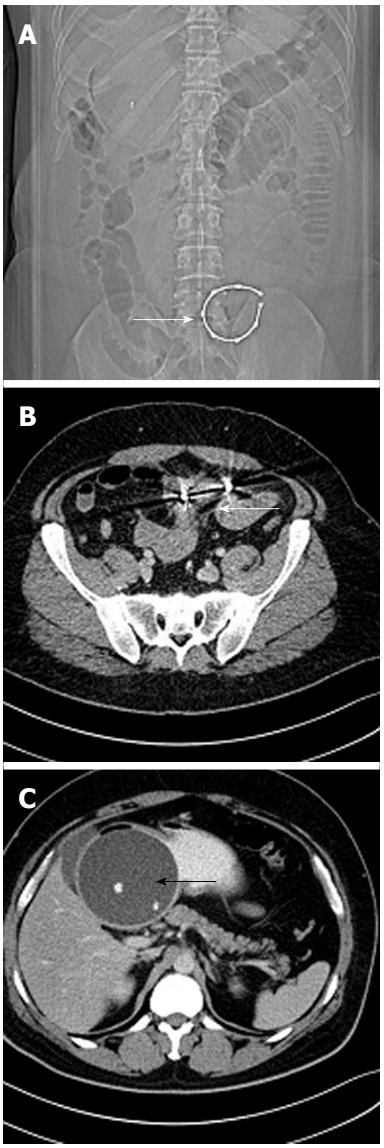

Figure 1 Abdominal computed tomography scan showing the safety ring migrated to the small bowel (A and B) (white arrows) and (C) the balloon was in the stomach (black arrow).

Patient was admitted for observation, advised null per oral, and started on intra-venous fluid. He becomes completely asymptomatic on conservative management. Next morning, patient underwent an upper gastrointestinal endoscopy. Balloon was seen in place but the safety ring was not seen in position, nor was it present in gastric cavity. Therefore, balloon was retrieved. Patient was stable clinically till night when he experienced a sudden and severe abdominal pain.

Plain X-ray film of abdomen was taken that revealed the presence of free air under the right dome of the diaphragm. Surgical team was informed immediately. Mean while NG tube was placed and IV antibiotics were initiated. Patient was transferred to the operation room for an emergency laparotomy. A 10 cm mid-line incision was given small bowel was examined.

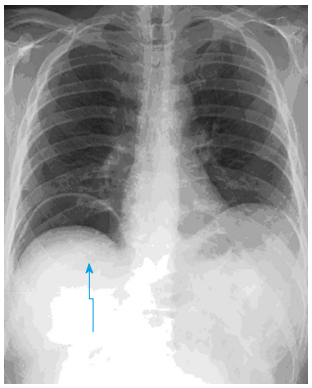

Figure 2 Free air under the diaphragm.

Two perforations were identified in distal jejunum at the site of ring entrapment. Small incision was made at the site of perforation and metallic ring was extracted followed by a successful primary repair of small bowel. Figure 2 shows free air under the diaphragm. Figure 3 shows endoscopic and gross eye views of both balloon and its broken ring after extraction.

DISCUSSION

Intra-gastric balloons were introduced in the early 1980s for the management of morbid obesity. These IGBs have attracted physicians since their first use[6].

Initial results were promising for this less invasive procedure in comparison with surgery for the treatment of morbid obesity[7-9]. Some published results reveal an average weight loss of 11-15 kg within 6 mo[10-13]. Standard IGBs are having significant undesired effects, *e.g.*, nausea or vomiting, and significant abdominal discomfort in initial phase. Balloon deflation and distal migration that may lead to bowel obstruction and a physical adaptation indicated by lack of further weight loss effects by these IGBs[14-17]. Complications of balloon insertion constitutes a diagnostic challenge because majority of patients were presented with non-specific abdominal pain, nausea or vomiting[18-23].

Spatz adjustable balloon system (SPATZ-ABS) is a vibrant bariatric therapy with significantly improved implantation time, having an adjustable size balloon according to desired weight, and a safety ring that prevents distal migration of device in case of rupture of balloon[24].

In our case, the safety ring was detached from the rest of the system and migrated down to the jejunum while the balloon remains in the stomach. It was retrieved endoscopically. The jejunal perforation caused by migration of the safety ring was managed by emergency surgery. This complication was unexpected as there was no clinical sign of intestinal obstruction. Ultrasonography alone was also not helpful in identifying this complication by SPATZ-ABS.

Because of non-specific clinical presentation and inadequacy of ultrasonography alone, we suggest that whenever there is suspicion of a balloon related complication, a combination of plain abdominal X-ray, ultrasound, an upper GI endoscopy and/or CT scan will be an appropriate approach for early detection and management of complication.

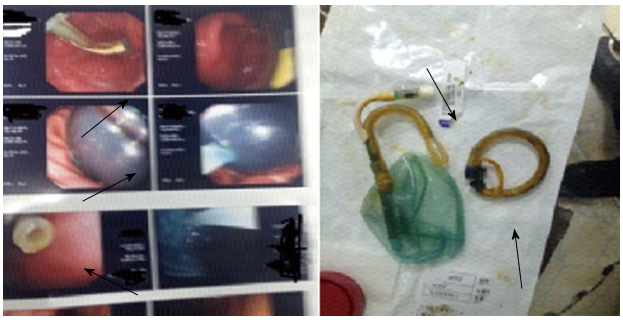

Figure 3 Endoscopic and gross eye views of both balloon and its broken ring after extraction.

COMMENTS

Case characteristics

A 45-year-old patient with history of intragastric Bio enteric balloon, experienced a recurrent cramp and abdominal pain, which became severe when perforation occurs.

Clinical diagnosis

No significant clinical signs, but when perforation occurs there was abdominal tenderness.

Differential diagnosis

Potential perforated duodenal ulcer, acute pancreatitis, acute intestinal obstruction or biliary colic.

Laboratory diagnosis

The CBC, LFT, KFT, and coagulation profile were all within normal parameters.

Imaging diagnosis

U/S abdominal was normal, computed tomography abdominal the ring was migrated down to the small bowel, when perforation occurred X-ray of the abdominal area showed free air under right dome of the diaphragm.

Pathological diagnosis

A pathology sample was not tested, but during surgery two small perforations were closed by sutures.

Treatment

NPO, endoscopic removal of the balloon, Laparotomy for repair of perforation, Pethedin inj, Paracetamol inj, Cefotoxim inj, Metronidazol infusion and *iv* fluid.

Related reports

From this case, any abdominal pain in a patient with an intragastric balloon should be taken seriously, and potential complications managed early.

Peer-review

This case report should be published.

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EDITORIAL

Use of *Clostridium botulinum* toxin in gastrointestinal motility disorders in children

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Abstract

More than a century has elapsed since the identification of *Clostridia* neurotoxins as the cause of paralytic diseases. *Clostridium botulinum* is a heterogeneous group of Gram-positive, rod-shaped, spore-forming, obligate anaerobic bacteria that produce a potent neurotoxin. Eight different *Clostridium botulinum* neurotoxins have been described (A-H) and 5 of those cause disease in humans. These toxins cause paralysis by blocking the presynaptic release of acetylcholine at the neuromuscular junction. Advantage can be taken of this blockade to alleviate muscle spams due to excessive neural activity of central origin or to weaken a muscle for treatment purposes. In therapeutic applications, minute quantities of botulinum neurotoxin type A are injected directly into selected muscles. The Food and Drug Administration first approved botulinum toxin (BT) type A in 1989 for the treatment of strabismus and blepharospasm associated with dystonia in patients 12 years of age or older. Ever since, therapeutic applications of BT have expanded to other systems, including the gastrointestinal tract. Although only a single fatality has been reported to our knowledge with use of BT for gastroenterological conditions, there are significant complications ranging from minor pain, rash and allergic reactions to pneumothorax, bowel perforation and significant paralysis of tissues surrounding the injection (including vocal cord paralysis and dysphagia). This editorial describes the clinical experience and evidence for the use BT in gastrointestinal motility disorders in children.

Key words: Botulinum toxin; Gastrointestinal motility disorders; Children; Swallowing disorders; Gastroparesis; Defecation disorders

Core tip: *Clostridium botulinum* toxin has been used to alleviate symptoms associated to muscle spams due to excessive neural activity of central origin or to weaken a muscle for treatment purposes. In therapeutic applications, minute quantities of botulinum neurotoxin type A are injected directly into selected muscles. Ever since, therapeutic applications of botulinum toxin have expanded to other systems, including the gastrointestinal tract. This editorial presents the current evidence and evaluates the clinical experience for the use of botulinum

toxin in gastrointestinal motility disorders in children.

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SWALLOWING DISORDERS

Cricopharyngeal achalasia

Cricopharyngeal achalasia is characterized by abnormal relaxation of the upper esophageal sphincter associated to abnormal coordination with pharyngeal contraction resulting in oropharyngeal dysphagia and at times resulting in aspiration. The disorder has been treated with medications, dilatations, botulinum toxin (BT) and myectomy. BT has been reported as safe and effective in patients with cricopharyngeal achalasia[1-3], particularly in those who failed medical therapy and are poor surgical candidates, as a diagnostic tool in complex cases[3], to alleviate symptoms until surgery can be safely performed[4] and to provide relief for residual symptoms after myotomy[5] with minimal side effects reported. In our experience the potential complications with the use of BT in cricopharyngeal achalasia can be important so we recommend its use for experienced hands, particularly ENT surgeons.

Esophageal achalasia

Esophageal achalasia is a disease of unknown etiology characterized by loss of esophageal peristalsis and failure of the lower esophageal sphincter (LES) to relax with swallowing. Decrease in nitric oxide synthase containing nerve fibers and interstitial cells of Cajal in the distal esophagus have been proposed as potential causes[6]. It is an uncommon condition in pediatrics and has an estimated incidence that ranges from 0.11-0.18/100000 children per year[7,8]. Symptoms vary with age of presentation. Progressive dysphagia, vomiting and regurgitation are common complaints in older children[9]. Initial diagnostic studies include barium swallow and upper endoscopy, but esophageal manometry is considered to the gold standard test for diagnosis and will provide diagnostic certainty in approximately 90% of the cases[10,11]. The goal of treatment in children with achalasia is to improve bolus transport across the LES by reducing the pressure at that level. Current treatment options include pharmacotherapy, pneumatic dilation, surgery or injection of BT and recently the Peroral Endoscopic Myotomy[12]. BT is endoscopically injected at the LES with a sclerotherapy needle in 4 different quadrants. The short-term efficacy of BT in treating esophageal achalasia has been well established in adults. Multiple double blind placebo controlled studies have revealed BT to be safe and effective in reducing symptoms and improving esophageal clearance in adults with esophageal achalasia[13]. It has been described to be as effective as pneumatic dilation[14-17] and comparable to surgical myotomy[18] in the short term (< 6 mo). It has been reported to improve residual symptoms after myotomy and pneumatic dilations[19]. It has been recommended primarily in those who are poor surgical candidates resulting in important symptomatic response[20]. BT has also been used as a diagnostic tool in cases where diagnosis of achalasia is not clear and to indicate definitive therapy[21]. Most of the information of BT use in children is found as case reports and case series. Most authors reported a short-lived (2-6 mo) improvement on symptoms[9,22-24]. Walton *et al*[22] reported a single case with sustained clinical improvement of 8 mo after a single BT injection. Khoshoo *et al*[25] reported BT as a safe and less invasive alternative for symptomatic relief of symptoms in 3 children with achalasia. They also observed weight gain prior to surgery and noted that it could also be a choice in patients with incomplete response following balloon dilatation or myotomy[25]. Hurwitz *et al*[24] found that among children receiving BT as initial treatment for achalasia, 83% responded to therapy with a mean duration of effect of 4.2 mo and more than half of responders required additional procedure 7 mo after receiving BT. Another study demonstrated an inverse relationship between pre-BT LES resting pressure and duration of response[23]. All authors agree that BT should be reserved for children with achalasia who cannot undergo pneumatic dilatation or surgery or to alleviate residual symptoms after these interventions.

BT has been also reported as useful in the management of esophageal spastic disorders in adults[26], to our knowledge no reports are available for this indication in children. The only fatality related to the use of botulinum toxin for gastrointestinal motility disorders has been reported in an adult patient with esophageal spasms who developed a fatal mediastinitis[27].

GASTRIC DISORDERS

Gastroparesis

Gastroparesis is defined as the presence of upper gastrointestinal symptoms with evidence of delayed gastric emptying by a standardized gastric transit study in the absence of mechanical obstruction. Symptoms classically include nausea, vomiting, early satiety, bloating, postprandial fullness, abdominal pain, and weight loss. The etiology of gastroparesis in the pediatric population is limited to a few studies. An observational descriptive analysis of a large pediatric population with gastroparesis reported that approximately 70% of the cases were idiopathic[28]. Another series found gastroparesis to be associated with post-viral gastroenteritis (18%), medications (18%), post-surgical (12.5%), mitochondrial disease (8%) and diabetes mellitus (2%-4%)[29]. Gastroparesis has been treated with medications and in some cases

with surgical interventions aiming to facilitate the transfer of bolus from stomach to small bowel. The endoscopic application of BT injections in gastroparesis has been well studied in adult patients. Multiple large uncontrolled studies have demonstrated symptom improvement with the use of BT[30-32]. However, two small randomized control studies showed no significant difference between BT and placebo on symptomatic as well as gastric emptying improvement[33,34], but some concerns have been raised about the power of such studies. In pediatrics, Rodriguez *et al*[35] assessed the long-term clinical outcomes after intra-pyloric BT injection in children with gastroparesis. After the first injection, 33% of patients reported no response and 67% described improvement in their symptoms. The mean duration of improvement was 3 mo and no significant side effects were reported[35]. From their analysis they also described that older age and vomiting were predictive of response to the initial injection, and male sex predicted response to repeated injections. There are currently no guidelines that indicate the timing of BT injections in pediatric patients with gastroparesis, but the consensus is that its use should be limited to patients that fail medical therapy with prokinetics and before more invasive interventions are considered (gastrojejunostomy, gastric electric stimulator). Although have not observed complications with its use in gastroparesis we have noticed short-lived vomiting in some patients followed by complete resolution of symptoms.

DEFECATION DISORDERS

Chronic constipation is one of the most common complaints at the pediatric offices. Although constipation may have several etiologies, in most children no underlying etiology can be found. Symptoms refractory to aggressive therapy with stool softeners and laxatives should prompt further work up to rule out etiologies like Hirschsprung's disease and internal anal sphincter (IAS) achalasia.

Hirschsprung's disease

Hirschsprung's disease (HD) is characterized by obstructive defecation due to distal colonic aganglionosis caused by a defect in cranio-caudal migration of neuroblasts leading to lack of relaxation resulting in functional obstruction. The diagnosis is confirmed by rectal biopsy demonstrating absence of ganglion cells in the submucosa and myenteric plexus. The treatment of HD consists in surgical removal of the aganglionic segment. Despite many improvements in diagnostic and surgical techniques, many patients continue to exhibit symptoms after surgical correction. The treatment of obstructive defecation initially consists of rectal dilatations to avoid stricturing of the surgical anastomosis. Some advocate performing a myectomy for those who fail medical therapy and dilatations, but results are variable with some reporting good outcomes[36] and others reporting only a moderate success[37] with complications like fecal incontinence. Due to the inconsistent efficacy and concerns of permanent incontinence, other non-invasive and self-limited alternatives have been contemplated, including use of topical nitric oxide[38] and BT. Langer *et al*[39] reported significant clinical improvement in 3/4 children as well as reduction of IAS resting pressure at 4-8 wk post-BT. Minkes *et al*[40] also reported clinical improvement in 14/18 children and described an association between clinical improvement and a post-BT decrease in IAS resting pressure. Another study showed an improvement in short and long-term obstructive symptoms, frequency of enterocolitis episodes and short-term decrease in hospitalization rates in 30 children with HD and prolonged use of BT[41]; 7 patients developed transient fecal incontinence; and, 1 patient reported anal pain after the BT injection. Elevated IAS resting pressure was associated with higher clinical success. A recent report by Han-Geurts *et al*[42] reported similar findings, with clinical improvement in 25/33 (76%) and decrease in hospitalizations due to enterocolitis. Importantly, they reported 2 children developing transient pelvic muscle paresis with walking impairment. General consensus is to use BT for those patients with obstructive defecation and elevated anal canal resting pressure. In our experience BT is more effective when IAS resting pressure is over 50 mmHg.

IAS achalasia

The hallmark of IAS achalasia is absent IAS relaxation with balloon rectal distention in the presence of ganglion cells on rectal biopsy. Some have called it ultra-short segment Hirschsprung's disease. The treatment of IAS achalasia has been aimed at relieving obstructive defecation with dilations or myectomy. IAS myectomy has been reported to be effective in relieving obstructive symptoms and helping achieve normal bowel control in children with IAS achalasia[43,44]. However, it is associated to fecal incontinence. BT has shown excellent results in relieving functional obstructive symptoms and has become the treatment of choice for IAS achalasia[41,45-47]. In several studies, transient fecal incontinence was the most common minor complication reported that resolved within 4 wk after BT injection[41,45,46]. Foroutan *et al*[48] demonstrated that BT has similar efficacy and less complications when compared to myectomy. Nevertheless, a recent meta-analysis found that regular bowel movements and short and long-term improvements were more frequent after surgery with no difference in the continued use of laxatives or rectal enemas, episodes of constipation and soiling and, overall complication rates between the two procedures[49]. BT should be considered the first option of treatment for IAS achalasia.

Chronic anal fissure

Chronic anal fissure is a common and benign anorectal condition associated to elevated anal canal

resting pressures, although other factors might also play a role. The classic symptom is pain on or after defecation that is often severe and may last from minutes to several hours. Most fissures occur in the posterior midline of the anal canal[50]. By definition, an acute anal fissure typically heals within 6 wk with conservative local management, while a chronic anal fissure fails medical management at times requiring more aggressive interventions[51]. Lateral internal sphincterotomy is a surgical technique commonly used to treat chronic anal fissure. It has been favored by most surgeons because it offers long-lasting relief in sphincter spasm by permanently weakening the IAS. However, it may lead to anal deformity and incontinence in 8%-30% of patients that can be permanent in a subset of patients[50]. BT injection to the IAS has been demonstrated to improve healing in chronic anal fissure in adult studies. In a randomized placebo controlled study BT demonstrated to be superior to placebo in healing of chronic anal fissure at two month follow up (73% *vs* 13%), only a small number of patients required a second injection and no relapses were reported after a 16-mo follow up[52]. Its use has also been shown to be effective when used in combination with topical nitroglycerin[53]. Pediatric studies have shown that BT injection to the external anal sphincter is an effective therapy in children with chronic anal fissures[54,55]. Nonetheless, there is discrepancy in the injection site when compared to adult studies. Prospective and long-term studies are needed to evaluate BT therapy in children with chronic anal fissures.

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REVIEW

Risk factors affecting the Barrett's metaplasia-dysplasia-neoplasia sequence

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Abstract

Esophageal adenocarcinoma has the fastest growing incidence rate of any cancer in the United States, and currently carries a very poor prognosis with 5 years relative survival rates of less than 15%. Current curative treatment options are limited to esophagectomy, a procedure that suffers from high complication rates and high mortality rates. Metaplasia of the esophageal epithelium, a condition known as Barrett's esophagus (BE), is widely accepted as the precursor lesion for adenocarcinoma of the esophagus. Recently, radio-frequency ablation has been shown to be an effective method to treat BE, although there is disagreement as to whether radio-frequency ablation should be used to treat all patients with BE or whether treatment should be reserved for those at high risk for progressing to esophageal adenocarcinoma while continuing to endoscopically survey those with low risk. Recent research has been targeted towards identifying those at greater risk for progression to esophageal adenocarcinoma so that radio-frequency ablation therapy can be used in a more targeted manner, decreasing the total health care cost as well as improving patient outcomes. This review discusses the current state of the literature regarding risk factors for progression from BE through dysplasia to esophageal adenocarcinoma, as well as the current need for an integrated scoring tool or risk stratification system capable of differentiating those patients at highest risk of progression in order to target these endoluminal therapies.

Key words: Barrett's esophagus; Esophageal adenocarcinoma; Endoscopy; Risk factors; Radiofrequency ablation; Antireflux surgery

Core tip: The transformation of Barrett's esophagus to dysplasia and finally to esophageal adenocarcinoma is a multifactorial process encompassing effects from multiple known and unknown risk factors. Previously, radiofrequency ablation was reserved for use in high risk patients with high-grade dysplasia, but recent evidence supports the expansion of this technique to be potentially used to treat additional patients at moderate risk of progression, such as those with long segments, long duration of symptoms, and those patients who are unable or unwilling to take proton-pump inhibitors's.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) has been estimated to affect nearly 20% of the United States population at any given time[1]. Of this group suffering from GERD, roughly 15% are estimated to have Barrett's esophagus (BE), a condition characterized by columnar-lined epithelium in the esophagus[2]. It is well established that BE is the link between GERD and esophageal adenocarcinoma (EAC), a neoplastic lesion with an extremely poor prognosis with 5-year survival rates of less than 15% and which currently has the fastest rising incidence rate of any cancer with approximately a 10-fold increased incidence rate among men aged 15-74 in the last 40 years[3-6]. Unfortunately, little progress has been made in treating this extremely aggressive cancer, with median survival time increasing only 3.2 mo over the last 30 years[7]. BE has been shown to be a paradigmatic model for progression from metaplastic disease through dysplasia to neoplasia[8]. In this review, we summarize the current literature regarding the etiology and pathophysiology of BE and EAC.

RESEARCH

We performed a literature review in the PubMed/Medline database using MeSH term "Barrett's Esophagus" combined with subheadings "etiology", "physiopathology", "therapy", "diagnosis" and "epidemiology" as well as MeSH term "Esophageal Neoplasms" with selected subheadings "diagnosis", "etiology", "physiopathology", "epidemiology" and "therapy" combined by Boolean operator AND with MeSH term "Adenocarcinoma" with selected subheadings "diagnosis", "epidemiology", "etiology", "pathophysiology" and "therapy". We reviewed abstracts published between 1980 and April of 2013 in English and selected articles relevant to topics discussed herein.

EPIDEMIOLOGY

Columnar lined epithelium has been shown to be present in almost 25% of individuals with GERD symptoms, and columnar lined epithelium with intestinal metaplasia is reported as affecting almost 15% of those with GERD symptoms. The probability of progressing to EAC from BE has been estimated to be approximately 0.5%/year[9,10], with the most convincing evidence provided in a meta-analysis of 47 studies by Yousef *et al*[11] showing a pooled cancer incidence of 6.4/1000 person-years for the 13 studies conducted in the United States and 6.1/1000 person-years for all 47 studies pooled. EAC incidence has increased roughly 10-fold in select demographics over the last 40 years, with only a small fraction being attributed to increasing obesity rates[12]. Recent data suggests this increase is slowing but still substantial, with average annual percentage increase in incidence rising 6.1% in men and 5.9% in women[13]. Other causes for this rapid increase in incidence have yet to be elucidated, but this continues to be a highly active area of research.

ETIOLOGY AND PATHOPHYSIOLOGY

BE is caused by reflux of gastric contents into the esophagus, which causes damage to the stratified squamous epithelium. Not surprisingly, it has also been shown that GERD symptoms increase odds of EAC by 7.7 fold, odds which increase to 43.5 fold when comparing patients with long-standing and severe GERD symptoms[13]. It is currently contested as to whether gastric acid, bile reflux, or the combination is responsible. Several studies have shown increased intraluminal bilirubin content, a proxy for duodenal juice content, in patients with BE, suggesting that bile acid plays an important role in BE development[14]. Likewise, gallbladder function was shown to be impaired in patients with BE and EAC in a real-time ultrasonography experiment following a 10-h fast leading to increased duodenogastric reflux[15]. Cholecystectomy has also been shown to increase risk of EAC, albeit slightly[16,17]. The body's compensatory mechanism can but does not always include metaplasia in the form of simple columnar epithelium, which is thought to be more tolerant to the low pH[18,19]. BE is the most predictive risk factor for the development of EAC, with a relative risk for developing esophageal cancer of 11.3 when compared to the general population[20]. Much research recently has been focused on determining what the risk factors are for developing BE. Age has been shown to be correlated with increased risk of developing BE, with a low of 2 diagnoses per 100000 person-years for those aged 21-30 years and peaking at 31 diagnoses per 100000 person-years in those aged 61-70 years[21]. Males also experience BE incidence rates roughly twice that of females, although the reason for this difference remains to be elucidated[21].

Obesity and its related conditions have been shown to be a risk factor for many diseases, and BE is no exception. A meta-analysis by Cook *et al*[22] suggests that increasing obesity is correlated with an increased risk for BE development but only indirectly due to obesity's effect on GERD development. This view is contested by El-Serag *et al*[23], who suggest that increasing visceral adipose tissue to subcutaneous adipose tissue ratio is correlated with the presence of BE [adjusted OR = 1.47 (95%CI: 0.92 to 4.09)]

as well as Kendall *et al*[24], whose data shows a significant correlation between all measures of obesity tracked (waist circumference, waist-hip ratio, sagittal abdominal diameter, and waist-height ratio) and presence of BE in males even after adjusting for GERD symptoms. It has been proposed that the association between obesity and risk of BE is due to several factors including increased intra-abdominal pressure leading to worsening GERD, as well as increased circulating levels of leptin, adiponectin, and other chemicals secreted by adipose tissue, although this link remains to be confirmed. Recently, low birth weight and preterm birth have been implicated as a risk factor for BE, with several studies reporting those born very small for gestational age, < 3rd percentile in one study and < 2000 g in another, having between a three and eleven-fold increase in odds when compared to those born at a normal weight for gestational age[25,26]. Hiatal hernia has been shown to be another risk factor for BE, with size of hiatal hernia correlating with increasing risk of both BE as well EAC[27,28]. Metabolic syndrome, another obesity related factor, has been shown to increase risk for BE by two-fold relative to those without metabolic syndrome[29].

It is being currently debated as to whether *Helicobacter pylori* (*H. pylori*) infection leads to increased or decreased risk of developing BE, but two meta-analyses, of 49 studies conducted by Fischbach *et al*[30] and 19 studies conducted by Islami *et al*[31], both suggest that, although significant selection and information bias may be present in these studies, *H. pylori* infection appears to be associated with a decreased risk of BE. Aggressive eradication of *H. pylori* infection over the last 30 years may provide an explanation for a small portion of the drastic increase in incidence.

Along with being male and older age[32-34], those with low dietary antioxidant intake have also been shown to not only have an increased risk of developing BE, but also have an increased risk of developing EAC[35,36]. Similarly, length of GERD symptoms is a risk factor for both development of BE as well as EAC[36,37]. The reasons for males experiencing high incidence rates is not well understood, but it appears to be due to other reasons than differential exposure to known risk factors[38,39]. Hormonal factors, studied by comparing patients undergoing hormone therapy, do not appear to account for the discrepancy in EAC incidence rates between males and females[40]. Heme iron intake in the diet has been suggested as a risk factor corresponding to EAC development as well[41]. Dietary iron has been shown to be a growth factor for *H. pylori,* making this association one in need of further investigation.

Many studies recently have elucidated relationships between various risk factors and the development of EAC, a goal that has potential to directly affect patient outcomes and change clinical practice with respect to ablative therapy. Sikkema *et al*[42] conducted a prospective cohort study in which they found statistically significant associations between many risk factors and progression to high grade dysplasia (HGD) and/or EAC including esophagitis and length of BE segment, with a risk ratio of 1.11 per centimeter increase in length, and known duration of BE of greater than or equal to 10 years with a risk ratio of 3.2. Also, previous partial gastrectomy is linked to EAC development[43]. Patients who underwent esophagectomy for EAC were shown in a case-control study to have a 45% prevalence of colonic polyps when compared to control patients who also underwent screening colonoscopies, of whom only 14% were shown to have colon polyps[44]. Whether there is a predictive relationship between presence of colon polyps and risk of EAC is still a contested topic and deserves further attention. Also, early research shows no evidence of viral genomic sequences present in tumors[45]. The single most predictive clinical factor for progression to HGD and/or EAC found to date is the presence of low grade dysplasia (LGD) found during biopsy with a relative risk of 9.7 (95%CI: 4.4-21.5) according to Sikkema et al and 5.5 (95%CI: 1.1-28.6) according to Oberg *et al*[46] compared to those without LGD.

Biomarkers have the potential to drastically improve our ability to risk stratify. p53 as well as KI-67, both proteins involved in cell cycle progression, have been shown to be expressed at higher levels in BE samples that progress to EAC[47-51]. Likewise, it has also been shown that cell-free circulating DNA methylation patterns correlate extremely closely (r = 0.92) with aberrant DNA methylation patterns in matched tumor tissue in patients with EAC and also that 911 loci for DNA methylation could perfectly discriminate between EAC and controls, suggesting that cell-free DNA methylation patterns could be used as a non-invasive method to screen premalignant lesions[52]. Promoter hypermethylation of p16 and APC is also strongly correlated with progression to EAC, with one study reporting hypermethylation of p16 and APC, either separately or together, in over 50% of HGD/EAC samples with hypermethylation of the same promoters totally absent in samples from patients with normal esophagus[53]. In a similar way, Mcm2 expression in BE is directly correlated with degree of dysplasia, with 91% of patients diagnosed with dysplasia or EAC in one prospective cohort showing Mcm-2-positive cytological brushings, while brushings from controls without BE showed no signs of Mcm-2 expression on the luminal surface[54]. COX-2 expression is upregulated in BE patients and degree of overexpression is correlated with risk of malignant transformation, suggesting that COX-2 expression could be used as a potential marker as well[55]. This increase in COX-2 expression has been shown to be strongly induced by deoxycholic acid incubation *in vitro* using OE-19 cells as a Barrett's model, suggesting a potential mechanism for this phenomenon[56]. Several bile acids have also been shown to induce the expression of other proteins important in cancer progression such as CDX2 as well as induce

NF-κB signaling[57]. Other notable biomarkers include increased DNA damage detected by Comet Assay, decreased Beclin-1 expression, increased cyclin A, cyclin B1, and cyclin D1 expression, and abnormal DNA content[49,58-65]. Notably, abnormal DNA content, measured by the number of chromosomes arms with loss, has been shown to be directly correlated with the progression from metaplasia, through low and high grade dysplasia, and finally to neoplasia[66]. Likewise, telomerase reverse transcriptase has been shown to be overexpressed in increasing levels along the metaplasia-dyplasia-neoplasia sequence of BE[67]. Whether these two markers can be used to differentiate between BE patients who will progress and those who will not remains to be studied. The field would benefit from further research into how these biomarkers can be integrated and utilized in a clinical setting as well as which can be used cost effectively to better predict risk of progression to EAC.

Interestingly, high serum leptin levels were associated with increased risk of EA, whereas increased levels of high molecular weight adiponectin conferred a protective effect, with a hazard ratio (HR) of 0.34 (95%CI: 0.14-0.82)[68]. The mechanism for this association might be due to leptin's effect on proliferation of adenocarcinoma cells independent of apoptosis or necrosis, as has been shown in BIC-1 and SEG-1 cells *in vitro*[69]. Type 2 diabetes mellitus has been shown to be more prevalent in those diagnosed with EAC, although the effect was attenuated after controlling for differences in BMI[70].

The consumption of several substances have shown to confer protective effects, with use of a multivitamin pill showing a HR of 0.38 (95%CI: 0.15-0.99) when compared to those not taking a multivitamin[71]. Vitamin D intake, however, was found to increase the risk of EAC, showing an OR of 1.99 (95%CI: 1.03-3.86), although vitamin D intake was not associated with BE or reflux esophagitis[72]. Taking proton-pump inhibitors (PPIs) has been shown to confer a protective affect against progressing from BE to EAC, with a hazard ratio of 0.41 (95%CI: 0.18-0.93) and 0.21 (95%CI: 0.07-0.66) for those using proton pump inhibitors at inclusion of the study or during the follow-up period, respectively; a finding supported by several other studies[73,74]. In addition to the use of proton-pump inhibitors, several studies recently have shown decreased rates of progression to EAC from BE when taking aspirin and/or statins, although the mechanism for this protection remains to be elucidated fully[75]. Sadaria *et al*[76] found that simvastatin attenuated growth and increased apoptosis in human esophageal adenocarcinoma (FLO-1) cells in tissue culture, providing one potential mechanism by which statins reduce risk of progression to EAC. One meta-analysis investigating this protective effect found a number needed to treat of 389 patients with statins to prevent one case of EAC[77]. ACE inhibitors could potentially provide a protective effect, although studies regarding this question were underpowered[78]. Medications that have relaxing effects on the lower-esophageal sphincter, specifically anticholinergics and theophyllines, have been associated with a roughly 1.5-2.5 fold increased risk of EAC, a relationship not seen for other types of cancers of the upper digestive tract[79,80].

As is expected, tobacco smoking has been shown repeatedly to increase the probability of progression to EAC. Interestingly, one study from the NIH Barrett's Esophagus and Esophageal Adenocarcinoma Consortium found an increased risk of progression to EAC with smoking and even showed a dose-response effect when considering pack-years, but there was a weaker association when considering cigarettes/day[81]. This study corroborates several other studies showing deleterious effects of smoking on risk of progression to EAC, estimating the risk at roughly double for those who smoke relative to those who do not smoke[82-85]. There appears to be no association between alcohol intake and risk of EAC according to several recent studies including meta-analysis, although this has been contested according to a matched case-control study out of North China[81,83,86-88].

Currently, no definitive genetic cause of BE or EAC has been identified. Several case reports, however, have found a remarkable history of BE and EAC among members of the same family, providing evidence that a subset of the population may be genetically susceptible to BE and potential progression to EAC[89-92]. Additionally, a single nucleotide polymorphism in the gene coding for epidermal growth factor (EGF) has been shown to be associated with decreased levels of EGF expression and has also been shown to be more prevalent in patients with BE and EAC[93]. Further research in this area could help identify specific genotypes that would allow clinicians additional tools when risk stratifying patients and making decisions regarding the management of patients with BE.

Surgical management of GERD has been shown to decrease odds of progression to EAC compared to no therapy, however a 2007 systematic review found that, in controlled studies, there was no statistically significant difference in EAC incidence rates between patients treated surgically and those treated medically. If data from uncontrolled case-series are included, the difference becomes significant. Interestingly, surgical management increased the probability of regression of BE and/or dysplasia by almost 15%[94]. This study shows puzzling results given the data from previous studies showing that fundoplication can reduce or even eliminate the reflux of bile acids into the esophagus, compared to medical therapy which only treats the reflux of hydrochloric acid[95]. One possible answer to this question could come from recent case-control data showing that, among patients who've undergone antireflux surgery, those with recurrent reflux symptoms are three times more likely to develop EAC than those without, underscoring the importance of addressing continuing reflux symptoms after antireflux surgery[96].

Randomized trials to date have only compared antireflux surgery to medical therapy in patients who were complete responders to medical therapy. This, unfortunately, is not the comparison of interest given the current role for surgery in GERD management. Patients selected for antireflux surgery in practice almost exclusively have failed medical therapy as their indication for surgical management. This suggests that there is some fundamental difference between patients who are responders and those who are not, and limits the usefulness of the comparison in these studies. The question of antireflux surgery *vs* continued medical management remains unanswered conclusively, but continues to be an active area of research and could benefit heavily from a randomized controlled trial comparing antireflux surgery to continued medical management in a population of patients who have continued reflux symptoms despite full dose medical therapy. Current data suggests that there is a role for antireflux surgery in the management of patients with BE, but the question of exactly which patients should be receiving these procedures remains to be answered.

CONCLUSION

As can be seen from the wealth of information outlined above, the risks associated with progression from BE to esophageal adenocarcinoma are multifactorial, with many different risk factors each contributing a relatively small portion to the overall risk of progression. This suggests that a single intervention aimed at reducing exposure to individual risk factors other than refluxed gastric contents is unlikely to have a drastic impact on increasing adenocarcinoma rates or to affect the risk for individual patients with Barrett's. Currently, no biomarkers have shown to be clinically useful in BE, but this continues to be an active area of research. More work is necessary to investigate the many risk factors at play and the populations that they apply to, in order to better understand the contributions to risk for any given clinical situation. Recent advancements in knowledge of risk factors and their contributions to progression have made clinical risk stratification models possible in order to target endoluminal therapies capable of eradicating Barrett's tissue and drastically decreasing risk of progression to adenocarcinoma. Currently, these tools are not widely available. Additional work is required to further develop and validate these tools in order to target patients at the highest risk of progression with either therapeutic intervention or endoscopic surveillance. One risk factor, the presence of LGD, has been very clearly shown to drastically increase the risk of progression to EAC by multiple studies. Given this information along with the known safety and efficacy of radiofrequency ablation and other endoluminal therapies, we believe that there is sufficient data to support the use of RFA in all Barrett's patients with LGD, even in the absence of additional risk factors. Additional stratification tools are required in order to dictate exactly which patients without LGD should receive RFA/endoluminal therapy and which should not, but given the evidence outlined above, patients with very long segment, patients who have had reflux symptoms for time periods of 10 years or greater, or patients who are unable or unwilling to take PPI's or are not antireflux surgery candidates should be considered carefully as potential candidates for endoscopic ablation.

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REVIEW

Endoscopic management of post-liver transplant biliary complications

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Abstract

Biliary complications are being increasingly encountered in post liver transplant patients because of increased volume of transplants and longer survival of these recipients. Overall management of these complications may be challenging, but with advances in endoscopic techniques, majority of such patients are being dealt with by endoscopists rather than the surgeons. Our review article discusses the recent advances in endoscopic tools and techniques that have proved endoscopic retrograde cholangiography with various interventions, like sphincterotomy, bile duct dilatation, and stent placement, to be the mainstay for management of most of these complications. We also discuss the management dilemmas in patients with surgically altered anatomy, where accessing the bile duct is challenging, and the recent strides towards making this prospect a reality.

Key words: Liver transplant; Biliary; Complications; Strictures; Bile leak; Management; Endoscopy; Endoscopic retrograde cholangiography; Biloma; Stone; Cast

Core tip: Biliary complications are being increasingly encountered in post liver transplant patients because of increased volume of transplants and longer survival of these recipients. Overall management of these complications may be challenging, but with advances in endoscopic techniques, majority of such patients are being dealt with by endoscopists rather than the surgeons. Our review article discusses the recent advances in endoscopic tools and techniques which have proved ERCP with various interventions, like sphincterotomy, bile duct dilatation, and stent placement, to be the mainstay for management of most of these complications. We also deliberate the management dilemmas in patients with surgically altered anatomy, where accessing the bile duct is challenging, and the recent strides towards making this prospect a reality.

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INTRODUCTION

Biliary tract complications (BTC) are described as Surgeons' "Achilles Heel" after liver transplantation (LT)[1]. They constitute a major source of morbidity after LT and pose a challenge in both diagnosis and treatment. The incidence of BTC varies from 5% to 32% in various studies and has been decreasing with time; however, newer challenges are emerging with the more widespread use of living donor, donation after circulatory death and split-liver transplants[2,3]. The different complications that can be seen post LT include biliary strictures, leaks, cast formation, papillary stenosis and other less common ones[4,5]. Conventionally, post-LT biliary complications can be referred to as early (within 30 d of LT), delayed (1-3 mo post-LT) and late (beyond 3 mo post-LT). Even though each complication has a predominant manifestation period, for management purposes the clinical presentation and diagnosis are more important. With the advancement of imaging techniques, most of these complications are diagnosed using non-invasive imaging like traditional ultrasound (US), computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) with more invasive techniques like percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiography (ERC) used for therapeutic purposes[6,7]. Over the last decade, there has been significant improvement in endoscopic techniques with an increase in the array of endoscopic assist devices, and consequently most of these complications are managed endoscopically, which will be the focus of this review.

TYPES OF SURGICAL RECONSTRUCTION AFTER LIVER TRANSPLANT

The technique of biliary reconstruction utilized during LT greatly influences the biliary tract complications seen in these patients[8-10]. It is necessary to be cognizant with the anatomy of the liver segments and its ducts, to be able to successfully diagnose and manage these complications. The two most common methods of biliary reconstruction include choledocho-choledochostomy (CC) or duct-to-duct anastomosis; and Roux-en-Y hepaticojejunostomy or choledochojejunostomy (RYC). It is imperative for endoscopists to have a thorough understanding of these anastomotic procedures as the former can be approached *via* conventional ERC whereas for the latter a percutaneous route is preferred. There is also an increasing usage of living, related-donor and split-liver transplants, because of limited availability of deceased donor liver transplants. During this procedure anastomosis is fashioned between donor's right hepatic duct to the recipient's common bile duct, which is even more complex than the traditional methods due to variability of the anatomy.

DIAGNOSIS AND EVALUATION OF BTC AFTER LT

Recognizing the risk factors for development of biliary complications is an important aspect of overall management, because if a risk factor is identified and appropriate remediation steps taken, the natural course of these complications may be altered. The common list factors are listed in Table 1 and discussed in detail at appropriate places in the article. Post-LT, patients with BTC can have varied presentations, which may range from asymptomatic transaminasemia to frank jaundice with abdominal pain and cholangitis. It is imperative to differentiate obstructive cholestasis from a non-obstructive cause like rejection - acute or chronic, drug induced cholestasis or recurrence of primary disease[11]. This is usually achieved with the help of imaging, which includes trans-abdominal ultrasound with Doppler, CT, MRCP, EUS, and HIDA scan (hepatobiliary iminodiacetic acid scan).

US with doppler can diagnose hepatic artery thrombosis in LT patients with a sensitivity of 91% and specificity of 99%[12]. Hepatic artery thrombosis is a risk factor for biliary leaks due to ischemic injury and hence, if detected on Doppler, warrants a confirmatory hepatic angiogram[2]. US can also be used to diagnose biliary strictures with a specificity of 98%; however, normal US findings do not exclude it and require further investigation with MRCP[13,14]. At present, MRCP is the initial imaging of choice to evaluate an LT patient for a biliary tract complications[15]. It provides detailed evaluation of both extra- and intra-hepatic biliary tree and can potentially avoid use of direct cholangiography[14]. It has several advantages over traditional and direct cholangiography, as it is non-invasive, there is no need of sedation, has minimal side effects and can demonstrate ducts both below and above a stricture. Several studies have been conducted to evaluate its role in LT patients with suspected biliary obstruction and in a meta-analysis, which included almost 400 LT-patients, MRCP was found to have a sensitivity of 96%, specificity of 94% with a positive likelihood ratio of 17 and a negative likelihood ratio of 0.04 for diagnosis of biliary obstruction[16-19]. However, it has limited role if LT was performed along with bilio-enteric anastomosis and for diagnosis of malignant strictures[16,20]. CT scan has limited role in evaluation of biliary tract complications in LT patients and maybe used to diagnose abscesses or fluid collections associated with biliary leaks.

TYPES OF BTC AFTER LT AND THEIR MANAGEMENT

Biliary strictures

Biliary strictures are the commonest complications after liver transplantation, with an incidence of 13% following deceased donor liver transplant (DDLT)

Table 1 List of risk factors responsible development of various biliary complications

Risk factor	Mechanism	Resultant biliary complication
HAT or stenosis	Being the main vascular supply to the bile duct, any compromise to integrity of HA or its branches induces acute and chronic ischemia of the biliary system	Anastomotic disruption Bile leak NAS AS Biliary cast syndrome
Type of transplant	Live-donor LT has higher overall biliary complications compared to Orthotopic LT	Bile leak HAT Unplanned re-explorations Portal vein thrombosis
Type of donor	DCD LT has higher biliary complication rate compared to DBD LT. This is because of increased risk of experiencing insufficient organ perfusion. Also increased risk if ABO blood group incompatibility between donor and recipient	Strictures (NAS) Bile duct filling defects (stones/sludge/clots/casts)
Type of anastomosis (biliary reconstruction)	Duct-to-duct CC anastomosis is preferred whenever possible, being simple and prevents enteric reflux into bile ducts, compared to RYC	Comparative biliary complication data is conflicting
Graft related factors	Use of grafts from older donors or grafts with increased steatosis (extended criteria), as well as increased cold (CIT) and warm ischemia times	Strictures (NAS and AS) Bile leak Bile duct filling defects (stones/sludge/clots/casts)
Surgical (or technical) factors-during both donor and recipient surgeries	Excessive dissection of periductal tissue during the procurement of native liver Excessive electrocautery to control bleeding during surgery Tension between the two ends of the biliary anastomosis Suture material used Denervation or injury to sphincter	Bile leak AS Mucocele Sphincter of Oddi Dysfunction
Placement of T-tubes (old strategy)	This increases chances of delayed healing, and may cause bile leaks.	Bile leak Hemobilia Infections (Cholangitis and Peritonitis)
Pre-LT factors	Infections (CMV or intra-abdominal infections) Diagnosis for LT: PSC or AIH	Infections (Cholangitis and Peritonitis) Strictures (NAS and AS) Bile duct filling defects (stones/sludge/clots/casts)
Post-LT factors	Immunosuppression: Emerging evidence that Sirolimus based regimen have higher risk of biliary strictures Infection, Acute cellular rejection, Obstruction, *etc.* Post-operative small bile leak is risk factor for future strictures Early HCV recurrence post-LT also increases inflammation and hence risk of strictures	Strictures (NAS and AS) Biliary cast syndrome

HAT: Hepatic Artery Thrombosis; NAS: Non-anastomotic stricture; AS: Anastomotic stricture; DCD: Donor after cardiac death; DBD: Donor after brain death; CC: Choledocho-choledochostomy; RYC: Roux-en-Y choledochojejunostomy.

but much higher (19%-32%) among living donor liver transplants (LDLT)[8]. They are encountered irrespective of type of anastomosis, although may be more common with Roux-en-Y hepaticojejunostomy or choledochojejunostomy reconstructions than duct-to-duct anastomoses[21]. They can be classified according to time of stricture development from LT as early (within 1 mo post-LT) *vs* late (more than 1 mo post-LT) or classified according to anatomical site into two categories-anastomotic strictures (AS) and non-anastomotic strictures (NAS) or ischemic strictures.

AS are usually single, localized to the site of anastomosis, short in length and occur within a year after LT[6,8] (Figure 1). Recent literature suggests their incidence to be < 10%, and they are formed as a result of ischemia, fibrosis or bile leak during or after the surgery. They are a reflection of intra-operative technical problems or small bile leaks or transient ischemia, resulting in peri-anastomotic fibro-inflammatory response leading to stenosis. Since bile leak is an important risk factor for development of AS, they need to be recognized early and managed appropriately. They can also form due to the sub-optimal surgical techniques like inappropriate suture material and excessive use of cautery for control of bleeding, in which case they are formed relatively early in the post-operative period[8]. Furthermore, there is emerging evidence that type of immunosuppression being used may have a role in development of AS, and need for early ERC for management of AS[22]. Most patients with very early stricture post-OLT may not have true AS, but a stenosis due to post-operative edema and inflammation, which responds very well to single dilatation and/or stenting session. True AS usually occurs between 3-12 mo after LT.

NAS, on the other hand, tend to be multiple, longer in length and are either intrahepatic or in the donor duct proximal to anastomosis, and defined as being present more than 0.5 cm away from anastomotic site. They tend to occur earlier than AS with mean time of presentation 3-6 mo post-LT and have an incidence of 5%-15%[23,24]. Although most NAS are multifactorial,

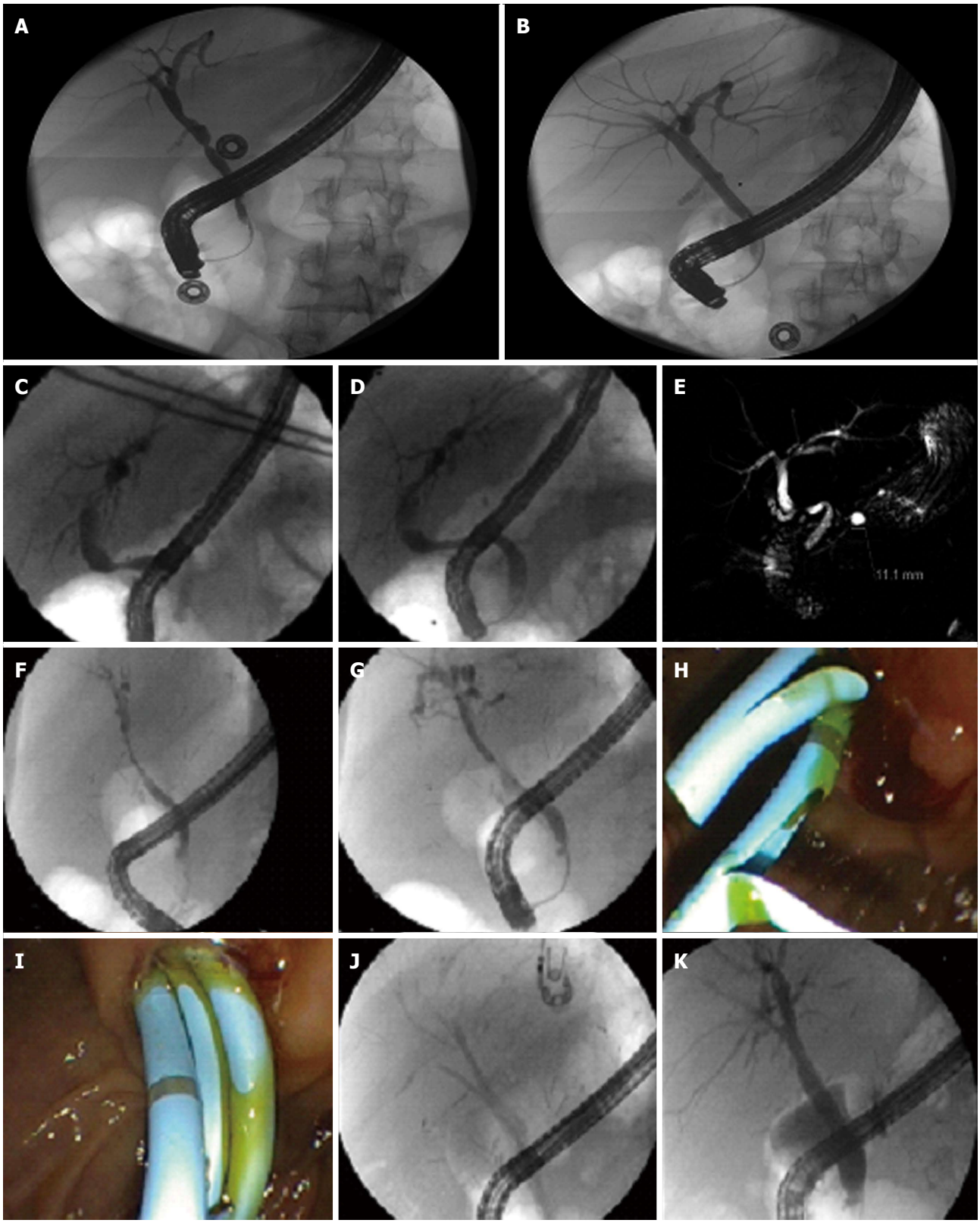

Figure 1 Different management strategies for biliary strictures. A: Post-LT anastomotic biliary stricture (as seen on ERC); B: managed with balloon dilatation only; C: Post-LT anastomotic biliary stricture (as seen on ERC); D: Managed with balloon dilatation; E: MRCP image of the same stricture; F: Long segment biliary stricture due to global hypotension post-LT; G: Dilatation performed with biliary balloon; H: Followed by placement of two plastic stents; I: Due to inadequate effect with two stents, sequential therapy strategy adopted with placement of three stents; J: Fluoroscopic image of three stents in right posterior and anterior hepatic and left hepatic ducts; K: Final cholangiogram suggesting a much improved bile duct diameter. ERC: Endoscopic retrograde cholangiography; LT: Liver transplantation.

they can further be divided into 3 sub-types based on their etiology: (1) macroangiopathic - secondary to hepatic artery thrombosis (HAT) leading to biliary destruction; (2) microangiopathic - secondary to

prolonged use of vasopressors in the donor, donation after cardiac death (DCD), prolonged warm and cold ischemic events; and (3) immunogenic - in patients with primary sclerosing cholangitis, ABO incompatibility, chronic rejection, CC chemokine receptor 5delta32 polymorphism or autoimmune hepatitis, which may act as an independent risk factor[8,23,25]. NAS can also be referred to as type Ⅰ (extra-hepatic), or type Ⅱ (intra-hepatic) and a combination of two[26]. Furthermore, Buis *et al*[27] proposed another classification of the anatomic regions of the biliary tree affected by non-anastomotic biliary strictures: hilar bifurcation (zone A), ducts between the first- and second-order branches (zone B), between second- and third-order branches (zone C) and in the periphery of the liver (zone D). Vascular NAS develops because the blood supply to donor bile duct comes from recipient hepatic artery, which is susceptible to ischemic injury post-transplant, while its native alternative supplies from smaller collaterals and branches of other arteries are transected during organ retrieval. The immunogenic NAS tend to occur later than vascular NAS. Because of their established relationship with ischemia, vascular patency of hepatic artery must be ascertained in these patients with a Doppler ultrasound. Patients who develop manifestations of NAS within the first year of transplant or have recurrent cholangitis, have the most unfavorable prognosis[28].

Management: Historically, post-LT biliary strictures were managed surgically *via* Roux-en-Y hepaticojejunostomy. However, over the past decade there has been tremendous improvement in endoscopic techniques, making endotherapy the treatment of choice for management of these strictures[29-31]. PTC and surgery are less often utilized, and usually reserved for cases where ERC cannot be used or has failed. Although not evidence-based, ursodeoxycholic acid is sometimes used to increase bile flow, and lower the chances of stone formation.

ERC is generally used to perform endoscopic biliary sphincterotomy (EBS) followed by balloon dilation and placement of biliary stent(s) to treat biliary strictures (Figure 1). Balloon dilation, if performed alone, has a high recurrence rate of 62% which decreases to 31% when performed with stent placement[32,33]. However, a recent prospective study by Kulaksiz *et al*[34] showed that dilation alone was as effective as dilation plus stent placement and in fact, stent placement was associated with a higher complication rate. However, more data is needed to clarify this discrepancy.

The most commonly used approach for treatment of AS consists of placement of large-bore 10-French plastic stents after balloon dilation and exchanging them every 3 mo (Figure 1). The median duration of plastic stent patency is around 3 mo (range 2-4 mo), as they are prone to debris deposition in their lumen resulting in obstruction, and risk of cholangitis. This approach has a success rate of 75% to 91% according to different studies for DDLT[32,35-38] but decreases to 37%-71% in patients with LDLT[39,40] because of the more complex duct-to-duct anastomosis. Factors limiting efficacy include peripheral location and presence of smaller and multiple biliary anastomotic strictures. It is also advised that balloon dilation should not be performed for very early strictures and for strictures in the setting of an anastomotic leak to prevent disintegration of biliary anastomosis. Severe complications of this technique are rare, although, a large study showed a complication rate of 6.6% per procedure which increases to 21% per patient as they get more than one procedure[41]. Some of the complications include pancreatitis, cholangitis, stent migration and hemorrhage. There was no death attributable to the procedure itself. An alternative approach to manage biliary strictures is to place maximum number of stents possible, which can then be exchanged at frequent intervals (Figure 1). This method is more aggressive but has shown to achieve a high long-term stricture resolution rate of 90%-94% with less frequent episodes of cholangitis[42,43]. This is a particular advantage of endoscopic therapy, as multiple stents cannot be placed using percutaneous catheter.

Metallic stents are generally useful only for malignant biliary obstruction as they provide effective palliation with a larger diameter (viz. 30-Fr) and longer patency[44]. They are either balloon-mouthed or self-expanding metallic stents (SEMS), but the fact that metal stents cannot be removed makes them less favorable in the setting of benign biliary diseases. Furthermore, possibility of reactive hyperplasia resulting in sludge/stone formation proximal to the stent poses a technical challenge, especially when SEMS cannot be removed. However, covered-SEMS (CSEMS = metallic skeleton with biocompatible and resistant synthetic covering viz. silicon, polyether polyurethane, polyurethane and expanded polytetrafluoroethylene) can be easily removed as the outer coating of the stents prevents tissue ingrowth, seen in about 20% patients. The major limitation with fully covered SEMS, however, is the relatively higher migration rate (6%-10%), which is now counterbalanced by development of partially-covered SEMS (PCSEMS), which provide advantages of covered stent but lower migration rates. Different types of metal stents are currently available, differing in their composition, like stainless steel or nitinol (which is a biocompatible metal alloy of titanium and nickel). Currently available SEMS are either fully covered (Viabil, Wallflex and Niti-S ComVi, *etc.*), or partially covered (Wallstent, Wallflex, *etc.*). Vandenbroucke *et al*[45] showed that Wallstents used in benign strictures after LT can be removed in 66% of patients and offer an option in patients with persistent proximal or anastomotic strictures who have multiple co-morbidities to undergo hepaticojejunostomy or re-transplantation. Similarly, Tee *et al*[46] showed benefit of such SEMSs in patients with refractory post-LT anastomotic biliary strictures. A recent meta-analysis by Kao *et al*[47] inferred that although SEMS appears to be promising

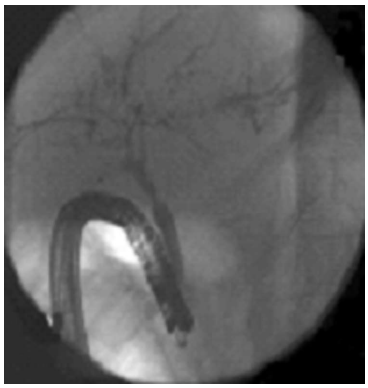

Figure 2 Diffuse non-anastomotic intra-hepatic biliary structuring seen in a donation after cardiac death liver transplant patient, not amenable to endoscopic therapy.

strategy in management of anastomotic biliary strictures in post-LT patients, but current evidence is not enough to suggest clear advantage of SEMS over multiple plastic stents.

NAS are generally more difficult to treat and even though there have been several advancements in endoscopy, overall endoscopic management of NAS remains sub-optimal and endoscopic therapy only acts as a bridging therapy to liver transplantation. This is due to the fact that balloon dilation of all NAS is not feasible (Figure 2) and stent occlusion is rather rapid because of the smaller caliber of the intrahepatic ducts where these strictures are commonly observed. Basic management principles including sphincterotomy and stent placement with scheduled exchange are similar to AS, but endoscopic therapy of NAS typically utilizes smaller diameter balloon dilation (of 4- to 6-mm compared with 6 to 8 mm for AS). Also, just like AS, strategies like use of multiple stents, and stents of progressively increasing diameter have been employed in management of NAS successfully. However, despite all these maneuvers, there is evidence that NAS requires longer time to respond to endoscopic therapy (dilatation + stenting) compared to AS (185 *vs* 67 d)[48]. Use of conventional stents like Amsterdam stent is less satisfactory since these stents are rigid and do not have side holes for draining bile. However, long and large-caliber (up to 20 cm with 10 Fr), flexible and fenestrated stents (Johlin pancreatic wedge stents) can be used. The flexibility helps them to adapt to the tortuous contours of the intrahepatic ducts and multiple side holes allow adequate bile drainage. Endoscopic therapy for NAS, for reasons explained above, has an overall low success rate of 25%-33% in LDLT and 60% in DDLT[40]. In cases of NAS associated with early HAT, aggressive management with either revascularization or early re-transplantation is the key to management, prior to development of intrahepatic complications like biloma and abscess formation.

Endoscopic therapy has generally been reserved for duct-to-duct anastomosis; however, with introduction of single (SBE) and double balloon enteroscopy (DBE), deep ERC can be performed even in patients with Roux-en-Y hepaticojejunostomy[49,50]. A large, multicentric study by Shah *et al*[51] showed that in patients with surgically altered biliary anatomy, SBE, DBE or rotational over-tube enteroscopy can be used to perform ERC successfully in 88% of patients in whom papilla is reachable. Once the duct is accessed, all interventions can be performed like stricture dilatation or stent placement. Another recent advancement has been the use of steerable ERC cannulas like Swing-Tip cannula, which is potentially helpful equipment in management of hilar strictures by using multiple guide wires, and repeated dilation of strictures with placement of stents. These cannulas also help to achieve faster cannulation of the bile duct[52].

Direct cholangioscopy using SpyScope technology has also been utilized to visualize biliary anatomy, and diagnose and manage biliary strictures. It has been studied to be safe and technically superior to conventional cholangiogram in different reports[53-56]. Siddique *et al*[57] demonstrated that direct choledochoscopy also helps in providing targeted treatment to patients. Exciting advancements in this field are happening, although not rapidly enough to make cholangioscopy a consistent tool in management algorithm of post-LT strictures. Balderramo *et al*[58] observed two distinct visual patterns of post-LT AS on direct cholangioscopy, described either as erythema or as edema, sloughing and ulceration, to help predict outcomes after endoscopic therapy. AS patients with only edema responded better with endoscopic therapy, while patients with sloughing and ulceration needed longer duration of stenting[58]. Different types of cholangioscopes (Polyscope) and techniques like use of methylene blue are combined with cholangioscopy to diagnose and delineate features of biliary strictures in patients post-LT[59,60].

Apart from endoscopic therapy, percutaneous transhepatic cholangiography (PTC) can also be used for treatment of AS. However, it is usually reserved for patients with bilio-enteric anastomosis or patients who have failed endoscopic treatment or are at higher risk of complications like bile leaks, infections and hemorrhage[11,61]. Surgery and re-transplantation are reserved for strictures refractory to endoscopic therapy, when all endoscopic and non-surgical options have been exhausted.

Biliary leaks and bilomas

Biliary leaks can be seen in 10%-25% of patients after LT. Although, their incidence has decreased in post-MELD era, it is seen more common after LDLT[62-64]. Biliary leaks mostly occur at 3 sites-anastomotic site, exit site of T-tube and at the site of cystic duct remnant[65]. The bile leaks at anastomotic site are reflection of dehiscence due to technical errors, tension or ischemia and devascularization of the tissue surrounding the biliary tree, in which case hepatic artery thrombosis is a common culprit and must be investigated with

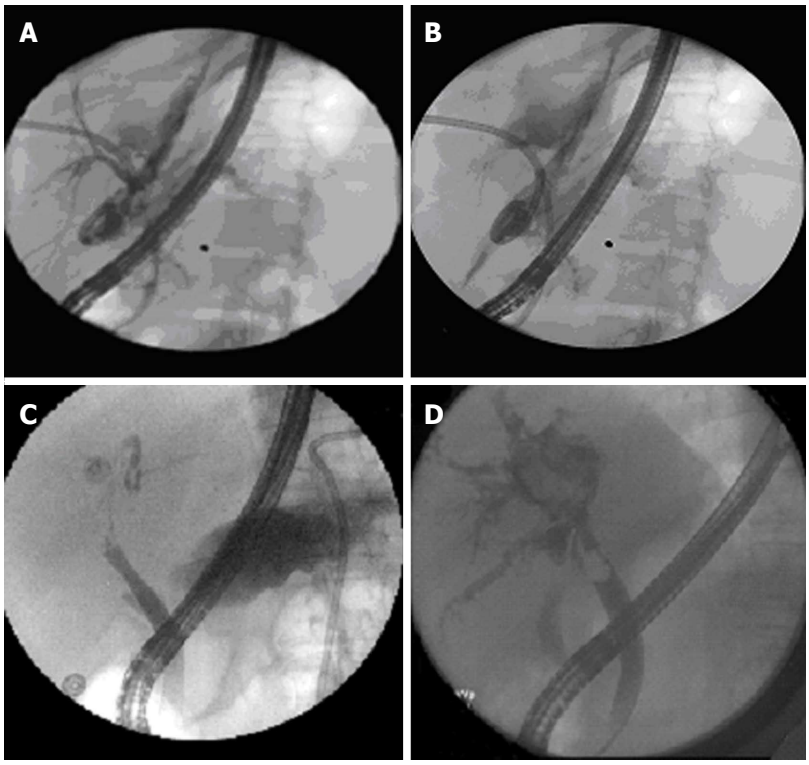

Figure 3 Management strategies for bile leak and biloma. A: Bile leak from split surface of the liver in a patient with split-liver transplant; B: Managed successfully with endoscopic plastic stent placement; C: In a separate patient, bile leak successfully managed by placement of a fully covered metal stent; D: In yet another patient, intrahepatic biloma, which becomes apparent on occlusion cholangiogram.

ultrasound Doppler. Less common sites of bile leak include ischemic injury to extra-hepatic bile duct (at non-anastomotic site), gallbladder fossa, aberrant bile duct (Luschka's duct) and cut surface of liver in LDLT or split livers (Figure 3). If bile extravasation occurs within the liver parenchyma or abdominal cavity, it may form collections called as biloma. Biliary leaks are generally divided according to time of occurrence into[66]: (1) early-occur within a month of the transplant and are usually associated with anastomotic leaks, ischemic injury and leakage around T-tube insertion site[2]; (2) late-occur more than a month after LT and noticed usually at the time of T-tube removal[67,68]. These are less common. Use of steroids or immunosuppressant medications post-LT is also alleged to hamper the healing process after T-tube removal.

Biliary leaks may present with abdominal pain or distension or patient might be asymptomatic, in which case, it is detected accidentally on abdominal imaging. One of the early indicators is the persistence of bile in the operative drain output. This can be confirmed with the help of a T-tube cholangiogram (in patients with a T-tube), or imaging like radionuclide scan (HIDA) or MRCP that can reliably detect a biloma and may localize the level of the leak[69].

Management: Most patients with biliary leaks can be managed endoscopically. ERC is most often used to perform biliary sphincterotomy and placement of biliary stent that can be kept in place for up to 2-3 mo (Figure 3). Although symptom resolution is fast after stent placement, the actual healing of leak may take up to 6-10 wk. Several studies suggest a success rate of 80%-90% using this strategy[8,70,71]. In case of an associated stricture, stent placement across the leak and stricture are prudent. In case of T-tube associated bile leaks confirmed on T-tube cholangiogram, leaving the drain open might suffice, without need for any further interventions. Naso-biliary drainage can also be performed in place of biliary stenting and Saab *et al*[72] in fact suggested that it might be the preferred strategy for management of biliary leaks. Although naso-biliary tubes can be useful for cholangiographic follow-up without further endoscopies and confirmation of leak sealing, however are very poorly tolerated. A small study showed that small leaks can be managed with sphincterotomy alone[73], however this is not the usual practice. In certain circumstances, along with bridging provided with the stent, drainage of the fluid collection might be needed, especially in large biloma with no communication with bile duct. This can be performed *via* EUS guided trans-gastric drainage or the traditional IR-guided drainage. Usually small bilomas resolve spontaneously, if there is adequate communication with duct, and some may require placement of a biliary stent. Despite these endoscopic advancements and options, there may be an occasional case where biliary leak cannot be treated endoscopically and thus requires surgery. These special cases include large anastomotic leaks, cases with Roux-en-Y anastomosis, early biliary leaks (< 1-2 wk after LT), bile duct necrosis or failure of primary therapy[3,69].

Sphincter of Oddi Dysfunction or papillary stenosis

Sphincter of Oddi Dysfunction (SOD) has an incidence of 2%-3.5% after LT. It is an incompletely understood and poorly defined syndrome of questionable significance[74]. It is thought to occur secondary to

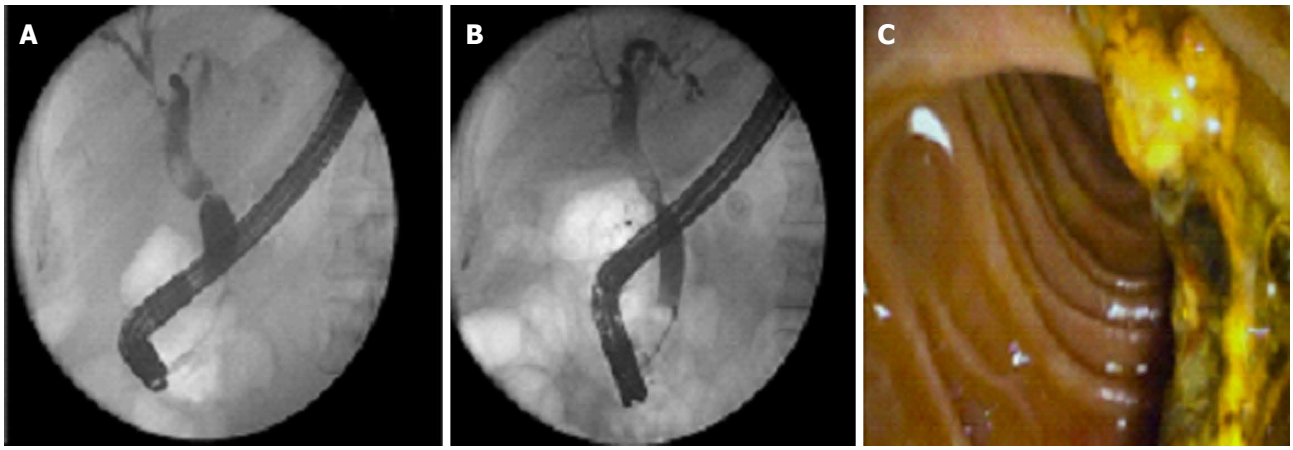

Figure 4 Management of common bile duct filling defects. A: Common bile duct (CBD) filling defect seen proximal to mid-CBD stricture in a post-liver transplantation patient; B: Successful removal of stone after dilatation the stricture; C: Endoscopic image of successfully extracted stone and sludge in this case.

denervation of Sphincter of Oddi during LT leading to a hypertonic sphincter. It can be divided into 2 types based on the mechanism of its pathogenesis: (1) SOD with stenosis - which occurs due to scarring and inflammation. The contributing processes can be CBD manipulation during LT, stone passage through papilla, or infection. Sphincter of Oddi has high basal pressure in this type; and (2) SOD with dyskinesia - which occurs due to functional disturbance of the sphincter resulting in intermittent biliary blockage. The sphincter in these cases has low basal pressure and absent phasic activity[74], and additional neurological or hormonal disturbances may be associated with development of functional disturbance[75].

Both types of SOD can lead to pain, recurrent pancreatitis and cholestasis without any apparent etiology, and hence need a high clinical suspicion for diagnosis. Biliary manometry can be utilized to confirm the diagnosis. Selective patients may be managed endoscopically, and ERC with sphincterotomy is usually reserved for patients with dilated bile duct with cholestasis liver chemistries, without any other obvious cause. It is aimed at cutting the sphincter muscles, resulting in reduction of the intra-luminal biliary and pancreatic hypertension, and symptomatic relief. However, the procedure has high risk of post-procedure pancreatitis and usually pancreatic duct stent is placed prophylactically[76]. In case of failure of endoscopic therapy, choledochojejunostomy is the last resort.

Biliary stones, sludge, casts, and blood clots

Biliary stones, sludge, casts, and blood clots are collectively referred to as "Common Bile Duct (CBD) Filling Defects" and can be seen in 3.3%-12.3% of patients after LT[77,78] (Figure 4). Stricture, infection and ischemia can result in biliary stones and sludge; and sloughed biliary epithelium, chronic rejection, infection, and bile stasis, have been associated with formation of biliary casts. They have been postulated to be related to strictures, bacterial infection, mucosal damage and ischemia[78-80]. These patients might present with abdominal pain, cholestatic liver enzyme pattern or may have recurrent episodes of cholangitis and pancreatitis[11]. However, many patients with choledocholithiasis may be completely asymptomatic, which is often attributed to the fact that transplanted graft is denervated, and may also be afebrile because of steroids and immunosuppressant medications they are on post-LT. Occasionally, CBD filling defects may form due to stagnation of bile proximal to a stricture, in which case management becomes challenging (Figure 4). Because of ischemic etiology to biliary cast syndrome, HAT exclusion with appropriate imaging becomes prudent.

Management: ERC with sphincterotomy has a success rate of 90%-100% in clearing biliary stones and sludge; however removal of biliary casts can be challenging and may require multiple procedures including sphincterotomy, balloon or basket extraction, stent placement and lithotripsy, or may need PTC eventually[77,79]. For removal of biliary casts, endoscopy has shown to successful in 25%-60% of patients across different studies[79,81]. In fact, in cases with severe biliary necrosis and casts, repeated interventions with baskets and dilatations are necessary, and placement of stents is not generally recommended in the early course, for risk of occlusion by biliary debris[82]. On the contrary, biliary duct stones are usually easily removed using ERC with biliary sphincterotomy and balloon sweeps (Figure 4). Occasionally, proximal stones may pose a challenge, and in those cases direct cholangioscopy can be performed to remove biliary stones. Also if filling defect lies proximal to a post-LT stricture, then stricture management becomes first step towards the goal of clearing the duct (Figure 4). Lithotripsy and Holmium Laser can be combined with this procedure for stone dis-impaction. Direct cholangioscopy can be performed using ultra-slim, pediatric endoscopes which can be directly advanced into the bile duct to examine duct anatomy and removal of biliary stones and casts[69]. Again, deep enteroscopy can be utilized to perform

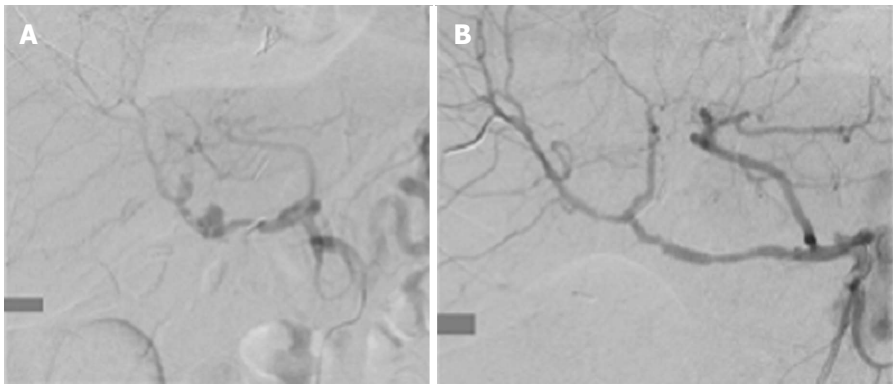

Figure 5 Rare cause of Hemobilia. A: Hepatic artery pseudoaneurysm fistulizing to the common bile duct, resulting in hemobilia; B: Managed with intravascular stent placement by interventional radiology.

ERC in patients with Roux-en-Y anastomosis to remove biliary stones or casts[83].

Mucocele

Mucocele of cystic duct results from collection of mucus from the cells lining the cystic duct remnant, and is an extremely rare entity in post-LT patients. Key to diagnosis is cognizance of this diagnostic possibility in a patient with post-LT obstructive jaundice or cholangitis with no apparent cause, and confirmation with MRCP, which would show an extrinsic mass (fluid collection) compressing the bile or hepatic ducts[84]. Patients usually require surgical or radiological drainage. To prevent this complication, usual operative practice involves either excising the cystic duct, or incorporating the distal end of the transected cystic duct into the suture line of the biliary anastomosis to ensure drainage[85].

Hemobilia

While hemobilia may not be a direct consequence or complication of liver transplant itself, it can happen after liver biopsy or PTC performed in post-LT period for management of various issues. Patients present with abdominal pain, jaundice and gastrointestinal bleeding, and upper endoscopy using regular forward-viewing gastroscope (or side viewing duodenoscope) typically reveals blood extruding from the ampulla. Management goals are hemostasis, as well as confirming clearance of bile duct of any clots, which would otherwise be a source of potential obstruction and cholangitis. Hemostasis may be achieved with a multi-prong strategy of coagulopathy correction, endoscopic therapy with use of epinephrine and electro-cautery if bleeding site is accessible, otherwise localization of bleeding with hepatic artery angiogram followed by embolization of feeding vessel radiologically[86]. Once hemostasis is achieved, clot retrieval and clearance of duct can be achieved with ERC if there is evidence of biliary obstruction. Figure 5 (used with permission from Farshad Aduli, MD) represents a case seen by authors, of post-LT hepatic artery pseudo-aneurysm fistulizing to the common bile duct resulting in hemobilia, which was managed by intravascular stent placement by interventional radiology.

SPECIAL ISSUES AFTER LT

Management of biliary complications in patients with Roux-en-Y Hepaticojejunostomy and Roux-en-Y gastric bypass

With the increase in number of liver transplants being performed and limited number of DDLT, there is increase in use of LDLT and split liver transplant strategies. This has resulted in more complex anatomy post-LT. Roux-en-Y Hepaticojejunostomy and Roux-en-Y gastric bypass are the 2 main altered surgical anatomies that are often encountered in post-LT patients. Roux-en-Y gastric bypass creates a common limb of 150 cm and a bilio-pancreatic limb of 150 cm, which makes conventional endoscopy and ERC challenging. Traditional PTC has been utilized for management of post-LT biliary complications in such patients with altered anatomy. However, as mentioned earlier, development of DBE, SBE and spiral enteroscopy has increased the endoscopic options that permit ERC in these patients[51,87,88]. Details of the success of this technique have been discussed earlier. However, it may not be possible to utilize this strategy in all patients, due to unfavorable surgical anatomy, adhesions, limited maneuverability of the scope around biliary anastomosis, and limited number of small-caliber ERC instruments that can be used through these devices. Also, these procedures require high skill and expertise and the learning curve is steep and hence available only at specialized centers. Another specialized technique that is being tried is formation of gastrostomy, either surgically or percutaneously using EUS, and then performing ERC through the gastrostomy port[89]. A single study using this approach achieved biliary intervention successfully in all patients as compared to 58% success rate with deep enteroscopy, and should be evaluated further[90]. Lastly, an alternative approach that may be potentially used in patients with altered anatomy is the use of direct

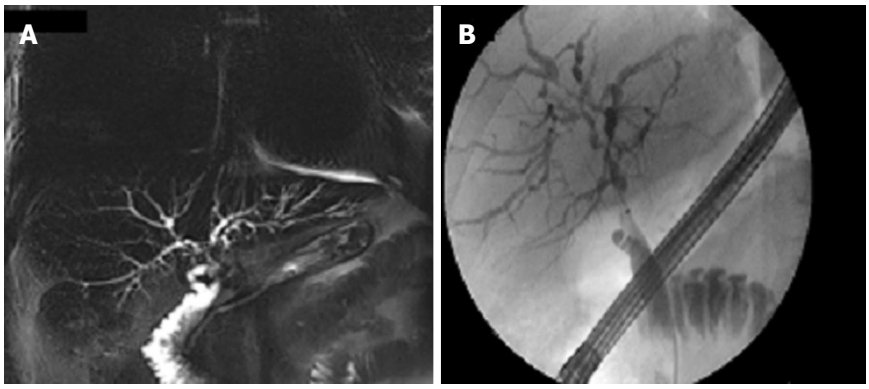

Figure 6 Don't forget the native disease. Recurrence of native disease can mimic biliary complications, hence appropriately investigated with magnetic resonance cholangiopancreatography (A) and/or endoscopic retrograde cholangiography (B). This patient was transplanted for primary sclerosing cholangitis, and had disease recurrence involving the intra-hepatics few years later.

cholangioscopy after percutaneous tract has been created. Direct visualization of bile ducts is possible using this method and can be used for removal of bile duct stones, dilation of stricture and placement of stents.

Biliary complications in recipients of LDLT and DCD transplants

Biliary complications after LT from living donors (LDLT) or grafts from donors after cardiac death (DCD) are more frequent than encountered with conventional donors after brain death (DBD). Complications that occur at a higher rate after LDLT included biliary leak (31.8% *vs* 10.2%), unplanned re-exploration (26.2% *vs* 17.1%), HAT (6.5% *vs* 2.3%) and portal vein thrombosis (2.9% *vs* 0.0%)[91]. However, there is suggestion that these complications may decrease as experience of LDLT center grows. The main reason for higher biliary complications is relatively smaller duct size, making the anastomosis technically difficult, and hence a higher chance of ischemic injury, especially in right-lobe LDLT[92]. Endoscopic management in LDLT recipients may be challenging given the complex nature of their duct-to-duct reconstruction, especially those involving smaller caliber ducts (< 4 mm), than when a hepatico-jejunostomy is used with these duct sizes. If attempted, smaller diameter stents (7.0-8.5 Fr) need to be used in these scenarios, and ERC performed more regularly because rates of re-stenosis are high with shorter duration of stenting. On the contrary, DCD is commonly associated with significant risk for both early and late biliary complications, including strictures, and many patients develop more than one biliary complication[93]. The major difference between pathogenesis of post-LT NAS in DCD is that the contributing mechanism is ischemic injury, which occurs before organ retrieval, rather than ischemia post-anastomosis in conventional DBD NAS[93]. There is also emerging evidence that the type of preservative solution (HTK solution) may also affect future incidence of biliary complications in DCD patients[94]. The endoscopic management principles remain the same, although intra-hepatic and small duct strictures may be more common making them less amenable to endoscopic management. There is evidence that although unilateral and easily approachable strictures may be managed endoscopically (with > 85% long-term survival), most DCD patients have diffuse intrahepatic structuring disease, due to global organ ischemia, which negatively impacts their long-term survival[95].

Sedation for ERC in post-LT patients

The sedation regimen for ERC in non-transplant setting may vary based on country, type of practice, endoscopist preference, age and co-morbidities of patient, and availability of anesthesia support. Conscious sedation (using opioids and/or benzodiazepines) is being increasingly less preferred for ERC, because it is long and uncomfortable procedure, and adequate patient relaxation and sedation is vital for the success of this critical procedure. Data suggests that propofol is superior to benzodiazepines for sedation during an ERC procedure, even in high-risk octogenarians[96]. Further studies proved that the combined use of propofol and midazolam or fentanyl for sedation has some benefits and no safety concerns, compared to using either drug alone[97]. There are adequate safety results for the administration of propofol by nonanesthesiologists[98]. For these reasons, at our center, like most of the other hospitals in the United States, ERC's are usually performed under anesthetist administered general anesthesia or monitored anesthesia care using propofol. Safety of opioids/benzodiazepines as well as propofol based regimens have been adequately demonstrated for GI endoscopic procedures, in several studies[99,100]. However, there is no such data available in post-LT patients, and is an area for further research. Nevertheless, in our experience of performing ERC's on post-LT patients over the last 6 years, we have not encountered any sedation related complication, and we attribute that to proper patient selection and careful optimization of patient co-morbidities before embarking on this critical procedure. Based on our experience, we endorse anesthetist administered anesthesia as a

routine sedation strategy for all post-transplant patients requiring ERC, taking into consideration the overall high-risk nature and length of this procedure, frequent need for multiple therapeutic interventions and patient co-morbidities.

CONCLUSION

Biliary complications are being increasingly encountered in post liver transplant patients because of increased volume of transplants being done and longer survival of these recipients. Overall management of these complications may be challenging, but with advances in endoscopic techniques, majority of such patients are being dealt with by endoscopists rather than the surgeons. ERC with various interventions, like sphincterotomy, bile duct dilatation, and stent placement, remains the mainstay for management of bile leaks, strictures and bile duct filling defects. Recurrence of native disease is the greatest mimicker of post-LT biliary complications, and hence must be investigated thoroughly with advanced imaging or endoscopic means (Figure 6). With increasing number of patients with altered anatomy, whether due to obesity epidemic or use of non-traditional anastomoses in liver transplant strategies like living-donor or split livers, ERC in these patients has been a perplexing issue and many require interventional radiology or surgical procedures. However, with ongoing attempts at developing improved tools and techniques to access the bile duct in patients with surgically altered anatomy, endoscopy will likely become unopposed frontier in this subgroup of patients as well.

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REVIEW

Role of stenting in gastrointestinal benign and malignant diseases

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Abstract

Advances in stents design have led to a substantial increase in the use of stents for a variety of digestive diseases. Initially developed as a non-surgical treatment for palliation of esophageal cancer, the stents now have an emerging role in the management of malignant and benign conditions as well as in all segments of the gastrointestinal tract. In this review, relevant literature search and expert opinions have been used to evaluate the key-role of stenting in gastrointestinal benign and malignant diseases.

Key words: Endoscopic stenting; Stricture; Leak; Complication; Cancer

Core tip: Endoscopic stenting plays an indispensable role in the treatment of benign and malignant digestive strictures and leaks. In this review, we summarize data from randomized clinical trials or prospective studies together with meta-analytical data, when applicable; to present the most updated recommendations in stenting of gastrointestinal diseases.

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INTRODUCTION

Stenting has become an optimal option for the treat-

ment of a variety of gastrointestinal malignant and benign diseases, which plays a vital role in alleviating obstructive symptoms such as dysphagia, pain, and improving patients' quality of life.

Over the past 30 years, dramatic changes have occurred in the composition and design of stents and their application to digestive disorders.

For example, stent composition began with plastic, evolved into self-expandable metal stents (SEMSs) and may soon evolve into biodegradable stents. At the same time, indications for stenting that began with esophageal cancer now include benign and malignant disorders involving a variety of sites in the gastrointestinal tract.

This paper will outline the indications and outcomes of stenting, the techniques of placement, composition and design of stents and prospects for new and improved stents.

TYPES OF STENTS AND PRINCIPLES FOR STENTING

A stent is a cylindrical medical device used to widen a narrow or stenosed lumen in order to maintain the patency of the lumen. The first stents were made of hard plastic and were used for obstructive esophageal cancers. Whereas early stents were mostly composed of plastic, the majority of contemporary stents are metal stents that are composed of either nitinol or stainless steel.

Nitinol mesh has improved the quality of the stents, replacing the other materials. This nickel-titanium shape-memory alloy is soft and flexible, with smoother wire ends, reducing the risk in and overgrowth.

Metal stents are available as uncovered, partially covered (PC), or fully covered (FC). An uncovered SEMS consists of a mesh that is bare and expands into the stenosis. A FCSEMS consists of a mesh stent that is covered by a membrane throughout its length. A PCSEMS consists of a stent with a membrane covering and uncovered proximal and distal ends of the stent.

Recently, FC self expanding plastic stent (SEPS) and biodegradable stent was developed. SEPS is made of woven plastic strands, while biodegradable stent is made from commercially available polydioxanone absorbable surgical suture material. Polydioxanone is a semicrystalline, biodegradable polymer. It degrades by hydrolysis of its molecule ester bonds, which is accelerated by low pH. The amorphous regions of the matrix deteriorate first and the crystalline portion deteriorates later.

Most of the metal stents on the market are mounted on a delivery system that consists of two coaxial tubes, but there is also a type of metal stent mounted on a delivery system with a user-friendly braided-suture release mechanism and it is deployed by pulling a ring attached to the suture string, thereby unraveling the string and slowly releasing the stent (Ultraflex esophageal or colonic stents, Boston Scientific/Microvasive, Natick, Massachusetts).

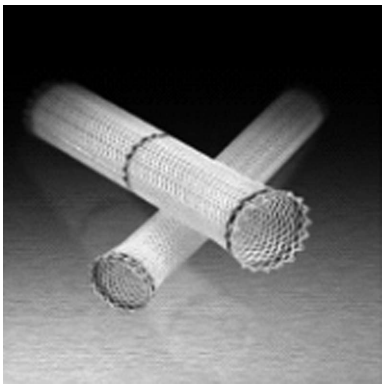

Figure 1 Boston scientific polyflex stent.

There are 2 types of delivery systems: through the scope (TTS), able to pass through the operative channel of the endoscope, and over the wire (OTW) that does not pass through the operative channel of the endoscope. The main differences between the delivery systems are the design of the handles, the lengths and the diameter, which determines the means of deployment.

Although the majority of deployment systems release the stent initially at the distal end of the catheter, there are some types of gastrointestinal stents available in both a proximal and distal release system (*i.e.*, Ultraflex esophageal stent NG/Boston Scientific and the esophageal Nit-S®/TaeWoong). In contrast to most SEMSs, which are sold in a constrained packing, the SEPS requires mounting onto the delivery catheter just before use. One important aspect of deployment is the variable degree of foreshortening that occurs with a majority of SEMSs and SEPS during the transition from the compressed to fully expanded state. The endoscopist must anticipate and allow for this foreshortening to ensure appropriate placement.

Before stenting firstly the lesion should be endoscopically or radiologically evaluated, the proximal and distal aspects of the lesion identified and a guide-wire advanced through the lesion, and the stent positioned across and then deployed under fluoroscopic and/or endoscopic guidance by release of the constraining mechanism.

Esophageal stents: Table 1

The SEPS Polyflex® (Boston Scientific) is a stent of polyester braid completely covered in silicone membrane. The stent need to be loaded prior to insertion into a large diameter delivery device (36-42 Fr) and is available in different sizes (diameters of 16, 18, and 21 mm and lengths of 9, 12 or 15 cm). Are available with proximal flare diameters of 20, 23 and 25 mm, the proximal end is flared for preventing distal migration with radio-opaque markers at the ends and in the middle for a more precise placement (Figure 1).

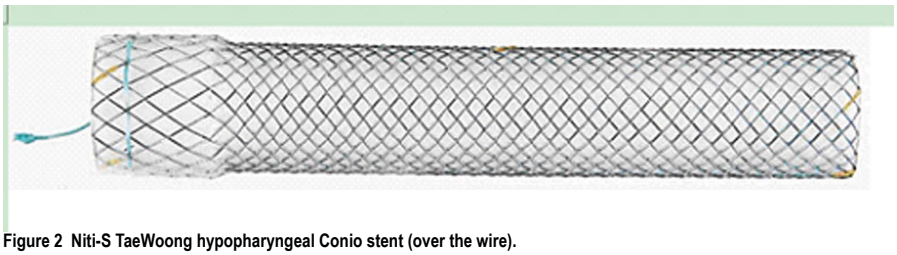

Figure 2 Niti-S TaeWoong hypopharyngeal Conio stent (over the wire).

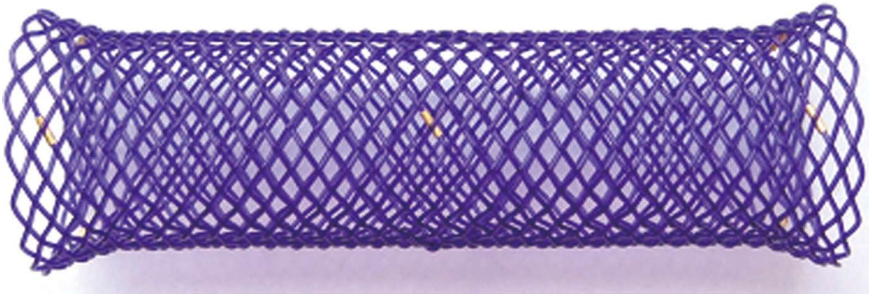

Figure 3 The Ella BD stent.

The most common used esophageal FC-SEMSs are: the Wallflex® (Boston Scientific), Niti-S® (TaeWoong), Evolution® (Cook Medical), Alimaxx-E® (Alveolus, Charlotte, NC, United States), SX-ELLA® stent Esophageal HV (Ella-CS, Hradec Kralove, Czech Republic) and the Hanaro® (M.I. Tech stent) and most of these stents are also available PC.

All these stents are made in nitinol and released OTW, the Alimaxx, Wallflex, Hanaro, SX-ELLA® and Evolution have a distal release, while Niti-S has both distal and proximal release.

The Alimaxx, Niti-S, Hanaro and Evolution are covered in silicone, while the Wallflex stent has the covering made of Permalume®, a particular type of silicone that diminish the food impaction. Actually the only FCSEMS with a possibility of a delivery-system TTS is the Niti-S.

The Wallflex, Alimaxx, Niti-S and Hanaro presents the same OTW release mechanism (the delivery system consists of a coaxial tubing assembly that constrains the stent on the delivery catheter shaft until the stent is released), an innovation, allowing a best control of the release, was recently projected by Cook Medical for the Evolution. The delivery system is composed by a "plastic handgun". With one hand and a squeeze of the trigger, the handle gives a precise control over stent deployment and recapturability. To shift between stent release and recapture, it needs switch the "directional button". There is furthermore a "point-of-no-return" reference mark that alerts when stent recapture is no longer possible.

The Ultraflex (Boston Scientific/Microvasive, Natick, Massachusetts) esophageal stent is another type of prosthesis that has a flared proximal end (23 or 28 mm), available uncovered and PC (the PCSEMS version have 1.5 cm of bare nitinol configured into wire loops at each end, thus sharp elements are absent) and is marketed with both a proximal and distal release design. This stent is highly flexible and is mounted on a delivery system with a user-friendly braided-suture release mechanism, deployed by pulling a ring attached to the suture string, thereby unraveling the string and slowly releasing the stent.

The Taewoong Medical produce specifically designed Niti-S stents. The Niti-S Conio Stent (Taewoong Medical, Seoul, South Korea) is a stent for hypopharyngeal stenosis. The stent have a body with a diameter of 12, 14 or 16 mm, and only the proximal crown has a diameter greater than the body of only 2 mm (14, 16 and 18 mm), to prevent distal migration and reduce the feeling foreign body (Figure 2). The Niti-S Beta stent (Taewoong Medical, Seoul, South Korea) is a newly design OTW stent with distal release with two rings in the body, for the anti-migration mechanism, produced for the treatment of complications of bariatric surgery. The biodegradable implant (ELLA BD stent) (Ella®-CS, Hradec Kralove, Czech Republic) is composed of polydioxanone which is a semi-crystalline polymer biodegradable (Figure 3).

The OTW delivery system has a diameter of 9 mm, the diameter of the stent is 25 mm, while the length varies between 6 and 13.5 cm. After the release in the esophageal lumen, the complete expansion of the stent occurs in 24-48 h. The degradation of the implant begins after 4 wk and the ninth week the radial force (RF) has been reduced by half, therefore the stent does not have to be removed.

The best way to release an esophageal stent is the combined endoscopic and fluoroscopic approach, expecially in presence of a leak, despite some expert endoscopist, only in selected cases, place the stent only with endoscopic control.

Table 1 Characteristics of the most commonly used esophageal stents

Producer	Model	Material	Diameter mm (body/flare)	Length (cm)	Type and characteristics
Merit Endotek	Alimaxx-E®	Nitinol	18/22	7-10-12	Fully-covered with anti-migration system
Merit Endotek	EndoMAXX®	Nitinol	19/24-23/28	7-10-12-15	Fully-covered with anti-migration system
Boston Scientific	Ultraflex®	Nitinol	18/23-23/28	10-12-15	Uncovered and partially-covered Possibility of distal or proximal release
Boston Scientific	Flamingo Wallstent®	Stainless steel	20/30	12-14	Partially-covered
Boston Scientific	Wallflex®	Nitinol	18/23-23/28	10-12-15	Partially and fully-covered
Boston Sientific	Polyflex®	Polyester	16/20-18/23	9-12-15	Plastic stent
Cook Endoscopy	Evolution®	Nitinol	20/25	8-10-12.5-15	Partially and fully-covered
Ella-CS	SX-ELLA® HV	Nitinol	20/25	8.5-11-13.5-15	Fully-covered with collar anti-migration system
Ella-CS	SX-ELLA® Flexella	Nitinol	20/25	8.5-11-13.5-15	Fully-covered Possibility of distal or proximal release Possibility of anti-reflux valve
Ella-CS	FerX-ELLA® Boubella	Stainless steel	20/25	9-10.5-12-13.5-15-16.5-19.5-21	Fully-covered Possibility of anti-reflux valve
Ella-CS	SX-ELLA® Danis	Nitinol	25/30	13.5	Fully-covered (with balloon/specific for variceal bleeding)
Ella-CS	SX-ELLA® Danis Seal	Nitinol	25/30	13.5	Fully-covered (specific for leaks)
Ella-CS	Ella BD stent®	Biodegradable polymer	18/23-20/25-23/28-25/31	6-8-10-13.5	-
Endochoice	Bonastent® ER	Nitinol	18/24	6-8-10-12-14-16	Fully-covered Possibility of anti-reflux valve
M.I. Tech	Hanarostent®	Nitinol	18/24-20/26-22/28	8-9-10-11-12-14-15-16-17	Partially and fully-covered Possibility of double covered configuration, anti-reflux valve and asymmetrical configuration
M.I. Tech	Hanarostent® ECBB	Nitinol	36-30-20-26	18-21-24	Fully-covered (Bariatric surgery)
Micro-Tech	MT® Esophageal stent	Nitinol	(Diameter central/extremities) 18/24-20/26-22/28	8-10-12	Uncovered, partially and fully covered Possibility of anti-reflux valve and radioactive system
Micro-Tech	MT® Cardia stent	Nitinol	16/22-18/24-20/26-22/28-24/30	9-10-11-12-13	Partially and fully-covered
Micro-Tech	MT® Retrievable stent	Nitinol	14/20-16/22-18/24-20/26-22/28-24/30	7-8-9-10-11-12	Fully-covered
TaeWoong Medical	Beta-Stent Niti-S®	Nitinol	18/24-20/26-22/28	10-12-14-15-16-18-20	Fully-covered (Fistula after bariatric surgery)
TaeWoong Medical	Mega-Stent Niti-S®	Nitinol	18/24-20/26-22/28	10-12-14-15-16-18-20	Fully-covered (Stricures or fistula after sleeve gastrectomy)
TaeWoong Medical	Niti-S Conio®	Nitinol	10/12-12/14-14/16	6-8-10-12-14-15	Fully-covered (Hypopharyngeal strictures)
TaeWoong Medical	Niti-S Cervical®	Nitinol	16/18-18/20	6-8-10-12-14-15	Fully-covered (Upper esophageal strictures) Possibility of distal or proximal release
TaeWoong Medical	Niti-S®	Nitinol	16/24-18/26-20/28	6-8-10-12-14-15	Partially and fully-covered Possibility of distal or proximal release for over-the-wire stent Possibility of TTS 10.5 Fr delivery system
TaeWoong Medical	Niti-S® double layer	Nitinol	16/24-18/26-20/28	6-8-10-12-14-15	Fully-covered with additional uncovered nitinol mesh Possibility of distal or proximal release Possibility of anti-reflux valve

Gastro-duodenal stents: Table 2

Different types of enteral stents are actually in use, all with a delivery system TTS (10 Fr) which needs a working scope channel of 3.8 mm.

All the commercialized stent are made in Nitinol, except for the Enteral Wallstent, known as a stainless steel stent, made with a mix of materials called Elgiloy® (Eligoy Inc., Elgin, IL, United States) (cobalt, chromium, nickel, iron, molybdenum, manganese). The Enteral Wallstent is characterized of an excellent RF but with the tendency of straightening, increasing the risk of stent impaction in the angulated sites.

An important role in the gastro-duodenal obstruction is played by two relevant features of the stents: the RF and the axial force (AF).

RF is the expanding force. AF is a force that maintains the stent straight after its placement. Combination of the two forces is more effective than only RF or AF, respectively. The AF straightens the stent, and plays a fundamental role in covered stents. The nature of the nitinol confers to these stents an optimal AF and RF.

Almost all of the TTS SEMS allow re-sheathing of the stent and TTS delivery systems also necessitate a kinking-resistant guide-wire. Delivery systems are

Table 2 Characteristics of the most commonly used duodenal stents

Producer	Model	Material	Diameter (mm) (body/flare)	Length (cm)	Type and characteristics
Boston Scientific	Wallstent®	Elgiloy	20/22	6-9	Uncovered
Boston Scientific	Wallflex®	Nitinol	22/27	6-9-12	Uncovered
Cook Endoscopy	Evolution®	Nitinol	22/27	6-9-12	Uncovered
Ella-CS	SX-ELLA® Eneterella	Nitinol	20-22-25 (no flare)	8.2-9-11.3-13.5	Uncovered
Endochoice	Bonastent® P	Nitinol	20	6-8-10	Uncovered
M.I. Tech	Hanarostent®	Nitinol	20/25-20/26	8-9-11-14	Uncovered and partially-covered
Micro-Tech	MT® Duodenal stent	Nitinol	20/26	6-8-10	Uncovered, partially and fully-covered
TaeWoong Medical	Niti-S® D-type unflared	Nitinol	18-20-22-24	6-8-10-12-14-15	Uncovered
TaeWoong Medical	Niti-S® S-type flared	Nitinol	18/26-20/28- 22/30-24/32-26/34-28/36	6-8-10-12-14-15-16	Fully-covered
TaeWoong Medical	Niti-S® Comvi unflared	Nitinol	18-20-22	6-8-10-12	Partially-covered

available in different lengths (135, 180 and 230 cm). An important characteristic of duodenal stents is the diameter. For obtaining an adequate food transit has to be used stents with a diameter > 20 mm. Some stents have distal flared extremity to improve the anchorage and can be covered and uncovered. The choice of a covered *vs* an uncovered stent depends by the endoscopist, evaluating fatures and site of the lesion. Uncovered SEMS are generally used, in this site, because of the low risk of migration. The flexibility of the uncovered stents allows following duodenal angulations, despite could exercitate high pressure on the angulated strictures. The mesh pressure on the mucosa induces epithelial regeneration, that leads to ingrowth, can contribute to stent occlusion. Then, the placement of a covered-SEMS is preferable in non-surgical patients, or patients with a high risk of mortality and morbidity, with a life expectance > 2-3 mo. Covered stent are generally indicated in the treatment of the tissue ingrowth inside an uncovered stent.

Materials used for covered stent are polyurethane, silicone, and expanded polytetrafluoroethylene. Covered SEMS are conceived to prevent tumor ingrowth and for closing fistula, if present; the only disadvantage of these stent is the tendency to migrate.

Two stents are currently marketed for the closure of fistulas post-sleeve gastrectomy, both over-the-wire (OTW): the Beta-stent® (Niti-S - TaeWoong), with lengths of 15, 18 and 23 cm and a diameter of 24 and 28 mm, and the Hanaro® stent (M.I. Tech) with lengths of 18, 21 and 24 cm and a width of 30 mm diameter. Both the two stents must be placed under fluoroscopic vision, after placing a stiff guide-wire in the duodenum, and present the proximal tourniquet on the crown for removal.

Duodenal stricture evaluation with X-ray enema before the endoscopy is generally not required. The passage of orally administered water soluble contrast through the duodenal stricture is generally delayed because of the gastrectasia, presence of residual food and delayed stomach emptying.

Furthermore, assessment of concomitant proximal jejunal strictures is not satisfactory due to the small amount of contrast that can pass the duodenal stricture. For these reasons stricture assessment during duodenal stenting procedure is preferred. Computed tomography is helpful to exclude the presence of peritoneal carcinosis.

To avoid aspiration, insertion of a naso-gastric tube 24 h before the procedure to empty the stomach, and the prone position during the procedure, are recommended.

Commercially available TTS SEMS require an operative endoscope (3.8 mm diameter working channel). Operative duodenoscopes offer a better visualization of the duodenal stricture lumen, the elevator helps the orientation of the catheter, grips of the guidewire, and the delivery system. Duodenoscopes are also useful for the treatment of a concomitant biliary stricture.

Duodenal stenting placement is performed under fluoroscopic guidance because both endoscopic and radiological controls are preferable. Stricture study is performed by contrast injection above the stenosis to assess diameter and length of the stricture; when the duodenal stricture is passed with an ERCP catheter, with or without a wire, contrast is injected downstream for evaluating the patency of the GI lumen, distally to the stenosis. Another accessory, that could be useful in the angulated stricture, is the sphincterotome. Balloon dilation before stent placement is not necessary (it increases the risk of perforation), and a stiff or super-stiff guide-wire is generally preferred. When the guide-wire is correctly in place distal to the stricture the stent catheter is advanced OTW. It is important the choice of a stent few centimeters longer than the stricture to be sure of a correct stenting of the stricture. If possible, the stricture can be measured by a centimeter guide-wire. The presence of a possible angulation of the bowel, immediately after the stricture, has to be considered. In this case the length of the stent should be chosen to avoid stent impaction on the gut wall. In presence of short stenosis of the upper duodenal genu, it is a 6 cm length stents, with the proximal extremity deployed through the pylorus, has to be chosen, avoiding covering the papilla for a possible further ERCP.

Table 3 Characteristics of the most commonly used colo-rectal stents

Producer	Model	Material	Delivery system and diameter	Diameters (mm) (body/flares-flanges)	Length (cm)	Type and characteristics
Boston Scientific	WallFlex®	Nitinol	TTS, 10 Fr	25 (body)-30 (proximal flange) 22 (body)-27 (proximal flange)	6, 9, 12	Uncovered
Boston Scientific	Ultraflex precision®	Nitinol	OTW, 16 Fr	25 (body)-30 (proximal flange)	5.7, 8.7, 11.7	Uncovered
Boston Scientific	Wallstent®	Stainless steel	TTS, 10 Fr	20 (22/minimal to no flare)	6, 9, 12	Uncovered
Cook Endoscopy	Evolution®	Nitinol	TTS, 10 Fr	25 (body) 30 (both ends flanged)	6, 8, 10	Uncovered
EndoChoice	BONASTENT®	Nitinol	TTS, 10 Fr and 12 Fr	22, 24, 26 (minimal flare)	6, 8, 10	Uncovered and partially covered
Ella-CS	SX-ELLA® Enterella	Nitinol	TTS, 10 Fr	22, 25 (no flare)	7.5, 8, 9, 11, 13.5	Uncovered and fully covered
Ella-CS	SX-ELLA® Enterella	Nitinol	OTW, 15 Fr and 18Fr	22, 25, 30 (no flare)	8.2, 9, 11.3, 13.5	Uncovered and fully covered
Endochoice	Bonastent® C	Nitinol	TTS, 10 Fr	22, 24, 26	6-8-10	Uncovered and fully covered
Leufen Medizintechnik	Aixstent®	Nitinol	OTW, 24 Fr	30 (body)-36 (both ends flared)	8, 10	Uncovered and partially covered
Micro-Tech	MT® Colon and rectum stent	Nitinol	TTS, 10 Fr	25 (body)-30 (both ends flanged)	8, 10	Uncovered
Micro-Tech	MT® Colon and rectum stent	Nitinol	OTW, 24 Fr	30 (body)-36 (both ends flanged)	8, 10, 12	Uncovered and partially covered
Micro-Tech	MT® Rectum stent	Nitinol	OTW, 24 Fr	20, 26, 30 (body)-24, 21, 36 (both ends flanged)	6	Fully covered
M.I.Tech	Hanarostent®	Nitinol	TTS, 10.2 Fr and 10.5 Fr	20, 22, 24 (body)-26, 28, 30 (both ends flared) (flanged and symmetric and asymmetric)	6-16	Uncovered and fully covered
M.I.Tech	Hanarostent®	Nitinol	OTW, 24 Fr	20, 22, 24 (body)-26, 28, 30 (both ends flared) (flanged and symmetric and asymmetric)	6-16	Uncovered and fully covered
M.I.Tech	Choostent®	Nitinol	OTW, 24 Fr	22, 24 (body)-30, 32 (both ends flanged) (symmetric and asymmetric)	6-16	Fully covered
S&G Biotech	EGIS® colorectal	Nitinol	TTS, 10 Fr and 12 Fr	18, 20, 22, 24, 26, 28, 30 (no flare)	6, 8, 10, 12	Uncovered and partially covered
Taewoong Medical	Niti-S® D-Type	Nitinol	TTS, 10.5 Fr	18, 20, 22, 24 (no flare)	6, 8, 10, 12, 14, 15	Uncovered
Taewoong Medical	Niti-S® D-Type	Nitinol	OTW, 16 Fr and 18 Fr	18, 20, 22, 24, 26, 28, 30 (no flare)	6, 8, 10, 12	Uncovered
Taewoong Medical	Niti-S® S-Type	Nitinol	TTS, 10.5 Fr	18, 20 (body)-24, 28 (both ends flanged)	6, 8, 10, 12	Fully covered
Taewoong Medical	Niti-S® S -Type	Nitinol	OTW, 16 Fr, 20 Fr and 22 Fr	18, 20, 22, 24, 26, 28 (body) 24, 26, 28, 30, 32, 34 (both ends flanged)	6, 8, 10, 12, 14, 15	Fully covered
Taewoong Medical	ComVi Niti-S®	Nitinol	TTS, 10.5 Fr	18, 20, 22 (no flare)	6, 8, 10	Partially covered
Taewoong Medical	ComVi Niti-S®	Nitinol	OTW, 14 Fr, 16 Fr and 18 Fr	18, 20, 22, 24, 26, 28, 30 (no flare)	6, 8, 10	Partially covered

TTS: Through the scope; OTW: Over the wire.

The majority of the delivery stent systems allow re-sheathing of a partially deployed stent, permitting further adjustments, before the release, if the position is not correct. If the stent is accidentally released beneath the stricture, it should be immediately replaced with a tooth-rat forceps. If the placed stent is shorter than the stricture, a second stent can be released, with the proximal part inside the first.

The correct position of the stent has to be radiologically documented immediately after the deployment, injecting contrast inside the stent. Completely stent expansion is generally obtained at 48 h.

Colo-rectal stents: Table 3

Over the years have been progressively introduced various types of stent. Material was initially steel (Z-stent® Cook Medical) or Elgiloy (Wallstent®, Boston Scientific) and subsequently the nitinol. The stents actually available are all in nitinol and can differentiate between them for the shape, the size, the type of mesh, the presence or absence of coverage, the catheter carrier (TTS or OTW) and the release system. The stent OTW, typically have a 16 Fr catheter and can be used, in consideration of the length and rigidity of the catheter carrier, only for strictures of the rectum

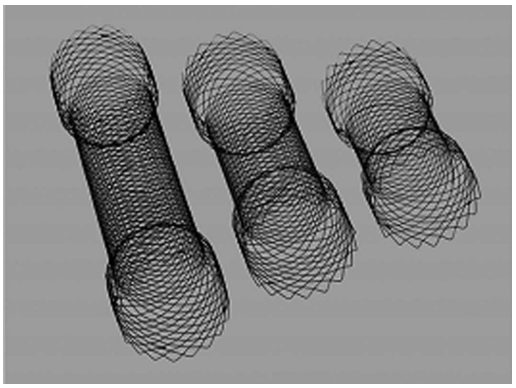

Figure 4 Colonic Evolution® stents.

or sigmoid typically within 30 cm from the anus. For stenosis located further upstream in the bowel, for anatomical reasons, it needs to use TTS stents. The Wallflex® (Boston Scentific) and Niti-S® (TaeWoong) are the most used stents to date and on which there are more data in the literature. The Evolution® stent (Cook) (Figure 4) instead is the most recently introduced on the market and which presents a delivery system that allows a best control of the various phases of the stent placement.

In the study of an occluded patient the diagnostic steps should go include the execution of a contrast medium CT scan that can be extremely useful both to evaluate the seat, the extension and nature of the stenosis, both to obtain a more comprehensive assessment of the situation abdominal (cecal diameter, exclusion of a bowel perforation or evaluation of liver metastases or peritoneal carcinomatosis). In general the onset of symptoms, their severity, and the distension of the cecum are the elements allowing the assessment in how many hours must be executed an attempt of endoscopic stent decompression. In most situations the endoscopic intervention can be performed within 6-8 h from the evaluation, for which reason even if the patient were to arrive later in the evening in the emergency room the stent placement could be deferred to the next morning. Logistically, it is necessary to have an X-ray room, a doctor and one or two experienced nurses or two doctors and a nurse, endoscopic instruments of different sizes to meet all anatomical situations and accessories needed for stent placement (guidewires, catheters, sphincterotome).

Stent TTS have a delivery catheter with a diameter of 10 Fr for which they pass in the channels of 3.8 mm diameter endoscope (standard colonscope, operative gastroscope and duodenoscope). Before placement of the stent is recommended the execution of a rectal enemas toileting which serve to clean the intestinal tract below the stenosis, thus facilitating the endoscopic exploration and identification of the stenosis. The procedure is almost always very well tolerated with minimal sedation with low doses of benzodiazepines. The anesthesia care should be required only for patients very sufferers or those with medical critical conditions.

For the possibility of ab-ingestis polmonitis, it is suggested to leave the stomach in a naso-gastric tube. It is also prudent to work with a very low level of endoscopic insufflation to avoid excessive distension of the colon upstream of the stenosis that could jeopardize the success of the maneuver.

It is preferable the patient lie supine to facilitate the radiological anatomy and identification of markers for the positioning of the stent. After reaching the stenosis, the next step is to cross the stricture with a guide-wire and an ERCP catheter. If the stenosis is very tight, long or very difficult to pass, it is suggested the use of a hydrophilic guide-wire, maybe with curved tip to avoid the risk of making false roads with a rigid (stiff) wire. In some occasional situations, in which the position of the stenosis is very lateralized respect to the endoscopic view for which the catheter fails to be directed in the stenosis, could be use a sphincterotome or, finally, the duodenoscope, having a different viewing angle, which allows to direct the tip of the catheter to the site of stenosis and facilitate the progression of the guide. Once passed the stenosis under radiological assistance, the wire must be withdrawn, injecting contrast medium to identify the correct position of the catheter, check the anatomy of the stricture and colon upstream. After that, a stiff guide-wire will be advanced across the catheter, far beyond the stenosis. This is useful to obtain a sufficient amount of guide-wire beyond the stenosis for all the maneuvers of the wire handling to give tension and straighten to the stent facilitating the advancement on the stricture. Dilation of the stricture before the release of the stent should be avoided because is a risk factor for intestinal perforation.

The choice of the stent will have to keep in mind the location and lenght of the stenosis. It is suggested to use stent with a length of at least 3-4 cm greater than that of the stenosis to allow a good adaptation of the stent also in very angled position where a stent too short might tend to straighten the curve inside and get in tension on the contralateral bowel wall, increasing the risk of dislocation and perforation. Once advanced the stent in the stenosis, the release should be supervised radiological and endoscopic (in the case of stents OTW is suggested to advance a small-caliber endoscope in parallel to the catheter carrying the stent). It is advisable to release the stent in a slow and gradual to always have full control of the maneuver. In the case of TTS stent is important that the endoscopist tends to progressively retract the catheter outside of the stent. Once completed the release, a last check radiological and endoscopic will be necessary to assess the proper expansion of the stent within the stenosis and evaluate the passage of air and fecal material through the stent.

ESOPHAGEAL DISEASES

The SEMSs have acquired a well-defined role in the

Table 4 Classification of dysphagia

Grade of dysphagia	Symptoms
0	No dysphagia
1	Occasional dysphagia for solid foods
2	Dysphagia for solid foods
3	Dysphagia for semi-solid food
4	Dysphagia for liquids

palliation of dysphagia in patients affected by esophageal malignant strictures, with a technical success greater than 95% with regard to their positioning and the ability to quickly resolve the dysphagia in almost all of the patients, reducing the rate of complications during the positioning phase thanks to the small diameter of the delivery catheter, and this, together with the use of an pediatric endoscope, makes unnecessary the preliminary expansion[1,2].

There are several types of esophageal SEMSs actually available for the treatment of malignant and benign esophageal stenosis[3].

The esophageal SEMSs are currently available uncovered, PC (only in the extremes do not have coverage) that FC[4].

The latter have attracted the interest of clinical researchers to evaluate their role in benign stenosis, esophageal mainly because complete coverage would allow their extraction after a certain time. In addition to the FCSEMS is necessary to consider the other two implants which are used in benign esophageal disease, the SEPS (Polyflex®, Boston-Scientific, Natick, MA, United States) and the biodegradable stent (Ella®-CS, Hradec Kralove, Czech Republic).

Benign esophageal diseases

Esophageal strictures: Before starting the endoscopic treatment is necessary to establish the real not malignancy of the stenosis, performing multiple biopsies and, when necessary, using endoscopic ultrasound (EUS) or other radiologic techniques. Essential is the classification of the dysphagia, so as to record the variation in the course of treatment (Table 4)[5].

The benign strictures are relatively frequent finding in clinical practice. In the past peptic strictures were prevalent, but are currently most commonly encountered those caused by caustic and radiotherapy. Esophageal strictures have been recently described in endoscopic mucosal resection, when circumferential and after endoscopic submucosal dissection[6].

Generally most of stenosis responds to a few[7] sessions of endoscopic dilatation, but from 25% up to 30 % requires a larger number of dilatation[8]. There are, however, "complex" strictures that do not respond to dilatation therapy, even if repeated over time (Table 5).

The anastomotic strictures, post-caustic ingestion stenosis and stenosis resulting from radiotherapic treatments, have a low rate of response to endoscopic

Table 5 Characteristic of "complex esophageal stenosis"

Length > 2 cm
Angulated
Irregular edges
Very low diameter

therapy: more than 40% tend to recur[9,10]. The most difficult to treat are the hypopharyngeal strictures, generally refractory.

It was moreover proposed the definition of "refractory stenosis" as: (1) absence of inflammation or motility disorders in presence of stricture; (2) impossibility of maintaining ⩾ 14 mm diameter after 5 sessions of dilation performed with a interval of 2 wk (refractory stenosis); and (3) impossibility of maintaining ⩾ 14 mm diameter for 4 wk after reaching a 14 mm diameter (recurrent stenosis)[11].

In addition to the expansion, have also been proposed other treatments, such as injection, at the level of the four quadrants of triamcinolon and, where appropriate, in particular in the anastomotic stenosis, the incisions of the fibrotic ring with a diathermic needle[12,13]. When these measures fail and dysphagia persists it is mandatory to evaluate the possibility to place a stent that, in addition to determining a laceration of the scarred submucosal layer and muscle of the esophageal wall, it maintains a constant pressure for the entire duration of its stay in the esophagus.

Anastomotic leaks

Total gastrectomy and esophagectomy are generally associated with high rate of morbidity and mortality even in specialized centres. The National Esophagogastric Cancer Audit of England and Wales published a rates of 8.3% of anastomotic leak after esophagectomy and 5.9% after total gastrectomy[14].

Although the improvements in the anastomotic techniques, anastomotic intrathoracic leak is generally associated with bacterial contamination, abscesses, and successive fistulas into pleural cavities. The continuous leakage of gastric juices and saliva into the pleural and mediastinal cavities can be life-threatening, with 30%-40% of post-surgical deaths[15].

Different treatments are described for the management of the esophago-gastric and the esophago-jejunal anastomotic leak. Some authors suggested the surgical treatment, but others prefrer a conservative approach with perianastomotic drainage, parenteral support and nasogastric decompression, and *iv* antibiotic therapy. All of these patients should be treated in appropriate critical care units[16].

The fibrin glue associated to metallic clips has been successfully used in small esophageal leaks[17,18]. An endoscopic stenting remains an attractive option, and SEPS and PC or FC-SEMS ensure good results, although the loading kit device and the delivery of the plastic stent can be difficult in non-expert hands. The leak

closure rates ranges from 60% to 100% with an healing rates > 90%[19,20]. Leak closure should be confirmed by contrast medium injected during the endoscopic procedure. Stents removal is planned at different times, depending by the size of the leak, but the stents are generally removed from 14 to 28 d from the placement with a previous clinical evaluation of healing of the absence or sepsis, radiologically documented.

The majority of the published studies suggest the stent placement immediately after the diagnosis of the leak for minimizing the contamination of the mediastinal cavity[21]. In some cases, the delayed placement can result in the healing of the anastomotic leak. Patients in which a covered stent is placed present an earlier oral intake (11 d *vs* 23 d), short ICU stay (25 d *vs* 47 d), and a less hospital stay (35 d *vs* 57 d). The in hospital mortality ranges from 0% to 20%, in different published series, lower if compared to the groups treated conservatively[22].

Acute and spontaneous esophageal perforations

Esophageal perforation is a life-threatening condition generally requiring surgical intervention. The management of the esopgaheal acute perforation (iatrogenic or spontaneous) is be divided into two groups: conservative and operative. Because of the rarity, the literature on this issue is based mainly on small series and case reports. Surgical repair seems to be the treatment of choice when an early diagnosis is made. The reported mortality in literature ranges from 0% (when the treatment starts within 24 h) to 30% if the treatment is delayed[23].

The conservative treatment is based on broad-spectrum *iv* antibiotic, parenteral nutrition and percutaneous drainage of the collections, when present. Ivey *et al*[24] showed as conservative therapy is appropriate only in presence of a perforation > 5 d; absence of sepsis; wide cavity at radiological imaging draining back into the esophageal lumen and absence of contamination of the pleural space[24]. A recent review advices that conservative treatment is feasible, with a survival rates of 60%-70% if the perforation are promptly diagnosed, but the need of the surgery is mandatory in case of failure[25].

Griffin *et al*[23] showed as in the management of spontaneous esophageal perforation (Boherhaave Syndrom's) they did not use stents. They suppose that the stent may prevent adequate drainage of sepsis, but can be subject to dislocation in absence of a stricture. Moreover, Authors recommend a non-operative management only in selected cases, especially when unfit for surgery[23].

Only three case reports are present in literature about the treatment of spontaneous esophageal perforations with the placement of the SEPS. In the first case the SEPS was placed at 24 h, in another case after 3 wk, in association of chest drainage, broad-spectrum *iv* antibiotic therapy and fibrin-glue injection, and, in the last case, the stent was placed 10 d later. All of the patients survived, and the immediate radiological study after stent placement did not show contrast medium outside from the esophageal lumen[26,27]. Oral intake was started in all of the three patients within 7 d, and were discharged between 7 and 21 d after stent placement.

The stent removal was scheduled between 5 and 10 wk. In two of the three treated patients, the stent was found into the gastric cavity.

Type of esophageal stents and outcomes

Self-expandable plastic stent: The SEPSs (Polyflex®) are usually placed with fluoroscopic assistance, but, in selected cases, deployment only under endoscopic view has been reported. A stent longer from 2 to 4 cm than the stenosis should be used for allowing a 1 to 2 cm extension above the edges of the lesion. Based on the RF of the SEPS, the completely expansion of the stent is obtained from hours to days[28,29].

The delivery device of the SEPS is larger and more rigid, if compared to other delivery system, with a non flexible tip. The assembly of the delivery device can sometimes be difficult in less well trained centres with low volume of cases, than these characteristics increase the challenging of the SEPS placement. The retraction rate of the SEPS is about 18% of the stent length before the release. The delivery system not allows the recapture. Because of the rigidity of the delivery system, it is suggested the neck hyperextension using a super-stiff wire. This may increase the risk of perforation, especially in presence of angulated strictures. This has been demonstrated in a prospective randomized trial (RCT) comparing 3 types of stents (Ultraflex, Niti-S and Polyflex); although dysphagia relief was achieved with all three types of stents, technical problems during stent release are encountered generally during SEPS placement than the other two SEMSs[30].

The SEPS presents some advantages if compared with PC-SEMS, as an easier removal and a less migration[31]. The soft material confers to the stent a well-balanced RF, adapting it to the wall of the esophagus, with a more probability of leak closure. The fully silicone covering does not allow granulation tissue ingrowth with minor overgrowth. It results in a possible successive easier repositioning and removal. The SEPS is available in different diameters and lengths, the exact diameter of stent has to be chosen on the basis of the size and site of the stricture (associated or not with a leak). There is no published evidence that the placement of large-diameter SEPS reduce the migration rate[32].

The SEPS presents other several drawbacks such as: the release takes place very fast, leading to the onset of severe sternal pain which can sometimes persist even 1 wk and the diameter of the introducer system that is excessive, especially in the presence of a "complex

stenosis".

The first study of the placement of SEPS in 15 patients reported a technical success, clinical success and a migration rates of 100%, 80% and 6.6% respectively[33].

Dua *et al*[34] in prospective study including 40 patients reported a clinical success of 40% and a migration rate of 22%, with a death due to a bleeding caused by erosion of the esophageal wall by SEPS[34].

A recent systematic review of the literature that has considered 10 studies with a total of 130 patients evidenced a technical and clinical success of 98% and 52%, respectively. The rate of migration (< 4 wk) was 24%, while complications were observed in 9% of patients with one death (0.8%)[35]. There is no consensus on the time to remove SEPS, but generally it is advisable the retrieval the stent after 6 wk, to prevent the onset of serious complications.

Partially-covered self-expandable metal stent

These stent should be not used in benign pathology because of the proliferation of granulation tissue through the proximal and distal uncovered mesh makes their removal difficult. One study that included 29 patients with benign esophageal strictures, reported the appearance of new stenosis the ends of the prosthesis in 41% of cases, migration in 31%, retrosternal pain and reflux in 21%, trachea-esophageal fistula in 6%[36]. Sometimes, in special cases where it cannot be used a stent completely covered for the high risk of migration, you can insert a PC-SEMS PC. To render its extraction after 6 wk, you can resort to the method indicated by Hirdes *et al*[37] aimed at eliminating the granulomatous tissue ingrowth present at the ends of the prosthesis: in it is placed a SEMS completely covered with similar diameter and length and leaving it up to a maximum of 2 wk. In this way the pressure of the stent will determine the necrosis of granulation tissue between the meshes, thus making possible the extraction of both stents[37].

FC self expandable metal stent

The complete coverage of the stent facilitates the extraction after a predetermined period of time, but could increase the risk of migration. This problem can be reduced if the endoscopist is able to perform an appropriate stent choice, in length and size. The capability of auto-conforming and the diameter should be considered in each individual case. A larger diameter will oppose effectively the migration and in presence of the fistula, and the perfect adhesion of the proximal crown to the wall to effective impermeability to liquids.

Eloubeidi *et al*[38] in 7 patients with benign strictures placed the Alimaxx-E (Alveolus, Charlotte, NC, United States) FCSEMS. The resolution of dysphagia was observed in 29%, while the migration occurred in 36% of the cases, half of the patients developed an ulcer distally to the FCSEMS and the 23% proximally, however these lesions were solved after the removal of the stent[38]. Additional studies have reported a migration rate to 37% up to 50%, a resolution of dysphagia to 21% up to 100 % of cases and the extraction of the stent was possible in all of the cases[39,40].

A meta-analysis that compared SEPS and FCSEMS in esophageal refractory strictures, included 8 studies with a total of 199 patients, found an improvement of dysphagia in the 55.3% patients treated with SEPS and in the 21.8% of the patients treated with FCSEMS, however these data must be accepted with extreme caution because in 6 of the 8 studies was used the SEPS[41].

The FCSEMSs are effective also in the treatment of benign fistulas, perforations and anastomotic leakage.

Van Heel *et al*[42] treated 33 patients with esophageal perforation (19 iatrogenic type, 10 Boerhaave's syndrome and 4 other pathologies), the closure of the perforation was obtained in 32 (97%) patients, recurrence occurred in 37% of cases, which required further stenting (3 patients were treated surgically), and the stents were removed within 6 wk of the placement without major complications[42].

A systematic review, that included 25 studies with a total of 267 patients, showed that the closure of the perforation was successful in 85% of patients, surgery was necessary in 13% and that patients treated with SEPS required a greater number of endoscopic reinterventions compared to patients treated with covered metal stents (26% *vs* 13%, $P < 0.001$)[43].

A particular problem is posed by the hypopharyngeal stenosis resulting from surgery and radiotherapy for cancer ear nose and throat[44,45]. Fibrosis caused by radiotherapy are interested in full thickness bowel and the remodeling of the stenosis is virtually impossible. Expansions of periodic increase fibrosis and therefore the risk of perforation. Generally, the appearance of a fistula requires, when possible, the surgery, with a considerable rate of mortality and morbidity. In these patients has proved useful the use of Niti-S Conio Stent (Taewoong Medical, Seoul, South Korea). The preliminary results are encouraging, but it is necessary to include a larger number of patients to assess the efficacy[46].

Biodegradable stent

The biodegradable implant (Hella® stent - Ella®-CS, Hradec Kralove, Czech Republic) was introduced in the clinical setting in 2008.

One study that included 21 patients with refractory strictures reported a significant improvement in dysphagia at a mean 53 wk of follow-up, 45% of the had not dysphagia at the end of the study, the migration rate was 9.5%, 3 patients complained of retrosternal pain after the release of the stent and one patient presented a slight bleeding after the procedure[47].

Van Boeckel *et al*[48] compared the outcomes

of SEPS (20 patients) and biodegradable stent (18 patients) in refractory strictures. In the group treated with SEPS, 6 (30%) patients were completely free of dysphagia with a median follow-up of 385 d while 10 (50%) had a recurrence of dysphagia, 1 severe bleeding and 1 perforation occurred. In the group treated with biodegradable stent, 6 (33%) patients were free of dysphagia with a median follow-up of 166 d, recurrence was observed in 12 (67%) patients and 2 severe bleeding and 2 cases of severe retrosternal pain occurred. The rate of endoscopic re-intervention was lower in the SEPS compared to the biodegradable stent grosup (15 *vs* 21)[48].

Malignant esophageal disease

Esophageal stents in malignant diseases are mainly placed in presence of unresectable carcinoma of the esophagus, with a short life expectancy, and suffer from marked esophageal stenosis or fistula[49]. Other malignant conditions in which patients are eligible for stent placement are extrinsic esophageal compression or fistula formation as a result of pulmonary cancer, mediastinal cancer or metastatic disease. The main advantages of stent therapy are successful insertion of the device in almost all cases with rapid (24-48 h) improvement of dysphagia. Disadvantages of the stent therapy are the re-occurrence of dysphagia in up to one-third of patients, and other stent related complications, including hemorrhage, pain and fistula[50]. Although most stents are placed in the distal or mid esophagus, insertion in the cervical esophagus is most rarely and it is considered equally effective with dedicated stent[51].

Both SEMS and SEPS are most used in esophageal malignant diseases. Actually to prevent tumor ingrowth PC or FC SEMS were used[51]. Although a FC-SEMS prevents tissue ingrowth over the full length of the stent, it presents a considerable migration risk[52].

Palliative treatment for malignant esophageal strictures

In the last 12 years, only five RCTs comparing different types of stent in patients with malignant esophageal strictures were published[53-56].

The first study randomized 100 patients to treatment with one of three SEMS: the PC-Ultraflex® stent (Boston Scientific, United States), the PC-Flamingo Wallstent® (Boston Scientific) and the FC-SEMS Gianturco Z-stent® (Wilson-Cook, Denmark). The three stents were equally effective in improving dysphagia scores without a significant difference in major complication rate.

The second trial randomized 53 patients with a distal esophageal tumor to a PC-Flamingo Wallstent® (Boston Scientific) or the more flexible PC-Ultraflex® stent (Boston Scientific). Clinical outcome was satisfactory in both groups without significant differences in improvement of dysphagia scores and complication rates.

A third study randomized 101 patients to a Polyflex® (Boston Scientific) or Ultraflex® stent (Boston Scientific), showing similar effectiveness in palliation of dysphagia. However, complications, especially late migration, occurred significantly more often after placement of a Polyflex® stent.

The fourth randomized study with 125 patients evaluated the Ultraflex® stent (Boston Scientific), the FC-double-layered Niti-S stent® (Taewong Medical, South Korea), and the Polyflex stent® (Boston Scientific). The Ultraflex® and Niti-S® stent were equally effective with equal overall complication rates, but recurrent dysphagia generally occurs more frequently with the Ultraflex® stent (52% *vs* 31%), mainly caused by a higher rate of food obstruction. The Polyflex® SEPS was associated with high failure of stent placement (17%) and increased migration risk. Because of a wider diameter of the Polyflex® delivery system, insertion is technically more difficult and dilation had to be performed more frequently. Furthermore, SEPS conform less easily to a stricture, making them more susceptible to slipping.

Observational series had initially demonstrated effectiveness of SEPS in malignant esophageal obstruction; however, the randomized studies revealed an unacceptable high complication rate[57,58].

A recently trial included 80 patients with dysphagia caused by malignant stenosis. Patients were randomized into two groups: PC-Evolution® stent (Cook Medical, Ireland) and Ultraflex® stent (Boston Scientific). The Evolution® stent was related with a significantly lower rate of stent dysfunction (8% *vs* 40%) and major complications (8% *vs* 25%). These data could not be confirmed in another single arm study, which included 44 patients with malignant dysphagia. In this study, the Evolution stent dysfunction rate was much higher (25%), mainly caused by tumor in- or overgrowth[59].

Stent innovations include anti-reflux and anti-migration features. The anti-reflux features were particularly developed for stents bridging the lower esophageal sphincter. This was generally done by attaching a valve to the distal end of the stent, inhibiting backflow from gastric contents into the esophagus. Theoretically, this should prevent reflux symptoms, esophagitis, and possibly aspiration. Although some studies have indicated that anti-reflux stents reduced gastro-esophageal reflux, a recent meta-analysis did not identify a significant difference in adverse events, symptoms and quality of life reflux-related[60]. Therefore, the use of anti-reflux stents has largely been abandoned. Antimigration features include uncovering of distinct areas of the metal mesh and a wider diameter of the stent flares, as well as addition of struts or rings to the outer side of the stent serving as anchoring devices. Both the Alimaxx-E® (Alveolus, United States) equipped with outer antimigration struts and the SX-ELLA® Esophageal HV stent (Ella-CS, Hradec Kralove, Czech Republic), with an anti-migration ring fall in the latter category. Several studies, however, have shown that, in spite of these design modifications, these stents frequently dislocate[61,62]. In addition, the SX-Ella stent

seems to be associated with a major number of adverse events, such as hemorrhage, fistula formation, and severe pain, which likely relate to excessive pressure of the anti-migration ring.

The Niti-S stent has a dog-bone shape to prevent migration. Two design of the stent are present in commerce: a fully-covered self expandable metal stent and a double-layered covering with an FC inner layer made of polyurethane and an outer uncovered nitinol mesh to facilitate the attachment of the SEMS to the wall. Several studies have reported good clinical efficacy and acceptable migration rates (up to 12%) with both types Niti-S® stents[63,64]. In one study, the double-layered version was associated with a significantly lower combined recurrent dysphagia and complication rate than the single layer version (12% *vs* 58%). However, the high complication rate of the single-layered Niti-S® stent used in that study was not confirmed in a recent large single arm study[65]. The FC-Wallflex® stent (Boston Scientific) is characterized by two migration-resistant features: distinct shouldering at both sides and internal covering. This stent has so far only been evaluated in one study for the treatment of neoplastic stenosis. Although the migration risk was low (9%), major complications were commonly seen (30%), which might be associated to the relatively high Wallflex® RF[66].

In summary, the available studies suggest that no major differences in efficacy and safety exist between different stents. However, there is still insufficient evidence to recommend one type of SEMS in the treatment of malignant dysphagia. Specific features reduce migration rates of FC-SEMS; however, they can also induce traumatic injury and lead to major adverse events.

Palliative treatment of malignant fistula

Fistulas usually result from infiltration of esophageal cancer to the respiratory tract or pleural cavity. Additionally, lung and mediastinal cancers can penetrate to the esophagus, also creating fistulas. Multiple series have reported on the use of covered SEMS to seal off fistulas, with closure rates ranging between 73% and 100%[67-69]. At the same time, it is also crucial that pleural and mediastinal fluid collections are drained aggressively. Both PC and FC-SEMS can be used as long as the covering completely seals the fistula. Unfortunately, randomized studies to recommend a specific type of SEMS are lacking. The largest non-comparative series to date reports on 61 patients with esophago-respiratory fistulas treated with covered SEMS. Ten patients also required a trachea-bronchial stent to seal the fistula. Complete fistula healing was reached in the 80% of the cases (49 subjects); the re-intervention was effective in the majority of 17 patients in whom the fistula had re-opened. Based on these data, and in the absence of effective alternative treatments, SEMS is considered the treatment of choice in malignant fistulas[70].

Bridge to surgery and SEMS

Nowadays, neoadjuvant chemoradiotherapy improves long-term survival after esophageal surgery[71]. Stent insertion before neoadjuvant therapy is an interesting new concept in the management of resectable esophageal malignancy. It could be useful as a bridge to surgery during the neoadjuvant chemotherapy, improving nutritional status by ensuring oral solid intake without the need for nasoenteral or percutaneous feeding tubes. Because esophagectomy is scheduled shortly after termination of neoadjuvant therapy, late stent-related complications can be averted. This approach has been evaluated in several studies, using different types of stents and various neoadjuvant regimes[72-74]. Stents were either extracted prior to esophagectomy or removed during surgery. They appear effective in improving dysphagia and maintaining nutrition. However, complications, although rare, may occur. These include esophageal perforation requiring urgent surgery, and stent migration. The latter has in case series been reported to result in small bowel perforation or obstruction. Furthermore, in one study, the number of patients proceeding to curative resection was surprisingly low due to progression or discovery of metastatic disease[75]. These findings indicate that adjunctive studies will clarify the use of the stents meanwhile the patient underwent neoadjuvant chemotherapy before implementing such use in regular practice. These studies should also clarify concerns about the possible spreading of viable tumor cells in the circulation after stent placement.

COMPLICATIONS OF ESOPHAGEAL STENTING

Recurrent dysphagia

Recurrent dysphagia remains a problem after stent insertion and occurs in almost one-third of patients. Endoscopic reintervention is successful in most cases[76]. In cases of tumor over- or ingrowth, insertion of a second stent is effective to restore luminal patency. This can also be considered in cases of stent migration. Conio *et al*[77] in 2010 described the possibility to treat the dysphagia because of the over- or ingrowth by placement of a SEPS. They evaluated 13 patients, previously treated with metal stent developing dysphagia because of tissue in/overgrowth, underwent self-expandable plastic stent (SEPS). Before SEPS placement, the dysphagia score ranged from 3 and 4. After 1 wk from the stent placement the dysphagia score was 0% in 100% of the cases. All of the patients were free of dysphagia till their death. Mean survival after self-expandable plastic stent placement was of 4 mo[77].

However, either endoscopic repositioning or exchanging for a new stent is preferable. Obstruction due to impacted food can easily be managed by endoscopic

stent clearance.

Another rare late complication is spontaneous stent fracture with collapse. The stent-in-stent technique seems safe and effective in these situations and can also be used to facilitate removal of the fractured SEMS[78].

Leak

Esophago-respiratory fistulas are mostly seen several months after stent placement. Due to the RF and resulting pressure necrosis, which is most extreme at the level of the flares, it is usually seen next to the proximal or distal margin of the stent. In these cases, placement of an additional covered-SEMS is an effective method.

Retro-sternal pain

Another complication is the development of retrosternal pain after stent insertion. Didden *et al*[79] found a 60% rate of moderate to severe pain in a prospective assessment of 50 patients after esophageal SEMS insertion for malignant stenosis.

Pain lasted for an average of 10 d and 91% of patients required analgesics, with good effect in all patients without the need for stent removal in any of them.

GASTRIC AND DUODENAL DISEASES

Benign diseases

Complications of bariatric surgery: The sleeve gastrectomy (SG), described for the first time by Gagner *et al*[80] in 2003 is currently a well standardized therapeutic option for the surgical treatment of different degrees of obesity[81,82]. The described complications of the SG include bleeding of the suture line and the stenosis, while the dehiscence of the suture line is the most serious event associated with a high morbidity rate and for whose management have been proposed different therapeutic approaches[83,84].

The re-intervention is often required even if burdened by a high rate of morbidity and mortality.

In recent years some endoscopic methods such as the use of covered-SEMS, have been mostly used for the treatment of anastomotic leakage with the aim of obtaining a non-minimally invasive surgical repair of the fistula[85,86].

The dehiscence of the suture line of the SG could be present in 0.5%-7% of the cases, even if could be underestimated; a detailed review of the American Society for Bariatric and Metabolic Surgery shows an overall rate of complications after SG variable between 0% and 24% with a percentage of dehiscence of 16%-20% of the cases[87]. The esophago-gastric junction and the proximal portion of the stomach near the corner of His are the points where most of you will be dehiscence[88,89].

The use of FC-SEMS in the treatment of dehiscence of the suture line of the SG was proposed by several authors in recent years[90].

The stent constitute a physical barrier between the fistula and the content intraluminal favoring the healing and the closure of the wall defect at the same time allowing the nutrition *per os*. The results of this method are reported in the literature as never variables, even if it is mostly case reports or small case series, so at present there are no extensive data statistically reliable.

Two stents are currently marketed for the closure of fistulas post-SG: the Beta-stent® (Niti-S - TaeWoong), and the Hanaro® stent (M.I. Tech). There are no data about, it is recommended the extraction of the stent between 6 and 8 wk. Currently there are no data comparing the two stents. The migration of the stent is the most common complication, reported in 30% of cases in some papers[87,91] and up to 42%-50% of cases in others[90,92]. The two ends of the stents slightly flared and high profile allow a good anchor. The body of the stents is longer than any of the esophageal stent allowing the opening of the proximal bell at the level of distal esophagus and the distal to the level of the duodenal bulb, by eliminating the pressure gradient, favoring the closure of the wall defect. The large diameter ensures excellent fit of the prosthesis to the wall of the gastric tube.

Malignant gastric outlet obstruction

Gastric outlet obstruction (GOO) is generally secondary to bilio-pancreatic and others. More rarely is due to gastric neoplasia[93]. Gastrojejunostomy (GJ) was the only therapeutic chance till the advent of the SEMS and is characterized by and higher mortality and morbidity, delayed symptoms resolution and longer hospitalization stay when compared to endoscopic stent placement[94,95].

In the last 20 years we observed an emerging role of self-expandable metal stent for palliation of GOO, substituting the GJ. A meta-analysis evaluating nine studies and 307 endoscopic and surgical intervention for palliation of malignant GOO evidenced better clinical success, minor morbidity and mortality, lower time-related procedure and hospital stay for endoscopic stent placement[96]. The rate of endoscopic clinical success was 84%-93%, with a technical success of 93%-97%[97,98].

The correct evaluation of the patients undergoing endoscopic stenting or surgical GJ plays a key role in the management of the malignant GOO. The GJ, in the opinion of some authors, is suggested in patients with a life expectancy more than 6 mo[99] despite a prospective randomized trial suggests GJ when the life expectancy is > 2 mo, and endoscopic SEMS when < 2 mo[100].

During the choice of the stent the endoscopist has to consider the site and the morphology of the stricture. The mean time for endoscopic duodenal SEMS placement is 17.5 min and the use of duodenoscope could

be useful because offer a better view of the duodenal stenosis, moreover, the scope elevator allows also the orientation of the device used, maintaining correctly in place the wire during devices exchange. The use of the duodenoscope is also suggested from some authors in presence of a challenging situation: a concomitant biliary obstruction[101,102].

The concomitant bilio-duodenal strictures are classified in three types: type Ⅰ: involving duodenal bulb/upper duodenal genu in absence of involvement of papillary area; type Ⅱ: involving the medium and distal portion of the duodenum and the papillary area; and type Ⅲ: involving the distal portion of the descending duodenum in absence of involvement of the papillary area[103].

In the type Ⅱ, when a duodenal SEMS is placed, a particular condition is created, the "jailed papilla". ERCP with biliary drainage through the metal mesh of the duodenal SEMS is possible fenestrating the SEMS with argon plasma coagulation (APC)[104]. In case of ERCP failure, percutaneous trans-hepatic biliary drainage is needed.

Actually the reported clinical success rate of duodenal stenting for GOO is 84%-93%, with a technical success of 93%-97%[98,99,101].

Tissue over- and ingrowth, food impaction and stent dislocation are the possible adverse events after SEMS placement, requiring endoscopic intervention in 20%-25% of the patients. Stent migration is more frequent for the covered than the uncovered SEMS[102].

Other complications of enteral SEMS are, bowel perforation and bleeding (< 1%), sometimes due to the uncovered ends of the SEMS[105,106]. The mesh pressure on the epithelium induces tissue regeneration, resulting in the ingrowth of the tissue, conditioning stent failure[107,108]. Then, the placement of a covered-SEMS is preferable in non-surgical patients, or patients with an high risk of mortality and morbidity, with a life expectance > 2-3 mo. Covered stent are usually placed inside of an uncovered stent, in presence of tissue ingrowth or for tumor recurrence and if a leak is present[109,110]. The disadvantage of the covered SEMS is the tendency to migration, even more rare for uncovered SEMS. The migration of a stent might be due to an inadequate stent diameter or after chemotherapy, if a reduction of the neoplastic mass is obtained[111].

COLON AND RECTUM DISEASES

Benign disease

Colo-rectal benign strictures are likely to endoscopic treatment: anastomotic strictures, post-ischemic, Crohn's disease strictures and post-actinic stenosis[112]. Among these, the most frequent is the anastomotic stenosis. It appears on 22%-30% of patients undergoing colorectal surgery and is the most benign colonic pathology treated endoscopically, especially with pneumatic (balloon) or mechanical (Savary) dilation.

Stenting in non neoplastic colorectal stricture is proving to be a viable therapeutic alternative with the intent to bring down the number of endoscopic sessions required to achieve the resolution of the stenosis itself. The data published so far on the use of stents in this setting are still limited and often conflicting.

In the benign stenosis the stents are used with the aim of solving the occlusion or sub-occlusion bowel, which is sometimes an emergency surgical. On the use of stents in benign colorectal diseases are still a few data and with time follow-up is limited, lacking in the literature randomized studies. The results on the efficacy and safety of stents in benign colorectal obstruction is controversial because of the high numbers of adverse events, especially considering the high migration rate[113].

Published studies have demonstrated that colonic stenting in the benign disease has a technical success variable from 85% to 100% with a complication rate of around 30%. The most serious complications observed, although rare, are leaks, bleeding and perforation but the most frequent adverse event is SEMS dislocation[114].

Furthermore, from the "case series" published on colo-rectal inflammatory diseases treatable with SEMS, diverticular stricture are those associated with the higher rate of complications. In fact, as noted by the study of Keränen *et al*[115] the endoscopic stenting in diverticular stenosis is burdened by a considerable risk of adverse events (as leaks, abscesses and perforations) with the need for surgical management in 70% of patients treated with stent[115]. Therefore, the use of stents in diverticular stricture is actually not recommended. The most frequent stricture treated by insertion of stent is than the anastomotic one.

Self-expandable plastic stent

Published data on the use of self-expandable plastic stent in non-neoplastic colonical and rectal diseases consists of case reports and series only[114,116].

Dai *et al*[114] described a series of 14 patients with benign colon and rectal diseases in which SEPS was implanted, anastomotic leak healing in 67% of the patients (4/6) and colonical disobstruction was obtained in the 50% of the patients (7/14). In 2 of 7 patients (28.5%) re-intervention was performed because stricture recurrence at 37 mo[114].

FC self-expandable metal stent

Actually, the biggest series on the use of the FC-SEMS was published in 2013 by the French Society of Digestive Endoscopy (SFED). The study includes 43 patients with bowel obstruction because of anastomotic, post-ischemic or post-radiotherapy stenosis. Stent placement was successful in the 100% of the patients. Clinical success was 81%. Stent migration was in 63% of the cases. The median left in place of the stent was of 21 d. Statistical analysis evidenced that FC-SEMS with a diameter less than 20 mm have a major risk of migration. Recurrence of occlusion was observed in

53% of the cases (23 patients). No predictive factors for occlusive or sub-occlusive symptoms recurrence were individuated at multivariate analysis[117].

Biodegradable stents

Although the use of this stent is limited to benign esophageal strictures, its application on colonic benign stenosis are reported.

Recently was reported its successful use for the treatment of a sigmoid stricture due to Crohn disease[118], however the majority of the published studies on the use this stent in colo-rectal benign strictures is referred to anastomosis.

Pérez Roldán *et al*[119] treated with the biodegradable stent 7 patients with postsurgical colorectal stricture and 3 with rectocutaneous fistula. In 9 patients the biodegradable stents were correctly placed; one early migration was observed. In one patients stent placement was not possible because of the distance to the anal orifice (30 cm) and the deformed anatomy site. Leak healing was obtained in 100% of the cases, despite recurrence was observed in one. Symptoms relief was observed in the 83.3% (6/7) of the occluded or sub-occluded patients; in the other case, the stent migrated 72 h after the placement[119].

Repici *et al*[120] studied 11 patients with anastomotic strictures within 20 cm from the anus, refractory to 3 sessions of endoscopic dilation. They obtained 100% of technical success. In the first 14 d after endoscopic stent placement Authors observed 4 dislocations, with subsequent stricture recurrence. Of the 7 cases with completely meshes biodegradation, 5 had no more symptoms and benign stenosis resolution. In 2 patients surgery was needed. The described clinical success was of 45%[120].

Malignant disease

The endoscopic colo-rectal stenting is indicated for bowel obstruction caused by neoplastic stenosis of the colon-rectum determining a bowel obstruction.

Endoscopic stent placement is also indicated for decompression before of elective surgery (bridge to surgery) in patients affected by colo-rectal neoplasia to avoid emergent surgery and as palliation in presence of patients unfit for surgery candidates because of advanced disease or their poor clinical conditions.

The very low stenosis, which are less than 5 cm from the anus are a contraindication to the stenting. In the case of very low stenosis the use of the stent is invariably associated with the appearance of tenesmus, anal pain and incontinence, making intolerable the presence of the stent in the distal rectum.

More than 20% of patients with acute colo-rectal neoplastic occlusion present metastases and 2/3 of them are unfit for surgery[121,122].

Then, the SEMS placement, especially in patients not suitable for surgery, allows a re-canalization of the bowel patency, avoiding surgery.

In patients with advanced colo-rectal neoplasia causing bowel obstruction surgical intervention with stoma creation is generally performed, with negative implications for patient quality of life[123]. The endoscopic stenting by use of SEMS is nowadays accepted in the palliative therapy of the colo-rectal cancer, becoming a valid alternative to surgical stoma.

Different studies evaluated the role of the SEMS in the palliation of colo-rectal cancer. Three randomized studies are present in literature comparing endoscopic stenting with surgery in patients unfit for surgery affected by colo-rectal neoplasia, causing bowel obstruction.

In these 3 RCTs studies the technical and clinical success was of 92% and 92% respectively, with a morbidity rate of 30% (11/37) in the patients underwent endoscopic stenting and 17% (6/36) in the patients underwent surgery, and a mortality of 8% (3/37) only in the stent group[124-126]. Two of the three Authors of the RCTs suggest superior efficacy and safety of the SEMS group if compared to surgery for palliation of colorectal cancer obstruction, differently to the reported data by the Dutch Stent-in I multicenter RCT. However, in palliated patients with a longer lifespan, SEMS placement in comparison to a colostomy, presents an improvement of the life quality, and with a reduction in cost and length of hospital stay[127,128]. Stents used were the WallFlex (Boston Scientific). The study was closed before the total patients enrollment for the high recorded numbers of perforations related to the SEMS placement, with 3 consequently deaths in 10 patients of the group undergone stenting. Authors had not a clear reason for justifying the high rate of perforations. They supposed a doubtful safety of the WallFlex.

Moreover, no supporting results have been showed by other studies in which WallFlex SEMS was tested as palliative treatment in referral centres. This studies show as the experience of the endoscopist could be an explanation for the high rate of adverse events reported by the Dutch group[129-131].

Bridge to surgery has to be seriously considered in presence of patients with acute obstruction and fit for surgery. SEMS placement provides to bowel patency restoration allowing colonical preparation for surgery and an eventual pre or intra-operative endoscopy for the research of synchronous neoplastic and non-neoplastic diseases. The curative intent for these patients is a single-step intervention with primary anastomosis, especially when a laparoscopic approach is possible.

However, the role of SEMS as bridge to surgery, has been widely debated, because several RCTs studies have shown conflicting and mixed results.

In the 6 RCTs in which endoscopic stenting was evaluated as bridge to surgery (171 patients) compared to emergency surgical resection (169 patients), the technical and clinical success of stenting was 79% and 77% respectively, with a morbidity rate of 33% in the

SEMS group and 53% surgical one with a comparable mortality rate (7% *vs* 8%)[132-137].

Notably evident is the difference in results between RCTs studies carried out in single centers *vs* those carried out in multicenters, particularly with respect to the stent placement outcomes and for the elevated number of stent-related perforations.

An elevated number of stent-related perforations were reported only in the studies specifically designed as multicenter trials and these studies were stopped prematurely.

In these trials, Pirlet *et al*[133] reported 3 stent-related perforations in 35 patients randomized to the stenting strategy and van Hooft *et al*[134] reported 6 stent-related perforations in 47 patients in the stenting group. The elevated number of perforations in these studies remains unexplained.

The worst results in SEMS placement outcomes come from RCTs which are specifically designed as multicenter trials involving low-volume centers. In the of Pirlet *et al*[133], of the nine participating centers, two of them enrolled 3 patients and one only 1 patient; in the study of van Hooft *et al*[134] 21 on 25 endoscopic centers were not referral.

The problem is that in planning RCTs regarding colonic stent placement, the need for involving multiple centers caused the inclusion of endoscopists with limited specific experience and low performance in placing stents. Therefore, this reality could result in confounding data on the real efficacy of the stenting strategy.

Huang *et al*[138] published a recent systematic review and meta-analysis evaluating safety and efficacy of colo-rectal stent placement as bridge to surgery compared to emergency surgery and considered for inclusion the 6 RCTs studies in english language and also another study in chinese language[138].

The technical success of colo-rectal stenting was of 76.9%, in absence of significant statistically difference in the postoperative mortality (10.7% *vs* 12.4%). The study evidenced lower morbidity (33.1% *vs* 53.9%, $P = 0.03$), higher rate of successful primary anastomosis (67.2% *vs* 55.1%, $P < 0.01$) and lower rate of definitive stoma (9% *vs* 27.4%, $P < 0.01$) for the group undergone stent placement[139].

None oncologic adverse events were recorded in the bridge to surgery group, but a major rate of lymphatic invasion was found[140-142]. No significant difference in survival were founded over 5 years (60% *vs* 58%)[143].

Colon stenting procedure does carry some risks, and complications are usually divided into early (within 30 d), including perforation, misplacement, and bleeding, and late, which include migration, reocclusion, tenesmus and delayed perforation.

The most common adverse event described in literature after stent placement as the migration (11%) SEMS obstruction caused by in and overgrowth tissue (12%) and bowel perforation (4.5%), as showed from a systematic review involving 88 published studies[144].

Stent obstruction is generally due to fecal impaction after tissue in or overgrowth, determining the long-term outcomes of the metal stent. The rate of SEMS obstruction by tissue in or overgrowth increases with the time because of the natural tendency of the neoplastic tissue to advance; then, SEMS occlusion is more frequent in patients in which the SEMS is placed for palliation. Literature data evidenced a 16% of SEMS occlusion when the treatment is made with palliative intent[145].

The endoscopic SEMS placement inside a stent is actually the best treatment to solve the stent obstruction due to the tissue in or overgrowth[146].

The migration of a SEMS could be asymptomatic or may cause occlusive or sub-occlusuve symptoms. More rarely is the bleeding. Tenesmus may be present when the SEMS reaches the rectum. Removal of a migrated stents from the rectal ampulla is not a challenging situation and can be also performed manually. Risk factors related to migration are the covering of the stent and the diameter < 24 mm. Some Authors stated that chemotherapy could be also related to the migration because of tumor reduction[147-149].

When the patient becoming symptomatic, the migration of the stent could be treated with the placement of a second one.

Bowel perforation is typically regarded as the only serious complication and is generally procedure or stent related. Most of the perforation occurred within 7 d after stent placement and may be caused by the SEMS delivery insertion into the stricture before the stent deployment, pneumatic dilatation of the stenosis or incorrect advancing of the wire. More rarely the perforation is due to the decubitus of the flared ends of the SEMS on the colonic wall. Over inflation with air can cause a perforation in a yet dilated colon far away from the site of obstruction, usually in the cecum[150-152].

Datye *et al*[152] reviewed the factors involved into the bowel perforation after stent placement, collecting the data from 82 published articles with 2287 patients. They showed a mortality rate related to perforation of 16.2% for patients who had stent-related perforation. The majority of adverse events (> 80%) were recorded within 1 mo from SEMS deployment, and 50% within 24 h from the procedure. Concomitant chemotherapy, steroids, and radiotherapy were significantly associated with perforation[153].

Bevacizumab therapy is considered now a considerable risk factor for post-stenting bowel perforation. The antiangiogenic effect could impair the colonic wall promoting the perforation at the site of maximal stent exercised pressure. Moreover, this perforation risk might be not dependent from the SEMS placement because is nowadays well known that spontaneous bowel perforation can occur during the addition of bevacizumab to chemotherapy.

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REVIEW

Recent advancement of therapeutic endoscopy in the esophageal benign diseases

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Abstract

Over the past 30 years, the field of endoscopy has witnessed several advances. With the advent of endoscopic mucosal resection, removal of large mucosal lesions have become possible. Thereafter, endoscopic submucosal resection was refined, permitting en bloc removal of large superficial neoplasms. Such techniques have facilitated the development of antireflux mucosectomy, a promising novel treatment for gastroesophageal reflux. The introduction and use of over the scope clips has allowed for endoscopic closure of defects in the gastrointestinal tract, which were traditionally treated with surgical intervention. With the development of per-oral endoscopic myotomy (POEM), the treatment of achalasia and spastic disorders of the esophagus have been revolutionized. From the submucosal tunnelling technique developed for POEM, Per oral endoscopic tumor resection of subepithelial tumors was made possible. Simultaneously, advances in biotechnology have expanded esophageal stenting capabilities with the introduction of fully covered metal and plastic stents, as well as biodegradable stents. Once deemed a primarily diagnostic tool, endoscopy has quickly transcended to a minimally invasive intervention and therapeutic tool. These techniques are reviewed with regards to their application to benign disease of the esophagus.

Key words: Per-oral endoscopic myotomy; Per-oral endoscopic tumor resection; Antireflux mucosectomy; Submucosal tumors; Subepithelial tumors; Over the scope clips; Stents; Gastroesophageal reflux disease

Core tip: Antireflux mucosectomy is an endoscopic antireflux procedure showing promising results in patients with refractory gastroesophageal reflux. Over the scope clips and esophageal stents permit safe endoscopic closure of esophagogastric defects, decreasing the requirement for surgical intervention. Per-oral endoscopic myotomy allows the precise performance of endoscopic myotomy for the treatment of spastic esophageal motility disorders with the efficacy of a surgical myotomy without the associated surgical morbidity. Per-oral endoscopic tumor resection enables en bloc endoscopic removal of subepithelial tumors (SETs) and is both a diagnostic and therapeutic intervention for esophageal SETs. These techniques will expand the boundaries of therapeutic endoscopy, decrease the need for surgical intervention, and improve patient outcomes.

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endoscopy in the esophageal benign diseases. *World J Gastrointest Endosc* 2015; 7(5): 481-495 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i5/481.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i5.481

ENDOSCOPIC ANTI-REFLUX PROCEDURES AND ANTI-REFLUX MUCOSECTOMY

Background

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal problems with an estimated increasing prevalence of over 25% in North America[1,2]. Consequently, it is a source of significant morbidity as well as considerable healthcare costs. In the United states alone, an estimated 9.3 billion dollars was incurred in direct healthcare cost as a result of GERD[3].

The standard surgical treatment for GERD is the Nissen fundoplication, where the fundus is wrapped around the lower esophagus to reinforce the lower esophageal sphincter (LES). This produces excellent short-term results and is generally safe with a post-operative complication rate of approximately 2%[4]. A recent multicenter randomized trial showed that there was no significant difference in symptom remissions at five years follow-up between oral esomeprazole therapy and laparoscopic Nissen fundoplication[5,6]. Studies with longer follow-up, have reported relapse rates of up to 50% at 12 years post-laparoscopic Nissen fundoplication[7,8]. Furthermore, reoperations in these patients has increased morbidity and relapse is still a possibility[9,10].

Recently, there has been great interest in pursuing endoscopic alternatives to laparoscopic antireflux surgery. There are three categories of such procedures; endoscopic devices for gastric plication, injection/implantable substances at the gastroesophageal junction (GEJ) and ablative therapies.

Endoscopic suturing devices allow plication 1-2 cm below the GEJ with the goal of reinforcing the LES, mimicking laparoscopic anti-reflux surgery. Depending on the device used, total procedure times vary from 30-60 min. However, due to safety, cost, and questionable long-term efficacy, many of these devices are no longer available. One currently available device is EsophyX® (EndoGastric Solutions, Washington, United States) which is marketed to deliver transoral incisionless fundoplication. Due to the fact that long-term efficacy data are not available, significant cost of the device, and the need to confirm safety and define optimal technique, it has not become widely used[11].

Injectable treatments where liquid chemical polymers are directly injected into the LES result in bulking and reinforcement of the natural barrier to reflux. These treatments demonstrated promising early results, but have been removed from the market due to safety concerns related to transmural injection resulting in mediastinits, pericarditis, and death[12-14].

Ablative therapy consists of thermal energy delivered to the GEJ, which results in tissue remodeling that provides reinforcement to the LES. Stretta® (Mederi Therapeutics Inc., Connecticut, United States) is a currently available device which delivers low radiofrequency energy. The Stretta device has been available in the United States since 2000 and has good safety data, contrary to many of the previously mentioned therapies. In short and mid-term follow-up, there is evidence of significant improvement in subjective and objective indicators of GERD. Long-term efficacy has not been consistently demonstrated with some series showing 60% of patients proceed to antireflux surgery, while other series have shown a more durable response[15-19].

Many of the studies on endoscopic antireflux procedures are limited to small single-center case series demonstrating good short-term improvement in symptoms. However, consistent long-term durable efficacy has not been shown, with the few randomized control studies failing to show improvement over sham control arms. Due to the lack of convincing evidence for adequate long-term symptom control, associated high-cost and some safety concerns endoscopic antireflux procedures have failed to become widely used.

With the introduction of strip biopsy by Tada *et al*[20] in 1984, endoscopic resection with local injection of hypertonic saline injection (ERHSE) by Hirao *et al*[21] 1988, cap EMR by Inoue *et al*[22] in 1990 and subsequent development of ESD in Japan, resection of superficial gastrointestinal neoplasia was revolutionized[20-24]. The safety and efficacy of EMR/ESD have been well reported and are now widely applied by endoscopists around the world[23-25]. A known complication of esophageal EMR/ESD, particularly when more than two-thirds circumferential, is stricture development[26-28]. The exact mechanism of stricture formation is unknown. However, from experimental models it has been shown to involve acute inflammation, angiogenesis, fibrous hyperplasia with replacement of the submucosa with dense collagen fibers, and ultimately, atrophy of the muscularis propria[29,30]. In 2003, Inoue *et al*[22] reported a case of circumferential EMR for short-segment Barretts with high-grade dysplasia that was found on endoscopy performed for objectively confirmed (24-h esophageal pH testing) reflux symptoms. A circumferential EMR was performed extending to include a 2 cm wide portion of the gastric cardia. It was hypothesized that this would improve the reflux symptoms by causing fibrosis at the gastric cardia resulting in reinforcement of the LES. As expected, excellent symptomatic and objective (normalization of 24-h esophageal pH testing) improvement resulted and the patient has remained off of PPI for over 10 years[31]. Then in 2014, Inoue *et al*[32] published a series of 10 patients that received the antireflux mucosectomy (ARMs) procedure for

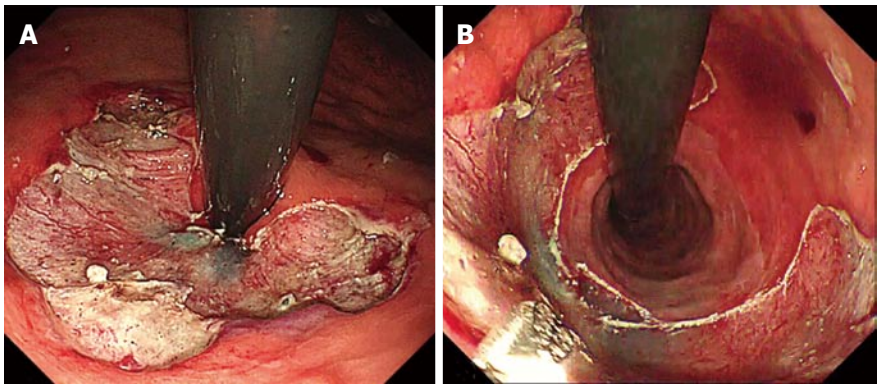

Figure 1 Completed antireflux mucosectomy. A: View on expiration; B: View on inspiration.

refractory GERD showing excellent results both subjectively and objectively.

Indications

Patients with GERD that are considered for ARMs are those without a large sliding hiatus hernia that have been objectively confirmed to be PPI refractory on 24-h esophageal pH testing. The presence of Barrett's esophagus does not preclude the performance of ARMs.

Technique

The ARMs procedure can be performed with ESD or EMR and is generally as follows: Step 1: Marking of area for mucosectomy. Mucosal reduction is planned along lesser curve of the gastric cardia in crescentic fashion (Figure 1A). When retroflexed in the stomach, the length of preserved mucosa on the side of the greater curve is estimated at twice the diameter of the endoscope (approximately 2 cm); Step 2: Submucosal injection. Both EMR and ESD can be used depending on the experience of the operator and the presence of mucosal lesions. Submucosal injection is made along the markings to ensure adequate lift to prevent deep injury or perforation; and Step 3: Mucosectomy. The mucosectomy is performed *via* EMR or ESD (Figure 1B).

Safety

In the first two cases of ARMs, circumferential mucosectomy was performed which resulted in stricture formation, however these were successfully treated with balloon dilation. Subsequently, all ARMS were performed in a hemi-circumferential or crescentic fashion that produced adequate fibrosis to alleviate GERD without stricture formation[32].

Efficacy

All patients had significant improvement in subjective and objective indicators of GERD. The DeMeester, heartburn and regurgitation scores all showed significant impressive improvement. Twenty-four hours esophageal pH testing showed the mean fraction of time at pH < 4 improved from 29.1% to 3.1%[32].

Conclusion

This series of ARMs showed promising safety and efficacy, however, the sample size was small, owing to the low incidence of GERD in Japan. Larger randomized sham-controlled studies with long-term follow-up are required to confirm these findings. Unique aspects of ARMs as an endoscopic treatment for GERD is that the safety of EMR/ESD has already been established, and endoscopists are already familiar with these techniques. These facts would allow ARMs to potentially be performed by most endoscopist with expertise in esophogastric EMR/ESD. In addition, there is no requirement for new, expensive specialized equipment. Thus, if future studies confirm the early promising results of ARMs, it has the potential to become a widely used endoscopic treatment for GERD, as it would meet the demands of safety, efficacy and cost-effectiveness.

OVER-THE-SCOPE CLIPS

Background

The over the scope clips (OTSCs) were initially introduced for closure of perforations and for mechanical hemostasis of complicated arterial bleeds of the gastrointestinal tract. The OTSC consist of a nitinol alloy with a similar shape to a bear trap. The clip, is preloaded on a clear applicator hood which is mounted onto the scope tip. The deployment system is analogous to that of a variceal banding device with the string running through the working channel of the endoscope and is fastened to a rotatable handle that is attached to the port of the working channel.

Indications

Specifically pertaining to the esophagus, the OTSC has successfully been used for refractory bleeds (non-variceal), closer of iatrogenic perforations, Boerhaave's syndrome, anastomotic leaks, tracheaesophageal fistula and securing fully covered self-expandable metal stents (SEMS)[33-43].

Technique

After mounting of the OTSC, the target area is identi-

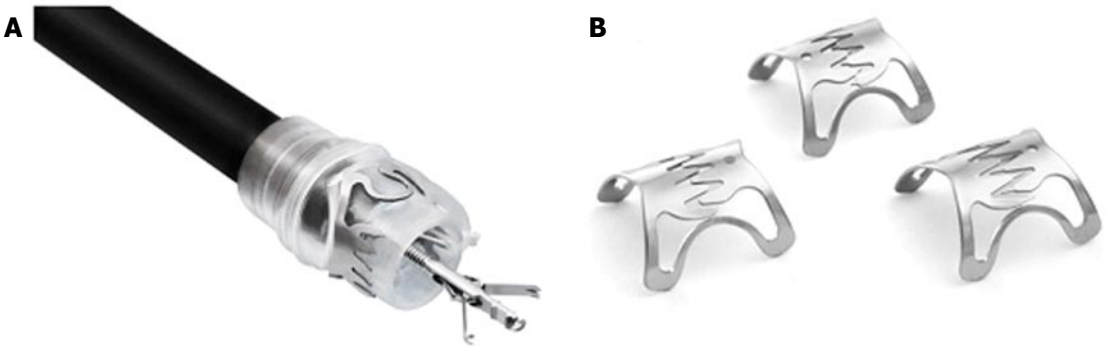

Figure 2 The over the scope clip device. A: Clip mounted onto the distal tip of an endoscope with Twin Grasper projecting from the working channel; B: The different over-the-scope clip tooth configurations available. (With permission from OVESCO Endoscopy, Germany).

fied, suctioned into the hood and the clip is deployed bringing the tissue into apposition. Alternatively, one of the available graspers or anchor can be used, allowing for dimproved apposition of the defect and better visualization of the tissue prior to clip deployment (Figure 2). Once the clip is deployed a permanent closing force of 8-9 Newtons (N) is applied to the tissue without causing necrosis[43]. Depending on the indication, different teeth are available; rounded (type a, Figure 2B left) for atraumatic application, pointed (type t, Figure 2B middle) and long pointed (type gc, Figure 2B right) for more tissue apposition. Some of the challenges with the OTSC device are that it limits sharp angulation which can make maneuverability in the esophagus more challenging and the attached OTSC device slightly impairs the endoscopic view.

Safety

Complications with the OTSC have been uniformly rare in all the published series, the majority reporting no or few complications[33-41,43-52]. However, isolated cases of esophageal perforation, inadvertent tongue piercing and intestinal obstruction (from accidental inclusion of opposing walls into the OTSC) have been reported[44,51,53].

Efficacy

The OTSC device has been shown to be safe and effective for refractory arterial GI bleeding and closure of iatrogenic perforations 20 mm and smaller[47,51]. The successful closure of anastomotic leaks and fistulas in case series has been largely favorable, but efficacy has varied widely between 38%-100% in published series, due to heterogeneity of cases, series size and operators experience[36-38,40-43,45,48-51,54,55]. However, two recent meta-analysis showed success rates of 80%-100% for both perforation and fistula closure, with failure usually associated with chronic fibrotic fistulas[52,56]. Most recently the European Society of Gastrointestinal Endoscopy released its position statement on iatrogenic endoscopic perforations and endorsed the use of the OTSC device for closure of iatrogenic esophageal perforations[57].

Conclusion

Multiple studies have reported that the OTSC device has good clinical efficacy for closure of esophageal, perforations, fistula and anastomotic leaks with few complications. Depending on the expertise available the OTSC device can be considered an early treatment option for esophageal perforation, leaks and fistula.

POEM

Background

Achalasia is an esophageal motor disorder resulting from inhibitory neuron dysfunction causing loss of peristalsis and impaired LES relaxation. This leads to impaired food bolus propulsion and stasis in the esophagus. Patients may experience dysphagia, regurgitation, chest pain, weight loss and heartburn[58-60]. The conventional treatments are laparoscopic Heller myotomy (LHM) and pneumatic dilation (PD). The first account of an endoscopic myotomy dates back to 1980 by Ortega *et al*[61] in Venezuela, where they described two 1cm long myotomies to a depth of 3 mm performed at the LES in 17 patients. In 1997, Pasricha *et al*[62] in the United States, described an experimental technique on a bovine model, where a mucosal incision was made five centimetres above the GEJ and a balloon was placed into the submucosal space to create a tunnel down to the GEJ, where a myotomy of the circular muscle was performed[62]. In 2010, Inoue *et al*[32] in Japan modified the endoscopic myotomy procedure such that it permitted safe and effective human application. Since the introduction of POEM, there has been an dramatic increase in POEM studies and the procedure is now being performed worldwide.

Indications

Currently, there are no universal guidelines for the indication of POEM. It is the opinion of the authors of this review that with the reported efficacy and safety from our center, that POEM can be considered a first line treatment for achalasia. POEM has been safety performed in patients with previous PD, LHM, Botox injection, and even previous POEM. In our center, it

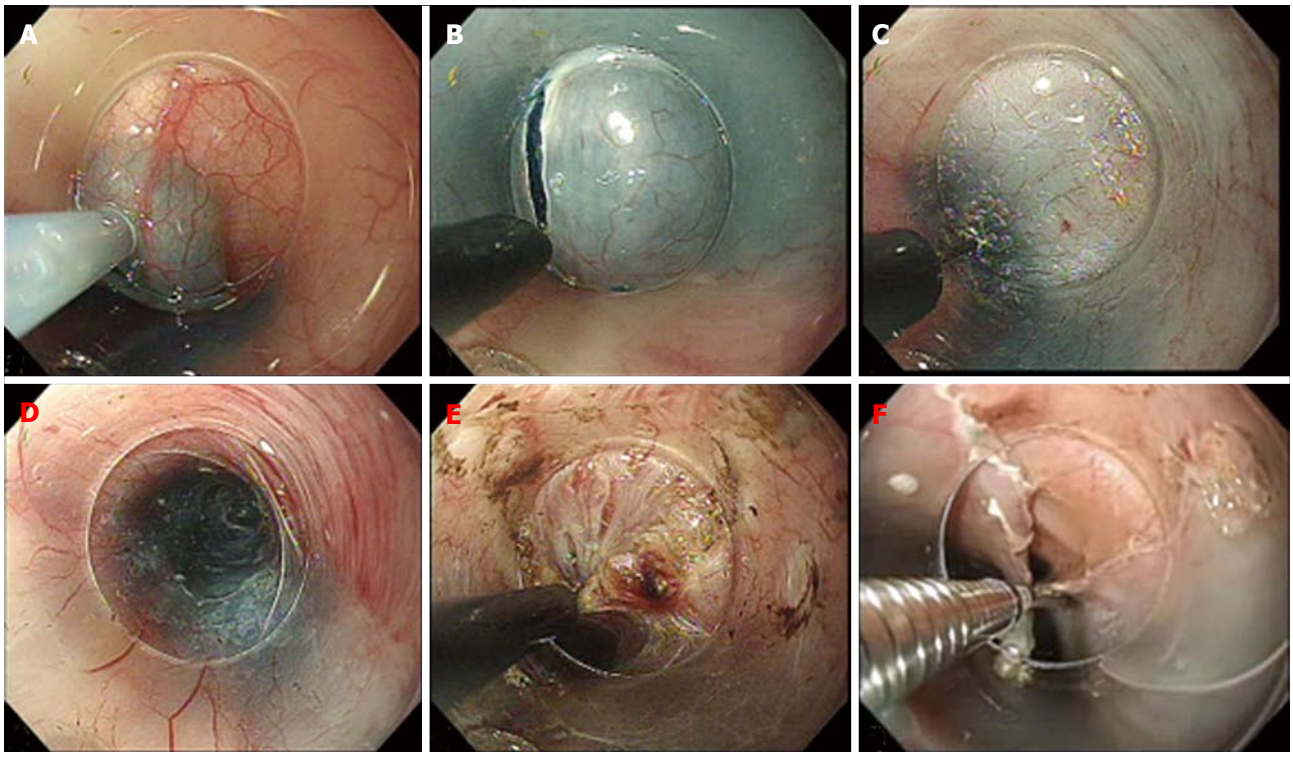

Figure 3 Steps in Per-oral endoscopic myotomy. A: Submucosal injection; B: Mucosal incision; C: Submucosal tunneling; D: Completed tunnel; E: Circular muscle myotomy; F: Closure of mucosal incision.

has also been safely performed in patients with type 1 and type 2 sigmoid achalasia as well as octogenarians. Other motility disorders such as diffuse esophageal spasm (DES), nutcracker esophagus, Jack-hammer esophagus, and hypertensive LES have also been successfully and safely treated with POEM.

Technique

The first successful case of POEM in a human was performed September, 2008 by Haruhiro Inoue. Since then, it has been widely accepted and performed with many slight variations to the original technique. The procedure as performed at our center is as follows (Figure 3): Step 1: Submucosal Injection and Incision. After the area of mucosal incision is chosen (approximately 13 cm above the GEJ for standard myotomy) 10 cc of saline with indigocarmine is injected into the submucosa and a 1.5-2 cm longitudinal incision is made with a triangle-tip knife (KD-640 L; Olympus). To avoid mucosal injury, the submucosal tunnel is dissected as close as possible to the circular muscle; Step 2: Creation of the submucosal tunnel. After enough space is created in the submucosa, mucosal entry is achieved and the tunnel is carefully extended down to the gastric side for approximately 3 cm; Step 3: Endoscopic myotomy. The circular muscle fibers are carefully dissected with the Triangle tip knife. When there is no abnormal contraction of the esophageal body or symptoms of chest pain, the standard myotomy is 8-10 cm; and Step 4: Closure of Mucosal entry. After completion of the myotomy and good hemostasis is confirmed, prophylactic antibiotic is instilled into submucosal tunnel and the mucosal entry site is clipped closed.

The main technical limitation to the performance of POEM is the presence of severe submucosal fibrosis which limits the ability to safety perform the submucosal tunnel and can occur when patients have had severe esophagitis, multiple previous endoscopic treatments, extensive esophageal EMR/ESD in the POEM field or radiation therapy.

Safety

Complications include; capnomediastinum, capnoperitoneum, intraprocedural and delayed bleeding, mucosal laceration/ischemia and GERD. The vast majority of complications reported have been treated conservatively and there have been no mortalities reported or requirement for conversion to open surgical procedure[63-73]. The most robust data comes from the international POEM survey (iPOEMS) database, reporting major complications occurred in 3.2% of 841 cases[74] which were treated conservatively without sequelae. In comparison, the large European trial comparing PD and LHM showed a 4% perforation rate for PD and a 12% rate of mucosal tear for LHM[75].

There is heterogeneity in reporting and classification of complications, partially accounting for the variability in reported complication rates (Table 1). Therefore, a standardized, internationally agreed upon adverse event reporting system for POEM is required. However, it is important to note that all the reported complications

Table 1 Series reporting Eckardt post Per-oral endoscopic myotomy for achalasia

Ref.	Country	No. of patients	Success rate (%)	Complications (%)	Mean follow-up (mo)
inoue *et al*[82] 2010[a]	Japan	17	100	0	5
von Renteln *et al*[79] 2012	Germany	16	94	12.5	3
Swanstrom *et al*[67] 2012	United States	18	100	16.7	11
Ren *et al*[85] 2012	China	119	94	55	3
Costamagna *et al*[65] 2012	Italy	11	100	0	3
Lee *et al*[66] 2013	South Korea	13	100	0	7
Hungness *et al*[76] 2013	United States	18	89	22	6
Teitelbaum *et al*[77] 2013	United States	12	100	NR	9
Zhou *et al*[83] 2013[b]	China	12	92	16.7	10
Von Renteln *et al*[64] 2013[c]	International	70	82.4	14.3	12
Sharata *et al*[84] 2013[d]	United States	31	100	12.5	6
Freidel *et al*[68] 2013	United States	45	95	33	3
Inoue *et al*[80] 2013	Japan	300	100	6	12
Sharata *et al*[73] 2014	United States	75	98	11	16
Bhayani *et al*[78] 2014	United States	37	100	13.5	6
Minami *et al*[63] 2014	Japan	28	96	0	3

[a]Eckard score was not used, but rather a dysphagia symptoms score which decreased from mean of 10 to 1.3; [b]All patient had previous laparoscopic Heller myotomy; [c]European and North American; [d]Included other spastic esophageal disorders, total 31 achalasia cases; Complications rate reported is for all 40 cases performed. NR: Not reported.

have been treated successfully endoscopically, with needle decompression or conservative management without any significant sequelae.

Efficacy

POEM is now being performed globally with excellent clinical results, with patients showing improvement of mean Eckardt scores from 5.4-8.8 pre-POEM to 0.4-1.7 post-POEM[63-68,76-81]. In addition, many series have reported decreases in LES pressure and barium column height[63-67,76-79,82]. Success rates, defined by a post-POEM Eckardt score $\leqslant$ 3, are summarized in Table 1. Multiple comparative studies have shown that POEM is at least as effective as LHM with shorter hospital stay and decreased post-procedure pain[76-78].

POEM has also been shown to be effective in patients with previous LHM. Zhou *et al*[83] reported a mean improvement in Eckardt score of 9.2 to 1.3, and Onimaru *et al*[81] reported a mean improvement in Eckardt score of 6.5 to 1.1. Patients who have failed Botox injections or PD have also seen comparable improvements post POEM[84].

Expanded Indications for other spastic esophageal motility disorders

Generally, other spastic disorders of the esophagus that have been treated surgically require a longer myotomy necessitating thoracotomy. This is another advantage of POEM, where a long myotomy can be performed without increased invasiveness or complications. From the iPOEMS database, the POEM procedure was performed in 25 DES patients, 106 Nutcracker patients, and 58 Hypertensive LES (HTLES) patients. Compared to achalasia, POEM was equally effective in Nutcracker esophagus and HTLES, but less effective for DES[74]. In the recent series by Sharata *et al*[73] that included 12 Nutcracker esophagus, 5 DES, and 8 HTLES patients, complete dysphagia relief was achieved in 70.8% of non-achalasia cases, while chest pain was relieved in 91.5%[73]. There are also two case reports demonstrating successful application of POEM for Jackhammer esophagus[86,87].

Areas of controversy

In our center, the majority of POEM cases were performed at 2 o'clock (anterior-lesser curve) or 5 o'clock (posterior-lesser curve) positions. In some cases, previous procedures such as LHM, POEM, or ESD (for esophageal lesion) had been performed, precluding safe submucosal tunnelling in the normal location and alternate positions were used. At present there are no studies to guide which site of standard myotomy is most optimal. This will hopefully be addressed with a large multicenter, randomized trial in the near future.

A selective circular muscle myotomy is normally performed in our center. Nevertheless, some centers prefer a full thickness myotomy. Li *et al*[88] compared full thickness myotomy with selective circular muscle myotomy and found no difference in either efficacy or adverse events. However, shorter operative times are observed with full thickness myotomy[88]. Until there is more evidence, we suggest an isolated circular myotomy to prevent potential damage to adjacent structures and.

Conclusion

Over 2000 POEM procedures have been performed worldwide. Most of the of the studies show excellent efficacy with low rate of major complications, all of which have been managed without sequelae. There is also growing evidence for the use of POEM for other spastic disorders of esophagus. Over time, POEM may arguably become the standard of care for achalasia and other spastic disorders of the esophagus.

PER-ORAL ENDOSCOPIC TUMOR RESECTION

Background

Subepithelial tumors (SETs) of the upper gastrointestinal tract are generally uncommon with an incidence of about 0.4% of all routine esophagogastric endoscopic examinations[89]. Gastric SETs have a malignancy rate of approximately 50%, in contrast, esophageal SETs are usually benign leiomyomas and only 1%-3% harbor malignancy[89-91]. Generally, SETs are asymptomatic and found incidentally on endoscopic or radiologic examination for unrelated symptoms or screening. However, larger SETs can cause dysphagia, chest pain, regurgitation and bleeding[92,93]. Traditionally, excision of symptomatic SETs has been performed with open surgical, laparoscopic or thoracoscopic techniques. These procedures are invasive, associated with significant health-care cost and morbidity[94-96]. In addition, if the lesion in question is benign it is difficult to justify surgical excision with associated surgical morbidity. With the introduction of POEM, the submucosal tunnelling technique has been subsequently applied for Per-oral endoscopic tumor (POET) resection by Inoue *et al*[97] in 2012. The technique has allowed SETs to be removed from the esophagus and gastric cardia, safety and effectively. Since its first description, multiple series have been published supporting its safety and efficacy.

Indications

Most of the SETs removed *via* POET have been benign. The presumptive diagnoses were made using a combination of endoscopy, endoscopic ultrasound (EUS) and CT scan. Indications for resection were presence of symptoms, enlarging tumor or unclear diagnosis in which resection was diagnostic.

Technique

An essential part of POET (and POEM) is use of low flow carbon dioxide insufflation to prevent complication from barotrauma as noted by Wang *et al*[98], where air insufflation was used in the first half of their series, which resulted in high rates subcutaneous emphysema, pneumothorax and pneumomediastinum. Subsequently, they used carbon dioxide insufflation for the remaining cases and did not have further adverse events related to insufflation[98]. The POET technique can be summarized as follows with the various steps shown in Figure 4: Step 1: Submucosal Injection and Incision. The area of mucosal incision is generally 5 cm proximal to the tumor and is made as described for POEM; Step 2: Creation of the submucosal tunnel. The submucosal tunnel is extended 1-2 cm distal to the tumor to ensure sufficient working space for the dissection of the tumour; Step 3: Tumour Resection. Once the mass is identified and the tunnel is sufficient, resection of the tumor can proceed. Careful dissection of the mass from the muscular layer should be performed to prevent rupture of capsule or perforation of the overlying mucosa. Tumors that extend to the deep muscular layer can be removed with a full thickness resection of the circular and longitudinal muscles. The free tumor can be withdrawn through the mucosal incision using a snare, grasping forceps or suctioning into the transparent hood; and Step 4: Closure of Mucosal entry. The tunnel is re-examined to confirm adequate hemostasis and the mucosal incision is closed with endoscopic clips. There are also reports of using endoscopic staples, OTSCs, as well as covered metal stents to seal the mucosal incision site[99-102].

Patients are managed analogous to post-POEM patients. Patients are kept nil per os for 24 h. Day 1 post-procedure the patient has an endoscopy as well as a contrast study to check for leak. Some centers perform routine post-procedure CT scan to check for insufflation related complications and perforation[103]. The patient's diet is advanced to clear liquids day-1 post-procedure, and advanced to regular diet by day 4 if asymptomatic. Endoscopy and endoscopic ultrasound are generally performed for follow-up on patients that underwent POET resection. If the lesion removed is malignant or with malignant potential, closer follow-up is performed and includes a CT scan to assess for tumor recurrence and the occurrence of distant metastasis[98,104].

Safety

Almost all of the reported complications have been insufflation related (subcutaneous emphysema, pneumoperitoneum and pneumomediastinum). All were managed with decompression or conservatively without sequelae. Analogous to POEM series, there is variability in reporting and classification of complications.

Efficacy

Nearly all series report 100% successful resection (refer to Table 2). With almost all being *en bloc* with intact capsule. A complete resection refers to an en bloc resection of the tumor with intact capsule. This factor is important to prevent seeding especially if the pre-procedure diagnosis is suggestive of a malignant or pre-malignant lesion. The limiting factor for resection of SETs *via* POET is size. The largest SET removed to date was 60 mm × 28 mm × 22 mm[100]. The tumor (known to be a leiomyoma) required fragmentation to be extracted. In addition, the mucosal incision could not be closed and necessitated placement of fully covered SEMS. Anecdotally, it appears that the upper limit for a complete resection is 4-5 cm depending if the shape of the tumor allows for extraction through the mucosal incision site. The efficacy data is summarized in Table 2[97-99,105-111] below.

Conclusion

Subepithelial tumors of the esophagus and cardia are usually incidental findings on endoscopic or radiologic examinations for unrelated symptoms, with

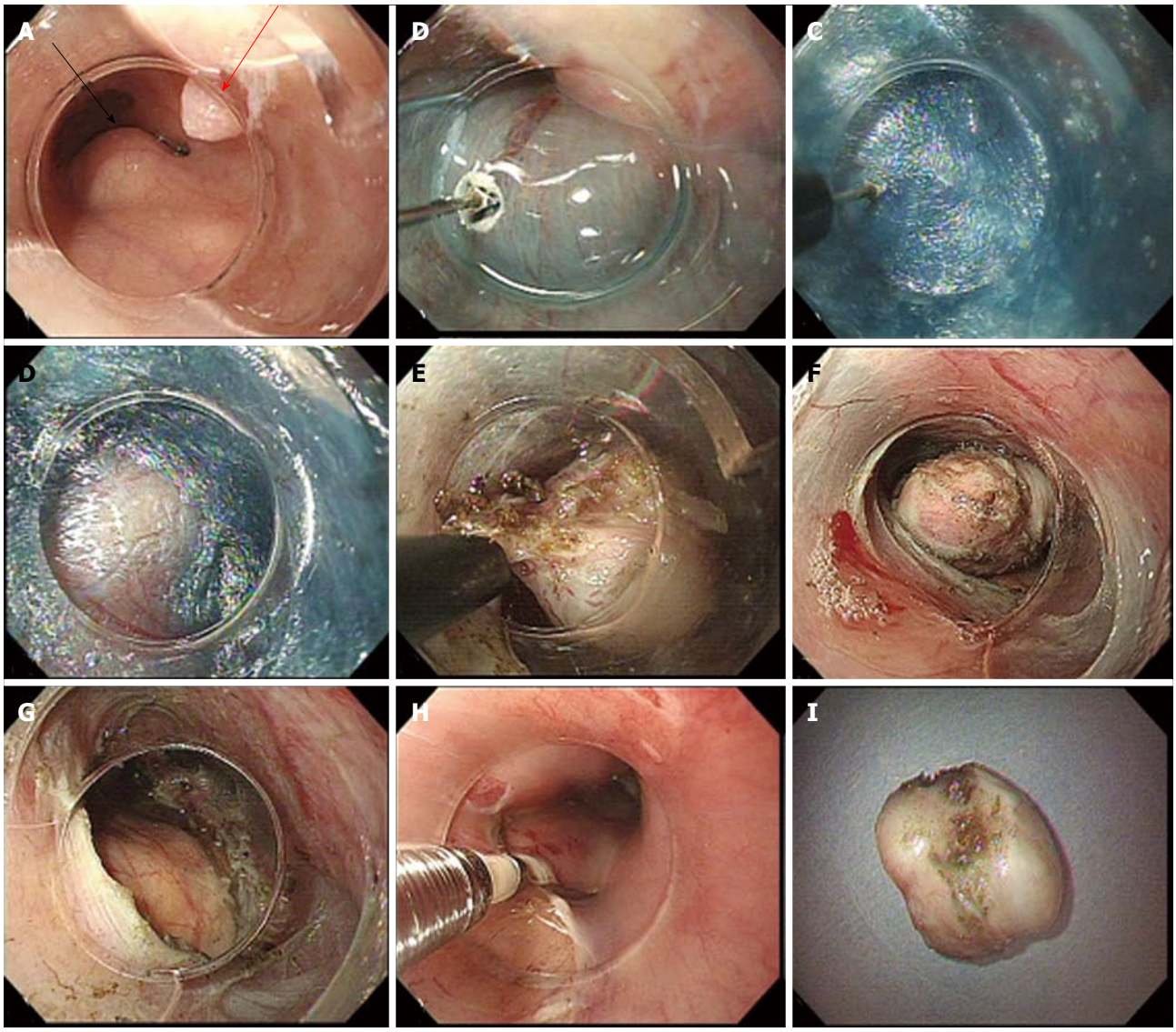

Figure 4 Per-oral endoscopic tumor resection of Leiomyoma. A: Subepithelial tumor (SET) (black arrow) and incidental papilloma (red arrow); B: Mucosal incision with TT knife; C: Creation of submucosal tunnel; D: First encounter with SET in tunnel; E: Dissection of tumor; F: Dissected SET; G: Completed full thickness resection; H: Closure of incision; I: Extracted SET with intact capsule.

the majority being benign. With the moderate yield of EUS, morbidity and costs and surgical resection, a minimally invasive diagnostic and therapeutic procedure is required for the management of SETs. The careful performance of POET is effective and safe, and with continued supportive evidence will likely be performed with increased frequency for resection of most esophageal and gastric cardia SETs, with surgical resection reserved for very large or malignant SETs.

STENTS

Background

When first introduced in 1959, esophageal stents were placed intra-operatively and were indicated only for palliation of dysphagia for non-operable malignant strictures[112]. Endoscopic stents were subsequently introduced in 1977, but were plagued with high complication rates[113]. Since then, SEMS have become widely used for palliation of dysphagia for non-operable malignant esophageal strictures with good safety, efficacy, and cost effectiveness data[114,115]. With the success of SEMS for malignant esophageal disease, there was an effort to expand the use of uncovered/partially covered SEMSS for the use of benign esophageal disease. However, it was found early on that SEMS resulted in increased complications when used for benign disease. Such complications included migration, tissue ingrowth, stent induced stenosis, development of tracheoesogeal fistula, and hemorrhage[116-118].

With the hope to ameliorate the serious issues encountered with SEMS when used for benign disease, manufacturers introduced the fully covered self-expandable metal stents (FCSEMS), fully covered self-expandable plastic stents (SEPS) and biodegradable

Table 2 Series reporting on safety and efficacy of per-oral endoscopic tumor resection

Ref.	Country	No. of patients	Mean tumor size (mm)	Complete resection[b] (%)	Piecemeal or disrupted capsule (%)	Complications (%)
Inoue *et al*[97] 2011[a]	Japan	9	29.4	100 (7/9)	0	0
Cai *et al*[105] 2012	China	1	20	100	NS	100
Gong *et al*[106] 2012	China	12	19.5	83.3 (10/12)	16.7 (2/12)	16.7
Xu *et al*[107] 2012	China	15	19	100	0	13.3
Liu *et al*[103] 2013	China	12	18.5	100	0	66.7
Xu *et al*[108] 2013	China	23	21	100	0	39
Wang *et al*[99] 2013	China	18	33	NS	NS	16.7
Chen *et al*[109] 2014	China	1	#1 = 25 #2 = 30	100	0	0
Kumbhari *et al*[100] 2014	United States	1	60	0	100	NS
Lu *et al*[110] 2014	China	42	12.1	97.7 (44/45)	2.3 (1/45)	15.6
Ye *et al*[104] 2014	China	85	19.2	100	0	9.4
Wang *et al*[98] 2014	China	57	21.5	100	0	21
Lu *et al*[111] 2014[c]	China	18	21	100	0	11.1

[a]The 2 subepithelial tumors (SETs) that could not be resected were 60 and 75 mm in size and an adequate endoscopic field for safe extraction was not possible; [b]Complete resection refers to *en bloc* extraction of the tumor with intact capsule and clear margins; [c]Series included only cardia and gastric SETs. NS: Not specified.

stents (BDS).

Indications

For patients with iatrogenic perforations, tracheoesophgeal fistula, and/or surgical interventions complicated by anastomotic leaks, the treatment has traditionally been surgical. However, with the advent of FCSEMS and fully covered SEPS, these have been increasingly used as means to prevent reoperation and to allow healing to take place. Another emerging use is for refractory benign esophageal strictures in which traditional management with dilation has failed.

Equipment

There are currently a variety of stents available depending on the country. Below is a brief summary (Table 3) of the general differences between the FCSEMS, SEPS and BDS with focus on benign esophageal strictures. Examples of each group are shown in Figure 5.

Technique

Once the stricture has been deemed refractory and stenting is considered, or a defect requires closure, then the choice of stent depends on the position and length of stricture/defect and preference of the endoscopist. The length of the stent should be at least about 3-4 cm longer the stricture/defect. The endoscopist should carefully assess the stricture/defect noting the proximal and distal margins, the distance from the upper esophageal sphincter and LESs. The stricture/defect should be greater than 2 cm distal from the upper esophageal sphincter, as if this distance is less it increase the risk of of pain, globus sensation, aspiration pneumonia or development of tracheoesophageal fistula. If the stent is to be deployed across the LES, a stent with an antireflux valve can be considered if available. Once the location of stent placement is chosen, the proximal and distal margins can be marked endoscopically (submucosal injection of radiopaque substance or placement of clips), by specific anatomic landmarks under X-ray or placement of radiopaque markers on the patient. If simultaneous endoscopic visualization is desired, an ultra-slim scope can be used transnasally. Under fluoroscopic control, the stent is deployed keeping adequate margins on both sides. Endoscopic clips, OTSCs or an endoscopic suturing device can used to decrease the risk of stent migration[34,119-122]. After deployment, the stents will radially expand and shorten reaching their final form.

Efficacy

Efficacy is defined as technical and clinical success. Technical success is defined as successful deployment of the stent and clinical success is the achievement of the intended clinical outcome (improvement in dysphagia, closure and healing of defect). FCSEMS and fully covered SEPS show excellent technical and good clinical efficacy for the closure of benign gastrointestinal disruptions with a technical success of 91% and clinical success of 81%[123]. In the cases where only partial closure fully covered achieved, surgical reinvention is still often avoided[123].

Unfortunately, for benign strictures, the clinical efficacy of FCSEMS and fully covered SEPS is less promising than for benign disruptions with a range of clinical success of 40%-50%[124,125]. Biodegradable stents were introduced with the hopes of improving the shortcomings of modest clinical efficacy of FCSEMS and fully covered SEPS. Unfortunately, the clinical efficacy of BDS has not differed significantly compared to its predecessors, with a mean clinical success rate of 47%[126]. However, in the pediatric population, with the use of custom made plastic stents higher efficacy has been demonstrated. Also, with the stents fastened to a nasogastric tube with an external silicon bar at the

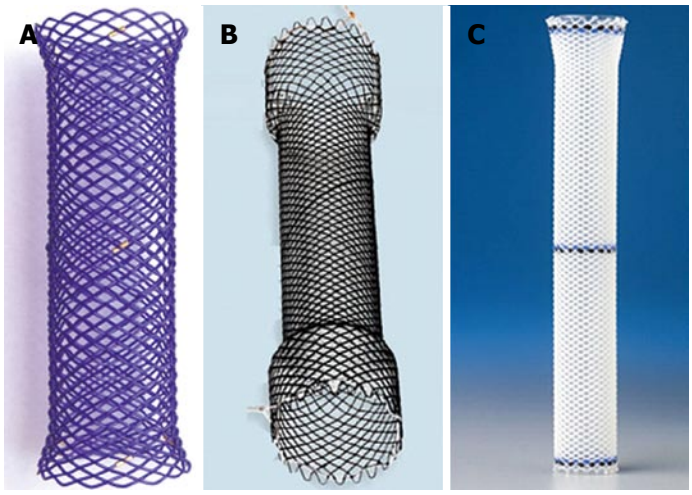

Figure 5 Examples of biodegradable stent, fully covered self-expandable metal stent and self-expandable plastic stent. A: Biodegradable stent (ELLA-CS, Czech Republic) composed of polydioxanone monofilament; B: Fully covered Evolution® stent composed of nitinol silicone coating (Cook, United States); C: Fully covered silicon constructed Polyflex® stent (Boston Scientific, United States).

Table 3 General differences between stents for benign esophageal disease

Stent type	Advantages	Disadvantages
FCSEMS	No requirement for pre-dilation	Expensive
	Recapture is possible	High migration risk
		Increased tissue hyperplasia
SEPS	Cheaper than other covered stents	High migration risk (potentially more than FCSEMS)
	Decreased tissue hyperplasia	Require manual loading
		Require pre-dilation
BDS	No need to remove	Expensive
	Less migration risk	Increased risk of post-procedure pain
		Require manual loading
		Require pre-dilation

FCSEMS: Fully covered self-expandable metal stents; SEPS: Self-expandable plastic stents; BDS: Biodegradable stents.

naris to avoid distal migration, much lower migration rates have been observed[127,128].

Safety

FCSEMS and fully covered SEPS have a modest complication rate, with the most common being stent migration at about 25%-30% with some evidence that the risk of migration is higher with SEPS[129,130]. The risk of migration may also be higher for proximal and anastomotic strictures[131]. Other rare complications of FCSEMS and fully covered SEPS include perforation, tissue hyperplasia, stent induced strictures, hemorrhage, and post-procedure pain. A very rare but dreaded complication is the development of an aortoenteric fistula, which is usually fatal[132-134]. BDS have a lower risk of migration of about 20% and fewer complications overall, but may have increased post-procedure pain[126,135,136].

Conclusion

There is mounting evidence for the efficacy of FCSEMS and fully covered SEPS for closure benign gastrointestinal disruptions with a moderate risk of stent migration. For refractory strictures, the efficacy is less promising likely owing to varying techniques, heterogeneity of patients and the severity of stricture pathology being treated. Depending on the individual case and the experience of the endoscopist, FCSEMS, fully covered SEPS, and BDS are potential options for select patients with refractory strictures. The particular choice of stent depends on the endoscopists preference and experience, perceived risk or migration, tissue hyperplasia and other complications. Hopefully with improvement in stent design, refinement in technique and patient selection, there will be improved clinical efficacy and safety for stents used for benign esophageal strictures.

SUMMARY

Endoscopy has drastically advanced from being primarily a diagnostic tool to becoming the favored modality for treatment of benign disease of the esophagus. Promising efficacy and safety data of POEM and POET is accumulating, and with careful application, these procedures may soon be heralded as the standard of care for various diseases. Despite being a novel procedure, there is extensive experience with the technique used in ARMs in the setting of EMR/ESD. With the early promising results of ARMs, it has the potential to become a prominent treatment of GERD if efficacy confirmed by larger randomized control trials. OTSC usage is becoming widespread and has a remarkably low complication rate with good efficacy in facilitating

the closure of esophageal perforations, fistula, and leaks. At present, the evidence for treatment of benign esophageal disruptions is promising and FCSEMS and SEPS should be considered in their treatment. However, for benign esophageal strictures the evidence for the use of FCSEMS, fully covered SEPS and BDS has been conflicting, but with further improvement in stent design and refinement of technique, there is potential for improved clinical efficacy.

With the ongoing introduction of novel procedures and equipment, it is critical that patient safety remain the top priority. International collaboration in the form of large multi-centered trials provide the opportunity to optimally study safety and clinical efficacy of newly introduced equipment and techniques.

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MINIREVIEWS

Peroral endoscopic myotomy

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Abstract

Peroral endoscopic myotomy (POEM) incorporates concepts of natural orifice translumenal endoscopic surgery and achieves endoscopic myotomy by utilizing a submucosal tunnel as an operating space. Although intended for the palliation of symptoms of achalasia, there is mounting data to suggest it is also efficacious in the management of spastic esophageal disorders. The technique requires an understanding of the pathophysiology of esophageal motility disorders as well as knowledge of surgical anatomy of the foregut. POEM achieves short term response in 82% to 100% of patients with minimal risk of adverse events. In addition, it appears to be effective and safe even at the extremes of age and regardless of prior therapy undertaken. Although infrequent, the ability of the endoscopist to manage an intraprocedural adverse event is critical as failure to do so could result in significant morbidity. The major late adverse event is gastroesophageal reflux which appears to occur in 20% to 46% of patients. Research is being conducted to clarify the optimal technique for POEM and a personalized approach by measuring intraprocedural esophagogastric junction distensibility appears promising. In addition to esophageal disorders, POEM is being studied in the management of gastroparesis (gastric pyloromyotomy) with initial reports demonstrating technical feasibility. Although POEM represents a paradigm shift the management of esophageal motility disorders, the results of prospective randomized controlled trials with long-term follow up are eagerly awaited.

Key words: Peroral endoscopic myotomy; Achalasia; Myotomy; Dysphagia

Core tip: Peroral endoscopic myotomy (POEM) is a minimally invasive, scarless approach to Heller myotomy for the palliation of symptoms of achalasia and spastic esophageal disorders. Current data demonstrates short-term success with minimal adverse events. POEM is no longer considered experimental with approximately 5000 procedures performed worldwide. In the future, a personalized approach to POEM will be undertaken with tailoring of the length of gastric myotomy based on intraprocedural physiological measurements. This will allow sufficient reduction in pressure at the lower esophageal sphincter for adequate relief of symptoms but also minimize gastroesophageal reflux.

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INTRODUCTION

Peroral endoscopic myotomy (POEM) is a minimally invasive endoscopic procedure intended for long-term recovery from symptoms of esophageal achalasia. Achalasia is a benign motility disorder of the esophagus which is characterized by incomplete relaxation of the lower esophageal sphincter (LES) and aperistalsis of the esophageal body. As the etiology of achalasia is not known, all treatment options are directed at decreasing the resting pressure at the LES.

The first reported endoscopic myotomy in humans was published in 1980[1]. In this report, the myotomy was carried out in an uncontrolled manner by incising the mucosa through to deeper layers of the lower esophageal sphincter with a needle knife. The method achieved technical success in all 17 patients although there was concern as the wound was directly exposed to esophageal and gastric contents and if too deep, there would be a direct perforation to the mediastinum and/or peritoneum. There were three minor bleeding episodes which were controlled endoscopically. The clinical, manometric and radiological postoperative results were promising. However, the direct incision method was not considered a reliable and safe approach and was therefore not adopted by the medical community.

Developments in natural orifice translumenal endoscopic surgery (NOTES)[2] have resulted in a submucosal endolumenal approach for the treatment of achalasia using POEM. Sumiyama *et al*[3] was the first to describe the idea of submucosal tunneling. However, Pasricha *et al*[4] initially described the concept of POEM in 2007 in an experimental preclinical model. This report demonstrated the safety and efficacy of performing a myotomy under endoscopic visualization in 4 pigs after the formation of a submucosal tunnel. Inoue *et al*[5] championed translating this innovative technique into clinical care in 2010 with the first human study reporting favorable results in 17 achalasia patients.

Multiple studies from Asia, Europe and the United States reveal that POEM is a safe and effective therapy for achalasia when performed by expert endoscopists. In addition, the recent white paper summary from the American Society of Gastrointestinal Endoscopy provided substantial data to support the notion that POEM is a promising therapeutic modality[6]. This review illustrates the patient selection and preparation, operative technique, clinical outcomes and future directions for POEM.

PATIENT SELECTION AND INDICATIONS

All patients with symptomatic, manometrically proven, primary idiopathic achalasia are eligible candidates to undergo POEM. Among initial published clinical studies, exclusion criteria included previous esophageal or gastric surgery (including Heller myotomy), sigmoid type esophagus, age under 18 years or inability to undergo general anesthesia. Other less common scenarios that rendered patients unsuitable for POEM included severe erosive esophagitis, significant coagulation disorders, liver cirrhosis with portal hypertension or prior therapy that may compromise the integrity of the esophageal mucosa or could have led to submucosal fibrosis (radiation, endoscopic mucosal resection, radiofrequency ablation, *etc.*). Previous therapy, such as uncomplicated pneumatic balloon dilation and botulinum toxin injection are not contraindications to POEM, although, in these cases inflammatory fibrosis is often encountered during submucosal dissection.

There are now multiple series reporting the technical success, efficacy and safety of POEM in patients who have undergone a prior Heller myotomy[7-9]. Successful POEM in the setting of a Roux-en-Y gastric bypass has also been reported[10] where the extensive adhesions and altered anatomy could have proven challenging for the surgical approach. POEM has also been studied in patients with with sigmoid-type achalasia with similar outcomes as those with a non-sigmoid type esophagus[11]. Age is no longer a contraindication to POEM with successful procedures being performed in those even at the extremes of age. In particular, several series have reported its successful use in the pediatric population[12,13].

Though POEM is classically done for the palliation of symptoms of achalasia, it is being increasingly used for the treatment of other foregut disorders. There are growing reports supporting its use in spastic esophageal disorders such as diffuse esophageal spasm (DES) and Jackhammer esophagus[14-19]. It is potentially more efficacious than even surgical myotomy as it allows myotomy not only of the LES, but also of the esophageal body, where hypertensive contractions occur[15,20,21]. Additionally, POEM has even been reported in the stomach (endoscopic pyloromyotomy) as a treatment strategy for selected patients with gastroparesis[22,23].

EVALUATION AND PREPARATION

It is obligatory that patients have a diagnosis of achalasia or spastic esophageal disorder firmly established based on clinical history, esophageal manometry, contrast esophagram and esophagogastroduodenoscopy (EGD). A standardized validated symptom assessment form is completed by all patients, with the majority of centers using the Eckardt score[24]. The Chicago classification of esophageal motility disorders mandates high resolution

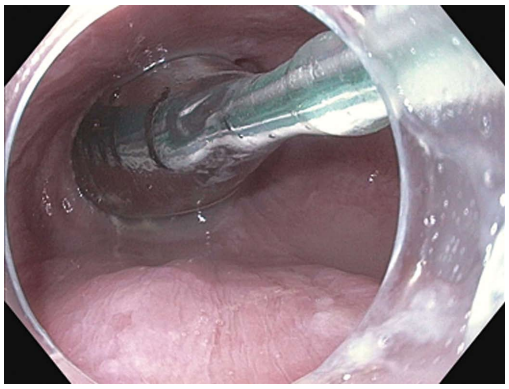

Figure 1 Endosocopic image of the endoluminal functional lumen imaging probe assessing the esophagogastric junction *via* impedence planimetry.

esophageal manometry (HREM) to identify the precise achalasia or spastic esophageal disorder subtype, although the clinical significance of this classification has been recently debated[25]. Computed tomography (CT) is not mandatory, however, some experts find it useful as it provides information on the anatomic features of adjacent structures as well as identifying congenital anomalies or ectopic varices. In addition, CT scan can be an adjunct to contrast esophagram in establishing the presence of a sigmoid-type esophagus.

Our institutional protocol is to perform an EGD on all patients 2 wk prior to their procedure. All patients are placed on a clear liquid diet 2 d prior to this endoscopy and an endoscopic assessment is made of the quantity of residual esophageal contents. If there is persistent solid residue, then even more stringent dietary restriction is advised prior to POEM. This will allow for a clear endoscopic view and may avoid aspiration during induction of anesthesia. Additionally, this evaluation allows for exclusion of underlying malignancy, erosive esophagitis, Barrett's esophagus and Candidal esophagitis. On occasion, a HREM catheter is inserted as passage without endoscopic guidance can be challenging in patients with a tight LES and/or sigmoid esophagus.

In case of use of anticoagulant or antiplatelet therapy, it is generally recommended that these medications be stopped with the exception of acetylsalicylic acid when prescribed as secondary prophylaxis. All patients have a blood type and screen performed on the day of the procedure.

POEM PROCEDURE

Our institutional protocol has been to perform POEM in the endoscopy suite. This is in contrast to most other centers where POEM is performed in the operating room[11,26]. We have performed over 50 cases in the endoscopy unit without a major intraprocedural adverse event. The procedure is performed with the patient in the supine position under general anesthesia with endotracheal intubation and complete paralysis. Our protocol is to use a specialized endotracheal tube that has a taper-shaped cuff with an evacuation port and suction lumen (TaperGuard Evac, Covidien, Mansfield, MA, United States). We have noted that approximately 100mls of fluid is aspirated through this specialized endotracheal tube during each procedure with no episodes of aspiration or pneumonia in our cohort[27].

Carbon dioxide (CO_2) insufflation is mandatory for safe POEM and to reduce the risk of mediastinal emphysema, tension pneumoperitoneum, pneumothorax and air embolization. An arterial line may be inserted such that an arterial blood gas can be performed and CO_2 levels monitored as needed. An indwelling urinary catheter is inserted and a forced air warming blanket is used to cover from the waist down.

The patient's abdomen remains in unrestricted view to allow for an immediate diagnosis of severe pneumoperitoneum. The abdomen is palpated periodically and if tidal volumes begin to diminish or the abdomen is markedly distended, decompression is accomplished using a Veress needle.

A thorough cleansing of the esophageal lumen is performed prior to commencement of the intervention. In certain cases, a therapeutic gastroscope with a 3.8mm working channel (GIF-Q260J; Olympus, Center Valley, PA, United States) equipped with a water jet is necessary. If adherent residue is present on the esophageal mucosa, a soft cleaning cap (Barrx RFA Cleaning Cap - Medium: CP-002A, BARRX Medical Inc., Sunnyvale, CA) can be used to safely scrape off the residue. Broad-spectrum intravenous antibiotics are administered.

Measurements of esophagogastric junction distensibility can be performed using the endoluminal functional lumen-imaging probe (EndoFLIP; Crospon, Galway, Ireland) (Figure 1). This provides a baseline by which the operator can assess the adequacy of the myotomy and may play a role in predicting which patients will likely be non-responders[28-30]. Subsequently, the esophagus is lavaged with 240 mL of sterile saline solution mixed with 180 mg of gentamicin.

A high-definition gastroscope fitted with a transparent cap is used. It is recommend to secure the cap on the endoscope tip with tape as anecdotal reports exist of dislodgement of the cap within the submucosal tunnel. A gastroscope that has a dedicated water jet channel such as the GIF-HQ190/GIF-H180J (Olympus, Center Valley, PA, United States) or EG2990i/EG2990k (Pentax Medical Corp., Montvale, New Jersey, United States) is recommended. For all our procedures, a bottle filled with saline and a second bottle of saline mixed with indigo carmine are attached to the water jet channel *via* a stopcock. Individual foot pedals activate each bottle[31] (Figure 2).

Four step approach to poem

The procedure can be split into four consecutive steps: the mucosal incision, formation of the submucosal tunnel, myotomy and closure of the mucosal incision[32].

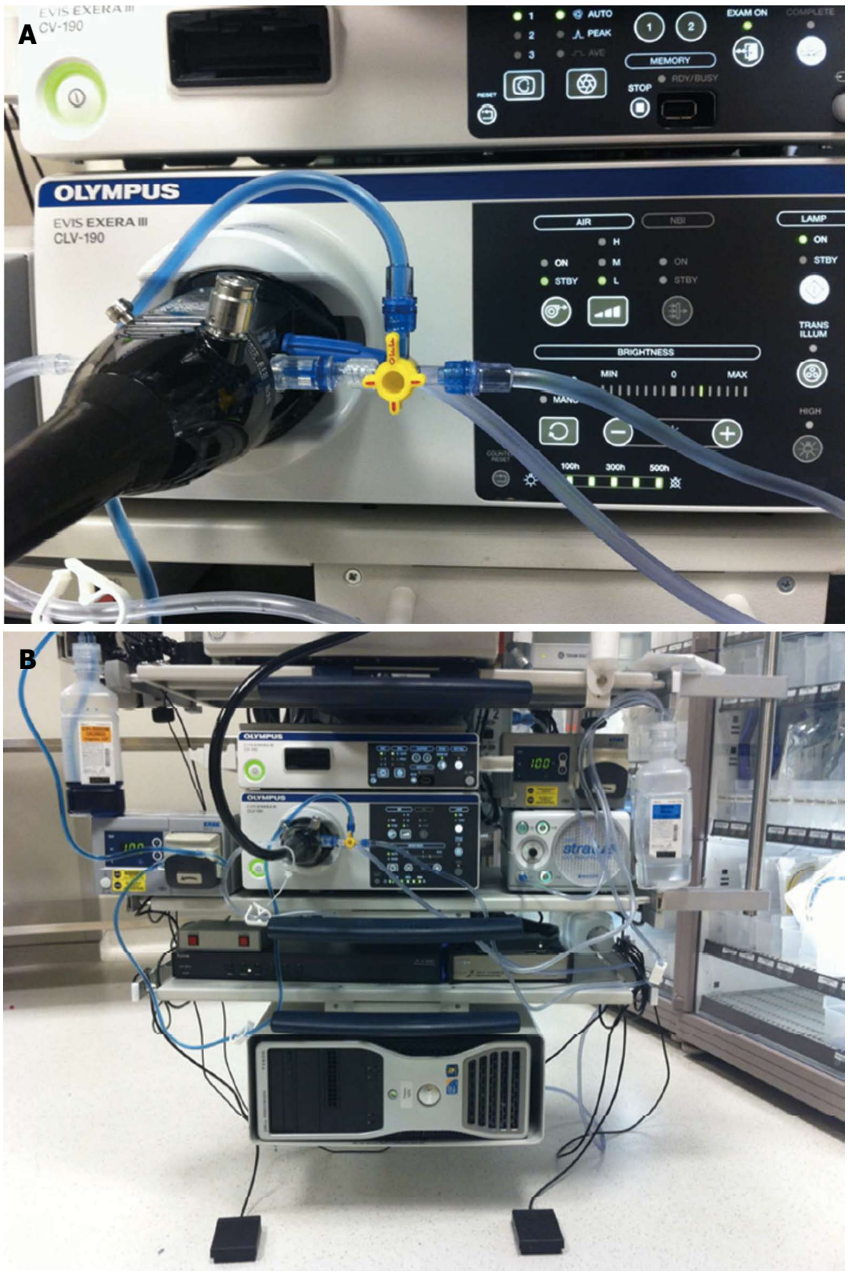

Figure 2 Endoscope setup for jet injection of dyed saline. A: One bottle of saline and a second bottle of saline mixed with indigo carmine are directly connected to the water jet channel *via* a stopcock; B: Separate foot pedals control injection of either pure saline for optimizing visual field or dyed saline for submucosal tunneling.

Step 1: Mucosal incision: The level of the esophagogastric junction (EGJ) is identified and determines the level submucosal tunneling is commenced. In most centers, an anterior (2 o'clock position) is used for the submucosal tunnel and myotomy. However, in some centers a posterior orientation (5 o'clock position) is favored. An anterior myotomy may decrease the damage to the angle of His, a barrier to post-operative GERD. If there is doubt as to the identification of the anterior and posterior walls, water can be injected into the esophageal lumen and will pool on the posterior aspect when the patient is positioned supine.

A submucosal cushion is then made 3 cm proximal to the proposed commencement of myotomy using 0.01% epinephrine, 0.25% indigo carmine and 0.9% saline solution. A 1.5 cm vertical mucosal incision is made using a hybridKnife (HK) (ERBE, Tubingen, Germany) or triangular tip (TT) knife (KD 640 L, Olympus, Center Valley, PA, United States) using a dry cut mode at 50 W on effect 3 (ERBE, Tubingen, Germany) (Figure 3). The gastroscope is then inserted into the submucosal space after dissection of the submucosal fibers at the level of the mucosal incision.

The length of the submucosal tunnel (and hence myotomy) must be determined prior to commencement of the mucosal incision. In patients with achalasia subtype Ⅰ and Ⅱ, a 6-10 cm esophageal myotomy is performed. In patients with spastic esophageal disorders, the length of myotomy is determined based on the proximal extent of the hypertensive contractions on HREM and/or the level of visible spastic contractions seen endoscopically.

Step 2: Creation of submucosal tunnel: The submucosal tunnel is created distally using a technique similar to endoscopic submucosal dissection. Using

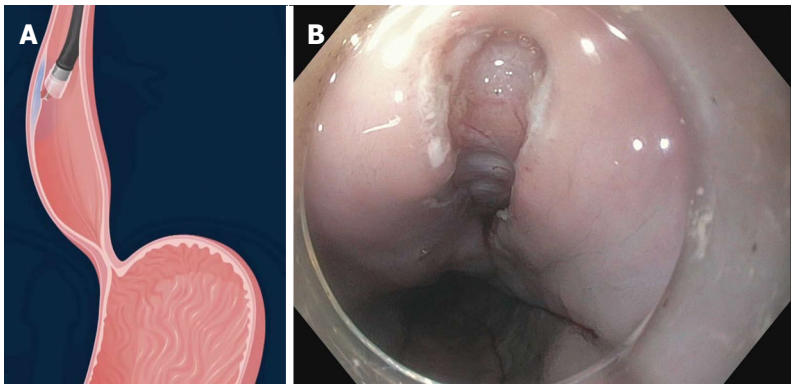

Figure 3 Longitudinal mucosal incision 1.5 to 2 cm on the anterior esophageal wall.

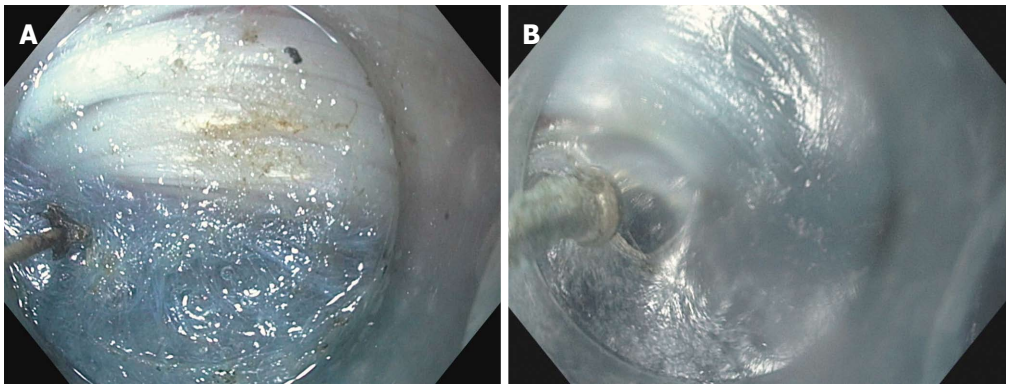

Figure 4 Creation of the submucosal tunnel. A: Dissection of the submucosal fibers using spray coagulation with the triangular tip knife (KD 640L, Olympus, Center Valley, PA, United States); B: Dissection of the submucosal fibers using the hybridKnife (ERBE, Tubingen, Germany) which allows for both submucosal dissection and fluid injection into the submucosal space.

a TT knife or HK, the submucosa is dissected with a no-touch technique using spray coagulation mode at 50 W on effect 2 (ERBE, Tubingen, Germany) (Figure 4). The dissection plane is located nearly on the surface of the muscularis propria. Recurrent jet injection of indigo carmine mixed with saline is done to increase the delineation between the submucosal fibers and muscularis propria whenever the planes become ambiguous (Figure 5). Care must be taken to avoid injury to the mucosal layer during creation of the submucosal tunnel as the mucosal layer is the only barrier between the esophageal lumen and mediastinum after myotomy. Large vessels in the submucosa are coagulated using the Coagrasper (Olympus, Center Valley, PA, United States) in soft coagulation mode at 80 W on effect 5 (ERBE, Tubingen, Germany).

An alternative technique for centers that do not have a water jet for injection is to use the HK (ERBE, Tubingen, Germany). This device obviates the need for multiple accessory exchanges between needle injector and knife as needless submucosal injection using a high-pressure water jet and electrosurgical dissection can both be performed. A randomized controlled trial demonstrated that the HK resulted in statistically significant quicker operating times as compared to using the TT knife. This was primarily the result of a statistically significant lower average number of accessory exchanges during the procedure (2 *vs* 19.2, $P < 0.0001$)[33]. However, the above-described water jet injection method obviates the need for these frequent exchanges as well.

Another technique uses a balloon, such as a standard biliary stone extraction balloon, to dissect the submucosal fibers without the use of electrosurgery. Operators who use this technique claim that it allows for a more rapid creation of the tunnel without substantial bleeding as the vessels are momentarily displaced rather than ruptured using this technique. Proponents of this technique also state that this method is particularly useful at the LES when the space between the muscle and mucosal layer is limited.

The submucosal tunnel is extended 3cm beyond the EGJ (Figure 6). This is essential as an adequate gastric myotomy is considered critical to eradicate the sling and clasp fibers which are considered essential to maintain LES continence[34,35]. The techniques to assess the location of the EGJ include: insertion depth, narrowing of the submucosal space and resistance of passage of the endoscope through the EGJ followed by prompt expansion of the space at the gastric cardia, change in vasculature, visualization of aberrant longitudinal muscle fibers at the EGJ and injection of epinephrine or indocyanine green (ICG)[36,37]. Many of these methods are subjective. Our preference is to use one of two objective techniques: double endoscope

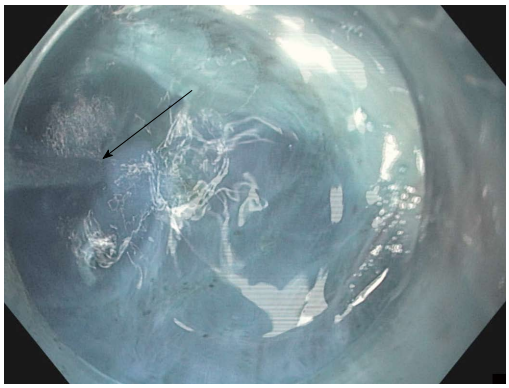

Figure 5 Repeated jet injection (arrow) of dyed saline is performed during submucosal tunneling to improve the demarcation between the submucosal layer and muscularis propria whenever the submucosal dissection plane becomes unclear.

transillumination technique or intraprocedural fluoroscopy[38,39].

Double endoscope transillumination for extent confirmation technique

After the submucosal tunnel is created, the gastroscope is withdrawn and an ultraslim, 5.9-mm endoscope is inserted through the mouth into the stomach and then retroflexed. The cap fitted gastroscope is reinserted alongside the ultraslim gastroscope into the submucosal tunnel. The brightness of the light of the ultraslim gastroscope is reduced while transillumination is switched on for the standard gastroscope within the submucosal tunnel. The transilluminated light is seen by the ultraslim gastroscope and hence allows exact appreciation of the extent of the tunnel into the proximal stomach (Figure 7).

Intraprocedural fluoroscopy

After the formation of a submucosal tunnel, a radiopaque marker (endoscopic clip placed at EGJ on the opposite side to the submucosal tunnel or fluoroscopically guided placement of a 19-gauge needle on the skin) is used to mark the EGJ. The endoscope is then re-inserted to the terminal aspect of the submucosal tunnel. Using a C-arm, a fluoroscopic image is obtained in the anterior-posterior axis. The distance between the jaws of the endoscopic clip or needle, and the endoscope tip is calculated using the known diameter of the endoscope as a scale (Figure 8). This allows for an objective measurement of the length of the submucosal tunnel below the EGJ.

Step 3: Myotomy: Selective myotomy of the inner circular muscle is performed 1cm below the end of the mucosal incision. The HK or TT knife is used to grasp and lift circular muscle fibers followed by cutting with spray coagulation current at 50 W on effect 2 (ERBE, Tubingen, Germany). Selective myotomy of the inner circular muscle, preserving the outer longitudinal esophageal muscular layer is usually preferred during POEM (Figure 9). The selective circular muscle myotomy is intended to prevent the endoscope entering the pleural space and decrease morbidity. However, it can be difficult to accomplish because the longitudinal muscle fibers of the esophagus are very thin, and therefore inadvertent splitting of these fibers often occur during POEM. Either trauma from maneuvering the endoscope in the tunnel, electrocautery damage, or CO_2 insufflation alone can result in splitting of the longitudinal muscle layer and adventitia and hence direct exposure to the mediastinum or peritoneum[32] (Figure 10). Moreover, the ability to differentiate between circular and longitudinal muscular layers becomes particularly challenging at the level of the EGJ and stomach. Therefore, some experts are of the opinion that a full-thickness myotomy at this level is mandated for adequate and long-term reduction of pressure at the LES.

Li *et al*[40] compared the outcomes between 131 patients that underwent selective inner circular muscle myotomy and 103 who underwent full-thickness myotomy. The average procedure times were briefer in the full-thickness myotomy cohort (42 min *vs* 49 min, $P = 0.02$). No difference was found in the frequency of adverse events between the cohorts. During follow-up, clinical success (Eckardt score $\leqslant 3$) persisted for 115/121 (95.0%) of patients in selective inner circular myotomy cohort and 95/99 (96.0%) of patients in full-thickness myotomy cohort ($P = 0.75$). There were no significant differences in absolute (pre and post) or mean reduction in LES pressures between groups (both $P > 0.05$). There was no statistically significant difference in the rate of clinical reflux events (21.2% *vs* 16.5%, $P = 0.38$). The authors concluded that there was no meaningful difference between the two methods in terms of symptom relief and manometric outcomes.

It is believed that selective inner circular myotomy adds an element of extra safety to POEM and hence may lead to easier dissemination, especially when performed by endoscopists with lesser experience. Although the myotomy is not the most challenging part of the procedure, it must be performed carefully such that there is adequate separation of muscle fibers and inadvertent damage to vessels is avoided. Once the myotomy is completed, smooth passage of the endoscope through the area of the LES into the stomach should provide confirmation of complete myotomy.

Step 4: Closure of the mucosal incision: Prior to closure of the mucosal incision, a careful inspection of the submucosal tunnel is performed and any oozing is controlled. Then the esophageal mucosa is interrogated and any laceration or mucosotomy is addressed. Lower esophageal sphincter relaxation is evaluated by retroflexed visualization of the gastric cardia. Repeat EndoFLIP measurements can now be performed to determine post myotomy distensibility.

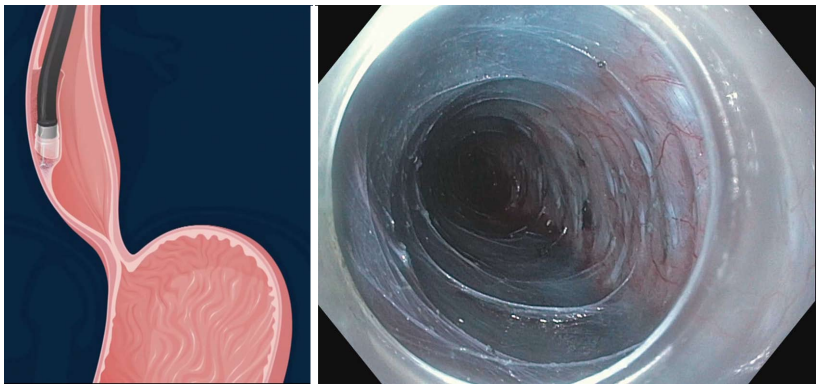

Figure 6 Submucosal tunnel after the submucosal fibers have been dissected away. The myotomy can now be commenced.

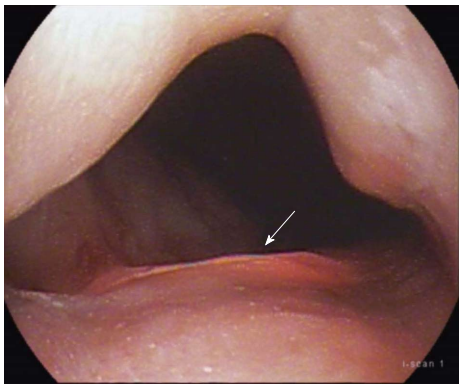

Figure 7 Transillumination can be seen 2 cm below the gastroesophageal junction indicating that the submucosal tunnel can be extended a further 1 cm prior to commencing the myotomy.

The mucosal entry can be closed with endoscopic clips[37,41] or the use of a flexible endoscopic suturing device (OverStitch; Apollo Endosurgery, Austin, TX, United States)[42] (Figure 11). When endoscopic clips are used, the initial clip is deployed at the most distal part of the mucosal incision to facilitate approximation of the incisional borders. Placement of subsequent clips is performed in a proximal direction until complete closure. Salvage closure techniques have been reported when standard methods fail. These include over-the-scope clip and a covered esophageal stent[43-45].

POSTOPERATIVE CARE

Patients are admitted overnight for observation and kept nil per oral. Intravenous prophylactic antiemetics and broad-spectrum antibiotics are prescribed. A contrast esophagram is obtained the following morning and a soft diet is commenced after exclusion of an esophageal leak. Routine thoracic CT scan is not warranted because of the high rate of minor and clinically irrelevant findings[46]. Patients are routinely prescribed broad-spectrum antibiotics for 5 to 7 d. Patients remain on soft diet for 2 wk after which a normal diet can be commenced. In order to avoid any potential damage to the esophageal mucosa, we prescribe twice daily proton pump inhibitor for 2 wk. Follow-up clinic visit to assess for delayed complications and assessment of clinical response (Eckardt score) occur at 3 mo post procedure. Additionally, repeat HREM and esophageal acid exposure testing are ordered routinely.

EFFICACY OF POEM

The published literature to date illustrates that POEM is highly effective in the short-term management of achalasia. In the almost all series, clinical success was defined as postprocedure Eckardt score $\leqslant$ 3. It should be noted that a patient could suffer dysphagia at each meal despite an Eckardt score of 3. Other metrics used are decrease in LES pressure, improvement in esophageal emptying and quality of life. It must be noted that most data are derived from studies that are uncontrolled and open label. Additionally, the follow-up interval is often short and frequently not standardized. Only one prospective multicenter study exists which reports outcomes to 12 mo[41]. The recent white paper summarized data from 14 studies with outcomes based on 804 patients[6]. Clinical success was reported in 82% to 100% of patients with significant reductions in Eckardt score and LES pressure. Several studies have described efficacy based on timed barium esophagram (an objective measurement of esophageal emptying)[42,47,48]. Recent reports have also documented a significant improvement in several measures of quality of life after POEM[42,49].

EndoFLIP has been increasingly reported as a method of assessing the adequacy of myotomy during the POEM procedure. This method involves using a balloon catheter outfitted with a series of electrodes that is placed across the EGJ and allows measurement of luminal diameter, cross-sectional area and balloon pressure *via* impedence planimetry (Figure 12). An index of EGJ distensibility can be determined and this has been shown to correlate better with postoperative symptoms than manometric pressure measurements[50]. Patients within a "sweet spot" of postoperative EGJ distensibility (4.5-8.5 mm^2/mmHg) are almost twice as likely to have optimal symptom outcomes as those outside this window[28].

The literature to date supports the notion that POEM is feasible, safe and efficacious in patients that have undergone prior botulinum toxin injections or pneumatic balloon dilation and is comparable to

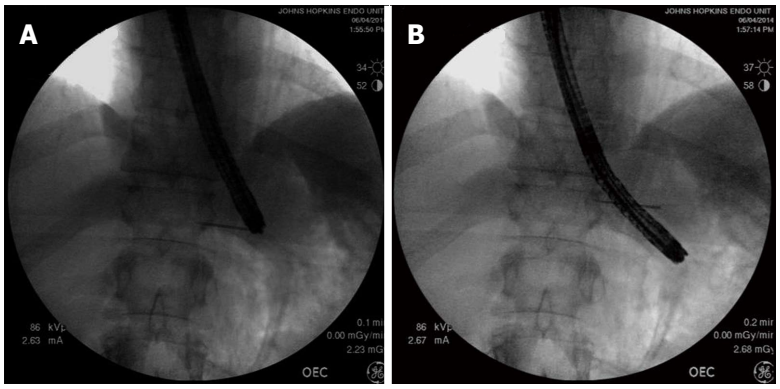

Figure 8 Using fluoroscopy to assess the adequacy of gastric myotomy during peroral endoscopic myotomy. A: The needle is fluoroscopically lined up with the tip of the endoscope and leveled with the EGJ; B: The endoscope has a diameter of 1 cm, and therefore, the endoscope tip is measured to be 3 cm below the needle marking the EGJ. EGJ: Esophagogastric junction.

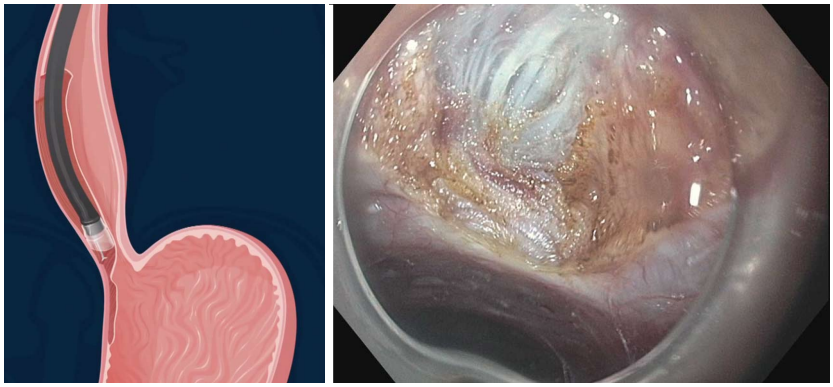

Figure 9 Selective myotomy of the circular muscle fibers. The longitudinal muscle fibers have been preserved.

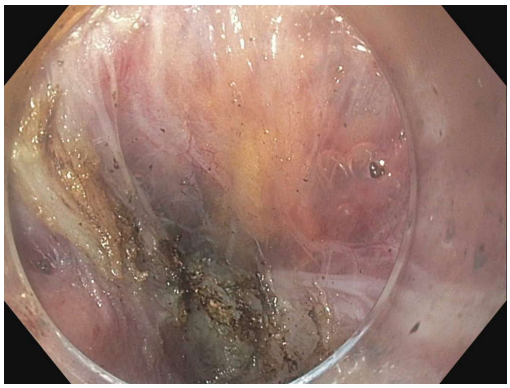

Figure 10 Splitting of the longitudinal muscle fibers despite attempted selective cardiomyotomy. Peritoneal fat can be seen through the translucent adventitia.

patients who are treatment naive[51-53]. In the IPOEMS survey, 40% of patients had undergone POEM after prior endoscopic therapy[36]. The consensus from POEM operators is that botulinum toxin injections injections induce submucosal fibrosis and results in a more challenging dissection (which can be overcome by operator experience) with undiminished efficacy[36]. POEM after prior pneumatic balloon dilation did not render the procedure more technically challenging or increase the rate of complications and the efficacy was undiminished[36].

Relapse or persistence of symptoms after a Heller myotomy happens in 10% to 20% of patients at 2-year follow-up[54]. There are 3 studies that specifically examined the utility of POEM in patients that have undergone a prior Heller myotomy. A prospective study of 12 patients by Zhou *et al*[8] with relapse or persistence of symptoms after Heller myotomy underwent technically successful POEM after a mean of 12 years from the time of the primary Heller myotomy. No major adverse events related to POEM were encountered. Treatment success was achieved in 11/12 (91.7%) patients (mean Eckardt score pretreatment *vs* posttreatment: 9.2 *vs* 1.3; $P < 0.001$) at a mean follow-up of 10.4 mo. Onimaru *et al*[7] reported their series of 11 patients who had relapse or persistent achalasia and had undergone Heller myotomy as initial therapy. Ten patients underwent salvage POEM which was performed successfully without adverse events. One patient responded to pneumatic dilation. At 3 mo follow-up, a significant reduction in Eckardt symptom scores (6.5 *vs* 1.1, $P < 0.001$) and LES resting pressures (22.1 *vs* 10.9 mmHg, $P < 0.01$) were noted. Finally, Vigneswaran *et al*[9] reported 5 patients who had symptom recurrence after Heller myotomy and subsequently underwent POEM. The average procedure time was 149 min. In all patients, there was a significant reduction in average postprocedure Eckardt score (6.8 *vs* 0.6, $P < 0.001$). Therefore, its appears that POEM may be a worthwhile treatment option for patients with relapse or persistent symptoms after Heller myotomy.

While POEM is usually performed for the management of achalasia, preliminary data suggest it is a

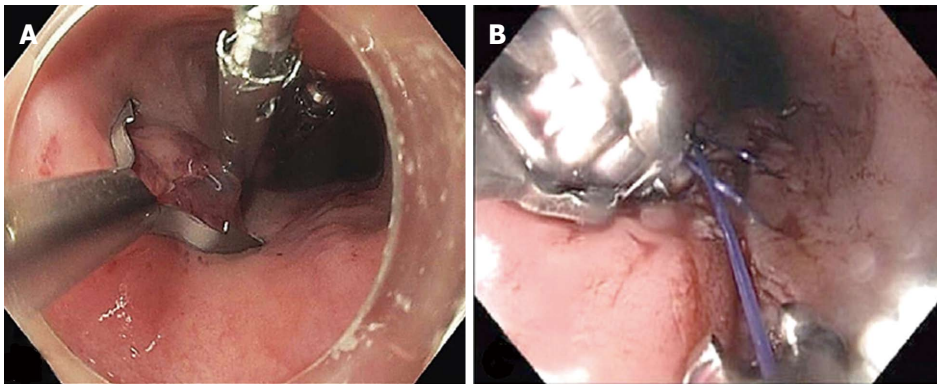

Figure 11 Closure of the mucosal entry after completion of the myotomy. A: A posterior mucosal incision was closed with three endoscopic clips; B: A posterior mucosal incision was closed with a running suture pattern using transoral flexible endoscopic suturing (OverStitch; Apollo Endosurgery, Austin, TX, United States).

viable option for the management of spastic esophageal disorders since it permits myotomy of the proximal esophagus (where hypertensive contractions occur). It is has been suggested that in those patients, a greater improvement in dysphagia is noted compared to chest pain in patients undergoing POEM[21,55]. Based on expert opinion, it is recommended that a longer esophageal myotomy be performed for spastic esophageal disorders and the level of commencement should be based on the findings of HREM and endoscopy[15].

ADVERSE EVENTS

POEM is a safe endoscopic technique associated with a low rate of perioperative and postoperative adverse events when performed by experienced operators.

Intraprocedural adverse events

Subcutaneous emphysema and pneumoperitoneum are often encountered during the procedure and are no longer considered adverse events. Pneumothorax is infrequently encountered and does not usually require treatment as CO_2 is rapidly absorbed. If there is respiratory compromise then a chest tube should be inserted and the procedure continued. In cases of tension pneumoperitoneum a Veress needle can be inserted through the abdominal wall. Excessive hypercarbia resulting from extended CO_2 administration may require the endoscopist to momentarily remove the endoscope from the patient for 5 to 10 min.

The most feared complication is an inadvertent mucosotomy which results in a perforation. As the submucosa and muscle have been dissected, even a small mucosotomy is potentially dangerous. Most mucostomies happen at the level of the LES and cardia as this is the site of narrowing in the submucosal tunnel. If a mucosotomy is identified it should be closed with endoscopic clips. Larger mucosotomies have been closed with a flexible endoscopic suturing device (OverStitch; Apollo Endosurgery, Austin, TX, United States)[56,57]. Other salvage techniques used have included fibrin glue[58] and over-the-scope clips[43]. If the mucosotomy is detected during submucosal tunneling then it should be addressed immediately as delayed closure may result in significant increase is the size of the mucostomy (Figure 13).

Bleeding during submucosal tunneling is not uncommon although the need for specialized interventions is rare (Figure 14). Careful step-wise dissection will allow vessels to be visualized and prophylactically treated using coagulation with the electrocautery knife itself (forced coagulation 25 W effect 2) or hemostatic forceps (Coagrasper; Olympus, Center Valley, PA, United States) for treatment of bigger vessels that are usually encountered in the gastric cardia. If bleeding appears to originate from a vessel along the mucosal surface, hemostasis can be achieved with gentle pressure using the tip of the endoscope for several minutes.

Late advers events

Delayed bleeding has been reported in 0.7% of patients in a large series of 428 patients[59]. Hematemesis with or without chest pain requires an emergent endoscopy and removal of the clips or sutures from the mucosal entry so that the submucosal tunnel and muscle can be assessed. In the aforementioned series, the bleeding point was identified in 2/3 cases and in the third patient there was no focus found and the patient was effectively treated with a Sengstaken-Blackmore tube. It is important to note that hematoma in the tunnel can result in pressure necrosis of the mucosal flap with potentially disastrous consequences. The safety of the Sengstaken-Blackmore tube in this setting is also debated as it can potentially result in pressure necrosis of the already devascularized mucosa.

The most common adverse event with POEM is gastroesophageal reflux (GER). When objective data are reviewed, such as erosive esophagitis on EGD and/or an abnormal acid exposure on a pH study, the prevalence of GER appears to be between 20% to 46%[6]. This is similar to the rates seen with Heller myotomy with partial fundoplication[60,61]. There is no consensus on how to manage patients with objective GER. One center reported the use of transoral endoscopic fundoplication in an patient with GER symptoms refractory to proton pump inhibitor[62].

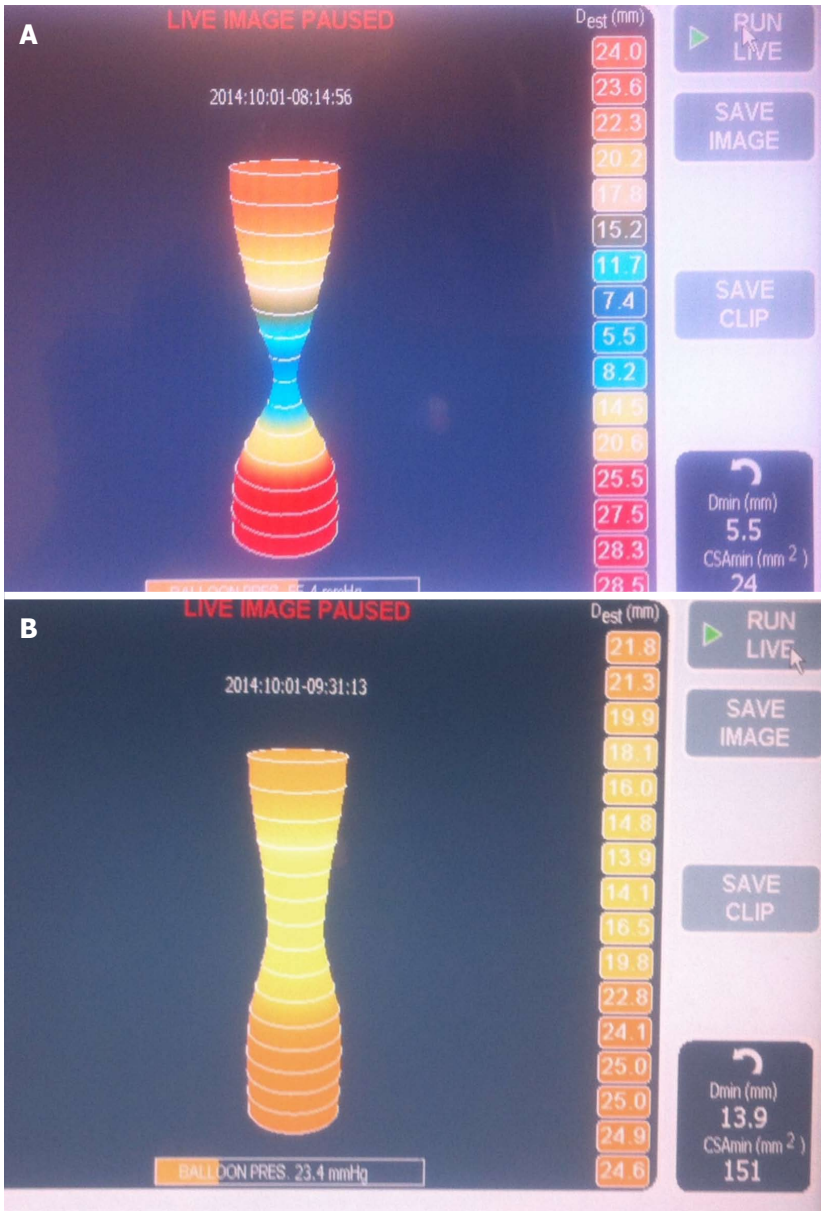

Figure 12 Endoluminal functional lumen-imaging probe (EndoFLIP; Crospon, Galway, Ireland). A: EndoFLIP measurements performed prior to commencement of POEM. A tight hourglass shape at the EGJ can be seen; B: On completion of the myotomy the waist is widened with a corresponding increase in the distensibility index. POEM: Peroral endoscopic myotomy; EGJ: Esophagogastric junction.

POEM IN THE MANAGEMENT ALGORITHM FOR ACHALASIA

For decades, pneumatic balloon dilation and Heller myotomy were the primary methods for the palliation of symptoms of achalasia. POEM appears to have potential advantages over these techniques. POEM appears to be associated with decreased need for retreatment and a lower rate of perforation than pneumatic balloon dilation although no comparative studies exist. There are several uncontrolled studies comparing POEM to Heller myotomy which reveal that they have similar short term efficacy and safety[47,63-65]. Aside from POEM, insertion of self-expandable metallic stents across the EGJ have been studied as an alternative management strategy. Although early reports show promise in terms of symptom palliation, stent migration and intolerance appear to be an issue[66-68].

At this stage, there are no gastrointestinal or surgical society guidelines that have incorporated POEM into their treatment algorithm for achalasia. The American College of Gastroenterology clinical guideline on the management of achalasia cautioned against the use of POEM until the results from further clinical studies are available[69]. Similarly, Vela *et al*[70] in his expert review, comments that POEM should only be performed in the context of clinical trials and that more data is needed before it can be incorporated into the treatment algorithm for achalasia patients. As POEM disseminates worldwide, it is inevitable that it will establish its place in management algorithms of the future.

GASTRIC PERORAL ENDOSCOPIC MYOTOMY (ENDOSCOPIC PYLOROMYOTOMY)

We have published the first human endoscopic pyloromyotomy for medication refractory gastropa-

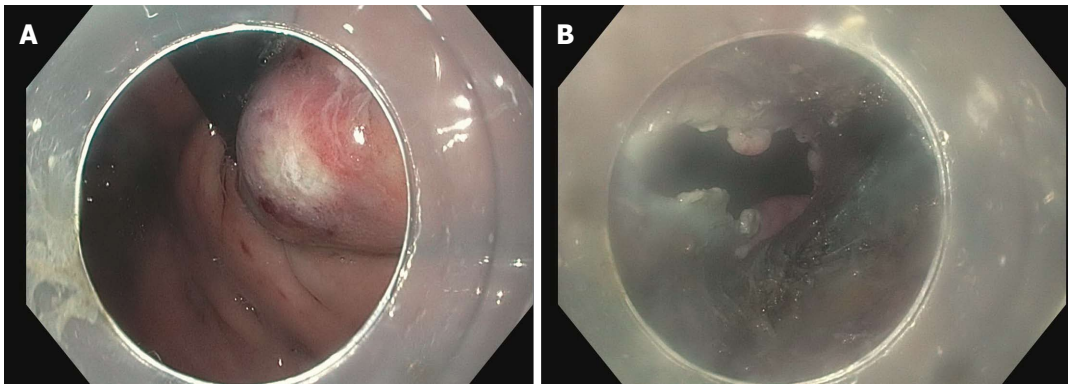

Figure 13 Inadvertent mucosotomy at the gastric cardia. A: Coagulation injury seen on the gastric mucosa at the level of the cardia during the process of submucosal tunneling; B: The procedure continued, however, on completion of the myotomy a frank 12 mm mucosotomy was now present.

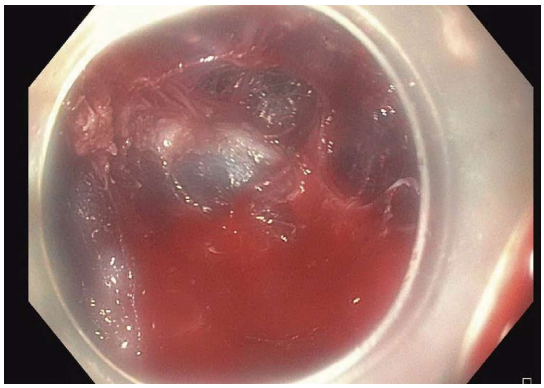

Figure 14 Bleeding encountered during gastric myotomy. This was treated with the use of coagulation graspers.

resis[22]. One year later Shlomovitz *et al*[23] reported gastric peroral endoscopic myotomy in 7 patients with gastroparesis. Six of the 7 patients experienced significant improvement in symptoms with normalization of gastric emptying seen in 4 out of 5 patients. This procedure appears viable and can be executed using similar techniques to that of esophageal POEM. It should be noted that only a subset of patients with refractory gastroparesis are likely to benefit from this approach.

COMMENCING A POEM PROGRAM

It is general consensus that institutions commencing a POEM program do it with institutional review board approval[36]. POEM is a technique that requires a unique set of skills combining good endoscopic manipulation and recognition of anatomical structures. In particular, knowledge of the EGJ anatomy and pathophysiology of achalasia is necessary. Of significant importance, is the maintenance of a consistent team throughout the learning curve. This includes nursing as well as anesthetic staff. Additionally, knowledge of the use of accessories necessary to deal with complications is mandatory. Expert operators propose that an efficient training method involves careful observation of POEM by an expert, experience using live animal models and then performing the procedure in humans with a proctor present.

The learning curve for POEM has not been clearly defined. Kurian *et al*[71] used the duration of the procedure per centimeter of myotomy and the incidence of inadvertent mucosotomies and calculated that the learning curve appeared to plateau at approximately 20 procedures. Teitelbaum *et al*[72] found that reduction in time for the mucosal entry and myotomy as well as reduction in the incidence of inadvertent mucosotomies occurred at a "learning rate" of 7 procedures. Expert operators comment that the creation of the submucosal tunnel, particularly at the LES, is likely the most difficult aspect of POEM.

FUTURE DIRECTIONS

Given that achalasia is a chronic disease, long-term outcomes for POEM are essential. Furthermore, POEM needs to be compared to Heller myotomy and pneumatic balloon dilation in multicenter prospective randomized controlled trials.

Progress is being made to simplify POEM in order to increase its efficiency and safety. We published our experience of a novel technique of "auto-tunneling" during POEM in 5 pigs[73]. After creation of the submucosal bleb at the site of the mucosal entry, a proprietary submucosal lifting gel (Cook Medical, Winston-Salem, NC, United States) was injected and resulted in a complete submucosal tunnel to the level of the EGJ. This and other innovative modifications may alleviate current technical challenges.

The most contentious issue surrounding POEM remains the frequency and clinical importance of gastroesophageal reflux. Rigorous evaluations of patients post POEM using pH measurements are required in patients from the East and West. Individualizing the length of the gastric myotomy based on the results of EndoFLIP may reduce the incidence of this problem. Additionally, performing a transoral partial fundoplication in all patients or those that have abnormal acid exposure on post procedure testing may improve outcomes.

Further investigation needs to be performed to

study other technical considerations for POEM. Is an anterior or posterior myotomy the preferred approach? Is it cost-effective and safe for POEM to be performed in the endoscopy unit? Is same day discharge suitable if an immediate contrast esophagram demonstrates no extravasation? These, as well as other questions, will need to be answered by high quality controlled trials.

CONCLUSION

POEM likely represents the first sentinel application in NOTES and has the potential to supplant the current treatment methods for achalasia. It fulfils an important clinical need as both pneumatic balloon dilation and Heller myotomy have their short comings. POEM is an elegant minimally invasive treatment with a short-term clinical response of 82% to 100% and with a low risk of adverse events. The results of prospective multicenter randomized controlled trials are awaited.

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MINIREVIEWS

Current status of peroral cholangioscopy in biliary tract diseases

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Abstract

Peroral cholangioscopy (POC) is an important tool for the management of a selected group of biliary diseases. Because of its direct visualization, POC allows targeted diagnostic and therapeutic procedures. POC can be performed using a dedicated cholangioscope that is advanced through the accessory channel of a duodenoscope or *via* the insertion of a small-diameter endoscope directly into the bile duct. POC was first described in the 1970s, but the use of earlier generation devices was substantially limited by the cumbersome equipment setup and high repair costs. For nearly ten years, several technical improvements, including the single-operator system, high-quality images, the development of dedicated accessories and the increased size of the working channel, have led to increased diagnostic accuracy, thus assisting in the differentiation of benign and malignant intraductal lesions, targeting biopsies and the precise delineation of intraductal tumor spread before surgery. Furthermore, lithotripsy of difficult bile duct stones, ablative therapies for biliary malignancies and direct biliary drainage can be performed under POC control. Recent developments of new types of conventional POCs allow feasible, safe and effective procedures at reasonable costs. In the current review, we provide an updated overview of POC, focusing our attention on the main current clinical applications and on areas for future research.

Key words: Peroral cholangioscopy; Biliary tract disease; Direct visualization; Indeterminate biliary strictures; Bile duct stones

Core tip: Peroral cholangioscopy is a rapidly developing endoscopic technique that provides the possibility to directly explore the bile duct, thereby increasing diagnostic accuracy in selected cases. Less expensive and safer than in the past, the field of applications of peroral cholangioscopy, through the development of new dedicated accessories, has been recently expanded and includes several therapeutic options such as the lithotripsy of difficult bile duct stones, ablative therapies for biliary malignancies and direct biliary drainage.

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INTRODUCTION

Since the 1970s, the dream of all biliopancreatic endoscopists was the ability to directly explore the bilio-pancreatic tree. The first cholangioscopic mother-baby scope system appeared to realize this ambition; however, the technique was too rudimentary, cumbersome, labor intensive and time-consuming because the scopes were very fragile, and two highly skilled endoscopists were required to perform the procedure. Therefore, the effect on clinical practice was marginal and was strictly confined to the research field[1].

In 2005, the advent of new types of peroral cholangioscopes led to renewed interest in endoscopic visualization of the biliary tree. Several technical improvements were introduced, and the leading one was the single-operator system. Furthermore, the endoscopic image quality was progressively improved, and the size of the working channel increased. All these technical improvements have led to an increased diagnostic accuracy.

The aim of the current review is to provide an updated overview on peroral cholangioscopy, focusing our attention on the main current clinical applications and on areas for future research.

TECHNICAL ASPECTS

Currently, two different systems for the direct visualization of the biliary tree are available. The first one, the so-called indirect peroral cholangioscopy, is based on a catheter with an optical probe inside that is inserted within the duodenoscope. SpyGlass® (Boston Scientific, Natick, MA, United States) is the most frequently used and widely diffused probe; the second system is based on an ultraslim upper endoscope (direct peroral cholangioscopy).

Indirect peroral cholangioscopy

The SpyGlass® system is inserted through the instrument channel of the duodenoscope, and the previous placement of a guidewire into the biliary tree is generally recommended. The insertion of the cholangioscope into the bile duct is one of the most challenging aspects of the technique because it can damage the cholangioscope. Once inside, the SpyScope has two dials that allow for four-way tip deflection. The SpyScope has a 10 French outer diameter, is 230 cm in length, and houses four channels: a 1.2-mm instrument channel, two 0.6-mm independent air and irrigation channels, and the 0.9-mm channel used for the fiberoptic probe. This latter channel is a 6000 pixel,

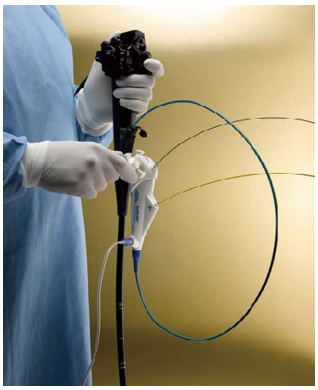

Figure 1 SpyGlass® (Boston Scientific, Natick, MA, United States).

reusable probe with a camera in its distal portion that conducts light and acquires and transmits images. The quality of the endoscopic images can be adjusted by moving the probe forward and backward throughout the procedure. The working channel allows the passage of biopsy forceps (SpyBite®) and dedicated accessories, such as the Holmium laser, for the intraductal fragmentation of non-removable stones (Figure 1).

Similar to the SpyGlass scope is the Polyscope® (Polyscope system; Polydiagnost, Pfaffenhofen, Germany), which consists of a detachable flexible endoscope system available in 8 Fr (185 cm length) with separate optical, working/irrigation (1.2 mm), illumination, and steering channels (Figure 2). There are few differences between the two systems, as summarized in Table 1, but potentially the most important one lies in the image quality because the optical fiber has 10000 pixels of definition; however, the angle of view (70°) is the same as in the SpyGlass scope.

Direct peroral cholangioscopy

Ultraslim endoscopes present larger outer diameters, generally 5-6 mm; therefore, they can be used only after a large endoscopic sphincterotomy and/or sphincteroplasty. The use of this system is definitely more challenging because of the significant difficulties that can be encountered in the initial insertion into the biliary tree as a result of the looping and in remaining anchored inside the duct. Therefore, a 0.025-0.035 inch diameter super-stiff guidewire previously placed within the intrahepatic duct is mandatory to introduce the scope into the acute angle of the biliary system from the second part of the duodenum. Once the duodenoscope is removed, the ultraslim endoscope is then advanced over the guidewire. Large loop development is common, particularly within the gastric fundus and the deep portion of the second part of the duodenal lumen. Hence, several accessories may be useful to successfully advance the ultraslim scope into the biliary tree. Recently, two techniques for an ultraslim endoscopic peroral cholangioscopy (POC) have been reported. The implementation of an intraductal 5 French balloon catheter that is inserted

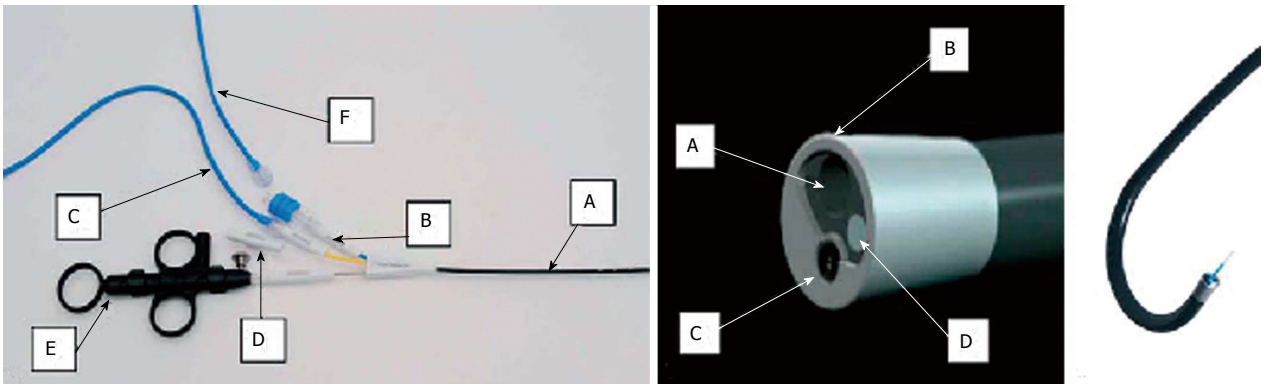

Figure 2 Polyscope system (Polydiagnost, Pfaffenhofen, Germany).

Table 1 Comparison of different equipment for indirect peroral cholangioscopy

Characteristics	Spyglass	Polyscope
Optics resolution	6000 Pixel	10000 Pixel
Working channel	1.2 mm	1.2 mm
Viewing angle	70°	70°
Outer diameter	10 Fr	8 Fr
Re-useable	Yes	Yes
Optical channel hermetically close	No	Yes (The optical fiber doesn't need to be sterilized; this prolongs its life cycle)
Steerability	4 way	1 way (With locking of the bending and rotating of the tip)
Compatibility with existing endoscopy tower	No (You have to buy a complete endoscopy tower system)	Yes (You can use, through adapters an existing endoscopy tower in the Hospital)

and fixed within a branch of the intrahepatic duct or proximally to a stricture has been proposed[2]. This technique facilitates the advancement of the ultraslim scope and the cannulation of the bile duct; however, it presents several drawbacks: the balloon must be withdrawn from the working channel of the scope for interventional procedures, and this maneuver can provide technical difficulties in maintaining the desired position; in addition, the balloon placement within the intraductal branches is not always easily reached. The implementation of the balloon doubles the success rate of direct peroral cholangioscopy from 45.5% with only the guide-wire in place to greater than 95% using a 5 F balloon catheter.

Notably, an anchoring balloon produced by Cook Medical (Winston-Salem, NC, United States) was removed from the market after a fatal complication because of an air embolus[3]. This development represents the most worrisome complication that can develop during a cholangioscopy; therefore, the use of CO_2 rather than room air is mandatory.

An overtube balloon-assisted cholangioscopy has also been proposed with successful results[4-9]. This device is generally adapted from the overtube of either a single or double-balloon enteroscope; however, these overtubes are too large in diameter for an ultraslim scope, making the manipulation cumbersome[4,10].

An overtube allows the right position to be obtained by securing the endoscope and preventing loop formation during advancement; it also provides an easier access to the papilla. Several techniques have been described to achieve easier cannulation of CBD, including the inflation of the overtube balloon in the distal gastric antrum rather than in the duodenal bulb, which may or may not make a J-turn maneuver right in front of the papilla[11].

CLINICAL APPLICATIONS

Twenty-five years ago, endoscopic retrograde cholangiopancreatography (ERCP) was the gold standard for the diagnosis of biliary diseases. Currently, that role has been almost completely replaced by other imaging modalities, including endoscopic ultrasound, magnetic resonance (MRI) and computed tomography (CT). However, the accuracy of these methodologies does not always allow for a definitive diagnosis. Therefore, the necessity of direct viewing and tissue sampling has always been claimed as a demanding goal in selected cases. Both direct and indirect cholangioscopy offer great advantages in terms of diagnostic and therapeutic options, as reported in the details in Table 2. Nevertheless, the main field of application of cholangioscopy is the work-up of indeterminate biliary strictures and, less frequently, the treatment of difficult bile duct stones.

Indeterminate biliary strictures

Direct visualization of biliary strictures is one of the most interesting applications of cholangioscopy, and it allows the physician to improve the diagnosis to plan the most suitable treatment. Indeterminate biliary strictures, in which a diagnosis has not been reached after standard procedures have been performed (*i.e.*, CT, RMN, or ERCP with brushing), is the initial and natural field of application of cholangioscopy.

Table 2 Diagnostic and therapeutic applications for cholangioscopy

Diagnostic applications		Therapeutic applications	
Common	Uncommon	Common	Uncommon
Indeterminate biliary strictures	Biliary cyst evaluation	Lithotripsy for choledocholithiasis	Biliary guidewire placement
Verification of bile duct stone clearance	Bile duct ischemia evaluation (post-liver-transplant)		Transpapillary gallbladder drainage
Staging of cholangiocarcinoma	Ductal involvement in ampullary adenoma		Foreign body removal (*e.g.*, stent)
	Hemobilia		

Currently, the visual criteria for malignancy are not fully standardized, and clinical experience interpreting cholangioscopic visual findings is still limited[12].

Criteria highly suggestive for malignancy include dilated and tortuous "tumor vessels" (also known as "capillary signs"), intraductal nodular or papillary masses, and oozing and irregular vascular patterns with an irregular surface. A benign condition should be considered when a smooth or fine granular surface structure without neovascularization or intraductal mass is observed[13,14]. The diagnostic accuracy of the "tumor vessel" sign for malignancy has been evaluated in 63 patients with indeterminate strictures, reporting a sensitivity of 61% and a specificity of 100% with excellent interobserver agreement (100%)[15].

A definitive diagnosis requires histological assessment. Several prospective trials have shown enthusiastic diagnostic accuracy results achieved with cholangioscopic-direct tissue sampling. Draganov *et al*[16] compared three sampling techniques during the ERCP: standard cytology brushing *vs* standard forceps biopsies *vs* SpyBite miniforceps biopsies. The authors enrolled 26 patients with biliary strictures, and the sample quality was adequate in 25 of 26 of the cytology brushings (96%), in 26 of 26 of the standard forceps biopsies (100%) and in 25 of 26 of the SpyBite miniforceps biopsies (96%). Three high-quality prospective trials showed a diagnostic accuracy of SpyBite forceps biopsy for indeterminate biliary lesions ranging from 72% to 85%, with a sensitivity of 49% to 82%, a specificity of 82% to 100%, a positive predictive value of 100% and a negative predictive value of 69% to 100% (Table 3)[12,16,17].

Although the high values of both the positive predictive value and specificity did not differ from those observed with traditional sampling techniques (*i.e.*, brushing and standard forceps biopsies), the interesting finding was the high sensitivity and negative predictive value, likely because of the possibility of directly targeting the altered mucosa. Although the SpyBite miniforceps biopsy showed expected disappointing

Table 3 Results of cholangioscopic-guided biopsies in indeterminate lesions

Ref.	Sensitivity	Specificity	Negative predictive value	Accuracy
Ramchandani *et al*[17]	82%	82%	100%	82%
Chen *et al*[18]	49%	98%	72%	75%
Draganov *et al*[16]	76.5%	100%	69.2%	84.6%

results for extrinsic lesions, with a sensitivity of only 8%, the sensitivity of the SpyGlass visual impression alone was less severely compromised (62%)[12].

Concerning extrinsic compression, the specificity is unavoidably reduced when direct visualization is solely used because it can be secondary to benign conditions, and in the case of several benign intraductal diseases, such as primary sclerosing cholangitis (PSC), it can present irregular biliary mucosa without harboring malignancy[18].

Nevertheless, it should be noted that in a prospective trial enrolling 53 patients with PSC and dominant stenosis, cholangioscopy, which was performed using a 9 Fr cholangioscope, was found to be significantly superior to ERCP for detecting malignancy in terms of its sensitivity (92% *vs* 66%), specificity (93% *vs* 51%), PPV (79% *vs* 29%) and NPV (97% *vs* 84%), respectively[19]. In patients with PSC, the main limitation is that the small diameter of their ducts frequently does not allow endoscope passage[19,20].

Image-enhanced cholangioscopy techniques have been proposed to improve diagnostic accuracy, particularly through new techniques that are currently being investigated, including chromocholangioscopy and narrow band imaging. Only limited experiences with chromocholangioscopy have been reported[21,22]. Hoffman *et al*[22] prospectively enrolled 55 patients who underwent chromoendoscopic cholangioscopy for biliary strictures or filling defects as a result of various etiologies (orthotopic liver transplantation, PSC, idiopathic). After the initial inspection of the bile duct, 15 mL of methylene blue (0.1%) was administered *via* the working channel of a Pentax "baby" cholangioscope, and the lesions were judged according to the macroscopic type and staining features. The authors identified characteristic surface and staining patterns in chronic inflammation, dysplasia and ischemic-type biliary lesions; in particular, they found that homogeneous staining predicted the presence of normal mucosa, the absence of staining predicted circumscribed lesions, and the diffused staining of such lesions represented neoplastic changes or inflammation. Unfortunately, these findings have not been confirmed by other studies, and their clinical usefulness remains limited.

Narrow band imaging (NBI) was developed by the Olympus medical system and is based on narrowing the bandwidth of spectral transmittance, resulting in optical color separation. In particular, the shorter band

(415 nm) is thought to provide information regarding the capillary and pit patterns of the superficial mucosa, whereas the longer band (540 nm) provides more information regarding thicker capillaries in slightly deeper tissues. NBI is available on a few models of cholangioscopes. The literature concerning NBI application in cholangioscopy is limited to case reports and small case series[23-25].

Based on these preliminary experiences, it appears that the addition of NBI to the usual inspection with conventional white light cholangioscopies increases the ability to identify unknown strictures and might be helpful in differentiating benign from malignant strictures. Azeem *et al*[26] recently published the results of a prospective study conducted on a total of 30 patients with PSC using NBI and high-resolution peroral video cholangioscopy with NBI-directed biopsies of suspicious lesions. The goal was the early detection of cholangiocarcinoma and high-grade dysplasia and the identification of candidates for liver transplantation. Even if there was a 48% increase in suspicious lesions biopsied with NBI compared to white-light imaging, the NBI-directed biopsies did not improve the dysplasia detection rate. Additional experience is required to assess the exact role of NBI in detecting dysplasia.

Theoretically, systems with a higher image quality definition should allow a better identification of such alterations; however, comparative studies focusing on this issue have not been conducted. In 2012, we published a case-series describing the clinical usefulness of peroral cholangioscopy that implements a new type of cholangioscope, the Polyscope®, which enhances image quality as a result of the 10000 pixel definition[27]. Peroral cholangioscopy was performed in 12 patients with different indications: 4 patients with strictures that developed after orthotopic liver transplantation and were suspected of being ischemic biliary lesions; three patients in which the indication was indeterminate biliary strictures, three patients in which retained bile duct stones were suspected, and finally two cases in which a cholangioscopy was performed for evaluating the intraductal spread of adenomatous tissue after ampullectomy. All the peroral cholangioscopies were successful, no procedure-related morbidity was reported and a correct diagnosis was reached in all the patients.

Missed stones and difficult bile duct stone treatment

The diagnosis of biliary stones is easily obtained using imaging techniques that are routinely available. However, these techniques are often insufficient because small stones can be missed and larger stones can block a duct, thus preventing the passage of contrast and avoiding detection during an ERCP. Indeed, it has been shown that previous ERCPs failed to correctly identify choledocholithiasis in 8%-16% of cases that were referred for a SpyGlass choledochoscopy[17,28]. In a study conducted in patients with primary sclerosing cholangitis, stones were not detectable in a cholangiography in approximately 30% of cases (7 out of 23 patients)[20]. In a multicenter study, stones were missed in 29% of cases that underwent an ERCP for different indications[12].

The most interesting feature of cholangioscopy is the possibility of fragmenting difficult-to-remove stones for which conventional techniques have failed. The "difficult stones" may result from several factors related to size, shape, texture or position. In these cases, intraductal electro-hydraulic (EHL) or laser lithotripsy (LL) under direct vision may be performed. Probes that pass through the accessory channels of cholangioscopies for EHL or LL are commercially available. These probes must be positioned close to the stones to increase effectiveness and reduce possible complications, thereby avoiding potentially dangerous shock waves delivered to the bile duct wall. Several studies have reported high success rates in clearing the bile ducts of stones after a cholangioscopic EHL or LL, ranging from 80% to 100%; these results are frequently achieved in only one session[12,29]. In the case of intrahepatic stones, the thinner LL probe is generally preferred to the EHL probe, whereas the EHL is the most widely used technique, particularly with the SpyGlass system, because of the dedicated irrigation channel providing the flowing water that is required to perform the EHL.

Uncommon applications of cholangioscopy

Several infrequent applications of cholangioscopy have been described, such as the study of cystic lesions of the biliary tree[30], the evaluation of ductal involvement in ampullary neoplasms[27], the diagnosis and treatment of cases of hemobilia as a result of rare causes[31,32], the identification of biliary varices in patients suffering from portal hypertension[33] and the use of different ablative therapies for intraductal tumor lesions, such as Nd-YAG laser photo-ablation, argon plasma coagulation or brachiotherapy for mucin-producing bile duct tumors[24]. Anecdotal cases of the cholangioscopy-assisted removal of stents that migrated proximally, targeted placements of guide-wires, transpapillary gallbladder drainage in cholecystitis and foreign body extractions have also been reported.

One interesting field of application of cholangioscopy is the evaluation of the biliary tract lesions in liver transplant patients or the treatment of liver complications after surgical resection or anti-tumoral therapies (*i.e.*, transarterial chemoembolization, TACE). In a study of 20 liver transplant patients, direct cholangioscopy helped identify the biliary stricture etiologies, such as ischemia, scar tissue, intraductal clots and retained suture material, that were otherwise missed by the ERCP[34].

The usefulness of cholangioscopy in the management of complications after the anti-tumoral treatment of hepatocarcinoma has also been reported by our group. In 2011, we described a choledochoscope-assisted percutaneous fibrin glue sealing of a bile leak

complicating a TACE of a nodule of hepatocellular carcinoma after conventional ERCP treatments had failed[35]. An inverse rendezvous procedure was successfully performed, allowing the insertion of the percutaneous wire-guided choledochoscope (Polyscope system) into the biloma and the injection of fibrin glue around the distal opening of the bile leak, allowing the direct closure of a fistula.

SAFETY

Peroral cholangioscopy is generally considered a safe procedure; however, cases of cholangitis, pancreatitis, bleeding and infection have been reported[15,36,37]. In particular, the most commonly reported complication is cholangitis, which is reported in up to 14% of cases[36]; hence, prophylactic antibiotics are mandatory. Chen *et al*[12] conducted a large, prospective, international, multicenter study using the SpyGlass system and reported an overall complication rate of 7.5% (17/226); the most frequent adverse event was early onset cholangitis. All the episodes were resolved without sequelae. Aspiration pneumonia is theoretically possible because of the large amount of normal saline generally used. Air embolism is a rare but fatal complication associated with direct peroral cholangioscopy[3]; therefore, CO_2 insufflation is strongly recommended rather than room air.

FUTURE APPLICATIONS

Cholangiocarcinoma has one of the worst prognoses of virtually all tumors, with a 5-year survival rate lower than 5%[38]. The early diagnosis of biliary preneoplastic lesions could reasonably identify patients who are at an increased risk of developing cholangiocarcinoma. Biliary duct pathology may be evaluated by intraductal endoscopy, but feasibility studies are required to test the diagnostic accuracy of cholangioscopy in the identification of preneoplastic lesions of the extrahepatic biliary tree. The improvement of image quality and the development of dedicated accessories will further promote the diffusion of peroral cholangioscopy.

Endoscopic drainage can be performed by direct cholangioscopy using a 5-Fr catheter or stent inserted in the 2.0-mm working channel, particularly in patients who require "ultra" selective guidewire access, such as for the orifice of the cystic duct or major intrahepatic branches[39]. Additionally, proximally migrated biliary stents, which cannot be removed *via* conventional ERCP, can be removed using 5-F baskets or other accessories under direct visual cholangioscopic control[40].

Cholangioscopy have been reported for the evaluation of recurrent pancreatitis because of T-tube remnants in the cystic duct stump that were previously not detected *via* ERCP, CT or MRI[41]. Although there are no published data on the therapeutic applications of cholangioscopy for the resection of a biliary lesion, a biliary polypoid lesion could be removed using a 5-F snare.

CONCLUSION

The introduction of peroral cholangioscopy has constituted a turning point for biliary endoscopy. In particular, the single-operator systems are able to address a new, enthusiastic approach to biliary tract diseases, with great advantages in everyday practice. The greatest interest has centered on the evaluation of indeterminate stenosis, in which a diagnosis has not been reached after standard procedures; this is the main field of application of POC. The development of standardized criteria for the differential diagnosis between benign and malignant strictures is the main goal for the future. Prospective multicenter studies are required to define criteria with high intra- and inter-observer agreements and adequate diagnostic accuracy. Peroral cholangioscopy currently remains a challenging and expensive technique in expert hands. However, the renewed interest of researchers, clinicians and the medical device industries, and the substantial technological improvements in image quality and dedicated accessories, might contribute in the near future to the dissemination of this technique.

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Endoscopic management of bariatric complications: A review and update

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Abstract

With over a third of Americans being considered obese, bariatric procedures have now become the most performed operation be general surgeons in the United States. The most common operations are the Laparoscopic Roux-en-Y Gastric Bypass, the Laparoscopic Sleeve Gastrectomy, and the Laparoscopic Adjustable Gastric Band. With over 340000 bariatric procedures preformed worldwide in 2011, the absolute number of complications related to these operations is also increasing. Complications, although few, can be life threatening. One of the most dreaded acute complication is the anastomotic/staple line leak. If left undiagnosed or untreated they can lead to sepsis, multi organ failure, and death. Smaller or contained leaks can develop into fistulas. Although most patients with an acute anastomotic leak return to the operating room, there has been a trend to manage the stable patient with an endoscopic stent. They offer an advantage by creating a barrier between enteric content and the leak, and will allow the patients to resume enteral feeding much earlier. Fistulas are a complex and chronic complication with high morbidity and mortality. Postoperative bleeding although rare may also be treated locally with endoscopy. Stenosis is a more frequent late complication and is best-managed with endoscopic therapy. Stents may not heal every fistula or stenosis, however they may prevent certain patients the need for additional revisional surgery.

Key words: Bariatric surgery; Bariatric complications; Endoscopic treatment; Sleeve gastrectomy; Roux-en-Y gastric bypass; Anastomotic leak; Self-expanding metal stent

Core tip: The majority of general surgeons and all bariatric surgeons will be faced with complications related to bariatric surgery. Understanding the new anatomy and most frequent complications is paramount to treating these patients appropriately. The use of endoscopic self-expanding stents alone or in combination with an operation can stabilize and occasionally completely heal anastomotic leaks and fistulas. Endoscopy can also be useful in the diagnosis and treatment of bleeding, stenosis, and ulcerations. This review will summarize the current literature on endoscopy for bariatric complications.

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INTRODUCTION

Obesity is a complex and chronic disease that is attributed to a combination of genetics and environmental factors. In the United States in 2011-2012, 69% of adults aged over 20 were considered overweight, 35.1% were obese, and 6.8% were morbidly obese. Similar trend are also seen in children (2-19 years) with obesity rate of 16.9% during the same period[1]. It is the second leading cause of preventable death in the United States, second only by smoking. The gap between these two has be diminishing and obesity is thought to overtake smoking in the near future[2]. Although lifestyle modifications have good short term results (1 year)[3], longer follow up has demonstrated a significant advantage to patients who have undergone a bariatric procedure[4]. The number of bariatric procedure performed worldwide in 2011 is estimated at 340768. The most commonly performed operations are the [Roux-en-Y gastric bypass RYGB (46.6%)], sleeve gastrectomy [SG (27.8%)], bilio-pancreatic diversion with duodenal-Switch [BPD/DS (2.2%)], and the Adjustable Gastric Band [AGB (17.8%)][5]. Over 90% these procedure are performed laparoscopically. The mean percentage of excess weight loss is 61.6%, 57%, 70.1%, and 47.5% respectively[6,7]. With an increase in the number of procedure being performed worldwide, as will the complications. These can be divided into intraoperative, perioperative, and late. The two latter can be further subdivided into local and systemic (Table 1). The sleeve gastrectomy is noteworthy as is does not create any mesenteric defects, thus the potential for internal hernia is eliminated.

Perioperative complications, although rare, are life threatening and must be diagnosed and treated promptly. Many of the clinical signs and symptoms are vague and subtle and can easily be overlooked. Late complications, although less life threatening, can be a diagnostic dilemma. Endoscopy is an excellent first line tool and may be simultaneously diagnostic and therapeutic. We will explore the pathophysiology, incidence and management of anastomotic/staple line leak, fistulas, stenosis, ulcers, and bleeding.

Table 1 Postoperative complications

	Local	Systemic
Intraoperative	Iatrogenic splenectomy (0.41%)	
Perioperative	Anastomotic leak (1.1%) GI hemorrhage (2.5%) Trocar injury (0.1%)	Deep vein thrombosis (1%) Pulmonary embolism (0.5%) Bowel obstruction (1.7%) Wound infection (3%) Pneumonia (0.2%) Cardiac event Mortality (0.2%-1%)
Late	Anastomotic stricture (3%-12%) Marginal ulcer (0.5%-20%) "Candy Cane" syndrome Gastroesophageal reflux	Bowel obstruction (2.5%) Incisional hernia (0.5%-8%) Internal hernia (1%-3%) Dumping syndrome (up to 30%) Cholecystitis (up to 30%) Anemia Vitamin deficiencies

ANASTOMOTIC AND STAPLE LINE LEAKS

Leaks occur when there is discontinuity of tissue apposition at the site where the tissue has been stapled and divided. It is generally felt that leaks within 48 h are caused by a technical failure. This can be a result of stapler misfire, wrong staple size for the tissue, or tissue trauma. Leaks occurring after several days are more likely due to tissue ischemia cause by tension on the anastomosis, distal bowel obstruction, or hematoma. In both situations, the intraluminal pressure exceeds the strength of the staple line[8]. Risk factors for leaks are increased age, male gender, sleep apnea (SA), and reversional surgery[9]. The incidence of leaks after RYGB has been as high as 8.3%, however most recent data would suggest the incidence to be closer to 1.1%[8,10,11]. The most common sites for anastomotic leak in the Roux-en-Y gastric bypass is the gastrojejunal anastomosis (GJA) 42.2%-67.8%, gastric pouch 10.2%, excluded stomach 3.4%, jejunojenual anastomosis 5.5%-7.8%, or in a combination or these sites in 14%[11,12]. As for sleeve gastrectomies, the most common location of staple line leak is the proximal third of the stomach occurring at the level of the cardiac notch in approximately 75%-87.5%[13,14]. Overall leak rate-related mortality is low (0.6%) in RYGB, however leak associated mortality is significantly higher (14.7%-17%)[9,15]. The results are similar in the sleeve gastrectomy population with an incidence of 1%-2.7%[14,16-18], overall leak-related mortality 0.14%, and leak associated mortality 9%[14].

Anastomotic leaks can be classified as acute < 7 d, early 1-6 wk, late 6-12 wk, chronic > 12 wk[17]. Regardless of the time at which the anastomotic leak occurs, a thorough clinical assessment must me performed. Diagnosis of these leaks can be quite difficult with the most commonly found abnormality being sustained tachycardia > 120 bpm[19,20]. Other symptoms that have been reported are abdominal pain, use of more analgesics than expected, no ambulation within 2 h of surgery, and shortness of breath[11]. Laboratory abnormalities may show leukocytosis or an elevated C-reactive protein, although these are not always present. The use of an upper gastrointestinal series with water-soluble contrast or computed

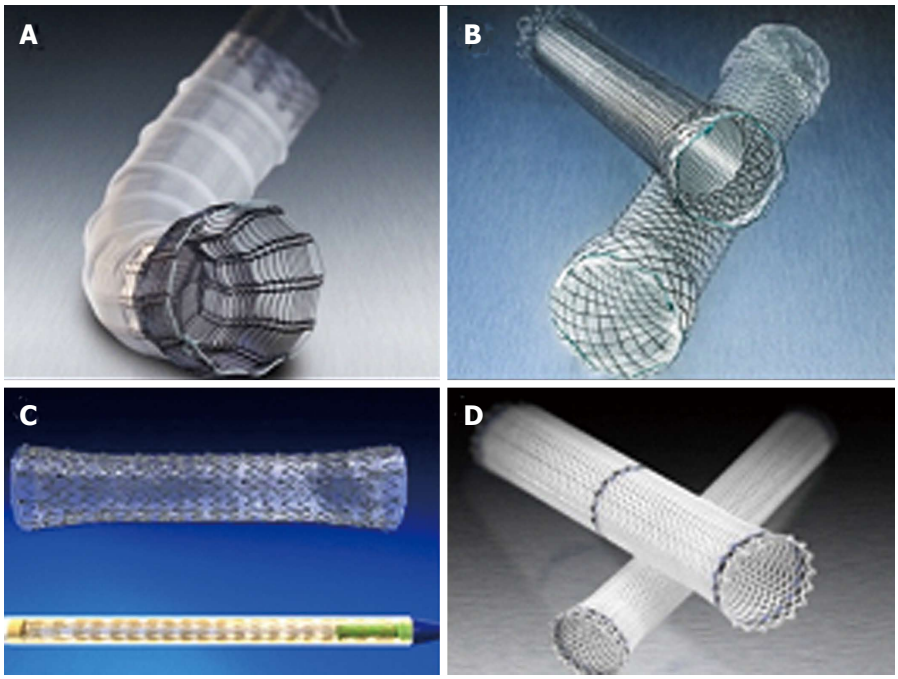

Figure 1 Self-expanding metal stents. A: Partially covered self-expanding metal stent; B: Partially and fully covered self-expanding metal stents; C: Fully covered self-expanding metal stent; D: Self-expanding plastic stent. Images courtesy of BostonScientific.com and Endotek.merit.com.

tomography may confirm the diagnosis, however these tests should not delay a return to the operating room. Most surgeons (86%) would take the patient to the OR with an unconfined and persistently symptomatic patient[17]. The majority (39%-81%) of patients with acute or early anastomotic leaks will ultimately return the the OR[11,12,19,20]. In the subgroup of patients who have minimal symptoms, are hemodynamically stable, and have a contained leak, conservative management may be warranted. Traditionally this management was NPO status, broad-spectrum antibiotics, percutaneous drains, and parenteral nutrition[11].

Endoscopic stents were initially designed as a tool of palliation for obstructing esophageal, gastric, and colorectal cancer. Some of the first published data for using stents across an anastomotic leak was in the thoracic population after esophageal resections. Leak rates as well as mortality after re-operation in this population was much higher therefore prompting a more conservative solution[21]. Most endoscopic stents used today are covered self-expanding metal stents (SEMS), partially covered self-expanding metal stents, and covered self-expanding plastic stents (SEPS) (Figure 1). These stents will provide a barrier between endoluminal bacteria and the acidic enteric content and the anastomotic disruption. Having an intraluminal device that will keep the anastomosis patent may also prevent wound contraction and the subsequent development of stenosis. The presence of these stents also confers the advantage of early enteral feeding. Healing success is defined as radiological confirmation of no leak after removal of stent. Stents are successful in 80%-94% of acute anastomotic leaks with stents left in place ranging from a mean of 41 d to 3.2 mo. Most patient may resume an oral liquid diet within 1-3 d. The most common side effects of the stent are early satiety, nausea, epigastric pain, and hypersialosis[22-24]. In a recent international expert panel consensus including 24 centres and over 12000 cases of laparoscopic sleeve gastrectomy (LSG), 93% of responders found the use of a stent for and acute proximal leak is a valid treatment option[17]. The most frequent complication of stent placement is stent migration seen in 16.9%-59%[25]. Most migrations are only a few centimetres, however this is enough to uncover the leak. The stents may also migrate distally with most passing per rectum. Only a few require an elective operation for stent retrieval. An urgent OR for erosion through the gastrointestinal wall and laceration of a blood vessel has also been described. Partially covered SEMS, larger diameter (18-22 mm), and longer length (15 cm) seem to have the least potential to migrate. The procedure of stent placement is most commonly performed in the operating room under general anesthesia with edotracheal intubation. The endoscope is use to identify the location of the leak and mark the location with radio-opaque clips. A guide-wire is also placed through the Roux limb. Under fluoroscopy, the stent deployment system is positioned across the leak and released. The length of the procedure can range from 23-47 min[24,26,27]. Endoscopic extraction is easiest with fully covered SEMS or SEPS. They can be grasped with large toothed graspers and extracted with firm steady pressure. Partially covered SEMS may have tissue ingrowth at either end. Two common techniques from removal are argon plasma coagulation and insertion of SEPS within the SEMS to induce tissue necrosis and easy extraction at a later date.

Figure 2 Resolution clip. Image courtesy of BostonScientific.com.

BLEEDING

Early bleeding after surgery can be intraluminal or extraluminal. The most frequent site of bleeding is the site of the anastomosis of staple lines. A risk factor for early bleeding is the presence of diabetes mellitus. The minority of bleeds will require an intervention more involved than a simple blood transfusion, and even fewer will require reoperation (21%)[28]. Bleeding is most often diagnosed with a postoperative decrease in hemoglobin. Uncommon clinical findings are hemoptysis, bright red blood pre rectum, or melena. A patient with hemodynamic instability, a distended or tender abdomen, or falling hemoglobin should be managed with an expeditious return to the operating room.

The gastroscope may be used may be used cautiously in the early post op with minimal air insufflation to avoid undue tension on the fresh anastomosis. The use of endoclips (Figure 2) alone or in combination with epinephrine is preferred to electrocautery[29].

FISTULAS

Anastomotic disruption with a more indolent and contained leak may ultimately form a fistula. A theory for the formation of a gastrogastric fistula is an incomplete transection of the gastric pouch and gastric remnant. The most common locations of an enteric fistula after bariatric surgery are gastrogastric, gastrocutaneous, duodenocutaneous, gastroperitoneal, and more rarely gastro-bronchial[8,26,30]. The incidence of gastric fistulas after bariatric surgery has not been well described, it may be in the order of 14.2% after an anastomotic leak[19]. The presence of a fistula will increase mortality with an order of magnitude of 8%-37.5%. It will also increased morbidity associated with a prolonged hospital stay, frequent hospital/clinic visits, and home care[31]. Success after stenting has been much less favourable than in the acute leaks. The success ranges from 19%-81%[19,26,32]. During an international expert panel for LSG, 89% of centres agree that stenting has a limited utility for chronic leaks (> 12 wk)[17]. Bège *et al*[25] have described a series of interventions starting with endoscopic drainage and debridement (± Amikacin 500 mg into the cavity), placement of a nasocystic tube, and placement of a plastic double-pigtail stent. A stent was inserted if the opening was more than 1 cm in diameter. The stent was secured proximally with endo-clips. If there was no resolution after 6 wk, therapeutic endoscopy was performed with placement of clips and/or injection of synthetic glue (N-butyl-2-cyanoacrylate) within the fistula cavity. Success after the first intervention was 64% of patients with late leaks/fistulas. Eisendrath *et al*[26] had a 61.9% success after stent alone, and an increased success rate of 80.9% the use after biologic glue, fistula plug, or clips.

ULCERS

Marginal ulceration may be seen in 0.49%-20% after RYGB[33-35]. The most common symptoms include epigastric pain, nausea, vomiting, food intolerance and bleeding. It is one of the most common finding on endoscopy in patients presenting with abdominal pain (52%)[36]. Risk factors include smoking (OR = 30.6), NSAIDs (OR = 11.5), diabetes (OR = 5.6), ischemia, increased stomach acid, bile acid reflux, *Helicobacter pylori* (*H. pylori*), steroids, alcohol, and foreign body[35,37-40]. Management is largely directed to the suspected etiology. Cessation of smoking, NSAIDs, and good blood glucose control is paramount. Proton pump inhibitors taken twice daily and tapered for 3-6 mo have had good results. If sampling of gastric fluid reveals normal or alkaline pH, sucralfate four times daily may have better results[41]. Biopsy proven *H. pylori* should be treated and visible suture should be removed. Non-healing ulcers should raise the possibility of a gastrogastric fistula.

STENOSIS/STRICTURE

This late complication can present with early satiety, nausea, vomiting, dysphagia, obstruction, retrosternal or abdominal pain[35]. These most commonly occur at the GJA and have an incidence of approximately 3%-12%[42-45]. Less frequently, stenosis can be seen at the enteroenteric anastomosis, the passage of the Roux limb through the mesocolon (Retrocolic approach only), and the Petersens defect. They most commonly present after 4-8 wk post op[46,47]. GJA with a linear stapler has a lower stricture rate of 2% compared to the 21 mm circular EEA stapler with a rate of 14%[19]. Risk factors include small (< 25 mm) circular stapler and marginal ulcers. The majority (90%) of patients will be amenable to endoscopic dilatation[47-49]. Dilatation may be attempted cautiously in as early as 4 wk post operatively. Frequently two, three or more dilatation may be required. With conscious sedation, the endoscope is passed to the level of the GJA. The diameter of the stricture is frequently be smaller than 3 mm and precludes passage of the endoscope. Caution must be applied when passing a guide wire

and the balloon dilator through the stenosis blindly. If any resistance is encountered, it should raise the possibility of passage into the blind limb. The balloon dilator is passed through the structured segment until its midpoint is at the maximal level of the stenosis. The smallest balloon is used initially and the size is progressively increased with every successful dilatation. This is felt to reduce the risk of perforation reported to be 3%-5%[46]. Dilatations of up to 15 mm, even in the first procedure, have been shown to be safe. The use of stents for treating strictures that have failed dilatation has not been fruitful. Puig *et al*[32] have had minimal success with only 2 of 16 patients not requiring and operative revision.

CONCLUSION

As the number obese patients increases, as will the number bariatric procedures. We will be left with a large number of patients with complications requiring adequate diagnosis and treatment. The surgeon is expected to promptly identify and appropriately manage early and late complications. Only surgeons who have performed the operations truly understand the new anatomy. Diagnostic and therapeutic endoscopy should be considered a first line tool in stable patients with perioperative complications such as anastomotic/staple line leaks, and bleeding. The placement of self-expanding metal or plastic stents in a patient with an anastomotic leak has shown favourable results. Late complication often present with vague complaints such as nausea, vomiting, or abdominal pain. Endoscopy is an excellent instrument for early diagnosis and treatment. SEMS, SEPS alone or in combination with metal clips, biologic glues, and biologic fistula plugs for treatment of fistulas should be considered first line therapy despite modest results. This strategy should greatly decrease the morbidity and mortality by reducing the rate of a revision surgery.

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Endoscopic submucosal dissection in early gastric cancer in elderly patients and comorbid conditions

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Abstract

The prognosis of early gastric cancer (EGC) is good if there is no concomitant lymph node metastasis. Therefore, the early detection of EGC is important to improve the prognosis of patients with gastric cancer. In Japan, 40% to 50% of all gastric cancers are EGC, and endoscopic submucosal dissection (ESD) is widely accepted as a local treatment for these lesions, particularly for large lesions that at one time were an indication for gastrectomy because of the difficulty of *en-bloc* resection. Consequently, this procedure can preserve the entire stomach and the patient's postoperative quality of life. ESD has become a general technique with improved procedures and devices, and has become the preferred treatment for EGC rather than gastrectomy. Therefore, ESD may demonstrate many advantages in patients who have several comorbidities, particularly elderly population, patients taking antithrombotic agents, or patients with chronic kidney disease, or liver cirrhosis. However, it is not yet clear whether patients with both EGC and comorbidities are feasible candidates for ESD and whether they would consequently be able to achieve a survival benefit after ESD. In this review, we discuss the clinical problems of ESD in patients with EGC and those comorbid conditions.

Key words: Endoscopic submucosal dissection; Gastric cancer; Elderly person; Antithrombotic agents; Liver cirrhosis; Chronic kidney disease

Core tip: Endoscopic submucosal dissection (ESD) is widely accepted as a local treatment for gastric cancer, particularly for early gastric cancer. Consequently, this procedure can preserve the entire stomach and the patient's postoperative quality of life. Therefore, ESD

may demonstrate many advantages in patients who have several comorbidities. However, it is not yet clear whether patients with both early gastric cancer (EGC) and comorbidities are feasible candidates for ESD and whether they would consequently be able to achieve a survival benefit after ESD. In this review, we discuss the clinical problems of ESD in EGC in elderly patients and patients with comorbid conditions.

Nishida T, Kato M, Yoshio T, Akasaka T, Yoshioka T, Michida T, Yamamoto M, Hayashi S, Hayashi Y, Tsujii M, Takehara T. Endoscopic submucosal dissection in early gastric cancer in elderly patients and comorbid conditions. *World J Gastrointest Endosc* 2015; 7(5): 524-531 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i5/524.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i5.524

INTRODUCTION

Gastric cancer is the fourth most common cancer and the second most common cause of cancer-related death in both sexes worldwide[1,2]. The incidence of gastric cancer has declined in younger populations along with decreasing infection rates of *Helicobacter pylori (H. pylori).* The infection rate of *H. pylori,* however, remains high in elderly Asian populations. In 2002, nearly 1 million new cases of gastric cancer were diagnosed, and more than half of these cases were from East Asia, including 41% from China and 11% from Japan[3]. Therefore, gastric cancer remains one of the most common cancers in Asian countries[4]. Patients with advanced gastric cancer have a poor prognosis; however, the prognosis of early gastric cancer (EGC) is good[5,6], and the 5-year gastric cancer-specific survival rate was reportedly 99% in cases that lacked concomitant lymph node metastasis[7]. EGCs account for 40% to 50% of all gastric cancers in Japan. Endoscopic resection (ER) is an alternative to surgery for treatment of mucosal neoplasms[8]. The criteria for ER for EGC was classified into the following three groups proposed by Gotoda *et al*[9] based on the characteristics of the initially detected tumor: "guideline group", "expanded guideline group" and "non-curative group". The guideline group was defined as mucosal differentiated cancer with the largest diameter measuring ≤ 20 mm. In Japan, ER is definitely indicated for this group. The expanded guideline group was defined as the following: (1) mucosal differentiated cancer measuring > 20 mm in diameter; (2) mucosal differentiated cancer with ulceration and measuring ≤ 30 mm in the largest diameter; and (3) differentiated cancer measuring ≤ 30 mm in the largest diameter with a submucosal invasion depth of < 500 μm. If the lesions did not meet these criteria, they were classified as the non-curative group. ER includes endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)[10]. EMR has been a standard technique for early gastric cancer with no risk of lymph node metastasis. EMR is, however, reportedly difficult to achieve *en-bloc* complete resection for the removal of lesions with the extended indication[11]. ESD is widely accepted as a treatment for EGC, particularly for larger lesions that at one time were an indication for gastrectomy because of the difficulty of *en-bloc* resection. Consequently, this procedure can preserve the entire stomach and improve the patient's postoperative quality of life. Moreover, ESD has become a standard technique with improved procedures and devices. Now, EMR has been replaced by ESD.

Because most patients with EGC are elderly, these patients commonly have several comorbidities that involve medical treatment, such as antithrombogenic agents to combat thrombosis, chronic kidney disease, or liver cirrhosis. In this review, we discuss the clinical problems associated with ESD in patients with EGC and comorbid conditions.

ELDERLY PATIENTS

Most patients with gastric cancer are diagnosed between their late 60s and 80s[12]. Therefore, most patients with EGC are elderly and therefore have an increased risk for procedure-related complications or events. EGCs generally grow slowly, and thus, we must determine a therapeutic strategy that considers the presence of comorbid diseases.

Most of elderly individuals have multiple chronic medical conditions[13]. Therefore, any indication for elderly patients with EGC must account for both life expectancy and concomitant conditions or diseases. However, there is little evidence that endoscopic resection is well tolerated in the elderly EGC patients who are most likely to benefit from resection.

Kakushima *et al*[14] previously reported the safety and efficacy of ESD for EGC in elderly patients aged 75 years or older (average age, 79 years old). Indeed, 57% of these patients also presented with comorbid diseases, but the *en-bloc* plus R0 resection rate and the complication rate in elderly patients were not significantly different from those of younger patients. Kakushima *et al*[14] concluded that ESD for gastric neoplasms is safe and effective in both elderly patients and younger patients. We also retrospectively validated whether gastric ESD was feasible even for elderly patients. In a study of 459 patients aged 75 years or older among 1188 EGC patients, perforation occurred in 20 patients (4.4%), and bleeding occurred in 12 patients (2.6%)[15]. The incidences of those complications were similar to those in the younger patients. Advanced age (*i.e.,* older than 75 years), however, is associated with an increased risk for postoperative pneumonia. Toyokawa *et al*[16] reported that the rate of late bleeding rate was significantly higher in elderly patients aged 75 years or compared with

Table 1 Endoscopic submucosal dissection in elderly patient *n* (%)

Ref.	Age (yr)	Patients *n*, lesions *n*	En-bloc resection, with R0, %	Perforation	Late bleeding	Pneumonia
Hirasaki *et al*[53]	≥ 75	53, 53	96, 81	1 (1.9)	(43%)[1]	NE
Kakushima *et al*[14]	≥ 75	42, 49	NE, 96	1 (2)	3 (7)	NE
Akasaka *et al*[15]	≥ 75	459, 459	NE	20 (4.4)	12 (2.6)	15 (3.3)
Toyokawa *et al*[54]	≥ 75	200, 229	92, 80	4 (1.7)	22 (9.6)	2 (0.87)
Abe *et al*[55]	≥ 80	440, 470	NE, 77.9	12 (2.8)	14 (3.2)	NE
Park *et al*[17]	≥ 70	132, 132	NE	6 (4.5)	5 (3.8)	6 (4.5)
Zhang *et al*[56]	≥ 75	171, 187	98, 94.1		(15.2%)[2]	NE

[1]Bleeding was defined in cases that required endoscopic management with methods such as clip placement and/or monopolar electrocoagulation to stop the bleeding, including early and late bleeding. One patient required surgery to treat the bleeding; [2]Immediate bleeding. NE: Not evaluated.

younger patients (9.6% *vs* 5.3%, $P = 0.0473$). After a multivariate analysis, the size of the resected specimen was the only significant risk factor for delayed bleeding. Recently, Park *et al*[17] reported that with expanded criteria as proposed by Gotoda *et al*[18], overall survival did not differ between elderly patients with EGC who underwent ESD and those who underwent surgery, although the risk of metachronous lesions was higher in patients who underwent ESD[17]. A propensity-matched analysis indicated that all of the adverse events observed in the ESD group were successfully treated and did not result in mortality. In contrast, two patients in the surgery group died of operation surgery-related complications, although no significant difference was observed between the two groups. Based on these data, we believe that gastric ESD in elderly patients is feasible and that EGC is manageable with this treatment (Table 1).

PATIENTS TREATED WITH ANTITHROMBOTIC AGENTS

In the last few decades, the number of patients treated with oral antithrombotic agents, including antiplatelet agents and anticoagulants, has increased worldwide in an effort to prevent or reduce thromboembolic events[19]. Recently, many novel oral anticoagulant drugs have been presented as alternatives to vitamin K antagonists and are either currently available or in the early or advanced stages of clinical development[20].

In patients who undergo minor surgical procedures, the discontinuation of antithrombotic therapy may not be required. However, patients who undergo major surgical procedures are required to discontinue the use of these drugs to minimize their risk for perioperative bleeding, as the continuation of antithrombotic agents in the perioperative period may lead to an increased risk of bleeding. In endoscopic procedures, antithrombotic agents may be discontinued when a patient is judged to have a low risk of thrombosis. The appropriate cessation of antithrombotic therapy has recently been reported to not increase the rate of delayed bleeding[21,22]. However, when gastric ESD is scheduled in a patient treated with oral anticoagulants (*e.g.*, warfarin) and judged by the prescribing doctor to have a high risk of thromboembolism, he or she will also undergo heparin replacement (HR). Similarly, when gastric ESD is scheduled in a patient treated with antiplatelet agents (*e.g.*, aspirin, ticlopidine, clopidogrel and cilostazol) and judged to have a high risk of thromboembolism, he or she will be placed on a continuous aspirin or cilostazol regime according to recently published guidelines from the Japan Gastroenterological Endoscopy Society[23]. In patients at high risk of thrombosis, the risks of both bleeding and thrombosis are unclear in patients who undergo endoscopic invasive procedures, such as gastric ESD.

Regarding antiplatelet agents, the continuous use of aspirin during the perioperative period of ESD has been reported to be acceptable, although the rate of delayed bleeding is slightly higher[24,25]. In an analysis of the combination of antiplatelet agents and anticoagulants, Koh *et al*[26] reported that antithrombotic therapy increased the risk of delayed bleeding. Takeuchi *et al*[27] also reported that the rate of postoperative bleeding in patients taking antithrombotic agents was 23.3%, which is significantly higher than the 2.0% observed in patients not treated with antithrombotic agents. Despite the discontinuation of antithrombotic agents, the authors found that combination therapy of low-dose aspirin (LDA) plus warfarin was a significant predictor of post-ESD bleeding (OR = 14.83, $P < 0.001$).

We believe that not only is LDA plus warfarin combination therapy a risk factor for late bleeding but also that HR is a risk factor for this condition. HR therapy is used as a bridge therapy along with invasive treatments to prevent antithrombotic events. We previously showed that the rate of delayed bleeding was high during gastric ESD (38%)[22] or colon polypectomy (20.0%)[28] under HR therapy.

However, few studies on the relationship between thrombotic events and endoscopic procedures have been conducted. The incidence rates of thrombotic events related to gastric ESD have been reported to range from 0 to 4.2%[21,22,24,27] (Table 2). We encountered one patient (4.2%) with delayed bleeding in the HR group who experienced a thrombotic event[22]. The patient's activated partial thromboplastin time was sufficiently prolonged under HR after successful endoscopic hemostasis for late bleeding. Although the patient discontinued the use of all antiplatelet agents, a cerebral infarction developed on post-operative day 13. Therefore, thrombosis during bleeding should be carefully considered, despite the presence of a sufficient anticoagulant effect during the perioperative period (Table 2).

Table 2 Endoscopic submucosal dissection in patients treated with antithrombotic agents *n* (%)

Ref.	Patients *n*, lesions *n*	En-bloc resection, with R0, %	Perforation	Late bleeding	HR No., bleeding	Thrombogenic event
Ono *et al*[21]	47[1], 56	96.4/82.1	1 (1.8)	6 (10.7)	1, 3 (33)	0 (0)
Lim *et al*[24]	274, ND	NE	0 (0)	26 (12.6)[2]	NA	1 (0.5)[3]
Koh *et al*[26]	175, ND	NE	NE	17 (9.7)[4]	NA	0 (0)
Takeuchi *et al*[27]	90, 90	NE	NE	21 (23.3)[5]	12, 21 (57)	1 (1)
Yoshio *et al*[22]	24, 24	100/100	0 (0)	9 (38)[6]	9, 24 (38)	1 (4.2)

[1]Forty-four low-risk patients stopped treatment with antithrombotic agents for 1 wk before and after endoscopic submucosal dissection (ESD). Three high-risk patients underwent intravenous heparin replacement during the cessation period; [2]A total of 274 patients were treated with antiplatelet medication, 102 of whom discontinued the use of these drugs for 7 d or more before ESD, whereas the remaining patients continued use; [3]One (1%) of the 102 patients who discontinued the use of antiplatelet medication developed an acute cerebral infarction; [4]Antithrombotic drug therapy was principally interrupted preoperatively and restarted when hemostasis was confirmed by second-look endoscopy. The rate of early postoperative bleeding during the first 5 postoperative days was 4%, and the rate of subsequent bleeding was 5.7%; [5]All patients commenced treatment with proton pump inhibitors immediately following surgery. Antiplatelet agents were discontinued for 7 d preoperatively until postoperative day 1, and anticoagulants were discontinued for 5 d preoperatively until postoperative day 1. A total of 46 patients received low-dose aspirin (LDA) only, 23 received LDA + thienopyridine, and 21 received LDA + warfarin. Anticoagulants were discontinued from preoperative day 4 to postoperative day 2. Heparin was substituted for anticoagulants after the latter were discontinued; [6]All patients underwent intravenous heparin replacement during the cessation period because of an increased risk of thromboembolism. HR: Heparin replacement; NA: Not applicable; NE: Not evaluated.

CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is associated with significant morbidity and mortality and is now recognized as a worldwide problem because the number of patients with CKD is sharply increasing[29]. In Japan, clinical practice guidelines have reported that the frequencies of stage 1, 2, 3, and 4/5 CKD in adults were 0.6%, 1.7%, 10.4% and 0.2%, respectively, in 2009. The total number of patients in stages 3 to 5 was estimated to be approximately 10.97 million[30]. Renal function linearly deteriorates with age. Therefore, the number of patients with CKD is higher in elderly populations, and consequently, the number of patients with gastric cancer and CKD is also believed to be increasing. Patients with CKD are more likely to experience multiple complications during the surgical procedure, such as procedure-related bleeding due to uremic platelet dysfunction and tissue vulnerability, compared with patients without CKD[31,32]. The safety and feasibility of gastric ESD for patients with CKD, however, are unclear.

Mannen *et al*[33] reported no significant risk factors for complications from gastric ESD among 17 patients with CKD. Goto *et al*[34] reported complications from gastric ESD in 7 patients with CKD who underwent hemodialysis (HD), one patient experienced delayed bleeding that required a blood transfusion, followed by shunt occlusion. Although all of the lesions were resected *en-bloc* with R0 resection, the authors concluded that ESD in patients with CKD should be carefully considered for substantial risks because late-onset complications may turn out to be severe. Kwon *et al*[35] also conducted a single-center retrospective study in which 17 patients with CKD were compared with 894 control patients who received gastric ESD. They reported no significant differences in *en-bloc* resection and perforation rates between patients with CKD and patients without CKD, but a tendency to hemorrhage was observed in patients with CKD. Numata *et al*[36] reported that the rate of post-ESD bleeding was 33% in 15 lesions in 12 patients with HD among the 63 patients with CKD, whereas the rate of post-ESD bleeding was only 9% in patients without HD. In addition, 2 deaths related to the ESD procedure were reported, but no deaths due to EGC occurred. Both of these patients were receiving HD, and the deaths occurred subsequent to the bleeding. The authors concluded that the cause of the bleeding was associated with other comorbidities, such as the use of anticoagulants during HD[36]. To focus on the eGFR, we also evaluated 144 patients with CKD in a multicenter survey that included municipal hospitals, where many patients with CKD were among those who underwent ESD[37]. In our study, we included patients with gastric cancer under the expanded criteria[7], and found that 20 patients did not achieve curative resection (13.9%), whereas additional surgeries were performed in 14 patients (9.7%). No ESD-related deaths were reported in these 144 patients. With respect to short-term outcomes, late bleeding was observed in 1.1% of patients in stage 3 (1/92), 13.0% in stage 4(3/23), and 13.8% in stage 5 (4/29). All incidences of bleeding were controlled by endoscopic hemostasis, but 5 patients required a blood transfusion (3.5%). In a univariate Poisson regression analysis including CKD stage, HD, diabetes mellitus, use of antithrombogenic

Table 3 Endoscopic submucosal dissection in patients with chronic kidney disease *n* (%)

Ref.	CKD, *n*/ lesions, *n*	Hemodialysis, *n*	HR, *n*	En-bloc resection, with R0, %	Perforation	Late bleeding
Goto *et al*[34]	7/9	7	ND	100/100	0 (0)	1 (14)
Kwon *et al*[35]	17[1]/19	8	ND	94.7/94.7	0 (0)	3 (17.6)[2]
Numata *et al*[36]	63 /79	12	2	89.9/89.9	3 (4.8)	11 (17.5)[3]
Yoshioka *et al*[37]	144/ 144	19	7	95.8/86.1	6 (4.2)	8 (5.6)

[1]Includes 2 patients with peritoneal dialysis; [2]Original paper reported 15.5%, which represented the percentage of perforation per lesion; [3]The rate of late bleeding was 33.3% (5/15) in hemodialysis patients and 9.4% (6/64) in non-hemodialysis patients; the difference was significant ($P < 0.05$). ND: Not described; HR: Heparin replacement.

Table 4 Endoscopic submucosal dissection in patients with liver cirrhosis

Ref.	Patients N (Child-Pugh A, B, C) /lesion, *n*	*En-bloc* resection, with R0, %	Perforation *n* (%)	Late bleeding *n* (%)	Median observation period (mo) Prognosis
Ogura *et al*[51]	15 (9, 6, 0)/18	88.9, 77.8	0 (0)	3 (20)	21.4 mo No recurrence but 3 patients underwent additional ER or surgery
Kwon *et al*[35]	18 (13, 3, 2)/22	90.9, 86.4	1 (5.6)	ND (approximately 9)	NE
Choi *et al*[57]	23 (20, 3, 0)/23	86.2, 82.6	0 (0)	1 (4.3)	17.5 mo (range, 2 to 72 mo) No local recurrence was found in either group during the follow-up period
Repici *et al*[58]	5 (4, 1, 0) /5	100, 100	0 (0)	2 (40)	22 mo (range, 18 to 36 mo) No recurrence
Kato *et al*[52]	69 (53, 15, 1)/69	99, 90	1 (1.5)	4 (5.8)	33.4 mo (range, 0.5-96.9 mo) The 5-yr overall survival rates were 60%

ND: Not described; NE: Not evaluated.

agents and HR, the critical factors related to bleeding were CKD stage and HD. In multivariate Poisson regression analyses, the risk ratio of bleeding was 11.4 in patients with stage 4 CKD and 11.0 in patients with stage 5 CKD. Thus, we concluded that CKD calculated from the eGFR would be an independent risk factor regardless of whether a patient undergoes HD[37].

Gastric ESD in patients with CKD is technically feasible, even in patients undergoing HD. However, bleeding in patients with CKD may lead to death due to other comorbidities, such as conditions that require the use of anticoagulants. Therefore, particular attention should be paid to late bleeding in patients with CKD, particularly patients with advanced CKD (Table 3).

LIVER CIRRHOSIS

Liver cirrhosis (LC) is a common disease, especially in Japan and other East Asian countries, due to the high prevalences of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections[4]. *H. pylori* and HBV/HCV, respectively, are the leading causes of bacterial and viral diseases in humans worldwide, particularly in East Asian. Consequently, it is not rare for patients to be affected by these two diseases. Patients with LC have a poor prognosis because of liver failure or the development of hepatocellular carcinoma (HCC)[38], esophagogastric varices[39], compromised host[40], or glucose intolerance[41]. In contrast, the prognosis of patients with EGC is good[7]. Therefore, it is difficult to determine whether patients with cirrhosis and EGC are suitable for ESD because this procedure may not increase the survival benefit for patients with LC. Until now, several studies have focused on the clinical outcomes of radical gastrectomy in patients with gastric cancer and comorbid LC[42-47]. These studies indicate that 10%-20% of patients with LC develop postoperative intractable ascites, and that the perioperative mortality rate is approximately 10%. However, few investigators have reported whether gastric ESD can be performed safely in patients with poor liver function or gastric varices. During gastric ESD, the rate of bleeding rate may increase because LC is frequently accompanied by complex alterations in the hemostatic system[48,49], and patients with LC have fewer platelets and a prolonged prothrombin time. More specifically, it is technically difficult to perform ESD when a varix is located near a gastric lesion. Kim *et al*[50], however, reported a successful ESD adjacent to a fundal varix after treatment with endoscopic variceal obturation using N-byutyl-2-cyanoacrylate (Histacryl®).

Ogura *et al*[51] performed a case series study on short-term ESD outcomes for 18 patients with LC. The authors reported that *en-bloc* resection was achieved in 88.9% of patients with EGC and cirrhosis but that the rate of late bleeding rate appeared to be higher (20%). Kwon *et al*[35] reported that the procedure time and short-term outcomes in patients with cirrhosis, such as the rates for *en-bloc* and complete resections, did not differ from those of the control group, even though the results of endoscopic mucosal resection were included. Immediate bleeding tended to occur more frequently in patients with both LC and CKD than in controls (47.5% *vs* 33.9%, $P = 0.077$). However, no significant difference was observed in the incidence of perforation[35]. We also evaluated outcomes of gastric ESD among 69 patients with LC. Based on a propensity-matched analysis, 53 (77%) of these patients had Child Pugh Grade A (CP-A) and 16 (28%) had Child Pugh Grade B/C (CP-B/C) compared with patients without LC[52]. In that study, short-term outcomes did not differ between the patients with LC and controls or between the patients with CP-A and those with CP-B/C. This study, however, revealed that the CP grade and HCC history were significantly independent risk factors for poor prognoses according to a Cox proportional hazards model. Patients with cirrhosis and CP-A demonstrated an overall survival that was nearly equivalent to that of patients without cirrhosis; however, patients with cirrhosis and CP-B/C or with histories of HCC had significantly worse long-term outcomes (the overall 3- and 5-year survival rates after ESD were 58% and 26%, respectively). Therefore, the long-term outcomes of patients with cirrhosis were likely influenced by liver

function or cirrhosis-related conditions rather than by gastric cancer. We concluded that patients with cirrhosis and CP-A appear to be good candidates for ESD but that patients with CP-B/C or with histories of HCC benefit less from ESD (Table 4).

CONCLUSION

This review demonstrated that gastric ESD could be performed safely, even in medically complex patients, such as elderly patients, those who are being treated with antithrombotic agents, and those with CKD or LC regarding the risk of complication, particularly bleeding. Although the short-term outcomes were not inferior, ESD was less beneficial to the survival of patients with a poor prognosis.

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Is it time to replace propranolol with carvedilol for portal hypertension?

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Abstract

Beta-adrenergic receptor antagonists (β-blockers) have been well established for use in portal hypertension for more than three decades. Different Non-selective β-blockers like propranolol, nadolol, timolol, atenolol, metoprolol and carvedilol have been in clinical practice in patients with cirrhosis. Carvedilol has proven 2-4 times more potent than propranolol as a beta-receptor blocker in trials conducted testing its efficacy for heart failure. Whether the same effect extends to its potency in the reduction of portal venous pressures is a topic of on-going debate. The aim of this review is to compare the hemodynamic and clinical effects of carvedilol with propranolol, and attempt assess whether carvedilol can be used instead of propranolol in patients with cirrhosis. Carvedilol is a promising agent among the beta blockers of recent time that has shown significant effects in portal hypertension hemodynamics. It has also demonstrated an effective profile in its clinical application specifically for the prevention of variceal bleeding. Carvedilol has more potent desired physiological effects when compared to Propranolol. However, it is uncertain at the present juncture whether the improvement in hemodynamics also translates into a decreased rate of disease progression and complications when compared to propranolol. Currently Carvedilol shows promise as a therapy for portal hypertension but more clinical trials need to be carried out before we can consider it as a superior option and a replacement for propranolol.

Key words: Portal hypertension; Chronic liver disease; Non-selective beta-blockers; Propranolol; Carvedilol

Core tip: Carvedilol is a promising agent among the beta blockers of recent time that has shown significant effects in portal hypertension hemodynamics. For primary prophylaxis of variceal bleeding, the effects of carvedilol were compared to band ligation in a few trials and showed some promise, but there has been no comparison with propranolol. Patients not responding to propranolol have shown clinical response to carvedilol, opening a new window of clinical application. For secondary prophylaxis of variceal bleeding, carvedilol has been shown to be effective. However no head-to-head trials comparing propranolol and carvedilol for variceal re-bleeding were found in literature.

Abid S, Ali S, Baig MA, Waheed AA. Is it time to replace propranolol with carvedilol for portal hypertension? *World J Gastrointest Endosc* 2015; 7(5): 532-539 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i5/532.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i5.532

INTRODUCTION

Liver cirrhosis remains the 12th leading cause of death worldwide according to estimates by the Global Burden of Disease Study[1]. Portal hypertension is an inevitable consequence of cirrhosis and underlies most of its complications like: variceal bleeding, ascites and hepatic encephalopathy[2]. Portal hypertension is characterised by a pathologic increase in the portal pressure gradient (the pressure difference between the portal vein and the hepatic veins) y greater than 5 mmHg. This causes the creation of porto-systemic collaterals leading to shunting of portal blood to the systemic circulation, bypassing the liver parenchyma. It has been shown that therapeutic reduction in portal pressure has been shown to improve clinical outcomes and reduces the incidence of recurrent haemorrhage, ascites, encephalopathy, and death[3-5].

Beta-adrenergic receptor antagonists (β-blockers) have been well established for use in portal hypertension for more than three decades. Non-selective β-blockers (NSBB) have been widely utilized since 1980, when the first article on their role in portal hypertension was published by Lebrec *et al*[6]. Portal hypertension results from fibrosis or regenerative nodules in the liver parenchyma increasing resistance to flow and causing mechanical obstruction; contraction of sinusoidal and perisinusoidal contractile cells (stellate cells and vascular smooth muscle cells) with intrahepatic imbalance between vasoconstrictors (such as endothelin 1 and angiotensin) and vasodilators; and splanchnic vasodilatation in secondary to a relatively ischemic liver or extrahepatic excess of NO, with sGC-PKG signalling and smooth muscle cell relaxation[7] (Figure 1).

NSBB have a dual mode of action decrease portal pressure, *i.e.*, reduction of cardiac output and splanchnic blood flow by β-1 receptor blockade, and β-2 receptor blockade, resulting in splanchnic vasoconstriction caused by unopposed effect of alpha 1 receptors[7]. NSBBs have been proven to decrease incidence of bleeding (primary prophylaxis) and re-bleeding (secondary prophylaxis) from esophageal varices[8-11]. It has been demonstrated that they also prevent bleeding from portal hypertensive gastropathy and development of spontaneous bacterial peritonitis[4,12,13]. Due to their widely diverse effects in patients with cirrhosis and widespread use, they have been dubbed as "aspirin" in clinical hepatology[14].

Different NSBBs like propranolol, nadolol, timolol, atenolol, metoprolol and carvedilol have been in clinical practice in patients with cirrhosis. Propranolol was the first, most widely studied NSBB and mainstream for treatment of portal hypertension. Carvedilol is a nonselective beta-blocker with intrinsic anti-alpha1-adrenergic activity. It has been a relatively newer addition to the NSBBs, in the arena of portal hypertension and has demonstrated promising results in terms of clinical outcomes.

Carvedilol has proven 2-4 times more potent than propranolol as a beta-receptor blocker in trials conducted testing its efficacy for heart failure[15]. Whether the same effect extends to its potency in the reduction of portal venous pressures is a topic of ongoing debate.

The aim of this article is to compare the hemodynamic and clinical effects of carvedilol with propranolol, and attempt assess whether carvedilol can be used instead of propranolol in patients with cirrhosis.

HEMODYNAMIC EFFECTS

To achieve successful protection against gastrointestinal bleeding, the portal pressure [usually measured as the hepatic venous pressure gradient (HVPG)] has to be decreased to ⩽ 12 mmHg or by 20% of baseline values[16]. Long-term follow-up of cirrhotic on beta blockers has shown that decrease of HVPG of above mentioned values results in lesser risk of developing variceal bleeding, ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome and hepatic encephalopathy[4].

Comparison of carvedilol to propranolol for portal hypertension was made in a recent systematic review with meta-analysis which included five head-to-head randomised trials[17-22]. This analysis favored carvedilol against propranolol, in terms of: (1) acute effects on reduction in HVPG [mean weighted difference in % of reduction in hepatic vein pressure gradient; -7.70 (95%CI: -12.40--3.00)]; (2) long term effects [mean weighted difference in % of reduction in hepatic vein pressure gradient was -6.81 (95%CI: -11.35--2.26)]; and (3) overall effects [(mean weighted difference in % of reduction in hepatic vein pressure gradient -7.24 (95%CI: -10.50--3.97)].

Additionally the same metaanalysis showed that Carvedilol had a lower relative risk of failure to achieve hemodynamic response than propranolol. The number of patients who achieved a reduction in HVPG to ⩾ 20% or to ⩽ 12 mmHg was reported in 4 of the 5 studies and was also markedly higher with carvedilol *vs* propranolol (57/94 *vs* 33/87). However, this favourable difference for carvedilol did not reach statistical significance.

Carvedilol caused more reduction in arterial blood pressure resulting in orthostatic hypotension as compared to propranolol. Propranolol caused a - 6.66 mmHg (95%CI: -10.17--3.15) mean reduction in arterial pressure whereas carvedilol caused a mean reduction of -10.40 (95%CI: -13.9--6.9). The reduction in mean arterial pressure was found to be significant

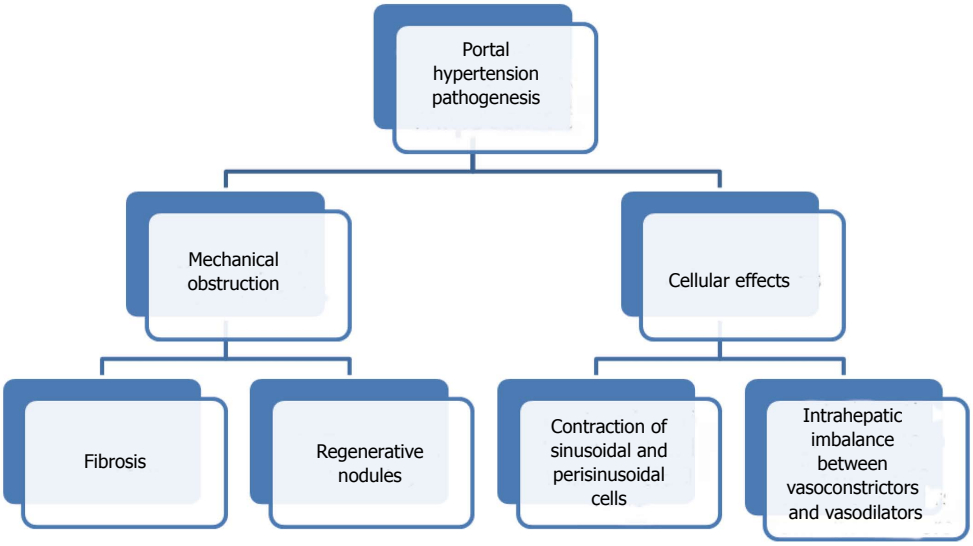

Figure 1 Pathogenesis of portal hypertension.

with both drugs, but the degree of reduction was in the order of one-third more with carvedilol compared to propranolol[17] (Figure 2).

Therefore carvedilol has been shown to be superior to propranolol in causing of acute, long-term and overall reduction of the hepatic venous pressure gradient, *i.e.*, portal venous pressure. The proportion of patients who demonstrated an adequate response is also higher for carvedilol.

Although the translation of these effects in terms of clinical benefit of reduced gastrointestinal bleeding events is significant, these changes in hemodynamic parameters come at the cost of orthostatic hypotension and fluid retention including ascites, with the use of carvedilol. However carvedilol can be a safe alternative in patients who are not hypotensive. In addition carvedilol has achieved significant hemodynamic response in more than half of the patients who were resistant to propranolol[23].

CLINICAL EFFECTS

Variceal bleeding

Pre-primary prophylaxis: Prevention of development of varices in patients with portal hypertension is known as pre-primary prophylaxis. Experimental models of portal hypertension have shown that B-Blockers delay the development of collaterals[24,25]. Escorsell *et al*[26] demonstrated that administration of β-blockers (timolol) to patients without varices caused a greater reduction in portal pressure than the reduction seen in patients with varices[26]. However this effect of use of timolol did not translate into prevention of variceal formation and variceal hemorrhage in a randomised study by Groszmann *et al*[27] which compared timolol with placebo in patients without varices. The study by Calés *et al*[28] using propranolol, for pre-primary prophylaxis did not show clinical benefit in terms of variceal development. To-date there were no studies using carvedilol for pre-primary prophylaxis.

Due to lack of any demonstrated clinical benefits of β-blockers in patients with portal hypertension without varices and adverse effects of these medications, none of the current guidelines (including Baveno V consensus[2], AASLD[29], and EASL/AASLD consensus[30]) recommend their use for pre-primary prophylaxis.

Primary prophylaxis: NSBB are recommended for use in primary prevention of variceal bleeding, as they have been associated with decrease in incidence of first bleeding episode and mortality benefits[2].

A meta-analysis of published randomised controlled trials on primary prophylaxis including 1859 patients, revealed pooled risk difference of 11% in incidence of variceal bleeding with use of propranolol against controls[31]. In another meta-analysis, D'Amico *et al*[32] demonstrated that in patients with varices of any size, β-blockers reduced the risk of a first bleeding episode from 25% to 15% within 2 years. The absolute risk difference was 9% (15% *vs* 24%) as compared to placebo. Moreover, the absolute risk reduction in mortality was found to be 4% (from 27% to 23%)[32].

Another meta-analyses has reported the usage of Beta blockers as primary prophylaxis to be associated with a 40% reduction in bleeding risk and a trend towards improved survival[33]. In a double-blind randomised trial, the Boston-New Haven-Barcelona Portal Hypertension Study Group compared propranolol with placebo for primary prophylaxis. There was significant difference in incidence of bleeding between the study groups favouring propranolol (incidence of bleeding 4% *vs* 22%; $P \leqslant 0.01$) during a mean follow-up of 16 mo. However there was no difference in mortality rates between the two groups[34].

Propranolol has been compared to esophageal band ligation (EBL) in terms of bleeding prevention

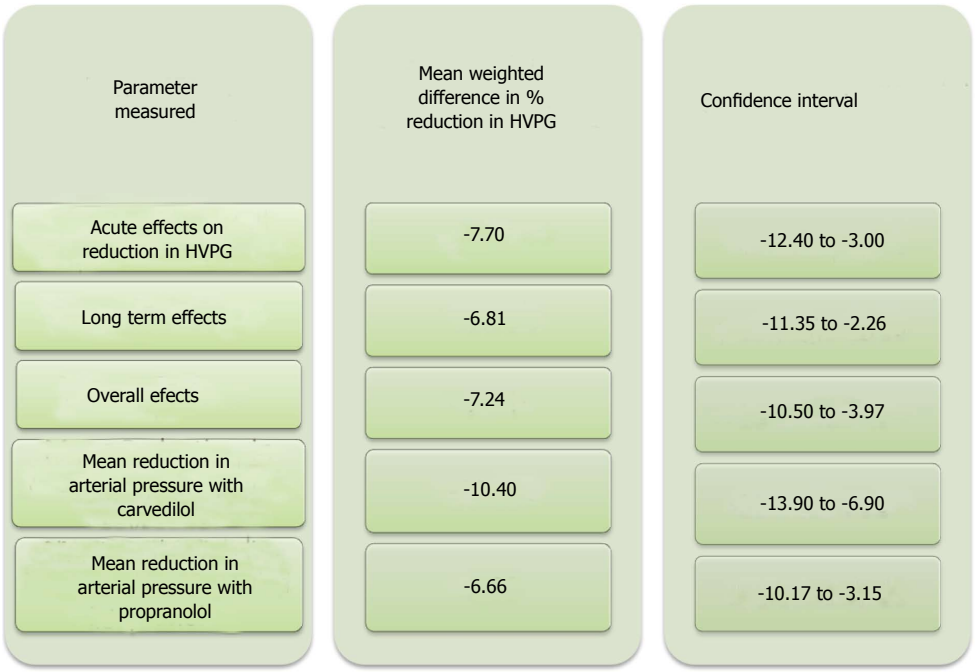

Figure 2 Hemodynamic effect of carvedilol compared to propranolol (Data from ref.[19]). HVPG: Hepatic venous pressure gradient.

and mortality reduction in patients with cirrhosis in several randomised controlled trials. A meta-analysis of sixteen randomised controlled trials found EBL causing significant reduction of the risk of first variceal bleeding compared to propranolol (relative risk difference 9.2%, 95%CI: 5.2%-13.1%, and POR 0.5, 95%CI: 0.37–0.68). However there was no statistically significant difference in Mortality between the two groups (POR 0.94, 95%CI: 0.70-1.28). On average, 3 endoscopic sessions were required to eradicate varices and at least 33 endoscopic procedures were needed to prevent one bleeding episode as compared with NSBBs[35]. However as NSBB are cheap, as haemodynamic monitoring is not required[36].

In a randomized control trial, Carvedilol has been compared with EBL and showed a significantly lower rate of first variceal bleeding (with minor adverse effects) in patients taking carvedilol 12.5 mg daily compared with EBL (10% *vs* 23%, HR = 0.41, 95%CI: 0.19-0.96)[37]. The lowest dose of carvedilol tested in this trial was 12.5 mg, which is known to cause a smaller reduction in HVPG than to actually cause prevention of first bleeding episode. So the results of this study need to be interpreted after considering its limitations[38].

Another randomised controlled trial by Shah *et al*[39] reported that both EBL and carvedilol groups had comparable variceal bleeding rates (8.5% *vs* 6.9%), bleeding related mortality (4.6% *vs* 4.9%) and overall mortality (12.8% *vs* 19.5%) respectively[39]. Although the study was underpowered, the authors suspect that carvedilol is not superior to EBL for primary prophylaxis of varices.

Use of carvedilol has been found to cause reduction of HVPG in patients failing to respond to propranolol, thus leading to lesser bleeding episodes in this group of patients. Bleeding rates followed up for 2 years were 11% with propranolol *vs* 5% with carvedilol and 25% with EBL (P = 0.0429)[23]. We did not find any studies comparing propranolol with carvedilol head-to-head for primary prevention.

Secondary prophylaxis: Secondary prophylaxis is prevention of recurrence after index variceal bleeding episode. The 1-year mortality after an episode of variceal bleeding is 40%[11]. Variceal bleeding recurs in 60% at 1-year with 6-wk mortality of 20% for every re-bleeding episode[2]. NSBBs have been widely used for prevention of re-bleeding and have been shown to decrease the rate of re-bleeding from varices to 42%, as compared to 63% in controls in several meta-analyses[32]. In addition these agents decrease overall mortality from 27% to 20%, and bleeding related mortality[40].

Carvedilol was compared with combination of nadolol and isosorbide-5-mononitrate in a randomized controlled trial in patients who previously had variceal bleeding. This study demonstrated that after a follow-up of 30 mo there was no significant difference in incidence of recurrent upper gastrointestinal bleeding between carvedilol and combination groups (62% *vs* 61%; P = 0.90). There was no significant difference between the Rate of recurrence of variceal bleeding between the carvedilol and combination groups (51% *vs* 43%; P = 0.46)[41]. Interim analysis of a multicentre randomised controlled study comparing carvedilol with endoscopic band ligation for secondary prevention of variceal bleeding, demonstrated no significant

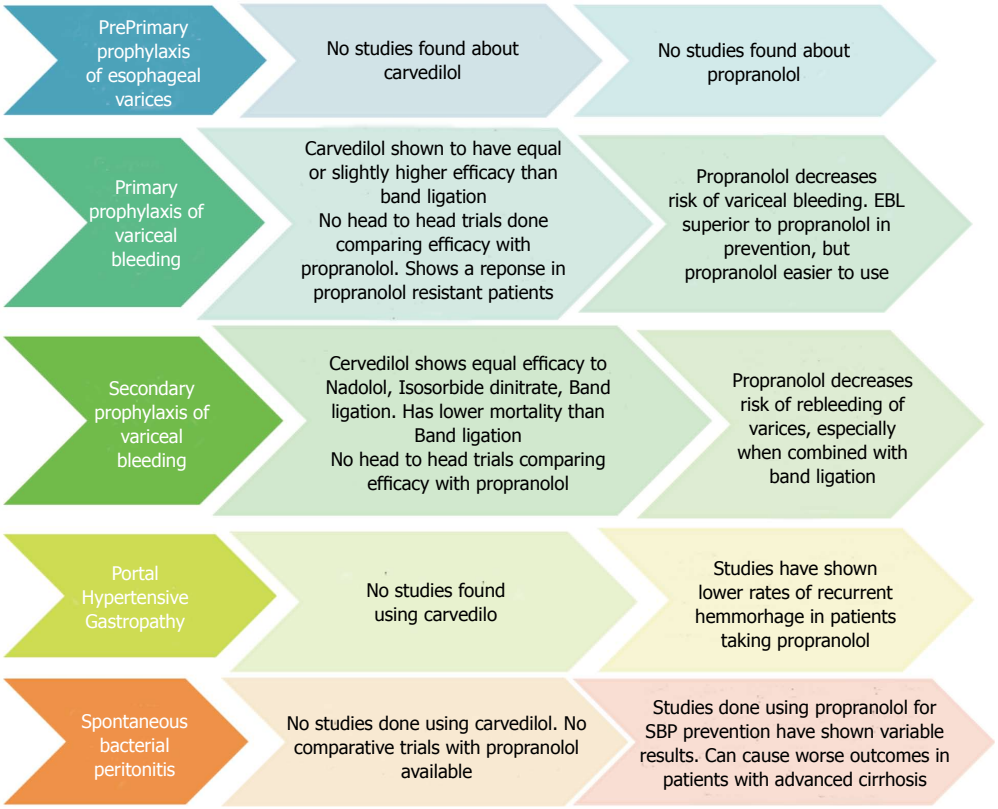

Figure 3 Current evidence about carvedilol and propranolol as prophylactic therapy.

difference between the groups in re-bleeding rates (37.5% *vs* 29%; $P = 0.72$). However the patients in carvedilol group had lower 1-year mortality rates as compared to EBL group (25% *vs* 51.6%; $P = 0.058$)[42].

The pioneer trial by Pagliaro *et al*[8] demonstrated that propranolol was effective in decreasing the incidence of variceal re-bleeding when compared to controls. A comprehensive meta-analysis of 12 randomised controlled trials for secondary prophylaxis of variceal bleeding showed that, use of β-blockers (11 using propranolol) was associated with increase in mean percentage of patients with no re-bleeding (21% mean improvement rate, 95%CI: 10%-32%, $P < 0.001$), the mean percentage of patients with no variceal re-bleeding (20% mean improvement rate, 95%CI: 11%-28%, $P < 0.001$), the mean survival rate (5.4% mean improvement rate, 95%CI: 0%-11%, $P < 0.05$, RR = 1.27), the mean percentage of patients free of bleeding death (7.4%, 95%CI: 2%-13%, $P < 0.01$, RR = 1.50)[40].

Baveno V consensus guidelines recommend a combination of β-blockers and variceal band ligation as the preferred therapy for secondary prophylaxis because it results in lower re-bleeding rates compared to either therapy alone[2]. Ahmad *et al*[43] compared combination of EBL and propranolol against propranolol for secondary prevention and found no statistical difference in re-bleeding (22% *vs* 38%) and mortality rates (23% *vs* 19%) between the groups. However the incidence of re-bleeding was higher in patients on propranolol alone[43].

Propranolol retains its place as the most widely used and studied drug for secondary prophylaxis with clear benefits as compared to placebo and combination with EBL. The evidence for carvedilol in variceal rebleeding recurrence is minimal but promising.

Portal gastropathy

Described as mosaic, snake-skin-like appearance of gastric mucosa with or without red punctuate erythema, portal hypertensive gastropathy (PHG) is estimated to be present in up to 80% of cirrhotic patients[44]. PHG can cause acute bleeding rarely with an incidence of 3% in three years, and in 2.5%-30% patients it may result in chronic insidious bleeding[45,46].

NSBBs have been shown to lower the incidence of bleeding in acute and chronic forms of haemorrhage from PHG. One of the earliest randomised controlled trials using propranolol showed lower haemorrhage rates, increase in haemoglobin level and an apparent improvement in the endoscopic appearance of the lesion when compared to placebo[47]. Pérez-Ayuso *et al*[12], in a randomised trial of used propranolol against no therapy in patients for secondary prophylaxis of bleeding from PHG. The study demonstrated higher number of patients remaining free of bleeding with propranolol in acute (85% *vs* 20%) and chronic setting (69% *vs* 30% at 30 mo). On multivariate analysis, the sole independent predictor of recurrent haemorrhage was the absence of propranolol[12].

Although the use of β-blockers for PHG is widespread, based upon current evidence strong recommendations can't be made for NSBB for this indication. We also did not find any studies using carvedilol to control bleeding from portal gastropathy.

Spontaneous bacterial peritonitis

NSBBs have been shown to have preventive effect on development of spontaneous bacterial peritonitis in a meta-analysis by Senzolo *et al*[13]. This analysis included three randomised controlled trials and two retrospective studies all using propranolol for prophylaxis of variceal bleeding, with respect to the incidence of SBP. Statistically significant difference of 12.1% ($P < 0.001$) was found in favour of propranolol in prevention of SBP.

A recently published thorough retrospective analysis of data from 607 patients with cirrhosis by Mandorfer *et al*[48] demonstrated no difference in incidence of SBP between NSBB users and patients who did not. Occurrence rates of SBP were similar between patients with and without NSBB treatment. However, NSBB use was associated with higher transplant-free survival in patients without SBP and reduced hospitalization rates[48].

In contrast, Mandorfer *et al*[48] demonstrated that in patients who have developed SBP, NSBB were associated with hemodynamic compromise and decreased blood pressures, reduced transplant free survival, increased hospitalization rates, and increased incidence of the hepatorenal syndrome and acute kidney injury. In another study, using a NSBB (propranolol) in patients with refractory ascites was found to reduce 1-year survival against those not using this drug (median survival: 5 mo *vs* 20 mo respectively)[49]. These results advocate against the use of NSBB in patients with advanced cirrhosis with ascites and SBP.

To conclude, the current evidence is variable about the role of NSBB in decreasing the incidence of SBP. However they can increase transplant-free survival in patients without SBP. In cases of advanced cirrhosis with ascites and the patients who have developed SBP, their use proves detrimental causing higher rates of hemodynamic compromise, time of hospitalization and risks of renal dysfunction. All the studies on NSBB use for SBP have used propranolol. We did not find any study about the use of carvedilol in patients with advanced cirrhosis and SBP, nor a head-to-head comparison of propranolol and carvedilol in this regard.

CONCLUSION

After reviewing the existing literature, it seems that Carvedilol has more potent desired physiological effects when compared to Propranolol. However, it is uncertain at the present juncture whether the improvement in hemodynamics also translates into a decreased rate of disease progression and complications when compared to propranolol (Figure 3).

There have been no clinical trials comparing carvedilol and propranolol for pre-primary prophylaxis. For Primary prophylaxis, the effects of Carvedilol have been compared to Endoscopic band ligation in a few trials and show some promise, but there has been no head to head comparison with propranolol. However, patients not responding to propranolol have shown clinical response to Carvedilol, opening a new window of clinical application.

For secondary prophylaxis, carvedilol has been compared to Beta blockers other than propranolol and Endoscopic Band Ligation, and seems to be equally effective. However, the most effective therapy to date remains a combination of Endoscopic Band Ligation, and no head to head trials have been conducted comparing carvedilol with propranolol. Similarly, there have been no trials exploring the role of carvedilol in portal hypertensive gastropathy and spontaneous bacterial peritonitis.

Thus, currently Carvedilol shows promise as a therapy for portal hypertension but more clinical trials need to be carried out before we can consider it as a superior option and a replacement for propranolol.

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ORIGINAL ARTICLE

Clinical Trials Study

Tripartite comparison of single-incision and conventional laparoscopy in cholecystectomy: A multicenter trial

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Data sharing: No additional data are available.

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Abstract

AIM: To compare the characteristics of two single-incision methods, and conventional laparoscopy in cholecystectomy, and demonstrate the safety and feasibility.

METHODS: Three hundred patients with gallstones or gallbladder polyps were admitted to two clinical centers from January 2013 to January 2014 and were randomized into three groups of 100: single-incision three-device group, X-Cone group, and conventional group. The operative time, intraoperative blood loss, complications, postoperative pain, cosmetic score, length of hospitalization, and hospital costs were compared, with a follow-up duration of 1 mo.

RESULTS: A total of 142 males (47%) and 158 females (53%) were enrolled in this study. The population characteristics of these three groups is no significant differences exist in terms of age, sex, body mass index and American Society of Anesthesiology (P > 0.05). In results, there were no significant differences in blood loss, length of hospitalization, postoperative complications.The operative time in X-Cone group was significantly longer than other groups.There were significant differences in postoperative pain scores and cosmetic scores at diffent times after surgery (P < 0.05).

CONCLUSION: This study shows that this two single-incision methods are safe and feasible. Both methods are superior to the conventional procedure in cosmetic and pain scores.

Key words: Cholecystectomy; Laparoscopic surgery; Single-incision laparoscopic cholecystectomy

Core tip: This is an article about single-incision laparoscopic surgery. It compares three methods in laparoscopic cholecystectomy. The study concludes that the three-device and X-Cone methods are safe and feasible for single-incision laparoscopic cholecystectomy. Compared with conventional laparoscopic cholecystectomy, single-incision laparoscopic surgery techniques have advantages in pain and cosmetic factors.

He GL, Jiang ZS, Cheng Y, Lai QB, Zhou CJ, Liu HY, Gao Y, Pan MX, Jian ZX. Tripartite comparison of single-incision and conventional laparoscopy in cholecystectomy: A multicenter trial. *World J Gastrointest Endosc* 2015; 7(5): 540-546 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i5/540.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i5.540

INTRODUCTION

Single-incision laparoscopic surgery (SILS) is an area of research interest in minimally invasive surgery. Its main advantage is a scar-free abdominal wall after surgery, as well as milder postoperative pain, faster recovery, shorter hospital stay, and better cosmetic outcomes. Since the first report of single-incision resection of gallbladder through the abdominal cavity by Navarra *et al*[1] in 1997, there has been a growing number of clinical reports on this topic[2-10]. At present, a variety of auxiliary means are used, such as the X-Cone method, triport method, Kirschner-aid exposure method, suspension sutures method, and three-device method[11-16]. However, there has been no comparative study of the various methods.

We enrolled 200 cases of laparoscopic cholecystectomy completed using the three-device and X-Cone methods in our two centers, as well as 100 cases of conventional laparoscopic cholecystectomy, to compare their technical characteristics and clinical outcomes, and demonstrate the safety and feasibility of the single-incision methods.

MATERIALS AND METHODS

Patients

Inclusion criteria were: patients with gallstones or gallbladder polyps; age 18-85 years; either sex; and body mass index (BMI) < 35 kg/m^2. Exclusion criteria were: complication by common bile duct or intrahepatic bile duct stones; acute cholecystitis; suspicion of complicated cholecystitis; BMI $\geqslant$ 35 kg/m^2; drug addiction; ASA physical classification > 3; previous upper abdominal surgery; pregnancy; presence of umbilical hernia; or previous umbilical hernia repair.

All 300 patients were admitted to the two clinical centers for laparoscopic cholecystectomy from January 2013 to January 2014. They were randomly assigned to three groups of 100. The case characteristics are shown in Table 1. All surgery was performed by three surgeons, each of whom had conducted > 1000 cholecystectomies, including $\geqslant$ 100 single-incision laparoscopic cholecystectomies.

The primary end points of this study were feasibility and safety of the three-device method and X-Cone method compared with conventional laparoscopic cholecystectomy, as indicated by intraoperative and postoperative adverse events up to 1 mo, operative time, and estimated blood loss. The secondary end points were: (1) pain as determined by a 10-point pain intensity scale performed at days 1 and 2, 1 wk, and 1 mo; (2) cosmesis evaluated *via* a body image questionnaire, photo series questionnaire, and cosmesis scale performed at 1 and 2 wk, and 1 mo; and (3) length of hospital stay and hospital costs.

Surgical methods

Umbilical disinfection was completed 1 d before surgery. Following routine anesthesia with tracheal intubation, second-generation cephalosporin was intraoperatively administered once. After pneumoperitoneum was established in patients undergoing three-device or conventional surgery, the patients were placed with their legs closed in the Trendelenburg position at approximately 30°, left tilted at approximately 20°. The surgeons stood on the left side of the patient, with the monitor on the right side. For patients undergoing X-Cone surgery, the legs were placed apart in the Trendelenburg position at approximately 30°, left tilted approximately 20°. The surgeons stood between the legs with the monitor on the patient's head side.

General anesthesia was induced with propofol (2 mg/kg) and sufentanil (0.5-2 μg/kg). Tracheal intubation facilitated by injection of Atracurium (0.5 mg/kg). Anesthesia during surgery was maintained with isoflurane 1.2% and administration of Atracurium (0.1 mg/kg) and sufentanil (0.1 μg/kg) and every 30 min. The patients were monitored by ECG, pulse oximetry, noninvasive blood pressure. Patients were recovered by administration of neostigmine (40 μg/kg) and atropine (20 μg/kg).

Three-device method: The umbilical incision was approximately 2.0 cm. Three trocars were directly placed into the incision. The locations are shown in Figure 1. The inferior 10-mm trocar was for insertion of the 30° laparoscope, while the two 5-mm trocars above were working ports for the scalpel and forceps,

Table 1 General data of the patients

	X-Cone method (n = 100) (No.1 group)	Three-device method (n = 100) (No.2 group)	Conventional method (n = 100) (No.3 group)	P value	Statistical methods and values
Sex					
Male	47	44	52		$\chi^2 = 1.31$
Female	53	56	48		
Age (yr)	39.5 ± 14.5	40.0 ± 12.5	41.7 ± 12.0	0.465	One-Way ANOVA F = 0.768
BMI (kg/m^2)	26.1 ± 5.5	28.2 ± 7.5	26.1 ± 8.4	0.06	One-Way ANOVA F = 2.847
Surgical risk grade (ASA)	1.6 ± 0.5	1.6 ± 0.4	1.6 ± 0.4	0.681	One-Way ANOVA F = 0.385
Diagnosis					
Stones	58	52	47		$\chi^2 = 2.43$
Polyps	42	48	53		

ASA: American society of anesthesiology; BMI: Body mass index.

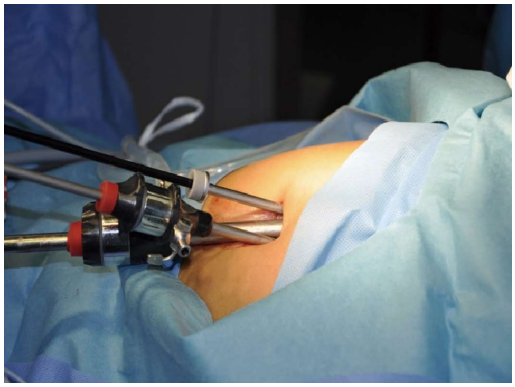

Figure 1 Diagram of the three-device method.

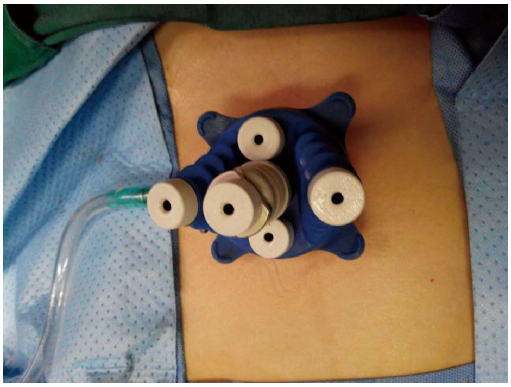

Figure 2 Device for the X-Cone method.

respectively. There was 1-2 mm of tissue between the three trocars to prevent leakage. The cystic artery was directly cut with the ultrasonic scalpel, and the cystic duct was closed with a 5-mm Hem-o-lok titanium clamp and transected with scissors. If the 5-mm Hem-o-lok was too small for the occlusion, the 5-mm trocar in the right working port was replaced with a 10-mm one for placement of a 10-mm Hem-o-lok. Once there was no abnormality of the abdomen, the gallbladder was removed. All equipment was removed first, and a pair of vessel forceps was inserted into the original 10-mm trocar to enlarge the incision in the abdominal cavity, and grasping forceps and a 10-mm trocar laparoscope were in turn placed to extract the gallbladder as a whole. The umbilicus white line was closed with a 3-0 Polysorb absorbable suture, and the umbilical skin incisions intradermally closed with absorbable sutures.

X-Cone method: A 3.0-cm curved incision was made around the upper or lower edge of the umbilicus. The subcutaneous tissue and anterior sheath were divided and the posterior sheath separated. As the middle space was pulled with hemostatic forceps, the X-Cone device (Karl Storz, Tuttlingen, Germany) was inserted (Figure 2). Pneumoperitoneum up to 12 mmHg was established through the pole of the X-Cone, and a 5-mm 30° laparoscope was inserted. The clamp and scalpel were placed into the other two ports. The surgeon pulled the gallbladder with curved traction forceps in the left hand and resected the gallbladder triangle with the ultrasonic scalpel in the right hand. The cystic artery was directly separated with the scalpel. After separation of the cystic duct, a 5 or 10-mm Hem-o-lok was used to close it and the cystic duct was then cut with scissors. The gallbladder was then removed as a whole from the gallbladder bed. The gallbladder was taken directly from the umbilical port. The umbilicus white line was closed with a 3-0 Polysorb absorbable suture, and the umbilical skin incisions intradermally closed with absorbable sutures.

Conventional method: A curved incision of 1.0 cm was made at the umbilical lower edge, an incision of 1.0-1.2 cm was made below the xiphoid, and a 0.5-cm incision was made 1-2 cm above the right clavicular line at the umbilical level. Two 10-mm trocars and one 5-mm trocar were placed into these incisions. The 10-mm umbilical trocar was for placement of the laparoscope, and the other two were working ports for placement of the ultrasonic scalpel and forceps.

Postoperative care: After completion of surgery in all three groups, the incisions were treated with a 50% dose of 75 mg ropivacaine for local anesthesia. Subsequently, the patients were extubated and closely

Table 2 Surgical data of the three groups

	X-Cone method (n = 100) (No.1 group)	Three-device method (n = 100) (No.2 group)	Conventional method (n = 100) (No.3 group)	P values	Statistical methods and values
Operative time (min)	56.3 ± 14.0	45.6 ± 12.0	42.1 ± 11.0	0.000 G1 *vs* G2 0.000 G1 *vs* G3 0.000 G2 *vs* G3 0.111	One-Way ANOVA F = 36.86
Blood loss[1] (mL)	16.4 ± 3.7	17.1 ± 4.5	15.8 ± 4.7	0.089	One-Way ANOVA F = 2.439
Conversion to multiple-incision LC	1	2	0	0.776	Fisher exact test
Complications					
Incision contusion	3	4	1	0.543	Fisher exact test
Wound infection	1	1	3	0.625	Fisher exact test
Bile duct injury	0	0	0	1.0	Fisher exact test
Bile leakage	2	2	1	1.0	Fisher exact test
Abdominal infection	0	0	0	1.0	Fisher exact test
Postoperative hospital stay (d)	1.66 ± 0.5	1.69 ± 0.5	1.68 ± 0.4	0.928	One-Way ANOVA F = 0.075
Hospital costs	11658 ± 1435	10406 ± 1246	10036 ± 1154	0.000 G1 *vs* G2 0.000 G1 *vs* G3 0.000 G2 *vs* G3 0.415	One-Way ANOVA F = 52.66

[1]Estimated intraoperative blood loss; LC: Laparoscopic cholecystectomy.

observed in the postanesthetic care unit and then transferred to the surgical ward once their Aldrete score was ⩾ 9. Postoperative electrocardiography was performed and oxygen was administered for 6 h, in combination with rehydration and bleeding control, as well as other fluid replacement. Liquid food and ambulation were allowed 6 h after surgery. In the postoperative period, Intravenous rotundine sulfate, at a dose of 1 mg/kg was administered according to patient request every 12 h until discharge home. Surgical dressings were changed on the first day after surgery. The patients were discharged on the second day after surgery. They were also asked to return for check-up at 1, 2 wk and 1 mo after surgery.

Statistical analysis

Data were analyzed using SPSS version 13 (Chicago, IL, United States). Base on Kolmogorov-Smirnov test, operative time, estimated blood loss, postoperative hospital stay, pain scores and cosmetic scores were all summarized using mean ± SD and compared among the 3 groups by using the One-Way ANOVA test (Tukey method). Intraoperative and postoperative adverse events was compared among the three procedures by Fisher exact test. χ^2 tests were performed to explore the effects of sex, and the clinical diagnosis. A value of $P < 0.05$ was considered to indicate significance.

RESULTS

A total of 300 patients were enrolled in this study and assigned to three groups of 100: three-device, X-Cone method, and conventional method. There were no significant differences in age, sex, BMI and ASA among the groups. The operation time, blood loss and complications are listed in Table 2. There were no significant differences in blood loss and postoperative hospital stay. The X-Cone method required longer operation time compared to the conventional (56.3 min *vs* 42.1 min, P = 0.000) and three-device methods (56.3 min *vs* 45.6 min, P = 0.000), while the latter two did not differ significantly in this regard (42.1 min *vs* 45.6 min, P = 0.111). Hospitalization costs were higher in the X-Cone group than the three-device group (P = 0.000) and the conventional group (P = 0.000). The conventional group was the cheapest group in the three groups.

In the X-Cone group, there were three cases of surgical incision contusion, and one case of wound hematoma. In the three-device group, two patients required additional working ports due to severe inflammatory adhesions, and there were four cases of incision contusion. In the conventional method group, all patients were successfully operated, and there were one case of incision contusion and three cases of incision wound infection under the xiphoid. No patient converted to laparotomy, and there was no serious complication such as bile duct injury or bile peritonitis. There was no postoperative bleeding or conversion to laparotomy. Percutaneous incision suture was successful without umbilical hernia.

The pain and cosmetic scores are listed in Table 3. The pain score was evaluated using a visual analog scale of 1-10 on days 1, 2 and 7, as well as 1 mo after surgery. There were differences in the pain scores on day 1 between the single-incision methods and

Table 3 Pain and cosmetic scores among the three groups

	X-Cone method (n = 100) (No.1 group)	Three-device method (n = 100) (No.2 group)	Conventional method (n = 100) (No.3 group)	P values	Statistical methods and values
Pain score[1]					One-Way ANOVA
1 d after surgery	3.4 ± 1.2	3.6 ± 1.2	4.2 ± 1.1	0	
				G1 *vs* G2 0.296	F = 11.16
				G1 *vs* G3 0.000	
				G2 *vs* G3 0.005	
2 d after surgery	2.8 ± 0.8	3.0 ± 1.0	3.2 ± 1.0	0.002	F = 6.34
				G1 *vs* G2 0.155	
				G1 *vs* G3 0.001	
				G2 *vs* G3 0.204	
7 d after surgery	2.2 ± 0.6	2.0 ± 0.6	2.3 ± 0.7	0.014	F = 4.35
				G1 *vs* G2 0.252	
				G1 *vs* G3 0.365	
				G2 *vs* G3 0.010	
1 mo after surgery	1.6 ± 0.4	1.5 ± 0.3	1.7 ± 0.5	0	F = 9.435
				G1 *vs* G2 0.123	
				G1 *vs* G3 0.048	
				G2 *vs* G3 0.000	
Cosmetic score[2]					
1 wk after surgery	8 ± 0.7	8 ± 0.5	6 ± 0.4	0	F = 423.61
				G1 *vs* G2 0.999	
				G1 *vs* G3 0.000	
				G2 *vs* G3 0.000	
2 wk after surgery	8 ± 0.8	8 ± 0.6	7 ± 0.3	0	F = 93.67
				G1 *vs* G2 0.966	
				G1 *vs* G3 0.000	
				G2 *vs* G3 0.000	
1 mo after surgery	9 ± 0.2	9 ± 0.3	8 ± 0.5	0	F = 308.9
				G1 *vs* G2 0.814	
				G1 *vs* G3 0.000	
				G2 *vs* G3 0.000	

[1]Pain score 1-10; [2]Cosmetic score 1-10.

the conventional method in favor of the former (P < 0.0001), there was no difference between the two single-incision methods (P = 0.296). The X-Cone group was the most comfortable on day 2, while the three-device group on day 7 after surgery. At 1 mo, single-incision methods were better than the conventional method.

The cosmetic scores were rated on a 1–10 scale with questionnaires, with 10 being satisfied and 0 being unsatisfied. At 1 wk (P = 0.000), 2 wk (P = 0.000) and 1 mo (P = 0.000) after surgery, the single-incision methods were significantly better than the conventional group in terms of cosmetic scores. The X-Cone group and the three-device group had no differences (P > 0.05).

DISCUSSION

SILS techniques have been extensively applied both at home and abroad in recent years[7,11,17-20]. It is performed using a 1-wound laparoscopic surgical procedure or by using speciic ports[21-24].Compared with conventional laparoscopic cholecystectomy, they are associated with fewer injuries and better cosmetic outcomes, as well as many other advantages[25-29]. Some investigators believe that single-incision laparoscopic cholecystectomy will replace conventional laparoscopic cholecystectomy, and become the new gold standard[13,14].

This was an unplanned preliminary analysis of a continuing clinical trial to establish the safety of SILS as an operative approach for treatment of gallbladder disease. This article presents preliminary data of a multicenter, prospective randomized, single-blinded study comparing two single-incision cholecystectomy (three-device and X-Cone methods) with conventional standard multiport laparoscopic cholecystectomy. Primary end points included feasibility and safety, with pain, cosmesis, and costs as secondary end points.

In terms of feasibility and safety, except for the two patients who had additional working ports due to severe inflammatory adhesions in the three-device group, all patients underwent surgery successfully. None of the 200 patients converted to laparotomy or had complications such as bile duct injury, suggesting that single-incision laparoscopic cholecystectomy was feasible and safe. The low conversion rate may differ from that in other studies[18,30], which was probably due to the fact that patients with acute cholecystitis were excluded from our study. There were no significant differences in the complication rates among the three groups. There were four cases of incision contusion in

the three-device group, and three and one cases in the X-Cone and conventional groups, respectively. To avoid conflict of instruments in the abdominal cavity with the single-incision method, repeated external squeezing of the surrounding tissue is often required, which may explain the incision contusion in the three-device and X-Cone groups. In addition, there were different numbers of cases of bile leakage in all groups, which were treated with repeated rinsing with saline until the liquid turned clear. There was no case of biliary peritonitis infection afterwards.

There was no significant difference in blood loss and postoperative hospital stay. The X-Cone method required a longer operation time compared to the conventional (56.3 min *vs* 42.1 min, $P = 0.000$) and three-device methods (56.3 min *vs* 45.6 min, $P = 0.000$). Although all three surgeons had conducted > 100 cases of gallbladder SILS, the X-Cone procedure was associated with inconvenient operation across multiple ports and conflicting handling of instruments such as curved apparatus and solid textures, which might have extended the operation time. In contrast, the three-device method and conventional technique did not differ significantly in this regard (45.6 min *vs* 42.1 min, $P = 0.111$). The space between the instruments in the three-device method comprises soft subcutaneous tissue, which allows for a wider range of motion for the instruments, which is conducive to surgery.

Regarding the pain and cosmetic scores, there were differences between the single-incision methods and the conventional method in the pain score on day 1 after surgery, in favor of the single-incision methods. The main complaint was pain below the xiphoid incision in the conventional group. As the pain scores declined on days 2 and 7, as well as 1 mo after surgery, the differences became insignificant. At 1 and 2 wk and 1 mo after surgery, the single-incision methods were significantly better than the conventional group in terms of cosmetic scores. No difference was noted between the three device and X-Cone methods.

There was no difference in the hospitalization costs between the three-device and conventional methods, but there was when compared with the X-Cone method, suggesting that the latter method had an impact on the overall hospital costs. In three-device techniques, conventional equipment and devices were used, resulting in no cost difference from the conventional method, so the three-device method has a more cost-effective. Hence, the three-device approach is more suitable for community hospitals in China.

The present study had the following limitations. First, patients with acute cholecystitis were excluded, and this explains the low laparotomy conversion and low complication rates. Second, although all three surgeons had conducted > 100 operations for gallbladder SILS, the X-Cone procedure was associated with inconvenient operation across multiple ports and conflicting handling of instruments such as curved apparatus and solid textures, which might have extended the operation time. Both of these limitations are routinely seen when a new technique is evaluated. Also, long-term complications were not addressed by this study. The frequency of events still needs to be evaluated by long-term trials.

In summary, both the three-device and X-Cone methods are safe and feasible for single-incision laparoscopic cholecystectomy. Compared with conventional laparoscopic cholecystectomy, SILS techniques have advantages in pain and cosmetic factors. Due to its use of conventional instruments and cost-effective nature, the three-device method is more suitable for community hospitals in China, while the X-Cone device, which allows the placement of more surgical instruments, is more advantageous in more complicated procedures such as laparoscopic liver resection.

COMMENTS

Background

Single-incision laparoscopic cholecystectomy is a new laparoscopic procedure in laparoscopic surgery. This technique has been denominated by some authors as "scarless". The best advantage is a scar-free abdominal wall after surgery, as well as milder postoperative pain, faster recovery, shorter hospital stay, and better cosmetic outcomes.

Research frontiers

It is a lot of studies about the single-incision laparoscopic surgery (SILS). But there has been no previous reported study of the comparison of these three methods in cholecystectomy.

Innovations and breakthroughs

In this study, the three-device and X-Cone methods are safe and feasible for single-incision laparoscopic cholecystectomy. Compared with conventional laparoscopic cholecystectomy, SILS techniques have advantages in pain and cosmetic factors.

Applications

These two SILS techniques were used more and more in different hospitals. Further study is needed to confirm whether these potential advantages of the SILS techniques can change the clinical course of patients with liver surgery.

Peer-review

This is a very interesting paper about the SILS in cholecystectomy. The most important innovations of this study that was applied in the manuscript is the comparison of three methods in cholecystectomy. In addition, it demonstated that single-incision three-device and X-Cone methods are safe and feasible for laparoscopic cholecystectomy.

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ORIGINAL ARTICLE

Observational Study

Biliary leakage after urgent cholecystectomy: Optimization of endoscopic treatment

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Abstract

AIM: To investigate the results of endoscopic treatment of postoperative biliary leakage occurring after urgent cholecystectomy with a long-term follow-up.

METHODS: This is an observational database study conducted in a tertiary care center. All consecutive patients who underwent endoscopic retrograde cholangiography (ERC) for presumed postoperative biliary leakage after urgent cholecystectomy in the period between April 2008 and April 2013 were considered for this study. Patients with bile duct transection and biliary strictures were excluded. Biliary leakage was suspected in the case of bile appearance from either percutaneous drainage of abdominal collection or abdominal drain placed at the time of cholecystectomy. Procedural and main clinical characteristics of all consecutive patients with postoperative biliary leakage after urgent cholecystectomy, such as indication for cholecystectomy, etiology and type of leakage, ERC findings and post-ERC complications, were collected from our electronic database. All patients in whom the leakage was successfully treated endoscopically were followed-up after they were discharged from the hospital and the main clinical characteristics, laboratory data and common bile duct diameter were electronically recorded.

RESULTS: During a five-year period, biliary leakage was recognized in 2.2% of patients who underwent urgent cholecystectomy. The median time from cholecystectomy to ERC was 6 d (interquartile range, 4-11 d). Endoscopic interventions to manage biliary leakage included biliary stent insertion with or without biliary sphincterotomy. In 23 (77%) patients after first endoscopic treatment bile flow through existing surgical drain ceased within 11 d following biliary therapeutic endoscopy (median, 4 d; interquartile range, 2-8 d). In those patients repeat ERC was not performed and

the biliary stent was removed on gastroscopy. In seven (23%) patients repeat ERC was done within one to fourth week after their first ERC, depending on the extent of the biliary leakage. In two of those patients common bile duct stone was recognized and removed. Three of those seven patients had more complicated clinical course and they were referred to surgery and were excluded from long-term follow-up. The median interval from endoscopic placement of biliary stent to demonstration of resolution of bile leakage for ERC treated patients was 32 d (interquartile range, 28-43 d). Among the patients included in the follow-up (median 30.5 mo, range 7-59 mo), four patients (14.8%) died of severe underlying comorbid illnesses.

CONCLUSION: Our results demonstrate the great efficiency of the endoscopic therapy in the treatment of the patients with biliary leakage after urgent cholecystectomy.

Key words: Urgent cholecystectomy; Acute cholecystitis cholecystectomy complications; Biliary leakage; Endoscopic retrograde cholangiography; Endoscopic treatment

Core tip: Biliary leakage can be a serious complication of urgent cholecystectomy even in the hands of an experienced surgeon. Endoscopic interventions replaced surgery as first-line treatment for most of the biliary ducts injuries and biliary leakage after cholecystectomy. Long-term follow-up results demonstrate the great efficiency of the endoscopic therapy in the treatment of the patients with biliary leakage after urgent cholecystectomy. Early cessation of bile output from the external abdominal drain strongly indicates healing of the leak and in those patients repeat cholangiography is not necessary, particularly if the presenting symptoms and/or signs of the biliary leakage disappeared.

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INTRODUCTION

Biliary leakage can be a serious complication of urgent cholecystectomy even in the hands of an experienced surgeon and can lead to considerable morbidity and prolonged hospitalization. Despite the fact that there are no properly controlled trials which could identify risk factors for bile duct injury, the risk of possible perioperative complications can be estimated based on patient characteristics (commorbidity, age, gender, body weight), intraoperative findings, and the amount of training and experience of the surgeon[1-3]. Large prospective and retrospective studies have defined the risk of biliary leakage arising from either open[4-6] or laparoscopic[6-9] cholecystectomy. The number of occurrences of biliary leaks during open cholecystectomy is not precisely known, but most large series demonstrated rates of 0.5% or less[10,11]. Despite several advantages over the open approach, laparoscopy, particularly in the cases of urgent cholecystectomy, provides a limited view of the biliary tract anatomy and can result in a higher rate of biliary leaking[7]. A two to four-fold increased incidence of biliary leakage following laparoscopic cholecystectomy was demonstrated[6,9,12].

The role of endoscopic retrograde cholangiography (ERC) in the management of biliary leakage is well established. Endoscopic treatment of biliary leakage includes biliary stent insertion with or without biliary sphincterotomy, biliary sphincterotomy alone or nasobiliary tube placement. All those methods have been demonstrated to be effective treatment for biliary leakage without need for further surgery[13-15]. However, the need for an endoscopic sphincterotomy, the choice between nasobiliary tube drainage and endoscopic biliary stenting and the preferable type of stent (short or long stent; larger or smaller diameter) are still the matter of extensive debate. Therefore, optimal endoscopic intervention is still not established and data regarding the long-term follow-up of those patients is missing.

The aim of this study was to determine the results of endoscopic treatment of postoperative biliary leakage occurring after urgent cholecystectomy with a long-term follow-up.

MATERIALS AND METHODS

This is an observational database study conducted in a tertiary care center with primary uptake area covering a population of approximately 300000 people (City of Zagreb, Republic of Croatia). The study was approved by the "Sestre milosrdnice" University Hospital Review Board. All consecutive patients who underwent ERC for presumed postoperative biliary leakage following urgent cholecystectomy between April 2008 and April 2013 were considered for this study. All the patients included in the study signed the informed consent statement. Patients with bile duct transection and biliary strictures were excluded. Biliary leakage was suspected in case of bile appearance from either percutaneous drainage of abdominal collection or abdominal drain placed at the time of cholecystectomy.

Information of all consecutive patients with postoperative biliary leakage, including cholecystectomy details such as indication for cholecystectomy, etiology and type of leakage, ERC findings and post-ERC complications, were reviewed from our electronic database. The grading of overall health and comorbidity

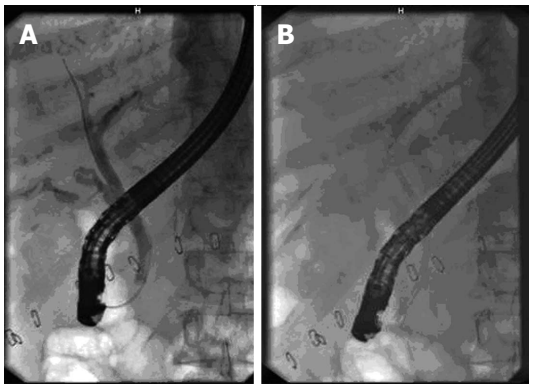

Figure 1 Radiograph at endoscopic retrograde cholangiography. A: Radiograph at endoscopic retrograde cholangiography showing biliary leakage into peritoneum from cystic duct stump; B: Radiograph showing 10 F biliary stent inserted above the level of the leak from cystic duct stump.

was performed according to the American Society of Anesthesiology classification[16]. All ERC successfully treated patients were followed-up after they were discharged from the hospital and the main clinical characteristics and laboratory data, including levels of bilirubin, alanine transaminase (ALT), aspartate aminotransferase, GGT, alkaline phosphatase, CRP and common bile duct diameter measured on transabdominal ultrasound were electronically recorded every month during first 6 mo, then every 6 mo.

ERC was performed with standard equipment (TJF 145, Olympus Optical Co., Japan), and by the well-trained endoscopists, each with at least five-year experience. Selective cannulation of the common bile duct was attempted with a standard wire-guided sphincterotome and 0.035-inch hydrophilic guidewire. If the efforts to enter the common bile duct were unsuccessful, a needle-knife papillotomy was performed. In all patients ERC was performed under intravenous sedation and analgesia (propofol and fentanyl) under direct anesthesiologist control. Pre-procedural antibiotics were administered (ciprofloxacin 400 mg *iv*).

Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis was identified by characteristic abdominal pain associated with serum amylase levels at least three times the upper limits of normal. Postprocedural bleeding was defined as one or more signs of ongoing bleeding, including fresh hematemesis or melena, hematochezia, aspiration of fresh blood *via* nasogastric tube, vital signs instability, and a reduction of hemoglobin level by more than 2 g/dL over a 24-h period.

In all patients with a cholangiographic evidence of a biliary leakage the placement of a plastic 10 F biliary stent without biliary sphincterotomy was performed. The standard procedure was to place proximal end of a biliary stent above the level of the leak in patients with the cholangiographic evidence of a leakage from the common bile duct or from cystic duct stump or cholecystohepatic duct of Luschka (Figure 1). If biliary leakage from the right hepatic duct or intrahepatic duct was confirmed, and in patients in whom biliary leakage was not located, only short plastic 10F biliary stent was inserted. In patients with a cholangiographic evidence of a biliary leakage and a common bile duct stone(s), biliary sphincterotomy was performed and after the stone was removed (with balloon catheter or Dormia basket), plastic 10F biliary stent was placed.

The clinical healing of the biliary leakage was determined by the complete absence of the symptoms, cessation of the output of the bile from the drain and by the removal of the drain without any further adverse outcomes. The failure of the endoscopic treatment was determined by the need for further intervention to control the leak including surgery and/or percutaneous drainage of the biliary tree.

Statistical analysis

All analysis were performed by an expert biomedical statistician with a statistical package (Statistica 10.0 for Windows, United States). Descriptive statistics were used in this case series to describe characteristics of the patients, procedures and outcomes. Continuous variables are expressed as medians with interquartile ranges for nonparametric values. Median time to biliary leakage closure and median time were estimated using a Kaplan-Meier survival curve. Spearman correlation coefficients were calculated to assess interrelationships of certain quantitative variables. A *P* values below 0.05 were considered statistically significant.

RESULTS

Study population

Among 2472 ERCP procedures that were performed in our center between April 2008 and April 2013, there were 34 patients who underwent ERC because of postoperative biliary leakage occurring after urgent cholecystectomy: 23 patients in whom urgent cholecystectomy was performed at our institution and 11 patients referred from our collaborating institutions (Figure 2). In the same period urgent cholecystectomy was performed in 1058 patients (31 patients with gallstones and hydrops of the gallbladder, 662 patients with acute or subacute calculous cholecystitis, 365 patients with gangrenous cholecystitis and one patient with Mirizzi's syndrome) at our institution. Since endoscopic treatment is a standard practice for management of post-cholecystectomy biliary leakage at our hospital, all the patients with suspected biliary leakage were referred to the endoscopy unit. Therefore, during a 5-year period biliary leakage occurred in 2.2% of all patients who underwent urgent cholecystectomy. In all those patients indications for urgent cholecystectomy were acute or subacute calculous cholecystitis (21 patients) or gangrenous cholecystitis (13 patients).

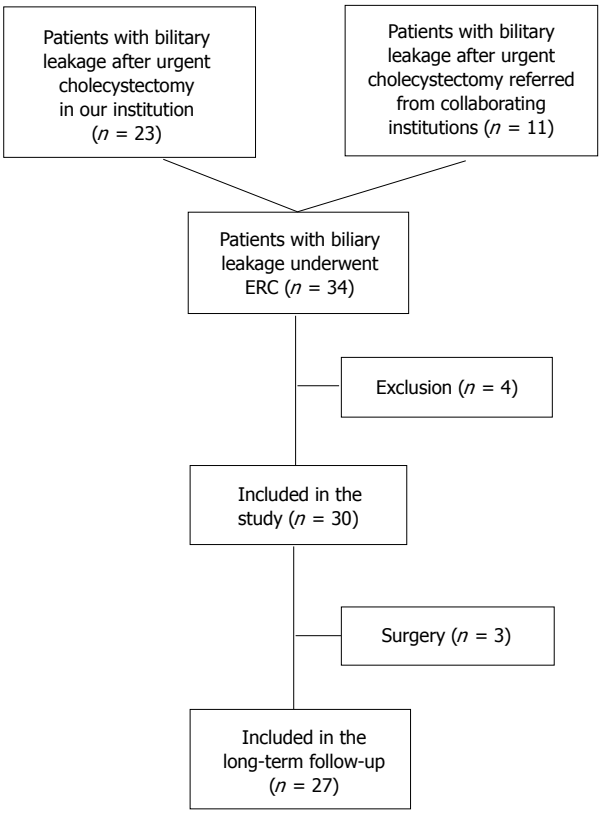

Figure 2 Schematic of subjects included in the study and long-term follow-up. ERC: Endoscopic retrograde cholangiography.

Endoscopic procedures

Initial ERC was successful in 32 out of 34 patients (94%). The reasons for failure of ERC in two patients were intradiverticular location of the papilla seen in one patient and the presence of a Billroth Ⅱ operation in a second patient. Patient with intradiverticular location of the papilla was successfully treated with the rendezvous technique[12] and this patient was included in the study. In two patients in whom ERC was successfully performed, the cholangiography demonstrated a complete transection of the common bile duct (first patients) and significant common bile duct stenosis because of multiple clips across the bile duct (second patient). Surgery was recommended for those patients as well as for the patient with the presence of a Billroth Ⅱ operation. Those three patients were excluded from the study. One patient, at the age of 79, with severe comorbidities, including heart failure with permanent atrial fibrillation, arterial hypertension, diabetes and renal insufficiency, died immediately after ERC (with stent in place) because of acute myocardial infarction and cardiac arrest. This patient was also excluded from the study.

The main clinical characteristics of 30 consecutive patients with postoperative biliary leakage included in the study are summarized in Table 1.

The median time from cholecystectomy to ERC was 6 d (interquartile range, 4-11 d) and 4 (13%) patients underwent ERC more than 2 wk after surgery.

Table 1 Clinical characteristics of 30 consecutive patients with post-cholecystectomy biliary leakage included in the study

Parameter	*n* (%)
Age (yr) (median)	62
Male/female	14 (46.7)/16 (53.3)
Cholecystectomy details	
Open	9 (30.0)
Laparoscopic	13 (43.3)
Laparoscopic to open conversion	8 (26.7)
Abdominal drain:	
Bile leak ⩽ 400 mL/d	24 (80.0)
Bile leak > 400 mL/d	6 (20.0)
Abdominal pain	20 (66.7)
Jaundice	8 (26.7)
Fever	14 (46.7)
Abdominal collection	8 (26.7)
Abdominal distension	6 (20.0)
Ascites	1 (3.3)
Comorbidity	
ASA 1-2	24 (80.0)
ASA 3-4	6 (20.0)

ASA: American Society of Anesthesiology.

Most common biliary leakage sites included leak from the cystic duct stump in 13 patients, the right hepatic duct or intrahepatic duct in 12 patients, leak from the common bile duct in three patients and from cholecystohepatic duct of Luschka in one patient (Table 2).

Endoscopic biliary sphincterotomy was performed in 17 patients: 11 patients with cholangiographic evidence of common bile duct stone(s), 3 patients with suspected but not proven common bile duct stone, and three patients in whom cannulation of the common bile duct was difficult (in two of them needle-knife papillotomy was performed). All those patients underwent plastic 10 F biliary stent placement. The proximal end of the biliary stent was placed above the site of the biliary leakage in 16 patients with leakage from the cystic duct stump, cholecystohepatic duct of Luschka and leakage from the common bile duct (based on the endoscopist's discretion, only in one patient biliary stent was placed below the site of the biliary leakage). In patients with biliary leakage from the right hepatic duct or intrahepatic duct and in patients in whom biliary leakage was not located on cholangiography, only short plastic 10 F biliary stent stranding the papilla was inserted.

After first endoscopic treatment bile flow through existing surgical drain ceased in 23 (77%) patients within 11 d following biliary therapeutic endoscopy (median, 4 d; interquartile range, 2-8 d). Those patients become asymptomatic with the normalization in laboratory data, and the biliary stent was removed on gastroscopy.

Mild post-ERC pancreatitis was observed in two patients after needle-knife papillotomy was performed. The occurrence of ERC-related pancreatitis did not affect the ultimate outcome in any of them. Post-ERC bleeding

Table 2 Endoscopic retrograde cholangiography findings in patients with post-cholecystectomy biliary leakage included in the study

1st ERC findings	*n* (%)
Number of patients	30
Bile leak characteristics	
Leak from the cystic duct stump	13 (43.3
Leak from the right hepatic duct or intrahepatic duct	12 (40.0)
Leak from the common bile duct	3 (10.0)
Leak from cholecystohepatic duct of Luschka	1 (3.3)
Could not be located	1 (3.3)
CBD stone(s)	11 (36.7)
Endoscopic management	
Biliary stent	13 (43.3)
EBS + stone extraction + biliary stent	11 (36.7)
EBS + biliary stent	6 (20.0)
Adverse effect	
Pancreatitis	2 (6.7)
Bleeding	1 (3.3)
1st ERC leakage resolution success rate	23/30 (76.7)
Repeated ERC findings	
Number of patients	7
Bile leak characteristics	
Leak from the right hepatic duct or intrahepatic duct	6 (85.7)
Could not be located	1 (14.3)
CBD stone(s)	2 (28.6)
Endoscopic management	
Biliary stent	5 (71.4)
EBS + extraction + biliary stent	2 (28.6)
Adverse effect	0
ERC leakage resolution success rate	27/30 (90)
Referred to surgery	3 (10)

ERC: Endoscopic retrograde cholangiography; EBS: Endoscopic biliary sphincterotomy; CBD: Common bile duct.

was observed in only one patient with liver cirrhosis and heart failure in which biliary sphincterotomy was performed (reduction of hemoglobin level by more than 2g/dL over a 24-h period). This patient was successfully treated conservatively and the occurrence of post-ERC bleeding did not affect the ultimate outcome of this patient. Duodenal perforation was not observed (Table 2).

Necessity for repetition of endoscopic procedure

In seven (23%) patients in whom persistent bile flow through existing surgical drain was demonstrated, suggesting the absence of the biliary leakage resolution, repeat ERC was performed within one to 4 wk, depending on the extent of the biliary leakage. In all those patients biliary stent was removed and replaced with a new one (Table 2). In two patients common bile duct stone was recognized and removed with a balloon catheter. After the repeat ERC was performed, four of those seven patients had cessation of bile flow through existing surgical drain within two to nine days (median, 5.5 d). Those four patients become asymptomatic with the normalization in laboratory data, and the biliary stent was removed on gastroscopy. There were no adverse events related to the repeat ERC.

Overall, 27 (90%) patients with biliary leakage after urgent cholecystectomy included in study were successfully treated with ERC, and all those patients were included in the long-term follow-up. ERC was repeated in 14.8% of patients, and 1.1 ERC procedure was needed for every patient with leakage resolution.

Three patients (10%) with biliary leakage after urgent cholecystectomy included in the study had more complicated clinical course. One of them had a continuous biliary leakage demonstrated as the high-output bile flow through existing surgical drain. In this patient second repeat ERC revealed large right hepatic duct biliary leakage. This patient was referred to surgery together with two patients in whom large symptomatic subphrenic abscess was confirmed along with a persistent biliary leakage through the surgical drain. Altogether eight patients had the abdominal fluid collection, and six were treated conservatively.

Table 3 Clinical characteristics of endoscopic retrograde cholangiography successfully treated patients with post-cholecystectomy biliary leakage in the long-term follow-up

Parameter	*n* (%)
Number of patients	27
Abdominal pain	0
Abdominal distension	0
Elevated bilirubin[1]	0
Elevated ALT[2]	13 (48.2)
Dilated common bile duct (> 6 mm)[3]	0
Death	4 (14.8)

[1]Bilirubin > 20 mmol/L; [2]ALT > two times above normal; [3]Measured by transabdominal or endoscopic ultrasound. ALT: Alanine transaminase.

Endoscopic treatment outcomes and long term follow-up

In all patients in whom endoscopic therapy led to the complete resolution of biliary leakage, median interval from the first endoscopic intervention and biliary stent placement to the stent extraction was 32 d (interquartile range, 28-43 d) (Figure 3). Median interval from the therapeutic ERC (first or repeated) to the stent extraction was 32 d, also (interquartile range, 28-42 d). Cessation of the bile flow through existing surgical drain occurred up to eleventh day after therapeutic ERC (first or repeated; median, 4 d, interquartile range, 2-8 d). There was no correlation between the volume of bile leak output on a surgical drain and the probability of bile leakage resolution after ERC ($r = 0.161$, $P = 0.537$).

Among 27 patients initially included in the long-term follow-up (median 30.5 mo, range 7-59 mo), four patients (14.8%) died. All of deceased patients died of severe underlying comorbid illnesses: malignancy (one patient), cerebrovascular accidents (one patient), heart failure (two patients). The main clinical characteristics and laboratory data of patients included in the long-term follow-up are demonstrated in Table 3. All those patients were asymptomatic with normal levels of bilirubin and without any signs of cholangitis and bile duct dilation. In 13 (48.2%) patients increase in ALT

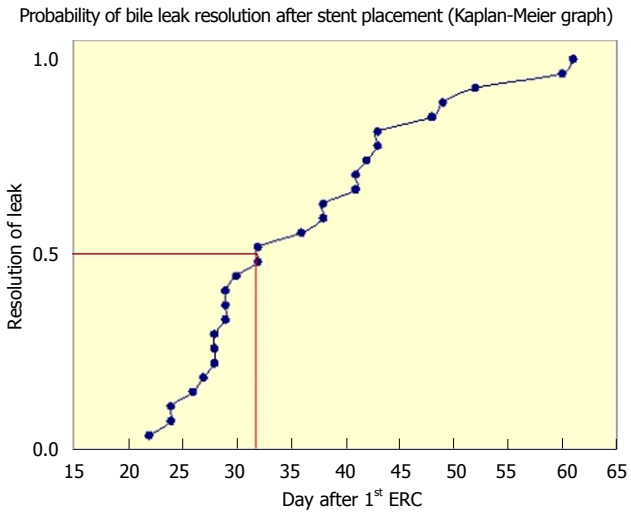

Figure 3 Kaplan-Meier graph demonstrates probability of resolution of bile leak after first endoscopic retrograde cholangiography with biliary stent placement for postcholecystectomy biliary leakage. ERC: Endoscopic retrograde cholangiography.

concentration (up to two times above the normal values) was observed. In all those patients endoscopic ultrasound revealed normal finding of common bile duct.

DISCUSSION

Postoperative biliary leakage is a serious complication that occurs in 0.2%-2.2% of all cholecystectomies[4-7,17], and even more frequently after laparoscopic cholecystectomy for acute cholecystitis[9]. In accordance with the results of our study, during 5-year period biliary leakage occurred in 2.2% of patients who underwent urgent cholecystectomy. This percentage is high with regard to the percentage of biliary leakage among patients who underwent either open or laparoscopic cholecystectomy that had been reported previously. It is possible to assume that mechanisms responsible for those findings in patients after urgent cholecystectomy include the presence of inflammation and edema (the cystic duct is indurated and shortened, lying in close contact with the common bile duct), or bleeding[6,9]. That may lead to the poor identification of anatomical structures including possible aberrant anatomy and dislodgement of suboptimally placed clips or a bile duct injury, where the experience of the surgeon is crucial[1,6,9,13].

Endoscopic interventions replaced surgery as first-line treatment for most of the biliary ducts injuries and biliary leakage following cholecystectomy. All of them are aimed towards decreasing the transpapillary pressure, allowing bile to flow through the path of decreased resistance. As a consequence, biliary leakage closes spontaneously. Recent data strongly suggest that biliary stent placement without biliary sphincterotomy is more efficient and has a lower complication rate than biliary sphincterotomy[18,19]. Since endoscopic treatment is a standard practice for management of postcholecystectomy biliary leakage at our institution, all the patients with suspected biliary leakage were referred to the endoscopy unit. Therefore, only patients with biliary leakage after urgent cholecystectomy were included in our study. To our knowledge this is the first long-term follow-up study investigating the efficiency of the endoscopic therapy in patients with biliary leakage occurring after urgent cholecystectomy. Our results clearly demonstrated the great efficiency of the endoscopic therapy in the treatment of the patients with biliary leakage. Among our group of patients closure of bile leaks was achieved with endoscopic therapy in great majority of patients (90%).

There are several limitations to this study. First, the number of patients was relatively small, although the study period included five years, but the protocol narrowed the inclusion criteria. Second, our management algorithm did not include some other available imaging methods like magnetic retrograde cholangiography because technical success of the initial ERC was rather high (94%) and this could be regarded as redundant.

There are no uniform recommendations regarding the need for repeat cholangiography at the time when previously positioned biliary stent need to be removed after resolution of biliary leakage. Namely, when endoscopic biliary stents are placed, the precise time when the leak closes cannot be determined. To our results, early cessation of bile output from the external abdominal drain strongly indicates healing of the bile leak. In majority of those patients presenting clinical symptoms and/or signs disappear very fast. Contrary, the persistent bile flow through existing surgical drain, in our study more than 11 d after endoscopic stent placement, indicates the persistent biliary leakage. In those patients, repeat ERC or some other procedure seems to be necessary. Reason for the persistent biliary leakage, as we found in our study, might be the presence of a previously unrecognized common bile duct stones, inadequately drained abdominal collection with inflammation and abscess formation or magnitude of bile duct defect.

Despite the fact that there are no uniform recommendations regarding the need for cholangiography at the time of stent removal, few studies demonstrated that repeat cholangiography is not necessary in patients in whom the presenting symptoms and/or signs of the biliary leakage had been disappeared. In those clinically well patients gastroscopy with biliary stent removal is effective if performed after the median time of 33 d following biliary stent placement[20-22]. In our study we clearly demonstrated that in asymptomatic patients following urgent cholecistectomy in whom early cessation of bile output from the external abdominal drain occurred (median, 4 d, interquartile range, 2-8 d), biliary stent removal on gastroscopy is safe after the median time of 32 d after biliary stent placement

without any need for repeat cholangiography.

During hospitalization, only one 79 years old patient with severe comorbidities, including heart failure with permanent atrial fibrillation, arterial hypertension, diabetes and renal insufficiency, died immediately after ERC (with stent in place) because of acute myocardial infarction and cardiac arrest. Among 27 patients included in the long-term follow-up four of them died. The main contributory factor that considerably affects patient's prognosis seems to be the comorbidity. Namely, among deceased patients all of them died of severe underlying comorbid illnesses, unrelated with cholecystectomy or endoscopic procedure.

In conclusion, despite the fact that the major limitation of our study is relatively small number of patients, long-term follow-up results demonstrate the great efficiency of the endoscopic therapy in the treatment of the patients with biliary leakage following urgent cholecystectomy. Early cessation of bile output from the external abdominal drain strongly indicates healing of the leak and in those patients repeat cholangiography is not necessary, particularly if the presenting symptoms and/or signs of the biliary leakage disappeared.

COMMENTS

Background

Biliary leakage can be a serious complication of urgent cholecystectomy even in the hands of an experienced surgeon. Endoscopic interventions replaced surgery as first-line treatment for most of the biliary ducts injuries and biliary leakage. Long-term follow-up results in this study demonstrate the great efficiency of the endoscopic therapy in the treatment of the patients with biliary leakage after urgent cholecystectomy.

Research frontiers

This paper describes a novel approach to endoscopic retrograde cholangiography procedure as a treatment for resolution of biliary leakage following urgent cholecystectomy.

Innovations and breakthroughs

This paper for the first time demonstrates the great efficiency of the endoscopic therapy in the treatment of the patients with biliary leakage after urgent cholecystectomy. Early cessation of bile output from the external abdominal drain strongly indicates healing of the leak and in those patients repeat cholangiography is not necessary.

Applications

Considering the tendency of early cholecystectomy in acute cholecystitis, and an increase in the number of laparoscopic procedures in the future, it is possible to expect a lot of patients with biliary leakage, especially after the urgent cholecystectomy. These results could be also applied to all patients with biliary leakage.

Peer-review

This is an interesting and practical paper about biliary leakage after surgery for acute cholecystitis. The subject is of paramount importance because most of the series mixed leakage after planned and emergency cholecystectomies.

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ORIGINAL ARTICLE

Prospective Study

Polyp detection rates using magnification with narrow band imaging and white light

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Author contributions: Gilani N and Ramirez FC designed and performed the research study; Stipho S, Panetta JD, Petre S and Young MA helped to collect the data; Gilani N and Ramirez FC performed statistical analysis and wrote the paper.

Ethics approval: This study was approved by Institutional Review Board at Phoenix VA Medical Center, Arizona, United States.

Clinical trial registration: Not applicable as this was a non-randomized study.

Informed consent: All patients in the study gave informed consent for the colonoscopy. Informed consent for the study was waived by the Institutional Review Board per request due to non-randomization.

Conflict-of-interest: None.

Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at (ngilani@hotmail.com). Consent for data sharing was not obtained from the participants but the presented data are anonymized and risk of identification is low.

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Abstract

AIM: To compare the yield of adenomas between narrow band imaging and white light when using high definition/magnification.

METHODS: This prospective, non-randomized comparative study was performed at the endoscopy unit of veteran affairs medical center in Phoenix, Arizona. Consecutive patients undergoing first average risk colorectal cancer screening colonoscopy were selected. Two experienced gastroenterologists performed all the procedures that were blinded to each other's findings. Demographic details were recorded. Data are presented as mean ± SEM. Proportional data were compared using the χ^2 test and means were compared using the Student's t test. Tandem colonoscopy was performed in a sequential and segmental fashion using one of 3 strategies: white light followed by narrow band imaging [Group A: white light (WL) → narrow band imaging (NBI)]; narrow band imaging followed by white light (Group B: NBI → WL) and, white light followed by white light (Group C: WL → WL). Detection rate of missed polyps and adenomas were evaluated in all three groups.

RESULTS: Three hundred patients were studied (100 in each Group). Although the total time for the colonoscopy was similar in the 3 groups (23.8 ± 0.7, 22.2 ± 0.5 and 24.1 ± 0.7 min for Groups A, B and C, respectively), it reached statistical significance between Groups B and C ($P < 0.05$). The cecal intubation time in Groups B and C was longer than for Group A (6.5 ± 0.4 min and 6.5 ± 0.4 min *vs* 4.9 ± 0.3 min; $P < 0.05$). The withdrawal time for Groups A and C was longer than Group B (18.9 ± 0.7 min and 17.6 ± 0.6

min *vs* 15.7 ± 0.4 min; $P < 0.05$). Overall miss rate for polyps and adenomas detected in three groups during the second look was 18% and 17%, respectively (P = NS). Detection rate for polyps and adenomas after first look with white light was similar irrespective of the light used during the second look (WL → WL: 13.7% for polyps, 12.6% for adenomas; WL → NBI: 14.2% for polyps, 11.3% for adenomas). Miss rate of polyps and adenomas however was significantly higher when NBI was used first (29.3% and 30.3%, respectively; $P < 0.05$). Most missed adenomas were ⩽ 5 mm in size. There was only one advanced neoplasia (defined by size only) missed during the first look.

CONCLUSION: Our data suggest that the tandem nature of the procedure rather than the optical techniques was associated with the detection of additional polyps' and adenomas.

Key words: Colonoscopy; Narrow band imaging; High-definition; Magnification; Screening; Yield

Core tip: The role of narrow band imaging for polyp detection is controversial. We studied 3 groups of 100 patients each, undergoing tandem colonoscopy by (1) white light followed by narrow band imaging; (2) narrow band followed by white light; and (3) white light followed by white light. Detection rate for polyps with white light used first was similar irrespective of the light used afterwards. Miss rate of polyps and adenomas was higher when narrow band imaging was used first (29.3% and 30.3%, respectively; $P < 0.05$). Our study suggests that the tandem nature of colonoscopy rather than the optical techniques, detects missing pathology.

Gilani N, Stipho S, Panetta JD, Petre S, Young MA, Ramirez FC. Polyp detection rates using magnification with narrow band imaging and white light. *World J Gastrointest Endosc* 2015; 7(5): 555-562 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i5/555.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i5.555

INTRODUCTION

Colonoscopy and polypectomy is aimed at prevention or identification of early colorectal cancer[1-3]. Colonoscopy however is not infallible in the detection of polyps and adenomas with reported miss rates in the order of 14% to 32% using tandem colonoscopy[4-10] and 23.3% for lesions (polyps and cancers) in resected colonic specimens[11]. Advances in the optics of endoscopy such as high definition, magnification and narrow band imaging have been introduced in clinical practice, and amongst others, are aimed at improving the yield of polyp and adenoma detection[12-20]. Our hypothesis was that narrow band imaging (NBI) detects more polyps and adenomas than white light (WL) when used in a tandem fashion during screening colonoscopy.

MATERIALS AND METHODS

As part of a quality improvement assessment of new technology, we sought to assess the yield of polyp and tubular adenoma detection when using wide angle magnification colonoscopy either with narrow band imaging or white light in average risk patients referred for their first colorectal cancer screening colonoscopy. These procedures were performed using the Olympus 180 H series colonoscopies (Olympus America Inc., Center Valley, PA). Cecal intubation was carried out using WL and without magnification. Once the cecum was reached, the electronic magnification featured at 1.5X was turned on. All these procedures were performed by one of two experienced board certified gastroenterologists (who had performed > 2500 and > 5000 colonoscopies each and > 250 colonoscopies using narrow band imaging) using one of the following strategies: (1) Group A: white light followed by narrow band imaging (WL → NBI); (2) Group B: narrow band imaging followed by white light (NBI → WL) and; (3) Group C: white light followed by white light (WL → WL) in a sequential and segmental fashion of tandem endoscopy every 15-20 cm. Measurements included: cecal intubation, withdrawal and total procedure times; grading of bowel preparation; anatomical location, size and histological diagnosis of polyps detected with white light or NBI, when using either of the strategies. Removed polypoid lesions, were classified based on histology as neoplastic (adenomas, hyperplastic and other tumors) and non-neoplastic (normal mucosa, hyperplastic mucosa, prominent lymphoid aggregates).

Patients underwent bowel cleansing with 4 L of polyethylene glycol solution and 4 bisacodyl tablets (20 mg total dose). Patients with suboptimal preparation (as determined by the colonoscopist during the insertion portion of the examination) were not included in the study. All procedures except four were performed using moderate sedation with incremental doses of midazolam and meperidine or fentanyl. Cecal intubation was confirmed by photo documentation of appendiceal orifice and ileocecal valve. Procedure times (cecal intubation, withdrawal and total procedure times) were documented by the Olympus stopwatch built in the processors. The watch was not stopped for rinsing and cleaning or while performing polypectomy. Polyp's size was estimated using an open biopsy forceps or the snare used for polypectomy. All polyps were removed during the withdrawal portion of the procedure even if visualized during the insertion phase. Colon was anatomically divided into proximal (proximal to splenic flexure) and distal (splenic flexure or distal to it) portions. Advanced neoplasia was defined as the presence of a tubular adenoma ⩾ 10 mm, villous component, or the presence of high grade dysplasia or

Table 1 Demographics, adequacy of bowel preparation, procedure-related times and polyps/adenomas detection

	Group A (WL → NBI)	Group B (NBI → WL)	Group C (WL → WL)	$P < 0.05$
Age (mean ± SEM) in years	62.2 ± 0.7	59.3 ± 0.6	62.0 ± 0.7	
Gender				
Men	99	98	98	
Women	1	2	2	
Cecal intubation time (mean ± SEM) in minute	4.9 ± 0.3	6.5 ± 0.4	6.5 ± 0.4	A *vs* C A *vs* B
Withdrawal time (mean ± SEM) in minute	18.9 ± 0.7	15.7 ± 0.4	17.6 ± 0.6	A *vs* B C *vs* B
Total procedure time (mean ± SEM) in minute	23.8 ± 0.7	22.2 ± 0.5	24.1 ± 0.7	B *vs* C
Bowel preparation				
Excellent	36 (%)	18 (%)	22 (%)	
Good	56 (%)	74 (%)	67 (%)	
Fair adequate	8 (%)	8 (%)	11 (%)	
Patients with polyps	78	67	73	
Total polyps detected	211	147	219	
Polyps/patient with polyps	2.7	2.2	3.0	
Of patients with adenomas	47	47	57	
Total adenomas detected	97	76	111	
Adenomas/patient with adenomas	2.1	1.6	1.9	

WL: White light; NBI: Narrow band imaging.

invasive carcinoma on histology.

The study was approved by the local Institutional Review Board and exemption for informed consent was granted due to non-randomized design and the fact that all patients underwent standard white light colonoscopy. However, informed consent for colonoscopy was obtained from all patients undergoing procedures.

Statistical analysis

SPSS 16.0 was used for statistical analysis. Data are presented as mean ± SEM. Proportional data were compared using the χ^2 test and means were compared using the Student's *t* test.

RESULTS

Three-hundred patients, 100 consecutive in each Group were studied. Table 1 shows the demographics, adequacy of bowel preparation and procedure-related times in each group. Although the total time for the colonoscopy was similar in the 3 groups, it reached statistical significance between Groups B and C ($P < 0.05$). The cecal intubation time in Groups B and C was longer than for Group A. The withdrawal time for Groups A and C was longer than Group B ($P < 0.05$).

In Group A, (WL → NBI) 211 polyps were detected in 78 patients (2.7 polyps/ patient); in Group B (NBI → WL) 147 polyps were detected in 67 patients (2.2 polyps/ patient) whereas in Group C (WL → WL) 219 polyps were detected in 73 patients (3.0 polyps/ patient). Adenomas were detected in 151 patients (50% of all patients) and similar in the 3 groups (47%, 47% and 57% for Groups A, B and C, respectively).

Yield for detection of polyps

As shown in Figure 1, in Group A (WL → NBI), the withdrawal with WL detected 181 polyps (62.4% distal and 37.6% proximal). Of those detected distally, 89.4% were ⩽ 5 mm in size; 7.1%, 6-9 mm in size and, 3.5%, ⩾ 1 cm. Of those detected proximally, 72% were ⩽ 5 mm in size; 17.7%, 6-9 mm and, 10.3%, ⩾ 1 cm in size. Switching to NBI detected 30 additional polyps (14.2% of all polyps detected in Group A) of which 70% were distal and 30% proximal. Ninety-five percent and 89% of the newly detected distal and proximal polyps were ⩽ 5 mm in size, respectively.

In Group B (NBI → WL), the first withdrawal with NBI detected 103 polyps (59.2% distal and 40.8% proximal). Of those detected distally, 91.8% were ⩽ 5 mm; 6.6%, 6-9 mm and, 1.6% was ⩾ 1 cm in size. Of those polyps detected proximally, 83.3% were ⩽ 5 mm; 14.3%, 6-9 mm and, 2.4%, ⩾ 10 mm in size. Switching to WL detected 44 additional polyps (30.8% of all polyps detected in Group B) of which 48% were distal and 52% proximal. Ninety-five percent and 92% of the newly detected distal and proximal polyps were ⩽ 5 mm in size, respectively.

In Group C, (WL → WL) the first withdrawal with white light detected 189 polyps (61.9% distal and 38.1% proximal). Of the polyps detected distally, 76.9% were ⩽ 5 mm in size, 17.1% were 6-9 mm and the remaining 6% were ⩾ 10 mm in size. Of the polyps detected proximally, 65.3% were ⩽ 5 mm in size, 23.6% were 6-9 mm and 11.1% were ⩾ 10 mm. When the second look with white light again was used, 30 additional polyps (13.7% of all polyps in Group C) were detected and of which 56.7% were proximal and 43.3% distal. Eighty-five percent and 76.5% of the polyps newly found in the distal and proximal colon were ⩽ 5 mm in size, respectively.

The newly diagnosed polyps detected with NBI (Group A, 14.2%) and white light (Group C, 13.7%) during the second look were significantly fewer than the ones detected using the WL after NBI (Group B, 30.8%) ($P < 0.05$). Overall, the second look of the tandem segmental colonoscopy detected 18% new polyps (104/577 polyps).

Yield for detection of adenomas

As can be seen in Figure 2, In Group A (WL → NBI), the first withdrawal with WL detected 86 adenomas: 50 (58.1%) proximal (64%: ⩽ 5 mm in size, 20%:

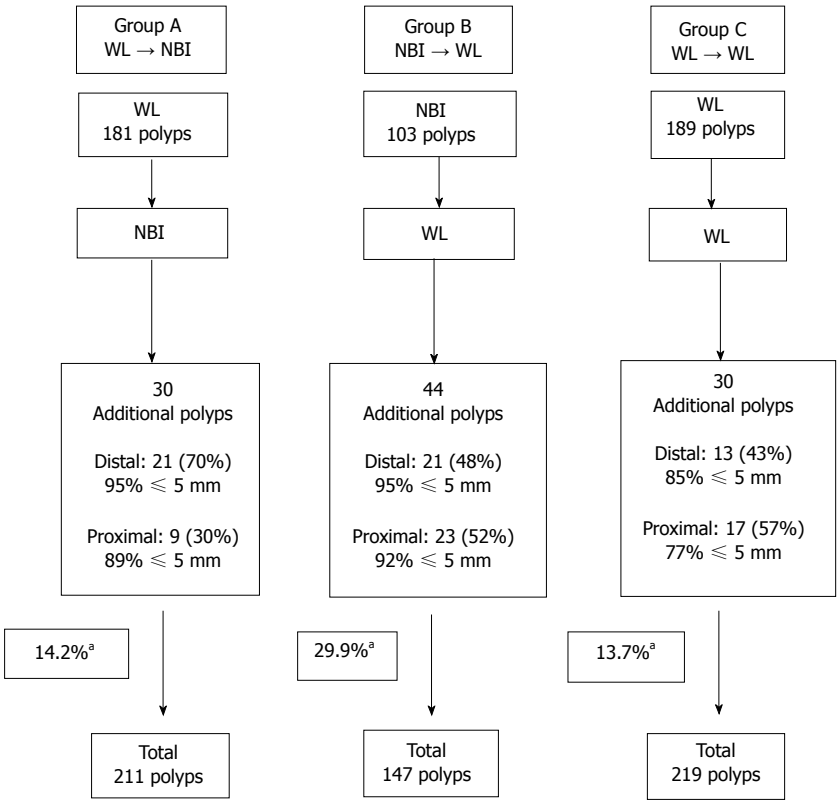

Figure 1 Yield of polyp detection. [a]*P* < 0.05, Group A and Group C *vs* Group B. WL: White light; NBI: Narrow band imaging.

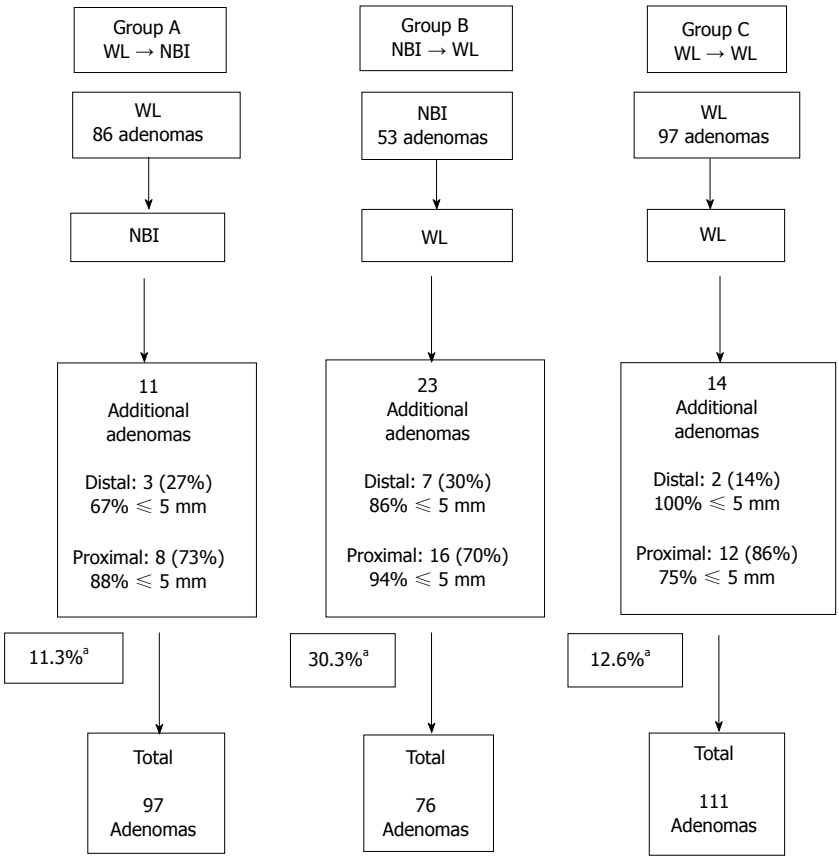

Figure 2 Yield of adenoma detection. [a]*P* < 0.05, Group A and Group C *vs* Group B. WL: White light; NBI: Narrow band imaging.

6-9 mm and, 14%: ⩾ 10 mm in size) and, 36 (41.9%) distal (77.8%: ⩽ 5 mm, 13.9%: 6-9 mm and 8.3%: ⩾ 10 mm). Switching to NBI detected 11 additional adenomas (11.3% of all adenomas detected in Group A): 8 (73%) proximal (88%: ⩽ 5 mm and 12%: 6-9 mm), and 3 (27%) distal (67%: ⩽ 5 mm and 37%: 6-9 mm).

In Group B (NBI → WL), the first withdrawal with

NBI detected 53 adenomas: 34 (64.2%) proximal (79.4%: ⩽ 5 mm, 17.6%: 6-9 mm and 2.9%: ⩾ 10 mm) and 19 (35.8%) distal (89.5%: ⩽ 5 mm, 5.3%: 6-9 mm and 5.3%: ⩾ 10 mm). Switching to WL detected 23 additional adenomas (30.3% of all adenomas detected in Group B): 16 (70%) proximal (94%: ⩽ 5 mm, 6%: ⩾ 10 mm) and 7 (30%) distal (86%: ⩽ 5 mm, 14%: 6-9 mm).

In Group C (WL → WL), there were 97 adenomas detected by white light during the first withdrawal: 61 (62.9%) proximal (70.5%: < 5 mm, 23%: 6-9 mm, 6.5%: > 10 mm) and 36 (37.1%) distal (58.3%: ⩽ 5 mm, 25%: 6-9 mm, 16.7%: ⩾ 10 mm). During the second withdrawal with white light, 14 additional adenomas were detected (12.6% of all adenomas detected in Group C): 12 (85.7%) proximal (75%: ⩽ 5 mm, 25%: 6-9 mm) and 2 (14.3%) distal (100%: ⩽ 5 mm).

The newly diagnosed adenomas detected with NBI (Group A, 11.3%) and WL (Group C, 12.6%) during the second look were significantly fewer than those detected using the WL after NBI (Group B, 30.3%) ($P < 0.05$). The second look of the tandem segmental colonoscopy thus, detected 16.9% new adenomas (48 out of 284 adenomas).

Yield for detection of advanced neoplasia

In Group A (WL → NBI), there were 8 patients (10 polyps) with advanced neoplasia (all defined by size ⩾ 10 mm only). None of these advanced neoplasias were detected during the second look performed by NBI. In Group B (NBI → WL), there were 3 patients (3 polyps) with advanced neoplasia (all defined by size ⩾ 10 mm only), and one of these (10 mm polyp in ascending colon) was detected during the second look using WL. In Group C (WL → WL), there were 9 patients (11 polyps) with advanced neoplasia including 1 villous adenoma in the sigmoid and 1 invasive carcinoma in the rectum (the remaining 9 adenomas were defined as advanced neoplasia by a size ⩾ 10 mm). None of the advanced neoplasias were detected during the second look with WL.

When NBI was used as the second look, it diagnosed 2 patients (1 adenoma each) that otherwise would have been diagnosed as having no adenomas at all and representing 4.3% (2 out of 47) of patients with adenomas. When WL was used as the second look, it identified 8 patients that otherwise would have been missed as having any adenomas (6 of these had single adenomas, and the other 2 had 2 adenomas each) and representing a pick up rate of 17% (8 out of 47 patients with adenomas). For Group C, when a second look with white light was performed, 5 patients (1 adenoma each) were detected that otherwise would have been missed as having any adenomas at all and representing 10.6% (5 out of 57) of patients with adenomas. The differences among the groups were not statistically significant. None of these patients in either group had advanced neoplasia that would have been undetected at all.

Yield for non-neoplastic polypoid lesions

Non-neoplastic polyps represented 17.8% (103/577) of all polyps and were similarly distributed among the 3 groups.

There was one case of post-polypectomy bleeding requiring admission and endoscopic intervention to secure hemostasis with endoscopic clips. There were no sedation-related complications.

DISCUSSION

The impact of new optical technologies such as high-definition, magnification and NBI on polyp detection rate is unknown. Tandem colonoscopy studies have yielded an additional detection rate up to 22% for adenomas and 27% for non-adenomas[9]. Our study showed that the detection rate of missed polyps and adenomas after a first look with white light was similar when using narrow band imaging (14.2% for polyps, 11.3% for adenomas) or white light (13.7% for polyps and 12.6% for adenomas) as the second look modality. We also found that when white light was used after narrow band imaging, the detection rate of missed polyps (29.9%) and adenomas (30.3%) was higher in comparison to where white light was used as first modality. The explanation for this unexpected finding is not completely clear. To further address this issue, we studied 100 additional consecutive patients undergoing screening colonoscopy using the following strategy (NBI → NBI → WL). Out of 198 polyps (92 adenomas) detected, the second look with NBI added 24 new polyps (7 adenomas) and the "third look" with WL added 28 additional polyps (15 adenomas) representing 12.1% polyps and 7.6% adenomas with the second NBI look and, 14.1% polyps and 16.3% adenomas with the "third look" using WL. Thus, the combined miss rate after a first look with NBI (26.2% and 23.3% for polyps and adenomas, respectively) was similar to the one reported in the present study when using the NBI → WL strategy. In our study, the bowel cleanliness was not associated with improved polyp detection. Another shortcoming of NBI appears to be relative poor visualization unless endoscope is held closer (more so than the WL) to the inspected area.

The adenoma miss rate in the tandem colonoscopy studies is inversely related to the size and directly related to the number detected during the first look[9]. In a prospective multicenter study[10] of tandem colonoscopy the miss rates for polyps, adenomas, polyps > 5 mm, adenomas > 5 mm and advanced neoplasia was 28%, 20%, 12%, 9% and 11%, respectively. The sessile or flat shape and left colonic location were associated with higher miss rates. Interestingly, in that study, not all recto-sigmoid polyps (thought to be hyperplastic) were removed. The explanation for rather significant and fairly similar miss rates reported by experienced endoscopists remains

speculative at best. Operator's-related factors that may influence the miss rate include: technique, rate of withdrawal, difference in recognition of pathology (only applicable when two different endoscopists with different levels of expertise are involved) and thus related to inter-observer variability, a more careful look performed by the second endoscopist because of the prior knowledge of the goals/objectives of the study (bias). Other factors may be polyp-related: location (*i.e.*, behind folds) that possibly becomes "more exposed" to the second look and, estimated polyp size; and/or, bowel preparation-related: a cleaner colon resultant from the cleaning performed during the first look. Optical enhancements in endoscopy are expected to reduce the miss rate of both polyps/adenomas; better predict histology and, enhance demarcation of neoplastic tissue and thus improve the rate of complete polypectomy. The development of these technologies in part, is in response to the lack of complete protection against interval cancer development[21], polyp detection and clearance such as adequacy of bowel preparation[22,23], operator's expertise and completeness (cecal intubation) of examination[24-28], adequate withdrawal times[29,30], incomplete polyp resection[31,32] and inherent limitations of the colonoscopy itself[33-35]. NBI was initially reported to increase the yield of detection of polyps and adenomas[12,15,17,19,20]. The studies investigating the role of NBI in the detection of colonic polyps have yielded controversial results. In a study[36], of 40 patients undergoing screening colonoscopy, NBI detected 51 additional polyps (41.5% of total polyps) and 29 adenomas (40.3% of total adenomas). The polyp/adenoma miss rate appeared somewhat higher than what has been reported in the literature (10%-20%), even if a potential gain provided by NBI from 5% to 15% was added. The study included WL → NBI arm but lacked NBI → WL and WL → WL) arms. In another study[15], NBI detected numerically more adenomas (23%) than conventional endoscopy (17%). However, procedures were not performed in a tandem fashion. There also appeared to be a learning effect upon adenoma recognition/detection due to involvement of multiple endoscopists, some with less experience even in conventional endoscopy. In a randomized controlled study[37], again, tandem colonoscopy was not performed, and thus the miss rate with each of the lights remained unknown. Nevertheless, in that study the authors found no difference in the detection rates of overall adenomas or adenomas of any size. To compare, detection rate for adenomas in our group of 300 patients was 50% (range: 47% to 57%) which is similar to the above mentioned study[37]. This may suggest that in the hand of experienced endoscopists with a high detection rate, NBI may not have an added benefit. In another randomized study comparing conventional *vs* pan-colonic narrow band imaging[38], NBI detected significantly more adenomas, especially diminutive (< 5 mm) in the distal colon without compromising the withdrawal time than conventional colonoscopy. The main limitation of the study again was the lack of tandem colonoscopy. Finally, a randomized tandem colonoscopy study[39] comparing NBI → WL *vs* WL → WL showed that there were no significant differences either in the miss or detection rates between two modalities (12.6% miss rate in NBI and 12.1% in WL group). Although, the miss rates in the, WL → WL group was similar to ours, the miss rate in the NBI → WL was lower than that found in our study.

The main limitations of our study are a non-randomized nature and being carried out by two experienced endoscopists at a single center, and thus the results may not be generalized.

In summary, the overall miss rate of adenomas by segmental tandem endoscopy was 17%; being highest (30%) after NBI had been used as the first modality. Most missed adenomas were in the proximal colon and were ⩽ 5 mm in size. When white light was used first, the detection rate of missed adenomas was similar with white light and NBI. In conclusion, our data suggest that the tandem nature of the procedure rather than the optical technique used was the most important factor for detecting missed pathology. We recommend taking extra time to "take a second look" at each segment during colonoscopy to increase the yield for detection of pathology.

COMMENTS

Background

Polyp detection is of paramount importance during colonoscopy. Conventional colonoscopy may miss polyps, some of which could be pre-cancerous. Narrow band imaging (NBI) is one of the several modalities that are being investigated to enhance polyp and adenoma detection rates.

Research frontiers

In narrow band imaging, light of specific blue and green wavelengths is used to enhance the details of certain aspects of the mucosa. NBI has been utilized to classify the colon polyps based on their pit patterns, to differentiate normal from dysplastic tissue in Barrett's esophagus and ulcerative colitis, and in some cases to improve the detection of colonic polyps/lesions.

Innovations and breakthroughs

The impact of new optical techniques such as high-definition, wide angle, magnification and NBI on polyp detection rate is unknown. The authors know, that a second look back-to-back colonoscopy when performed by a second endoscopist (tandem colonoscopy), may yield additional polyps. The study showed, that the additional detection of missed polyps and adenomas after a first look with white light (WL) was similar when either NBI (WL → NBI) or white light (WL → WL) were used as a second look. This suggests that NBI did not increase the rate of detection of polyps/adenomas but that the tandem nature of the procedure did.

Applications

This study suggests that white light may be a relatively better modality in comparison to narrow band imaging when routinely used for purposes of polyp detection during colonoscopy.

Terminology

NBI: Light of specific blue and green wavelengths that can be used in endoscopy to enhance the details of certain aspects of the lining of gastrointestinal tract; Adenoma: A potentially pre-cancerous polyp.

Peer-review

The authors present a well-designed study investigating the use of second look with narrow band *vs* white light endoscopy and the effect on polyp detection rates.

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CASE REPORT

Chronic abdominal pain secondary to mesenteric panniculitis treated successfully with endoscopic ultrasonography-guided celiac plexus block: A case report

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Abstract

Mesenteric panniculitis is a chronic illness that is characterized by fibrosing inflammation of the mesenteries that can lead to intractable abdominal pain. Pain control is a crucial component of the management plan. Most patients will improve with oral corticosteroids treatment, however, some patients will require a trial of other immunosuppressive agents, and a minority of patients will continue to have refractory disease. Endoscopic ultrasound guided celiac plexus block is used frequently to control abdominal pain in patients with pancreatic pathology. To our knowledge there are no case reports describing its use in mesenteric panniculitis patients with refractory abdominal pain.

Key words: Endoscopic-ultrasound; Abdominal pain; Celiac plexus; Mesenteric panniculitis

Core tip: Mesenteric panniculitis is a rare disorder that can present with refractory and disabling abdominal pain, we describe a novel intervention using endoscopic ultrasonography guided celiac plexus block to control the refractory abdominal pain in a patient with mesenteric panniculitis. This approach is based on the anatomical supply of the epigastric area where the pain is originating.

Alhazzani W, Al-Shamsi HO, Greenwald E, Radhi J, Tse F. Chronic abdominal pain secondary to mesenteric panniculitis treated successfully with endoscopic ultrasonography-guided celiac plexus block: A case report. *World J Gastrointest Endosc* 2015; 7(5): 563-566 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i5/563.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i5.563

INTRODUCTION

Mesenteric panniculitis is a rare, benign condition

characterized by acute inflammation of the mesenteric adipose tissue that can progress to chronic fibrosis[1]. The disease was first described by Jura[2] in 1924, he used the term retractile mesenteritis to describe this condition. Subsequently, the term mesenteric panniculitis was developed by Aach *et al*[3] to describe the acute inflammatory phase of the disease. Since then, this has been widely used and adopted term to describe this disease. Mesenteric panniculitis is also known as mesenteric lipodystrophy, primary liposclerosis, isolated lipodystrophy, lipogranuloma, and Weber-Christian disease[4]. The etiology of this disorder remains largely unknown; an association with inflammatory disorders, infection, malignancy (particularly lymphoma)[5], trauma, and abdominal surgery has been described[6]. The prevalence of the disease is estimated to be around 0.6%, and it is more common in Caucasians. The clinical course of mesenteric panniculitis is indolent and favorable[7].

The disease usually progresses slowly and may subside spontaneously[7], around 30%-50% of patients are asymptomatic[5]. However, 20% of patients will have more symptomatic debilitating disease[8]. The most common symptom is chronic abdominal pain, some patients may present with acute abdomen[9]. Abdominal pain can be accompanied by other non-specific symptoms including fever, nausea, vomiting, anorexia and non-intentional weight loss[10]. The diagnosis is usually suggested by high resolution computed tomography (CT) scan[11]. Histological confirmation is rarely required[1]. The majority of patients will respond to systemic corticosteroids[8]. However, some patients will require a more intense immunosuppressive therapy like azathioprine or cyclophosphamide. Only a minority of patients will continue to have refractory disease despite immunosuppressive therapy[12]. Other modalities including progesterone, colchicine, tamoxifen, antibiotics and emetine, or radiotherapy have been used in refractory disease with limited success[13,14]. Surgical resection is reserved for the treatment of complication like intestinal obstruction or ischemia[7]. Refractory abdominal pain can be a major source of morbidity in these patients[15].

CASE REPORT

We report here on a 62-year-old caucasian male who presented with right upper quadrant abdominal pain for several months prior to his first presentation to our institution in 2005. The abdominal pain was not associated with changes in bowel habits, nausea, vomiting, or constitutional symptoms. Initial investigations including complete blood count, liver and kidney function tests, and abdominal ultrasonography were normal. The patient underwent cholecystectomy in 2005 for possible biliary cause of pain, but the pain persisted after surgery. Subsequently, imaging study using CT imaging scan demonstrated thickening and irregularity of the mesentery surrounding the pancreatic head. The radiologic findings were in keeping with the diagnosis of mesenteric panniculitis (Figure 1). Extensive investigations ruled out luminal pathology, pancreatic or adrenal diseases, intermittent porphyria, vascular etiology, and other conditions.

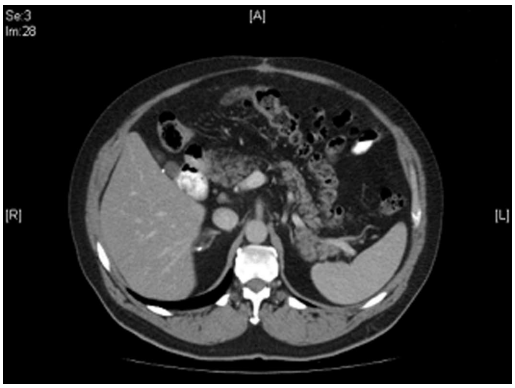

Figure 1 Computed tomography of the abdomen. Computed tomography scan of the abdomen showing mesenteric irregularity and thickness.

Given the radiologic findings and the patient symptoms, the patient was started on prednisone 40 mg once daily for two months. This was associated with a significant improvement in the severity of abdominal pain. However, prednisone therapy was complicated by severe systemic side effects, including worsening of pre-existing depressive disorder, hypertension and cataracts. For this reason, the patient was subsequently weaned off corticosteroids. He remained symptom free for 6 mo after discontinuation of steroid therapy, and then had recurrence of abdominal pain. Because of the chronicity and severity of the symptoms, the patient underwent diagnostic laparoscopy primarily to rule out malignant process. The operative findings showed thickening of the mesentery with no discrete visible masses. Samples from the thickened mesentery were obtained. The pathology results confirmed the diagnosis of mesenteric panniculitis (Figure 2). The patient was started on a steroid-sparing agent (azathioprine) for 6-mo with no response. Further attempts using 3 to 6 mo courses of tamoxifen and subsequently thalidomide failed to improve his symptoms. Different non-opiate analgesic agents were unsuccessful in controlling his symptoms, including acetaminophen and non-steroidal anti-inflammatory drugs. Eventually the patient was started on opioids (oxycodone and morphine) and a serotonin-norepinephrine reuptake inhibitor for pain control. A follow-up CT imaging of the abdomen showed similar findings.

After discussion with the patient, the patient was referred for endoscopic ultrasonography (EUS) guided celiac plexus block in an attempt to control relief the intractable abdominal pain and minimize the use of narcotics.

After obtaining consent from the patient, the linear echoendoscope was advanced through the oral cavity

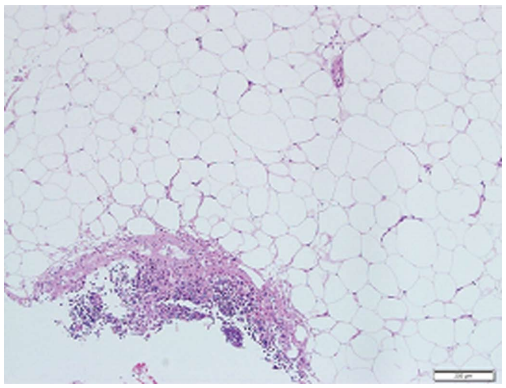

Figure 2 Mesenteric biopsy. Mesenteric biopsy showing fibrotic band of dense collagen infiltrated by mixed inflammatory cells (lymphocytes, plasma cells and neutrophils). There is fat necrosis, no vasculitis or malimgnancy seen. There is no cellular atypia or lipoblast identified in the biopsy.

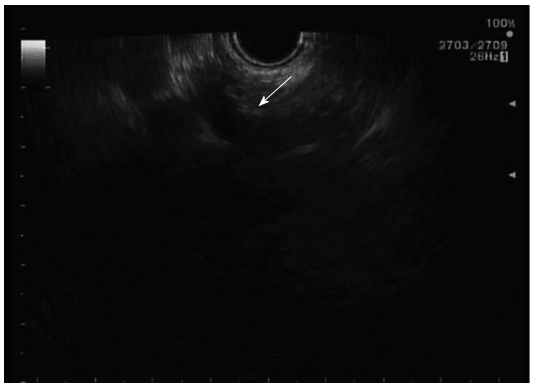

Figure 3 Ultrasonographic image of celiac plexus. This image is showing the celiac artery and celiac plexus (arrow).

into the stomach; the celiac trunk was identified using the ultrasound images (Figure 3). A 19-gauge needle (Echotip; Wilson-Cook) was used to inject 40 mg of Triamcinilone and 10 mL of 0.25% bupivicaine on both sides of the celiac trunk. This protocol is similar to that described by Gress *et al*[16]. Intravenous crystalloids were administered during the procedure to prevent hypotension caused by the procedure. The patient tolerated the procedure well and was discharged home within few hours.

Within the first week after the procedure, the patient noticed a dramatic improvement in his symptoms. Within 2 mo, he was weaned off narcotics with complete resolution of his symptoms. However, symptoms recurred 6 mo after the procedure. Given the initial response to this therapy, the procedure was repeated using identical protocol. Few days after the procedure, the patient developed a back injury that led to a surreptitious diagnosis of a 1 cm schwannoma at T12-L1 spinal levels. Surgical resection of the spinal cord tumor was done soon after celiac block, which confounded the assessment of pain. Three months after the second EUS-guided celiac plexus block, the patient was pain free and off all analgesics.

DISCUSSION

To our knowledge, there are no published reports of applying this unique intervention to control refractory abdominal pain in a patient with mesenteric panniculitis. Mesenteric panniculitis is a rare disorder that is characterized by chronic inflammation leading to fibrosis of the mesentery. Patients' presentation varies from asymptomatic incidental radiologic findings to severe abdominal pain, vomiting, changes in bowel habits, and constitutional symptoms[17,18]. Associated malignancy is not uncommon, with one report showing that 70% of included patients had radiological findings consistent with malignant disorders[19].

Due to the low incidence of this condition, the prognosis of the disease is not well defined. One report with more than 5 years of follow-up showed that mortality rate approaches 45%, majority of fatalities (50%) were related to co-existing malignancy[20]. Several case reports showed that immunosuppressive medications are effective in controlling disease activity[4,21,22]. However, there are no published reports on the utility of celiac plexus block for controlling refractory symptoms.

Celiac plexus is composed of sympathetic efferent fibres, which are derived from the greater, lesser, and least splanchnic (T5-T12) nerves[23]. The visceral afferent fibres supplying the distal esophagus down to the transverse colon pass through the celiac plexus, before ending in the spinal cord. Therefore, pain originating from pancreatic disease may respond to celiac plexus block. In fact, the most studied application of EUS-guided celiac block is in pancreas-related pain[1,24-26]. The application of this procedure in other disorders is very limited. There are few case reports on the use EUS-guided block in the management of pelvic cancer pain[27], acute intermittent porphyria[28], and pain caused by diabetic gastroparesis[29]. No published literature on the utility of this intervention in patients with mesenteric panniculitis related pain.

Theoretically, pain originating from upper abdominal organs could be alleviated by this procedure. However, this was not tested in clinical trials or observational studies. More research in this area is required in order to ascertain or dispute our observation.

COMMENTS

Case characteristics

Recurrent right upper quadrant abdominal pain.

Clinical diagnosis

Mesenteric panniculitis.

Differential diagnosis

Upper endoscopy ruled out an intraluminal pathology, computed tomography (CT) scan finding was not suggestive of neuroendocrine or pancreatic malignancy, diagnostic laparoscopy done to rule out intra-abdominal malignant process.

Laboratory diagnosis

Extensive investigations including complete blood count, Lipase, Liver enzymes, kidney function, porphyria screening, radiological imaging with CT scan, the

diagnosis was confirmed with histology.

Imaging diagnosis

Imaging study using CT scan demonstrated thickening and irregularity of the mesentery surrounding in keeping with the diagnosis of mesenteric panniculitis.

Pathological diagnosis

Mesenteric biopsy showing fibrotic band of dense collagen infiltrated by mixed inflammatory cells (lymphocytes, plasma cells and neutrophils) in keeping with the diagnosis of mesenteric panniculitis.

Treatment

The patient was treated with multiple pharmacological agents including prednisone, azathioprine, tamoxifen and thalidomide that failed control his symptoms. Subsequently, responded to endoscopic ultrasonography (EUS)-guided celiac plexus block.

Related reports

Nicholson *et al* reported that mesenteric panniculitis in merseyside: a case series and a review of the literature in 2010.

Experiences and lessons

Mesenteric panniculitis is a rare disorder that can present with refractory and disabling abdominal pain, the authors describe a novel intervention using EUS guided celiac plexus block to relieve refractory abdominal pain in a patient with mesenteric panniculitis.

Peer-review

Novel intervention for a rare disease is based on the anatomical supply of the epigastric area where the pain is originating.

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CASE REPORT

Anaemia in Waldmann's disease: A rare presentation of a rare disease

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Author contributions: All authors performed the research, designed, wrote, critically analysed the manuscript; El-Etreby SA, Altonbary AY and Bahgat MH were responsible for medical assessment and follow up of the patient; Mazroa JA was responsible of radiological assessment; Elkashef W examined the pathological specimens; El Sorogy M performed the surgical procedure; finally, El-Etreby SA and Bahgat MH analyzed the data, revised the draft and approved of the final version of the paper to be published.

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Ethics approval: The study was reviewed and approved by the Mansoura Faculty of Medicine Institutional Review Board, Mansoura University, Egypt.

Informed consent: The study participant, or her legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest: None.

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Abstract

A 32-year-old female presented with 5-year history of iron deficiency anemia, marked pallor and edema of both lower limbs. Laboratory investigations including complete blood count, blood film, iron studies, lipid profile, ascitic fluid analysis, test of stool for occult blood and alpha 1 anti-trypsin. Upper, lower gastrointestinal (GIT) endoscopies, and enteroscopy were performed. Imaging techniques as abdominal ultrasonography and computed tomography were done. Echocardiography, lymph node biopsy and bone marrow examination were normal. The case was diagnosed as Waldmann's disease with protein losing enteropathy and recurrent GIT bleeding. Management started with low fat diet with medium chain triglyceride, octreotide 200 μg twice a day, tranexamic acid and blood transfusion. Then, exploratory laparotomy with pathological examination of resected segment was done when recurrent GIT bleeding occurred and to excluded malignant transformation.

Key words: Waldmann's disease; Lymphangiectasia; Gastrointestinal bleeding; Iron deficiency anemia

Core tip: To our knowledge, this is the first "Egyptian" case of primary intestinal lymphangiectasia. In addition, its presentation is rare with blood loss anemia in contrast to the more common presentation with hypoproteinemia and edema. So, we are reporting a case with a rare clinical presentation of a rare disease. Double balloon enteroscopy was so beneficial in the diagnosis of the case superior to capsule endoscopy

because the advantage of biopsy and histopathologic examination. There is controversy about medical treatment options, surgical treatment may be preferred in localized lesions otherwise, has no role. Prognosis may be favorable.

El-Etreby SA, Altonbary AY, El Sorogy M, Elkashef W, Mazroa JA, Bahgat MH. Anaemia in Waldmann's disease: A rare presentation of a rare disease. *World J Gastrointest Endosc* 2015; 7(5): 567-572 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i5/567.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i5.567

INTRODUCTION

Waldmann's disease; also called primary intestinal lymphangiectasia (PIL) is a rare form of protein losing enteropathy caused by leakage of lymph inside the small intestinal lumen from dilated lacteals. The manifestations begin before the age of 30 years in 90% of cases, often in childhood. Whether bleeding into gastrointestinal tract a feature of PIL or not is still controversial. Here, we present a case of a young women with chronic blood loss anemia (iron deficiency and positive fecal occult blood test) caused by Waldmann's disease.

CASE REPORT

A 32-year-old female with 5 year history of iron deficiency anemia was referred to our Gastroenterology Unit for further evaluation. History was irrelevant apart from easily fatigability and repeated blood transfusions as well as iron therapy. Examination revealed marked pallor and edema of both lower limbs.

Laboratory findings of a 32 years old female with Waldmann's disease are shown in Table 1.

Upper and lower GI endoscopies were done twice within two-month period and did not reveal any gross pathology. So, Fujinon's Double Balloon Endoscopy System (with 2.8 mm forceps channel) was used to examine the small bowel through oral route down to 310 cm from the ligament of Trietz. Multiple lymphangectasias (Figure 1) were seen starting at about 100 cm, extending all through the assessed parts; some of them were actively bleeding. The most affected area (at about 100 cm) was tattooed with India Ink. Histopathological examination of the lesions revealed multiple dilated vascular and lymphatic spaces and few lymphocytes with no evidence of malignancy, picture consistent with capillary telangiectasia.

Abdominal ultrasonography, abdominal computed tomography (CT), echocardiography, inguinal lymph node biopsy, and bone marrow examination were performed to exclude secondary causes of lymphangiectasia. All tests were normal except for mild splenomegaly (due to multiple hemangiomas).

Table 1 Laboratory results for the patient

Test	Result	Normal reference
Complete blood count		
Hemoglobin	5.2 g/dL	12-18 g/dL
HCT	18.30%	37%-51%
MCV	70.2 pg	80-97 flpg
MCHC	28.4 g/dL	31-36 g/dL
Platelets	284	140-440 cell/cm^3
WBCs	3.8	4.1-10.9 cell/cm^3
Lymphocytes	500	600-1400
Blood film		
Hypercellular bone marrow with no blast cells		
Blood chemistry		
s. Albumin	2.1 g/dL	3.5-5 g/ dL
AST	30 IU/L	Up to 40 U/L
ALT	25 IU/L	Up to 45 U/L
s. cholesterol	107 mg/dL	Up to 200 mg/dL
s. triglyceride	54 mg/dL	Up to 160 mg/dL
s. iron	23 ng/dL	28-170 ng/dL
s. ferritin	12 ng/mL	40-430 ng/mL
TIBC	750 ng/dL	261-478 ng/dL
s. TSH	1.2 mIU/L	0.3-3.04 mIU/L
Stool tests		
Occult blood	Positive	
α-1 AT clearance	2 folds above normal range	

HCT: Hematocrit; MCV: Mean corpusclar volume; MCHC: Mean corpuscular hemoglobin concentration; WBCs: White blood cells; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TIBC: Total iron binding capacity; TSH: Thyroid stimulating hormone; α-1 AT: Alpha 1 antitrypsin.

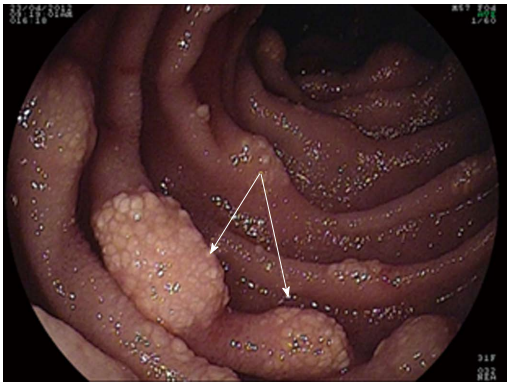

Figure 1 Multiple jejunal lymphangiectasia.

Management started with low fat diet with medium chain triglyceride, octreotide 200 μg/twice a day, tranexamic acid and blood transfusion till an acceptable level of hemoglobin was achieved (about 9 g/dL). She was discharged on diet regimen and regular follow up.

Nine months later during routine follow up, clinical examination showed marked pallor (Hb 6 g/dL) and abdominal ultrasonography revealed moderate ascites and mild right sided pleural effusion. Ascitic fluid was milky and turbid. Chemical analysis of ascitic fluid sample revealed glucose of 108 mg/dL, total protein of 1170 mg/dL, lactate dehydrogenase of 195 U/L, triglycerides of 1232 mg/dL (diagnostic of chylous ascites), WBCs of 250 cell/cm^3 mainly lymphocytes,

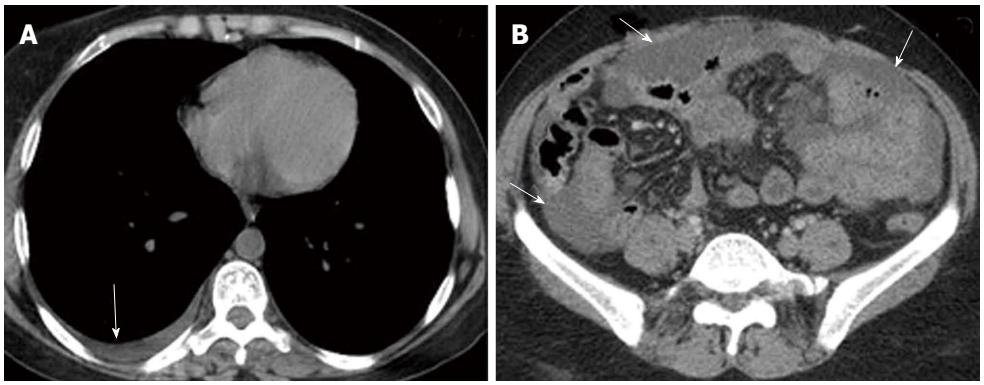

Figure 2 Pre contrast axial computed tomography scan showing (A) mild right-sided pleural effusion and (B) mild ascites.

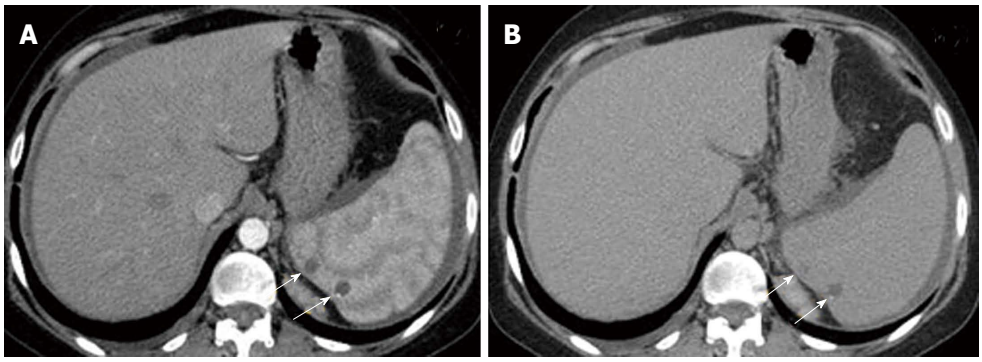

Figure 3 Triphasic post contrast axial computed tomography showing. Multiple splenic hemangiomas in portal (A) and delayed (B) phases respectively showing filling in (arrows).

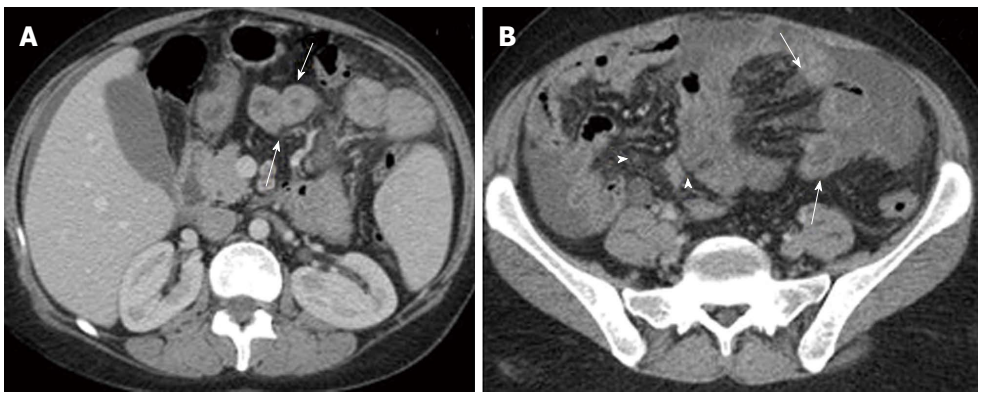

Figure 4 Triphasic post contrast axial computed tomography (portal phase) showing. A: Dilated small intestinal wall (arrows); B: Mesenteric hypodense bands indicating obstructed lymphatics (arrows), and dirty fat appearance due to mesenteric oedema (arrow heads).

and RBCs of 0.01×10^6. Cytological examination of ascitic fluid revealed no atypical or malignant cells. ZN stain and adenosine deaminase were negative. Triphasic CT scan was performed by 8 multi-slice G.E. CT scanner. It revealed right pleural effusion, mild ascites; both had uncomplicated fluid density: 0-20HU (Figure 2) and multiple splenic hemangiomas (Figure 3). Regarding small intestine, CT revealed dilated small intestinal loops with diffuse, nodular wall thickening (reaching up to 9 mm), mesenteric hypodense bands representing dilated lymphatic channels and mesenteric edema (Figure 4). Neither lymphadenopathy nor hepatomegaly was detected.

Surgical opinion was sought and malignant transformation was suspected. So, exploratory laparotomy was done through midline incision. Findings include minimal ascites, multiple cysts related to the small intestinal wall and its mesentry and a discolored segment of the proximal jejunum previously marked with India Ink by enteroscopy (Figure 5) but no masses were found. Resection anastomosis of the discolored segment was done. Histopathological examination revealed large gaping vascular spaces lined by flat endothelial cells and filled by lymph fluid, picture consistent with primary intestinal lymphangectasia (Figure 6).

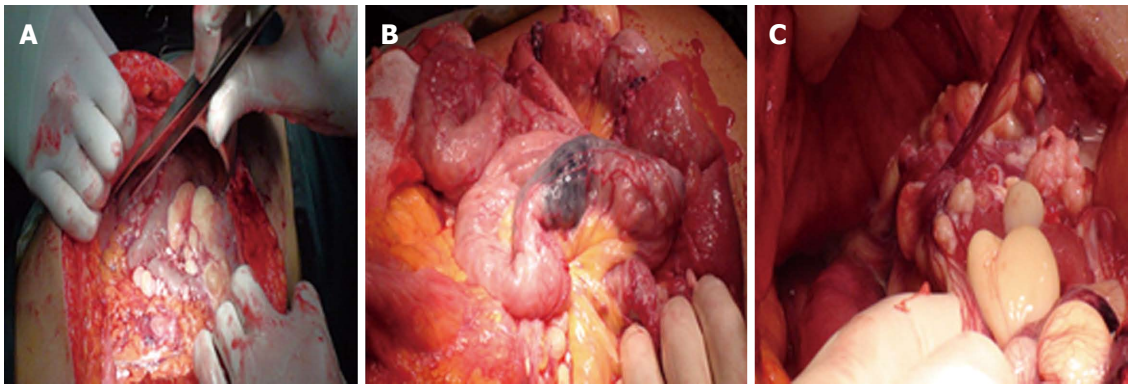

Figure 5 Exploratory laparotomy, multiple cysts was seen related to the small intestinal wall and its mesentry and a discolored segment of the proximal jejunum.

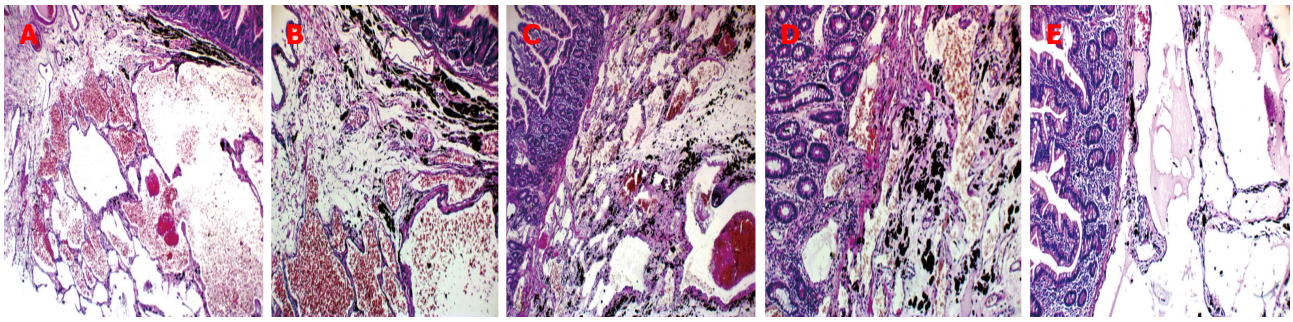

Figure 6 Histopathological examination of the resected part of small intestine. A: The sub-mucosa shows large gaping vascular filled by RBCs (HE × 40); B: The vascular spaces are lined by flat endothelial cells (HE × 100); C: Black staining is due to labeling material (India Ink) (HE × 100); D: The sub-mucosal vascular are see encroaching upon the mucosal lining (HE × 100); E: Some vascular spaces lined by flat endothelial cells and filled by lymph fluid (HE × 100).

Postoperative outcome was favorable and she was discharged home after 5 d.

On the 20th postoperative day, patient achieved marked improvement of her general condition, disappearance of edema lower limb, ascites, and pleural effusion. Laboratory investigations were; s. albumin 4.1 g/dL, HB 10.9 g/dL, platelets count 147 cell/cm^3, WBCs 4900 cell/cm^3 with normal distribution. Six months later, she remained asymptomatic with weight gain of 5 kg and rather stable hemoglobin level.

DISCUSSION

Protein losing enteropathy (PLE) is a rare cause of hypoproteinemia due to gastrointestinal (GI) loss of serum protein. This rare condition has many reported causes (Table 2) including the rare Waldmann's disease (PIL) in which GI protein loss results from leakage of lymph through the ectatic intestinal lacteals[2].

PIL predominantly affects young children although it may also be diagnosed in older age. There is slight male preponderance with 3:2 ratio. On the other hand, race is not a predictor of PIL[3,4].

Patients usually present with bilateral lower limb edema[2-7]. Other manifestations like pain, loose motion, and malnutrition are less common[8]. Rare manifestations include abdominal mass, Mechanical ileus[9-11], chylous reflux[12,13], iron deficiency with anemia[14], necrolytic migratory erythema[15], recurrent hemolytic uremic syndrome[16], and osteomalacia[17]. Recurrent gastrointestinal bleeding was even more rare being reported in only 2 cases[18,19].

Work up of diagnosis consist of laboratory, imaging studies and GIT endoscopy with confirmatory histopathological examination[20].

The most common laboratory finding is hypoproteinemia. Hypo-albuminemia is most prominent and lymphopenia. Cholesterol levels are not usually elevated. PLE can be confirmed by presence of excess fecal α1-antitrypsin[21,22].

Abdominal CT scan may show dilated thickened small intestinal loops, ascites, halo sign and edematous mesentery. It also helps rule out secondary causes[23,24].

Diagnosis can only be confirmed by finding dilated lacteals both on endoscopic and histopathologic examination[25,26]. Video capsule endoscopy imaging provides the same information and allow exploration of the whole small bowel but does not allow biopsies[27].

PIL has to be differentiated from secondary causes of intestinal lymphangiectasia such as Crohn's disease, intestinal tuberculosis, and Whipple's disease as well as from causes of PLE without lymphangiectasia such as Mentrier's disease and systemic lupus erythematosus (SLE)[20].

Medical management relies on diet modification with low fat replaced by medium-chain triglycerides

Table 2 Causes of protein losing enteropathy[1]

Erosive gastrointestinal disease
Inflammatory bowel disease
Gut malignancy
Non steroidal anti-inflammatory drug enteropathy
Erosive gastropathy
Acute graft vs host disease
Pseudomembranous enterocolitis
Ulcerative jejunoenterocolitis
Intestinal lymphoma
Sarcoidosis
Non erosive gastrointestinal disease
Celiac disease
Hypertrophic gastropathies
Eosinophilic gastroenteritis
Connective tissue disorders
Small intestinal bacterial overgrowth
Amyloidosis
Microscopic colitis
Tropical sprue
Whipple's disease
Parasitic diseases
Viral gastroenteritis
Increased interstitial pressure
Intestinal lymphangiectasia
Congestive heart failure
Constrictive pericarditis
Congenital heart diseases
Fontan procedure for single ventricle
Portal hypertensive gastroenteropathy
Hepatic venous outflow obstruction
Enteric lymphatic fistula
Mesenteric venous thrombosis
Sclerosing mesenteritis
Mesenteric tuberculosis or sarcoidosis
Neoplasia involving mesenteric lymph nodes or lymphatics
Chronic pancreatitis with pseudocysts
Congenital malformations of lymphatic
Retoperitoneal fibrosis

thus preventing fat overloading of intestinal lacteal[28,29].

Response to other medications, such as[30-31] octreotide[32-36] and steroids[37] is variable.

Small intestinal resection is indicated in localized forms of the disease[38,39].

Natural history of PIL is greatly variable; depending on involvement of intestine either generalized or localized with blockage of mesenteric lymphatic drainage. Prognosis may be favorable unless it is complicated by intestinal B-lymphoma or effusion in serous sacs[20,40].

COMMENTS

Case characteristics

A 32-year-old female presented with 5-year history of iron deficiency anemia, marked pallor and edema of both lower limbs.

Clinical diagnosis

Examination revealed marked pallor and edema of both lower limbs.

Differential diagnosis

Primary intestinal lymphangiectasia has to be differentiated from secondary causes of intestinal lymphangiectasia such as Crohn's disease, intestinal tuberculosis, and Whipple's disease as well as from causes of protein losing enteropathy without lymphangiectasia such as Mentrier's disease and systemic lupus erythematosus.

Laboratory diagnosis

Patient hemoglobin level and serum albumin were 5.2 g/dL, 2.1 g/dL respectively. α-1 AT clearance was 2 folds above normal range and stool test for occult blood yield positive result.

Imaging diagnosis

Computed tomography of the abdomen revealed dilated small intestinal loops with diffuse, nodular wall thickening, mesenteric hypodense bands representing dilated lymphatic channels and mesenteric edema.

Endoscopy diagnosis

Double balloon enteroscopy was performed, and revealed presence of multiple lymphangectasias, some of them were actively bleeding.

Pathological diagnosis

Histopathological examination of the lesions revealed multiple dilated vascular and lymphatic spaces and few lymphocytes with no evidence of malignancy, picture consistent with capillary telangiectasia.

Treatment

Management started with low fat diet with medium chain triglyceride, octreotide 200 μg/twice a day, tranexamic acid and blood transfusion till an acceptable level of hemoglobin was achieved (about 9 g/dL). But the results was unsatisfactory.

Related reports

Only two cases with primary intestinal lymphangiectasia were presented in literatures by gastrointestinal bleeding.

Term explanation

Chronic blood loss anemia (iron deficiency and positive fecal occult blood test) could be a one of manifestation of primary intestinal lymphangiectasia.

Experiences and lessons

This case report represents a case of primary intestinal lymphangiectasia with rare presentation, recurrent gastrointestinal bleeding and iron deficiency anemia. Also, it yields our experience with different treatment modalities that could be used.

Peer-review

The article highlights the clinical characteristics, diagnostic modalities and treatment options available for primary intestinal lymphangiectasia.

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Unreported complication of Bravo pH capsule dislodged into the pyriform sinus

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Abstract

We report an unexpected, previously unreported complication of Bravo pH capsule dislodgement. During Bravo pH testing of a 44-year-old man with gastroesophageal reflux disease, we were unable to endoscopically visualize the capsule attached to the esophageal wall after deployment. After multiple attempts to detect the capsule, it was visualized in the left pyriform sinus. As there was significant risk for pulmonary dislodgement, ENT and pulmonary physicians were immediately consulted to review options for safe removal. Ultimately, ENT successfully retrieved the capsule with a foreign body removal forceps. The Bravo pH test is generally a well-tolerated diagnostic tool used to confirm the presence of abnormal esophageal acid reflux. While few complications have been reported, technical difficulties can occur, including poor data reception, misplacement, and early dislodgement. Rarely, more serious complications can occur, ranging from esophageal wall trauma to capsule aspiration. Gastroenterologists performing this procedure should be aware of the low, but non-trivial, risk of complications.

Key words: Gastroesophageal reflux disease; Esophageal pH monitoring; Bravo capsule; Dislodgement; Esophagogastroduodenoscopy

Core tip: We report an unexpected, and so far unreported, complication of a Bravo pH capsule dislodgment. While Bravo probe placement is generally a well-tolerated procedure, dislodgment into the pyriform sinus in this case necessitated immediate action by an interdisciplinary team. Complications of Bravo capsule use range from technical difficulties, such as poor data reception and non-deployment, to more serious events such as esophageal wall trauma and capsule aspiration. Gastroenterologists performing this procedure should be aware of the risk of potential complications.

Kumar A, Kramer E, Chokhavatia S. Unreported complication of Bravo pH capsule dislodged into the pyriform sinus. *World J Gastrointest Endosc* 2015; 7(5): 573-574 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i5/573.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i5.573

LETTER TO THE EDITOR

We report an unanticipated, previously undocumented complication of Bravo capsule dislodgement. A forty-five year old patient with gastroesophageal reflux disease (GERD), non-compliant with medical therapy, presented with increasing cough, hoarseness, and other acid reflux symptoms. To verify presence of acid reflux, he underwent upper endoscopy and Bravo pH testing at our hospital. The gastroesophageal junction (Z line) was visualized at a distance of 40.0 cm from dentition. The Bravo device was deployed at 34.0 cm from dentition (6 cm above the Z line). When the capsule was not endoscopically visualized to be adherent to the esophageal wall, the endoscope was advanced beyond 34.0 cm to assess for possible device movement to the distal esophagus or stomach. When the capsule was not visualized at these locations, the endoscope was withdrawn. When the scope was withdrawn from the upper esophageal sphincter, the device was seen in the left pyriform sinus (Figure 1). The nonadherent capsule likely was either pulled up by the endoscope during withdrawal or coughed up by the patient. ENT and pulmonary physicians were immediately consulted for assistance in ensuring safe removal of the capsule from this precarious location, as there was significant risk for pulmonary dislodgement. After the anesthesiologist performed endotracheal intubation, ENT successfully retrieved the capsule with a foreign body removal forceps without further complications.

The Bravo pH test is generally a well-tolerated diagnostic tool that can verify the presence of abnormal esophageal acid reflux and determine if treatment refractory symptoms are due to persistent acid reflux in patients with GERD. As the deployment of the Bravo pH device is typically a innocuous procedure[1], very few complications have been reported. Technical difficulties most commonly include non-deployment, non-attachment, misplacement, premature dislodgement, and insufficient data reception. Infrequently, patients develop significant chest pain after capsule placement[2], necessitating removal. Rarely, more serious complications can occur in less than 2% and include esophageal wall trauma, excessive bleeding, and capsule aspiration[3]. In one reported case, the patient aspirated the capsule into the bronchus immediately after deployment, causing retching, heavy coughing, and desaturation to 74%[4]. After initial pushing into stomach with a transnasal video-endoscope, this capsule was removed with grasping forceps.

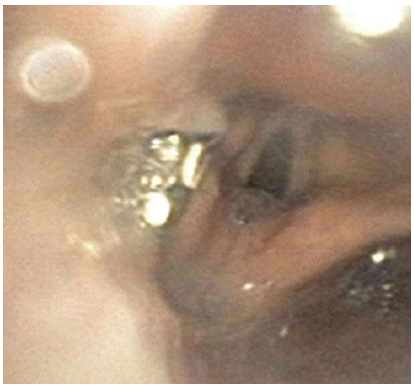

Figure 1 Bravo pH capsule in left pyriform sinus.

Gastroenterologists using the Bravo pH test should be cognizant of the low but non-trivial risk of complications, ranging from technical difficulties to aspiration of a dislodged capsule. Providers can use reports of documented complications to troubleshoot and resolve difficulties that may arise during deployment of Bravo pH capsules.

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EDITORIAL

Endoanal ultrasonography in fecal incontinence: Current and future perspectives

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Abstract

Fecal incontinence has a profound impact in a patient's life, impairing quality of life and carrying a substantial economic burden due to health costs. It is an underdiagnosed condition because many affected patients are reluctant to report it and also clinicians are usually not alert to it. Patient evaluation with a detailed clinical history and examination is very important to indicate the type of injury that is present. Endoanal ultrasonography is currently the gold standard for sphincter evaluation in fecal incontinence and is a simple, well-tolerated and non-expensive technique. Most studies revealed 100% sensitivity in identifying sphincter defect. It is better than endoanal magnetic resonance imaging for internal anal sphincter defects, equivalent for the diagnosis of external anal sphincter defects, but with a lower capacity for assessment of atrophy of this sphincter. The most common cause of fecal incontinence is anal sphincter injury related to obstetric trauma. Only a small percentage of women are diagnosed with sphincter tears immediately after vaginal delivery, but endoanal ultrasonography shows that one third of these women have occult sphincter defects. Furthermore, in patients submitted to primary repair of these tears, ultrasound revealed a high frequency of persistent sphincter defects after surgery. Three-dimensional endoanal ultrasonography is currently largely used and accepted for sphincter evaluation in fecal incontinence, improving diagnostic accuracy and our knowledge of physiologic and pathological sphincters alterations. Conversely, there is currently no evidence to support the use of elastography in fecal incontinence evaluation.

Key words: Endoanal ultrasonography; Fecal incontinence; External anal sphincter; Internal anal sphincter; Obstetric anal sphincter injuries; Three-dimensional endoanal ultrasonography; Elastography

Core tip: Clinicians need to be more alert to fecal incontinence, which is a serious under-reported problem. Endoanal ultrasonography is currently the gold standard for sphincter evaluation in these patients. The most important cause of fecal incontinence is obstetric injury and the most relevant questions and controversies are related to this. The diagnosed of sphincter injury after delivery and after complete primary repair is much lower to that found by ultrasonography, and many

of these women developed fecal incontinence. The clinical evaluation, technical aspects, advantages and limitations and the current role of three dimensional ultrasonography and real-time elastography will also be discussed.

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FECAL INCONTINENCE: WHAT SHOULD WE KNOW BEFORE PERFORMING ENDOANAL ULTRASONOGRAPHY?

Fecal incontinence (FI) has a profound impact in a patient's personal life, impairing social interaction, professional and sexual activity and carries a substantial economic burden due to health costs.

The prevalence varies from 2.2% to 25 % in the community[1] and up to 50% of the nursing home residents[2]. Although a relevant problem, it is an underdiagnosed condition, since many affected patients are reluctant and embarrassed to report it. In a study by Sultan *et al*[3], none of the women that developed FI after vaginal delivery spontaneously reported their symptoms or sought medical attention. So, it is essential that health professionals, mainly those who look after women ask about symptoms of FI, especially in the postpartum period.

Loss of continence can result from several mechanisms, dysfunction of the anal sphincters, abnormal rectal compliance, decreased rectal sensation, altered stool consistency, or a combination of any of these abnormalities. FI is often multifactorial condition, may be the consequence of local, anatomical or systemic disorders, non-traumatic or traumatic lesions. Not every patient with sphincter injury develops incontinence, and, in addition, patients can have incontinence without sphincter injury. There are several women that only develop FI several years (20 or 30 decades) after delivery.

Patient evaluation should always include a detailed clinical history, inspection of the perianal area and a digital rectal examination. The type of incontinence (urge or passive), obstetric history (vaginal deliveries, use of forceps, perineal laceration), previous anorectal surgery, coexisting comorbidities, anal resting tone and squeeze pressure are fundamental to understand the mechanism behind the impairment and this information should never be neglected. Patients with urge incontinence often have weakness of the external anal sphincter (EAS) and reduced squeeze pressures or reduced rectal capacity with rectal hypersensitivity. Patients with passive FI, often have weakness of the internal anal sphincter (IAS) and lower resting pressure[4]. Taking all this information into consideration before endoanal ultrasonography (EAUS) is performed, can indicate the type of injury found.

There are several clinical scores that can be used to access severity, like the American Medical System, Pescatori score, Vaizey scale, Rockwood score or the Cleveland Clinic (Wexner) Incontinence Score[5]. These scores allow a more objective and reproducible assess of FI severity and a comparison of patients and treatments, namely the outcomes of both conservative and surgical treatments.

EAUS IN FECAL INCONTINENCE

EAUS is currently the gold standard technique for sphincter evaluation in FI[6]. The first studies in EAUS were performed by Law *et al*[7,8], in the early 1990s, comparing EAUS with electromyography, EAUS proved to be better tolerated and a useful technique for assessing defects of the anal sphincters. Most studies revealed 100% sensitivity in identifying sphincter defect. It is important to search for sphincter discontinuity, sphincter thinning and perform perineal body measurement. Discontinuity of the sphincter indicates a tear, and scarring is characterized by loss of the normal texture that usually has low reflectiveness. IAS tears appear normally as hyperechoic breaks and EAS tears appear as relatively hypoechoic areas (Figure 1). IAS thickness measurement in adults is abnormal if less than 2 mm (suggestive of degeneration) and generalized EAS atrophy is difficult to evaluate in EAUS. Perineal body measurement improves visualization of anterior sphincter lesions in females. A perineal body thickness of 10 mm or less is considered abnormal, whereas 10 mm to 12 mm is associated with sphincter defect in one-third of patients and those with 12 mm or more are unlikely to harbour a defect unless they previously have undergone reconstructive perineal surgery[9-11].

During the exam, the number, the circumferential extent (radial angle in degrees or in hours of the clock) and longitudinal extent (proximal, distal or full length) of the defect should be reported.

There are several possible pitfalls during EAUS that can simulate sphincter tears. A correct diagnose is important for FI assessment and for choosing the best therapeutic approach; a proper training in EAUS is fundamental. In many cases, it is not the endoscopic ultrasound practitioner that is performing the EAUS. These are two different techniques and specific training is needed for endoscopic ultrasound practitioners enrolled in EAUS.

Anal sphincteroplasty should be considered in patients with FI who do not respond to conservative therapy and who have an anatomic sphincter defect. Short-term outcomes suggest good-to-excellent results,

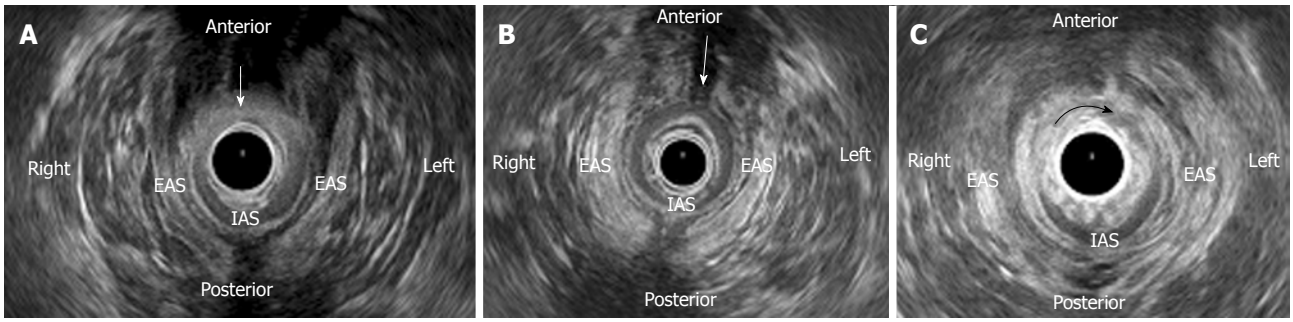

Figure 1 Endoanal ultrasound images of patients with fecal incontinence. A: A combined defect (arrow) of the external anal sphincter (EAS) from 10 to 2 o'clock and of the internal anal sphincter (IAS) from 9 to 3 o'clock positions, in a woman due to an obstetric anal sphincter injury; B: An anterior EAS defect (arrow), in a woman due to an obstetric anal sphincter injury; C: An IAS defect (arrow) from 8 to 4 o'clock position, in a man as a complication of a previous anorectal surgery (due to fistula).

but the benefits tend to deteriorate with long-term follow-up[4].

EAUS and endoanal magnetic resonance imaging (MRI) are comparable for the diagnosis of EAS defects, but IAS defects are less well assessed on MRI[12]. EAUS is simple, well-tolerated and non expensive. Endoanal MRI is expensive, not generally available, unsuitable in claustrophobic patients and those with metal implants. Endoanal MRI is superior to two-dimensional (2D) EAUS for identifying EAS atrophy. EAUS cannot distinguish fatty infiltration from normal muscle tissue and the boundaries of the EAS are harder to determine. Comparison between endoanal MRI and three-dimensional (3D) EAUS capacity for EAS atrophy evaluation revealed conflicting results. Cazemier *et al*[13] showed that both techniques are comparable in detecting EAS atrophy, although there is a substantial difference in grading. West *et al*[14] demonstrated that no 3D EAUS measurements are suitable parameters for assessing EAS atrophy. It is important to recognize atrophy because it is associated with a poor clinical outcome of sphincter repair.

EAUS and anorectal manometry are complementary investigations. EAUS allows anal sphincter morphology assessment and manometry anal sphincter function evaluation. Studies comparing both techniques show good correlation between them in partial or complete defects of the anal sphincter[15].

Most studies show poor agreement between digital anorectal examination and EAUS. In a study by Sultan *et al*[16] the clinical examination was only 50% accurate at predicting anal sphincter defects and Jeppson *et al*[17] show a specificity of 32% for digital anorectal examination in detecting anal sphincter defects seen on EAUS; however, Dobben *et al*[18] reported increased correlation between digital examination and EAUS based on size of the sphincter defect. Notwithstanding, performing digital anorectal examination is important in the evaluation of a patient with FI, helping to differentiate other potential causes such as tumor or fecal impaction.

It is important to ask patients about the presence of FI directly rather than relying on spontaneous reporting[4] and initial patient evaluation should include a detailed clinical history, inspection of the perianal area and a digital rectal examination. Manometry is important for anal sphincters function evaluation, anal sphincter resting and squeeze pressures are the key parameters[4]. EAUS is the gold standard for diagnosing anal sphincters tear and IAS degeneration. If EAS atrophy is suspected, endoanal MRI should be performed. Needle electromyography of the anal sphincter should be considered in patients with clinically suspected neurogenic sphincter weakness, particularly if there are features suggestive of proximal (*i.e.*, sacral root) involvement[4].

OBSTETRIC ANAL SPHINCTER INJURIES: A REAL PROBLEM

The most common cause of FI is anal sphincter injury related to vaginal delivery in female, due to direct anal sphincter laceration or indirect damage to sphincter innervation.

Two EAUS-based scoring systems have been proposed to define the severity of anal sphincter damage, both of them in women with obstetric anal sphincter injuries (OASIS). Starck *et al*[19] introduced a specific score, with 0 indicating no defect and 16 corresponding to a defect > 180° involving the whole length and depth of both sphincters. Norderval *et al*[20] reported a simplified system, including fewer categories and not recording partial defects of the IAS. The maximal score of 7 denotes defects in both the EAS and the IAS exceeding 90° in the axial plane and involving more than half of the length of each sphincter. Both scoring systems have demonstrated a good correlation between the extent of sphincter defects and the degree of FI. Scoring systems may help the clinician in choosing the appropriate treatment for patients with FI, but studies are needed.

Obstetric tears are divided into several subclasses, initially described by Sultan[21], and then adopted by the Royal College of Obstetricians and Gynaecologists (RCOG): injury to the perineal skin grade 1; injury to

the perineum involving the perineal muscles grade 2; involving the anal sphincter < 50% EAS grade 3a; > 50% EAS grade 3b; involvement of the IAS grade 3c; involvement of the anal sphincter as well as the anorectal epithelium grade 4[19]. OASIS encompasses both third- and fourth-degree perineal tears. They are identified in 0.6%-9.0% of vaginal deliveries where mediolateral episiotomy is performed, but the detection in EAUS is much higher[22].

A landmark study by Sultan *et al*[3] in 1993, using EAUS reported occult anal sphincter injury in 35% of women, six weeks after their first vaginal delivery. The incidence of *de novo* defects in multiparous females was 4.2%. The incidence of occult sphincter damage after vaginal delivery was unknown, previously to this study. Only 3% of primiparous women had an injury during delivery that was apparent in clinical examination. Results also suggested that the structural injury to the sphincters was permanent, since they were also present at 6 mo. Notably, only one third of women with sphincter defects in EAUS had FI.

In 2003, Oberwalder *et al*[23] published a meta-analysis of 717 vaginal deliveries (including the study by Sultan[21]) and found an incidence of occult sphincter damage of 26.9% in primiparous women and 8.5% of new defects in multiparous women. In one third of these women, postpartum sphincter damage was symptomatic.

Perhaps women with occult sphincter defect, but without FI can have sufficient residual sphincter function[21] or, since several mechanisms contribute to continence, they may compensate for this injury. The peak of incidence of FI is in the fifth and sixth decades of life in women, so the cumulative effect of deliveries, aging, menopause, progression of neuropathy may contribute for sphincter weakness in the long term and FI developing several years (20 or 30 decades) after delivery.

The clinical relevance of screening for occult anal sphincter laceration is controversial, mainly in asymptomatic defects. In a prospective cohort study by Frudinger *et al*[24], including primiparas with occult anal sphincter lacerations, at 10-year follow-up, only women who were symptomatic in the immediate postpartum period had deterioration over time of FI. Conversely, a randomized control trial by Faltin *et al*[25] showed that EAUS after childbirth improves the diagnosis of anal sphincter tears, and their immediate repair decreases the risk of severe FI. In this study, 752 primiparas with no clinically recognized anal sphincter laceration (occult) were assigned to undergo or not an EAUS immediately after delivery and diagnosed lacerations were repaired. In the EAUS group significantly fewer women reported severe FI at 3 and 12 mo compared to those who did not undergo EAUS. Using these data, it was estimated that 29 women would have to undergo EAUS to prevent one case of severe FI.

The current guidelines of the RCOG from 2007[22] state that "As there are clear difficulties with availability, access to staff trained in EAUS on the labour ward, image quality and patient acceptability, the use of EAUS in detecting anal sphincter injury immediately after delivery should be viewed as a research tool at present". There is no recommendation about screening women later after vaginal delivery for occult sphincter defects. Thus, data are controversial for asymptomatic patients. There are no cost-benefit studies of EAUS in this setting, or whether asymptomatic patients could benefit from it. Currently, the major investment should be in improving the identification of OASIS immediately after delivery. It is unclear, if occult sphincter defects are missed tears or true "occult" defects; probably the vast majority are not diagnosed clinically at time of delivery.

If an OASIS is identified immediately after vaginal delivery, it should be repaired. The RCOG[22] recommend that for repair of the external anal sphincter, either an overlapping or end-to-end (approximation) method can be used; if the IAS is identified, it is advisable to repair separately with interrupted sutures. Repair should be conducted in an operating theatre, under regional or general anaesthesia, by appropriately trained practitioners. Although primary reconstruction of the sphincters, more than 50% of women experience some change in continence (mainly to flatus) and the effect deteriorates with time[26]. Having a persistent sonographic defect after primary repair of OASIS has been shown to be associated with ongoing incontinence symptoms[27,28]. Studies show a high frequency of endosonographic sphincter defects after primary repairs, between 54% and 93% of women[29-32]. In a study using EAUS performed 2-7 d after delivery in women who had undergone a primary repair of an OASIS, 90% had endosonographic sphincter defects. In this study the extent of the endosonographic defects were mainly determined by the surgical experience of the doctor performing the repair, and not by the clinical degree of the tear[19].

The current guidelines of the RCOG[22] also do not make recommendations about using EAUS for confirming a complete primary repair. According to these guidelines "If a woman is experiencing incontinence or pain at follow-up, referral to EAUS and anorectal manometry should be considered". Considering the very high rate of sphincter defects detected by EAUS after primary repair, the high percentage of women that have some continence alteration and the difficulty in assessing the complete reparation of defects immediately after delivery, is EAUS confined to symptomatic women enough? In 2006, Starck *et al*[32] conducted a prospective study that included women who had suffered an OASIS at delivery and underwent EAUS at 1 wk, 3 mo and 1 year after primary suture. There was a positive correlation between the endosonographic sphincter defect score at 1 wk, 3 mo and 1 year and the Wexner incontinence score at 1 and 4 years. Endosonographic sphincter defect score at 1 wk was the variable that was most predictive of the Wexner score at 4 year. There are no systematic reviews or randomised

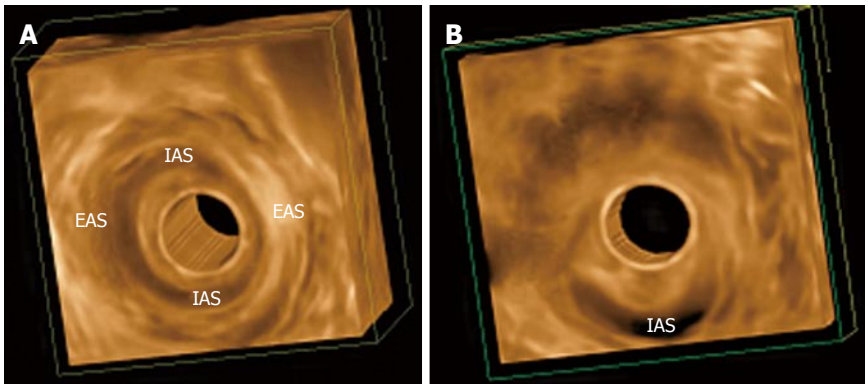

Figure 2 Three-dimensional endoanal ultrasonography images. A: Normal appearance of the external anal sphincter (EAS) and internal anal sphincter (IAS); B: An IAS defect in woman as a complication of a previous anorectal surgery (due to fistula).

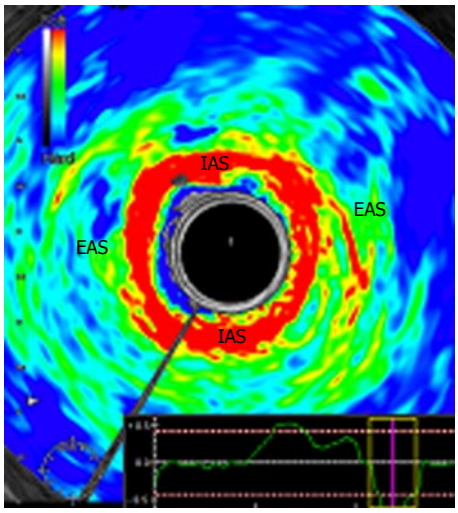

Figure 3 Normal appearance of the internal and external anal sphincters in endoanal ultrasound real-time elastography. The internal anal sphincter appears in red (softer) and external anal sphincter in green/blue (harder). EAS: External anal sphincter; IAS: Internal anal sphincter.

controlled trials to suggest the best method of follow-up after obstetric anal sphincter repair[22].

EAUS can also be important to aid decision for future delivery. According to the RCOG guidelines[22], "all women who have sustained an OASIS in a previous pregnancy and who are symptomatic or have abnormal EAUS and/or manometry should have the option of elective caesarean birth. Between 17% and 24% of these women with previous third-degree tear developed worsening fecal symptoms after a second vaginal delivery".

THREE-DIMENSIONAL EAUS

Three-dimensional EAUS has been used in the evaluation of the anal canal since the late 1990s[33,34]. Before 3D, imaging of the anal canal was mainly limited to the axial plane, impairing accurate longitudinal measurement, which is important for complete surgical repair. Three-dimensional EAUS produces a digital volume that can be seen from any plane, allowing length, thickness, area, and volume measurement (Figure 2).

Christensen *et al*[35] conducted a study to investigate the differences of 3D and 2D EAUS in visualizing damage to the anal sphincter complex. The agreement between the two observers that evaluated the images was better when using 3D (98.2% using 3D and 87.9% using 2D), so 3D improved diagnostic confidence.

The studies involving 3D EAUS also allowed for a better understanding of sex differences in sphincter configuration and between parous and non-parous females, continent and incontinent patients[36]. FI was not associated with loss of sphincter volume, but anterior sphincter length and EAS thickness is smaller[36]. Williams *et al*[37] assessed changes to anal canal morphology after delivery, in the absence of sphincter trauma, and there was a decrease in the length of the anterior portion of the EAS following childbirth.

ULTRASOUND REAL-TIME ELASTOGRAPHY

Real-time elastography (RTE) has been evaluated previously in tumours and inflammatory tissues, and has proven to provide valuable additional information.

In 2010, Allgayer *et al*[38] performed the first study to access RTE in FI, 50 patients were included. The IAS, a smooth muscle, consisted of softer areas (red) than the EAS and, conversely, the EAS, a striated type of muscle, contained harder elements (blue) than the IAS (Figure 3). There was an absence of a correlation of elastogram color distributions of the IAS and EAS with major clinical, functional and gray-scale B-mode parameters, so RTE did not seem to provide additional information in the diagnostic workup of FI. However, there was a non-significant increase in the percentage of blue (hard) areas in the IAS in patients neoadjuvantly irradiated for rectal or cervical cancer compared to non-irradiated patients. To confirm this data, the authors performed a larger study[39], but RTE with quantitation of sphincter elastic properties yielded no further diagnostic and prognostic information compared to

conventional EAUS in irradiated and non-irradiated patients and, therefore, cannot be regarded as a new tool in the assessment of those patients.

Hence, currently there is not evidence to support the use of RTE in FI evaluation.

CONCLUSION

FI is a serious clinical and social problem, frequently under-reported, and clinicians need to be more alert to it in the routine clinical practice. EAUS is a fundamental tool when assessing these patients.

The most important cause of FI is obstetric injury and the more relevant questions and controversies in EAUS are related to this aetiology. The diagnosed of sphincter injury after delivery and after complete primary repair is much lower to that found by EAUS, and many of these women developed FI, later in life.

While three-dimensional EAUS is currently accepted for sphincter evaluation in FI, there is presently no evidence to support the use of elastography.

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REVIEW

Cholangiocarcinoma and malignant bile duct obstruction: A review of last decades advances in therapeutic endoscopy

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Abstract

In the last decades many advances have been achieved in endoscopy, in the diagnosis and therapy of cholangiocarcinoma, however blood test, magnetic resonance imaging, computed tomography scan may fail to detect neoplastic disease at early stage, thus the diagnosis of cholangiocarcinoma is achieved usually at unresectable stage. In the last decades the role of endoscopy has moved from a diagnostic role to an invaluable therapeutic tool for patients affected by malignant bile duct obstruction. One of the major issues for cholangiocarcinoma is bile ducts occlusion, leading to jaundice, cholangitis and hepatic failure. Currently, endoscopy has a key role in the work up of cholangiocarcinoma, both in patients amenable to surgical intervention as well as in those unfit for surgery or not amenable to immediate surgical curative resection owing to locally advanced or advanced disease, with palliative intention. Endoscopy allows successful biliary drainage and stenting in more than 90% of patients with malignant bile duct obstruction, and allows rapid reduction of jaundice decreasing the risk of biliary sepsis. When biliary drainage and stenting cannot be achieved with endoscopy alone, endoscopic ultrasound-guided biliary drainage represents an effective alternative method affording successful biliary drainage in more than 80% of cases. The purpose of this review is to focus on the currently available endoscopic management options in patients with cholangiocarcinoma.

Key words: Cholangiocarcinoma; Malignant bile duct obstruction; Interventional endoscopy; Endoscopic therapy; Self-expandable metal stent

Core tip: Cholangiocarcinoma are an heterogeneous group of tumor and represent a challenge in medicine because of the difficulty in establishing the diagnosis and an high recurrence rate after surgery which represents the only curative treatment. Endoscopy has gained a

pivotal role in the management of the disease, before surgery if patient is amenable to surgical intervention or in those unfit for surgery. New stent prototype able to release drugs and/or photodynamic therapy have been commercialized with promising results. When endoscopy fails, endoscopic ultrasound-guided biliary drainage represents an effective alternative method affording biliary drainage.

Bertani H, Frazzoni M, Mangiafico S, Caruso A, Manno M, Mirante VG, Pigò F, Barbera C, Manta R, Conigliaro R. Cholangiocarcinoma and malignant bile duct obstruction: A review of last decades advances in therapeutic endoscopy. *World J Gastrointest Endosc* 2015; 7(6): 582-592 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i6/582.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i6.582

INTRODUCTION

Cholangiocarcinoma (CC) is an epithelial malignancy with markers of cholangiocyte differentiation arising within the biliary tree. It is characterized by a marked genetic heterogeneity which explains its high therapeutic resistance[1]. CC is rare but related mortality is high because it is most often diagnosed at a locally advanced stage, not amenable to curative surgery.

Although the incidence of CC is rapidly increasing it remains a rare disease. Data about endoscopic therapeutic options are often comprised into large databases of malignant obstructive jaundice mainly due to pancreatic head cancer. This may have influenced the reported outcomes and benefits of endoscopic treatment modalities[2].

Currently, classification of CC is based on anatomical site, defining intrahepatic, perihilar and distal CCs[2]. Intrahepatic CC is defined as a tumor located proximally to the branch of the right and left lobe bile ducts; the extrahepatic and perihilar cholangiocarcinoma is localized to the area between the second branches bile ducts and the insertion of the cystic duct into the common bile duct (Figure 1); whereas distal CC is confined to the area between the origin of the cystic duct and the ampulla of Vater[3].

Several progresses in the management (diagnosis, treatment and palliation) of CC have befallen in the last decades. However, surgical resection or liver transplantation represents the only potential curative alternative for all subtypes of CC[2]. Unfortunately, involvement of the vascular structures and lymphnodes is associated with very low 5-year survival rates even after curative-intent surgery[2] and, overall the clinical results of patients undergoing liver resection are disappointing with a survival rate of 20%-35% within 5-year[4-9]. Palliative therapy, in patients not amenable of surgical intervention includes systemic chemotherapy and loco regional therapies (TACE, RFA) to reduce masses but increased survival rate has not yet been shown[2].

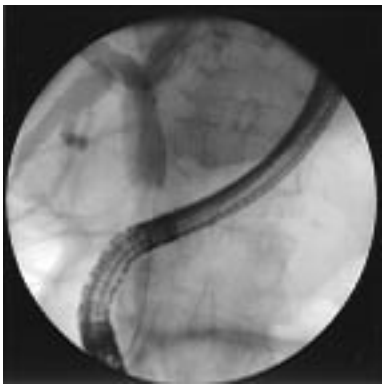

Figure 1 Distal cholangiocarcinoma during endoscopic retrograde cholangiography.

The main onset of CC is unpainful icterus in > 90% of patients and preoperative biliary drain (endoscopic or percutaneous), has been introduced because jaundice is thought to increase the risk of postoperative complications, but the advantages of this procedure are still unclear[10]. Moreover, in patients who will undergo neo-adjuvant therapy the work-up preceding chemotherapy includes biliary stenting. In the last decades advances in stenting materials and acknowledgement of the benefits in the post-surgical outcome due to pre-operative biliary drainage has led endoscopic retrograde cholangiography (ERC) to a pivotal role in the work up of CC, both in patients amenable to surgical intervention and in those unfit for surgery.

EPIDEMIOLOGY

The reported incidence in the United States is one or two cases per 100000 person/year, also in Europe is 1.5 per 100000 person/year, and it accounts for approximately 3% of all gastrointestinal malignancies. CC is the most common primary malignancy of the liver after hepatocellular carcinoma. An increase in intrahepatic CC mortality has been registered worldwide particularly in western compared with central and northern Europe. The increased incidence of intrahepatic CCs may in part be attributed to new diagnostic methods for obstructive jaundice allowing to identify biliary malignancies which previously would have gone undetected. In spite of this, the rising incidence of intrahepatic CC has not been associated with an increased proportion of early stage or small size lesions[11-15].

Perihilar disease represents about 50%, distal disease 40% and intrahepatic disease less than 10% of CC cases. Age-adjusted rates of CC are reported to be the highest in Hispanic and Asian populations (2.8-3.3 per 100000 person/year) and lowest in non-Hispanic white people and black people (2.1 per 100000 person/year)[2].

RISK FACTORS

The main risk factors are considered primary sclerosing

cholangitis (PSC) and choledochal cysts. The per-year cumulative risk of CC in patients with PSC is 1.5% after the development of jaundice and the prevalence of CC in patients with PSC ranges between 8% and 40%. A recent study from the Netherlands showed that the risk of CC for patients with PSC is 9% after 10 years from the time of the diagnosis[13]. However for the majority of patients a specific risk factor has not been identified. Recently, cirrhosis and viral hepatitis have also been proposed as potential risk factor, particularly for intrahepatic CCs[2]. Another risk factor for the development of CC are choledochal cysts (incidence of CC is between 10% and 20%), significantly reduced by early diagnosis and surgical ablation[15]. The carcinogenetic pathway is not clear although biliary stasis and reflux of pancreatic fluids are suspected through chronic inflammation way[1]. Unfortunately, CC can also occur years after resection of the cyst suggesting some genetic abnormality predisposing to the development of biliary neoplasia[16].

MANAGEMENT

CC have an remarkably poor five-year survival rate estimated from 5% to 10%. Some difference could be detected if survival is stratified by location of the lesion: the percentage of patients amenable of surgical resection is higher if the location is distal CCs compared to proximal (intrahepatic and perihilar) tumors. Nakeeb *et al*[17] published a large series about resectability rates for distal, intrahepatic, and perihilar lesions: 91%, 60%, and 56%, respectively[17]. Moreover patients who undergo a potentially curative resection, at pathology examination achieve tumor-free margins barely in 20% to 40% of proximal and 50% of distal location[18]. These percentage are even lower if a proximal tumor-free margin of at least 5 mm is requested as a curative criteria.

Surgery data for CCs have increased over year, largely owing to more aggressive surgery strategies and extended criteria for resectability.

Criteria for resectability of CC in the United States include[19]: (1) absence of retro-pancreatic and celiac nodal metastases or distant liver metastases[20]; (2) absence of portal vein or main hepatic artery involvement; (3) absence of extrahepatic adjacent organ invasion; (4) absence of spread disease; however, resectability is finally determined at surgical exploration, particularly with perihilar tumors[21]. Due to their location within the upper hepatoduodenal ligament, these tumors often extend into the liver and major vascular structures, and preoperative evaluation of resectability is often difficult. Thus, surgical exploration is indicated for proximal bile duct carcinomas whenever feasible.

Whether preoperative biliary decompression using an endoscopically or percutaneously placed stent should be carried out in patients who present with obstructive jaundice is still controversial and will be discussed below. Obstructive jaundice is the most common presenting symptom of CC. If biliary drainage is advantageous or not is still under debate. Cholestatic malabsorption, liver dysfunction, and biliary cirrhosis develop rapidly with unresolved obstruction and severe liver dysfunction is one of the main factors that increase postoperative morbidity and mortality following surgical resection[21].

The European Society of Gastrointestinal Endoscopy (ESGE) focused his attention on the treatment options in order to select the most appropriate procedure (with or without sphincterotomy) and stent choice (plastic or metal, short or long) on the basis of patient's disease stage and tumor location.

ENDOSCOPIC TREATMENT IN PATIENTS ELIGIBLE FOR SURGERY

Preoperative biliary drainage was introduced to improve the postoperative outcome, for the reason that patients with jaundice had an increased risk of postoperative complications[10-22]. In various experimental studies and retrospective case series, preoperative biliary drainage reduced morbidity and mortality after surgery[23-25]. Nevertheless, two meta-analyses of randomized trials and a systematic review of descriptive series showed that the overall complication rate in patients undergoing preoperative biliary drainage was higher than in those who were referred straight to surgery[26]. In patients, fit for surgery for malignant common bile duct (CBD) obstruction, introduction of a plastic biliary stent followed by postponed surgery was associated with a higher morbidity compared with surgery within 1 wk. This was partly explained by complications associated with the biliary drainage procedure itself. Nevertheless, in many institution preoperative biliary drainage has been incorporated into the work-up of cancer of the pancreatic head or distal CBD[27]. In 2010 van der Gaag *et al*[10] conducted a large multicenter randomized trial in which 202 patients were randomized to receive whether preoperative biliary drainage followed by surgery within 4-6 wk, or surgery alone within 1 wk of diagnosis. Serious complications were registered in 39 percent in the immediate surgery group and 74 percent in the group with biliary drainage (RR = 0.54, $P < 0.001$)[28]. Neither mortality nor length of hospital stay were reduced in patients who underwent preoperative drainage. Moreover, the presence of a stent within the biliary tree could decrease the accuracy of diagnostic imaging to predict tumor resectability and the surgeon's ability to determine the proximal tumor extent during intervention.

The ESGE recommends preoperative biliary drainage only in patients who will undergo neo-adjuvant therapies or in patients with biliary sepsis, or in patients with troublesome itching or predicted delay in surgical intervention[29-50].

How to achieve biliary drainage: endoscopically or *via* a percutaneous approach? Retrospective series and at least two prospective trials conducted in patients with

obstructive jaundice from a malignant hilar obstruction (mainly proximal CCs or gallbladder cancer) suggest that successful palliation of jaundice is more likely and the incidence of post-procedure cholangitis may be lower with the percutaneous as compared to the endoscopic approach[31-33].

Endoscopic biliary drainage can be obtained using either plastic or self-expandable metal stents (SEMSs). Many stents (plastic and metal, both covered and uncovered), are available and both produce similar short-term results with respect to clinical success, morbidity, mortality, and improvement in quality of life[50]. A systematic review concluded that neither stent type offered a survival advantage[34]. Accordingly, in patient candidate for surgery the choice of stent should be guided by tumor location and extension.

The use of a plastic stent is inexpensive and effective, and the stent can be easily removed or replaced. Plastic stents, however, eventually develop occlusion by sludge and/or bacterial biofilm, and maintaining biliary drainage with plastic stents usually requires repeated endoscopic procedures. Plastic stents are available in multiple diameters ranging from 7 to 11.5 French, though 10 French stents are the most commonly used for distal common bile duct obstruction[35]. SEMSs provide a larger opening diameter than plastic one thus enabling prolonged patency and rapid biliary drainage[50]. However, the cost of metal stents is considerably higher and their removal may be challenging. The indications for using SEMSs in patients candidate to surgery is not well established yet. The main reason for the preferential use of plastic stents in patients with pancreatic cancer was the notion that uncovered SEMS could hinder pancreatoduodenectomy by interfering with transection of the bile duct proximal to the neoplasia[36]. With growing experience it has been shown that, when 2 cm or more of the common hepatic duct can be exposed proximally to the SEMS, the surgical procedure is not more complex than in the presence of a plastic stent[35].

Which kind of metal stent? SEMS models have been significantly developed and changed in the last decade: out of five types in use ten years ago, only single one is still available[29-37]. The distinguishing features of the various available SEMSs are prices, shortening ratio, radio-opacity, covering, radial force, flexibility, size of open cells of the mesh, anchoring mechanism and design of the tip[29-37]. *In vitro* measurements of radial expansion force and of flexibility have shown markedly different results between the various SEMSs, including covered and uncovered models of otherwise identical SEMSs[38]. The opening procedure shorten SEMSs by 0%-50%: different models with different shortening ratio are available. If the stricture is long and narrow the deployment could be difficult and irregular. Large open cells in the mesh may allow tissue to ingrow into the stent lumen, getting an inefficacious biliary drainage either immediately after the insertion or during follow-up[39-41]. Some special SEMS models, studied for hilar strictures, have a section with larger mesh cells in order to allow the introduction through the mesh of a new stent to reach another biliary branch[29]. In case of covered SEMSs, anti-migration mechanisms are particularly important: these may include flared ends or external fins, but some complications have been registered like bleeding of the bile duct wall caused by decubitus ulcers[42]. Recently models with soft ends and slip-knot to facilitate removal have been commercialized reducing the risk of bleeding or perforation if the wires are sharp and not fused.

ENDOSCOPIC TREATMENT IN PATIENTS WITH LOCALLY ADVANCED DISEASE

The long-term prognosis in CC patients who have undergone potentially curative surgical resection remains poor: these discouraging results have prompted interest in the use of neo-adjuvant therapy in patients amenable to surgery in order to improve survival. Such a strategy has also been proposed in locally advanced cases aiming to downstage the disease to allow surgical resection. This topic is valid for distal as well as for hilar CC. Recently in case of bilateral extension beyond the secondary radicles curative resection has been proposed after application of neoadjuvant therapy PDT oRFA (its applications and results will be discussed later).

The choice of the best stent to be used in this selected patient is less controversial than in those eligible for surgery. The efficacy of plastic stents is generally poor: more than one half of patients treated with plastic stents during neo-adjuvant therapy requires repeated stent replacement owing to stent occlusion or cholangitis[43]. Several studies have demonstrated that the use of SEMSs leads to improved outcome during neo-adjuvant therapy. Aadam *et al*[44] reported a 7 times higher complications rate and a 3 times higher hospitalization rate in patients treated with plastic stents as compared with patients treated with metal stents.

Uncovered and covered SEMSs are available. Uncovered SEMSs have a mesh design that allows them to be embedded in the biliary duct wall but it also makes them susceptible to tissue in-growth, which can lead to occlusion in as many as 20% of cases. Covered SEMSs were designed to prevent tissue in-growth but, as expected their use is associated with an increased rates of migration[45]. In an effort to guarantee patency and decrease rates of migration, partially covered SEMSs have been developed. In a recent meta-analysis, Saleem *et al*[46] concluded that covered SEMSs supply a significantly longer patency than uncovered SEMSs (average 60 d), but at the price of a higher migration rate[46-48]. Similar rates of cholecystitis were also found (approximately 2% in each group). Through subgroup analysis, Saleem *et al*[46] did not find any difference in rates of migration or stent patency comparing partially covered SEMSs to fully covered SEMSs. Contrastingly, in a retrospective cohort study analyzing the outcome

of 749 patients by Lee *et al*[47] no difference in stent obstruction was found (covered SEMSs 35%, uncovered SEMSs 38%) . While obstruction due to tumor in-growth was more frequent in patients treated with uncovered SEMSs (76% *vs* 9%, $P < 0.001$), other mechanisms of obstruction occurred in patients treated with covered SEMSs, including sludge formation and food debris. Conversely, higher rates of migration (36% *vs* 2%, $P < 0.001$) and of acute pancreatitis (6% *vs* 1%, $P < 0.001$) were found in patients treated with covered SEMSs[47]. This study was retrospective and open, and follow-up was not standardized. In a recent study, Kitano *et al*[48] used a covered SEMS modified to reduce migration. The anti-migration characteristics consisted of low axial forces and uncovered flare ends, and was compared to uncovered SEMSs of similar design. One hundred and twenty patients were included in this prospective randomized multicenter study and the covered SEMS group had a substantial longer stent patency (mean of 219.3 d *vs* 166.9 d, $P = 0.047$) and less need for re-intervention (23% *vs* 37%, $P = 0.08$) compared to uncovered SEMSs. The tumor ingrowth was also lower in the covered SEMS group (0% *vs* 25%, $P < 0.01$)[47,48].

Even if a lower complication rate and a lower hospitalization staying has been described in patients with SEMS compared with plastic stents, the management of long standing metallic stent is challenging due to ingrowth of neoplastic tissue. Usually patients with positioned SEMS underwent neoadjuvant therapy to achieve a tumor downstaging and even if a 5-year survival rate is not influenced a prolonged survival is described and stent obstruction occurs frequently. Management of stent obstruction is challenging especially in hilar CC when previous bilateral SEMS have been positioned, due to the difficulties in bypassing the stent with the guidewire without enter the stent mesh. If not possible an option could be the ballon dilation of stent mesh.

ENDOSCOPIC TREATMENT IN PATIENTS WITH ADVANCED DISEASE

Placement of a stent is currently considered the treatment of choice for palliation of malignant obstructive jaundice in patients with advanced CC since it is associated with similar rates of jaundice relief and survival but less morbidity compared to the surgical approach[49-59]. Successful endoscopic deployment of a stent (or multiple stents as needed to span the malignant stricture) is possible in 70% to 100% of patients. Pre-procedure CT and/or MRI is often used in an attempt to identify the dominant biliary system in the event that only one side can be drained endoscopically.

Endoscopic stenting has been compared to the percutaneous approach. Retrospective series and trials conducted in patients with obstructive jaundice from a malignant hilar obstruction (mainly proximal CCs or gallbladder cancer) suggest that successful palliation of jaundice is more likely and rates of early cholangitis may be lower with the percutaneous as compared to the endoscopic approach[60,61]. However, other complications may be more frequent (*e.g.*, bile leaks and bleeding), potentially increasing morbidity and mortality. Furthermore, percutaneous stents usually imply an open external drainage, at least initially, and this is often inconvenient to the patient. As a result, in most institutions an initial endoscopic attempt at drainage is usually preferred whenever possible.

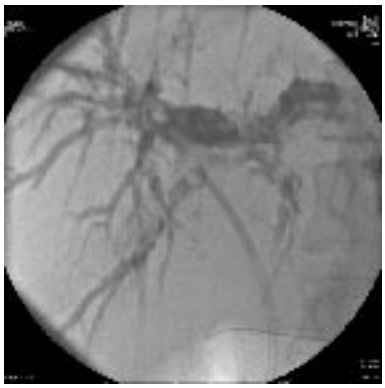

Figure 2 Endoscopic retrograde cholangiography with a plastic stent in the right hepatic duct. However the left hepatic duct remains dilated.

Palliative endoscopic biliary decompression can be achieved using either plastic or SEMSs. In the last two decades, SEMSs have been increasingly used and have been demonstrated to be more effective than plastic stents allowing a more rapid biliary drainage and consequently a lower incidence of septic complications since the first procedure[51,52]. A systematic review concluded that none stent improves survival rate however uncovered metal stents have a lower risk of causing cholecystitis and pancreatitis and migration rate is significantly lower than in covered group[31].

Whether to use unilateral or bilateral stents in patients with hilar obstruction is debated. The issue should be to drain as much as possible but this does always mean that you need to put a stent in every single duct. In many cases, unilateral stent placement will be sufficient to relieve jaundice and frequently, a dominant duct could be identified during ERC procedure, as the more effective to be drained (Figure 2)[32]. However, unilateral drainage alone may not relieve jaundice completely and may increase the risk of cholangitis especially if contrast medium have been injected and not drained. Studies comparing these approaches have reached variable and dubious conclusions. Many endoscopists place bilateral stents (plastic or metal); certainly a minimum of two stents (left and right branches) is need in an attempt to maximize biliary drainage (Figure 3). The choice to use more than two stents is linked to patient disease features and endoscopist skill.

RADIOFREQUENCY ABLATION

Radiofrequency ablation (RFA) has been used to treat

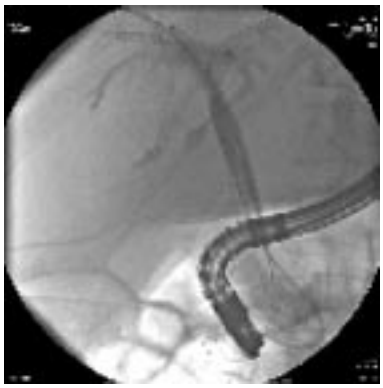

Figure 3 Use of covered self-expandable metal stent in patients with hylar cholangiocarcinoma.

liver malignancies since the early 1990s[61-65]. More recently this technique has been applied in malignant biliary strictures[62].

Habib TM Endo-HPB EMcision is an endoscopic bipolar catheter studied to be introduced through biliary malignant strictures, so that radiofrequency energy can be delivered locally before stent positioning. Potential advantages of the device use could be longer stent patency by ease down tumor growth. Endo-HPB is a 8 F, 1.8 m coaxial over the wire catheter that is designed to be inserted through a 3.2 mm working channel of the endoscope. At the distal end of the catheter, two ring electrodes spaced 8 mm apart produces a heating zone length of approximately 25 mm.

RFA in bile duct appears to be safe however its efficacy in long term and its role, alone or combined with SEMS is unclear. Sharaiha *et al*[64] recently compared RFA combined with SEMS with SEMS alone in 66 patients. Twenty-six were treated with RFA and SEMS and 40 only with stent placement. The author confirms a statistically significant improvement in malignant strictures diameter after RFA treatment[63-65]. Randomized controlled trials are needed.

ALTERNATIVE STENT DESIGN AND STRATEGIES

Recently Shah[65], proposed drug-eluting stents designed to improve SEMS patency by delivering a chemotherapeutic agent such as paclitaxel to prevent tumor in-growth and stent occlusion[66]. Unfortunately, in a multicenter prospective study comparing drug-eluting covered SEMSs with covered SEMSs no significant difference in stent patency was found[67].

PHOTODYNAMIC THERAPY AND DRUG ELUTING STENT

Photodynamic therapy (PDT) is a new palliative technique for malignant bile duct stenosis that seems to improve pain relief, increase biliary patency and increase survival.

Recently Bae *et al*[2] proposed a photosensitizer-embedded self-expanding metal stent (PDT-stent) which provides a photodynamic treatment without the need of systemic injection of photosensitizer and the treatment could be repeated more than one time due to the incorporation of the polymeric photosensitizer into the mesh of the stent. Photo-fluorescence imaging of the PDT-stent demonstrated homogeneous distribution of polymeric Pheo-A (PPA) on stent surface and the stent maintained its photodynamic power at least for 8 wk, for repeated PDT procedure if necessary after stent positioning. The PDT-stent after light exposure created cytotoxic free radical such as singlet oxygen in the close tissues, inducing destruction of neoplastic cells on animal models[66,67].

EUS GUIDED BILIARY DRAINAGE

Endoscopic biliary drainage with stent positioning is technically successful in > 90% of procedure. In the case of failure, endoscopic ultrasound (EUS)-guided biliary drainage has recently emerged as an effective alternative method providing technical success in > 80% of cases[49]. EUS-guided biliary drainage was first reported in 2001 by Giovannini *et al*[67] and can be approached into 3 different ways: (1) EUS-guided transluminal biliary drainage including choledoco-duodenostomy and hepatico-gastrostomy; (2) EUS-rendezvous technique; and (3) EUS-antegrade approach[67,68].

For EUS-guided transluminal biliary drainage, the biliary duct is punctured from the proximal duodenum with a 19 G fine needle aspiration (FNA) under EUS guidance followed by cholangiography. Progressively a guidewire is driven into the biliary system and dilation of the needle way is carried out. After fistula creation with a cystotome, or a bougie dilator, the stent is deployed between the biliary duct and the duodenal lumen for biliary drainage.

In EUS-rendezvous technique, the biliary duct is approached under EUS and X-ray guidance *via* 19 G FNA needle. Progressively, a guidewire is driven into the biliary system then through the bile duct, through the ampulla within the duodenum. After guidewire positioning, ERCP is performed using guidewire and the guidewire is retrieved, once biliary cannulation is carried out or the stenosis has been exceeded. Therefore, EUS- rendezvous technique is feasible only in patients in which the endoscopic access to the ampulla is preserved[68].

In EUS-anterograde approach, the intra-hepatic biliary duct is accessed from the small bowel with creation of a temporary fistula between the small bowel and the intra-hepatic biliary duct then the stent placement is achieved through the fistula. This technique is appropriate for patients with surgically altered anatomy or duodenal obstruction which prevent ampullary access.

Published studies regarding choledoco-duodenostomy

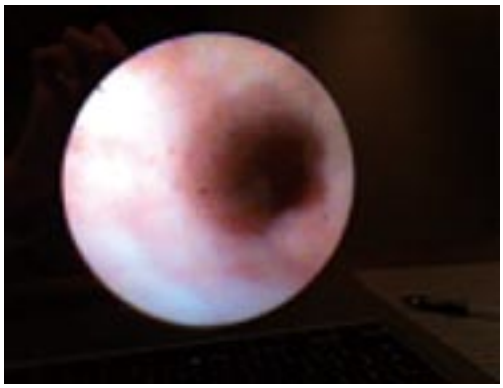

Figure 4 Visualization of biliary epithelium during SpyGlass.

and hepatico-gastrostomy show technical success rates of 94% and 87% with early complication rates of 19% and 27%, respectively, despite the fact that different biliary access and fistula dilation methods have been utilized. Regarding stent type, covered SEMS have generally been preferred over plastic stents, especially in more recent studies. Radial expansion of covered SEMSs can reduce risk of complications such as bile peritoneal leak or pneumoperitoneum because the fistula is immediately plugged by the covered SEMS. On the other hand, stent migration is reported after endoscopic procedure. For this purpose, the development of stents specifically designed for these procedures could further improve the results.

One of the most challenging aspects of EUS-rendezvous technique is the guidewire manipulation, which requires skill, tact sensitivity and good cooperation with a second operator[66]. Similarly, EUS-antegrade approach requires careful guidewire manipulation, however a major care is the risk of bile leak into the peritoneal cavity through the dilated fistula even if no report of biliary peritonitis have been issued, and the overall success and complication rates are 77% and 5 %, respectively[69-73].

NEW TECHNIQUES

Cholangioscopy

Peroral cholangioscopy, "mother-baby" technique, was utilized in the mid-1970s for the diagnosis and definition of bile duct narrowing. Nevertheless this technique revealed many limitations in visualization of the wall and required the cooperation of two skilled operators[74,75]. The "SpyGlass system" (Boston Scientific Corp, Natick, MA, United States) introduced in 2006 has enlarged the role of cholangioscopy from a diagnostic to a therapeutic one. The new system has overcome the need of two endoscopists and it has been launched as a single endoscopist cholangioscope. It allows the direct visualization of biliary tree (Figure 4) and consequently its use in the diagnostic work up of CC is well established. Sethi *et al*[74] reported a diagnostic accuracy of SpyGlass around 57% and these data were confirmed also in other series with an overall diagnostic accuracy, in differentiating neoplastic *vs* non neoplastic lesions, varied from 77% to 90%[75-79]. Although it is considered limitative to banish a cholangioscope to a diagnostic role in CC work up, more data are needed about its role in therapeutic endoscopy and biliary drainage. One of the main indications is the lithotripsy for difficult to remove, biliary stones[80]. Recently Dong Choon Kim described the use of an ultraslim endoscope (GIF-XP260N; Olympus, Tokyo, Japan) for intraductal stones fragmentation under endoscopic visualization[81].

Fluorescence in situ hybridization

Fluorescence *in situ* hybridization (FISH) assesses the presence of chromosomal aberrations, in number or structures, and uses fluorescence-labeled probes to evaluate increases or decreases in chromosome number if referred to numerical abnormalities or to specific structural abnormalities in case of clonal diversity[82,83]. This technique is performed on ERC brushing smears.

Previous studies have demonstrated that FISH polysomy combined with cytology improves sensitivity. Some studies have considered the positive FISH results based on polysomy only, whereas some have considered trisomy or tetrasomy as a positive test results as well. Recently a review was published by Navaneethan *et al*[82] with a pooled sensitivity and specificity was 51% and 93% in detection of CC in patients with PSC. Vasilieva *et al*[83] in 2013 published data about the use of structural abnormalities as markers of clonal diversity and different clinical features of the disease. However more data are needed, the use of fish does not increase sensitivity significantly. A future role of the FISH will be the possibility to delineate the oncogenesis, to understand the response or not to chemotherapy[83,84].

CONCLUSION

Cholangiocarcinoma and bile duct tumors are an heterogeneous group of tumor with different biological behavior and prognosis according to their location and growth pattern. CC presents a special challenge in gastroenterology, oncology, and visceral surgery because of the difficulty in establishing the diagnosis, local complications in the biliary pathways, and a high recurrence rate after resection. Diagnosis is usually defined in advanced disease stage, due to paucisintomaticity of tumor and to low sensitivity of imaging technique for detection of lesions at early stage. The only curative treatment for CC is surgery, but 40%-85% of all patients have recurrent disease even after radical excision. Because of this high recurrence rate and because the majority of patients undergo palliative therapy (chemotherapy or endoscopic therapy) to try to downstage the tumor and adjuvant treatments are now under intense discussion. Moreover because of the low prevalence of the disease, there have been only a few studies of palliative chemotherapy for CC. On the basis of one positive phase 3 study, chemotherapy with

gemcitabine and cisplatin is considered the standard and now plays an established role in palliative care[84].

Endoscopy, as explained in this review has gained in the last decades a key role in the work up of CC, both in patients amenable to surgical intervention as well as in those unfit for surgery or not amenable to immediate surgical curative resection owing to locally advanced disease. Endoscopy allows successful biliary drainage and stenting in more than 90% of cases. The development of new stents, metallic, covered, with different mesh materials, different mesh shape is a constant work in progress to reduce complications in patients with advanced disease, to avoid repeated endoscopic procedure and to improve long term results. Moreover in the last two years new stent prototype able to release drugs and/or photodynamic therapy have been commercialized with promising results but very few data are available, not enough to be validated. When endoscopy fails, endoscopic ultrasound-guided biliary drainage represents an effective alternative method affording successful biliary drainage in more than 80% of cases. Also in this field new dedicated stents fit for trans-duodenal biliary drainage or trans-hepatic biliary drainage are under construction.

This a new field that need constant updating and future studies should address the efficacy of combined local and systemic treatments.

In conclusion the final messages are: (1) The benefit of adjuvant chemotherapy has not yet been confirmed and require further investigation; and (2) Endoscopic biliary drainage by means of ERC is an integral component of the treatment of CC.

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REVIEW

Management of primary achalasia: The role of endoscopy

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Abstract

Achalasia is an oesophageal motor disorder which leads to the functional obstruction of the lower oesophageal sphincter (LES) and is currently incurable. The main objective of all existing therapies is to achieve a reduction in the obstruction of the distal oesophagus in order to improve oesophageal transit, relieve the symptomatology, and prevent long-term complications. The most common treatments used are pneumatic dilation (PD) and laparoscopic Heller myotomy, which involves partial fundoplication with comparable short-term success rates. The most economic non-surgical therapy is PD, with botulinum toxin injections reserved for patients with a higher surgical risk for whom the former treatment option is unsuitable. A new technology is peroral endoscopic myotomy, postulated as a possible non-invasive alternative to surgical myotomy. Other endoluminal treatments subject to research more recently include injecting ethanolamine into the LES and using a temporary self-expanding metallic stent. At present, there is not enough evidence permitting a routine recommendation of any of these three novel methods. Patients must undergo follow-up after treatment to guarantee that their symptoms are under control and to prevent complications. Most experts are in favour of some form of endoscopic follow-up, however no established guidelines exist in this respect. The prognosis for patients with achalasia is good, although a recurrence after treatment using any method requires new treatment.

Key words: Achalasia; Endoscopic treatment; Dilation; Botulinum toxin; Myotomy

Core tip: We propose a treatment and monitoring algorithm for achalasia based on the most relevant published evidence and an exhaustive summary of all the available endoscopic techniques.

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INTRODUCTION

Achalasia is a primary oesophageal motor disorder of unknown aetiology characterised manometrically by insufficient relaxation of the lower oesophageal sphincter (LES) and a loss of oesophageal peristalsis[1] secondary to the degeneration of the myenteric plexus[2]. It should be suspected in patients who present with dysphagia, regurgitation of undigested food debris, respiratory symptoms, chest pain, and weight loss[3]. It is described at any age, but occurs most frequently between the ages of 20 and 40. There does not appear to be any association with sex or ethnicity. The annual incidence is 1 in 100000 persons and the prevalence is 10 in 10000[4,5]. Following clinical suspicion and diagnostic confirmation by means of a barium swallow and manometry, the indication of oesophagogastroduodenoscopy (EGD) in the initial phase is essential for differential diagnosis, ruling out pseudoachalasia due to malignant neoplasms and the presence of oesophageal squamous cell carcinoma as complications of achalasia. Diagnosis using high-resolution manometry and multi-channel intraluminal impedancemetry appears to have a higher diagnostic sensitivity than conventional manometry in diagnosing this disease. It also allows the identification of subtypes: Type I is associated with absent peristalsis and no discernible esophageal contractility in the context of an elevated integrated relaxation pressure (IRP). Type II is associated with abnormal esophagogastric junction (EGJ) relaxation and panesophageal pressurisation in excess of 30 mmHg. Type III achalasia is associated with premature (spastic) contractions and impaired EGJ relaxation[6].

EGD forms an essential part of the diagnostic algorithm of achalasia, although in the earliest stage it has a low sensitivity for detecting this condition as up to 40% of patients with achalasia will have a normal endoscopy[7]. The presence of oesophageal dilation on the oesophagogram, a narrowing of the oesophageal junction into a "bird beak" shape, aperistalsis, and difficulty in evacuating the barium column from the oesophagus support the diagnosis[4]. The objective of treatment is to relieve the symptoms, improve oesophageal evacuation, and prevent the development of complications. Therapeutic options include medical treatment, endoscopic treatment, including pneumatic dilation (PD) and botulinum toxin injection (BTI), and surgical LHM treatment[5]. Other treatments with a promising future which are currently being researched are POEM, oesophageal stents, and ethanolamine injection.

ENDOSCOPIC THERAPY FOR ACHALASIA

Pharmacological endoscopic therapy

BTI (Botox, Allergan, Inc.) has been the most frequently used pharmacological endoscopic treatment for achalasia since 1995. Botulinum toxin is a neurotoxin which blocks the release of acetylcholine from nerve endings by cleaving the SNAP-25 protein. This causes a chemical denervation of the LES muscle, which can last several months, reducing its basal pressure[8,9]. The technique involves injecting 80 to 100 U of toxin in four quadrants (20-25 U in each) using a sclerotherapy needle, at a distance of 1 cm above the squamocolumnar junction. Higher doses have not been shown to be more efficient[10]. The initial response rate is very high, approximately 80%-90% in the month of treatment, but the therapeutic effect disappears over time such that < 50% of patients are asymptomatic after one year of monitoring[10-12]. This suggests that repeated treatments with the toxin are required every 6-12 mo. The predictive factors of a better response to treatment with BTI are: age > 40 years, achalasia type II, and a decrease in base line pressure of the LES after treatment[12]. BTI has not been shown to halt progressive oesophageal dilation, so it does not prevent long-term complications of achalasia. It is a simple, safe and effective technique with few side effects, although chest pain following injection has been described in 16%-25% of cases. Complications such as mediastinitis or allergic reactions to egg protein are rare, and systematic neurotoxicity with generalised paralysis does not occur due to the low doses used. However, repeated botulinum toxin treatments cause an intramural inflammatory reaction at the level of the LES as well as submucosal fibrosis which may make it more difficult to carry out subsequent surgical myotomy[13-15]. Treatment with BTI should therefore be reserved exclusively for patients of advanced age, those with high surgical risk, severe comorbidities, short life expectancy, and those who are not candidates for PD or surgical myotomy or on a waiting list for surgery[16].

PD

PD is the most effective non-surgical procedure in the treatment of achalasia[4,17]. The aim of dilation treatment is to rupture the muscle fibres of the LES by means of the force exerted by air balloons positioned and inflated at this level. Both the use of bougies as well as standard

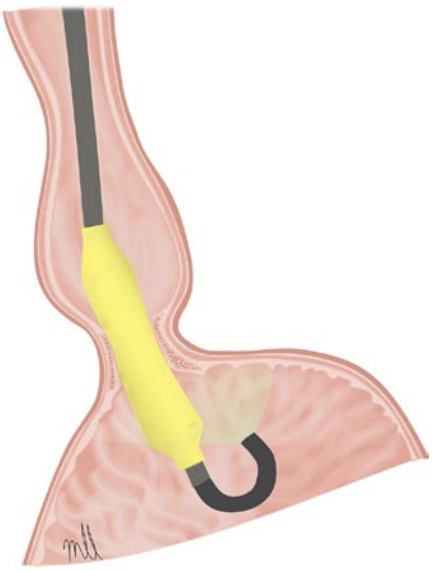

Figure 1 Witzel dilator.

balloon dilation through the endoscope channel (TTS balloon) have not been shown to be particularly effective in achieving this goal, which is necessary to significantly relieve symptoms[4]. The most commonly used dilation treatment for this disease is Rigiflex balloon dilation. Another type of balloon dilation used less frequently is the Witzel dilator, which has also been shown to be effective although it is less widely used and fewer papers have been published on it[18,19].

Pneumatic dilation with a Witzel balloon: Pneumatic dilation with a Witzel balloon is a relatively safe method of treating achalasia with a similar rate of complication to Rigiflex dilation, and a high level of efficacy in the medium to long term[18-20]. The Witzel dilator is a 15-cm polyurethane balloon with a maximum diameter of 4 cm, which is inserted attached to the endoscope until it is positioned at the level of the cardia using direct vision and retroflexion (Figure 1). According to the technique recommended by Alonso Aguirre[20] the balloon is inflated to 200 mmHg for 1 min and, depending on patient tolerance (if the dilation is performed under conscious sedation), it is inflated again once or twice to a maximum pressure of 200 or 300 mmHg. If the dilation is performed under deep sedation, the balloon is inflated to 200 mmHg for 2 min. In a study published for our centre in 2009[18], we observed a success rate of 85% after the first and second dilations (only required in 23% of cases). During the first 5 years of follow-up, 80% maintained the response, and the proportion decreased to around 60% after 10 years. The only variable related to a positive response in the long term was age (> 40 years). A small number of complications were reported: perforation in 4.2%, all treated conservatively, and the appearance of gastro-oesophageal reflux (GER) in the 10% who responded to treatment with proton pump inhibitors (PPI).

Dilation with Rigiflex balloon: The procedure has been standardised with the use of the Microinvasive Rigiflex balloon system (Boston Scientific Corp, Massachusetts, United States). These polyethylene balloons are available in 3 diameters (30, 35, and 40 mm), mounted on a flexible catheter which is positioned in the oesophagus using a guide placed with the help of an endoscope. Balloon inflation at the level of the LES can be controlled using radiology, radiopaque marking, or endoscopy (Figure 2).

The protocol for inflating the balloon varies in function from centre to centre. In general, the balloon is inflated gradually until it reaches a pressure of approximately 7-15 psi, which is maintained for 15-60 s. Using radiology, it is possible to check how the central notch on the balloon, which corresponds to the LES, disappears as the balloon is progressively inflated[21]. This is the most important factor in order for the expansion to be effective, rather than the duration of balloon inflation[22]. Following PD, some authors recommend ruling out perforation by carrying out a radiological check using Gastrografin followed by a barium oesophagogram[4,23]. This technique can usually be performed on an outpatient basis. The patient may be discharged after 6 h, once complications have been ruled out[4,21]. According to some authors, it is possible to choose whether to perform a single dilation session[24], or to carry out successive dilations, progressively increasing the diameter of the balloon in each session (beginning with 30, then 35, and finishing with 40 mm)[25], with 4-6 wk between sessions, based on alleviation of symptoms, reduction of manometric pressure in the LES[24,26], or the improvement of oesophageal evacuation[27,28]. Overall, the results of the studies published show that PD is effective, with response figures of 40%-78% at 5 years and between 12%-58% at 15 years[29-31]. By using the strategy recommended in the clinical practice guidelines[4], higher response rates of up to 97% at 5 years and 93% at 10 years can be achieved[32]. The predictive factors for a failure of treatment with PD are: young patients (age < 40 years)[18,33,34], male sex, dilation using a 30-mm balloon, presence of pulmonary symptoms, failure of treatment after one or two dilation sessions[24,29,35,36], post-treatment determination of a pressure measurement in the LES > 10-15 mmHg, failure of the balloon to relax completely[37], or delayed oesophageal evacuation in a barium oesophagogram carried out in vertical position[26,38-41]. PD is the most cost-effective treatment for achalasia for a period of 5 to 10 years after the procedures[42,43]. Candidates for PD should be those for whom surgery is not contraindicated as a definitive treatment, given that the most severe complication for this technique is oesophageal perforation, which occurs in approximately 1.9% (range 0%-16%)[28,39]. Many perforations tend to occur after the first dilation and are believed to be related to incorrect positioning and balloon relaxation during dilation[44]. Early diagnosis

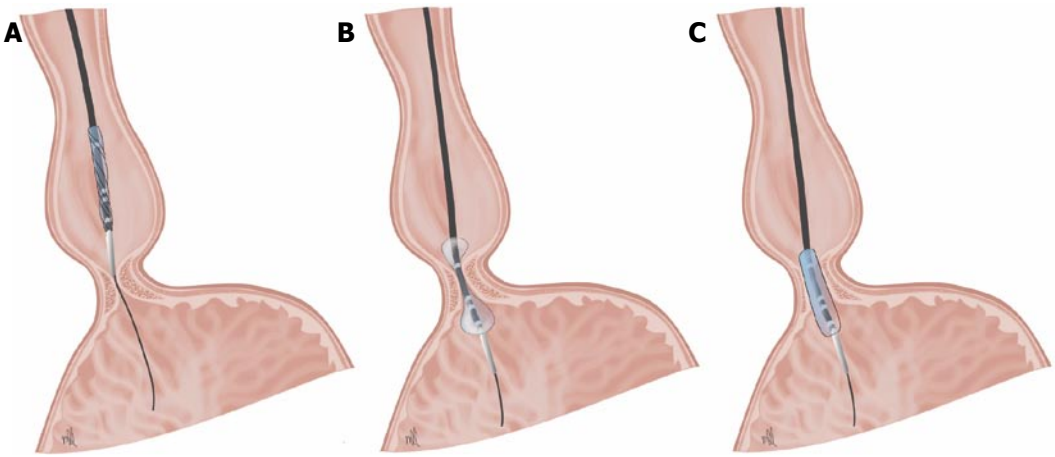

Figure 2 Dilation with Rigiflex balloon positioned at the level of the lower oesophageal sphincter. A: Step 1: positioning the balloon in the esophagogastric junction (EGJ); B: Step 2: deflated balloon in the EGJ; C: Step 3: inflated balloon in the EGJ.

of this complication favours an improved course. Small perforations can be managed conservatively with parenteral nutrition and antibiotics[45], however perforations which are larger, symptomatic, or with suspected contamination of the mediastinum must be repaired surgically *via* thoracotomy[4,21]. Other complications include GER, which is generally mild and transient, appears in 15%-35% of patients, and usually responds to treatment with PPI[46]. Serious GER complications following dilation are rare. Mild but frequent complications include chest pain, aspiration pneumonia, bleeding, fever, tearing of the oesophageal mucosa without perforation, and oesophageal haematoma.

Comparison of the different therapeutic modalities

Botulinum toxin *vs* pneumatic dilation: The results of individual randomised controlled trials comparing BTI and PD have shown that there are no significant differences between the two techniques in terms of remission of symptoms in the short term (4-6 wk), but there is a rapid relapse 6-12 mo after BTI. The success rate in the year of treatment varies from 65.8%-70% for PD and 24%-36% for BTI. However, it can be concluded that PD is more effective in the long term than BTI[11,47-50].

Botulinum toxin *vs* laparoscopic Heller myotomy: There are few studies comparing BTI with LHM. The study by Zaninotto *et al*[51] reports comparable efficacy at 6 mo, although at 2 years only 34% of patients treated with BTI remain asymptomatic, as compared with 87.5% of patients treated with LHM[51].

Role of combination therapy: Therapy with BTI in combination with any other type of endoscopic or surgical treatment for achalasia can increase the response rate. Although it is still not routinely recommended in clinical practice[52], Mikaeli *et al*[53] published a higher remission rate during follow-up in patients who had first been treated with toxin and then with PD (77%) compared to those who had only received treatment with PD (62%)[53]. Other authors have reported a higher percentage of remission after 2 years in those who had received PD first followed by BTI (56%) compared to those who had only received dilation (35.7%), or only toxin (13.79%)[54].

Pneumatic dilation *vs* laparoscopic Heller myotomy: The question of whether to choose surgical treatment or PD as the primary treatment option when treating achalasia remains controversial today. Numerous studies use the strategy of repeating dilation sessions depending on the symptomatic response, if there is no improvement in the manometric tests or in the evacuation of barium contrast. This strategy enables the response rates to be increased to levels comparable with those obtained with LHM[32,55,56]. The only randomised comparative study between PD and surgery, carried out by the European Achalasia Trial Investigators Group in 2011[57] showed similar results for both techniques with a follow-up period of 2 years. 201 patients were randomised to receive dilation with Rigiflex (n = 95) or LHM with partial fundoplication (n = 106). The success rate was comparable for both techniques after 1 year and after 2 years: 90% and 86% respectively for PD, and 93% and 90% for LHM (P = 0.46). The meta-analysis published in 2009 by Campos *et al*[49] includes non-randomised studies of case series. They reported overall response figures of 68% in the 1065 patients dilated with Rigiflex and 89% in the 3086 patients who underwent surgery. In a study by the Cleveland Clinic (Cleveland, OH, United States)[28], 106 patients were treated with PD and 73 patients with LHM. The success rate, based on clinical data or necessity of re-treatment, was similar for both groups: 96% for dilation *vs* 98% for surgery after 6 mo, decreasing to 44% *vs* 57% after 6 years. The advantages of endoscopic treatment are that it includes the possibility of outpatient care, is less invasive than surgery, involves fewer complications and less risk of subsequent reflux and haemorrhage. However,

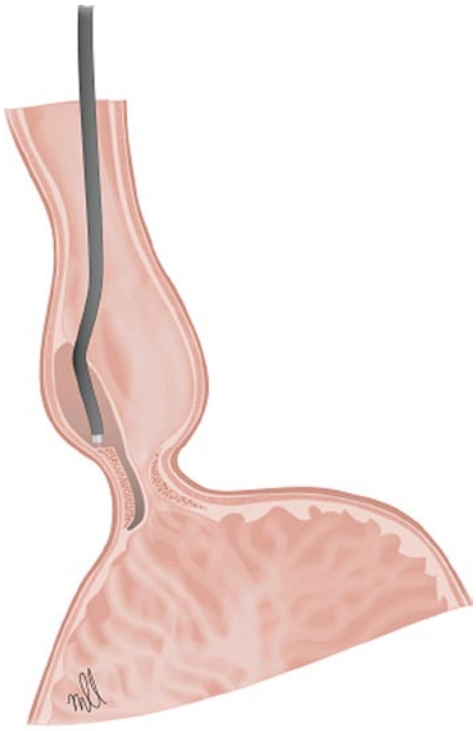

Figure 3 Peroral endoscopic myotomy.

in addition to the fact that more than one treatment session is frequently required, there are still no studies with long-term follow-up which have demonstrated the superiority of PD[21,58]. A recent meta-analysis published by Weber *et al*[59] found that both techniques, PD and LHM, were effective in the treatment of achalasia, however myotomy was found to be more durable[59]. There is some controversy around whether the initial PD obstructs the subsequent performance of laparoscopic myotomy[58,60]. The type of treatment must be selected consensually, taking into account the preferences of the patient as well as the experience of each centre[1,61]. These techniques should preferably be carried out by centres with a high volume and experience in LHM[58].

New treatments for achalasia

Peroral endoscopic myotomy: POEM is a minimally invasive procedure carried out *via* endoscopy. It combines the surgical principles of laparoscopic myotomy with the latest advances in endoscopic submucosal dissection[62].

The technique is performed under a general anaesthetic with endotracheal intubation and the patient in supine position. A liquid diet is indicated for 24-48 h prior to the procedure and antibiotic prophylaxis is administered on the day of the intervention, which is maintained during hospitalisation and in some cases for up to 7 d. Different authors agree on the use of CO_2 insufflation to minimise the risk of pneumomediastinum and air embolism. A submucosal injection of 10 mL of saline solution with 0.3% indigo carmine is administered in the central oesophagus, about 13 cm away from to the EGJ, in a 2 o'clock position. A longitudinal incision of 2 cm is made above the surface of the mucosa to gain access to the submucosal space (Figure 3). Thus a descending anterior submucosal tunnel through the EGJ is created, which reaches approximately 3 cm into the proximal stomach. Once the submucosal tunnel is complete, the circular muscle fibres are cut 2-3 cm in distal direction from the access to the mucosa, approximately 7 cm above the EGJ. Myotomy continues distally until it reaches the gastric submucosa, and extends about 2-3 cm in distal direction to the EGJ. Once the circular muscle fibres in the lower part of the oesophagus have been identified and cut, the site of access to the mucosa is closed using haemostatic clips[63].

The first reference to endoscopic myotomy for achalasia appears in 1980 in a case series published by Ortega *et al*[64]. Later, as endoscopic surgery through natural orifices (NOTES) progressed, Pasricha *et al*[12] demonstrated its feasibility using a porcine model. The technique was adopted in clinical practice in 2010 by Inoue *et al*[65]. The study evaluated 17 patients, aiming for a significant reduction in the index of symptoms of dysphagia in all of them (average score from 10 to 1.3; $P = 0.0003$), as well as the basal pressure of the LES (from 52.4 to 19.9 mmHg; $P = 0.0001$). The operating time ranged from 100 to 180 min, with an average myotomy length of 8.1 cm. No serious complications related to the procedure were described. One patient presented with a complication of pneumoperitoneum. After a follow-up of 5 mo, only one patient reported symptoms of reflux, which were shown in gastroscopy to be an oesophagitis Los Angeles Grade B, which was treated satisfactorily by taking a protein pump inhibitor[65,66]. In 2011, Swanström *et al*[67] published their experience with POEM in 5 patients. No leaks were detected in a barium oesophagogram 24 h after the procedure, nor were any complications described immediately post-operation, with all patients presenting a rapid relief of dysphagia without reflux symptoms[66,67]. In 2012, von Renteln *et al*[68] presented the results of the first prospective POEM trial in Europe. The myotomy was performed in 16 patients achieving a clinical response of 94% after 3 mo. The LES pressure was reduced from 27.2 to 11.8 mmHg ($P < 0.001$), with no patients developing reflux symptoms after the treatment[63,68]. Some authors have studied the applicability of the techniques to patients previously subjected to endoscopic treatment (BTI, PD). Sharata *et al*[69] demonstrated clinical success in this context in 12 patients. Only one case of intramural bleeding, which required a new endoscopy for haemostasis, and one case of dehiscence of the mucosectomy, which was treated with haemostatic clips, were described. All patients demonstrated symptomatic relief, with an average decrease in the Eckardt score from 5 to 1. Comparing these results with those of the 28 patients without previous endoscopic treatment, no significant differences were found to exist between the two groups[66,69]. In 2012, Zhou *et al*[70] published their experience with 12 patients with a history of

LHM in which they successfully performed endoscopic myotomy. No serious complications with the technique were described, achieving an average improvement in the index of symptoms from 9.2 to 1.3 ($P < 0.001$). The basal pressure of the LES was reduced from 29.4 to 13.5 mmHg ($P < 0.001$). Only one patient reported reflux symptoms, presenting a positive response to intermittent treatment with PPI[66,70].

The first study to retrospectively compare POEM and surgical myotomy was published in 2013. No significant differences were observed in terms of the length of the myotomy, complication rate, or hospital stay[63,71]. Bhayani *et al*[72] have recently presented the results of a study in which 101 patients were prospectively included, 64 treated with Heller myotomy and 37 with POEM. The authors conclude that the two techniques are comparable in terms of efficacy and safety, with similar results in post-operative manometry and pathological acid exposure, as assessed on an outpatient basis using a pH meter[72].

In summary, POEM is posited as a useful technique, although it is an expensive procedure which requires significant expertise. The studies published show excellent results in the short term as far as dysphagia relief and improvement of the manometric pressure data for the LES are concerned. The complication most frequently described is pneumoperitoneum, which can generally be resolved by conservative means. The presence of GER following POEM ranges between 5.9% and 46%, depending on the series, but in general it is a question of mild symptoms which can be adequately controlled with medical treatment. On the basis of the published data, it is no surprise that the majority of experts on POEM, including surgeons with extensive experience in surgical myotomy, appreciate the advantages of achieving results like those for LHM by minimally invasive means. Endoscopic myotomy could eventually become a first-line treatment for achalasia, except for those with significant comorbidity or advanced achalasia at the megaoesophagus stage. This technique is not a future anymore, but a present. However, new randomised studies are needed which will allow us to evaluate POEM in the long term and to compare the technique with the remaining treatment modalities.

Oesophageal prostheses: Self-expanding metallic prostheses have been used safely and effectively to treat malignant pathologies of the oesophagus and tracheoesophageal fistula, oesophageal perforations, and anastomotic leaks. However, given the high risk of complications (migration, perforation, indentation, and restenosis), its use in benign pathology is more controversial. Various authors have defended the use of removable prostheses in the management of benign stenosis of the oesophagus, arguing that it constitutes a reasonable alternative in the treatment of patients with achalasia[73,74]. The ideal prosthesis would be placed at cardia level to keep open the EGJ, thus limiting gastroesophageal reflux[75].

In 2009, Zhao *et al*[76] published their experience in 75 with a diagnosis of achalasia who were treated with the temporary placement of a self-expanding metallic prosthesis of 30 mm in diameter, with a follow-up of 13 years. The placement of the prosthesis is guided by a fluoroscopy and is extracted *via* gastroscopy 4-5 d later. The procedure was performed successfully in all patients, achieving a clinical response of 100% one month after removing the prosthesis and 83.3% in the follow-up of over 10 years. No perforations or mortalities associated with the treatment were reported, with the percentage of migration of the prosthesis at 5%, reflux at 20%, and chest pain at 38.7%. The authors conclude that the use of a temporary self-expanding metallic prosthesis is a safe and effective approach in the treatment of achalasia, with a satisfactory long-term clinical remission rate[76]. In 2010, Cheng *et al*[73] compared the efficacy of different self-expanding metallic prostheses in the long-term treatment of achalasia. They designed a study with 90 patients and separated them into three groups according to the diameter of the prosthesis used (20, 25, and 30 mm). They concluded that the prosthesis with a diameter of 30 mm is associated with a lower incidence of migration and with higher clinical response rates, comparable in the short term with those described for surgical myotomy[73]. The same authors published a prospective randomised study in 120 patients, in which they evaluated the long-term efficacy of a specially designed, partially covered and removable metallic prosthesis, and compared it with PD. They achieved a success rate over 10 years of 83% with the 30-mm prosthesis, while the response rate for the 20-mm prosthesis and PD was 0%[75,77].

Although the results seem promising, they reflect the experience of a single centre, which is why this technique should not be generally recommended. Further randomised studies are required which evaluate its long-term efficacy and safety[75].

Treatment of achalasia with sclerotherapy: Ethanolamine oleate: The injection of a sclerosing agent such as ethanolamine oleate at the level of the LES could be an alternative therapy for patients with refractory achalasia who are not candidates for PD or surgery. Its effect is based on the local inflammatory effect of this substance, but there are still insufficient studies and it is only to be recommended in selected cases[78,79].

THERAPEUTIC MANAGEMENT ALGORITHM

Achalasia therapy is based on achieving the relaxation or mechanical disruption of the LES. Since achalasia is a rare disease, there are few randomised and controlled clinical trials which would enable us to define

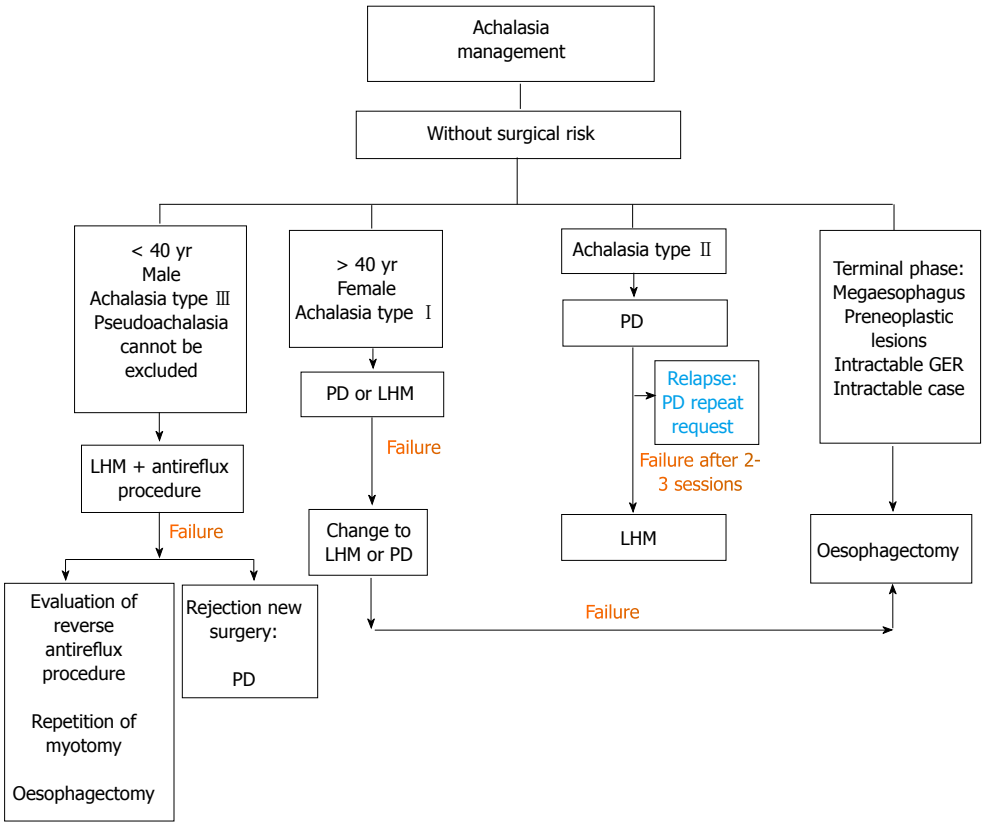

Figure 4 Management algorithm in patients without surgical risk. PD: Pneumatic dilation; LHM: Laparoscopic Heller myotomy.

the optimum strategy. Furthermore, the safety and maintenance of efficacy of the different treatment options vary greatly.

The choice of initial treatment of achalasia is complex and all options are determined by the combination of numerous factors such as the age of the patient, sex, surgical risk, comorbidity, type of achalasia[7], patient preferences, oesophageal anatomical distortion, and the experience of the hospital. Moreover, identifying factors which predict the success of the therapies can inform our recommendations. In Figures 4 and 5, we propose an algorithm for the management of this disease based on the most recent published recommendations[3-5,21,58,80,81]. In general, LHM is the most durable technique in the long term for treating achalasia, however PD is the non-surgical procedure of choice, and it is the most cost-effective strategy. Both techniques are recommended as an initial therapy for treating achalasia in healthy patients who can undergo surgery (Figure 4). The success rate in the short term is comparable for the two techniques.

PD is the most economical non-surgical option, primarily for type Ⅱ. The subtype of achalasia, diagnosed using high-resolution manometry at the beginning of the study, can predict the response of the treatment[58]. Thus we have seen that the success rate with PD is significantly higher for achalasia type Ⅱ (96%) than for type Ⅰ (56%) and type Ⅲ (29%)[82]. The sessions are repeated according to an "on demand" strategy, based on the recurrence of symptoms, and long-term remission can be achieved with it. Criteria for failure include a lack of symptom relief after 2-3 sessions or following the use of the largest diameter balloon chosen. In these cases, the patient must undergo surgery (Figure 4). In high-risk patients, PD can be a reasonable alternative if carried out in hospitals with surgical experience, because of the possibility, however infrequent, of perforation (Figure 5).

Surgical myotomy, using the technique described by Heller a century ago, is the most effective treatment option in the long term[83]. In the last 20 years, this procedure has been carried out safely and successfully using the minimally invasive laparoscopic approach[84], and more recently using robotic assistance. In the majority of cases, it is recommended to also use an anti-reflux fundoplication technique, preferably partial (Dor anterior or Toupet posterior) owing to the fact that it results in significantly lower rates of post-operative dysphagia. It is the procedure of choice in adolescents and young adults, especially male[85], in cases where pseudoachalasia cannot be ruled out and, possibly, in patients with achalasia type Ⅲ (Figure 4)[82], patients with pulmonary symptoms, and those who have not responded to initial treatment with one or two sessions of dilation[37,58,86,87]. The predictors of a poor response after surgery include severe pre-operative dysphagia and preoperative low pressure of the LES (< 30-35 mmHg)[88]. The main predictor of patients

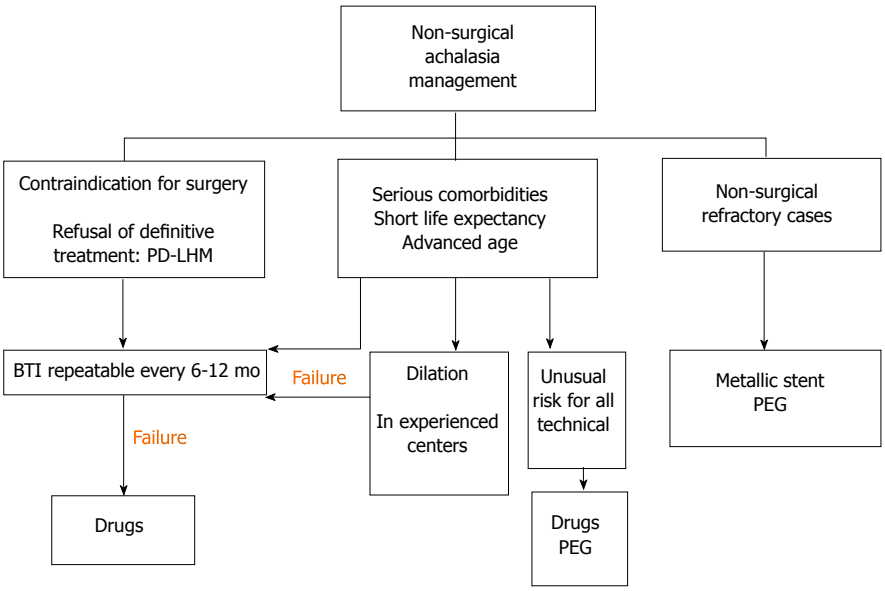

Figure 5 Non-surgical management algorithm. PEG: Percutaneous endoscopic gastrostomy; BTI: Botulinum toxin injection; PD: Pneumatic dilation; LHM: Laparoscopic Heller myotomy.

who will require an additional intervention after the Heller myotomy is an oesophageal dilation of > 6 cm (megaoesophagus) in diameter prior to surgery.

Robotic surgery (Da Vinci® Surgical System, Intuitive Surgical, Mountain View, CA) has been used to treat achalasia as it meets the limitations of conventional laparoscopic surgery, making it more ergonomic for the surgeon and minimally invasive. This involves a computer-assisted surgical device with remote handling. The benefits of amplifying the three-dimensional image enable complex surgical procedures such as fundoplication LMH to be performed more accurately, helping to prevent oesophageal perforation, and to identify residual circular muscle fibres[89].

BTI is the first-line treatment for patients of advanced age, those with severe comorbidities, those with a short life expectancy[16], or those on a waiting list for surgery (Figure 5). It is recommended for patients who are not eligible for more definitive therapies (PD or LHM). Pharmacological treatment with nitrates, calcium channel blockers, and "nitric oxide donors" (sildenafil) may reduce pressure in the LES, but the efficacy is generally unsatisfactory and incomplete. It is recommended for patients who do not want or cannot undergo a more definitive treatment and for whom BTI has failed (Figure 5). Sublingual nifedipine is the most widely used drug. In a review, Cochrane, Wen *et al*[87], identified only two randomised studies evaluating clinical success of nitrates in achalasia and concluded that they cannot give solid recommendations for use. In our experience, it can be a treatment option prior to the extension of the myotomy or the election of oesophagectomy. BTI and medical treatment should only be used in high-risk patients (Figure 5), and as an intermediate step prior to other, more durable treatments[3].

POEM is a new treatment[90] which has shown good results in the short term, including following a myotomy with anterior fundoplication[91]. It is profiled as a viable option for patients following the failure of a myotomy, in the absence of more controlled studies, long-term results, and comparison with current techniques.

Despite the improvement in symptoms offered by PD and LHM, 10%-15% will present progressive deterioration of the oesophageal function, and up to 5% may require an oesophagectomy in the terminal stage when they do not respond to any treatment (Figure 4)[92]. The ideal method of reconstruction following oesophagectomy has not yet been established, the options being gastric, colonic, or jejunal[3]. The treatment option for refractory achalasia is (Figure 5)[93] the minimally invasive Ivor-Lewis oesophagectomy. The success rate is close to 90%, although there is a significant risk of respiratory complications, anastomotic strictures, and leaks, dumping syndrome, regurgitation, and bleeding. The placement of percutaneous endoscopic gastrostomy (PEG) can be considered a suitable alternative in patients with an unusually high risk for other techniques. However, it does not tend to reduce the symptoms or risks of aspiration of salivary retention.

ROLE OF ENDOSCOPY IN THE DIAGNOSTIC THERAPEUTIC PROTOCOL OF ACHALASIA

Evaluation to guide treatment

The success of the treatment must be documented using objective parameters. Since there are deficiencies in the correlation between the latter and clinical symptoms, an adequate strategy includes periodic monitoring to detect symptomatic recurrences at an early stage. The symptoms can also reappear due to an initial incomplete myotomy, the growth of new muscular

fibres, or stenosis. The first clinical evaluation should be performed at an early stage (1-3 mo) after the initial intervention, and every 1-2 years thereafter[88]. The most widely used system for scoring symptoms is the Eckardt score[94]. The Eckardt score (maximum score, 12) is the sum of the symptom scores for dysphagia, regurgitation, and chest pain (0, absent; 1, occasional; 2, daily; and 3, each meal), and weight loss (0, no weight loss; 1, < 5 kg; 2, 5-10 kg; and 3, > 10 kg). This register allows new explorations, barium oesophagram, and EGD to be indicated. In addition, regular monitoring is important not only to ensure clinical control, but also to decide on the need for retreatment and to prevent complications at a later stage. Regardless of the subtype of achalasia, the long-term positive response variable most widely used in Europe is post-treatment LES pressure < 10 mmHg[24,88,95]. Other centres use the timed measurement of the barium column after the PD as a predictor of success. In this respect, a decrease by > 50% with respect to the basal pressure within 1 min is associated with a clinical improvement[41,96]. Some institutions perform oesophageal manometry intraoperatively or immediately after the dilation[97,98]. However, the pressure of the LES could be falsely raised as a result of oedema or intramural haematoma following the intervention. There is a new method for the intraoperative evaluation of the diameter of the EGJ (EndoFLIP). It is an endoluminal probe, which produces functional images of the diameter of the EGJ in real time using impedance planimetry. However, more studies are needed to determine the best parameter for retreatment[99]. There is no treatment for the neural lesion considered to be responsible for achalasia, which is why oesophageal peristalsis is rarely normalised following any of the therapies. However, some cases have been described in which recovery of peristalsis occurs, both following myotomy and following dilation[100-104]. Different authors have associated this with close monitoring of patients and the early indication of treatment, thus avoiding progression to advanced stages with oesophageal atony.

Endoscopic surveillance of complications

The primary role of endoscopy is to detect, prevent, and treat immediate and long-term complications deriving from the disease itself and the therapies applied. Endoscopy immediately after an endoscopic intervention is only indicated for the treatment of complications arising from the techniques used. However, there are currently no guidelines for monitoring squamous cell carcinoma or other late complications such as oesophageal and peptic stenosis, or megaoesophagus. More data are needed to determine which follow-up guidelines will improve the overall result in this disease, since prospective monitoring studies over > 30 years have shown a benefit in long-term survival in only 13% of cases[105].

The most prevalent complications in the long term when the treatment has been effective are mainly due to GER, which occurs in almost 25% of patients after a follow-up of > 15 years[106]. Following PD, the symptoms are generally relieved and temporary, and can be easily controlled with PPI. However, more severe complications have been described following surgery, including the incidence of reflux symptoms of 18% (range 5%-55%)[49]. These complications can be markedly reduced by adding a Dor fundoplication to the LHM[107]. The second most frequent complication is the progressive dilation of the oesophagus which leads to sigmoid megaoesophagus, and appears in 10% of cases of > 10 years of progression[88]. The most feared complication is oesophageal cancer, the prevalence of which ranges from 0.4%-9.2%, squamous cell cancer being more frequent[108-111] than Barrett's adenocarcinoma (associated with GER after myotomy). In this case, and although more studies are required, the majority of experts, including the latest guidelines from the American Society of Gastrointestinal Endoscopy[112], advocate some form of endoscopic surveillance 15 years after the initial diagnosis, and in patients with oesophageal stasis[5,113], but the subsequent monitoring interval has not been defined.

CONCLUSION

Achalasia is a primary oesophageal disorder for which there is no curative treatment. Pneumatic dilation and surgical myotomy are recommended initial therapies in healthy patients because they offer the best results in the long term. Botulinum toxin injection and medical treatment have transitory effects, and should be reserved for high-risk patients or as an intermediate measure before more definitive treatment. Other new options without definitive location in the therapeutic algorithm are peroral endoscopic myotomy, metallic stents, and ethanolamine injection. In refractory cases and in terminal stages, oesophagectomy is an option. Follow-up after the treatment is indicated to detect recurrences, indicate retreatment, and prevent late complications.

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REVIEW

Endoscopic management of biliary complications after liver transplantation: An evidence-based review

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Abstract

Biliary tract diseases are the most common complications following liver transplantation (LT) and usually include biliary leaks, strictures, and stone disease. Compared to deceased donor liver transplantation in adults, living donor liver transplantation is plagued by a higher rate of biliary complications. These may be promoted by multiple risk factors related to recipient, graft, operative factors and post-operative course. Magnetic resonance cholangiopancreatography is the first-choice examination when a biliary complication is suspected following LT, in order to diagnose and to plan the optimal therapy; its limitations include a low sensitivity for the detection of biliary sludge. For treating anastomotic strictures, balloon dilatation complemented with the temporary placement of multiple simultaneous plastic stents has become the standard of care and results in stricture resolution with no relapse in > 90% of cases. Temporary placement of fully covered self-expanding metal stents (FCSEMSs) has not been demonstrated to be superior (except in a pilot randomized controlled trial that used a special design of FCSEMSs), mostly because of the high migration rate of current FCSEMSs models. The endoscopic approach of non-anastomotic strictures is technically more difficult than that of anastomotic strictures due to the intrahepatic and/or hilar location of strictures, and the results are less satisfactory. For treating biliary leaks, biliary sphincterotomy and transpapillary stenting is the standard approach and results in leak resolution in more than 85% of patients. Deep enteroscopy is a rapidly evolving technique that has allowed successful treatment of patients who were not previously amenable to endoscopic therapy. As a result, the percutaneous and surgical approaches are currently required in a minority of patients.

Key words: Biliary stricture; Bile leakage; Liver transplantation; Endoscopic retrograde cholangio-pancreatography; Plastic stents; Fully-covered self-expandable metal stents

Core tip: One third of liver transplant recipients are

affected by biliary tract complications which are the major source of morbidity in these patients. Biliary-biliary (as opposed to bilio-enteric) anastomoses are first treated by endoscopy, with resolution of > 85% and > 75% of cases in deceased and living-donor transplant recipients, respectively. New stenting protocols and new designs of fully covered self-expandable metal stents are at the frontline of efforts aiming to reduce patient burden during treatment. Here, we discuss the latest developments in the endoscopic approaches to these complications.

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INTRODUCTION

Liver transplantation (LT) has become a standard of care in patients with end-stage liver disease. After LT, approximately one third of patients are affected by biliary tract complications and these result in significant morbidity and decreased patient survival[1]. Due to the scarcity of organ donors and the increasing number of patients waiting for LT, living donor liver transplantation (LDLT) has emerged as an alternative to deceased donor liver transplantation (DDLT). Even though surgical techniques are constantly improving, biliary complications are more frequent following LDLT compared with DDLT[2]; LDLT also remains characterized by its technical complexity and ethical controversies.

Biliary complications following LT include biliary leaks, strictures, choledocholithiasis and other less common conditions[3,4]. Approaches commonly used for treating biliary complications involve endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC) and surgery. ERCP is commonly regarded as the first choice treatment modality in most circumstances; if it fails PTC is often used, reserving surgery for severe complications or refractory conditions not manageable by less invasive techniques[5-8].

Here we review the literature focusing on the endoscopic management of biliary complications, the different strategies for treating strictures and biliary leaks and summarize their outcomes.

ETIOLOGY, RISK FACTORS AND DIAGNOSIS

Biliary reconstruction in LT

It is essential for endoscopists to have a clear comprehension of the different types of surgical reconstruction during LT. Biliary reconstruction is performed at the end of LT, once all vascular anastomoses have been completed. An end-to-end choledoco-choledocal anastomosis is the first choice procedure in most institutions following whole organ LT in patients with healthy native bile ducts of suitable caliber[6,9]. This technique produces physiological bilioenteric continuity, preserves the function of the sphincter of Oddi and allows for potential future endoscopic treatment of biliary complications. Bilioenteric reconstruction (Roux-en-Y hepaticojejunostomy) is performed in cases of previous biliary tract disease (*e.g.*, sclerosing cholangitis, biliary atresia), large disparity in size or small caliber of the bile ducts, and may be preferred in cases of retransplantation because of inadequate recipient duct length[10]. Due to the shortage of cadaveric livers, LDLT has gained popularity in adult patients. With LDLT, the living donor's right or left lobe or the left lateral segment is transplanted. Ductal anastomoses are more difficult to perform than in DDLT due to the small caliber of the intrahepatic ducts. In reduced size split-liver transplantation, a liver from a dead donor is splitted into two organs to permit two recipients to receive a graft; the anastomoses of both right and left lobe are alike to those of LDLT.

Risk factors for biliary complications

Biliary complications may be promoted by multiple risk factors related to recipient, graft, operative factors and post-operative course: (1) among recipient-related factors, advanced recipient age and more advanced liver function impairment contribute to the development of biliary complications[11,12]; (2) among graft-related factors, prolonged cold and warm ischemia time, extended donor criteria grafts and donation after cardiac death, as opposed to brain death, are associated with a higher incidence of ischemic-type biliary lesions (ITBL)[13,14]. Nonetheless, a recent report by Vanatta *et al*[15] showed that, by carefully selecting donors and recipients, overall patient and graft survival as well as the incidence of ITBL were similar following donation after cardiac *vs* brain death[15]; (3) operative risk factors are different for DDLT and LDLT for various reasons: LDLT by itself is an important risk factor for biliary complications due to the small duct size, the presence of multiple biliary duct outlets and the devascularization of the bile ducts during hilar dissection of the graft[16-18]. In DDLT, T-tube placement for duct to duct (DD) reconstruction allows minimizing the incidence of anastomotic strictures[19] and it is unequivocally recommended by some authors[20]; however, this results in biliary leakage following T-tube removal in 5%-33% of cases[19]; (4) during the postoperative course, early hepatic artery thrombosis may lead to the severest forms of non-anastomotic strictures, at multiple sites of the donor biliary system, because blood supply to the bile ducts is fragile. This may result in partial or total biliary necrosis with the formation of typical biliary casts and multiple intraluminal filling defects at

cholangiography[5,21]; and (5) other documented factors, including ABO incompatibility, cytomegalovirus infection and chronic/acute rejection episodes have been reported to be potential risk factors for biliary complications in historical publications; more recently these factors have been strongly associated with non-anastomotic, rather than anastomotic, complications[22-24].

Diagnostic approach

The clinical presentation of biliary complications varies considerably; patients could present no symptom at all, jaundice, abdominal pain, biliary leak or cholangitis. In asymptomatic LT recipients, a biliary complication usually is first suspected because of elevations of serum bilirubin, alkaline phosphatase, and/or gamma-glutamyl transferase levels. In the case of cholestasis, the initial diagnostic step is to discriminate obstructive *vs* nonobstructive causes, like LT rejection (acute or chronic), recurrence of primary disease and drug-induced cholestasis.

The initial evaluation should include a liver ultrasound (US) with a Doppler evaluation of the hepatic vessels, due to the frequent association of biliary complications with the presence of hepatic artery thrombosis or stenosis[6,25]. If hepatic artery stenosis or occlusion is suspected by Doppler US, multidetector computed tomography should be used as the second-line modality of choice for the rapid assessment of major vascular complications requiring pre-treatment confirmation. If hepatic artery thrombosis is confirmed, angiographic intervention should be performed urgently to re-establish hepatic artery flow[26,27]. Magnetic resonance cholangiopancreatography (MRCP) has substantially facilitated the accurate recognition of biliary tract complications (sensitivity and specificity of 93%-97% and 92%-98%, respectively, compared with ERCP as the reference standard)[28-31]. MRCP provides the endoscopist with a map of the whole biliary tract and, unlike ERCP, consistently demonstrates ducts even upstream from a tight stricture, therefore it is especially useful for hilar or intrahepatic anastomotic strictures. When findings at MRCP were compared to other approaches, including ERCP, PTC, and surgery to diagnose post-LT biliary complications, the sensitivity, specificity, positive predictive value, and negative predictive of MRCP were 98%, 94%, 94%, and 98%, respectively[31]. Its main disadvantages include a low sensitivity in the case of sludge or small stones (< 5 mm). MRCP is noninvasive and is the technique of choice for diagnosing post-LT biliary complications.

Etiology and types of biliary strictures

Post-LT biliary strictures are usually classified as anastomotic strictures (ASs) or non-anastomotic strictures (NASs), also called ischemic type biliary strictures (ITBS)[32-34]. Biliary strictures complicate around 2%-14% of LT and can be categorized in to early or late (occurring within or after the first month following LT, respectively). Strictures which appear soon after LT are commonly referable to technical problems, whereas late strictures are generally attributable to vascular insufficiency and problems with healing and fibrosis. In a recent systematic review, 1844 (12.8%) of 14359 LT patients had biliary strictures. The appearance of a stricture varies widely, from 7 d to 11 years after LT[35].

Anastomotic strictures: ASs can present at any time after transplantation but most of them are diagnosed within one year following LT with a mean interval between LT and diagnosis of 5-8 mo. ASs complicate around 6%-12% and 34% of deceased and living donor LT procedures, respectively[33,36,37]. ASs pathogenesis is believed to include inadequate mucosa-to-mucosa anastomosis, local tissue ischemia, and the fibrotic nature of the healing process[33,38]. ASs are solitary and short in length (Figure 1A and B). They may involve a choledocho-jejunostomy or a choledocho-choledochostomy; they are considered clinically relevant only if cholestasis or cholangitis are present. A slight and transient narrowing of the biliary lumen occurs frequently within the first one to two months following biliary anastomosis due to postoperative edema and inflammation, but it is uncertain how many of these cases progress to clinically significant ASs (Figure 1A)[33]. ASs can generally be effectively treated by endoscopic means and do not decrease graft or patient survival.

Non-anastomotic strictures: Post-LT strictures are classified as NASs if they are located more than 5 mm proximal to the anastomosis (Figure 1D). They account for 10% to 25% of all strictures complicating LT, with an incidence in the range of 0.5% to 10%[19,38-40]. NASs are considered to derive from ischemic damage to the duct as it may occur following hepatic artery thrombosis. Conditions associated with NASs include a prolonged ischemia time (cold and warm), transplantation after cardiac death donation, prolonged vasopressor support for the donor, ABO-type incompatibility, primary sclerosing cholangitis, autoimmune hepatitis or hepatitis C virus infection in the recipient[41-48]. Furthermore, nowadays a wider acceptance of older and extended criteria donors has been suggested to contribute to an increased incidence of NASs[19]. True NASs, usually referred to as ITBSs, characteristically are diffuse and include the hilum and sectorial or segmental intrahepatic branches. The treatment of NASs is technically more difficult than that of ASs and, in the case of hepatic artery thrombosis, the endoscopic treatment is mostly ineffective if the arterial blood flow cannot be restored.

Etiology and types of biliary leaks

Biliary leakage is the second most common complication after LT, with an incidence of 2%-21%[19,49,50]. In a recent meta-analysis, the rate of biliary leakage after LT

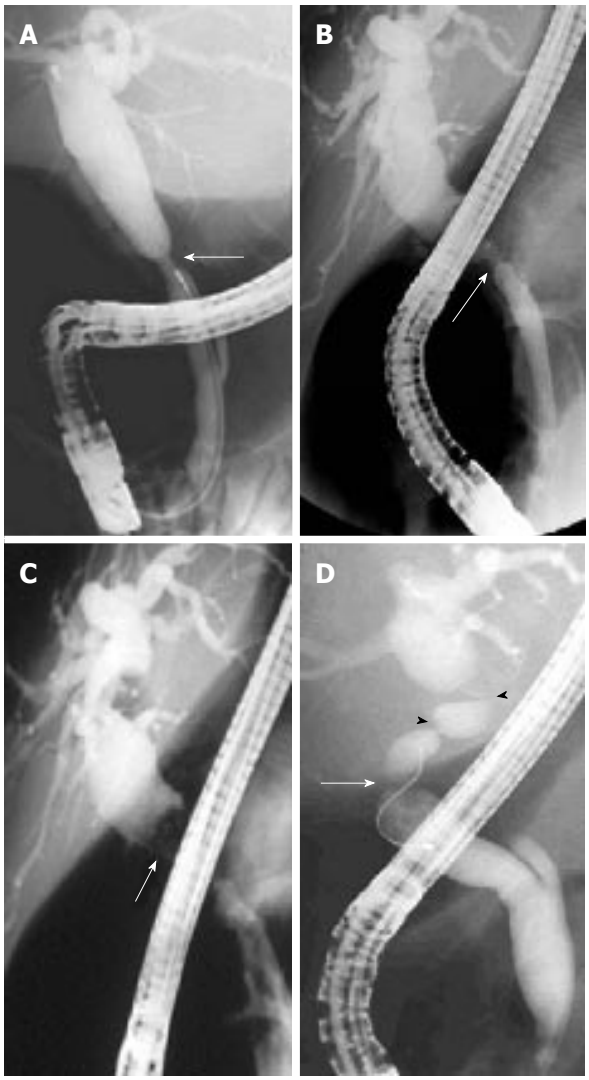

Figure 1 Biliary strictures at endoscopic retrograde cholangiopancreatography. A: Early and incipient anastomotic stricture (arrow) with upstream biliary dilation; B and C: Late and high-grade anastomotic stricture (arrow) > 1 year after deceased-donor liver transplantation, with a large stone located upstream from the stricture (arrow); D: Combination of anastomotic (arrow) and non-anastomotic (arrow heads) strictures.

was 8.2%, without significant difference between DDLT (7.8%) and LDLT (9.5%)[35]. Leakage may develop at the level of the anastomotic site, from the cystic duct remnant, from the cut surface of partial liver grafts in the case of LDLT, and following T-tube removal (Figure 2). Bile leaks can be classified into two categories: early bile leaks, which present within 4 wk following LT (these usually occur at the anastomotic site and are often related to technical issues, not to the type of biliary reconstruction), and late bile leaks, which present beyond this time (they are usually related to T-tube removal, resulting from delayed T-tube tract maturation possibly related to immunosuppression). A bile leak should be suspected in any patient who develops abdominal pain, fever or any sign of peritonitis following LT, especially after T-tube removal. Bile leaks can derive in collections of fluids and abscesses that might be related to strictured or disconnected ducts. Depending on the size of the leakage and the clinical presentation, bile leaks can be managed conservatively, nonsurgically or surgically[4,51].

Etiology and type of intraluminal biliary filling defects

Stones, sludge and casts occur in approximately 5% of patients after LT, with stones accounting for 70% of the cases. Biliary stone disease is associated with disorders that can reduce the flow of bile such as ASs or NASs. In addition, medications such as cyclosporine may play a role in bile lithogenicity by inhibiting bile secretion and promoting functional biliary stasis. Sludge is described as a thick collection of mucus, calcium bicarbonate and cholesterol crystals, which, when left untreated, can transform into biliary stones (Figure 3A).

Casts refer to the presence of multiple hard pigmented dark material that mold the bile ducts (Figure 4). These are thought to develop due to bile duct mucosal damage related to obstruction, ischemia, or bacterial infection. A history of hepatic artery thrombosis and a prolonged cold ischemia time are associated with debris formation[52-54]. This disorder occurs in 2.5% to 18.0% of LT recipients[32,54]. Casts are associated with increased morbidity, graft failure, retransplantation and mortality.

Sphincter of oddi dysfunction

Sphincter of oddi dysfunction (SOD) describes a clinical syndrome of biliary or pancreatic functional obstruction that may be responsible for cholestasis, pain, or pancreatitis.

It is hypothesized that, in the post-LT setting, denervation of the ampulla (secondary to surgical intervention) might generate a hypertonic sphincter, resulting in increased intraductal biliary pressure. This complication has been reported in 2% to 7% of patients who have undergone LT[55,56]. Typically, patients present with cholestasis, dilation of the distal bile duct and no obstacle detected at cholangiography.

ENDOSCOPIC MANAGEMENT

Managing post-LT biliary complications needs a multidisciplinary team involving transplant surgeons, hepatologists, endoscopists, and interventional radiologists. Endoscopic therapy is the first line therapy in most cases with a duct-to-duct anastomosis. With recent developments in enteroscopy, many patients with Roux-en-Y hepaticojejunostomy can also be treated endoscopically[57], with PTC being mostly reserved for the salvage of failures. The spectrum of endoscopic therapies includes biliary sphincterotomy, balloon dilation of strictures, basket and balloon extraction of stones, sludge, and casts, and the placement of one or multiple, side-by-side, biliary plastics stents. Additionally, cholangioscopy allows the characterization of strictures by observation and tissue sampling, and therapy of difficult casts or stones by intraductal lithotripsy[58-62]. Endoscopic therapy is usually highly successful and has a low incidence of procedure-related complications,

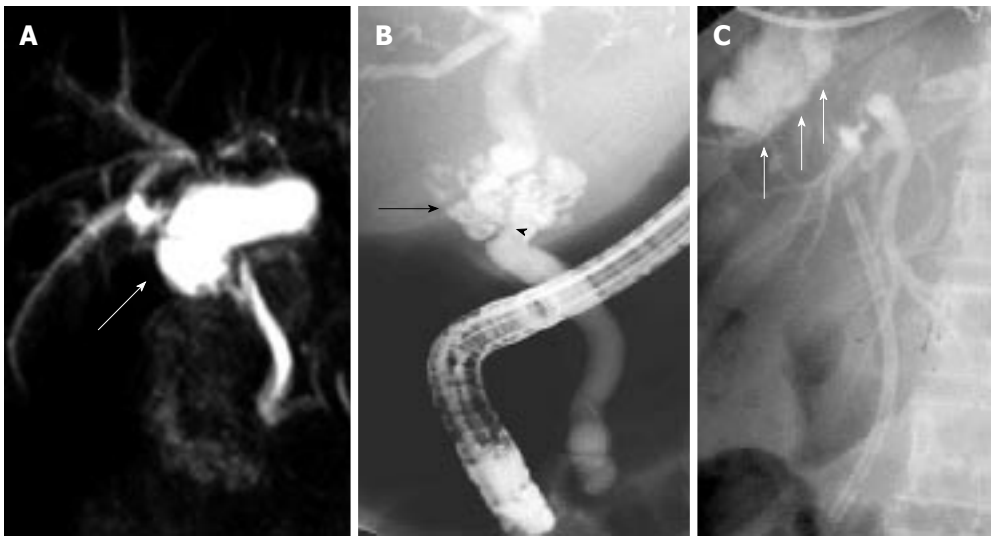

Figure 2 Biliary leaks. A: Biloma (arrow) resulting from anastomotic leakage early after liver transplantation as shown at magnetic resonance cholangiopancreatography; B: Anastomotic leakage (arrow) at the level of an anastomotic stricture (arrow head) early after liver transplantation as shown at endoscopic retrograde cholangiopancreatography (ERCP); C: Multiple leak sites from the cut surface in a split liver transplantation patient (arrows) as shown at ERCP with a plastic biliary stent in place.

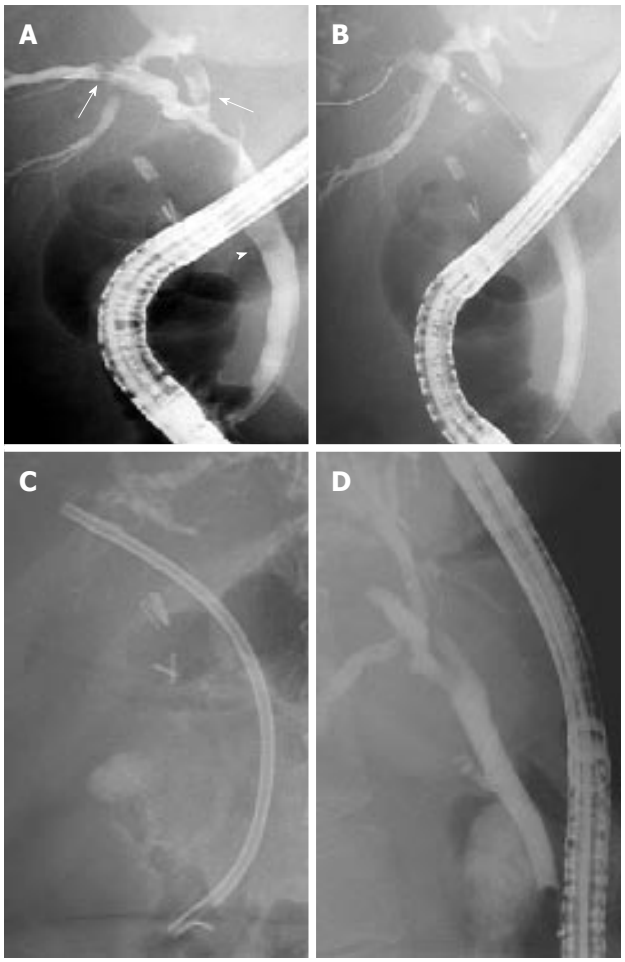

Figure 3 Endoscopic treatment of an anastomotic biliary stricture with upstream sludge and downstream stone after living donor liver transplantation. A: Anastomotic biliary stricture with upstream sludge (arrows) and downstream stone (arrowhead); B: Stricture dilation using a 10-mm in-diameter balloon; C: 10-F plastic biliary stent in place; D: Absence of residual stricture at late follow-up.

reserving surgery as a last option intervention if endoscopic and/or percutaneous treatment is not feasible or is ineffective.

Biliary leaks

Traditionally, post-LT biliary leaks have been treated surgically with anastomotic revision or conversion to a Roux-en-Y hepaticojejunostomy if a duct-to-duct anastomosis is not technically feasible. With advances in endoscopic therapy, ERCP has now become the initial therapeutic option in the management of biliary leaks. Usually the leakage of bile is treated through biliary sphincterotomy followed by the placement of a transpapillary stent (Figure 2C) for 2 to 3 mo (in contrast to post-cholecystectomy leaks, where the stent can be removed in 4 to 6 wk) with the aim of ensuring the proper healing of the leaks. Prolonged stenting is advised because healing may be delayed by immunosuppressors. If the leak is associated with a biliary stricture, this can be prudently dilated before inserting one or more plastic stents upstream from both the stricture and the leak[63]. Biliary stenting provides faster leak resolution than sphincterotomy alone and it is equally effective whether sphincterotomy is performed or not. At the time of stent removal, a careful anatomical evaluation should be performed and duct cleansing should always be performed because biliary abnormalities (mostly sludge, stones, or persistent leak) can be found at this time in a significant proportion of patients[64]. Endoscopic therapy solves the leakage of bile in more than 85% of patients[38,63-66]. Recently, fully covered self-expandable metal stents (FCSEMS) have been used in a pilot study of 17 LT recipients with biliary leaks[67]. FCSEMS offered minimally invasive and low-morbidity short-term control of leaks but it resulted in a relatively high stricture rate. In this series of 17

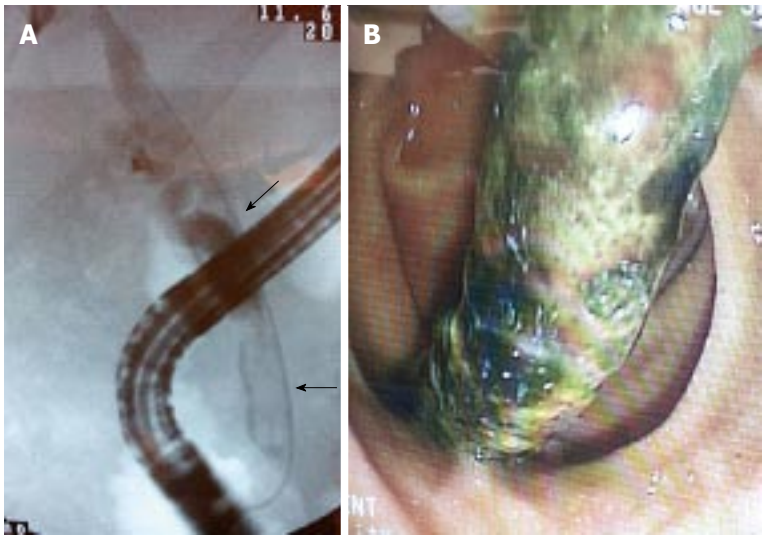

Figure 4 Elongated intraductal filling defects in the choledocus and common hepatic duct suggestive of biliary casts (arrows) (A) and endoscopic view of the successfully removed cast (B).

patients, 8 (47%) patients developed common bile duct strictures following FCSEMS removal; of these, 6 (35%) required repeat endoscopic treatment for a clinically significant stricture, therefore the use of current FCSEMS models cannot be recommended in the post-LT population. In specific situations, endoscopic therapy can be impossible or fail, for example, in the case of large anastomotic leaks associated with hepatic artery compromise or surgically altered anatomy (Roux-en-Y anastomosis). These patients will most often require surgical management.

Biliary strictures

Anastomotic strictures: No standard protocol has emerged for the endoscopic therapy of ASs. By analogy with the more frequent postcholecystectomy biliary stricture, endoscopic therapy of ASs usually requires biliary sphincterotomy plus balloon dilatation (BD) and stent placement (Figure 5). The use of BD alone in early onset anastomotic strictures (the first 2 mo following LT) may be effective. However, despite good initial success, BD alone led to a high rate of recurrent stricture formation[68]. Therefore, the combination of BD and stenting is a more adequate approach[33,65,68-71].

Multiple 10-Fr plastic stents are usually maintained until stricture resolution or for a minimum of 12 mo, with stent exchange scheduled every 3-4 mo to reduce the chance of stent blockage and cholangitis. In a recent systematic review that included 440 LT-related ASs treated with multiple simultaneous plastic stents[72], the mean AS resolution rate was approximately 85% for early as well as late ASs. Higher ASs resolution rates (97% *vs* 78%) and lower ASs recurrence rates (1.5% *vs* 14%) have been reported with stenting durations > 12 mo *vs* < 12 mo. This was observed despite the fact that shorter stenting durations were applied for early *vs* late ASs. Most cases of ASs recurrence were successfully managed with repeat plastic stenting.

Recently, different strategies of AS treatment have been described to decrease patient burden: (1) long-term maximal stent therapy with stent exchange only when signs or symptoms of biliary obstruction are detected: this strategy has allowed minimizing the number of ERCPs needed to treat ASs without compromising success or patient safety. With this protocol, complete AS resolution was reached in 94% of patients and recurrence rate at a median follow-up of 11 mo was 3%[73]. The authors reported in a total of 83 patients 2 cases of post-ERCP pancreatitis, 2 cases of periprocedural bacteremia but no episodes of cholangitis caused by stent occlusion; (2) stent exchange every 2 wk: ERCP with rapid-sequence balloon dilation followed by stenting with multiple stents over a short time period[74]. With this approach, mean stenting duration was 107 d and long-term stricture resolution was achieved in 33 (87%) of 38 patients; ERCP-related complications occurred in 2 (5%) patients. During a mean follow-up of one year after stent removal, 5 (13%) patients had a stricture recurrence, successfully retreated by endoscopic means in 4 cases; and (3) temporary placement of covered self-expandable metal stent (SEMSs). Covered SEMSs offer the advantage of longer stent patency and larger nominal diameter compared with a single plastic stent. Covered SEMSs should be maintained in place for a minimum of 3 mo as shorter stenting durations result in lower ASs resolution (72% *vs* 90%)[75-79]. In the systematic review cited above[72], covered SEMSs had a much higher stent migration rate (16%) compared with simultaneous multiple plastic stenting. Furthermore, covered SEMS carry a low but real risk of tissue ingrowth and stent impaction. Therefore, the authors concluded that current evidence does not suggest a clear advantage of SEMS use over multiple simultaneous plastic stenting in the management of ASs. In a large prospective study that was not included in the systematic review[80], the AS resolution rate using FCSEMSs was 68% of 42 LT patients and the migration rate was 17% and 75% at 3 and 6 mo, respectively. In this study, cholangitis was reported in 24% of patients with LT-related ASs and it

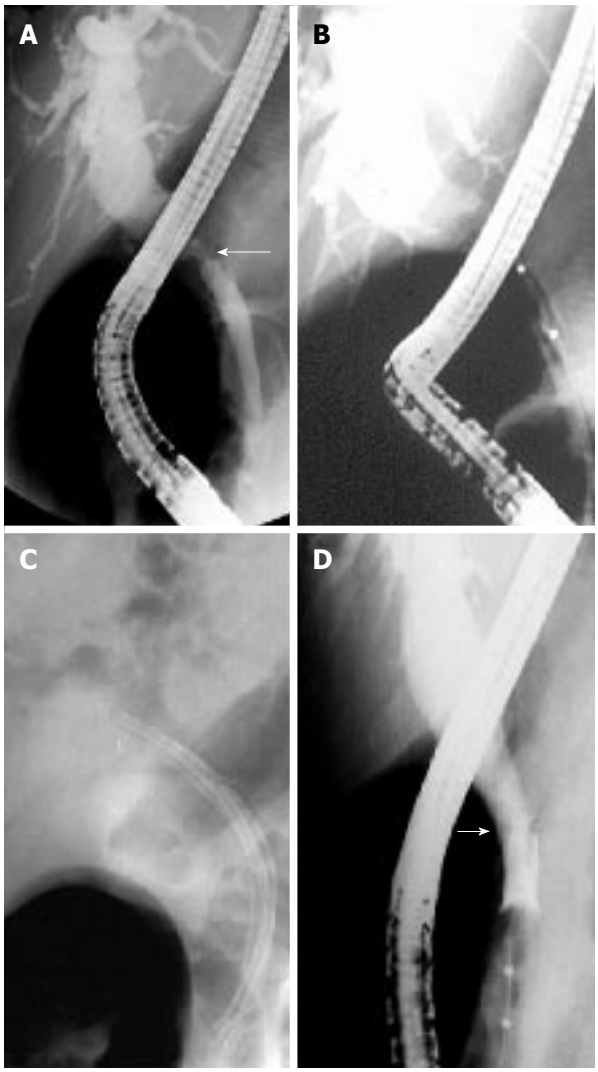

Figure 5 Endoscopic treatment of an anastomotic biliary stricture after deceased donor liver transplantation. A: Late, high-grade, anastomotic stricture (arrow) with a stone partially concealed by the endoscope; B: Stricture dilatation with a 4-mm in-diameter balloon; C: Three 10-Fr plastic stents in place, no residual stone; D: Balloon occlusion cholangiogram showing stricture disappearance at the end of treatment (arrow).

was strikingly associated with stent migration. Finally, a recent randomized trial compared a new design of FCSEMS *vs* multiple simultaneous plastic stenting in 20 patients with LT-related ASs[81]. ASs resolution rates were similar with both stent models but complication rate and hospital stay duration were non-significantly higher with the plastic stent *vs* FCSEMS, suggesting that some FCSEMS designs that effectively prevent stent migration might be a cost-effective alternative to plastic stenting.

Endoscopic management of ASs seemed to be more challenging in LDLT *vs* DDLT due to the complexity of duct-to-duct anastomosis. However, using an aggressive strategy of maximal endoscopic stent placement, two studies reported high (75%-100%) AS resolution rates in LDLT patients[82,83]. The long-term resolution rates of biliary leaks and/or strictures reported in selected retrospective studies are summarized in Table 1[37,82-87].

Table 1 Retrospectives series showing living donor liver transplantation endoscopic anastomotic strictures treatment results

Ref.	Patients (*n*)	Stenting (m)	Success (%)	F/U (m)	Relapse (%)
Yazumi *et al*[37] (2006)[1]	75	6	68	20 (1-50)	10
Gómez *et al*[84] (2009)	10	NR	20	30.5 (2-23)	NR
Seo *et al*[87] (2009)	29	3-6	64.5	31	30
Chang *et al*[86] (2010)	113	3-6	26.5	33 (3-96)	NR
Kim *et al*[85] (2011)	112	12.7	36	42.8 ± 15.2	11.5
Chan[82] (2013)	8	NR	75	18 ± 8.7	NR
Hsieh[83] (2013)[2]	38	5.3	100	74	21

[1]Combination of percutaneous transhepatic biliary drainage plus endoscopic retrograde cholangiopancreatography (ERCP) in 9 patients and inside stents technique; [2]Combination of percutaneous transhepatic biliary drainage plus ERCP in 6 patients. NR: Not reported.

Factors identified as independent predictors of failed endoscopic treatment of LDLT-related ASs include higher LT recipient age, longer operation duration, and a pouched morphology of the AS[84,88]. Recurrent ASs occur in approximately 21% of patients and may be retreated by endoscopy[83]. PTC plays an important role when a guide wire cannot be inserted through the anastomotic stricture at the time of ERCP (*e.g.*, disconnected duct, some refractory angulated or twisted strictures). For these patients, the rendez-vous technique (PTC + ERCP) may be useful to insert a stent above the stricture. This approach has been demonstrated to be feasible and relatively safe for the management of biliary strictures complicating LDLT with duct-to-duct anastomosis[89]. The endoscopic treatment of some ASs can be unsuccessful and may need long-term stenting or surgical hepaticojejunal anastomosis[87,90].

Non-anastomotic strictures: The endoscopic therapy of NASs or ITBSs often involves the hilum and intrahepatic ducts and is notably more demanding than the therapy of ASs. The stenosis at the level of the sectorial or segmental branch ducts can result in a cholangiographic appearance that simulates primary sclerosing cholangitis. It is challenging to make general recommendations for managing NASs and treatment should be individualized. Treatment success depends upon stricture grade, number, and location. Extra-hepatic strictures generally respond better to therapy and altogether, in the few published reports of endoscopic treatment, the success rates ranged between 50% and 70%[50,91]. Finally, a few patients (especially the ones with complex ischemic intrahepatic strictures) may need surgical revision or retransplantation.

In patients who have undergone Roux-en-Y hepaticojejunostomy, a potential alternative to PTC is the use of various techniques of enteroscopy. In 25 pediatric patients with hepaticojejunal anastomoses, the bilioen-

teric anastomosis could be reached in 17 patients, a stent could be placed in 9 patients and AS resolution was obtained in 5 (20%) patients, showing the difficulty of this procedure[92]. In a series of 44 adults with choledochojejunal AS following various hepato-biliary-pancreatic surgery, temporary stenting (including stent removal) was achieved in 32 (73%) patients and restenosis occurred in 7/32 patients[93].

Other complications

Biliary stones, sludge and casts: In LT recipients, the endoscopic management of stones is similar to that performed in the nontransplant setting although the approach may be complicated by the presence of a stricture downstream from the stone. In such circumstances, delayed stone extraction (following biliary stenting) or advanced endoscopic techniques like intraductal lithotripsy or direct choledocoscopy may be required to achieve stone removal. In patients with serious coagulation disorders or thrombocytopenia where sphincter ablation may be relatively contraindicated, balloon dilatation of the intact sphincter can be applied.

For biliary casts, the endoscopic approaches are alike to those utilized in stone disease. However, the success rate is significantly lower owing to the multiplicity of filling defects located in intrahepatic bile ducts[39]. Treatment usually requires multiple ERCPs, possibly complemented with PTC and it may require retransplantation in a significant proportion of cases[39,94] Cholangioscopy might aid to discriminate biliary casts from strictures[59].

Sphincter of Oddi dysfunction and papillary stenosis

As for SOD in the non-LT setting, biliary sphincterotomy is the common treatment and provides a high success rate[39]. The question of whether these patients are at similar risk of post-ERCP pancreatitis as those who are affected in the non-LT setting has not been formally studied; however it seems reasonable to consider prophylactic pancreatic stenting in addition to standard rectal administration of NSAIDs when performing sphincterotomy in these patients[95].

SUMMARY

Biliary complications remain a burden in LT patients and continue in some cases to be a challenging aspect of the multidisciplinary care of LT patients. As biliary complications are the most frequent complication following LT, the index of suspicion for requesting further investigations should be low. MRCP is the most useful examination to establish the diagnosis, especially because the low sensitivity of US may be more detrimental in LT as compared to the average patient. Successful endoscopic treatment is achieved in most cases, with the notable exceptions of ASs in LDLT patients, NASs and biliary casts. For ASs, temporary simultaneous multiple plastic stenting for a minimum of 12 mo (except in some cases of early AS) remains the standard of care; FCSEMS have yielded disappointing results up to now. In patients with choledocojejunostomy, deep enteroscopy techniques may allow successful treatment but success rates are lower. Nowadays PTC and surgery are reserved for a small minority of patients.

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REVIEW

Review of diagnostic and therapeutic endoscopic retrograde cholangiopancreatography using several endoscopic methods in patients with surgically altered gastrointestinal anatomy

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Abstract

The endoscopic approach for biliary diseases in patients with surgically altered gastrointestinal anatomy (SAGA) had been generally deemed impractical. However, it was radically made feasible by the introduction of double balloon endoscopy (DBE) that was originally developed for diagnosis and treatments for small-bowel diseases. Followed by the subsequent development of single-balloon endoscopy (SBE) and spiral endoscopy (SE), interventions using several endoscopes for biliary disease in patients with SAGA widely gained an acceptance as a new modality. Many studies have been made on this new technique. Yet, some problems are to be solved. For instance, the mutual unavailability among devices due to different working lengths and channels, and unestablished standardization of procedural techniques can be raised. Additionally, in an attempt to standardize endoscopic procedures, it is important to evaluate biliary cannulating methods by case with existence of papilla or not. A full comprehension of the features of respective scope types is also required. However there are not many papers written as a review. In our manuscript, we would like to evaluate and make a review of the present status of diagnostic and therapeutic endoscopic retrograde cholangiopancreatography applying DBE, SBE and SE for biliary diseases in patients with SAGA for establishment of these modalities as a new technology and further improvement of the scopes and devices.

Key words: Double balloon endoscopy; Single balloon endoscopy; Spiral endoscopy; Endoscopic retrograde cholangiopancreatography; Roux-en-Y reconstruction

Core tip: This study is a review of the status of diagnostic and therapeutic endoscopic retrograde cholangiopancreatography using several endoscopic methods in patients with surgically altered gastrointestinal

anatomy, evaluating the results from multiple centers over the world. The descriptions of features of the respective endoscopes including the introduction of new endoscopes are summarized. Assessment of the procedures is concretely made by type of reconstruction methods and by type of applied endoscopes, which suggests the present and future challenges to be overcome.

Shimatani M, Takaoka M, Tokuhara M, Miyoshi H, Ikeura T, Okazaki K. Review of diagnostic and therapeutic endoscopic retrograde cholangiopancreatography using several endoscopic methods in patients with surgically altered gastrointestinal anatomy. *World J Gastrointest Endosc* 2015; 7(6): 617-627 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i6/617.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i6.617

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is now one of the most effective diagnostic and therapeutic modalities in patients with biliary diseases. The success rate is > 90% for patients with normal anatomy[1,2], however, ERCP in patients with surgically altered gastrointestinal anatomy (SAGA) is far more challenging because of the inability of the endoscope to reach the blind end due to the long bowel passage, and of the complicated angulation. Some acute angled surgical limbs preclude the scope maneuverability and hinder the scope advancement.

The success of ERCP in patients with SAGA is affected by methods of surgical operations[3], and it often fails despite all the efforts. Consequently, many patients with SAGA are indicated for surgical or percutaneous operations, which is more invasive with greater risk of complications for patients than endoscopic therapy[4]. As an alternative procedure, percutaneous transhepatic cholangiography (PTC) is widely accepted, though is technically limited in such cases as; the absence of the dilated intrahepatic ducts, a contraindication due to the abdominal dropsy or compromised coagulation. In addition, PTC cannot establish an access to the pancreatic duct system[4]. Then surgery is left as the only alternative[5], though it brings about greater adverse events, longer hospital admission, and increased financial costs. Thus, the endoscopic interventional approaches have come to be preferred.

Since Katon *et al*[6] introduced the first endoscopic approach to Billroth-Ⅱ gastrectomy in 1975. In the late 1990s early 2000s, a number of papers studied on ERCP by using forward-viewing endoscopes or standard side-viewing duodenoscopes in various attempts, and the success rates widely ranged in 50%-92%[7-12]. As for Roux-en-Y reconstruction, Gostout *et al*[13] first reported the endoscopic approach in 1988. Since then, many attempts had been made by using duodenoscopes, pediatric colonoscopes, and oblique-viewing endoscopes, though the success rate was 33%-67% which was not satisfactory[12,14-16]. However, the advent of recently developed balloon assisted endoscopy (BAE) and spiral endoscopy (SE) radically gained the efficacy of endoscopic interventions in post-operative patients with not only Billroth-Ⅱ gastrectomy but also with Roux-en-Y reconstruction.

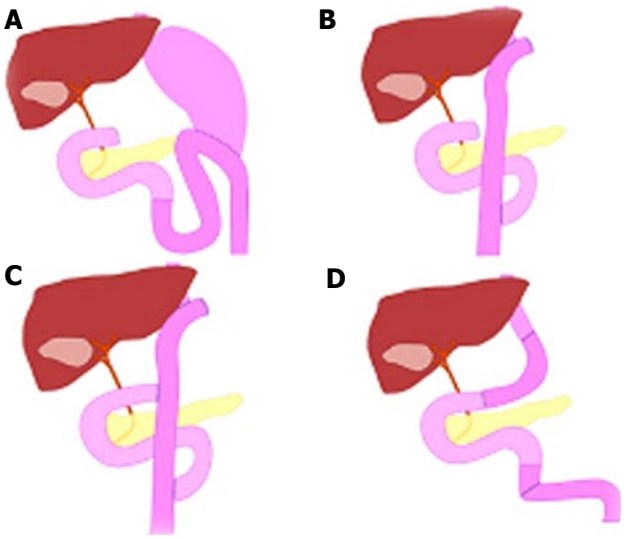

Figure 1 Schema of types of surgical anatomic reconstruction from gastrectomy. A: Billroth Ⅱ reconstruction; B: Roux-en-Y reconstruction; C: Double-tract reconstruction; D: Jejunal pouch interposition.

SURGICALLY ALTERED ANATOMY

In Japan, pancreaticoduodenectomy for treatment of pancreatic carcinoma and a total or partial gastrectomy for treatment of gastric diseases are often encountered. There are four common types of surgical anatomic reconstruction from gastrectomy; Billroth-Ⅱ reconstruction, Roux-en-Y reconstruction, double-tract reconstruction and jejunal pouch interposition (Figure 1). The number of Billroth-Ⅱ reconstruction has decreased due to the effective treatment of peptic ulcer disease whereas that of Roux-en-Y reconstruction has increased due to the recent spread of laparoscopic surgery. There are three common types of surgical anatomic reconstruction from pancreaticoduodenectomy; the Whipple Method, the (modified) Child surgery, the Cattell Method, and the Imanaga Method (Figure 2). Currently in Japan, the modified Child surgery is the first line reconstruction method for pancreaticoduodenectomies.

In United States in contrast, Roux-enY gastric bypass (RYGB) for morbid obesity[17-20], hepaticojejunostomy for living donor liver transplantation (LDLT)[21,22] or treatment of biliary injury or disease[23,24], and pancreaticoduodenectomy for ampulla neoplasia and pancreatic carcinoma[25,26] are more frequently encountered types of surgically altered anatomies. Because the severe morbid obesity is rarely encountered in Japan, RYGB for obese is not common and neither is hepaticojejunostomy for LDLT.

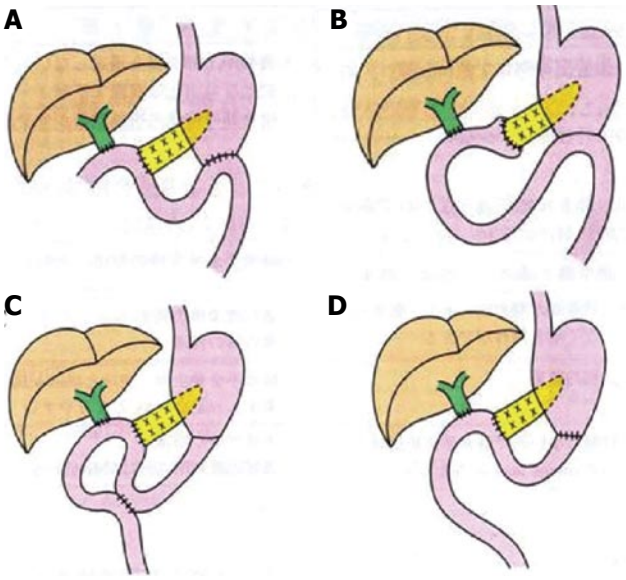

Figure 2 Schema of types of surgical anatomic reconstruction from pancreaticoduodenectomy. A: The Whipple Method; B: The (modified) Child surgery; C: The Cattell Method; D: The Imanaga Method.

Figure 3 Double-balloon endoscopy. The short type double balloon enteroscope (EC- 530B; FUJIFILM, Osaka, Japan) with a working channel of 2.8 mm diameter and a working length of 152 cm.

ENDOSCOPES

The invention of deep endoscopy has revolutionized the management of patients with mid-small-bowel diseases. Since the first introduction of double-balloon endoscopy (DBE) by Yamamoto[27] in 2001 (Figure 3), two additional techniques have become available, single-balloon endoscopy (SBE)[28,29] (Figure 4) and spiral endoscopy (SE)[30,31] (Figure 5). DBE and SBE entail a similar mechanism of advancement consisting of sequential bowel pleating by a push-pull technique that uses a balloon-fitted overtube with or without a second balloon inserted over the tip of a dedicated endoscope. The maneuver of the balloon or balloons in combination helps to hold and fix the intestine allowing the deep insertion by shortening the intestine. The inserting method of DBE (Figure 6) and SBE (Figure 7) is as shown in schemas. This technique enables the scope advancement selectively or retrogradely to reach the blind end in altered gastrointestinal anatomy with a high success rate. In contrast, SE is based on a different concept of insertion that pleats small bowel onto the endoscope to advance it through the lumen useing a rotating overtube [Discovery SB overtube (DSB); Spirus Medical, Inc., Stoughton, MA, United States]. This technique uses a spiral or raised helix-fitted overtube coupled with the endoscope, advanced as a unit into the small bowel by continuous rotation of the overtube in a manner similar to use of a corkscrew. An inner sleeve allows the independent motion of the overtube from the endoscope during advancement and withdrawal. The main difference between BAE and SE is that the latter uses a more or less continuous pleating of the small bowel by a clockwise rotation of the overtube rather than the push-pull technique. Unfortunately, SE is not currently commercially available.

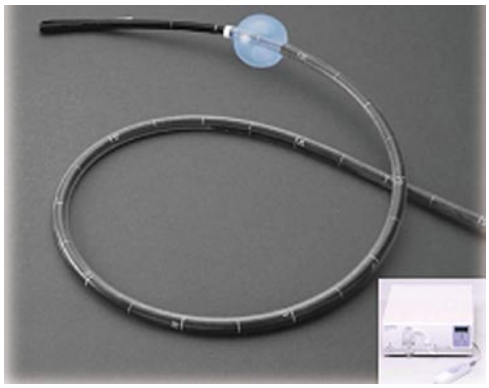

Figure 4 Single-balloon endoscopy. The standard type double balloon enteroscope (SIF- Q260; Olympus Systems, Tokyo, Japan) with a working channel of 2.8 mm diameter and a working length of 200 cm.

Figure 5 Spiral endoscopy. Discovery SB overtube over the snteroscope.

Characteristic of DBE

There are two types of DBE. One is with a 2.2 mm working channel for observations, introduced in 2003. The DBE, EN-450P (FUJIFILM, Osaka, Japan) and the other is for treatments with a 2.8 mm working channel. For the treatment-type scope, it can be sorted into two types. The first type was introduced in 2004, the standard type DBE, EN-450T5 (FUJIFILM, Osaka, Japan) with a 2.8 mm working channel and a 200 cm working length. The second type is the short type DBE, EC-450BI5 (FUJIFILM, Osaka, Japan) with a 2.8

Table 1 Information of balloon assisted endoscopy in Japan

	FUJIFILM					OLYMPUS		
	EN-450P/20	EN-450T5	EN-580T	EC-450BI5	EI-530B	SIF-Q260	SIF-Y 0004 (the first generation)	SIF-Y 0004 (the second generation)
	Standard type	Standard type	Standard type	Short type	Short type	Standard type	Short type	Short type
Release date (yr)	2003	2004	2013	2005	2011	2007	Prototype	Prototype
Direction of view	Forward view	Forward view	Forward view	Forward view	Forward view	Forward view	Forward view	Forward view
Angle of view	120°	140°	140°	140°	140°	140°	120°	120°
Outer diameter (mm)	8.5	9.4	9.4	9.4	9.4	9.2	9.2	9.2
Total length (mm)	2300	2300	2300	1820	1820	2305	1840	1840
Working length (mm)	2000	2000	2000	1520	1520	2000	1520	1520
Working channel (mm)	2.2	2.8	3.2	2.8	2.8	2.8	3.2	3.2
Passive bending part	No	No	No	No	No	No	No	Yes

mm working channel and a 152 cm working length that was introduced in 2005 as a colonoscope, and subsequently in 2011 another short type DBE EI-530B (FUJIFILM, Osaka, Japan) was introduced with a 2.8 mm working channel and a 152 cm working length as a pancreatobiliary scope. The short type DBE with the 152 cm working length is preferred and used rather than the standard type DBE with the 200 cm working length to perform ERCP in patients with (SAGA), because the 152 cm working length of the short type DBE allows the availability of almost all the ERCP-related devices, whereas the 200 cm working length limits the use of those devices.

In 2013, the treatment-type scope (EN-580T; FUJIFILM, Osaka, Japan) with a 3.2 mm working channel was introduced after further improvement, though it remained as the standard type with a 200 cm working length. For the use in ERCP in patients with SAGA, further development of short type DBE is strongly expected.

Characteristic of SBE

In 2007, Olympus introduced the standard type SBE (SIF-Q260; Olympus Medical Systems, Tokyo, Japan) with a 2.8 mm working channel and a 200 cm working length. Currently in Japan, only the standard type SBE is commercially available. Though, the short type SBE with a 3.2 mm working channel and a 152 cm working length (SIF-Y0004; Olympus Medical Systems, Tokyo, Japan), has been newly developed as the first-generation prototype. Some papers have been already written about the use of this scope for ERCP reporting that the 3.2 mm-working channel of the short type SBE allowed a smooth pushing-in and pulling-out action of devices, facilitating the employment of devices including a covered metallic stent that had been not applicable with the 2.8 mm working channel, which consequently enabled almost all the treatments that were equivalent to those of the conventional ERCP[32-35]. Additionally, the short type SBE (SIF-Y0004; Olympus Medical Systems, Tokyo, Japan) has been recently introduced as the second-generation prototype. This new endoscope is equipped with a passive bending part. This device helps the scope to pass and advance smoothly in the small intestine, which makes a special feature of this scope, as well as the 3.2 mm working channel that facilitated almost all the treatments equivalent to those of conventional ERCP. Some papers have been already written about ERCP using this scope[34,35], implying that deep insertion to the blind end using the second-generation prototype was easier than that using the first-generation prototype. With the equipment of this new device, the excelling performance in deep insertion to the blind end seems to be highly expected. Characteristics of BAE are summarized in Table 1.

ENTERING THE AFFERENT LIMB BY TYPE OF SURGICAL RECONSTRUCTION

The method of insertion to the blind end differs according to the type of surgical reconstruction. A full comprehension of every feature of respective reconstruction method is essential.

Billroth Ⅱ gastrectomy

In a case with Billroth Ⅱ gastrectomy, there are short afferent loop (SAL) and long afferent loop (LAL). The latter contains a jejunojejunostomy called the Braun anastomosis between the afferent and the efferent limbs. As for SAL, the angulation of gastrojejunostomy is acute, and it is difficult to identify the intestinal orifice that is possibly-be-the afferent limb, as well as to insert. The afferent limbs often appear in the upper left direction over the normal anastomosis in the monitor with its lumen closed. Generally, identification of the afferent limb is challenging due to the complicated angulation of gastrojejunostomy, however once the scope is inserted, the blind end can be reached using conventional scopes such as duodenoscopes or forward-viewing endoscopes in a short time owing to the short length of afferent limb. Ciçek *et al*[36] reported that the success rate of reaching the blind end in patients with simple Billroth Ⅱ gastroenterostomies using the duodenoscope was 83%.

In LAL, identification of the afferent limb is easy and the angulation is obtuse, which facilitates the scope insertion to the afferent limb because two intestinal orifices should be visible from the gastric lumen and either can be inserted easily. However due to the

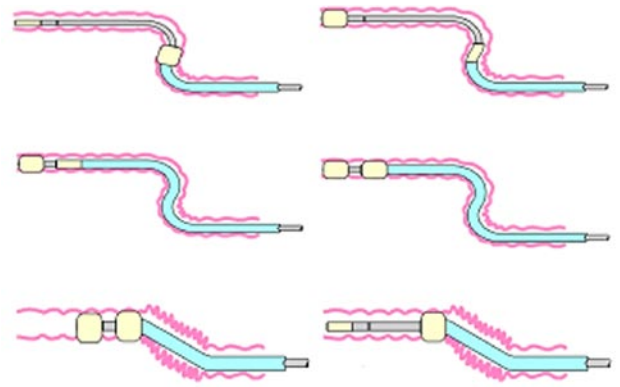

Figure 6 Schema of double-balloon endoscopy insertion.

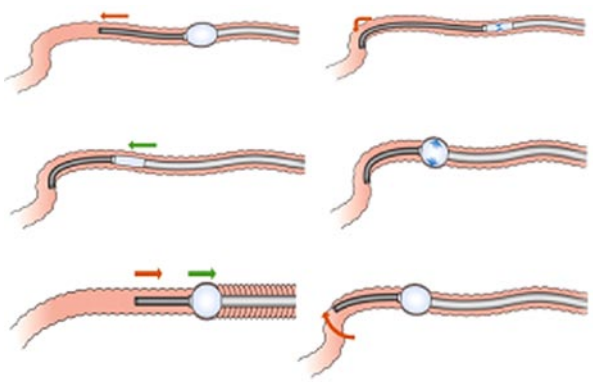

Figure 7 Schema of single-balloon endoscopy insertion.

longer length of the afferent limb it requires a longer duration to reach the blind end. It also precludes the advancement to the blind end. Thus, deep insertion using the conventional scopes is quite difficult.

In patients with both a Billroth Ⅱ gastroenterostomy and an additional Braun anastomosis, Çiçek *et al*[36] reported that the success rate was lowered to 29% for reaching the blind end. Whereas, Wu *et al*[37] reported the success rate of reaching the blind end in patients with both a Billroth Ⅱ gastroenterostomy and an additional Braun anastomosis was 90% even by using duodenoscopes by inserting the middle entrance of the lumen. Lin *et al*[38] reported the success rate of reaching the blind end using a duodenoscope was 69%. Furthermore in all the unsuccessful cases DBE was employed for the reattempted session and could successfully access the blind end. Also, in our previous report using short type DBE, the success rate of reaching the blind end was 100%[39]. In cases with Braun anastomosis, we would also attempt the insertion to the middle entrance as Wu *et al*[37] reported. The Braun anastomosis shows like a maze. It is often considered as a disadvantage for endoscopic insertion, however when the efferent limb was entered by error, the scope can always return from the Braun anastomosis to the efferent limb. Applying the technique to insert the middle entrance, the Braun anastomosis is not necessarily a disadvantage for the scope insertion, rather can be an advantage.

Roux-en-Y reconstruction

In a case with Roux-en-Y reconstruction, identification of the afferent limb in Y anastomosis is very difficult. Also, the insertion is possibly hindered by the acute angulation of the afferent limb and the severe adhesion as a consequence of the long intestine to the blind end. In comparison with the cases of Billroth Ⅱ gastrectomy, entering the afferent limb in cases with Roux-en-Y reconstruction is considered much more difficult. There are three challenges to be overcome for a successful insertion in cases with Roux-en-Y reconstruction.

The first challenge is identification of the afferent limb. It is difficult to identify the afferent limb in jejunojejunal anastomoses. Because of the maze-like feature of that area, endoscopists often lose their way or misjudge the orientation. Recently, Yano *et al*[40] reported a method using an intraluminal injection of indigo carmine to identify the afferent limb. The success rate was 80%, which suggests it should be helpful in identification of the afferent limb. However, the success rate based on our experience was approximately 50%. (unpublished observations) The divergence of the results could be reasoned that Yano *et al*[40] performed the procedure with the patient in a left-lateral position, whereas we performed in a pronation. Different postures in patients could have caused the divergence between the results.

The second challenge is the management of the complicated angulation in jejunojejunal anastomosis and the length of the afferent limb. It requires endoscopist's experience and skill to control the of sharp angulation of jejunojejunal anastomosis in order to reach the afferent limb, which in some patients forms an angle of up to 180 degrees. Shah *et al*[41] reported the success rate of deep insertion could be raised by change of patient's position from the typical semi-prone to a left-lateral or supine position during the procedure. Roux-en-Y gastric bypass (RYGB) is a particularly challenging postsurgical anatomy in terms of the length of the afferent limb. It consists of the long limb (often > 100 cm) that is traversed from the gastrojejunal orifice to the jejunojejunal anastomosis to reach the afferent small-bowel limb[14]. This reconstruction method is frequently performed in the United States for morbid obesity. Therefore, it was reported laparoscope-assisted ERCP was more efficient than endoscope-assisted ERCP for RYGB[42,43]. The RYGB is infrequently performed in Japan. We assume that the primary disease and application of surgery method differ to some extent in gastrointestinal anatomy between the United States and Japan.

Adhesions are the third challenge, which are frequently observed in patients with SAGA. In Japan, lymphadenectomy of malignant tumors is likely to be performed, which often results in post-surgical severe adhesion. They often preclude the scope advancement, and if scope insertion to this lesion is forced by power, it increases a risk of perforation and bleeding. Therefore

a careful maneuver and the discretion to withdraw are necessary for endoscopists.

In order to challenge these three obstacles, various attempts have been made and reported. Hintze *et al*[12] reported that the success rate of reaching the ampulla in Roux-en-Y anastomoses was 33%, compared with 92% in Billroth Ⅱ anatomy. Wright *et al*[14] reported a use of colonoscopy to access the biliary orifice and a guide wire for a duodenoscope to attempt ERCP in 15 patients with long-limb Roux-en-Y anastomoses. Kikuyama *et al*[16] used the oblique-viewing endoscope in couple with an overtube and reported a high success rate, though it was based on the small case series. Generally the results were not sufficiently practical or satisfactory.

Recently, two multicenter studies have been reported on the use of overtube-assisted endoscopy in the United States. One multicenter study[41] observed 129 patients (180 procedures) focusing only on Roux-en-Y reconstruction, and reported that the success rate of reaching the papilla or the hepaticojejunostomy site was 71% using several scopes such as DBE, SBE and SE. They concluded there was no divergence in the result caused by the type of applied scopes, however, in the 3/4 of unsuccessful cases where endoscopy-ERCPs failed were simply due to the failure of reaching the blind end, which suggested that the success of endooscopy-ERCPs were significantly affected by the result of the deep insertion to the blind end. It indicates that insertion to the blind end is quite challenging and prerequisite for performing ERCP in cases with Roux-en-Y reconstruction. The other multicenter study[44] focused on ERCP in 79 patients using the short-type DBE for several anatomical variations. The success rate of reaching the blind end was 90% (based on success rates of 82% for Roux-en-Y gastric bypass, 95% for pancreatoduodenectomy, and 100% for Billroth Ⅱ gastrectomy, hepaticojejunostomy, Roux-en-Y hepaticojejunostomy, Roux-en-Y gastrojejunostomy, choledochojejunostomy, and Roux-en-Y pancreaticojejunostomy). They reported a very high success rate of 90% to reach the papilla or the hepaticojejunostomy site applying only the short type DBE. They raised two points as reasons for their good result owing to several advantages regarding the short DBE, which is quite agreeable: (1) DBE might have better maneuverability than the long conventional DBE, which is especially useful in patients with post-surgical severe adhesions; and (2) DBE allowed endoscopists to apply a power pressure more effectively to the endoscope, which might have raised the success rate of reaching the papilla or anastomosis.

REACHING THE BLIND END WITH OVERTUBE-ASSISTED ENDOSCOPY

Reaching the blind end with BAE

SBE and DBE are based on the same concept of insertion. The difference is the presence or absence of the balloon at the tip of the endoscope. The absence of a balloon fitted to the tip of the endoscope impairs the stability in case with severe adhesions around the blind end. The slippery feature of intestine prevents the tip of the endoscope from being fixed still and orienting into the required direction to follow the overtube, which eventually hinders the deep advancement of overtube. Tsujikawa *et al*[28] suggested that the DBE was advantageous in cases with sharp angulations of the small intestine, because the balloon on the tip of the DBE could help pass around such angulations better than the hook-shaped tip of the SBE. In comparison with DBE, it is assumed that SBE is more disadvantageous in a performance of deep insertion. Shah *et al*[41] reported the success rates of reaching the blind end in patients with Roux-en-Y gastric bypass using standard type SBE (n = 22) or DBE (n = 15), using both the standard and the short type DBE, was 73% in the SBE group and 87% in the DBE group. It suggested that DBE showed a better performance in deep insertion to the blind end. However, the new short type SBE with the passive bending part has been introduced in order to improve the success rate of insertion to the blind end. Obana *et al*[33] reported the success rate of insertion to the blind end using the short type SBE without the passive bending part was 73%, which was relatively low. Recently we have reported the success rate using the short type SBE with the passive bending part was 92%[34]. We assume that the success rate of deep insertion to the blind end might have been raised by the use of short type SBE equipped with the passive bending part. Today several challenges are yet to be overcome for deep insertions using BAEs into the blind end.

Reaching the blind end with SE

SE is based on the totally different concept of insertion from that of BAE. Previous small studies have suggested that SE allow more efficient advancement into the small bowel than BAE, however, there are not much paper written regarding the insertion to the blind end in patients with (SAGA) using SE. Therefore, sufficient data are not available to evaluate the SE in point of success rate of deep insertion, complication morbidity and efficacy. To evaluate the efficacy and the safety of this method, more studies and assessment in a larger number of cases are necessary.

OVERTUBE-ASSISTED ERCP

Many studies of DBE-assisted ERCP have been made since 2007[39,41,44-61]. And studies of SBE-assisted ERCP were subsequently introduced in 2009[62-69], followed by the studies of SE-assisted ERCP in 2011[70-72]. As the DBE was introduced prior to the development of the SBE and SE, there existed more number of reports of successful ERCP using DBE in patients with PD than that of the SBE and SE. In comparison of the results before and after the advent of BAE and/or SE, it is obvious that

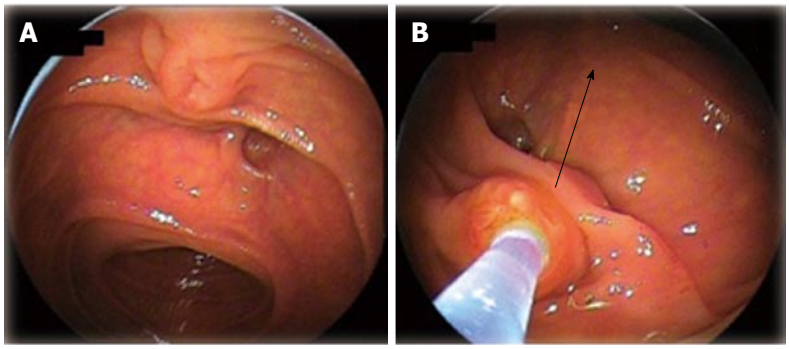

Figure 8 Biliary cannulation using double-balloon endoscopy in a patient with papilla. A: Papilla when the blind end was accessed; B: Locating papilla in 6 o'clock direction in the monitor, and performing cannulation adjusting the axis of catheter into 12 o'clock direction along the biliary duct.

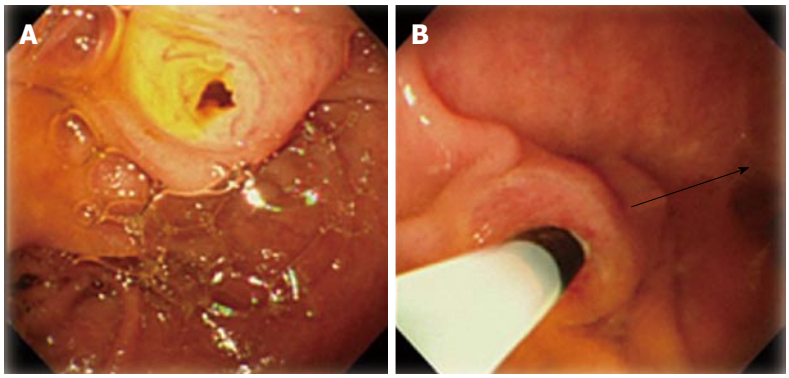

Figure 9 Biliary cannulation using single-balloon endoscopy in a patient with papilla. A: Papilla when the blind end was accessed; B: Locating papilla in 8-9 o'clock direction in the monitor, and performing cannulation adjusting the axis of catheter into 3 o'clock direction along the biliary duct.

the success rate has radically improved to a satisfactory level.

DBE-assisted ERCP

There are a lot of studies on DBE-assisted ERCP with wide ranging results. The success rate of ERCP-related interventions varied 60%-100%[39,41,44-61], which was probably because many studies were based on a small number of cases. We have reported a large case single center study[39], as a single center study in which we evaluated 103 procedures DBE-assisted ERCP by type of reconstruction method in 68 patients. The overall success rate for ERCP was 95% (based on success rates for Roux-en-Y reconstruction, Billroth Ⅱ reconstruction, and pancreatoduodenectomy of 91%, 100%, and 100%, respectively). In all successful ERCP cases, endoscopic therapeutic interventions were successfully accomplished. One multicenter study[41] reported the overall ERCP success rate was 63%. The success rate of ERCP using SBE and DBE was similar between Roux-en-Y gastric bypass and other long-limb surgical bypass. It also reported that the success rate of ERCP in cases where the blind end was successfully reached was 88%, which was satisfactory though they explained the success rate was lowered because many cases had contained papilla. Itoi *et al*[63] reported the success rate of ERCP using the standard type SBE was 72.3% mentioning that the biliary approach in patients with naïve papilla was difficult[63]. It is agreeable, however, in our previous study[39], the success rate of cannulation into papilla was 97%, suggesting the different type of applied scopes could affect the divergence of the results. For instance, because the position of the working channel of DBE is located at 6:30, an attempt to bring the papilla in a 6 o'clock direction in monitor will allow a down-angled maneuver that helps to fix the papilla still by a direct power pressure, which facilitates a stable cannulation (Figure 8). Whereas, the position of the working channel of SBE is located at 9 o'clock, which makes difficult to fix the papilla, precluding a stable cannulation as a consequence (Figure 9). Whereas Shah *et al*[41] concluded the type of scopes did not affect their result, though they used mostly the standard type DBE and SBE with the 200 cm working length in many cases. Namely, it could be inferred that not only using the DBE but the short type was the best appropriate scope for cannulation in cases with papilla. Siddiqui *et al*[44] reported the overall ERCP success rate using only the short-type DBE was 90% raising a reason for the excellent result as; the short DBE allowed the use of commercially available ERCP cannulas for performance of wire-guided cannulation, and therapeutic instruments could be applied to carry out successful therapeutic treatments.

SBE-assisted ERCP

Dellon *et al*[64] evaluated a use of the standard type SBE for diagnostic and therapeutic ERCP. They observed 4 patients with Roux-en-Y anatomy in total. (1 patient with RYGB, 2 patients with Roux-en-Y anatomy caused by bile duct injury, and 1 patient with Roux-en-Y anatomy after liver transplantation). The overall success rate of the therapeutic ERCP on the first session was 50%. In this report, the standard type SBE with 200 cm working length that was only applicable to limited variety of devices was used for the therapeutic ERCP,

Table 2 Review studys evaluating endoscopic retrograde cholangiopancreatography using several enteroscopy in patients with altered gastrointestinal anatomy

Ref.	No. of cases	Type of scope	Enteroscopy success (%)	Success rate of ERCP	Overall ERCP success (%)
Mehdizadeh *et al*[48]	5	Standard type DBE	67	100	67
Mönkemüller *et al*[53]	18	Standard type DBE	94	85	83
Maaser *et al*[4]	11	Standard type DBE	100	64	64
Kuga *et al*[59]	6	Standard type DBE	100	83	83
Tsujino *et al*[49]	12	Short type DBE	100	94	94
Siddiqui *et al*[44]	79	Short type DBE	89	90	81
Shimatani *et al*[39]	103	Short type DBE	97	96	94
Tomizawa *et al*[69]	22	Standard type SBE	68	73	50
Itoi *et al*[63]	13	Standard type SBE	92	83	77
Dellon *et al*[64]	4	Standard type SBE	75	67	50
Yamauchi *et al*[32]	31	Short type SBE	90	89	81
Obana *et al*[33]	19	Short type SBE	79	66	53
Shimatani *et al*[34]	26	Short type SBE	92	92	85
Lennon *et al*[70]	29	Standard type SBE	55	87	48
Shah *et al*[41]	27	Standard type DBE	85	85	63

ERCP: Endoscopic retrograde cholangiopancreatography; DBE: Double balloon endoscopy; SBE: Single-balloon endoscopy.

which could have caused the unsatisfactory success rate of SBE-assisted ERCP.

However, along the recent development of the short type SBE, several reports have been made on the short type SBE-assisted ERCP. The overall success rate of ERCP was 78%-90%, which was higher than that of ERCP using the standard type SBE. It could be reasoned that the 152 cm working length allowed the use of more variety of available devices.

SE-assisted ERCP

Although only published in abstract form, some studies on SE-assisted ERCP have been made. In a multi-center study, Shah *et al*[41] reported 129 patients with surgically altered anatomy who underwent ERCP using SBE (*n* = 15), DBE (*n* = 22), and SE (*n* = 13). The ERCP success rates of each method were 60%, 63%, and 65%, respectively. Lennon *et al*[70] discussed the comparison of SE and SBE. They concluded there was no significant difference between SE and SBE, and their overall ERCP success rate was 44%.

A review of studies evaluating overtube assisted ERCP in patients with (SAGA) *via* various techniques is summarized in Table 2.

COMPLICATIONS

It is assumed that the morbidity of complications is affected by type of applied endoscopes and by method of surgical reconstruction. The common complications for overtube-assisted ERCP are comparable with those of conventional ERCP such as bleeding, perforation, and post-ERCP pancreatitis. There are few studies made only in a small case series, however, the actual rates of perforation, bleeding, and pancreatitis associated with overtuve-assisted ERCP is unknown.

Performing ERCP in Patients with SAGAposes a greater risk of complications than in patients with NGA[73,74]. The risk of retroperitoneal perforation in patients with Billroth II surgery has been reported as high as 7%-10%[74]. Regarding Roux-en-Y reconstruction, our previous study retrospectively observed 55 procedures, reporting that procedural complications developed in 5 of 55 procedures (9%)[39]. Shah *et al*[41] retrospectively observed 129 patients, reporting that procedural complications were observed in 16 of 129 patients (12%), including pancreatitis (mild = 4, severe = 1), mild bleeding (*n* = 1), abdominal pain requiring hospital admission (*n* = 3), and throat pain requiring physician contact (*n* = 4). Two perforations were also observed and 1 case of death occurred. However, apart from those, studies based on only small case series can be found[75,76]. In order to evaluate the safety and efficacy of the procedure, it is necessary to analyze and evaluate data of complications out of large case studies from multiple centers prospectively, particularly for Roux-en-Y reconstruction.

CONCLUSION

The endoscopic approach to PD in patients with (SAGA) has radically become practical. Development of new modalities such as DBE, SBE, and SE is in progress as a consequence of an increased demand for the endoscopic interventions. For the safety and a higher success of the procedures, further development of the scopes and devices, standardization of technical maneuverability, establishment of guidelines in decision making of indicated and contraindicated cases, and assessment of complications from a larger multi-center study are necessary.

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REVIEW

Endoscopic ultrasound guided interventional procedures

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Abstract

Endoscopic ultrasound (EUS) has emerged as an important diagnostic and therapeutic modality in the field of gastrointestinal endoscopy. EUS provides access to many organs and lesions which are in proximity to the gastrointestinal tract and thus giving an opportunity to target them for therapeutic and diagnostic purposes. This modality also provides a real time opportunity to target the required area while avoiding adjacent vascular and other structures. Therapeutic EUS has found role in management of pancreatic fluid collections, biliary and pancreatic duct drainage in cases of failed endoscopic retrograde cholangiopancreatography, drainage of gallbladder, celiac plexus neurolysis/blockage, drainage of mediastinal and intra-abdominal abscesses and collections and in targeted cancer chemotherapy and radiotherapy. Infact, therapeutic EUS has emerged as the therapy of choice for management of pancreatic pseudocysts and recent innovations like fully covered removable metallic stents have improved results in patients with organised necrosis. Similarly, EUS guided drainage of biliary tract and pancreatic duct helps drainage of these systems in patients with failed cannulation, inaccessible papilla as with duodenal/gastric obstruction or surgically altered anatomy. EUS guided gall bladder drainage is a useful emergent procedure in patients with acute cholecystitis who are not fit for surgery. EUS guided celiac plexus neurolysis and blockage is more effective and less morbid vis-à-vis the percutaneous technique. The field of interventional EUS is rapidly advancing and many more interventions are being continuously added. This review focuses on the current status of evidence vis-à-vis the established indications of therapeutic EUS.

Key words: Endosonography; Pancreatic pseudocyst; Celiac plexus; Choledochostomy; Cholecystostomy; Photochemotherapy; Abdominal abscess; Common bile duct; Pancreatic duct; Endoscopic ultrasound-guided fine needle aspiration

Core tip: Therapeutic endoscopic ultrasound (EUS) has found role in management of pancreatic fluid collections, biliary and pancreatic duct drainage in cases of failed endoscopic retrograde cholangiopancreatography, drainage of gallbladder, celiac plexus neurolysis/blockage, drainage of mediastinal and intra-abdominal abscesses and collections and in targeted cancer chemotherapy

and radiotherapy. The field of interventional EUS is rapidly advancing and many more interventions are being continuously added. This review focuses on the current status of evidence vis-à-vis the established indications of therapeutic EUS.

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Endoscopic ultrasound (EUS) is an important diagnostic and therapeutic technique in the field of gastroenterology. The ability to visualise and access organs in vicinity of the gastrointestinal tract has opened this exciting field with many interventional EUS procedures now overtaking conventional approaches for treatment of various gastrointestinal diseases. While advances have been made in all aspects of diagnostic and therapeutic EUS, the present review will focus on advances in therapeutic EUS and use of EUS in drainage of pancreatic collections, celiac plexus neurolysis, biliary/pancreatic duct drainage, and in the drainage of intra-abdominal abscesses.

EUS GUIDED DRAINAGE OF PANCREATIC FLUID COLLECTIONS

Pancreatic fluid collections

Acute and chronic pancreatitis can be complicated by collections of varying nature composed of pancreatic juice and varying amounts of necrotic debris in patients with acute necrotising pancreatitis[1]. The morphological characteristics of pancreatic collections complicating acute pancreatitis seem to change with time and the amount of solid necrotic debris lessens with time[2]. Pancreatic fluid collections need to be drained if they get infected or become symptomatic and cause abdominal pain, gastric outlet obstruction or biliary obstruction. Radiological, surgical and endoscopic approaches have been used to drain pancreatic collections[3,4]. Broadly, collections needing drainage early in the course of illness when a wall has not yet formed are drained *via* percutaneous interventions while endoscopic drainage is feasible late in the course when wall has formed[5]. The distinction between the types of collection is important before drainage as the nature and outcome of drainage depend to a large part on the amount of solid debris present in the pancreatic fluid collections (PFCs)[6-8]. While non-necrotic collections have an excellent outcome with endoscopic drainage, the fate of necrotic collections is not as good. In one report while treatment success was 93.5% in pseudocyst drainage it was much lower at 63.2% for drainage of walled off necrosis[9]. Morphologic features like size and amount of debris predict the number of procedures needed as increasing size and amount of debris predict more number of procedures[8].

Endoscopic drainage vs EUS-guided drainage

While many centres continue to perform pancreatic pseudocyst drainage endoscopically, there is some evidence to suggest that EUS-guided drainage may be preferable. Two randomised trials have indicated a higher technical success especially in non-bulging lesions (Table 1)[10,11]. EUS-guided drainage is preferable in certain other clinical scenarios like presence of portal hypertension, collaterals around the collection, and presence of calcification in the wall[14,15]. A meta-analysis of available studies suggest that the technical success rates are higher for EUS guided drainage but the short term and long term results appeared to be similar[12]. In one of the report comparing the endoscopic and EUS guided drainage, median hospital stay was reported as similar with the two modalities[11]. Both reports indicate that the procedure time was not significantly different with either of the modality[10,11].

EUS guided drainage of PFCs

The drainage using EUS is done by using a linear echoendoscope which is advanced into the stomach or duodenum. The window is assessed using colour Doppler for any regional vascularity as well as the distance between the gastrointestinal tract wall and the cyst is measured. A 19 gauge EUS fine needle aspiration (FNA) is utilised to access the collection and contents aspirated for visual assessment as well as for analysis (cultures, amylase and carcinoembryonic antigen levels). Following this a guidewire is coiled into the cyst cavity and the tract is dilated[6,7,16]. Following this various modifications are available for the drainage of PFCs including single or multiple stentings, multistep procedure with initial nasocystic drain followed by placement of stent or insertion of fully covered self-expanding metallic stents[17]. Also, after resolution of PFC, removal of transmural stents may result in recurrence of PFCs[18]. Long term indwelling plastic stents, especially in patients with disconnected duct, is a preferred approach currently in these patients[19]. Multiple authors have reported good results of EUS guided drainage and Table 2 shows important studies reporting outcomes with EUS-guided drainage of PFCs[20-36].

Innovations

Use of metallic stents: Use of self expanding metallic stents (SEMS) has recently been advocated as they may provide a better drainage because of wider diameter and thus a quicker resolution of the symptoms[37]. Various removable stents with anti-migration features have been introduced for drainage of PFCs. Fully covered stents with dumbbell like shape have been introduced which provide lumen apposition and have lesser chances of migration[38]. Various innovations like insertion of plastic pigtail stents to prevent migration

Table 1 Comparison between endoscopic *vs* endoscopic ultrasound-guided drainage of pancreatic pseudocysts

Ref.	Patients and methods	Results
Park *et al*[10]	Randomised trial of conventional *vs* EUS guided drainage of pancreatic pseudocysts (n = 60)	EUS guided drainage has higher technical success (94% *vs* 72%). EUS preferable in non-bulging collections. Complications and pseudocyst resolution similar
Varadarajulu *et al*[11]	RCT of conventional *vs* EUS guided drainage (n = 15 each)	Higher technical success in EUS guided procedure (100% *vs* 33%) with lesser complications
Kahaleh *et al*[12]	Conventional drainage in bulging pseudocysts and absence of portal hypertension *vs* EUS guided in rest (n = 99)	No differences in short term or long term success and similar complications
Barthet *et al*[13]	Algorithm based approach of transpapillary (for small), EUS guided (nonbulging) or Conventional drainage of pseudocysts	EUS guided approach needed for atleast half of the patients

EUS: Endoscopic ultrasound; RCT: Randomized controlled trials.

Table 2 Endoscopic ultrasound guided drainage of pancreatic fluid collections (excluding self expanding metallic stents)

Ref.	Number	Outcome
Giovannini *et al*[20]	35 patients: 15 pseudocyst and 20 WON	Technical success: 94.3% Clinical success: 88.5%
Hookey *et al*[21]	116 patients (51 EUS guided transmural drainage)	Technical success: 93.8% Clinical success: 90.6%
Krüger *et al*[22]	35 patients (both pseudocysts and abscess)	Technical success: 94% Clinical success: 88%
Antillon *et al*[23]	33 patients: all pseudocysts	Technical success: 94% Clinical success: 90%
Lopes *et al*[24]	62 procedures: 36 pseudocysts and 26 abscesses	Technical success: 94% Clinical success: 84.3%
Ardengh *et al*[25]	77 patients with sterile PFCs	Technical success: 94% Clinical success: 91%
Varadarajulu *et al*[26]	60 patients: 36 pseudocyst and 24 with abscess/WON	Technical success: 95% Clinical success: 93%
Ahn *et al*[27]	47 patients with pseudocyst	Technical success: 89% Clinical success: 100%
Will *et al*[28]	132 patients: 31 pseudocysts (n = 32), 115 abscesses/WON	Technical success: 97% Clinical success: 96%
Seewald *et al*[29]	70 patients: including pseudocyst, WON, abscess	Technical success: 97.5% Clinical success: 83%
Puri *et al*[30]	40 patients with pseudocyst	Technical success: 100% Clinical success: 97%
Kato *et al*[31]	67 patients with pseudocyst	Technical success: 88% Clinical success: 83%
Künzli *et al*[32]	108 patients	Technical success: 97% Clinical success: 84%
Siddique *et al*[33]	87 patients with WON	Technical success: 99% Clinical success: 73.5%
Hocke *et al*[34]	30 patients with WON	Technical success: 96.7% Clinical success: 83.4%
Jürgensen *et al*[35]	35 patients with WON	Technical success: 100% Clinical success: 97%
Yasuda *et al*[36]	57 patients with WON	Technical success: 100% Clinical success: 75%

WON: Walled off necrosis; EUS: Endoscopic ultrasound; PFCs: Pancreatic fluid collections.

have been employed with these stents[39]. The major benefit of SEMS is likely to be in walled off necrosis (WON) as they may provide ease of repeated access for necrosectomy, however this remains to be proven in prospective studies. Table 3 depicts the studies where metallic stents were used in management of PFCs.

Non-fluoroscopic drainage: It has been demonstrated that EUS-guided drainage is feasible even without fluoroscopic control[6,48]. Seicean *et al*[48] have demonstrated the utility of EUS in drainage of PFCs in 24 patients and documented complete resolution in 83.3% cases. However difficulty arose in PFCs with thickened wall for which fluoroscopic control was recommended by the authors. We have also demonstrated the efficacy of EUS in draining non-bulging PFCs in 20 patients in absence of fluoroscopic control. Only one patient needed percutaneous intervention amongst these 20 patients[6]. In another report of EUS guided drainage of 22 patients with PFCs, drainage was technically feasible in 19 patients even in absence of fluoroscopy. Success after single procedure was noted in 59% patients[49].

Creation of multiple drainage routes: In management of walled off necrosis, creation of a single enteral opening may not provide adequate drainage of the collection. In this regard it may be better to have multiple access sites into the cavity which may help in improving drainage and irrigation of the cavity. Dual modality drainage involving percutaneous and endoscopic drainage simultaneously has been advocated for achieving this end[50]. A purely endoscopic procedure: EUS guided multi transluminal gateway technique has been evaluated and reported to have a high success (91.7%) vis-à-vis convention drainage (52.1) in a non-randomised study[51]. Prospective reports validating this approach are awaited.

Forward viewing echoendoscope: A multicentre randomised trial reported use of a forward viewing echoendoscope for drainage of PFCs. The technical success rates, mean procedure times, ease of access and complication rates were similar to the oblique-viewing echoendoscope indicating lack of any benefit with use of forward viewing echoendoscope for drainage of PFCs[52].

Table 3 Use of metallic stents for endoscopic ultrasound guided drainage of pancreatic fluid collections

Ref.	Population	Stent	Design	Outcome
SEMS				
Talreja *et al*[17]	18 patients with PFCs	FCSEMS (biliary stent)	Prospective cohort	95% success
Belle *et al*[40]	4 patients with WON	PCSEMS	Case series	100% clinical success
Fabbri *et al*[41]	22 patients with infected PFCs	FCSEMS (biliary)	Case series	77% clinical success
Penn *et al*[39]	20 with PFCs	FCSEMS (biliary) with plastic pigtail	Case series	Technical success 100%, clinical success 85%
Weilert *et al*[42]	18 patients with PFCs	FCSEMS	Case series	Clinical success in 78%
LACSEMS				
Shah *et al*[43]	Pseudocyst and WON (n = 33)	AXIOS (EUS guided in 30/33)	Prospective cohort	91% technical success, 93% resolution of PFC
Walter *et al*[44]	46 patients WON and 15 pseudocyst	AXIOS stent	Prospective cohort	Technical success: 98%, clinical success: 93% in pseudocyst and 81% in WON
Gornals *et al*[45]	9 patients with PFCs	AXIOS	Case series	Technical success in 88% and 100% clinical success
Itoi *et al*[46]	15 patients with pseudocysts	AXIOS	Retrospective case series	100% clinical success
Yamamoto *et al*[37]	9 PFCs, 5 pseudocyst and 4 WON	FCSEMS (Nagi stent)	Retrospective case series	77.8% clinical success
ESOPHAGEAL SEMS				
Sarkaria *et al*[47]	17 patients with WON	Esophageal FCSEMS	Retrospective case series	88% clinical success

SEMS: Self expanding metallic stents; PFCs: Pancreatic fluid collections; FCSEMS: Fully covered SEMS; WON: Walled off necrosis; LACSEMS: Lumen apposing covered SEMS.

Others

Access to the cavity may be difficult in patients with thick wall between the gastric/duodenal lumen and the cavity and therefore the tract may be difficult to dilate. To overcome this use of wire guided bent needle knife to obtain a wide access has been used[53]. A double guidewire technique utilising a double lumen catheter has been advocated to avoid the hassle of repeated need for cannulation of pseudocyst for placing multiple endoprosthesis[54]. A modification of the dual-lumen biliary brush catheter has also been used to place multiple guidewires into the cyst cavity and thereby allowing placement of multiple stents[55]. A novel exchange free access device has also been used for EUS guided drainage of PFCs and has an inner trocar for puncture and an outer dual balloon for dilatation of the tract reducing the need for multiple exchanges[56,57]. Numerous other innovations like use of hydrogen peroxide and streptokinase have been used but comparative data vis-à-vis control group is not yet available[58,59].

Drainage of PFCs is an important therapeutic application of EUS with excellent technical and clinical outcomes. We believe that merely dividing walled off PFCs into pseudocysts and WON may be too simplistic and it would be better to have three subgroups including acute postnecrotic pseudocyst (< 10% solid debris), walled off liquid necrosis (10%-40% solid content) and walled off solid necrosis (> 40% solid debris) as this has implications on management and success of endoscopic drainage[60]. We have previously shown that the amount of necrosis predicts the therapy needed in PFCs. Whilst those with < 10% debris need only one session of drainage, those with 10%-40% solid debris needed ≥ 2 sessions and the group with even higher (> 40%) debris needed direct endoscopic debridement or surgical necrosectomy[8]. Based on this, we follow an algorithmic approach (Figure 1) for management of PFCs at our institution.

EUS GUIDED BILIARY ACCESS

Endoscopic retrograde cholangio-pancreaticography (ERCP) is the standard approach to drain an obstructed biliary tract but may fail due to a number of factors like inaccessible papilla or a failure to cannulate it. In these situations, radiological or surgical drainage is needed. EUS guided biliary drainage is emerging as an alternative to a failed ERCP[16]. EUS guided approaches include transmural drainage (hepaticogastrostomy or choledochoduodenostomy), a rendezvous procedure or an antegrade approach[61]. EUS guided transluminal drainage (EUS-TLD) is achieved by bile duct puncture from the stomach or the duodenum using EUS-FNA needle. Occasionally choledochoantrostomy or hepaticoesophagostomy has also been described for achieving biliary drainage[62-64]. After obtaining a cholangiogram a guidewire is placed into the biliary system and the tract dilated followed by insertion of stent to achieve drainage of biliary system into the stomach or the duodenum. While duodenal station is used to achieve access into the common bile duct, gastric station allows access to the left lobe intrahepatic biliary radicals[61]. Access to right sided biliary system has also been described[65]. Table 4 depicts the major reports of EUS guided transluminal access to biliary

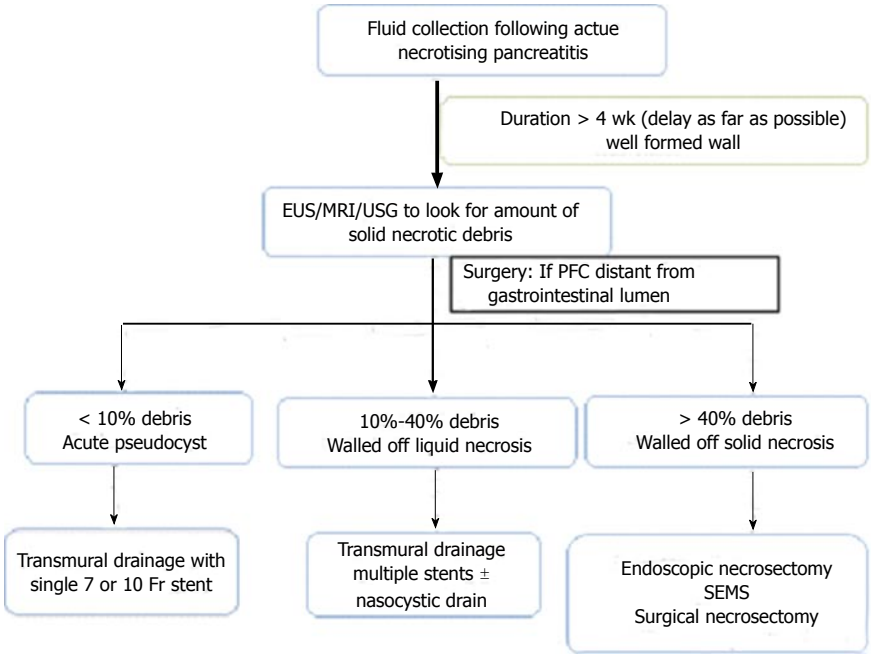

Figure 1 Proposed endoscopic treatment algorithm for walled off pancreatic necrosis. EUS: Endoscopic ultrasound; MRI: Magnetic resonance imaging; PFC: Pancreatic fluid collection; SEMS: Self expanding metallic stents.

Table 4 Endoscopic ultrasound guided transluminal biliary drainage

Ref.	Number	Etiology	Technical success	Clinical success	Complication rates
Takada *et al*[66]	26 17 CCD, 6 HG, 2 CCA, 1 HJ	Malignant	90.6%	100%	20.7%
Kawakubo *et al*[67]	64 CCD: 44 HG: 20	Malignant	95%	100%	19%
Prachayakul *et al*[68]	21 CCD: 6 HG: 15	Malignant	95.2%	90.2%	9.5%
Hara *et al*[69]	18 CCD	Malignant	94%	94%	11%
Song *et al*[70]	15 CCD	Malignant	86.7%	100%	23.1%
Kim *et al*[71]	13 CCD: 9 HG: 4	Malignant	92.3%	91.7%	30.7%
Park do *et al*[72]	57 CCD: 26 HG: 31	Both benign and malignant	96.5%	89%	20%
Komaki *et al*[73]	15 CCD	Malignant	93%	100%	26.7%
Hara *et al*[74]	18 CCD	Malignant	94%	100%	17%
Khashab *et al*[64]	20 HG: 3 CCD: 15 HE: 2	Malignant	95%	86.3%	10%
Vila *et al*[75]	60 HG: 34 CCD: 26	Both benign and malignant	64.7% and 86.3%	63.2%	15.1%
Attasaranya *et al*[76]	25 HG: 16 CCD: 9	Both benign and malignant	77%	96%	35%

CCD: Cholecystoduodenostomy; HG: Hepaticogastrostomy; CCA: Cholescystoantrostomy; HJ: Hepaticojejunostomy.

system. EUS guided rendezvous is achieved by creation of a temporary access to the biliary tree using EUS guided approach in patients with failed cannulation but with accessible papilla. The guidewire is then negotiated across the obstruction into the duodenum through the papilla and is then retrieved using snare and thereby providing a conduit for further ERCP[61]. This approach is, therefore, useful in failed ERCP but accessible papilla. The approach from the stomach and first part of duodenum is considered to be stable but the ampullary direction of guidewire is achieved best from the stomach and second part of duodenum[61]. Table 5 depicts the major reports of EUS guided rendezvous procedures and their outcomes. EUS guided antegrade approach is the use of temporary EUS guided access created from the duodenum or stomach for placement of stents or balloon dilatation without the scope reaching the papilla. The reported success rate for this procedure is 77% and the complication rate is 5%, however large studies are lacking[61].

EUS-TLD is associated with significant complications including perforation, bile leak, bleeding, and stent dysfunction or migration. The use of EUS-TLD has also been reported to be as efficacious as transpapillary drainage in patients with previous duodenal stents with a higher stent patency rate with EUS-TLD[84]. SEMS are preferred over plastic stents as they provide a larger diameter and therefore are likely to remain patent for longer periods and the risk of bile leaks is likely to be less with SEMS. SEMS also make a reinsertion of stent easier as stent can be placed into the previous SEMS[85]. Both EUS-TLD and placement of duodenal SEMS in patients with obstructive jaundice and duodenal obstru-

Table 5 Endoscopic ultrasound rendezvous procedures for biliary drainage

Ref.	Number	Technical success	Clinical success	Complications
Khashab *et al*[64]	13 (EH: 11, IH: 2)	100%	100%	15%
Tarantino *et al*[77]	4 (EH: 4)	50%	100%	13%
Dhir *et al*[78]	20	100%	100%	15%
Dhir *et al*[79]	17 TH, 18 EH	100% for EH and 94.1% for TH	100%	Higher for TH *vs* EH
Park do *et al*[80]	20 (14 IH and 6 EH)		80%	10%
Kawakubo *et al*[81]	14 (9 EH and 5 IH)	100%	100%	14%
Dhir *et al*[82]	58 (all EH)	-	98%	3.4%
Iwashita *et al*[83]	40 (31 EH and 9 IH)		73%	13%

EH: Extrahepatic; IH: intrahepatic.

ction due to unresectable periampullary lesions has been reported as a single step procedure with use of linear echo-endoscope[86].

EUS guided approaches have also been compared with percutaneous approach for biliary drainage. In a randomised study comparing percutaneous and EUS guided approaches in 25 patients with unresectable biliary obstruction, the technical success, clinical success, cost and complications were similar amongst both the groups suggesting that either could be used as an alternative for biliary drainage[87]. However a recent report comparing 51 patients who underwent percutaneous transhepatic biliary drainage (PTBD) with 22 patients who underwent EUS-TLD indicated that the technical success was higher for PTBD. The authors however recommended EUS-TLD as the initial procedure of choice as it needed lesser re-interventions reducing costs of therapy as also a lower adverse event rate[88]. In a similar report where 50 patients were retrospectively evaluated success of internal stenting as well as complication rates were more favourable in the EUS-TLD group. While internal stenting could be achieved in 92% patients in EUS-TLD group, it could be achieved only in 46% of PTBD group[89]. Amongst EUS guided approaches, transhepatic access seems to increase the risk of complications vis-à-vis transduodenal access of the biliary tree[78]. An approach has been suggested for the use of various EUS guided methods for achieving biliary drainage in different clinical settings. If ampulla is inaccessible, EUS-TLD is the initial choice. If papilla is accessible rendezvous should be attempted but if it is not possible to cross the lesion/stricture then EUS-TLD can be undertaken. Antegrade approach may be better suited for surgically altered anatomy where the procedure is needed for benign lesions[61].

EUS GUIDED GALL BLADDER DRAINAGE

The emergent gall bladder drainage is usually done radiologically but availability of EUS has made it possible to drain the gall bladder endoscopically. This may be indicated in situations like acute cholecystitis in patients who are unsuitable for surgery and have not improved with antibiotics[90]. In a systematic review of endoscopic drainage of gallbladder using nasogallbladder drainage in 194 patients and gallbladder stenting in 127 patients the technical success rates were 81% and 96%, clinical success rates were 75% and 88% and complication rates were 3.6% and 6.3%, respectively[90,91]. In a randomised study of patients with acute cholecystitis who were assigned to undergo either an EUS guided drainage or a percutaneous drainage of gall bladder the technical success rates were similar as were the complication rates suggesting that EUS guided approach is feasible for gall bladder drainage with outcomes comparable to the percutaneous approach[92]. Major reports (> 10 patients) on EUS guided drainage of gall bladder are shown in Table 6.

Table 6 Endoscopic ultrasound guided gall bladder drainage for acute cholecystitis

Ref.	Number	Technical success	Clinical success	Complications
Jang *et al*[92]	30	97%	100%	7%
Lee *et al*[93]	9	100%	100%	11%
Song *et al*[94]	8	100%	100%	37%
Jang *et al*[95]	15	100%	100%	13%
de la Serna-Higuera *et al*[96]	13	85%	85%	15%

Gall Bladder drainage can be achieved by use of either plastic or metallic stents or use of naso-gallbladder drains[94,95]. The complications may include bile leak, perforation and pneumo-peritoneum. In a report evaluating long term outcomes in 56 patients with acute cholecystitis who had underwent EUS guided gallbladder drainage the stent patency was 86% over 3 years. Four patients had late adverse events including distal stent migration in 2 patients and acute cholecystitis due to stent occlusion in 2 patients. The stent occlusions were treated endoscopically[97]. A single step procedure for insertion for lumen opposing metallic stent using AXIOS system has also been reported[98]. EUS guided gallbladder drainage has also been used as an approach for drainage in unresectable pancreatic cancer with use of anti-migratory fully covered metallic stents[99]. EUS guided gall bladder drainage may be of value in situation where a percutaneous procedure is dificult or more risky (presence of ascites and coagulopathy) but comes at an increased risk associated with sedation in patients with various comorbidities and the risk of bile leak.

EUS GUIDED PANCREATIC DUCT DRAINAGE

EUS guided pancreatic ductal (PD) drainage may be indicated for patients with failed transpapillary

drainage like in failed cannulation of non-negotiable strictures in chronic pancreatitis or pancreatic fistulae or pancreaticogastric or pancreaticojejunal stenosis after pancreatic surgery[100]. Both trans-enteric stenting and rendezvous procedures can be accomplished after EUS guided access to the pancreatic duct has been obtained. Once an access has been achieved using EUS-FNA needle and a guidewire is placed into the PD, and dilatation of the tract is done. SEMS are not used to drain the pancreatic duct for the associated risk of obstructive pancreatitis due to blockage of the side branches of the pancreatic duct. Complications associated with EUS guided PD drainage include leakage of pancreatic juice, pancreatitis, perforation or bleeding[101,102]. In a systematic review of 9 studies including 205 patients the pancreatic duct drainage was successful in 58%-100% with clinical success in 74% and a complication rate of 20%[102]. Success rates were lesser in a nationwide retrospective study form Spain[75]. Both rendezvous and transenteric drainage has been reported to have similar efficacy although it may be difficult to do a rendezvous in tight strictures[103,104]. The EUS guided PD access can be utilised for taking brushings to confirm malignancy in pancreatic stricture[105]. Access may be easier to obtain in dilated duct[104]. Some data is available about long term clinical success which indicates that at a median follow-up of 37 mo pain relief was present in 72% patients[106]. Another report indicated complete pain relief in 83% of patients[107]. It is important to suspect underlying malignancy in those with lack of pain relief[108]. Anterograde pancreatic drainage including stricture dilatation and removal of stone has also been reported[109,110]. To summarise EUS guided pancreatic duct drainage can be of use in rescue management of failed ERCP or in patients with surgically altered anatomy but the technique is still evolving and better accessories are needed.

USE OF EUS IN MANAGEMENT OF MALIGNANT DISEASE

Brachytherapy

Recently EUS guided brachytherapy has also been evaluated with radioactive seeds being placed into the tumour of interest under EUS guidance with the help of linear echoendoscope[111,112]. The most popular radioactive seeds are Iodine 125, palladium 103 and iridium 192. In pancreatic cancers where the cells divide quite rapidly, iodine is the radioactive material of choice as it has got a long half life of 60 d. The radioactive spill over the region of interest is definitely an issue of concern but in human tissue the penetration distance of the radiation into surrounding tissue is very small. The seeds of EUS guided brachytherapy were sowed by Sun *et al*[111] with their study in pigs. Sun *et al*[111] published the use of iodine 125 in unresectable pancreatic cancer in 15 patients. The result revealed a median survival of 10.6 mo with 27% patients having partial tumour response[111]. In another study in 22 patients with advanced pancreatic cancer where combination of gemcitabine and Iodine 125 brachytherapy was used, the overall survival rate didn't improve[112].

Fiducial marker placement

For external beam radiation to the cranium, bony landmarks are used for guiding the therapy while in intraabdominal malignancy fiducial markers are placed inside the tumour for guiding therapy. These markers are radioactive spheres, coils or seeds. Earlier fiducials were placed under surgical or radiological guidance but with advent of interventional EUS, these fiducials can be placed under EUS guidance also. Pishvaian *et al*[113] reported EUS guided fiducail placement in 13 patients with technical success achieved in 11/13 patients. An average of 3-4 fiducials were placed in each patient. There have been multiple studies where EUS guided fiducials have been placed successfully in pancreatic cancers, esophageal cancers and neuroendocrine tumours[114-116]. To compare the 2 types of fiducials a study was conducted in 39 patients with advanced pancreatic cancer. Traditional fiducials of 5 mm length and viscoil fiducials of 10 mm length were compared. It was observed that traditional fiducials had better visibility scores as compared to viscoil fiducials and the migration rate between the two types of fiducials was similar[117].

EUS guided ethanol ablation

Ethanol causes cell death by membrane lysis, vascular occlusion and protein denaturation and has been used for ablation of solid and cystic lesions of thyroid, liver, adrenals, *etc*. EUS guided ethanol ablation has been used recently for ablation of pancreatic lesions, neuroendocrine tumors (NETs) and metastatic abdominal lesions. EUS guided fine needle injection therapy using alcohol is safe and better than percutaneous approach as it is delivers alcohol to target tissue with more accuracy, identify surrounding structures and perform injection therapy in real time monitoring.

In a study by Gan *et al*[118] including 25 patients with pancreatic cysts who underwent ablation with variable concentrations of alcohol (5%-80%), the results revealed complete resolution in 8 patients and epithelial ablation in 5 patients who underwent surgery. In another study ethanol injection was compared with saline injection alone. In this study 25/42 patients were initially treated with alcohol and rest 17 with saline. After 3 mo, patients in both the groups were treated with ethanol injection. The results showed that 80% ethanol injection resulted in a greater decrease in size as compared to saline injection. Nine patients who were followed up for 2 years had no recurrence of cyst[119]. In another study of 42 patients with cystic tumours of the pancreas who were initially injected with 99% ethanol followed by paclitaxel. Complete resolution

Table 7 Antitumour agents, their composition and area of use

Name of the agent	Drug	Ref.	Reported use
CYTOIMPLANT	Allogenic mixed lymphocyte culture	Chang *et al*[130]	Advanced pancreatic cancer
TNFerade	cDNA expressing TNF-α (adenovector)	Hecht *et al*[131], Chang *et al*[132] and Citrin *et al*[133]	Pancreatic, esophageal and rectal cancer
ONY X-015	Adenovirus	Mulvihill *et al*[134]	Advanced pancreatic cancer
Oncogel	Paclitaxel and ReGel	Linghu *et al*[135], Matthes *et al*[136] and Vukelja *et al*[137]	Pancreatic, esophageal cancer
Gemcitabine	Gemcitabine	Levy *et al*[138]	Advanced pancreatic cancer
DC's	Dendritic cells	Irisawa[139], Hirooka *et al*[140]	Advanced pancreatic cancer

was achieved in 29 patients. No complications were observed[120]. EUS guided ethanol ablation of pancreatic neuroendocrine tumours has been reported in patients who are not good candidates for surgery either because of age or comorbidities. There have been published reports where even multiple NETs have been injected with alcohol and ablation has been achieved with patient remaining symptom free post injection. But there is a risk of recurrence and metastasis. So long term follow up studies are required to adequately define the role of ethanol ablation in NETs[121-125].

Multiple metastatic lesions have also been ablated with EUS guided ethanol injection but its role in these situations need to assessed in larger studies. These include hepatic metastases from carcinoma colon, pelvic lymph nodal metastases from rectal cancer, left adrenal metastases from non-small cell carcinoma lung, hepatic metastases from pancreatic carcinoma and ablation of a gastrointestinal stromal tumour in a patient whose comorbidities precluded surgery[126-129].

Delivery of antitumor agents

Pancreatic carcinoma has got a poor response to chemotherapeutic agents and radiation. In presence of locally advance disease and borderline resectability, neoadjuvant chemotherapy has been tried, but it carries a poor response rate as the tumour is hypovascular and produces a desmoplastic reaction around it leading to poor delivery of drugs. So various local antitumour agents have been tried in patients with advanced pancreatic carcinoma for palliation and in locally advanced lesions for downstaging before surgery (Table 7).

The problem with all these studies is that they were small and all these agents in this role are still in experimental stage. So we need much more large prospective studies before these techniques can be put into clinical practice.

Tumour ablation

Thermal injury leading to coagulation necrosis has been the principle of radiofrequency ablation (RFA). This principle has been exploited for treatment of solid tumours like hepatocellular carcinoma (HCC) and liver metastases. Percutaneous, open or laparoscopic approach have been associated with morbidity and mortality. Recently EUS guided RFA has been performed under real time guidance in porcine models. Studies of EUS RFA done in porcine models have used the technique for ablation of lymph nodes and pancreatic lesions[141,142]. Majority of pigs tolerated the procedure well except for few complications.

EUS photodynamic therapy

Photodynamic therapy is another modality for tumour ablation. Here a photosensitizer drug is injected and application of light is done to the area of interest. The tumour cells are killed by direct cytotoxic effects, vascular changes and inflammatory reaction[143,144]. A study in porcine models where EUS guided photodynamic therapy has been done to liver, pancreas and kidney showed that 100% necrosis was seen in pancreas only[145].

EUS guided laser therapy

It is an evolving technique and recently a case was reported where EUS guided laser ablation of a left lobe HCC was performed using 22 G needle and patient was followed up for 2 mo with no recurrence of the lesion[146].

EUS-GUIDED INRAABDOMINAL ABSCESS DRAINAGE

EUS guided internal drainage of abdominal and pelvic abscesses has emerged as an alternative to traditional percutaneous drainage. Abscesses in areas close to the gastrointestinal lumen including mediastinum, lesser sac, perihepatic and subphrenic space, and pelvis can be drained using EUS guidance. The procedure involves the usual steps described earlier for PFC drainage: access using 19 G EUS-FNA needle, use of guidewire, dilatation of tract and placement of drainage catheter or pigtail stents. The suggested dilatation diameters for esophagus is 6 mm, for colon and jejunum is 6-8 mm, for duodenum 8-10 mm and in stomach 8-15 mm[147]. Table 8 shows various reports of EUS guided drainage of pelvic abscesses.

Mediastinal abscesses have also been drained under EUS guidance including placement of lumen opposing stents[154,155]. A few reports have also involved aspiration of splenic abscess in setting of pancreatitis[156,157]. Liver abscess have also been drained using EUS guidance

Table 8 Endoscopic ultrasound guided drainage of pelvic abscesses

Ref.	Number	Site	Technical success	Clinical success	Complications
Hadithi *et al*[148]	8	Abdominal (pelvic)	100%	100%	0
Puri *et al*[149]	30	Pelvic (4 prostatic)	93.3%	83.5%	0
Ramesh *et al*[150]	38	11 transcolonic, 27 transrectal	100%	87%	10.5%
Puri *et al*[151]	14	Pelvic	100%	93%	0
Varadarajulu *et al*[152]	25	Pelvic	100%	96%	0
Giovannini *et al*[153]	12	Pelvic	100%	75%	25%

and placement of lumen apposing stent has also been done[158,159].

EUS GUIDED CELIAC PLEXUS BLOCK

Percutaneous celiac plexus neurolysis (CPN) has been used for management of pain in pancreatic cancer and sometimes for chronic pancreatitis. EUS guided CPN has emerged as a more effective technique in recent times[160]. Using the linear echoendoscope at the level of gastroesophageal junction the aorta is located and celiac artery traced. While alcohol is used to obtain CPN, bupivacaine is used for celiac plexus block (CPB). Although triamcinolone is often added to bupivacaine but a randomised study found no benefit with addition of triamcinolone[161]. The average efficacy of CPB for pain relief is around 3 mo. Transient hypotension and diarrhea may occur as side effects of the procedure. The EUS guided technique avoids passage through the vertebrae and muscles at the back as required for a CT guided celiac block and therefore unlikely to have related adverse events like paraparesis[162]. Interestingly, ganglion cells have now been visualised on EUS and it may be better to target ganglions directly[163,164]. In a randomised trial comparing CPN with celiac ganglia neurolysis (CGN), the positive response was higher in the CGN group (73.5% *vs* 45.5%). Half of the patients in CGN group obtained complete relief vis-à-vis 18% in CPN group[165].

Multiple comparative reports have emerged which have compared radiologic *vs* EUS guided CPN. EUS guided CPN provided a more long lasting pain relief (30% up to 24 wk) while with CT guided CPN only 12% had some relief at 12 wk[166]. In a trial comparing one *vs* two injections for pain relief during CPN, no incremental benefit in pain relief was observed with two injections[167]. EUS guided CPB was more efficacious for pain relief in patients with chronic pancreatitis in a randomised comparison with percutaneous CPB[168]. Only a subset of patients with EUS guided CPN obtain complete pain relief and the duration of pain relief is variable. The predictors of pain relief are not established. Also the benefit of performing CPN rather than CPB in chronic pancreatitis is not clear[169].

It is apparent that the availability of interventional EUS has allowed gastroenterologists to make forays into areas which traditionally remained the domain of surgeons and interventional radiologists. With further improvements in accessories and development of EUS-natural orifice transluminal endoscopic surgery, the endosonologist will have to do multiple roles[170].

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MINIREVIEWS

Role of wireless capsule endoscopy in the follow-up of inflammatory bowel disease

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Abstract

The introduction of wireless capsule endoscopy in 2000 has revolutionized our ability to visualize parts of the small bowel mucosa classically unreached by the conventional endoscope, and since the recent introduction of colon capsule endoscopy, a promising alternative method has been available for the evaluation of large bowel mucosa. The advantages of wireless capsule endoscopy include its non-invasive character and its ability to visualize proximal and distal parts of the intestine, while important disadvantages include the procedure's inability of tissue sampling and significant incompletion rate. Its greatest limitation is the prohibited use in cases of known or suspected stenosis of the intestinal lumen due to high risk of retention. Wireless capsule endoscopy plays an important role in the early recognition of recurrence, on Crohn's disease patients who have undergone ileocolonic resection for the treatment of Crohn's disease complications, and in patients' management and therapeutic strategy planning, before obvious clinical and laboratory relapse. Although capsule endoscopy cannot replace traditional endoscopy, it offers valuable information on the evaluation of intestinal disease and has a significant impact on disease reclassification of patients with a previous diagnosis of ulcerative colitis or inflammatory bowel disease unclassified/indeterminate colitis. Moreover, it may serve as an effective alternative where colonoscopy is contraindicated and in cases with incomplete colonoscopy studies. The use of patency capsule maximizes safety and is advocated in cases of suspected small or large bowel stenosis.

Key words: Small bowel capsule endoscopy; Colon capsule endoscopy; Crohn's disease; Ulcerative colitis; Indeterminate colitis; Postoperative; Ileal pouch-anal anastomosis; Refractory pouchitis

Core tip: Wireless capsule endoscopy is a valuable diagnostic tool for the evaluation of lesions located on the small intestine and large bowel mucosa since the recent introduction of colon capsule endoscopy. It plays an important role in the early recognition of recurrence on postsurgical Crohn's disease patients, offers valuable

information on the evaluation of intestinal disease, and aids significantly in patient management, treatment tailoring and disease reclassification in patients with a previous diagnosis of ulcerative or indeterminate colitis. Patency capsule maximizes safety and is advocated in suspected small or large bowel stenosis.

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INTRODUCTION

The follow-up of patients with known inflammatory bowel disease consists in close disease monitoring for the maintenance of clinical remission, early detection of biochemical or clinical relapse and early recognition, as well as prevention, of disease and treatment related complications. Since various studies[1-4] have provided strong evidence that the inflammation of the intestinal mucosa is not firmly associated with patients' symptoms and laboratory markers of inflammation, the treatment goal has evolved to a new concept, the achievement and maintenance of deep remission. Its definition includes the concurrent abatement of symptoms, a score < 150 as measured with Crohn's Disease Activity Index (CDAI), mucosal healing, a term referring to the endoscopic restoration of normal mucosal appearance of a previously inflamed region and the complete absence of ulceration as well as macroscopic and histological signs of inflammation[5], and diminution of inflammatory markers. In the absence of a consensus on mucosal healing definition in ulcerative colitis patients, this could involve the disease's clinical and endoscopic remission[6-8]. In Crohn's disease patients, deep remission is associated with a better health-related quality of life and minimization of disease related complications requiring hospitalization or surgery[6].

Despite its invasive character, colonoscopy is considered the gold standard method for the evaluation of intestinal mucosa lesions as it provides accurate assessment of disease extension and localization, offering the ability of tissue sampling of abnormal mucosal segments. By contrast to colonoscopy, the introduction of wireless capsule endoscopy in 2000[9], a non-invasive well-tolerated diagnostic method, allowed the visualization of parts of the small intestine beyond the reach of conventional endoscopes and also the large bowel mucosa, since the recent introduction of wireless colon capsule endoscopy. Current research does not support the use of colon capsule endoscopy over colonoscopy for the evaluation of mucosal healing and disease activity[10] although results of a recent study[11] demonstrate that colon capsule endoscopy findings can result in changes of the initial diagnosis, in favor of Crohn's disease. The aim of this review is to evaluate the importance of wireless capsule endoscopy in mucosal healing assessment, treatment management and disease reclassification of inflammatory disease patients, their follow-up in the post-operative period, as well as to highlight its possible future roles.

CAPSULE ENDOSCOPY: BENEFITS, DRAWBACKS, LIMITATIONS AND SAFETY

Capsule endoscopy is a non-invasive, well-tolerated method, allowing direct visualization of the small bowel mucosa and having a significant higher diagnostic yield compared to other diagnostic methods[12].

Its main disadvantages (Table 1) are the procedure's higher cost compared to other modalities, the inability of tissue sampling, the significant incompletion rate which in several trials[13-15] is reported to range from 15% to 30%, the risk of aspiration and the risk of capsule retention, which in Crohn's disease patients is estimated to be 2.6%[15] and may require surgery for the removal of the retained capsule.

The use of capsule endoscopy is contraindicated in patients with known stricturing or obstructing disease and in selected cases, radiology may still be necessary to exclude the presence of strictures. It is considered to be a safe technique[16] and the administration of a dissolvable patency capsule to patients with suspected strictures prior to the procedure, provides adequate assessment of the gastrointestinal patency and maximizes safety[17,18]. In cases of known gastroparesis or in patients unable of swallowing, the videocapsule can be administered endoscopically. The relative contraindication of wireless capsule administration in patients with electromedical devises is in question, as according to recent research[19] it is considered safe.

CAPSULE ENDOSCOPY SCORING INDEXES FOR THE ASSESMENT OF MUCOSAL INFLAMMATION

In an effort to maximize objectivity on the interpretation of small bowel capsule endoscopy findings and the need of a common language to report severity of small bowel inflammation, two diagnostic scoring systems have been developed, Lewis score (LS) and Capsule Endoscopy Crohn's Disease activity Index (CECDAI).

Developed by Gralnek *et al*[20] in 2008, LS[20], an incorporated feature of Given's Rapid Reader software, offers a quantitative assessment of inflammation severity using the Capsule Endoscopy Structured Terminology[21] for the description of lesions and a grading system for the assessment of inflammation severity. Capsule transit time is used to divide the small bowel in three tertiles and based on the severity of 3 endoscopic variables - villous edema, ulcers and stenosis - each tertile score is calculated individually. The final score ranges from 8 to 4800 points and is the sum of the tertile with the

Table 1 Advantages and disadvantages of wireless capsule endoscopy

Advantages
Non-invasive well-tolerated method
Allows direct visualization of distal and proximal parts of the small bowel (SBCE) and large bowel mucosa(CCE)
Disadvantages
High cost compared to other modalities
Inability of tissue sampling
Significant incompletion rate (15%-30%)
Risk of capsule retention (2.6%)
Risk of aspiration

SBCE: Small bowel capsule endoscopy; CCE: Colon capsule endoscopy.

greatest score added to the stenosis score. A score below 135 points represents a normal appearing mucosa or clinically insignificant findings.

CECDAI, a quantitative method developed by Gal *et al*[22] in 2008, employs the variables of inflammation, extent of disease and the presence of strictures as well as a grading system for the assessment severity. Small bowel is divided in proximal and distal segments after the midpoint determination with the use of small bowel transit time. Segmental scores are gauged separately by multiplying the inflammation score by the extent-of disease score and adding the stricture score. The sum of segmental scores represents the final CECDAI score. Both scores should be interpreted with regard to the patient's history, as they cannot identify the underlying reason of mucosal inflammation. The use of LS and Capsule Endoscopy Crohn's Disease Activity Index is advocated, as they provide an objective non-invasive method for the evaluation of small bowel inflammation and follow up of Crohn's disease[22-24] and correlate closely with highly sensitive markers of intestinal inflammation such as fecal calprotectin[25], a protein released from neutrophils and inflamed mucosa. Fecal calprotectin is not able to determinate the cause of intestinal inflammation, however fecal calprotectin levels are demonstrated to correlate closely with intestinal inflammation[26-29] and are proved to be a valuable selection tool prior to capsule endoscopy studies as despite the presence of symptoms, patients with fecal calprotectin levels between 50 and 100 μg/g, are shown to have negative for findings studies[30].

THE ROLE OF WIRELESS CAPSULE ENDOSCOPY IN THE ASSESSMENT OF MUCOSAL HEALING AND TREATMENT TAILORING

Clinical remission is not strongly associated with the diminution of inflammatory markers[4] although C-reactive protein (CRP) is demonstrated to be a useful marker in the evaluation of moderate to severe Crohn's disease[31]. Moreover, clinical and laboratory improvement of patients under treatment is not associated with mucosal healing[31]. Patients continue to have small bowel aphthous ulcerations in video capsule endoscopy studies (Table 2) one month after clinical remission and it is estimated that approximately 6 mo are necessary for the complete endoscopic restoration of small bowel mucosa[4,32]. In a multicenter prospective study[3] including 40 patients with known or suspected non-stricturing, non-penetrating Crohn's disease, only one third of the patients who achieved clinical response improved their endoscopic image in capsule endoscopy studies. A cohort of 43 patients with symptomatic small bowel Crohn's disease, under biologic or immunomodulatory treatment, evaluated mucosal healing and deep remission rate on baseline and after 12 and 52 wk on treatment[1,33]. Their baseline demographics, quality-of-life questionnaires, Harvey-Bradshaw index, CRP and fecal calprotectin levels were collected and Capsule Endoscopy Crohn's Disease Activity Index was used to assess ileitis severity. Active small bowel Crohn's disease was present in 39 patients (90%) on baseline and 28 patients (65%) had an endoscopic re-assessment during week 52. Despite the clinical and biochemical improvement, no patient achieved complete mucosal healing on week 12[1]. Twelve patients achieved deep remission on week 52 (42%)[33]. The correlation between capsule endoscopy findings, clinical symptoms (Crohn's Disease Activity Index and Inflammatory Bowel Disease Questionnaire) and laboratory markers of inflammation (CRP) was evaluated in 19 patients with known, moderately active Crohn's disease under treatment[2]. All patients had a proven functional patency to minimize the risk of capsule retention, and small bowel capsule endoscopy studies at baseline, after 4, 12 and 24 wk on treatment. Mucosal inflammation was evaluated with the use of LS. At baseline, no correlation was found between clinical symptoms, markers of inflammation and LS, and capsule endoscopy findings were not associated with patients' symptoms on 4 and 12 wk of treatment, leading to the conclusion that capsule endoscopy is a reliable, independent and objective diagnostic modality for the assessment of mucosal healing and response to therapy, and on the prognosis of prolonged clinical disease remission[32]. In addition, data obtained of two recent retrospective studies[34,35] indicate that capsule endoscopy findings assist on decision making, treatment changes or initiation of new pharmaceutical agents, in a significant proportion of inflammatory bowel disease patients.

THE ROLE OF WIRELESS CAPSULE ENDOSCOPY IN THE POSTOPERATIVE PERIOD OF INFLAMMATORY BOWEL DISEASE PATIENTS

Recurrence

The introduction of biologic therapy for the treatment of inflammatory bowel disease did not eliminate

Table 2 Key studies describing the role of wireless capsule endoscopy on the assessment of mucosal healing in Crohn's disease patients under treatment

	Ref.	Treatment	Indication	Patients (*n*)	Conclusion
CD	Niv *et al*[2]	Yes	SB mucosa evaluation of known CD patients	19	Musocal findings are independent from clinical and laboratory parameters
CD	Hall *et al*[1]	Yes	SB mucosal healing and deep remission rates assessment on 12 wk of treatment of known symptomatic CD patients	43	Symptomatic and biochemical response to treatment is not mirrored by mucosal healing
CD	Hall *et al*[33]	Yes	SB mucosal healing and deep remission rates assessment on 52 wk of treatment of known symptomatic CD patients	43	Symptomatic and biochemical response to treatment appears to be mirrored by endoscopic remission in 42% of individuals
CD	Efthymiou *et al*[3]	Yes	SB mucosal healing assessment of known symptomatic CD patients	40	Clinical response does not correlate closely with mucosal healing in patients with CD of the small bowel
CD	Tsibouris *et al*[32]	Yes	Assessment of detection rate of small bowel ulcerative lesions and completion rate in CD patients in acute phase and remission	102	SB aphthous ulcers are present a month after entering clinical remission

CD: Crohn's disease; SB: Small bowel; CRP: C-reactive protein.

the need for surgical intervention[36-40]. Eventually, 20%-30% of ulcerative colitis patients[41,42] and up to 75% of Crohn's disease patients[43], will require surgery for the management of uncontrolled inflammatory bowel disease and disease related complications. A common and undesirable postsurgical outcome is the development of disease recurrence. In Crohn's disease patients, recurrence rate increases with time[44] and is demonstrated to be higher in smokers[45], patients with ileocolonic involvement[46], perforating disease[47] and 5-ASA-treated patients with end-to-end anastomosis[44]. The introduction of Rutgeerts endoscopic scoring system[48] has provided a valuable modality for the quantified assessment of postoperative recurrence of the ileocolonic anastomosis or neoterminal ileum, and a valuable prognostic tool of Crohn's disease recurrence[48-50], since endoscopic recurrence precedes the development of symptoms[48] and does not correlate with CDAI[51]. The follow-up of postoperative patients is directed towards recognition of endoscopic recurrence (Table 3), as severe endoscopic recurrence rate is estimated at 50.2% (95%CI: 28-73; range: 30-79) and early identification and initiation of treatment may prevent clinical recurrence[52,53].

In a prospective study of 22 Crohn's disease patients, capsule endoscopy was reported to have comparable results with other noninvasive tests on the detection of recurrence[54]. Moreover, based on the results of a prospective study[55] including 35 patients who had undergone ileocolonic or partial ileal resection, wireless capsule endoscopy was not shown to be superior to ileocolonoscopy for the detection of recurrence on the neoterminal ileus although it enabled the visualization of lesions beyond colonoscope's reach in two out of three patients and aided significantly in the detection of recurrence in two patients missed by ileocolonoscopy. However, capsule endoscopy was the diagnostic modality preferred by patients in a small prospective study[56] including 24, symptom-free Crohn's disease patients under no prophylactic treatment, who had undergone ileocolonic anastomosis. In the same study, the authors concluded that capsule endoscopy was more effective in the detection of a significant number of Crohn's disease recurrence missed by colonoscopy and an effective diagnostic alternative for the visualization of the neoterminal ileum of patients with incomplete colonoscopy studies. Current research supports the use of baseline capsule endoscopy, shortly after the resection, for the detection of true cases of recurrence, as many ulcerations near the anastomotic site are formed due to factors related to surgery, such as disturbed blood flow and sutures[57], but its preoperative use is reported to be of little value for the prognosis of recurrence[58]. The use of wireless capsule endoscopy in suspected or known luminal stenosis is contraindicated[54,57].

Anemia

Based on the results of a small study of 17 ulcerative colitis patients with ileal pouches and persistent iron deficiency anemia[59], the authors concluded that wireless capsule endoscopy is a well-tolerated procedure to provide additional information on the reason of anemia. Patients with persistent anemia, 12 mo after ileal pouch-anal anastomosis (IPAA) or continent ileostomy, were evaluated with upper gastrointestinal endoscopy, pouch endoscopy and videocapsule endoscopy, and they had laboratory screening to exclude celiac disease. The reason of anemia was identified in 5 patients (29.4%). In one patient, arterio-venous malformations of the small bowel were only recognized by capsule endoscopy.

Pouchitis in patients with IPAA

Surgical removal of the colon and rectum with the creation of an artificial pouch, the IPAA, may be the only treatment option for ulcerative colitis patients with medically uncontrolled disease, who are unwilling to receive immunomodulatory or biologic therapy, or suffering from severe disease complications.

Table 3 Key studies on the role of wireless capsule endoscopy on postoperative Crohn's disease recurrence

Patient group	Ref.	No. of patients	WCE findings/(*n*)	Ileocolonoscopy findings/(*n*)
CD	Bourreille *et al*[55]	32	21/(32)	19/(32)
CD	Pons Beltrán *et al*[56]	24	15/(22)	6/(19)
CD	Biancone *et al*[54]	22	16/(17)	21/(22)
CD	Kono *et al*[57]	19	14/(18)	NA

CD: Crohn's disease; WCE: Wireless capsule endoscopy; WCE findings: Number of patients with findings on WCE; WCE (*n*): Total number of patients who had undergone WCE; Ileocolonoscopy findings: Number of patients with findings on ileocolonoscopy; Ileocolonoscopy (*n*): Total number of patients who had undergone ileocolonoscopy; NA: Not available.

Pouchitis is the most common complication, with a cumulative probability of nearly 50% ten years after IPAA performed[60] requiring investigation for the recognition of the underlying cause.

Results based on trials of ulcerative colitis patients with IPAA and symptomatic pouchitis[35,61,62] (Table 4), support the use of capsule endoscopy for the evaluation of small bowel mucosa on the suspicion of Crohn's disease and on differentiating intermediate colitis.

THE ROLE OF WIRELESS CAPSULE ENDOSCOPY ON DISEASE RECLASSIFICATION

Inflammatory bowel disease patients may undergo multiple imaging studies, endoscopic procedures and biopsies before reaching a definitive Crohn's disease or ulcerative colitis diagnosis, while 10%-15% of patients will remain unclassified[63]. Capsule endoscopy has become an important tool for the reclassification of disease (Table 5) in patients with an initial diagnosis of ulcerative colitis or inflammatory bowel disease unclassified/indeterminate colitis. The importance of wireless capsule endoscopy in the diagnostic workup of inflammatory bowel disease was demonstrated in a recent study of 23 known ulcerative colitis patients[64] where small bowel lesions (13 patients, 57%) and erosions (8 patients, 35%) were identified in the majority of them.

Corresponding results from the initial experience with small bowel capsule endoscopy[65] have demonstrated that the identification of small bowel lesions by wireless capsule in patients with isolated colitis, lead to further investigation with ileocolonoscopy with biopsies, and a change of diagnosis in favor of Crohn's disease. In a retrospective trial[62] including 120 patients with known ulcerative colitis or indeterminate colitis undergone capsule endoscopy, 19 patients (15.8%) had findings suggestive of small bowel Crohn's disease involvement. Interestingly, patients with the highest proportion of small bowel disease were those with a history of colectomy (7 out of 21 patients, 33%) compared to the patients who did not undergo colectomy (12 out of 99 patients/12%), indicating the importance of capsule endoscopy studies prior to colectomy in ulcerative colitis patients. Similarly, data obtained from a study of 30 inflammatory bowel disease unclassified patients with negative serology[66] showed that wireless capsule endoscopy findings resulted in disease reclassification in favor of Crohn's disease in five of them. Another significant conclusion of this study was that negative for findings capsule endoscopy studies, do not exclude small bowel Crohn's disease, as further investigation with ileocolonoscopy and biopsies in six patients led to a diagnosis of Crohn's disease in five patients and ulcerative colitis in one patient. In two studies that enrolled pediatric patients[67,68] capsule endoscopy resulted in reclassification of more than half of the ulcerative colitis, inflammatory bowel disease unclassified/indeterminate colitis patients to Crohn's disease.

Table 4 Key studies on the role of wireless capsule endoscopy on pouchitis patients

Patient group	Ref.	No. of patients	WCE findings/(*n*)	CD reclassification
UC (IPAA)	Calabrese *et al*[61]	16	15/(15)	None
UC (IPAA)	Mehdizadeh *et al*[62]	21	7/(21)	7
UC (IPAA)	Long *et al*[35]	23	13/(23)	3

UC: Ulcerative colitis; IPAA: Ileal pouch-anal anastomosis; WCE findings: Number of patients with findings on WCE; WCE (*n*): Total number of patients who had undergone WCE; CD: Crohn's disease; WCE: Wireless capsule endoscopy.

POSSIBLE FUTURE INDICATIONS OF WIRELESS CAPSULE ENDOSCOPY IN THE FOLLOW UP OF INFLAMMATORY BOWEL DISEASE PATIENTS

Research on the prognostic value of mucosal healing on treatment response[69-72], has shown that assessment of mucosal healing on certain time points can predict the likelihood of prolonged deep remission. The data of 127 patients[73] who had participated in the SONIC trial, were used to estimate the prognostic value of ileocolonoscopy findings on treatment response. Patients Simple Endoscopic Score for Crohn's Disease and the Crohn's Disease Endoscopic Index of Severity were calculated on baseline, after week 26 and week 50. Namely, the endoscopic response and mucosal healing in week 26 identified the patients who would be on corticosteroid-free clinical remission on week 50. The study's results provided confirmatory evidence that assessment of mucosal healing in certain time points during therapy has a significant prognostic value on the response of treatment.

Growing evidence[74-76] in the corresponding literature, indicate the strong association between disease location and disease complications. Patients with ileal

Table 5 Key studies evaluating the role of wireless capsule endoscopy on disease reclassification

Patient group	Ref.	No. of patients	SB findings of inflammation	Reclassified to CD
UC/IC	Gralnek *et al*[68]	4	2	2
UC	Higurashi *et al*[64]	23	13	None
UC/IC	Cohen *et al*[67]	7	5	5
UC/IBDU	Mehdizadeh *et al*[62]	120	19	NA
IBDU	Maunoury *et al*[66]	30	5	5
UC/IC	Mow *et al*[65]	21	12	5

UC: Ulcerative colitis; IC: Indeterminate colitis; IBDU: Inflammatory bowel disease unclassified; SB: Small bowel; CD: Crohn's disease; NA: Not available.

Crohn's disease were shown to have a greater risk of stricturing and penetrating disease development as well as disease progression compared to those with colonic involvement.

There is no supporting evidence for the use of wireless capsule endoscopy on treatment response, on risk stratification and as a prognostic tool for prolonged remission, but given videocapsule endoscopy's non invasive nature and the advantage of detailed imaging of the entire small intestine, it could be a promising tool towards this direction.

Wireless capsule endoscopy could play an important role in the early detection of ulcerative colitis related panenteritis[77], a new and rare entity related to colectomy which typically occurs after colectomy, and its histological picture is not compatible with Crohn's disease. In a small case series of 6 patients[78], the use of ileocolonoscopy identified ulcerative colitis related panenteritis findings in 5 patients, resulting in treatment step-up and clinical improvement. One patient had to be evaluated with capsule endoscopy to confirm small bowel mucosa inflammation leading to the conclusion that video capsule endoscopy could offer an alternative method for the early detection of this rare complication.

CONCLUSION

Wireless capsule endoscopy is a valuable, non-invasive tool for the follow-up of inflammatory bowel disease, offering direct and detailed visualization of the entire intestine. Even though it cannot replace the role of traditional endoscopy, its use is advocated when there is high suspicion of small bowel disease involvement and as an alternative method in incomplete colonoscopy studies or when colonoscopy is contraindicated. Wireless capsule endoscopy's important disadvantages comprise the inability of tissue sampling and the limited, or in selected cases, prohibited application on patients with known stenosis or obstruction of the intestinal lumen, due to the high risk of capsule retention. Unnecessary capsule endoscopy studies can be avoided with the use of fecal calprotectin levels to identify patients who will probably not benefit from the procedure, and the use of patency capsule to identify patients that are likely to experience capsule retention. Lewis Score and Capsule Endoscopy Crohn's Disease Activity Index are validated, objective and reliable scoring systems developed to minimize interobserver agreement and provide a standardized reporting system of small-bowel inflammation. Assessment of mucosal inflammation has a positive impact on treatment tailoring and is proven to be a reliable prognostic tool for disease remission. Videocapsule endoscopy studies in the postoperative period of ulcerative colitis and inflammatory bowel disease unclassified/indeterminate colitis patients provide valuable information on the differential diagnosis of Crohn's disease as well as postoperative complications, and can aid significantly in the early recognition of recurrence for the timely initiation of immunomodulatory or biologic treatment, before obvious clinical and laboratory relapse. Wireless Capsule endoscopy may have potentially significant roles in the prognosis of treatment response as well as the occurrence of potential complications and the early diagnosis of ulcerative colitis related panenteritis, a recently described rare entity, affecting patients with ulcerative colitis after colectomy.

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ORIGINAL ARTICLE

Retrospective Study

Role of double-balloon enteroscopy in malignant small bowel tumors

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Author contributions: Pérez-Cuadrado Robles E, Esteban Delgado P and Bebia Conesa P contributed equally to this work; Martínez Andrés B, Franulic Guggiana M, Alcaraz Mateos E and Fernández Caballero M designed and performed the research; Rodrigo Agudo JL and Chacón Martínez S analyzed the data; Latorre R, Soria F, Herrerías Gutiérrez JM and Pérez-Cuadrado Martínez E wrote the paper.

Ethics approval: This study was a retrospective and descriptive study without prospective interventions or control group. Thus, we have not considered necessary to submit the manuscript to the Institutional Review Board.
Informed consent: All patients provided written consent to undergo DBE under general anesthesia or deep sedation. However, in this retrospective study of 627 patients with a long span of time (2004-2014) the informed consent to be enrolled in the study was waived. All data are anonymized and there were no prospective interventions.
Conflict-of-interest: None to declare.
Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at kikemurcia@gmail.com. Consent was not obtained but the presented data are anonymized and risk of identification is low.

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Abstract

AIM: To assess the double-balloon enteroscopy (DBE) role in malignant small bowel tumors (MSBT).

METHODS: This is a retrospective descriptive study performed in a single center. All consecutive patients who underwent a DBE with final diagnosis of a malignant neoplasm from 2004 to 2014 in our referral center were included. Patient demographic and clinical pathological characteristics were recorded and reviewed. MSBT diagnosis was achieved either by DBE directed

biopsy with multiple tissue sampling, endoscopic findings or histological analysis of surgical specimen. We have analyzed double-balloon enteroscopy impact in outcome and clinical course of these patients.

RESULTS: Of 627 patients, 28 (4.5%) (mean age = 60 ± 17.3 years) underwent 30 procedures (25 anterograde, 5 retrograde) and were diagnosed of a malignant tumor. Patients presented with obscure gastrointestinal bleeding (*n* = 19, 67.9%), occlusion syndrome (*n* = 7, 25%) and diarrhea (*n* = 1, 3.6%). They were diagnosed by DBE biopsy (*n* = 18, 64.3%), histological analysis of surgical specimen (*n* = 7, 25%) and unequivocal endoscopic findings (*n* = 2, 7.1%). Gastrointestinal stromal tumor (*n* = 8, 28.6%), adenocarcinoma (*n* = 7, 25%), lymphoma (*n* = 4, 14.3%), neuroendocrine tumor (*n* = 4, 14.3%), metastatic (*n* = 3, 10.7%) and Kaposi sarcoma (*n* = 1, 3.6%) were identified. DBE modified outcome in 7 cases (25%), delaying or avoiding emergency surgery (*n* = 3), modifying surgery approach (*n* = 2) and indicating emergency SB partial resection instead of elective approach (*n* = 2).

CONCLUSION: DBE may be critical in the management of MSBT providing additional information that may be decisive in the clinical course of these patients.

Key words: Double balloon enteroscopy; Malignant small bowel tumors; Obscure gastrointestinal bleeding; Gastrointestinal stromal tumor; Occlusion syndrome

Core tip: Malignant small bowel tumors (MSBT) are a heterogeneous and relatively rare group of neoplasms. Double balloon enteroscopy (DBE) may have a critical role in the management of MSBT because of its diagnosis and therapeutic capabilities. DBE procedure may delay or avoid emergency surgery, clarifying the tumor location and characteristics. We have assessed DBE impact in these lesions in a large series of patients of a single referral center.

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INTRODUCTION

Small bowel tumors (SBT) are relatively rare, accounting for 3% to 6% of all gastrointestinal neoplasms[1]. Malignant SBTs (MSBT) are described in the 3.6%-14.5% of patients of double balloon enteroscopy (DBE) series[2-4]. The difference in incidence in these studies is because many authors considered benign and malignant tumors and included duodenal neoplasms. MSBT are a heterogeneous group with different predominant histological types within different studies[5-10]. We will focus on malignant primitive SB tumors such as adenocarcinoma, stromal, neuroendocrine, lymphoproliferative and metastatic tumors. Moreover, these lesions may have a poor prognosis in its natural course so that early diagnosis and treatment may be critical[11,12]. These tumors are often diagnosed late because of their nonspecific clinical presentation[13-16], when they have few therapeutic possibilities[17,18].

Obscure gastrointestinal bleeding (OGIB) is the most common clinical presentation in some studies[4,19,20], while a suspected mass is reported to be the first DBE indication by other authors[2,21]. Therefore, MSBT represent a real diagnostic challenge for the physician. DBE is a well-established procedure in diagnosis and treatment of SB disorders. However, there are few data to date reporting DBE role in MSBT[20,22-24]. Our study was conducted to assess the impact of DBE in these neoplasms.

MATERIALS AND METHODS

This is a retrospective descriptive study. All consecutive patients with MSBT who underwent a DBE procedure in our institution were investigated. Patient demographic and clinical pathological characteristics were recorded. MSBT diagnosis was achieved either by DBE directed biopsy with multiple tissue sampling, endoscopic findings or histological analysis of surgical specimen.

DBE procedure

DBE procedure (Fuji Film, Saitama, Japan) was performed by expert endoscopists as described by Yamamoto *et al*[25]. Fujinon EN-450 P5, EN-450 T5 and EN-580T enteroscopes were used. There was no special preparation for the anterograde approach besides an 8-12 h fast. For the retrograde approach, bowel preparation was performed as in colonoscopy. All patients provided written consent to undergo DBE under general anesthesia or deep sedation. Capsule endoscopy (CE) and radiological studies such as CT scan were also considered, when available.

Endoscopists were aware of prior findings reported by CE or other techniques. DBE approach was selected based on the information prior to DBE procedure including previous CE, clinical and/or radiological findings. When the location was uncertain, the oral approach was preferred.

DBE data including indication, approach, endoscopic findings, tumor location, time of the procedure, biopsy histological diagnosis, therapeutics and complications were collected. Tattoo injection was performed to mark the maximum length of bowel inspected or the location

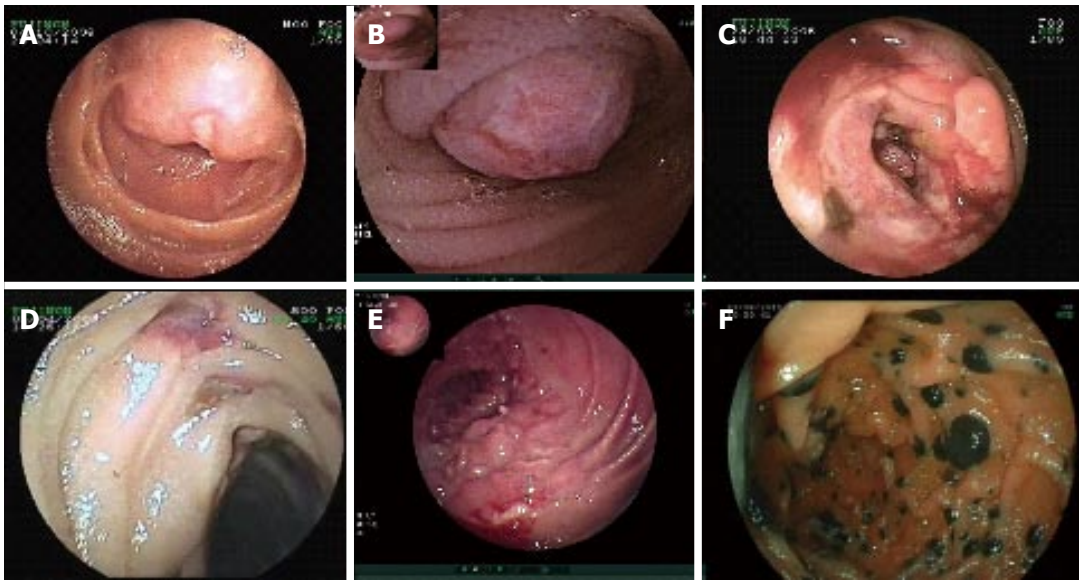

Figure 1 Endoscopic images of different types of malignant small bowel tumors. A: Ulcerated jejunal gastrointestinal stromal tumor; B and C: Stenosing adenocarcinomas; D: Kaposi sarcoma; E: Mucosa-associated lymphoid tissue lymphoma; F: Melanoma.

of the lesion and to guide the elective or emergency surgery.

Finally, we analyzed how DBE procedure influenced MSBT management and outcome. In this sense, avoiding or modifying the elective or emergency surgery approach was considered as the main evaluation criterion.

Descriptive statistics were used to describe clinical pathological features, endoscopic and radiological findings. Categorical variables were calculated as percentages and continuous variables were expressed as mean values (SD).

RESULTS

Of 627 consecutive patients who underwent 880 DBEs from January 2004 to September 2014 at our referral center, 89 (14.2%) were confirmed to have a SBT. Twenty-eight patients (4.5%) (mean age ± SD: 60 ± 17.3 years) underwent 30 DBEs (25 anterograde, 5 retrograde) (median time: 65 min, range 20-160) and were diagnosed of a MSBT. We only include the malignant tumors localized distal to Treitz. There was a male preponderance in gender (*n* = 20, 71.4%).

Patient's characteristics are shown in Table 1. The most common clinical indication was OGIB (67.9%). Patients presented with overt-OGIB (*n* = 9, 32.1%), occult-OGIB (*n* = 10, 35.7%), occlusion syndrome (*n* = 8, 28.6%) and diarrhea (*n* = 1, 3.6%). In addition, 10 patients (35.7%) had weight loss and 6 patients (21.4%) transfusion requirements.

DBE was indicated following CE in 17 cases (60.7%) and this procedure confirmed the MSBT in 14 cases (82.4%). The capsule was retained in 4 cases due to SB stenosis identifying the tumor in two of them and retrieved by DBE in all patients. CT scan (*n* = 8, 28.6%) and other radiological studies (*n* = 2, 7.1%) were previously performed and a suspected mass was identified in 6 cases (21.4%). CT scan also detected a SB complete stenosis in four cases and DBE clarified that only in three of them there was a complete stenosis without overpassing it with the endoscope. Among patients with obstructive symptoms, radiological imaging was the first SB study in 6 (75%) cases and direct DBE was performed in 2 (25%) patients.

DBE directed-biopsy was attempted in 25 patients (89.3%) and benign/reactive mucosa was found in 5 of them (1 midgut neuroendocrine tumor, 1 adenocarcinoma and 3 GIST) so that 20 patients (71.4%) were finally confirmed to have a MSBT by DBE biopsy (Table 2). Two patients (7.1%) had moderate bleeding after DBE biopsy that stopped after endoscopic treatment. Directed-biopsy by DBE was not attempted in 3 patients (10.7%) with GIST (*n* = 1), neuroendocrine tumor (*n* = 1) and metastatic disease (*n* = 1) because of active bleeding that required emergency surgery within GIST and neuroendocrine tumors and because it was considered unnecessary for diagnosis in the other case. In addition, histological analysis of surgical specimen and endoscopic findings lead to diagnosis in 7 (25%) and 1 (3.6%) patients, respectively.

Seven different histological types of MSBT were found. Most of them were located in jejunum (*n* = 20, 71.4%) followed by ileum (*n* = 8, 28.6%). We have only included malignant tumors located between distal to Treitz and terminal ileum. Endoscopic findings of different MSBT are shown in Figure 1.

The most common malignant tumor was GIST (*n* = 8, 28.6%) followed by adenocarcinoma (*n* = 7, 25%). GIST was also the most common MSBT within OGIB patients (36.8%). In two GIST an enteric fistula was identified by DBE with passage of contrast into the peritoneum so that emergency surgery was indicated after tattoo injection. One of them deceased

Table 1 Patient characteristics by histological type of malignant small bowel tumor

	GIST	Adenocarcinoma	Lymphoma	Neuroendocrine tumor
No. patients (% of MSBT)	8 (28.6%)	7 (25%)	4 (14.3%)	4 (14.3%)
Sex (M/F)	7/1	3/4	2/2	4/0
Mean age (SD) (yr)	64 ± 15	59 ± 16	48 ± 22	55 ± 24
Clinical presentation				
Overt-obscure OGIB	4	1	1	1
Occult-obscure OGIB	3	3	2	2
Diarrhea	0	0	0	1
Occlusion syndrome	1	3	1	0
Duodenum/jejunum/ileum	0/7/1	0/6/1	0/3/1	0/0/4

MSBT: Malignant small bowel tumor; GIST: Gastrointestinal stromal tumor; OGIB: Obscure gastrointestinal bleeding.

in the intensive care unit. Another patient with severe anemia and transfusion requirements underwent a DBE that confirmed an ulcerated jejunal GIST with active bleeding. Argon plasma coagulation was successfully performed so that emergency surgery was delayed. The positive detection rate by directed-biopsy within GIST was 57.1%.

Adenocarcinoma was mainly located in jejunum (*n* = 5, 71.4%). One patient underwent DBE because of one CT suspected jejunal mass and chronic anemia. Finally two synchronic jejunal adenocarcinomas were found modifying the surgery approach. Three patients with adenocarcinoma (42.9%) had impassable SB stenosis despite multiples endoscopic maneuvers and an enteral stent was successfully placed in one case[26]. There were 2 patients with liver metastasis at diagnosis and 3 patients did not underwent surgery because of comorbidities. Finally, 4 patients (57.1%) with adenocarcinoma underwent elective surgery.

Among lymphoma tumors (*n* = 4, 14.3%), there were 2 MALT, 1 non-Hodking diffuse large B lymphoma and 1 Burkitt lymphoma. One patient with a jejunal MALT lymphoma had refractory celiac disease. Three patients were treated by chemotherapy and the remaining patient refused treatment.Half of patients (*n* = 2) with neuroendocrine tumors had multiple small tumors besides the main ileal lesion undiagnosed by previous enhanced CT scan.

A jejunal Kaposi sarcoma actively bleeding was identified in a patient with acute overt-OGIB and endoscopic hemostasis was successfully performed. All patients with SB metastasis had the primary lesion already diagnosed (colonic adenocarcinoma, choriocarcinoma, lung adenocarcinoma and melanoma). DBE modified surgical approach in one patient with

Table 2 Final diagnosis and histological analysis by double balloon enteroscopy directed-biopsy

	DBE biopsy	Final diagnosis (% of MSBTs)
MSBT	20/25 (80%)	28
GIST	4/7 (57.1%)	8 (28.6%)
Adenocarcinoma	6/7 (85.7%)	7 (25%)
Lymphoma	4/4 (100%)	4 (14.3%)
Neuroendocrine tumor	2/3 (66.7%)	4 (14.3%)
Metastatic	3/3 (100%)	4 (14.3%)
Kaposi Sarcoma	1/1 (100%)	1 (3.6%)

DBE: Double balloon enteroscopy; MSBT: Malignant small bowel tumor; GIST: Gastrointestinal stromal tumor.

clinical occlusion syndrome suspected because of metastasis in whom a total DBE confirmed that the obstruction was due to adherences.

Tattoo injection was performed in 21 cases (75%) and guided elective (*n* = 8, 28.6%) or emergency surgery (*n* = 5, 17.9%). There was no complication related to therapeutics.

In summary, DBE modified the clinical course and outcome in 7 patients (25%), delaying or avoiding emergency surgery (*n* = 3), modifying surgery approach (*n* = 2) and indicating emergency SB partial resection instead of elective approach (*n* = 2). It's interesting to note that within these 7 patients, in only 3 cases (42.9%) surgery was delayed or avoided due to endoscopic therapy. Two patients with actively bleeding GIST and Kaposi sarcoma in whom argon plasma coagulation was successfully performed and one patient with a stenosing adenocarcinoma who underwent a DBE with an enteral prosthesis placed.

DISCUSSION

Regarding the diagnostic performance of deep enteroscopy in SB tumors, Chen *et al*[3] in an Asiatic retrospective study reported 440 DBEs in 400 patients, diagnosing 67 SB tumors by DBE, with 16.8% overall diagnostic yield. Eleven patients with negative DBE were diagnosed of a SBT by CE or surgery. The positive detection rate among the 78 patients with SBT was higher with DBE than with CT scan (85.9% *vs* 72.9%, respectively). Adenocarcinoma (29.5%), GIST (24.4%) and lymphoma (15.4%) were the most common tumors reported by this author. They were mostly located at the jejunum (60.3%), and the MSBT detection rate was 14.5%. Cangemi *et al*[2], in an American research study, with 1652 DBE performed in 1106 patients reported a SBT detection rate of 12.1%. However, the MSBT rate was about 5%. The most common lesions were neuroendocrine tumor (19.4%), GIST (7.5%) and lymphoma (7.5%).

A study from United States[27] analyzes the impact on incidence and survival rates for SBT after the emergence of CE and deep enteroscopy. In order to assess the potential impact of this technology, they compared

the incidence rates from 1992-2000 and 2001-2009 to determine if there were different diagnostic yields between both periods. SBT remain uncommon in United States, and its incidence significantly increased from 2.5 during the 1992-2000 time frame to 3.1 per 100000/year in the later period of time ($P < 0.004$). The survival was significantly better in the 2001-2009 cohort (52.6% *vs* 63.1% 5-year survival, $P < 0.001$). Stage-specific analysis showed a significant rise in more distant disease only in African-Americans after 2000, which may reflect factors in tumor biology, treatment, and/or access to care of these patients.

In the present study, we reported on 28 patients (4.5%) with MSBTs, all distal to Treitz. When DBE was carried out, there was a suspicion of SBT in all cases. The histological type distribution is quite different between different countries. Adenocarcinoma[3,20,28], neuroendocrine SBT[1,4] and lymphoma[21] have been reported to be the most frequent histological type by different authors. These differences are probably due to the different geographical distributions and clinical presentations of different studies of patient's populations. In our study, GIST was the most common MSBT followed by adenocarcinoma.

DBE allowed histopathological diagnosis in most patients (71.4%), except in GI stromal tumors. The histological detection rate in GIST was low (57.4%) but higher than reported by other authors[22,29]. In addition, there were some extremely rare tumors detected, such as jejunal Kaposi sarcoma.

MSBTs were more common among men (71.4%). These tumors may be presented with complete SB stenosis and/or acute overt OGIB, requiring early management by emergency DBE[30-32] or surgery[33]. This procedure may define the characteristics of SB stenosis or bleeding in order to make a surgery decision and/or perform endoscopic treatment[34,35].

There has been recently reported[5] that in patients presented with OGIB, DBE following a positive CE may be the first option, but direct surgery may also be indicated. Interventional digital subtraction angiography has also been reported to be effective in GIST with bleeding[36].

Among patients with a high clinical suspicion of a SBT in the setting of a negative CE result, radiological imaging or deep enteroscopy are equally indicated. CT scan or MR is the preferred initial test in patients with obstructive symptoms. We have performed a DBE following a positive CE in all cases to have a histological and endoscopic diagnosis.

We are also convinced that the entire exploration of the SB in selected cases such as patients with neuroendocrine tumors may be crucial, because this may impact further management. In our series, we have reported multiple adenocarcinomas or neuroendocrine tumors in the same patient. In addition, the histological analysis may have different diagnostic yields within different lesions of the same MSBT. In other cases, to achieve the primary MSBT location for histological and endoscopic diagnosis may be enough.

Thus, DBE has proven to be accurate in management of MSBT. In our study, DBE modified the outcome of 7 patients (25%), not only because of diagnosis capabilities but also of therapeutics interventions.

However, there were some limitations of our study as the retrospective design and potential referral bias.

In conclusion, DBE is critical in the management of MSBT and may have an impact delaying or avoiding emergency surgery. This procedure clarifies the tumor location and characteristics allowing tattoo injection to guide a possible surgery and provides additional information to other procedures that may be decisive in the clinical course of these patients.

COMMENTS

Background

Malignant small bowel tumors (MSBT) are a heterogeneous group of rare tumors. However, the incidence of these neoplasms is increasing correlated to the expansion of deep enteroscopy and video capsule endoscopy.

Research frontiers

There're different histological subtypes of MSBT with different prognosis and management. The real incidence of each histological type and clinical characteristics are not well-established. Studies to date have reported different distributions of these neoplasms depending on the *geographical area*. Recently, double-balloon enteroscopy (DBE) following capsule endoscopy was confirmed as a valid strategy in patients with a suspected MSBT presenting with obscure gastrointestinal bleeding (OGIB).

Innovations and breakthroughs

Most of studies to date report series from Asia or United States. There're few large European reports of MSBT. In addition, there's no consensus regarding the most common histological type or clinical presentation by different authors. The present study represents a large series of a referral center in DBE. The authors have considered only patients with jejunal of ileal tumors in order to clarify the DBE role in these cases. OGIB was the most common clinical presentation and gastrointestinal stromal tumors the most common type.

Applications

This study clarifies the DBE role in MSBT. The present data might suggest that DBE might impact in about 25% of patients with MSBT by modifying surgery approach.

Terminology

DBE is an endoscopic technique originally described by Yamamoto that allows the entire examination of the small bowel, with two balloons fitted onto the tips of the scope and over tube.

Peer-review

This study clarifies the role of DBE in the management of MSBT on proper scientific level.

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ORIGINAL ARTICLE

Retrospective study

Evaluation of the margins of differentiated early gastric cancer by using conventional endoscopy

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Author contributions: Yoshinaga S performed endoscopic examinations and therapies, and also wrote this manuscript mainly; Oda I, Abe S, Nonaka S, Suzuki H, Takisawa H and Saito Y performed endoscopic examinations and therapies; Taniguchi H evaluated resected specimens pathologically and took pictures of resected specimens.

Ethics approval: We explain all patients about comprehensive prior consent arrangements that we use every data and figures except genetic materials for studies. Therefore, Institutional Review Board of our hospital did not review this study.
Informed consent: All study participants, or their legal guardian agreed to this aforementioned comprehensive prior consent.
Conflict-of-interest: The authors have no conflict of interest directly relevant to the contents of this study.
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Abstract

AIM: To evaluate the determination of the margin of differentiated-type early gastric cancers by using conventional endoscopy.

METHODS: We retrospectively evaluated 364 differentiated early gastric cancers that were endoscopically resected as en-bloc specimens and diagnosed pathologically in detail between November 2007 and October 2008. All procedures were done with conventional endoscopes and all endoscopic samples, before and after indigo carmine dye, were re-evaluated using a digital filing system by one endoscopist. We analyzed the incidence of lesions with unclear margins and the relationship between unclear margins and relevant clinicopathological findings.

RESULTS: The rate of lesions with unclear margins was 20.6% (75/364). Multivariate regression analysis suggested that the factors that make the determination of the margin difficult were normal color, presence of components of flat area (0-IIb), a diameter ⩾ 21 mm, ulceration, and components of poorly differentiated adenocarcinoma in the mucosal surface.

CONCLUSION: As many as 20% of differentiated early gastric cancers show unclear margins. Consideration of the factors associated with unclear margins may help endoscopists to accurately determine the margins of the lesion.

Key words: Early gastric cancer; Conventional endoscopy; Determination of the margin

Core tip: As many as 20% of differentiated early gastric cancers show unclear margins by using conventional endoscopy. Consideration of the factors associated with unclear margins, such as normal color, presence of components of flat area (0-IIb), a diameter ⩾ 21 mm, ulceration, and components of poorly differentiated adenocarcinoma in the mucosal surface, may help endoscopists to accurately determine the margins of the lesion.

Yoshinaga S, Oda I, Abe S, Nonaka S, Suzuki H, Takisawa H, Taniguchi H, Saito Y. Evaluation of the margins of differentiated early gastric cancer by using conventional endoscopy. *World J Gastrointest Endosc* 2015; 7(6): 659-664 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i6/659.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i6.659

INTRODUCTION

Since Gotoda *et al*[1] described the incidence of lymph node metastasis from early gastric cancer and with the development of endoscopic submucosal dissection (ESD), early gastric cancer is often resected endoscopically. When endoscopic resection of early gastric cancers is performed, it is important to accurately determine the margin of the lesion. A vague determination of the location of the margin may allow residual cancer to remain, leading to recurrences and additional resections. Recently, imaged enhanced endoscopy (IEE) procedures, such as narrow band imaging (NBI), auto fluorescence imaging (AFI), or flexible spectral imaging color enhancement (FICE) have been developed; however, these methods have not been adopted everywhere. Therefore, an accurate understanding of the use of conventional endoscopes is still relevant.

In this study, we evaluated the determination of the margin of differentiated-type early gastric cancers by using conventional endoscopes and investigated the factors that may make the margin unclear.

MATERIALS AND METHODS

A total of 381 differentiated early gastric cancers were resected endoscopically between November 2007 and October 2008. We excluded 17 early gastric cancers that could not be evaluated in detail because of piecemeal resection, severe burning effects, or other confounding factors. A total of 364 early gastric cancers were included in this study. We reviewed the clinical records, endoscopic images, endoscopy reports, and pathology reports for every patient and analyzed the incidence of lesions with unclear margins and the relationship between unclear margins and the following clinicopathological findings: age, sex, tumor location, tumor color, macroscopic type, component of flat area, tumor size, ulcer finding, component of poorly differentiated adenocarcinoma in the mucosal surface, and intestinal metaplasia around the lesion.

Endoscopic procedure

All patients drank a solution containing 40000 units of pronase (Pronase MS®; Kaken Pharmaceutical Products, Tokyo, Japan), 4 mL of 2% dimethicone (Gascon®; Kissei Pharmaceutical Co., Tokyo, Japan) and 2 g of $NaHCO_3$ to dissolve mucus and bubbles before examination. All procedures were done with conventional endoscopes (GIF-Q240, Q260, H260; Olympus Optical Co., Tokyo, Japan) and without magnifying endoscopy, NBI, or AFI. All endoscopic images were recorded by using a digital filing system (NEXUS; Fuji Film Medical Co., Tokyo, Japan). All endoscopic images before and after indigo carmine dye (0.2%) were reviewed in this study by using a digital filing system by one individual (S.Y) who has 10 years of experience as an endoscopist.

Definitions

Lesions with an unclear margin were defined as lesions with an undelineated margin or an inaccurate marking. An undelineated margin was determined by reviewing the endoscopic images. The identification by the endoscopist of a difference between the lesion and surrounding mucosa in terms of colors, surface morphology, and a height more than two-thirds the size of the circumference was considered a delineated margin (Figure 1). If it was not possible to make a distinction, it was classified as an undelineated margin lesion (Figure 2). We also evaluated the markings made before resection to recognize the tumor margin. We defined an accurate marking if all markings were made outside of the tumor in the resected specimen (Figure 3A). If not, we defined it as an inaccurate marking (Figure 3B). The tumor color and location were also determined endoscopically. The stomach is anatomically divided into three parts: the upper third (U), middle third (M), and lower third (L). The cross-sectional circumference of the stomach is divided into four equal parts; the lesser and greater curvatures, and the anterior and posterior walls based on the Japanese Classification of Gastric Carcinoma[2]. The main macroscopic type of the tumor was classified based on the Paris classification[3], and the components of flat area (0-IIb) of the tumor, tumor size, ulceration findings, components of poorly differentiated adenocarcinoma in the mucosal surface, and metaplasia around the tumor were determined histopathologically.

Statistical analysis

Statistical analysis were made by using the Student's *t* test for evaluating the patients' ages and the tumor sizes, and by using the χ^2 test with Yate's correction and the Fisher exact test for evaluating any other factors.

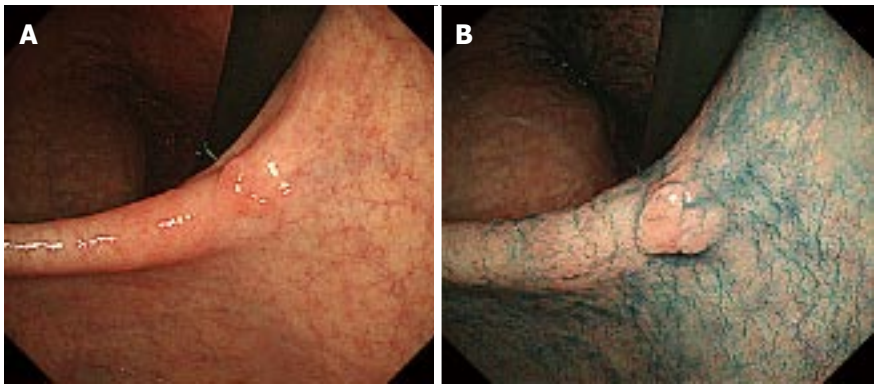

Figure 1 A case of a delineating lesion (0-IIa). Before (A) and after (B) indigo-carmine dye, the margin of the tumor was clear.

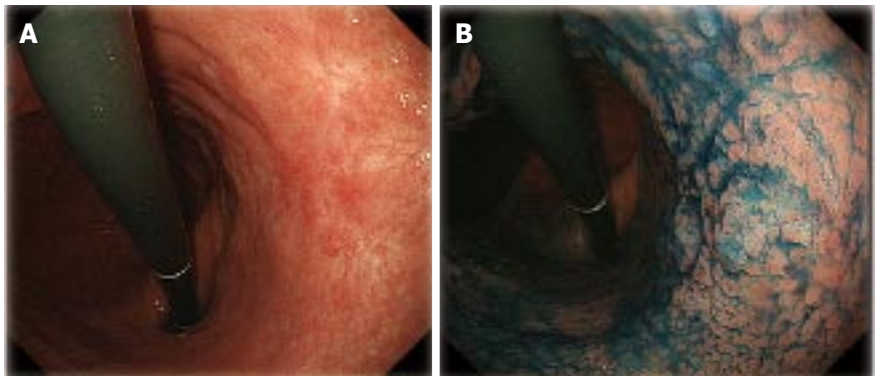

Figure 2 An undelineated margin lesion. A: A case of an undelineating lesion (0-IIc) with ulceration findings; B: After indigo-carmine dye, the margin of the tumor was still unclear.

A level of $P < 0.05$ was considered to be statistically significant. After evaluating the factors that made the determination of the margin difficult, we decided to use logistic regression analysis for further analysis of those factors.

RESULTS

Incidence of lesions with unclear margin

The characteristics of the 364 candidate lesions reviewed during this period are described in Table 1. There were 27 undelineated margin lesions and 337 delineated margin lesions. There were 62 lesions with inaccurate markings and 302 lesions with accurate markings (Table 1). Consequently, 14 lesions were found to have overlapping results. Therefore, there were 75 lesions with unclear margins (Figure 4). The rate of those lesions in this group was 20.6% (75/364).

Factors that made determination of the margin difficult

Factors that had significant correlations with unclear margins were tumor location (three parts), color, components of the flat area (0-IIb), tumor size, ulceration, and components of poorly differentiated adenocarcinoma in the mucosal surface (Table 2). After evaluating those 6 factors by multivariate regression analysis, the factors that made the determination of the margin difficult were normal coloration (OR = 2.095; 95%CI: 1.040-4.217; $P = 0.0383$), components of flat area (0-IIb) (OR = 4.900; 95%CI: 1.610-14.913; $P = 0.0051$), the diameter $\geqslant$ 21 mm (OR = 3.852; 95%CI: 2.165-6.852; $P < 0.0001$), ulceration findings (OR = 2.307; 95%CI: 1.156-4.604; $P = 0.0178$), and components of poorly differentiated adenocarcinoma in the mucosal surface (OR = 6.650; 95%CI: 2.590-17.073; $P < 0.0001$) (Table 3).

DISCUSSION

After ESD was developed, early gastric cancer was often resected endoscopically, especially in Japan. Previously reported[4-6] accuracy rates for the delineation of the margin by using conventional endoscopy were almost 80% to 85%, although the criteria for the determination of the margin were not commonly specified in those reports. In this study, we defined the accuracy rate not only by endoscopic images but also by pathological study of the specimens, and the accuracy rate was almost the same as that shown in previous reports. Asada-Hirayama *et al*[7] reported a similar study to ours, and in their result, the accuracy rate for the delineation of the margin was 92.6%, which was much higher than that seen in previous reports, including our study. However, they evaluated only markings on the resected

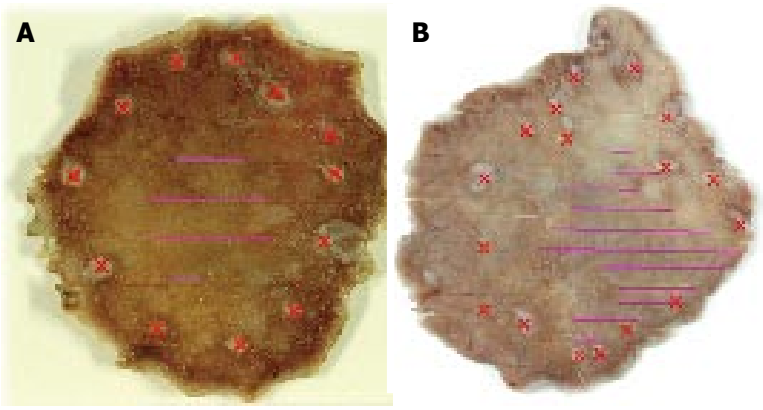

Figure 3 Cases of accurate and inaccurate markings. A: A case of accurate markings. The purple lines indicate the tumor area. The red crosses indicate the marking; B: A case of inaccurate markings. The purple lines indicate the tumor area. The red crosses indicate the marking.

Table 1 The characteristics of 364 lesions

Age (yr)	
Median ± SD	70 ± 9
Range	30-92
Sex	
Men (%)	293 (80.5)
Women (%)	71 (19.5)
Tumor location (three parts)	
U (%)	74 (20.3)
M (%)	144 (39.6)
L (%)	146 (40.1)
Tumor location (cross-sectional parts)	
Less (%)	140 (38.5)
Gre (%)	59 (16.2)
Ant (%)	64 (17.6)
Post (%)	101 (27.7)
Color	
Reddish (%)	213 (58.5)
Discolored (%)	87 (23.9)
Normal color (%)	64 (17.6)
Margin of the lesion	
Delineated	337 (92.6)
Undelineated	27 (7.4)
Main macroscopic type	
0-I (%)	11 (3.0)
0-IIa (%)	154 (42.3)
0-IIb (%)	6 (1.6)
0-IIc (%)	193 (53.0)
Components of flat area (0-IIb)	
Presence (%)	17 (4.7)
Absense (%)	347 (95.3)
Tumor size (mm)	
Median ± SD	16 ± 13
Range	2-100
Ulceration finding	
Presence (%)	62 (17.0)
Absense (%)	302 (83.0)
Components of poorly differentiated adenocarcinoma in the mucosal surface	
Presence (%)	26 (7.1)
Absense (%)	338 (92.9)
Metaplasia around the lesion	
Presence (%)	337 (92.6)
Absense (%)	27 (7.4)
Marking	
Right	302 (83.0)
Wrong	62 (17.0)

SD: Standard deviation; U: The upper third of the stomach; M: The middle third of the stomach; L: The lower third of the stomach; Less: The lesser curvature; Gre: The greater curvatures; Ant: The anterior wall; Post: The posterior wall.

specimens and they used not only conventional endoscopes, but also magnifying endoscopes with NBI. Although there was no significant difference in the accuracy between the 2 kinds of endoscopes in their study, this factor might have influenced the margin delineation rates.

Tanabe *et al*[6] reported the factors that make the delineation of the margin difficult as (1) large lesions (> 31 mm); (2) flat lesions or those with a flat area; (3) adenocarcinoma with low-grade atypia; (4) gastric mucin phenotype (G-type) adenocarcinoma or gastric predominant gastric and intestinal mucin phenotype (G > I-type) adenocarcinoma; and (5) carcinoma cells invading the middle to deeper portion of the mucosa under normal covering epithelium. In our study, 2 factors, lesion size and flat area, were almost the same as the factors that Tanabe *et al*[6] reported, and Asada-Hirayama *et al*[7] reported similar results. To achieve a complete resection, we should observe for those factors that demonstrate a more difficult to differentiate margin, and if the lesion might have such characteristics, we should examine the margin more carefully to ensure an accurate determination. Conventional endoscopy can demonstrate the tumor size and ulceration findings, but sometimes it is difficult to identify components of the flat area. To solve this difficulty, IEE, such as a magnifying endoscope, NBI[8,9], FICE[10], and an acetic acid-indigo carmine mixture (AIM)[11], might be useful. Yao *et al*[8] reported magnifying endoscopy with NBI may allow reliable delineation of the lateral extent of carcinomatous tissue, and in this study, a demarcation line was identified in 97 of 100 carcinomas (97%). Additionally, Nagahama *et al*[9] reported that magnifying endoscopy with NBI could determine margins in 72.6% of the lesions that show unclear margin using conventional endoscopes. AIM was developed by Kawahara *et al*[11] and they reported the diagnostic accuracy of AIM observation was 90.7%. In contrast, the diagnostic accuracy of indigo carmine observation was 75.9% in that study. AIM is also easy to use without special equipment. Kadowaki *et al*[12] mentioned that magnifying endoscopy with NBI and acetic acid is easier compared to other magnifying endoscopy methods to recognize the demarcation of

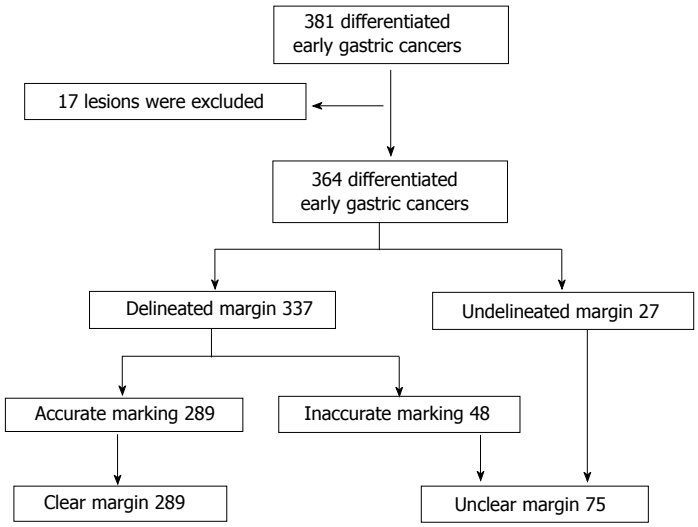

Figure 4 Flow chart of this study.

Table 2 The comparison between "clear margin" and "unclear margin"

	Clear margin (n = 289)	Unclear margin (n = 75)	
Age (yr)			
Median ± SD	70 ± 8	72 ± 10	NS
Range	37-92	30-90	
Sex			
Men (%)	237 (82.0)	56 (74.7)	NS
Women (%)	52 (18.0)	19 (25.3)	
Tumor location (three parts)			
U (%)	54 (18.7)	20 (26.7)	P = 0.0128
M (%)	108 (37.4)	36 (48.0)	
L (%)	127 (43.9)	19 (25.3)	
Tumor location (cross-sectional parts)			
Less (%)	113 (39.1)	27 (36.0)	NS
Gre (%)	47 (16.3)	12 (16.0)	
Ant (%)	51 (17.6)	13 (17.3)	
Post (%)	78 (27.0)	23 (30.7)	
Color			
Reddish (%)	165 (57.1)	48 (64.0)	P = 0.0049
Discolored (%)	79 (27.3)	8 (10.7)	
Norm-colored (%)	45 (15.6)	19 (25.3)	
Main macroscopic type			
0-I (%)	10 (3.5)	1 (1.3)	NS
0-IIa (%)	120 (41.5)	34 (45.3)	
0-IIb (%)	3 (1.0)	3 (4.0)	
0-IIc (%)	156 (54.0)	37 (49.3)	
Components of flat area (0-IIb)			
Presence (%)	7 (2.4)	10 (13.3)	P = 0.0002
Absense (%)	282 (97.6)	65 (86.7)	
Tumor size (mm)			
Median ± SD	15 ± 11	25 ± 17	P < 0.0001
Range	2-68	3-100	
Ulceration finding			
Presence (%)	43 (14.9)	19 (25.3)	P = 0.0319
Absense (%)	246 (85.1)	56 (74.7)	
Components of poorly differentiated adenocarcinoma in the mucosal surface			
Presence (%)	11 (3.8)	15 (20.0)	P < 0.0001
Absense (%)	278 (96.2)	60 (80.0)	
Metaplasia around the lesion			
Presence (%)	266 (92.0)	71 (94.7)	NS
Absense (%)	23 (8.0)	4 (5.3)	

SD: Standard deviation; U: The upper third of the stomach; M: The middle third of the stomach; L: The lower third of the stomach; Less: The lesser curvature; Gre: The greater curvatures; Ant: The anterior wall; Post: The posterior wall; NS: Not significant.

Table 3 The multivariate regression analysis of the factors that make the determination of the margin difficult

Factors	OR	95%CI	P value
Lcation in the U and M parts	1.769	0.940-3.331	NS
Norm-colored	2.095	1.040-4.217	0.0383
Components of flat area (0-IIb)	4.900	1.610-14.913	0.0051
Tumor size ⩾ 21 mm	3.852	2.165-6.852	< 0.0001
Ulceration finding	2.307	1.156-4.604	0.0178
Components of poorly differentiated adenocarcinoma in the mucosal surface	6.65	2.590-17.073	< 0.0001

OR: Odds ratio; NS: Not significant; U: The upper third of the stomach; M: The middle third of the stomach.

early gastric cancers for non-expert endoscopists as well as expert endoscopists. Utilizing these advanced imaging techniques may make it easier and clearer for all endoscopists to recognize the demarcation of early gastric cancers.

Our study had a few limitations. First, we did not compare endoscopic figures with resected specimens in detail, so there was no evidence that the determination of the margin was completely correct. However, in our study, to evaluate the accuracy as precisely as possible, we strictly determined the criteria of "undelineated margin lesions" using not only endoscopic images but also pathological study of the specimens as well as was done in the study of Nagahama *et al*[9]. Second, our study was a retrospective study, and therefore, the individuals who performed the endoscopic resection and those who re-evaluated the lesions were not the same in almost all cases, and the margins that the 2 endoscopists considered were not same. To solve these 2 limitations, future studies could prospectively demarcate the tumor margin to be able to compare it with the endoscopically resected specimens, and the same endoscopists should evaluate the accuracy of the determination.

In conclusion, approximately 20% of differentiated early gastric cancers showed an unclear margin.

Factors such as normal color, components of flat area (0-IIb), diameter ⩾ 21 mm, ulceration findings, and components of poorly differentiated adenocarcinoma in the mucosal surface can make the determination of the margin difficult. During endoscopic resection, endoscopists should carefully evaluate the margin of the lesion while considering the risk factors for unclear margins.

COMMENTS

Background

When endoscopic resection of early gastric cancers is performed, it is important to accurately determine the margin of the lesion. A vague determination of the margin may result in residual cancer cells, which may cause recurrences and require additional resections.

Research frontiers

Recently, imaged enhanced endoscopy (IEE) procedures, such as narrow band imaging (NBI), auto fluorescence imaging (AFI), or flexible spectral imaging color enhancement (FICE) have been developed. Especially, magnifying endoscopy with NBI may allow reliable delineation of the lateral extent of carcinomatous tissue, and it could determine margins in the lesions that show unclear margin using conventional endoscopes. However, these methods have not been adopted everywhere.

Innovations and breakthroughs

In this study, the authors evaluated the determination of the margin of differentiated-type early gastric cancers by using conventional endoscopy. In order to evaluate the accuracy as precisely as possible, the authors more strictly determined the criteria of "undelineated margin lesions" using not only endoscopic images but also pathological study of the specimens than similar studies.

Applications

The result of this study is an important benchmark to evaluate the new modalities describe above. And when these new modalities are not available, the authors should carefully evaluate the margin of the lesion while considering the risk factors for unclear margins.

Terminology

Endoscopic submucosal dissection is a newly developed technique in the field of endoscopic treatment for gastrointestinal neoplasms because of its high rate of *en bloc* resection. IEE is a dye-based or an equipment-based image enhanced technology to increase the contrast of structures, thus making the mucosal topography, morphology and borders of lesions viewable in finer detail. NBI is one of the equipment-based image enhancement technologies, which improves the contrast of the microvascular structure and fine mucosal patterns in the mucosal surface layer using the narrow-band illumination focused two beams of 415 nm and 540 nm. AFI is one of the equipment-based image enhancement technologies based on the detection of natural tissue fluorescence emitted by endogenous molecules such as collagen, flavins, and porphyrins. FICE is one of the equipment-based image enhancement technologies, which enhance images by extracting spectral images at the desired wavelengths by applying signal processing to the white light generally used by endoscope. An acetic acid–indigo carmine mixture is one of the dye-based image enhancement technologies using both acetic acid for color contrast and indigo carmine for shape contrast.

Peer-review

It is a retrospective study and evaluation of various endoscopic criteria for unclear margins in early gastric cancer may not be perfect. Still this study provides useful guide for future prospective studies to define unclear margins in early gastric cancers.

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CASE REPORT

Metallic stent insertion with double-balloon endoscopy for malignant afferent loop obstruction

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Informed consent: All study participants, or their legal guardian, provided written informed consent prior to study enrollment.
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Abstract

Progress in double-balloon endoscopy (DBE) has allowed for the diagnosis and treatment of disease in the postoperative bowel. For example, a short DBE, which has a 2.8 mm working channel and 152 cm working length, is useful for endoscopic retrograde cholangiopancreatography in bowel disease patients. However, afferent loop and Roux-limb obstruction, though rare, is caused by postoperative recurrence of biliary tract cancer with intractable complications. Most of the clinical findings involving these complications are relatively nonspecific and include abdominal pain, nausea, vomiting, fever, and obstructive jaundice. Treatments by surgery, percutaneous transhepatic biliary drainage, percutaneous enteral stent insertion, and endoscopic therapy have been reported. The general conditions of patients with these complications are poor due to cancer progression; therefore, a less invasive treatment is better. We report on the usefulness of metallic stent insertion using an overtube for afferent loop and Roux-limb obstruction caused by postoperative recurrence of biliary tract cancer under short DBE in two patients with complexly reconstructed intestines.

Key words: Afferent loop obstruction; Double balloon endoscopy; Overtube; Metallic stent; Biliary tract cancer

Core tip: Malignant afferent loop and Roux-limb obstruction are intractable complications caused by

postoperative recurrence of biliary tract cancer. Metallic stent insertion using an overtube under double-balloon endoscopy is a safe and feasible treatment option in such cases.

Fujii M, Ishiyama S, Saito H, Ito M, Fujiwara A, Niguma T, Yoshioka M, Shiode J. Metallic stent insertion with double-balloon endoscopy for malignant afferent loop obstruction. *World J Gastrointest Endosc* 2015; 7(6): 665-669 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i6/665.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i6.665

INTRODUCTION

Malignant afferent loop obstruction is a potentially life-threatening adverse event of Billroth II gastrectomy and pancreaticoduodenectomy. The occlusion is generally caused by a recurrent tumor, and often presents as chronic, progressive, partial obstruction[1-3]. This type of complication is expected to increase along with therapeutic advances for malignant tumors, thus necessitating the development of safe, effective treatments.

The general condition of patients with malignant afferent loop obstructions is poor due to cancer progression, and thus a less invasive treatment is preferred. Malignant afferent loop obstructions can be treated with surgery, percutaneous transhepatic biliary drainage, percutaneous enteral stent insertion, or endoscopic therapy[4-6]. Endoscopic stents for digestive tract obstruction are a minimally invasive, useful, and safe treatment[7-9]. The primary obstacle for endoscopic stent treatment in postoperative digestive tract obstruction is the difficulty in approaching the obstructing lesion. Of note, there are reports on the use of double-balloon endoscopy (DBE) for complicated postoperative bowel reconstructions[10,11]. Furthermore, a short DBE, which has a 2.8 mm working channel and 152 cm working length, is useful for endoscopic retrograde cholangiopancreatography in these patients[12]. However, because of the large diameter of the system for delivery of metallic stents (MS) indigestive tract obstructions, they cannot be deployed through the narrow working channel of a short DBE. Therefore, new methods are needed to deploy an MS with DBE.

We report on the usefulness of MS insertion using an overtube under a short DBE for afferent loop and Roux-limb obstruction caused by postoperative recurrence of biliary tract cancer in two patients with complexly reconstructed intestines.

CASE REPORT

Case 1

A man in his sixties underwent Roux-en-Y hepaticojejunostomy because of cholangiocarcinoma. Chemotherapy was performed one year later for recurrence of peritoneal dissemination. Two years after chemotherapy, the patient developed a fever and elevated serum transaminase levels. Laboratory tests were as follows: white blood cell (WBC) counts, 9410/μL (normal: 4500-8500/μL); C-reactive protein, 4.7 mg/dL (normal: < 0.26 mg/dL); total bilirubin, 1.2 mg/dL (normal: 0.2-1.2 mg/dL); γ-glutamyltranspeptidase (γGTP), 256 IU/L (normal: 5-40 IU/L); aspartate aminotransferase (AST), 38 IU/L (normal: 10-35 IU/L); and alanine aminotransferase (ALT), 17 IU/L (normal: 7-42 IU/L). Abdominal computed tomography (CT) showed the reconstructed jejunum that was expanded at the site of hepatectomy, mild expansion of the intrahepatic bile ducts and stenosis of the reconstructed jejunum (Figure 1A). The patient was diagnosed with malignant Roux-limb obstruction due to peritoneal dissemination and cholangitis.

Ultrasound-guided drainage was performed for the dilated jejunal Roux-limb, but repeated inflammatory aggravation with drain obstruction occurred. Therefore, a short DBE was performed with the patient under conscious sedation. The short DBE (EC-450BI5; Fujifilm, Tokyo, Japan) was inserted into the Roux-limb obstruction (Figure 1B), and a 0.035 inch guide-wire (Radifocus; Terumo, Tokyo, Japan) was passed through the site of the stricture. Then, a standard endoscopic retrograde cholangiopancreatography injection catheter (MTW Endoskopie, Düsseldorf, Germany) was inserted, and passage through the stenosis was confirmed by radiography. The guide-wire was exchanged with a 0.035 inch Jagwire (Boston Scientific Co., Natick, MA, United States), and an overtube was left to prevent bowel expansion. The DBE was then removed. Finally, an MS (2.2 cm × 6.0 cm, Wallflex duodenal stent; Boston Scientific Co.) was inserted through the overtube in combination with an over-the-wire technique (Figure 1C) and deployed (Figure 1D). There were no perioperative or postoperative adverse events.

After stent insertion, the patient's cholangitis, general condition, and laboratory tests improved as follows: WBC count, 7960/μL; C-reactive protein, 1.86 mg/dL; total bilirubin, 0.7 mg/dL; γGTP, 96 IU/L; AST, 25 IU/L; and ALT, 19 IU/L. On CT, dilation of the Roux-limb disappeared, and chemotherapy resumed. However, this patient died because of peritonitis carcinomatosa 141 d after stent insertion.

Case 2

A man in his sixties underwent pancreaticoduodenectomy because of Vater's papilla cancer. He developed a fever and jaundice approximately 10 mo after the operation. Laboratory tests were as follows: total bilirubin 9.9 mg/dL; γGTP, 401 IU/L; AST, 273 IU/L; and ALT, 283 IU/L. Abdominal CT showed ascites, dilation of the afferent loop, and a surrounding soft density (Figure 2A). The patient was thus diagnosed with malignant afferent loop obstruction due to peritoneal dissemination and cholangitis.

A short DBE (EC-450BI5; Fujifilm) was performed,

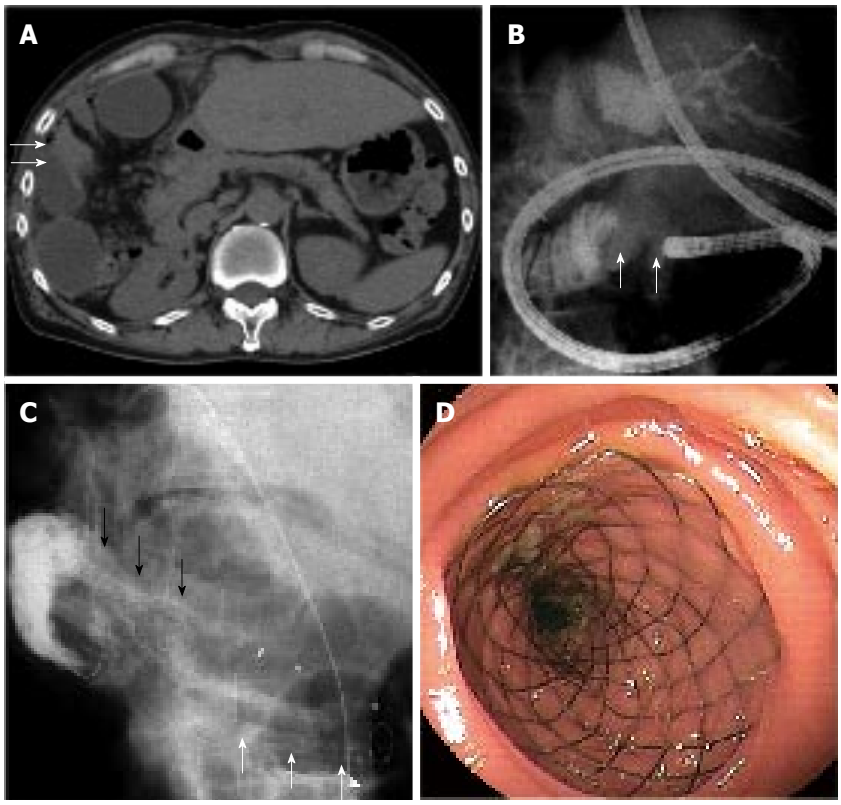

Figure 1 Metallic stent insertion with double-balloon endoscopy for malignant afferent loop obstruction in case 1. A: Abdominal computed tomography showed the reconstructed jejunum that was expanded at the site of hepatectomy, expansion of intrahepatic bile ducts, and the stenosis of the reconstructed jejunum (arrows); B: The stenosis (arrows) was seen when the double-balloon endoscopy (DBE) reached the Roux-limb obstruction; C: An overtube was left to prevent bowel expansion. The DBE was then removed and an metallic stent (MS) (black arrows) was inserted through the overtube (white arrows) in combination with the over-the-wire technique; D: A Wallflex duodenal MS with a diameter of 2.2 cm and a length of 6.0 cm was deployed.

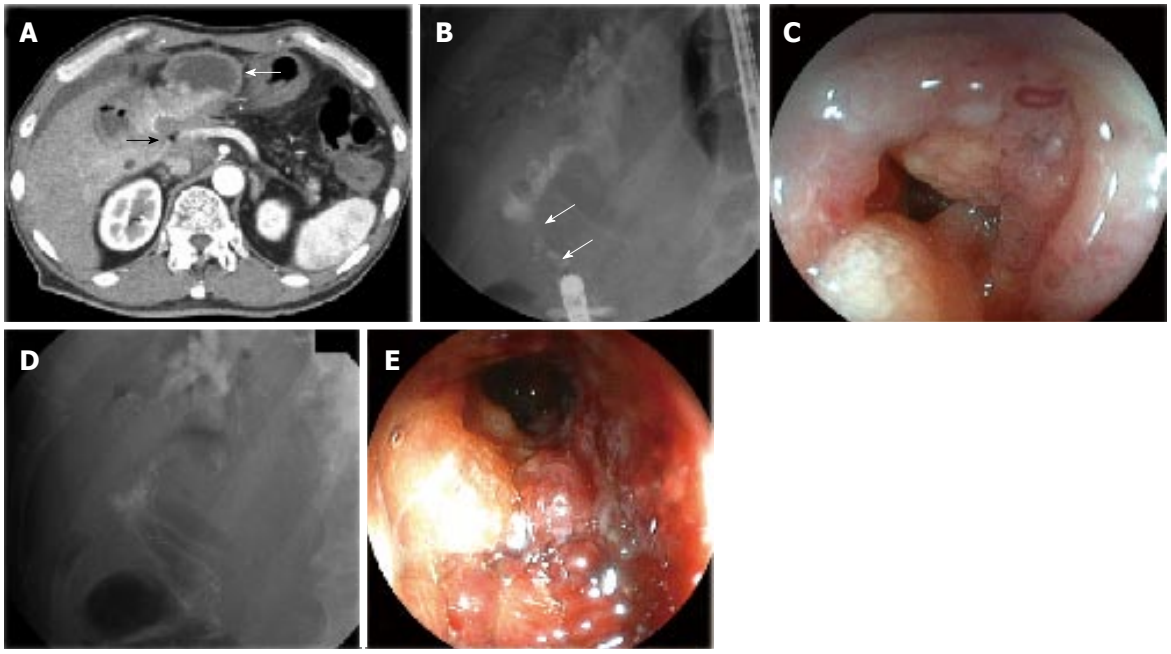

Figure 2 Metallic stent insertion with double-balloon endoscopy for malignant afferent loop obstruction in case 2. A: Computed tomography showed ascites, dilation of the afferent loop (white arrow), and a surrounding soft density (black arrow); B: The double-balloon endoscopy reached the afferent loop obstruction (arrows); C: Stenosis with irregular mucosa was seen; D and E: A Niti-S duodenal metallic stent with a diameter of 2.2 cm and a length of 6.0 cm was inserted and deployed.

which revealed stenosis with irregular mucosa at the afferent loop obstruction (Figure 2B and C). An MS (2.2 cm × 6.0 cm, Niti-S D-type stent; Taewoong Medical Inc., Seoul, South Korea) was inserted and deployed as

described in case 1 (Figure 2D and E). There were no perioperative or postoperative adverse events.

After insertion of the MS, the patient's general condition and laboratory tests improved: total bilirubin, 1.5 mg/dL; γGTP, 296 IU/L; AST, 92 IU/L; and ALT, 77 IU/L. Chemotherapy was resumed, however this patient also died from peritonitis carcinomatosa 140 d after stent insertion.

DISCUSSION

Afferent loop and Roux-limb obstruction are rare adverse events that result in the obstruction of the postoperative intestinal tract. When jaundice and/or fever occur in a postoperative cancer patient with intestinal tract reconstruction, it is important to consider afferent loop or Roux-limb obstruction due to recurrence. Obstructions are typically treated with surgery; however, the general condition of many of these patients is so poor that surgery is not possible. In such cases, insertion of an MS through the stenosis is a useful treatment.

Although percutaneous stent deployment has been reported[13,14], the endoscopic approach allows for direct identification of the stenosis. There are few reports using this method, due to the difficulty in reaching the stenosis with an endoscope, and the need for a scope with a large enough working channel diameter to permit insertion of an MS. In the cases reported here, malignant afferent loop and Roux-limb obstructions were confirmed by DBE and the stenoses were penetrated with a guide-wire. The endoscope was then removed, leaving the overtube to prevent bowel expansion and deploy the MS with an over-the-wire technique. With this method, the stents were safely and easily inserted through the stenoses using a DBE, eliminating the need for a new endoscope. DBE was chosen over a colonoscope in these cases, as it can cause patient discomfort and poses a risk to the patient's health. Stents were safely inserted without a high degree of difficulty and did not produce major adverse events. Moreover, the patients were able to leave the hospital early.

There are other treatments for afferent loop obstruction, such as percutaneous transhepatic biliary drainage or endoscopic ultrasound-guided transhepatic drainage. When a hepatic-jejunal anastomotic stricture coexists, these methods may be particularly useful. However, biliary access can be challenging in patients without dilation of intrahepatic biliary ducts or in patients with ascites. In our cases, we could confirm the absence of judge hepatic-jejunal anastomotic strictures because the bile ducts were easily contrasted by cystography from the afferent loop. Thus, treatments should be selected depending on the patient's condition.

In conclusion, MS insertion using an overtube for afferent loop and Roux-limb obstruction from postoperative recurrence of biliary tract cancer under short DBE is safe and feasible. However, it is necessary to accumulate more cases to determine the true rates of adverse events and confirm the effectiveness of this approach in comparison with surgery and other treatments.

COMMENTS

Case characteristics

Two men in their sixties who underwent Roux-en-Y hepaticojejunostomy after presenting with cholangiocarcinoma and a fever (Case 1) and pancreaticoduodenectomy due to Vater's papilla cancer after presenting with fever and jaundice (Case 2) are reported here.

Clinical diagnosis

Case 1: Fever; Case 2: Fever and jaundice upon physical exam.

Differential diagnosis

Pseudocyst; ileus.

Laboratory diagnosis

Case 1: WBC, 9410/μL; C-reactive protein, 4.7 mg/dL; total bilirubin, 1.2 and 9.9 mg/dL; γ-glutamyltranspeptidase, 256 and 401 IU/L; aspartate aminotransferase, 38 and 273IU/L; and alanine aminotransferase,17 and 283 IU/L, for case 1 and case 2, respectively.

Imaging diagnosis

Computed tomography (CT) in case 1 revealed expansion at the site of hepatectomy in the reconstructed jejunum, mild expansion of intrahepatic bile ducts, and stenosis of reconstructed jejunum; in case 2, CT revealed ascites, dilation of the afferent loop, and a surrounding soft density.

Treatment

Metallic stent insertion with double-balloon endoscopy for malignant afferent loop and Roux-limb obstruction.

Related reports

Afferent loop and Roux-limb obstructions caused by postoperative recurrence of biliary tract cancer are rare and intractable.

Term explanation

Malignant afferent loop obstructions are rare adverse events due to the obstruction of the postoperative intestinal tract of Billroth II gastrectomy and pancreaticoduodenectomy.

Experiences and lessons

Metallic stent insertion using an overtube for afferent loop and Roux-limb obstruction caused by postoperative recurrence of biliary tract cancer under short double-balloon endoscopy is safe and feasible.

Peer-review

The technique is interesting and clinically relevant, and will be of interest to this journal's readership.

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EDITORIAL

Gastrointestinal endoscopy biopsy derived proteomic patterns predict indeterminate colitis into ulcerative colitis and Crohn's colitis

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Abstract

Patients with indeterminate colitis (IC) are significantly younger at diagnosis with onset of symptoms before the age of 18 years with significant morbidity in the interim. The successful care of IC is based on microscopic visual predict precision of eventual ulcerative colitis (UC) or Crohn's colitis (CC) which is not offered in 15%-30% of inflammatory bowel disease (IBD) patients even after a combined state-of-the-art classification system of clinical, visual endoscopic, radiologic and histologic examination. These figures have not changed over the past 3 decades despite the introduction of newer diagnostic modalities. The patient outcomes after restorative proctocolectomy and ileal pouch-anal anastomosis may be painstaking if IC turns into CC. Our approach is aiming at developing a single sensitive and absolute accurate diagnostic test tool during the first clinic visit through endoscopic biopsy derived proteomic patterns. Matrix-assisted-laser desorption/ionization mass spectrometry (MS) and/or imaging MS technologies permit a histology-directed cellular test of endoscopy biopsy which identifies phenotype specific proteins, as biomarker that would assist clinicians more accurately delineate IC as being

either a UC or CC or a non-IBD condition. These novel studies are underway on larger cohorts and are highly innovative with significances in differentiating a UC from CC in patients with IC and could lend mechanistic insights into IBD pathogenesis.

Key words: Indeterminate; Ulcerative; Crohn's colitis; The colitides; Proteomics; Diagnostic accuracy

Core tip: This Editorial is introductory, dedicated to a novel and innovative study with clinical relevance regarding precision of indeterminate colitis (IC) into accurate diagnosis of either ulcerative colitis (UC) or Crohn's colitis (CC). To date, it is very difficult to predict the clinical course of IC, whether it will evolve into UC or CC. About 90% of IC is diagnosed at the time of colectomy for fulminant colitis and subsequent management critically depends on the correct eventual diagnosis. The outcome after colectomy and pouch anastomosis may be painstaking if IC turns into CC. The undergoing studies of proteomic analysis on colon biopsy specimens, if successful will permit delineate IC into UC or CC precision which could be of great help in decision making regarding treatment indication. Although the present data is convincing and support differentiated between UC and CC, this data requires validation and confirmation on a large scale by clinical studies. Hopefully, this editorial will stimulate research into this field to trying to overcome the diagnostic accuracy challenges in inflammatory bowel diseases.

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INTRODUCTION

In endoscopic medicine, predicting the phenotypic outcomes of "indeterminate colitis (IC)", given its unpredictable clinical presentation and disease course, is challenging[1,2]. Inadequate differentiated diagnoses of the two predominantly colonic inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's colitis (CC), may lead to the inconclusive IC diagnosis even when a state-of-the-art classification system of combined clinical, endoscopic, radiologic and histologic tools[1,2] are used. Unless there is a unique and yet unclassified class of colitis, the field needs to develop supplemental molecular biomarker tools for precise and rapid distinction between UC and CC for patients that will otherwise be diagnosed with IC. Previous studies using mucosal biopsy[3,4] have been successful as prognostic indicators for IBD whether the colitis is in a quiescent or active state, but have not been able to distinguish UC from CC[3,4]. Patients with IC are significantly younger at diagnosis (M ± SEM, 9.53 ± 4.8 years)[5-8] with onset of symptoms before the age of 18 years[9-13]. IC shows an equal gender distribution[8,14,15]. In contrast, UC is predominant among males and the mean age at onset is 36-39 years[14-18]. These figures have not changed over the past 3 decades despite the introduction of newer diagnostic modalities[1,2,5,10,13,19]. Even after long-term surveillance, a substantial number of patients with IC still have an unchanged diagnosis[5,19,20], with significant patient suffering in the interim[5,19,20]. The continued presence of an IC diagnosis over a long period of time supports part of our hypothesis that IBD may represent a spectrum of diseases rather than just two entities, Crohn's disease (CD) and UC[21].

The need for IC classification into either UC or CC is important for proper care in patients suffering from IBD, with obvious therapeutic and prognostic implications[22]. Early and accurate diagnosis and sub-classification of UC and CC is therefore the cornerstone for personalized and evidence-based interventional care[23-25]. These two pathologies have differing therapeutic strategies and prognoses. Most patients with UC, or IC likely to develop UC[22], will require pouch surgery for resolution[26-30]. Pouch surgery is well-established[22] and restores gut continuity, defecation, deferral, and discrimination, but is only successful if the UC and/or IC likely to develop UC diagnosis is correct[31,32]. However, IC and UC are mistakenly diagnosed in patients with CC[1,33]. Current data show that 15% of IBD patients who undergo pouch surgery for presumed definitive UC (or IC likely to develop UC) subsequently are diagnosed with *de novo* CD in the ileal pouch[34,35]. Identifying patients with CC and positive outcomes after pouch surgery is a painstaking clinical experience[4,34,35]. Ileal pouch anal anastomosis is acceptable standard care for UC patients, and restorative proctocolectomy should be contraindicated for CC patients[4,36,37] .

Pouch complications are significantly higher in patients with CC (± 64%) and IC (± 43%) *vs* patients having UC (± 22%) ($P < 0.05$)[23,38,39]. This diagnostic dilemma holds potential morbidity from unnecessary and/or inappropriate surgery, and underscores the need for a research strategy focused on developing molecular biometrics to improve diagnosis of colitides at initial endoscopic biopsy[21,40-44]. De novo CD in the ileal pouch is the diagnosis most feared by IBD patients and doctors due to its intractable nature and associated complications which often necessitate excision of the pouch with a permanent end-ileostomy[45-49].

ADVANCES

Mass spectrometry (MS) and imaging mass spectrometry (IMS)[21] are non-invasive technologies that can measure individual molecules in complex endoscopic and surgical clinical specimens[40,41]. These analyses

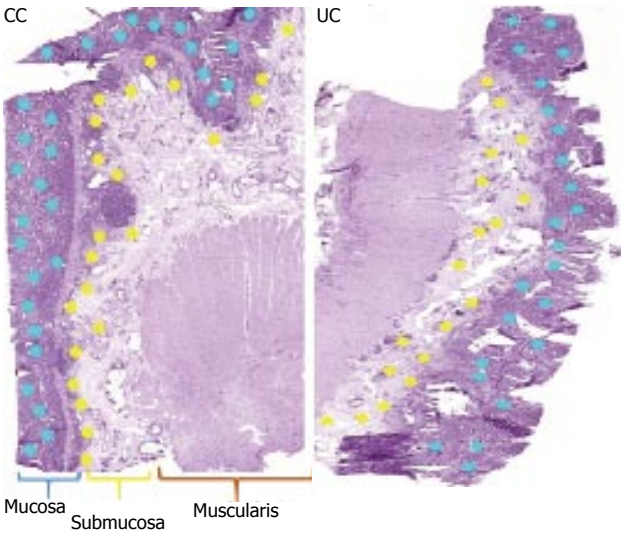

Figure 1 Illustrates histology-directed tissue compartment proteomics profiling using matrix-assisted-laser desorption/ionization mass spectrometry. Digital photomicrographs acquired form histology and matrix-assisted-laser desorption/ionization sections are used to identify and designate sites of interest for profiling. Using bioinformatics technology comparisons are performed in both the training and independent test set samples between inflamed mucosa and inflamed submucosa Crohn's colitis (CC) *vs* ulcerative colitis (UC). Tissue showing marked areas of pathological interest. Rings demonstrate matrix spots in mucosal (blue) and submucosal (yellow) layers (our unpublished data).

provide quantitative and qualitative data about cellular systems, and can differentiate diseased from normal tissue, and can identify diseases within the same organ[40,41,50]. These characteristics offer significant diagnostic and prognostic potential for clinical medicine and could supplement known clinicopathologic variables for delineating IC into UC or CC at a patient's first clinical visit. Due to the current alarming epidemiologic studies indicate that the incidence and prevalence of IBD is widening worldwide, especially in developing nations[9,21,51-60], established techniques like MS and IMS, which are affordable, non-invasive, easier, accurate and faster at screening for potential delineation of IBD, ought to be considered for clinical applications in IBD laboratories. The basic steps of the MS/IMS methodology of histology-directed proteomic patterns profiling are outlined in Figure 1.

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REVIEW

Advances in endoscopic retrograde cholangiopancreatography for the treatment of cholangiocarcinoma

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Abstract

Cholangiocarcinoma (CCA) is a malignancy of the bile ducts that carries high morbidity and mortality. Patients with CCA typically present with obstructive jaundice, and associated complications of CCA include cholangitis and biliary sepsis. Endoscopic retrograde cholangiopancreatography (ERCP) is a valuable treatment modality for patients with CCA, as it enables internal drainage of blocked bile ducts and hepatic segments by using plastic or metal stents. While there remains debate as to if bilateral (or multi-segmental) hepatic drainage is required and/or superior to unilateral drainage, the underlying tenant of draining any persistently opacified bile ducts is paramount to good ERCP practice and good clinical outcomes. Endoscopic therapy for malignant biliary strictures from CCA has advanced to include ablative therapies *via* ERCP-directed photodynamic therapy (PDT) or radiofrequency ablation (RFA). While ERCP techniques cannot cure CCA, advancements in the field of ERCP have enabled us to improve upon the quality of life of patients with inoperable and incurable disease. ERCP-directed PDT has been used in lieu of brachytherapy to provide neoadjuvant local tumor control in patients with CCA who are awaiting liver transplantation. Lastly, mounting evidence suggests that palliative ERCP-directed PDT, and probably ERCP-directed RFA as well, offer a survival advantage to patients with this difficult-to-treat malignancy.

Key words: Endoscopic retrograde cholangiopancreatography; Cholangiocarcinoma; Stents; Self-expandable metal stents; Photodynamic therapy; Photodynamic therapy; Radiofrequency ablation; Radiofrequency ablation

Core tip: Endoscopic retrograde cholangiopancreatography (ERCP) is a valuable treatment modality for patients with cholangiocarcinoma (CCA), as it enables

luminal drainage of blocked bile ducts and hepatic segments by using plastic or metal stents. While there remains some debate as to if bilateral hepatic drainage is required and/or superior to unilateral drainage, the underlying tenant of draining any persistently opacified bile ducts is paramount to good ERCP practice. Although ERCP interventions cannot cure CCA, advancements in the field of ERCP, including ERCP-directed photodynamic therapy and radiofrequency ablation, likely confer a survival advantage and improve upon the quality of life of patients with incurable disease.

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INTRODUCTION

Cholangiocarcinoma (CCA) is the second most common primary neoplasm of the liver[1]. It arises from malignant transformation of cholangiocytes, which are the epithelial cells that line the biliary tree. CCA may be classified based on location as intrahepatic, perihilar, or extrahepatic[1]. Perihilar lesions are further sub-classified depending on their proximal tumor extension according to the classification proposed by Bismuth[2]. Seventy percent of tumors present with bilateral hilar involvement - termed "Klatskin tumors" - and are unresectable cancers[2]. Although CCA is a rare malignancy with 3500 to 5000 cases diagnosed annually in the United States[3], mortality from this cancer is high due to a typically late presentation and limited curative therapies[3].

In patients with inoperable, incurable CCA, initial management usually involves drainage of malignant biliary obstruction and palliation of jaundice. Nevertheless, systemic or locoregional therapies do exist that offer the potential for tumor control, in part to mitigate the complications of further biliary obstruction. Chemotherapeutic agents and radiation therapies have been utilized to achieve this end, although their efficacy is limited, with partial response rates with chemotherapy demonstrated to be 35.9%, and with a stable disease rate of only 26.9%[4].

Over the past two to three decades, the management of CCA has evolved. While surgery remains a curative option for early disease, most cases of CCA are unresectable at the time of presentation. The typical presenting sign of CCA is jaundice. As such, decompressive biliary drainage techniques can help bridge symptomatic patients to surgery, and they can also be used for palliation by treating jaundice and pruritus and by reducing the risk of cholangitis. Various strategies have been employed for biliary drainage, including surgical drainage, percutaneous drainage, and endoscopic decompression *via* nasobiliary drainage or internal biliary stenting. Other mainly palliative modalities for treatment of CCA involve chemoradiation, transarterial chemoembolization, and ablative therapies such as brachytherapy, photodynamic therapy (PDT), and radiofrequency ablation (RFA), which can be applied intraoperatively, percutaneously, or endoscopically[5]. Herein, we will focus on endobiliary therapies for the treatment of CCA and its complications, and the majority of this review will pertain to interventions delivered *via* endoscopic retrograde cholangiopancreatography (ERCP).

BILIARY DECOMPRESSION

While surgical resection is the only treatment that offers curative intent to patients with CCA, the morbidity and mortality associated with liver resection is significantly higher in patients with obstructive jaundice than in patients with normal liver function[6]. Therefore, preoperative biliary drainage is routinely performed to reverse cholestatic liver dysfunction and reduce mortality after selective hepatectomy[7].

Historically, surgical bypass (hepaticojejunostomy or choledochojejunostomy) was the primary modality of biliary drainage prior to percutaneous and endoscopic advancements[8-11]. With advances in endoscopic therapy, particularly the development and refinement of ERCP, endoscopic decompression of obstructive jaundice due to malignant biliary stricturing from CCA should be considered the standard of care[12-16]. While adverse events are influenced by the clinical scenario, the risks associated with ERCP are well documented and uncommon. An American Society for Gastrointestinal Endoscopy guideline on "Complications of ERCP" reports a post-ERCP pancreatitis rate of about 3.5% (range 1.6%-15.7%), a rate of hemorrhage of 1.3%, and a perforation rate of 0.1%-0.6%[17]. Typically, the rate of post-ERCP cholangitis is 1% or less, but this risk does increase in situations of ERCP for drainage of malignant biliary obstruction[17].

In circumstances where biliary decompression is not possible or is incomplete by ERCP, percutaneous transhepatic biliary drainage (PTBD) can be an effective adjunctive therapy. However, PTBD is also associated with its own risks, including intra-procedural death in 1.7% of cases[18].

Many variables must be considered when endoscopic biliary drainage is pursued in patients with obstructive jaundice from CCA. Decisions include whether to use plastic stents (PS) *vs* self-expandable metal stents (SEMS) and whether to pursue unilateral *vs* bilateral biliary stenting.

UNILATERAL *VS* BILATERAL BILIARY DRAINAGE

In patients with Bismuth I perihilar cholangiocarcinoma,

which involves the extrahepatic bile duct but not the biliary confluence, a single stent that crosses the malignant stricture is usually adequate[12]. However, when considering patients with obstructive jaundice from more advanced CCAs that might involve the biliary confluence but not the second-order radicals (Bismuth Ⅱ), or for those that involve the right (Bismuth ⅢA), left (Bismuth ⅢB), or bilateral (Bismuth Ⅳ) hepatic ducts and higher-order branches, it has been suggested that drainage of as little as 25% of the liver can result in resolution of jaundice[19]. Thus, placement of a single stent into one lobe of the liver can result in sufficient biliary decompression in many cases. In some circumstances, segments of the liver that are inaccessible may be atrophied due to chronic involvement of tumor, making additional stenting unnecessary. However, in cases of Bismuth type II, Ⅲ, or Ⅳ CCA, the optimal location and number of stents remains controversial and has been addressed by a number of studies[12-16,20-31].

Deviere *et al*[12] demonstrated in 1988 that bilateral biliary stenting was associated with significantly improved survival and decreased development of cholangitis compared to unilateral stenting. However, in that study, contrast was injected into both lobes of the liver in all patients making the need for bilateral stenting more critical. In instances where one or more segments of the liver are injected with contrast, cholangitis may develop if adequate drainage is not achieved. This concept underscores an important point that - given the advancements in radiographic imaging - whenever possible, a thinly-sliced computed tomography (CT) scan performed on a multidetector scanner or a contrasted magnetic resonance imaging scan with magnetic resonance cholangiopancreatogram (MRCP) should be obtained prior to ERCP. High resolution cross-sectional imaging can identify areas of obstruction that can be selectively targeted for biliary decompression during ERCP, thereby avoiding over-opacification of the intrahepatic bile ducts[32,33].

In 1998, Chang *et al*[20] reviewed fluoroscopic images from ERCPs conducted for biliary decompression in 141 patients with hilar CCA. Those patients who had either a single lobe opacified and drained (unilateral stenting) or both lobes opacified and drained (bilateral stenting) had a significantly lower incidence of cholangitis and mortality compared with those patients who had both lobes of the liver opacified and only one side drained. These findings highlight that the decision to pursue unilateral *vs* bilateral stenting is greatly influenced by procedure-related issues, such as the extent of intrahepatic biliary opacification as well as the ease/difficulty of cannulating and subsequently draining various intrahepatic segments.

Other reports have suggested that drainage of more than 50% of the liver volume is associated with improved survival[34]. In a large retrospective review of 480 patients receiving endoscopic biliary drainage for hilar CCA, bilateral stenting (with either SEMS or PS) resulted in significantly longer overall stent patency compared with unilateral stenting [18 wk *vs* 17 wk for PS (P = 0.0004) and 27 wk *vs* 20 wk for SEMS (P < 0.0001)][26]. This finding had previously been reported in a smaller retrospective review of 46 consecutive patients undergoing palliative endoscopic biliary stent placement for malignant hilar obstruction. In a subgroup with hilar CCA, significantly greater overall stent patency was found in the group receiving bilateral stenting compared to the unilateral stenting group (P = 0.009)[27].

In 2001, De Palma *et al*[21] randomized patients in Italy with malignant hilar obstruction (about 57% from CCA) to unilateral or bilateral stenting for biliary decompression following a diagnostic cholangiogram. On intention-to-treat (ITT) analysis, patients who received unilateral 10-French (Fr) PS had significantly greater rates of successful stent insertion and drainage and also significantly lower rates of cholangitis (8.8% *vs* 16.6%, P = 0.013) compared to those who got bilateral PS. There were no significant differences between the two groups with respect to 30-d mortality, late complications, and median survival. It is important to note that successful stent insertion was significantly lower in the group randomized to bilateral PS (76.9%) as compared to the unilateral PS group (88.6%, P = 0.041). Bilateral stenting of complex hilar strictures from CCA is challenging and often requires significant device manipulation and repeated opacification of the biliary tree in order to access undrained hepatic segments using a guidewire. In fact, on per-protocol analysis (when only patients with successful unilateral and bilateral drainage were included) there was no difference in outcomes between these two groups, but this secondary analysis was underpowered to detect significant differences.

In considering these somewhat disparate data, it is probably best to be guided by the central tenet of endoscopic retrograde cholangiography, that drainage of any opacified large bile ducts or hepatic segments that do not drain spontaneously should be pursued. In a patient with complex perihilar stricturing, use of cross-sectional imaging to guide ERCP and limit contrast opacification can reduce the risk of cholangitis and other procedure-related complications. Planning an ERCP using cross-sectional imaging can also help one avoid opacifying atrophic segments that are less likely to be functional, which might also be more difficult to access and completely drain. When ERCP is performed using this type of a planned and deliberate approach, unilateral biliary stenting might be sufficient to relieve jaundice from a malignant hilar obstruction.

Lastly, effective treatment of patients with CCA requires multidisciplinary consultation. In patients with potentially resectable disease, the choice of which lobe or segments to drain may not be as simple as going after the largest volume of obstructed liver on cross-

sectional imaging. Indeed, presurgical biliary drainage of the lobe or segments of the liver that will remain after operative resection is key to avoiding atrophy of the liver remnant. If the bile ducts of the designated remnant liver are obstructed and not accessible by ERCP, drainage *via* PTBD should be pursued. In these situations, drainage of the portion of the liver targeted for resection might not be required, as atrophy of these segments is desired (and sometimes pursued by selective portal vein embolization) so as to cause hypertrophy of the future liver remnant, which reduces the risk of post-resection hepatic decompensation[35,36].

PLASTIC *VS* SELF-EXPANDABLE METAL STENTS

The issue of the most appropriate means of biliary decompression is further complicated by the decision to utilize either PS or SEMS. Plastic stents are smaller in caliber and tend to form biofilms, resulting in earlier obstruction than SEMS. On average, PS need to be exchanged at least every 3 mo, while SEMS may remain patent for 6 to 12 mo or longer. Raju *et al*[37] demonstrated median SEMS patency of 5.6 mo compared with 1.9 mo for PS, and they found SEMS to be more cost effective because of reduced need for re-intervention. The advantage of PS is that they are removable, and thus their use may be more attractive in patients with good functional status who might outlive a palliative SEMS. Metal stents are available in uncovered, partially-covered, or fully-covered versions. While fully-covered SEMS are potentially removable, their use across a perihilar stricture can be problematic as they can inadvertently obstruct other intersecting normal bile ducts due to their coating. Covered SEMS are also more prone to migration. Uncovered SEMS are less likely to migrate as tumor ingrowth keeps these stents in place, although tumor ingrowth can also lead to stent occlusion. In clinical practice, many interventional endoscopists tend to favor plastic biliary stenting in situations where the diagnosis remains in question, when surgery might still be possible, and in those patients who are likely to outlive the patency of permanent uncovered SEMS.

Multiple non-randomized and randomized trials have demonstrated greater patency with use of SEMS in patients with inoperable CCA, as compared to plastic stenting[13-16,23,25-30,38-40]. Peters *et al*[16] conducted a small prospective pilot study in 1997 to assess the efficacy of SEMS for palliation of jaundice in patients with malignant hilar strictures. Of the 17 patients included, 11 had CCA, and 9 demonstrated adequate drainage following SEMS placement as reflected by a significant decrease in bilirubin. The 2 patients who did not obtain relief from jaundice had extensive intrahepatic disease. Median stent patency was 12 mo with median survival of 10 mo. While these authors concluded that SEMS appeared to provide durable palliation for high-grade malignant biliary strictures, they cautioned against direct comparison with PS until a controlled trial comparing the two modalities had been completed.

In 2003, Kaassis *et al*[13] published a randomized study that found no significant survival difference in patients with malignant common bile duct strictures who underwent SEMS placement compared with patients who underwent PS placement. However, time to the first episode of biliary obstruction was significantly longer in the group receiving SEMS (P = 0.007). Metal stenting was also noted to be more cost-effective in patients without hepatic metastases, who had longer survival (5.3 mo *vs* 2.7 mo in patients with metastases). These authors recommended that plastic stenting was more appropriate in patients with advanced disease, signified by metastases, due to their shorter expected survival[13].

A large retrospective review of 480 patients who received endoscopic biliary drainage in the setting of hilar CCA over a 15-year period demonstrated greater functional success (defined by a decrease in bilirubin to less than 75% of pre-treatment level) with SEMS placement (97.9%) compared with PS placement (84.8%, P < 0.001)[26]. Furthermore, there were significantly greater rates of early complications (8.3% *vs* 2.0%) and late complications (56.4% *vs* 24.4%) in the group that received PS compared to the group that received SEMS. Interestingly, multivariate analysis using Poisson regression showed that SEMS placement (P < 0.01) and bilateral deployment (P < 0.01) were the only independent prognostic factors associated with stent patency[26].

In 2012, Sangchan *et al*[30] conducted an open-label randomized controlled trial in Thailand that compared PS to SEMS placement for unresectable hilar CCA. 180 patients underwent ERCP with randomization to unilateral placement of a 10-mm-wide SEMS *vs* a 7-Fr or 10-Fr PS into the hepatic duct with the largest area of obstruction based on pre-procedural CT or MRCP. On ITT analysis, the rate of successful drainage in the SEMS group was significantly greater than in the PS group (70.4% *vs* 46.3%, P = 0.011)[30]. Median survival time for the SEMS group (126 d) was also significantly longer compared with the PS group (49 d, P = 0.0021).

In 2013, a randomized controlled trial conducted in Japan compared SEMS to PS for drainage of malignant biliary strictures[15]. This study found the 6-month stent patency in the SEMS group was significantly greater (81%) compared with the PS group (20%, P = 0.0012). Kaplan-Meir analysis demonstrated a 50% patency rate of 359 d in the SEMS group as compared to 112 d in the PS group (P = 0.0002). Furthermore, the mean number of interventions for stent failure was significantly lower in the SEMS group (0.63 times/patient) compared to the PS group (1.80 times/patient, P = 0.0008). Lastly, the overall total cost for the treatment was significantly lower in the SEMS group than in the PS group (P = 0.0222).

Overall, these studies support the use of SEMS over

PS for long-term palliation of patients with malignant biliary obstruction, including from unresectable CCA. Typically, uncovered SEMS should be used for palliation when strictures are found across the biliary confluence, and these SEMS likely have even greater utility and cost-effectiveness when expected survival exceeds 3 mo, such as in those patients without metastatic disease. However, with the advent of ERCP-directed ablative therapies for unresectable CCA, a substantial proportion of patients might now expect to outlive even the patency of SEMS. In these patients, a strategy of repeated ERCPs for plastic stent revision and possibly repeated ERCP-directed ablations for locoregional tumor control is reasonable, particularly while they maintain good functional status and quality of life.

PERCUTANEOUS TRANSHEPATIC BILIARY DECOMPRESSION

Biliary decompression and stent placement for malignant biliary strictures can also be achieved by a percutaneous approach. In most centers, PTBD is performed by interventional radiologists. Decompression tubes may be inserted into dilated proximal biliary radicals to facilitate drainage of static bile above the level of obstruction. Alternatively, stenting across a malignant stricture can also be achieved by PTBD, which then allows for bile drainage internally into the duodenum. However, several studies have evaluated the use of PTBD with mixed results[14]. Complications associated with PTBD include vascular injury, risk for tumor seeding, and discomfort at the external drain site[28]. Additionally, PTBD has reported intraprocedural hemorrhage and sepsis rates of 2.5% and a death rate of 1.7%[18].

Hamy *et al*[23] evaluated 35 patients with malignant hilar obstruction (most had CCA) who received a palliative SEMS *via* a percutaneous-transhepatic route. They found a 97% rate of adequate biliary drainage with a median survival of 182 d and a 25% rate of recurrent jaundice after 180 d. These results were corroborated by a large retrospective multicenter study of 84 patients that compared the efficacy of percutaneous-transhepatic to endoscopic SEMS placement for initial malignant biliary decompression[28]. In this study, the rate of successful initial biliary decompression was higher in the percutaneous group (92.7%) as compared with the endoscopically-placed SEMS group (77.3%)[28]. However, overall stent patency and survival-once decompression was achieved-were similar between the groups, suggesting that a well-placed stent, irrespective of how it was placed, is the key to durable biliary decompression and improved survival in patients with malignant biliary obstruction.

Oftentimes, the decision to pursue biliary drainage *via* ERCP or PTBD is determined by clinical reasons, such as in patients with surgically altered gastroduodenal anatomy in whom PTBD might offer easier or more reliable access for therapeutic biliary interventions, or by local expertise. PTBD can be a valuable adjunctive therapy to drain obstructed bile ducts not accessible by ERCP, particularly in patients who might be surgical candidates and require drainage of the future liver remnant so as to prevent atrophy. In our experience, most patients favor endoscopic biliary drainage whenever possible, as it obviates the need for an external catheter for drainage or access. In general, if an experienced biliary endoscopist is available who can perform complex ERCP (as treatment of a hilar tumor is considered a level-3-complexity ERCP by American Society for Gastrointestinal Endoscopy guidelines[41]), we suggest attempting biliary decompression *via* ERCP. If adequate biliary drainage by ERCP is not achieved, then PTBD is an important adjunctive therapy in this patient population that should be pursued. Furthermore, once a PTBD track is mature (which typically requires 3-4 wk), a rendezvous-ERCP procedure can be performed to internalize biliary drainage of a previously inaccessible segment, after which the PTBD catheter can be removed.

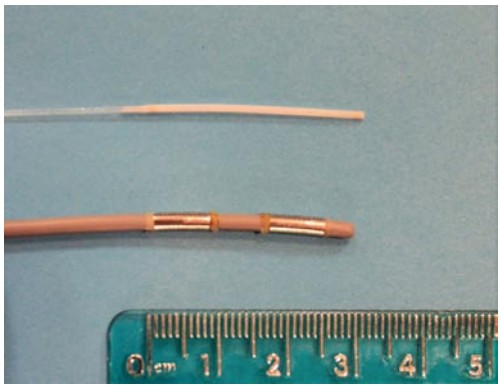

Figure 1 Endoscopic retrograde cholangiopancreatography-directed ablative therapies. Photodynamic therapy is applied *via* a laser fiber (above), whereas radiofrequency ablation is delivered using an 8-Fr catheter with two sets of bipolar rings (below).

ERCP-DIRECTED PHOTODYNAMIC THERAPY

PDT is a well-studied ablative therapy that induces tumor necrosis and apoptosis in treated portions of the biliary tree. The intravenous photosensitizer used in the United States is porfimer sodium (Photofrin, Pinnacle Biologics, Bannockburn, IL). While use of this drug for PDT in patients with CCA is done so off-label in the United States, Medicare and most private insurers in the United States do cover this procedure for palliation of unresectable CCA[42]. Porfimer sodium is typically administered intravenously, at 2 mg/kg, ideally 48 h (but possibly up to 72 h) before ERCP. At the time of ERCP, a 10-Fr bougie catheter (SBDC-10, Cook Medical, Bloomington, IL) or a choledochoscope (SpyGlass, Boston Scientific, Natick, MA) is advanced over a wire to

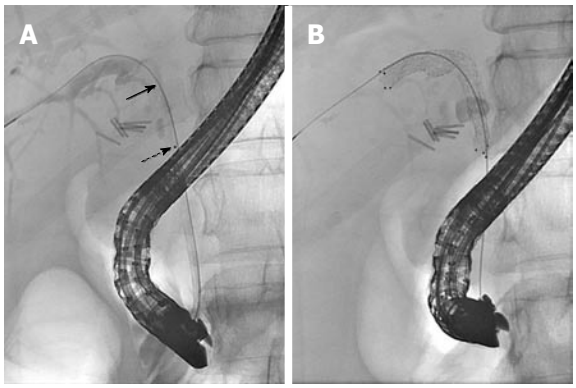

Figure 2 Endoscopic retrograde cholangiopancreatography-directed photodynamic therapy followed by unilateral metal stenting. A: Fluoroscopic view of a photodynamic therapy laser fiber delivered through a 10-Fr-bougie catheter during endoscopic retrograde cholangiopancreatography. The portion of the fiber that emits laser light is demarcated by the black dot (dashed arrow). The proximal-most tip of the fiber is not visible fluoroscopically (solid arrow) but is located near the biliary confluence; B: An 8 mm x 6 cm uncovered self-expandable metal stent was placed across a malignant stricture that involved the right hepatic duct and common hepatic duct.

the level of the malignant stricture and used to pass a laser fiber. This laser fiber (Figures 1 and 2) is then used to deliver activating light (at 630 nm for 750 s, with a light dose of 180 J/cm^2)[43]. When the photosensitizer is activated, oxygen free radicals are released that result in local tissue destruction. Since its first description for biliary tumor ablation in 1991[44], multiple studies have demonstrated that PDT can enable local tumor control and also can result in improved quality of life in this difficult-to-treat patient population[42,45-61]. Metal stent patency has also been shown to be significantly greater with PDT applied immediately prior to stent placement *vs* metal stent placement alone (median time of 244 d *vs* 177 d, respectively, $P = 0.002$)[49].

In 2003, Ortner *et al*[52] conducted a prospective, open-label, randomized, multicenter study of patients with unresectable CCA that compared PDT (using porfimer sodium) in addition to endoscopic or percutaneous stenting by using two 10-Fr endoprostheses *vs* stenting alone and demonstrated significant improvement in survival times (median 493 d *vs* 98 d, respectively, $P < 0.0001$)[52]. Improvement in cholestasis and quality of life indices were also reported. Another randomized controlled trial by Zoepf *et al*[60] in 2005 compared PDT (using Photosan-3, SeeLab, Wesselburenerkoog, Germany) and stenting *vs* stenting alone in patients with unresectable CCA. These investigators demonstrated significantly improved survival in the group that received PDT (21 mo) compared to the group that received only stents (7 mo, $P = 0.0109$). In this study, PDT was delivered *via* ERCP (transpapillary) or by percutaneous biliary access.

The survival benefit associated with PDT in patients with unresectable CCA has also been demonstrated by multiple heterogeneous cohort studies, which were mostly retrospective in nature[45,47,54,62,63]. In 2012, Leggett *et al*[50] conducted a meta-analysis that included six studies that contributed 170 patients with unresectable CCA who received PDT and biliary stenting *vs* 157 patients with CCA who underwent stenting alone. This meta-analysis found that PDT was associated with a statistically significant survival advantage (weighted mean difference of 265 d, $P = 0.01$) and significantly improved quality of life as reflected by improvement in Karnofsky score (weighted mean difference of 7.74, $P = 0.01$). While there appears to be sufficient data to support that at least one round of PDT offers a survival advantage to patients with incurable CCA, it is not clear if multiple rounds of PDT (done every few months) adds to the survival advantage[62]; nor is it clear if bilateral PDT is superior to unilateral PDT in the case of Bismuth IV tumors.

The merits of PDT are tempered somewhat by its potential side-effects. Although a study evaluating the safety and long-term efficacy of PDT using porfimer sodium reported no treatment-related mortality or grade-4 toxicity, complications including photosensitivity resulting in burns (Figure 3) and to a lesser extent bleeding, stenosis, and bile leak have been reported[46]. Cholangitis is usually the most commonly encountered problem that arises in patients with CCA who have undergone biliary intervention, and as expected cholangitis following PDT does occur. A major drawback with ERCP-directed PDT is the need for patients to avoid direct or indirect sunlight for 4-6 wk, which may significantly affect their quality of life. Efforts to limit light toxicity have also resulted in use of a newer photosensitizer meta-tetra(hydroxyphenyl)chlorin (Foscan, Biolitec AG, Jena, Germany) that has demonstrated efficacy in a small study while potentially removing the detrimental side-effects of prolonged skin photosensitivity[48]. Another major drawback of PDT is that the cost of a single-dose of porfimer sodium in a 75 kg patient is about USD $37208, which can be prohibitively high[43].

Nevertheless, PDT has several advantages including: (1) porfimer sodium preferentially accumulates in malignant cells, potentially reducing damage to non-malignant epithelium; and (2) laser light can refract through bile, which can transmit the PDT effect to malignant strictures that are not directly adjacent to (and might be inaccessible to) the laser fiber[43]. Because PDT is dependent on the transmittance of laser light, and does not require the laser fiber to directly make contact with tumor tissue, successful delivery of PDT through metal stents has been reported with appropriate adjustment of the light dose[64].

ERCP-DIRECTED RADIOFREQUENCY ABLATION

Percutaneously- and intraoperatively-directed RFA have been demonstrated by several studies to be efficacious for local tumor control in patients with

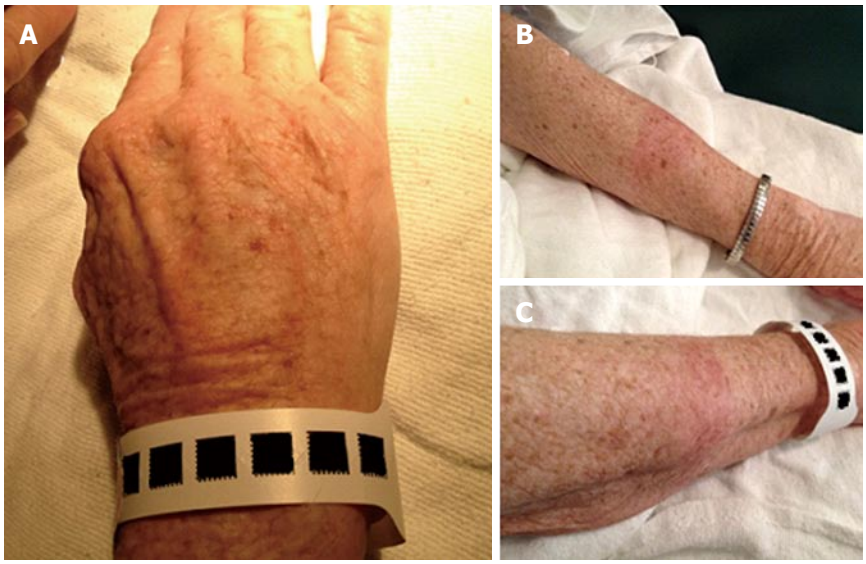

Figure 3 Photosensitivity following photodynamic therapy. A patient with unresectable cholangiocarcinoma was treated with photodynamic therapy. After 4 wk, a test dose of 10 min of exposure to direct sunlight on small areas of uncovered skin resulted in moderate burns on hands (A) and forearms (B, C). Two additional weeks of avoidance to even indirect sunlight was required.

inoperable CCA[65-70], including as an adjunct to surgery[71-73]. RFA has been used for local control of tumor recurrence following surgery in patients who may no longer be good operative candidates or for whom no other surgical intervention is possible[68,72], including those who have already undergone protocol liver transplantation for CCA[74]. However, complications following the percutaneous delivery of RFA are not trivial and have included gastrohepatic fistula[75], hemorrhage necessitating transarterial embolization[76], hepatic vein pseudoaneurysm[77], acute liver failure or abscess formation[78], and needle-tract seeding of tumor[79].

ERCP-directed RFA was developed to enable endoscopists to treat malignant biliary strictures *via* a mechanism of coagulative necrosis induced by thermal energy that is delivered *via* contact using a bipolar catheter[43]. One commercially available RFA catheter (Figure 1) is an 8-Fr device with two electrodes spaced 8 mm apart at the end of the catheter that can be passed over a guidewire (Habib EndoHPB; EMcision, London, United Kingdom)[80]. This device passed United States Food and Drug Administration 510[k] premarketing clearance in 2009. This RFA catheter can be passed through the accessory channel of a duodenoscope and into the bile duct (Figure 4). Fluoroscopic guidance is used to center the two sets of bipolar rings across a malignant stricture for RFA treatment (Figures 5 and 6).

In 2011, Steel *et al*[81] conducted a single-center open-label pilot study that demonstrated that ERCP-directed RFA could be performed safely and efficaciously in patients with malignant biliary strictures from unresectable pancreas cancer or CCA. In this initial study, all but one of 21 patients who had RFA followed by SEMS placement maintained stent patency at 30 d. One patient had asymptomatic biochemical pancreatitis, 2 patients required percutaneous gallbladder drainage, and 1 patient developed rigors. At 90-d follow-up, 3 patients had occluded biliary stents. Subsequently, in a retrospective series of 12 patients (9 with CCA) with malignant intraductal or perihilar biliary strictures, Tal *et al*[80] performed 19 successful RFA applications *via* ERCP followed by PS placement. These investigators used a setting of 8 W for treatment of intrahepatic and perihilar biliary strictures and 10 W for extrahepatic bile duct strictures using an ERBE electrosurgical generator (VIO 200D, ERBE Elektromedizin, Tübingen, Germany). However, biliary bleeding was observed at 4-6 wk in 3 patients (2 of whom died of hemorrhagic shock), and cholangitis developed in 4 patients, which was amenable to stent exchange. Finally, Figueroa-Barojas *et al*[82] reported on the use of ERCP-directed RFA in 25 patients with malignant biliary structures (11 patients had CCA). Procedures were performed using a RITA 1500X RF generator (Angiodynamics, Latham, NY) set at 7-10 W for a time period of 2 min. These investigators reported a resultant significant increase in mean bile duct diameter of 3.5 mm ($P < 0.0001$)[82]. In this series, 5 patients presented with pain after the procedure, one patient developed mild post-ERCP pancreatitis, and one patient developed cholecystitis following endobiliary RFA.

In 2014, Sharaiha *et al*[83] published a retrospective series of 66 patients with malignant biliary strictures (36 with CCA) who underwent either SEMS placement alone or RFA followed by SEMS placement. They reported 100% technical success in both groups. While these investigators found that rates of stent patency were similar between the two groups, on multivariate analysis, RFA was found to be an independent predictor of survival (HR = 0.29, 95%CI: 0.11-0.76, $P = 0.012$). Finally, RFA has been described as a means of treating tumor ingrowth of uncovered SEMS in the bile duct[84].

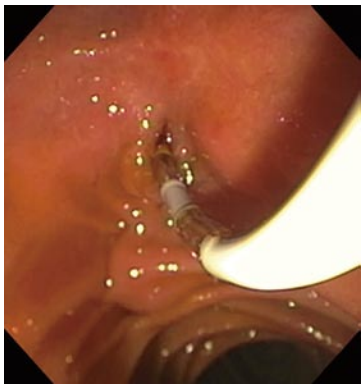

Figure 4 Endoscopic view of a radiofrequency ablation catheter being inserted into the bile duct by using a duodenoscope. A biliary sphincterotomy had been performed during a prior endoscopic retrograde cholangiopancreatography procedure in this patient with an unresectable cholangiocarcinoma to enable easier access to the bile duct. Note: this is not a depiction of radiofrequency ablation (RFA) actively being performed, as RFA is not typically applied with the bipolar coils exposed in the duodenal lumen, in order to avoid thermal injury to the duodenal wall.

Typically, the RFA catheter can be passed into a blocked stent and used under fluoroscopic guidance to ablate any tumor ingrowth, which is then removed by retrieval balloon sweep. This ablation may be followed by placement of an indwelling plastic stent or a second uncovered SEMS, in appropriate situations (Figure 6).

When compared to PDT, the advantages of endobiliary RFA include being able to provide ablative treatment without the patient having to come in 2 d in advance for infusion of a photosensitizer, easier delivery of the RFA catheter that can be done over a guidewire, and no requirement to avoid sunlight for several weeks to prevent photosensitivity. However, RFA requires direct contact with neoplastic tissue for ablation, thus it does not offer the "field effect" conferred by the laser light used in PDT, which can refract through bile to treat inaccessible blocked bile ducts.

In 2014, Strand *et al*[43] demonstrated comparable survival following ERCP-directed RFA *vs* ERCP-directed PDT. In this retrospective cohort study, 48 patients with unresectable CCA underwent RFA (n = 16) or PDT (n = 32) followed by plastic or metal biliary stenting. Overall median survival in both treatment groups was not statistically different (9.6 mo following RFA and 7.5 mo following PDT, P = 0.799). Furthermore, patients who underwent RFA had a lower mean number of plastic stents placed per month (0.45 *vs* 1.10, P = 0.001) but also had more episodes of stent occlusion (0.06 *vs* 0.02, P = 0.008) and cholangitis (0.13 *vs* 0.05, P = 0.008) per month, as compared to patients who received PDT.

In addition to the differing advantages and disadvantages of RFA *vs* PDT that were mentioned earlier, a major discriminating factor between these two ablative technologies is cost. Strand *et al*[43] noted that because both procedures required ERCP with sent exchange, the true cost differential is the difference between the cost of a dose of porfimer sodium (USD $37208) and the cost of the RFA catheter (USD $1295), which is $35913[43]. In the current environment of falling reimbursements and the need for cost-containment, this is a significant difference that favors ERCP-directed RFA.

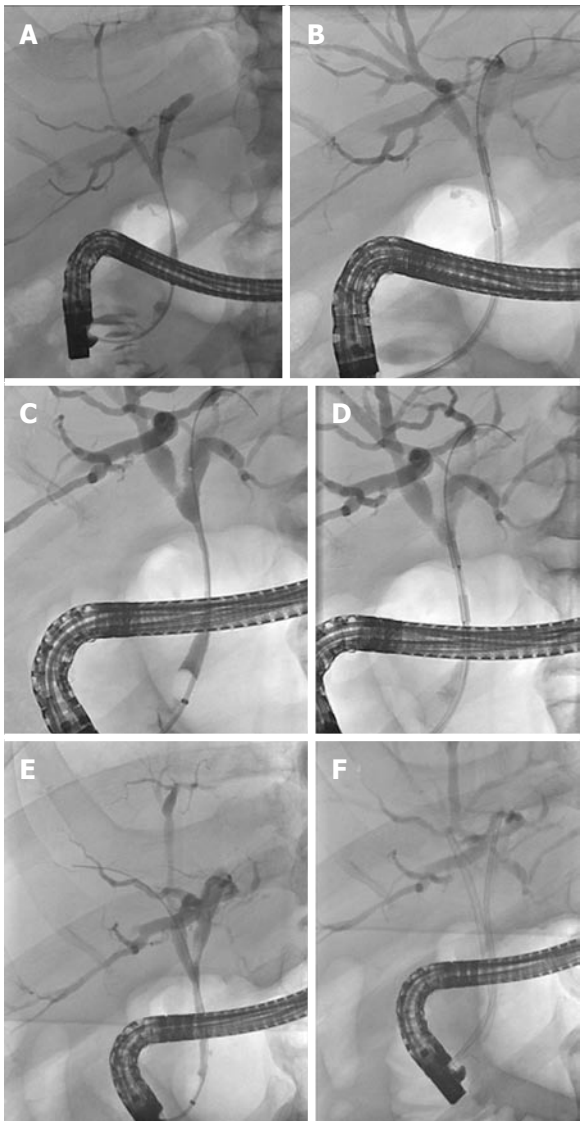

Figure 5 Effect of repeated endoscopic retrograde cholangiopancreatography-directed radiofrequency ablation on a malignant extrahepatic biliary stricture in a patient with unresectable cholangiocarcinoma. A long perihilar stricture is seen involving the extrahepatic duct (A) in a patient who had exploratory laparotomy that showed locally advanced and unresectable Bismuth I cholangiocarcinoma. A cholecystectomy had been performed at the time of laparotomy. Endoscopic retrograde cholangiopancreatography (ERCP)-directed radiofrequency ablation (RFA) was applied to this malignant stricture (B) followed by biliary stenting (not shown). Following two rounds of RFA done at about 3 mo intervals, a third ERCP showed moderate improvement in the stricture's diameter (C). Repeat ERCP-directed RFA was performed (D). After 4 rounds of RFA therapy, an ERCP 1 year later showed marked improvement of the extrahepatic bile duct with no high-grade stricture seen (E), and RFA was not repeated during this procedure. A 10-Fr plastic stent was placed into the right hepatic duct and a 7-Fr plastic stent was placed into the left hepatic duct for more durable biliary drainage (F), as this was an otherwise healthy patient with excellent functional status who would likely outlive metal stenting. While patients with Bismuth I cholangiocarcinoma often do well with a single extrahepatic biliary stent, this patient had previously had premature stent failure and cholangitis with a single plastic stent, thus two biliary stents were required.

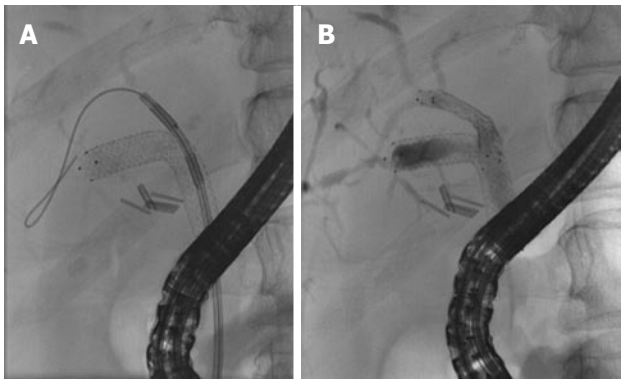

Figure 6 A patient with unresectable cholangiocarcinoma was previously treated with photodynamic therapy followed by placement of an uncovered metal stent (see Figure 2). For persistent symptomatic biliary obstruction due to undrained segments in the right liver, a wire was passed into the previously undrained segments which allowed for 6-Fr bougie dilation followed by 4-mm balloon dilation across the lattices of the existing large-cell uncovered self-expandable metal stent (SEMS) (not shown). After dilation, the 8-Fr radiofrequency ablation (RFA) catheter was deployed over the wire and through the SEMS, and RFA was applied to a malignant stricture that was obstructing drainage (A). Lastly an 8-mm uncovered SEMS was deployed through the previously placed 8-mm uncovered SEMS (B) enabling durable drainage of more of the right liver.

ERCP-DIRECTED NEOADJUVANT ABLATIVE THERAPY FOR CCA PRIOR TO LIVER TRANSPLANTATION

Experience with liver transplantation (LT) for unresectable CCA had previously been disappointing due to frequent cancer recurrence and poor 5-year survival rates[3]. To improve outcomes following LT for CCA, a protocol for neoadjuvant chemotherapy followed by LT was first developed at the University of Nebraska and then at the Mayo Clinic[3,85]. Patients who met the following criteria were included in this LT protocol: (1) perihilar location of suspected CCA; (2) a malignant-appearing stricture on cholangiography with malignant endoluminal brushing or biopsy, carbohydrate antigen 19-9 level > 100 U/mL (in the absence of cholangitis), mass on cross-sectional imaging, and/or polysomy on fluorescence *in situ* hybridization; (3) unresectable disease or disease arising in primary sclerosing cholangitis; (4) completion of neoadjuvant therapy before LT; and (5) medical suitability for LT[85]. Neoadjuvant therapy from the early "Mayo" protocol included administration of external beam radiation therapy (XBRT) and 5-fluorouracil, followed by brachytherapy[85-87]. Use of intraluminal brachytherapy and XBRT in patients with unresectable CCA has been reported for palliation of jaundice and as a treatment to temporarily obviate the need for biliary stenting[88,89]. Furthermore, a retrospective study by Darwish Murad *et al*[85] of 287 patients, 75% of whom received brachytherapy as part of neoadjuvant therapy prior to LT, demonstrated a 5-year ITT survival rate of 53% and post-transplant recurrence-free survival of 65%[85]. In this large series of patients, recurrence-free survival for patients who had received brachytherapy was similar to those who had not (HR = 1.05; 95%CI: 0.60-1.85)[85]. Other studies have also shown no mortality benefit from the addition of brachytherapy[90,91]. In an effort to mitigate side-effects associated with brachytherapy and the complexities associated with delivery of radioactive ribbons in the endoscopy or radiology suite, other endobiliary therapies for neoadjuvant locoregional CCA tumor control prior to LT have been adopted.

In particular, PDT, as mentioned previously, has been demonstrated to be a safe and potentially efficacious modality for locoregional control of perihilar CCA in palliative patients. In a proof-of-concept study performed at our institution, Cosgrove *et al*[42] reported on 4 patients with unresectable CCA who had undergone protocol-driven neoadjuvant chemoradiation followed by ERCP-directed PDT to provide endobiliary and local tumor control in patients who were awaiting LT[42]. Although the sample size of this study was small, none of the patients who received PDT had progressive locoregional disease or distant metastases during the pre-transplant period, and all patients underwent successful LT. ITT disease-free survival was 75% at a mean follow-up of 28.1 mo. Based on these data regarding PDT, as well as our comparable experience with RFA for patients with incurable CCA[43], our institution's protocol allows for the use of either PDT or RFA as an alternative to brachytherapy for locoregional tumor control in patients with inoperable CCA who are awaiting LT. Prospective trials to study these ERCP-directed neoadjuvant modalities for locoregional control in patients with CCA are indicated.

CONCLUSION

CCA is a malignancy with high morbidity and mortality due to its typically late presentation with obstructive jaundice, and its associated complications of cholangitis and biliary sepsis. ERCP is a valuable treatment modality for patients with CCA, as it enables internal luminal drainage of blocked bile ducts and hepatic segments by using plastic or metal stents. While there remains debate as to if bilateral (or multi-segmental) hepatic drainage is required and/or superior to unilateral drainage, the underlying tenant of draining any persistently opacified bile ducts is paramount to good ERCP practice and good clinical outcomes. Endoscopic therapy for malignant biliary strictures from CCA has advanced to include ablative therapies *via* ERCP-directed PDT or RFA. As chemoradiation is of limited efficacy in providing tumor control for this cancer, these endoscopic modalities, which offer the potential for locoregional control and hopefully more durable biliary drainage, are a much needed addition to our therapeutic endobiliary armamentarium. While ERCP techniques cannot cure CCA, advancements in the field of ERCP have enabled us to improve upon the quality of life of patients with incurable disease. ERCP-directed PDT has been used in lieu of brachytherapy to provide neoadjuvant local

tumor control in patients with CCA who are awaiting LT. Lastly, mounting evidence suggests that palliative ERCP-directed PDT, and probably ERCP-directed RFA as well, can offer a survival advantage to patients with this difficult-to-treat malignancy.

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REVIEW

Role of endoscopic ultrasonography in the loco-regional staging of patients with rectal cancer

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Abstract

The prognosis of rectal cancer (RC) is strictly related to both T and N stage of the disease at the time of diagnosis. RC staging is crucial for choosing the best multimodal therapy: patients with high risk locally advanced RC (LARC) undergo surgery after neoadjuvant chemotherapy and radiotherapy (NAT); those with low risk LARC are operated on after a preoperative short-course radiation therapy; finally, surgery alone is recommended only for early RC. Several imaging methods are used for staging patients with RC: computerized tomography, magnetic resonance imaging, positron emission tomography, and endoscopic ultrasound (EUS). EUS is highly accurate for the loco-regional staging of RC, since it is capable to evaluate precisely the mural infiltration of the tumor (T), especially in early RC. On the other hand, EUS is less accurate in restaging RC after NAT and before surgery. Finally, EUS is indicated for follow-up of patients operated on for RC, where there is a need for the surveillance of the anastomosis. The aim of this review is to highlight the impact of EUS on the management of patients with RC, evaluating its role in both preoperative staging and follow-up of patients after surgery.

Key words: Rectal cancer; Staging; Endoscopic ultrasonography; Accuracy; Therapeutic strategy

Core tip: In the era of tailored management of patients with rectal cancer (RC), endoscopic ultrasonography (EUS) has become crucial for the appropriate preoperative

staging of these patients. This review highlights the impact of EUS on the management of patients with RC, evaluating its role in both preoperative staging of RC and follow-up of patients after surgery. Finally, possible new application are discussed, on the basis of the technologic innovation and the evolution of the therapeutic strategies.

Marone P, de Bellis M, D'Angelo V, Delrio P, Passananti V, Di Girolamo E, Rossi GB, Rega D, Tracey MC, Tempesta AM. Role of endoscopic ultrasonography in the loco-regional staging of patients with rectal cancer. *World J Gastrointest Endosc* 2015; 7(7): 688-701 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i7/688.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i7.688

INTRODUCTION

Every year approximately 40000 patents are diagnosed with rectal cancer (RC), and the incidence of RC in the European Union is 15-25/100000 per year, with an estimated mortality of 4-10/100000 per year[1]. The prognosis of RC is strictly related to both T and N stage of the disease at the time of diagnosis[2]. This is traditionally staged according to local invasion depth (T stage), lymph node involvement (N stage), and presence of distant metastases (M stage) (Table 1)[3,4]. Staging RC is crucial for choosing the best multimodal therapy (Table 2)[2]: patients with high risk locally advanced RC (LARC) undergo surgery after neoadjuvant chemotherapy plus radiotherapy (NAT); those with low risk LARC are operated on after a preoperative short-course radiation therapy. The latter is used as a valid alternative to NAT in elderly patients, or for patients unfit for preoperative chemotherapy because of severe comorbidities. Finally, surgery alone is recommended only for early RC. Total mesorectal excision (TME) is the standard surgical approach, with or without sphincter preservation. Extended abdomino-perineal resection is performed in distal RC which requires sphincter demolition. Local excision is performed in small T1 cancers with favorable histology by means of trans anal endoscopic microsurgery (TEM) or trans anal minimally invasive surgery. Local excision is also performed in selected patients showing complete clinical response after NAT. Therefore, precise staging of patients has a pivotal role for the selection of different therapeutic options and team work among the members of the multidisciplinary team is mandatory to improve patients outcome[2].

Several imaging methods are used for staging patients with RC: computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and endoscopic ultrasound (EUS)[1]. The latter has a high accuracy for loco-regional staging of RC, since it is capable to evaluate precisely the mural infiltration of the tumor (T), especially in the early RC.

Table 1 The 2010 AJCC staging system for primary rectal cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*: Intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor directly invades or is adherent to other organs or structures
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional nodal metastasis
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (*i.e.*, liver, lung, ovary, non-regional node)
M1b	Metastases in more than one organ/site or the peritoneum

From ref.[3].

Table 2 Therapeutic strategy

cT1 cT2 cN0 cCRM-	Surgery alone
Any cT cN+	CRT
cT2 cT3 cN0 cCRM+	
cT2 cT3 cN0 cCRM-	SCRT

C: Clinical stage; CRM: Circumferential resection margin; CRT: Standard chemotherapy + radiation therapy; SCRT: Short term chemotherapy + radiotherapy. From ref.[2].

On the other hand, EUS is less accurate in restaging RC after NAT and before surgery. Recently, EUS has been used in clinical trials where patients have been selected for less invasive therapies: polypectomy for T1 RC; TEM for T1/T2-N0 cancers, and NAT + TEM for T2N0 tumors. Finally, EUS is indicated for following-up patients operated on for RC, where there is a need for surveillance of the colorectal anastomosis, which is at risk for local recurrences[2,5-7].

This review evaluates the role of EUS in the loco-regional staging of patients with RC, analyzing both accuracy and limits of this imaging method, which is part of the multidisciplinary approach for patients with RC. In particular, the aim of the review is to highlight the impact of EUS on the management of patients with RC, evaluating its role in both preoperative staging and follow-up after surgery. Finally, possible new applications are discussed on the basis of the

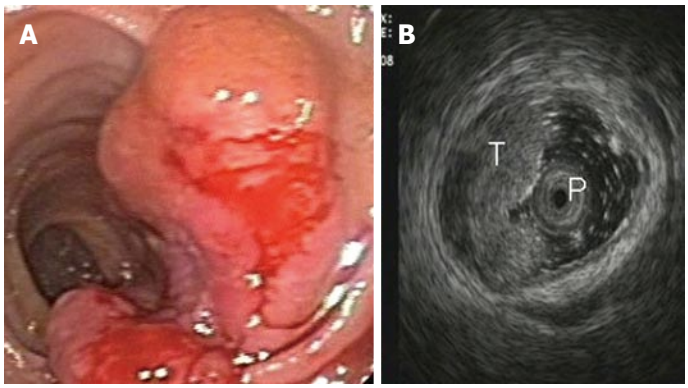

Figure 1 Stage T1 rectal cancer: (A) endoscopic and (B) ultrasonographic view. Endoscopic ultrasound with radial miniprobe (12 MHz), showing a small tumor located within the mucosa and superficial submucosal layers, and preservation of the outer layers of the rectal wall. T: Tumor; P: Radial probe.

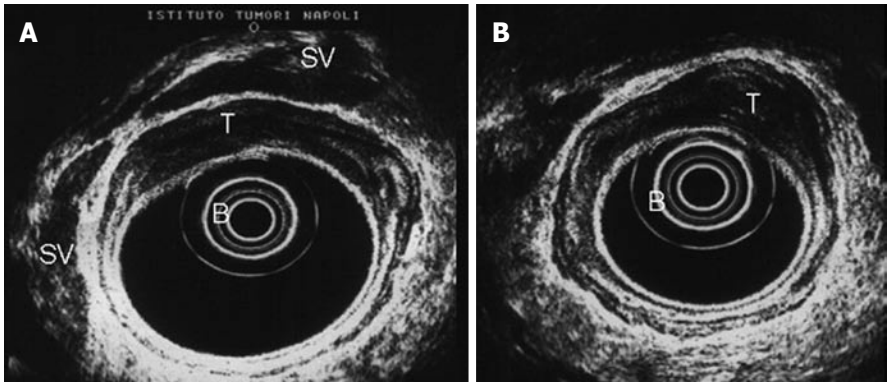

Figure 2 Stage T2 rectal cancer: Ultrasonographic view. The tumor infiltrated the entire wall, without invading the smooth outer margin of the muscularis propria (fourth layer). Endoscopic ultrasound with radial array transducer UM 20 (7.5-12 MHz). B: Ballon; T: Tumor; SV: Seminal vesicles.

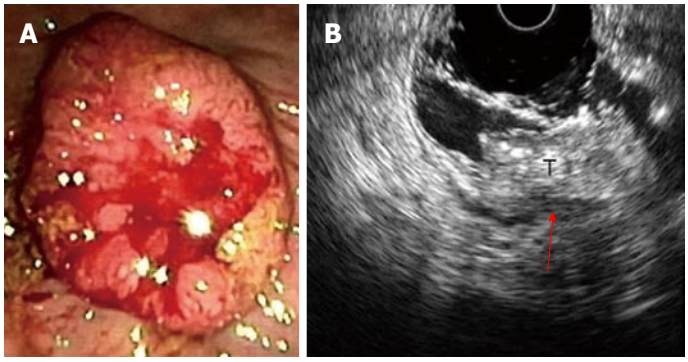

Figure 3 Stage T3 rectal cancer: (A) endoscopic and (B) ultrasonographic view. Endoscopic ultrasound with radial array transducer UM160 (5-20 MHz), showing increased wall thickness for the presence of a mass with inhomogeneous echogenicity, invading all the layers of the wall and minimal infiltration of the perirectal fat. T: Tumor; Red arrow: Infiltration of the perirectal fat.

technological innovation and the evolution of the therapeutic strategies[7-10] (Figure 1).

EUS Accuracy in staging rectal cancer T staging

At the time of EUS, RC usually appear as a hypoechoic mass, with loss of the normal echo-layers of the wall, which is inhomogeneous and irregular because of the fusion of the layers infiltrated by the tumor[5,9-11]. According to the infiltration depth, there are four different echoendoscopic T stages (uT) (Table 3, Figures 1-5). In patients with RC, EUS assesses the tumor penetration depth into the rectal wall, with an overall accuracy for T stage of about 84%, ranging from 63% to 96%, while the reported accuracy of CT and MRI are 65%-75% and 75%-85%, respectively (Table 4)[12-45]. In a systematic review of 31 articles published over a period of 20 years, Skandarajah *et al*[46] reported that EUS has an overall accuracy of 82% for T stage and it is useful for discriminating early superficial RC. In another review of 42 studies, which analyzed the accuracy of EUS in patients with RC, confirmed by pathological exam of the surgical specimen, Puli *et al*[47,48] concluded that EUS has a sensitivity of 81%-96% and a specificity of 91%-98%, showing a higher sensitivity for LARC (95%), compared with early cancer (88%). In a multicenter, prospective, study conducted in 384 hospitals in Germany over a 8-year period, Marusch *et al*[49] analyzed the diagnostic accuracy of rectal EUS in the clinical staging of 7000 patients with RC who had not received NAT. This allowed uT *vs* pT comparison, which showed a uT-pT correspondence of 65%. The latter was related to the hospital volume, with uT-pT correspondence of 63% for hospitals undertaking ≤10 EUS/year, 65% for those performing 11-30 EUS/year,

Table 3 T staging (uT) of rectal cancer at endoscopic ultrasound, according to the infiltration depth

uT1 = tumor invasion limited to the mucosa and the submucosa; this is further divided into T1m, if the tumor infiltrates the mucosa, with normal muscolaris mucosa, and T1sm, when there is submucosal invasion (Figures 1 and 7)
uT2 = tumor infiltration of the muscolaris propria, with the tumor mass extended through the first 4 layers of the rectal wall. The outer layer corresponding to the muscolaris propria is smooth, meaning that the tumor is still limited to the rectal wall (Figure 2)
uT3 = tumor invasion of the perirectal fat, with an irregular 4th layer, which means that the tumor has spread outside the rectal wall (Figures 3 and 4)
uT4 = tumor infiltration of adjacent structures and organs, which are strictly connected to the rectal hypoechoic mass (Figure 5)

From ref.[9].

Table 4 Endoscopic ultrasound accuracy of T and N stage of rectal cancer

Ref.	Pts no.	T Stage	N Stage	P/R	Tipe of EUS probe
Saitoh *et al*[13]	88	90%	75%	-	Flexible, radial, (7 MHz) Rigid, radial (5-7.5 MHz)
Feifel *et al*[14]	79	89%	-	P	Rigid, linear (3-7 MHz)
Yamashita *et al*[15]	122	78%	-	R	Rigid, linear (5.5-7 MHz)
Beynon *et al*[16]	100	93%	83%	-	Rigid
Rifkin *et al*[17]	102	72%	81%		Rigid, radial (7 MHz)
Hildebrandt *et al*[18]	113	-	78%	P	Rigid, radial (7 MHz)
Tio *et al*[19]	91	88%	-	-	Rigid
Katsura *et al*[20]	120	92%	-		Rigid, radial, (7 MHz)
Glaser *et al*[21]	154	86%	81%	P	Rigid, radial (7 MHz)
Herzog *et al*[22]	118	89%	80%	P	Rigid, radial (7 MHz)
Cho *et al*[23]	76	82%	70%	P	Flexible, radial (7 MHz)
Thaler *et al*[24]	36	88%	80%	P	Rotating wall transducer IR 1510 AKTM (Kretz) (5, 7.5, 10 MHz)
Nielson *et al*[25]	100	85%	-	-	Probe (7 MHz)
Sailer *et al*[26]	160	77%	83%	P	Rigid
Nishimori *et al*[27]	70	76%	69%		Flexible
Norton *et al*[28]	121	92%	65%	P	Flexible, radial (7.5-12 MHz)
Kim *et al*[29]	89	81%	63%		Rotating transducer (7.5 MHz)
Marone *et al*[30]	63	81%	70%	R	Flexible, radial (7.5-12 MHz)
Akasu *et al*[31]	154	96%	72%	R	Flexible, radial (7.5-12 MHz
Garcia-Aquilar *et al*[32]	545	69%	64%	P	Rigid, radial (7-10 MHz)
Harewood *et al*[12]	80	91%	82%	P	Flexible, radial (7.5-12 MHz)
Marusch *et al*[33]	422	63%	-	P	Rigid
Kauer *et al*[34]	458	69%	68%	R	Probe (7.5-10 MHz)
Vila *et al*[35]	120	83%	72%	P	Flexible, radial
Landman *et al*[36]	938	-	70%	P	Probe (10 MHz)
Halefoglu *et al*[37]	34	85%	76%	P	Probe (7-10 MHz)
Lin *et al*[38]	192	86%	78%	P	Flexible, radial (7.5-12 MHz)
Fernández-Esparrach *et al*[39]	90	95%	65%	P	Flexible, radial (5-20 MHz)
Ünsal *et al*[40]	31	80%	70%	R	Radial
Zhu *et al*[41]	110	91%	85%	-	Rigid, radial (5-10 MHz)
	4976				
Mean		84	74		
Range		63-96	63-85		

uTN stage compared with pTN stage; no previous neoadjuvant therapy (NAT). P: Prospective; R: Retrospective; Pts: Patients; EUS: Endoscopic ultrasound.

and 73% for hospitals where more than 30 EUS/year were performed. Furthermore, the poorest uT-pT correspondence was found for T2 and T4 RC, with understaging occurring in 18% of cases and overstaging in 17% of patients[49]. These results were similar to those of a previous multicenter, prospective, study conducted by the same authors who reported that EUS had overall accuracy of 63% for T staging of RC. The diagnostic accuracy was 51% for pT1 RC, 58% for pT2 lesions, 73% for pT3 tumors, and 44% for pT4 cancers, with overstaging in 24% of cases and understaging in 13% of patients[33]. According to the results of both studies, EUS staging of RC in clinical practice does not have the same accuracy reported in the literature and the authors believe that EUS is a useful tool for guiding the therapeutic strategy of RC only when it is performed by experts[33,49]. Lower accuracy of EUS was also reported in a series of 545 patients with RC, where this method showed an overall accuracy of 69% for T stage and 64% for N stage[32]. A possible limitation of this study was the exclusion from the analysis of those patient who underwent NAT. This could have affected the accuracy of EUS for T stage, especially for T3 RC which is usually visualized the best at the time of EUS. Another pitfall of the study could be the different experience of the operators, which influenced the

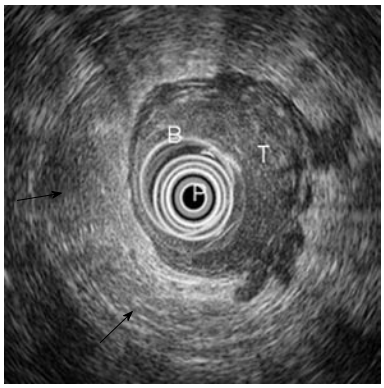

Figure 4 Stage T3 rectal cancer: Ultrasonographic view. Endoscopic ultrasound shows advanced cancer of the rectum with large hypoechoic and inhomogeneous thickening of the rectal wall, loss of the five-layered wall structure and deep infiltration of the perirectal fat. Endoscopic ultrasound with radial array transducer UM160 (5-20 MHz). B: Ballon; P: Transducer; T: Tumor; Black arrow: Perirectal fat.

accuracy of EUS, as highlighted by Marusch *et al*[33,49]. Indeed, Kauer *et al*[34] observed that there is a high inter-observer variability (61%-77%), according to the experience of the operator. These authors reported that EUS has an overall accuracy of 69% for T staging of RC, with T3 tumors better (86%) staged and T4 cancer the least (36%) accurately classified. Differentiating T1 from T2 was difficult in this retrospective series, where overstaging (19%) was much more frequent than understaging (12%)[34].

Superficial RC limited to the mucosa can be resected endoscopically. Whenever a trans anal resection is planned, it is recommended to perform a preoperative EUS staging of the tumor, as suggested by Kneist *et al*[50]. These authors evaluated the accuracy of EUS in 552 patients undergoing trans anal excision of RC and they reported that EUS has a sensitivity of 95% and a positive predictive value of 93% in staging early RC[50]. Similarly, Glancy *et al*[51] demonstrated that EUS has an overall accuracy of 95% in staging early superficial RC suitable for local treatment. This high accuracy rate was confirmed by Zorcolo *et al*[52], who reported that EUS allows a precise distinction between early and advanced RC, with sensitivity of 96%, specificity of 85%, and overall accuracy of 94%. The latter is lower in our personal series, where we reported that EUS has an accuracy rate of 81% in differentiating early (T1) from advanced RC (T2), with the same occurrence of overstaging and understaging (9%)[30]. Finally, a recent meta-analysis analyzed the results of 11 studies, which discussed the efficacy of preoperative EUS in staging patients with early RC: the sensitivity of EUS in diagnosing T0 was 97%, with a specificity of 96%[48]. These data support the conclusion that EUS accurately diagnoses T0 RC, helping physicians to choose endoscopic treatment for patients with early RC.

Several studies have shown that EUS accuracy for T stage is strictly related to the depth of infiltration and the accuracy is lower for T2 stage than for early

Table 5 Accuracy of endoscopic ultrasound for each single T stage

Ref.	Year	No.	pT1	pT2	pT3	pT4
Akasu *et al*[31]	1997	164	86%	56%	93%	75%
Marone *et al*[30]	2000	63	80%	78%	84%	80%
Lin *et al*[38]	2011	192	86%	94%	86%	65%
Fernández-Esparrach *et al*[39]	2011	90	95%	76%	76%	95%
Zhu *et al*[41]	2013	110	93%	88%	88%	96%
Range		619	80%-95%	56%-94%	76%-93%	65%-96%
Mean			88%	78.4%	85.4%	80.2%

uTN stage compared with pTN stage; No previous neoadjuvant therapy (NAT).

(T1) or advanced (T3-4) RC (Table 5)[31,30,38,39,41]. These assumptions are supported by the results of another meta-analysis which examined 42 studies, with a total number of 5039 patients: the pooled sensitivity and specificity of EUS for T1 stage was 88% and 98%, respectively; for T2 stage, EUS had pooled sensitivity and specificity of 80% and 96%, respectively; for T3 stage, the pooled sensitivity and specificity of EUS were 96% and 91%, respectively; finally, for T4 stage, EUS had pooled sensitivity of 95% and specificity of 98%, respectively. The authors of this meta-analysis concluded that EUS should be the imaging method of choice for T staging of RC[47]. Despite the high accuracy that EUS has for T stage, this imaging method is not capable of differentiating peri-tumoral inflammation and edema from neoplastic infiltration. One of the mayor limits of EUS, is overstaging T2-T3 RC, with the risk of overtreatment[30,32,53-59]. In T3 stage cancer infiltrates the rectal wall up to the perirectal fat, with different penetration depth. The precise evaluation of the infiltration depth into the perirectal fat is an important prognostic factor for T3 RC. Harewood *et al*[56] demonstrated that T3 RC are not all equal, with minimally invasive disease carrying a more favorable prognosis. In a series of 42 patients with T3 RC, who underwent surgery without receiving NAT, EUS overstaged the minimally invasive (invasion < 2 mm beyond muscolaris propria at EUS) T3 cancer in 50% of cases, in comparison with advanced (invasion > 2 mm beyond muscolaris propria at EUS) T3 RC. These were overstaged only in 4% of cases. The reported EUS accuracy for differentiating T1/T2 and T3/T4 was 88%, with an overall accuracy of 76% for T stage and 63% for N stage. Since the overstaging rate of minimally invasive T3 RC was high, the authors recommend to exclude these patients from NAT, which should be used only for patients with advanced T3 RC[56]. These data highlight the importance of proper measurement of the infiltration depth of RC at EUS, because this information is crucial for establishing the prognosis and guiding the multimodal therapy. According to Esclapez *et al*[57], an ultrasonographic maximum tumor thickness cutoff point of 19 mm could be useful to classify patients preoperatively and select them for primary surgery or

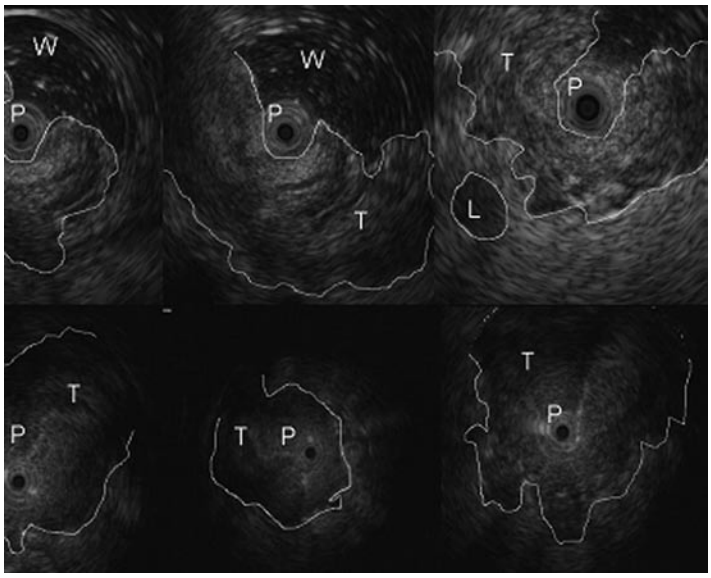

Figure 5 Stage T4 rectal cancer: Miniprobe ultrasonographic view. Endoscopic ultrasound with radial miniprobe (12 MHz) shows an advanced, stenotic rectal cancer with large hypoechoic and inhomogeneous thickening of the rectal wall, loss of the five-layered wall structure and invasion of adjacent organs. T: Tumor; P: Miniprobe; L: Metastatic lymph node; W: Water.

Table 6 N staging at endoscopic ultrasound, according to the number of metastatic lymph nodes

uN1 = 1-3 positive nodes
uN2 = More than 4 metastatic lymph nodes

From ref.[9].

NAT. Indeed, these authors showed that tumor thickness of more than 19 mm in uT3 RC was associated with a higher rate of postoperative recurrence[57].

In approximately 14% of RC there is a stricture that cannot be traversed by the echoendoscope, leading to inaccurate staging and potential errors because EUS evaluates only the distal portion of the cancer[5,50,51]. The presence of a stricture is a limitation for staging RC at EUS: this determines not only inaccurate T staging, but also incomplete N staging because perirectal lymph nodes cannot be examined. Moreover, a stricture often does not permit perpendicular position of the ultrasonographic beam and an adequate focal distance of the probe from the tumor leading to misstaging. All these pitfalls can lead to an incorrect staging of the tumor, which can then affect the therapeutic strategy[5]. Marone *et al*[60] reported that EUS has an overall accuracy of 83% in a series of 127 patients with RC, who underwent surgery without receiving NAT. When the T stages were analyzed separately, EUS showed an accuracy of 76% for T1, 72% for T2, 91% for T3 and 67% for T4 stages. Overall, EUS misstaged T in 16% of cases, with 11% of overstaging and 5% of understaging errors. The presence of a stricture lowered the accuracy rate of EUS for T stage from 93% to 56%; similarly the distance of RC from the anal verge affected the accuracy of EUS for T stage, which decreased from 92% for tumors located > 5 cm from the anal verge to 67% for cancer sites < 5 cm from the anus[60]. Therefore, the presence of a stricture and tumor distance of less than 5 cm from the anal verge are two factors limiting the accuracy of EUS in staging RC.

Recently, the capability of EUS in assessing MRF and predicting the circumferential resection margin (CRM) of RC has been evaluated by Granero-Castro *et al*[61]. In a series of 76 patients with mid-low RC, preoperative staging was performed by means of both MRI and EUS and the patients underwent surgery without receiving NAT. A comparison between preoperative (EUS and MRI) CRM status and pathologic examination after TME surgery was eventually made: overall accuracy of EUS and MRI in assessing CRM status was 84% and 92%, respectively, with similar negative predictive values (97%). When focusing on low RC, the overall accuracy of EUS increased to 87%, whereas MRI lowered its accuracy rate to 87%, with a negative predictive value of 96% for both imaging methods. These data suggest that EUS should be used together with MRI for predicting CRM involvement in low anterior RC.

N STAGING

EUS allows the assessment of perirectal lymph nodes for metastatic infiltration: these are metastatic when they appear as roundish or oval, homogeneous echo-poor nodules with a short axis of at least 5 mm (Figure 6)[5,7,9,10]. According to the number of metastatic lymph nodes, there are two different N (uN) echoendoscopic stages (Table 6).

The incidence of malignant metastatic lymph nodes in patients with RC is strictly related to T stage and varies from 6%-11% for T1, 10%-35% for T2 and 26%-65% for T4 RC[3,5,7,8]. Determination of lymph nodes involvement during EUS is difficult and less precise, with a variable accuracy of 63%-85% (Table 4)[12-45]. Kauer *et al*[34] reported that EUS has an overall accuracy of 68% in diagnosing metastatic lymph nodes associated to RC, with a sensitivity of 52% and a specificity of 82%. A recent meta-analysis of 35 published studies evaluated the accuracy of EUS in diagnosing metastatic lymph nodes of patients with RC[7]. EUS showed sensitivity of 73% and specificity of

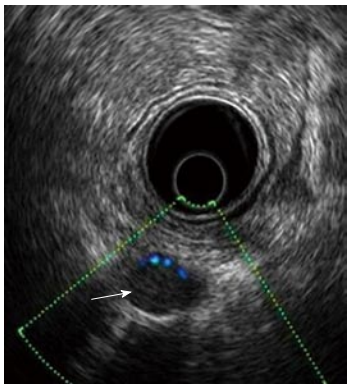

Figure 6 Perirectal metastatic lymph node: Ultrasonographic view. Endoscopic ultrasound with radial array transducer UM160 (5-20 MHz). White arrow: Perirectal metastatic lymph node.

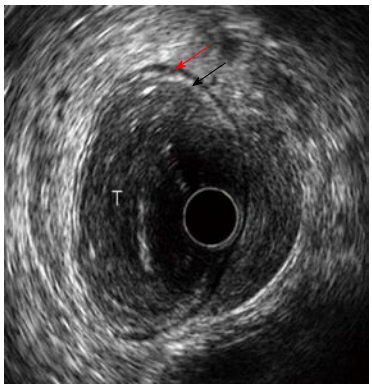

Figure 7 Stage T1 rectal cancer: miniprobe ultrasonographic view. Endoscopic ultrasound with radial miniprobe (12 MHz), showing a small tumor located within the mucosa and superficial submucosal layers, with preservation of the outer layers of the rectal wall. T: Tumor; Red arrow: Muscularis propria layer; Black arrow: Submucosa layer.

76% for N staging and the data analyzed supported the hypothesis that EUS is more accurate in excluding nodal invasion, rather than diagnosing it. Indeed, determination of nodal invasion is less accurate because of difficulty in discriminating between inflammatory and metastatic nodes, which leads to false positive diagnosis and possible overtreatment. The size of lymph nodes could be indicative of neoplastic invasion: nodes greater than 5 mm can be metastatic in 50%-70% of cases, whereas those smaller than 4 mm harbor malignancy in less than 20% of cases[16]. These data have been partly confirmed by Akasu *et al*[59], which observed that the incidence of nodal metastases is strictly related to the size of the lymph node in patients with RC: 9.5% for nodes less than 2 mm; 47% when the lymph node measures 3-5 mm and 87% for nodes larger than 6 mm. However, despite this correlation between size of the node and incidence of metastatic invasion, there are several reports of metastatic lymph nodes smaller than 5 mm in patients with RC, with an overall incidence of 18%[20,62-64]. There is a clear correlation between T stage of RC and risk of metastatic invasion of perirectal lymph nodes. The more advanced the RC, the higher the risk of metastatic lymph nodes: less than 5% with T1m and more than 80% with T3 RC[65,66]. The latter results were confirmed by Landmann *et al*[36], who reported that the accuracy of EUS for N staging decreases from 84% in pT3 RC to 48% in pT1 cancers. The low detection rate of metastatic lymph nodes in T1 RC is probably explained by the fact that in these cancers possible metastatic nodes are small, with a size variable from 0.3 to 3.3 mm. Therefore, EUS can misstage early RC where the presence of neoplastic invasion is possible even in small lymph nodes: this exposes a patient who undergoes local excision to pelvic recurrence because of misstaged early cancer. To avoid this, it was proposed to decrease the dimensional cut off of 5 mm to 3 mm, with increased sensitivity, but reduced specifity and overall accuracy for N staging at EUS. Indeed, with a 5 mm cut off, EUS has an overall accuracy of 89% for N stage in T1 RC, with sensitivity of 39% and specificity of 89%. On the other hand, reducing the cut off to 3 mm, EUS shows an increased (75%) sensitivity for N stage in T1 RC, with significantly reduced specificity (49%) and overall accuracy (53%)[31,36,45]. These data confirm that the size of the lymph node cannot be the only parameter to be used for assessing neoplastic nodal invasion in patients with RC[36,45,59,67].

EUS accuracy for N staging can be ameliorated associating other parameters to the dimensional criterion used for defining malignant lymph nodes. These ultrasound features include lymph node short axis size, echogenicity, shape, and border. Among them, those which better correlate with malignancy are: enlarged node ($\geqslant$ 1 cm in short axis), hypoechoic appearance, round shape, and smooth border[11]. The presence of two or more features is associated with EUS sensitivity of 77%, specificity of 29%, and accuracy of 54%. Three or more features give EUS a sensitivity of 68%, and a specificity of 52%, with an accuracy of 61%. Finally, with four or more features EUS shows sensitivity of 23%, specificity of 100% and accuracy of 61%. Simultaneous presence of all these features in a lymph node is related to 100% of positive predictive value, but this is a rare occurrence (less than 25% of cases)[65]. Despite all the efforts to find the right criteria, determination of lymph nodes involvement during EUS is less accurate and useful than T staging. The most important limitation is the difficulty in both discriminating between inflammatory and metastatic lymph nodes and recognizing small metastatic nodes. These limitations can be overcome by EUS-guided FNA, which allow sampling of the suspicious perirectal nodes, leading to correct N staging. However, even with EUS-guided FNA, the overall accuracy of EUS for N stage remains low, because distant metastatic lymph nodes are undetectable by EUS, since they are out of the scanning area. Indeed, incomplete evaluation of the iliac nodes is the most frequent cause of incorrect staging of patients with RC, leading to mistreatment in 6% of cases[16,45,62,63,66-70]. Recently, Kim *et al*[64] suggested that tridimensional EUS could obviate the low accuracy of

EUS for N staging. However, these results need to be confirmed.

PITFALLS IN STAGING RECTAL CANCER

Sometimes, EUS staging of RC can be incorrect and the cancer is misstaged because of overstaging rather than understaging. At EUS, hypoechoic fibrosis and/or inflammation cannot be differentiated by the hypoechoic mass of the tumor leading to overstaging. On the other hand, understaging occurs when the microscopic neoplastic invasion into the next layer is undetectable during EUS, especially when an entire layer is distended by the invading tumor which abuts into the adjacent layer, without showing clear infiltration. Moreover, a stricture which cannot be traversed limits the accuracy of EUS, while location, shape and size of the tumor can alter the direction of scanning and result in overstaging. Similarly, the T stage can influence the results of EUS staging, as in the case of T2 cancer for which EUS staging is less accurate. Finally, EUS is operator dependent and there is a substantial difference in accuracy between novice and experienced endoscopists, since the latter have learned over the time how to avoid technical problems, like oblique scans, overfilling of the balloon and inadequate water filling of the rectum[5].

MINIATURE ULTRASONIC PROBES

Dedicated echoendoscopes have some limitations due to the fact that combining endoscopy and ultrasonography in one instrument increases the diameter of such scopes (12-13 mm). Because of the large diameter, complete passage of severe strictures is often impossible. Furthermore, conventional EUS often requires a second examination, separate from the previous routine endoscopy. The miniature ultrasonic probes (diameters about 2 mm; frequencies 12-20-30 MHz) can be passed through the working channel of standard endoscopes to provide high frequency ultrasound images (Figures 1, 5 and 7). These miniprobes allow simultaneous endoscopic and ultrasonographic evaluation of the lesions, complete assessment of strictures that cannot be traversed by conventional echoendoscopes and accurate staging of superficial lesions[8]. The rarity of lymph node metastases in T1m or T1sm 1 RC supports the indication for endoscopic resection of these lesions, which require accurate preoperative staging. This has been performed by Harada *et al*[71], using a 15-MHz ultrasound miniprobe in 35 patients with submucosal invasive colorectal cancer. The accuracy of miniprobes was low (37%) in categorizing the different depth of submucosal invasion, while it was high (86%) in differentiating between mucosal/superficial submucosal infiltration (M and SM) and deep submucosal invasion (SM2, SM3, MP, and S)[71]. These data support the indication for ultrasonographic staging of early colorectal *via* miniprobes in order to plan endoscopic resection. In a prospective study of 131 consecutive patients with adenocarcinoma or broad-based polyps of colorectum, EUS accuracy for T staging with miniprobes was 96%, with 4% of overstaging and 2% of understaging[72]. The overall accuracy of N staging using miniature ultrasonographic probes was 87% (sensitivity 95%, specificity 71%, positive predictive value 87%, negative predictive value 88%). These data confirm that miniprobe ultrasonography has a high overall accuracy for both T and N staging of colorectal cancer and it may be useful for selecting patients fit for local resection. Finally, Gall *et al*[73] conducted a meta-analysis of ten studies with a total of 642 patients to evaluate the accuracy of miniprobe EUS in staging RC. The pooled sensitivity and specificity were respectively 91% and 98% for T1 cancers, 78% and 94% for T2 tumors, 97% and 90% for T3/T4 RC. Eight percent of T1/T2 cancers were upstaged to T3/T4 tumors and 5% of T3/T4 RC were downstaged. Finally, the pooled sensitivity and specificity for N staging were 63% and 82%, respectively. These data confirm that miniprobe EUS is highly effective for clinical staging of RC, allowing identification of those patients who may be suitable for nonsurgical treatments.

EUS-FNA for staging rectal cancer

According to a recent study, EUS-FNA is useful for assessing primary and metastatic rectal cancers. In this setting, EUS-FNA had sensitivity, specificity, positive and negative predictive values of 89%, 79%, 89% and 79% respectively. This technique improves staging of suspected nodal or distant metastases, but it is indicated only when cytologic results will change the therapeutic strategy[74,75]. This is the conclusion of Harewood *et al*[12], who reported that standard EUS modified therapeutic strategy of LARC in 25 patients, while only in 1 case EUS-guided FNA was crucial for choosing the correct therapy. According to Shami *et al*[76], EUS-guided FNA has a clinical impact of 19% on staging and subsequent management of patients with RC. In this cancer the incidence of lymph node metastases is strictly related to T stage, with a higher risk of nodal metastasis with more advanced T stages. Peritumoral lymph nodes are highly predictive of cancer invasion: the majority of perirectal nodes detected by EUS are metastatic in patients with RC. This is the explanation for the low clinical impact of EUS-guided FNA in staging patients with RC. Moreover, T3 RC is an indication for NAT, independently from N stage, which has no influence on the therapeutic strategy of patients with LARC[12,75]. EUS-guided FNA seems to offer the most potential for the management of T1-2 stage disease, where the presence of metastatic perirectal lymph nodes modifies the therapeutic strategy. Therefore, its use should be confined to this subgroup of patients[12,67,75,77]. This indication is confirmed by Levy and colleagues who evaluated the role of EUS guided FNA in N staging of 32 patients with RC and suspicious iliac lymph nodes[70]. In approximately 50% of cases, the sampled nodes were positive for neoplastic invasion and determined

a change in the therapeutic strategy. Of note, CT scan did not detect half of the lymph nodes which were malignant at EUS–guided FNA. These data support the need to properly investigate the iliac lymph nodes during staging of patients with RC.

EUS in comparison with CT and MRI for staging rectal cancer

In RC, EUS has been compared with digital examination, CT scan and MRI. EUS is superior to rectal digit examination, showing a higher accuracy (91%-92% *vs* 52%-60%). CT scan is unable to correctly define the single layers of the rectal wall and therefore is not indicated for T staging of RC, while it is crucial for diagnosing distant metastases[77]. EUS is more accurate than CT scan in loco-regional staging of RC, showing an accuracy rate of 87% for T stage and 62% for N stage, compared to that of CT scan (76% for T stage and 62% for N stage)[6,63,77]. Similarly, EUS was considered more precise (85% *vs* 77%) than MRI in determining the T stage of RC[77]. However, recent technology has allowed MRI to define the status of MRF and subsequently delineate the possible threatened CRM, making this imaging method crucial for loco-regional staging of RC[44]. A systematic review of 31 articles published over a 20-year period evaluated the role EUS and MRI in loco-regional staging of RC[46]. While EUS is more useful for staging early RC, with an overall accuracy of 82%, MRI is indicated for staging advanced disease, providing a better definition of both the mesorectum and the MRF. The latter is crucial for choosing the best therapeutic strategy. In another systematic review, Kwok *et al*[78] evaluated the role of CT scan, EUS and MRI in the preoperative staging of RC. In determining T stage, EUS was more accurate than CT scan and MRI. The latter, with the adjunct of an endorectal coil, has the same accuracy of EUS for T stage, while it is more precise in determining nodal metastases. Both EUS and MRI with an endorectal coil are limited by the presence of strictures when staging RC. An MRI with a pelvic phased-array coil is not invasive, has a high spatial resolution and appears to be a promising image method for loco-regional staging of RC[37,79]. Yimei *et al*[80] evaluated the reference value to surgeons of both EUS and MRI, reporting that EUS has higher sensitivity (P = 0.044) and specificity (P = 0.039) than MRI, showing elevated accuracy for early stage RC. This makes EUS staging crucial for the identification of those patients who are suitable for less invasive surgery. On the other hand, MRI is useful for the proper diagnosis of LARC which need to undergo multimodal treatment. MRI has been preferred to EUS because it is better tolerated, can be used in stenotic tumors and it can define the infiltration depth of MRF and assess the CRM. The latter is a crucial information for choosing the best therapeutic strategy. However, Cesmeli *et al*[81] point out that EUS is still important in the preoperative staging of early RC, because of its ability to delineate the different layer of the rectal wall, allowing the selection of those patients suitable for local excision. EUS can also improve N staging by performing FNA, whenever N stage can change the therapeutic strategy[81]. In a series of 49 patients, EUS and MRI showed similar accuracy (88%), in predicting pathologic CRM of low RC[82]. Therefore, EUS and MRI are complementary and should be both used for preoperative staging of patients with RC. The fact that staging accuracy is improved by combination of MRI and EUS is supported by the results of a recent study in which the authors compared feasibility and accuracy of both 1.5 Tesla MRI and three-dimensional (3D) EUS for staging patients with RC before and after preoperative chemotherapy[83]. The stage accuracy by MRI, 3D-EUS and the combination of MRI and 3D-EUS was 65%, 70% and 74%, respectively, before chemotherapy and 65%, 78% and 83%, respectively, after chemotherapy. The post chemotherapy staging by MRI alone was improved by a combination of MRI assessment of the lymph nodes and 3D-EUS assessment of the perirectal tissue penetration (P= 0.046). These results confirmed that staging accuracy is improved by combining MRI with EUS.

According to the data of the literature, EUS and MRI are superior for T- staging, while CT and PET/CT are the main stay for metastatic work-up. EUS is superior in staging early cancers and defining the infiltration of the anal sphincter, while MRI is excellent for staging T4 and clarifying both the MRF status and the infiltration of the elevator muscle; CT and EUS are complementary, rather than competitive in loco-regional and distant staging of RC[84-86]. Therefore, the best approach for RC is the combination of all different imaging methods, which are complementary: they should be utilized according to the clinical condition of the patient, the availability of each single test and the personal preference. Cost-benefit studies have demonstrated that the most cost-effective association of imaging methods is EUS plus CT scan[87].

Accuracy of eUS in staging locally advanced rectal cancer after chemoradiation

Loco-regional staging of RC after NAT is affected by local effects of the treatment which determines peritumoral inflammation, edema, necrosis, and fibrosis of the neoplastic tissue. This reduces the accuracy of EUS, leading to overstaging errors (Table 7)[88-90]. EUS staging of RC after NAT is inaccurate, as shown by Vanagunas and colleagues in a series of 82 patients with LARC[90]. After NAT, EUS correctly predicted complete response to chemoradiation in only 63% of cases and its overall accuracy for pathologic T-stage was 48%, with 14% of understaging and 38% of overstaging. These data suggest that EUS staging of RC after NAT is inaccurate, and its routine use for restaging patients should be discouraged. Similary, Marone *et al*[91] and Maor *et al*[92], demonstrated that EUS restaging of LARC after NAT has low accuracy. Both studies compared two groups of patients with LARC: one operated on without receiving NAT and another one who underwent surgery after NAT. The results of the studies were similar, showing

Table 7 Accuracy of endoscopic ultrasound in staging locally advanced rectal cancer after chemo-radiation

Ref.	Year	No.	T	Mistakes		N
				Over	Under	
Vanagunas *et al*[90]	2004	82	48%	38%	14%	77%
Mao *et al*[92]	2006	25	72%	8%	12%	80%
Radovaanovic *et al*[94]	2008	44	75%	18%	7%	68%
Marone *et al*[91]	2011	85	61%	28%	7%	59%
Mean		236	64%	23%	10%	71%
Range			48%-75%	8%-38%	7%-14%	59%-80%

uTN stage compared with pTN stage; Previous neoadjuvant therapy (NAT). Over: Overstaging; Under: Understaging.

that EUS restaging of LARC after NAT has low accuracy (60%-70%) and is able to predict a complete response in only 50% of cases. Further confirmation of this low accuracy came from a study where the authors compared sensitivity and specificity of EUS and MRI, in patients with LARC after NAT[93]. Both EUS and MRI had low accuracy (46% *vs* 44%) for T stage of LARC after NAT. Better accuracy of EUS restaging was reported by Radovanovic and colleagues who demonstrated that EUS has an accuracy of 75% for T stage after NAT, with 18% of overstaging and 7% of understaging[94]. The majority of overstaging occurred in patients with uT3 tumors, eventually found to have pT0-pT2 RC. EUS was able to correctly stage only one of the patients who had complete response after NAT. Despite the fact that EUS restaging accuracy for LARC was higher, the results of this study confirm that EUS is not useful after NAT.

EUS DIAGNOSIS OF LOCAL RECURRENCE IN PATIENTS OPERATED ON FOR RC

After surgery, local recurrence of LARC has an incidence of about 25%, which decreases to 10%, if NAT has been administered before surgery (10%). The risk of local recurrence is strictly related to T stage and it is higher for more advanced T stages, occurring mostly in the first two postoperative years[95-97]. Early identification of local recurrence and its immediate treatment could potentially improve patients survival. EUS has a high sensitivity, but low specificity in defining local recurrences. A limitation of EUS is its inability to clearly differentiate postoperative changes and benign lesions from cancer recurrence[95-97].

EUS-guided FNA increases the specificity of EUS (57% *vs* 97%). To date, there are no guidelines which define the role of EUS in the follow-up of patients operated on for RC, since there are no clear data that echoendoscopic follow-up and/or EUS-guided FNA influence patients survival after surgery for RC[95-97].

Future perspectives

The recent development of new technology for EUS generates novel applications for echoendoscopic diagnosis and staging of gastrointestinal tumors. Tridimensional EUS (3D-EUS) seems to improve the spatial visualization of RC allowing better evaluation of tumor resectability[98]. 3D-EUS is more accurate than 2D-EUS and CT scan in T staging of RC, for which the three imaging methods have an accuracy of 78%, 69% and 57%, respectively[64]. 3D-EUS visualization of the outer margin of the rectal wall is well related to neoplastic infiltration and metastatic nodal invasion diagnosed by pathological examination of the surgical specimen. Some data suggest that 3D-EUS allows correct visualization of MRF, which was not well delineated by 2D-EUS. Proper measurements of the tumoral area before and after NAT could be a useful criterion for evaluating the response of RC to NAT[98-100].

Elastography is a new technique which has been recently added to the armamentarium of EUS and allows measurement of tissue elasticity useful to differentiate normal from tumoral tissue. Preliminary data have shown that simultaneous elastography during EUS improves its accuracy for T staging of RC[98]. Finally, EUS with contrast medium administration (contrast harmonic EUS or CH-EUS) and simultaneous Doppler visualization allows the study of tumoral vascularization and irroration. These data are useful for the evaluation of both tumoral response to NAT and efficacy of anti-angiogenic treatments, because this combination of techniques shows accurately those changes in the vascular pattern of RC which reflect its response to therapy. Miyata *et al*[101] evaluated the micro-vascularization of lymph nodes by means of CH-EUS in order to differentiate benign from malignant nodes: sensitivity, specificity, and accuracy of CH-EUS for malignant lesions were 95%, 97%, and 97%, respectively. These data show that CH-EUS is accurate in detecting minimal changes of tumoral vascularization in lymph nodes which harbor neoplastic invasion. This information could address the correct use of FNA-guided EUS, whenever it is needed[101,102]. To date, there are still little data on the clinical application of simultaneous use of these new methods together with standard EUS. Therefore, further clinical trials are needed for the evaluation of indication, accuracy, clinical impact and limitation of CH-EUS and Doppler-EUS.

CONCLUSION

Prognosis of patients with RC is strictly dependent from the stage of the disease at the time of diagnosis. Multidisciplinary approach to patients with RC is the standard of care in order to reduce local recurrences and improve survival outcomes. A strong cooperation among members of a multidisciplinary team is mandatory to improve patients outcomes, because the latter are strictly dependent from the chosen therapeutic strategy. This is the results of an accurate loco-regional staging, especially if metastatic disease has been excluded. CT scan, MRI, PET are the imaging method used for staging RC and give information on both loco-regional and distant disease. In the last decades, EUS has been

used in combination with these imaging methods for staging RC in order to better define both the T stage and the involvement of loco-regional lymph nodes. EUS has significant clinical impact on patients with RC, allowing to identify those who are candidate for local excision and/or direct surgery, without receiving NAT. LARC is well defined by EUS, even if the identification of both MRF and possible threatened CRM is more precisely obtained by MRI. The latter lacks accuracy for mid - low anterior RC, which could be better staged by EUS, as recent data suggested. Therefore, EUS and MRI are complementary and they should be used simultaneously, with a significant increase of the overall accuracy for the T stage of RC. EUS is superior in identifying early cancers and infiltration of anal sphincter, while MRI is excellent in recognizing T4, in relationship to MRF infiltration of the elevator muscle. While EUS and MRI are superior for T- staging, CT and PET/CT are the main stay for metastatic work-up.

Restaging after NAT is mandatory for establishing a correct prognosis of patients with RC and choosing the most effective treatment. This should be tailored according to the results of NAT, whose experimental drugs can be tested in clinical trials and evaluated by means of restaging RC. The latter is not performed by means of EUS because this imaging method has low accuracy in restaging RC, due to the difficulty in differentiating inflammation and tissue fibrosis from actual residual cancer.

EUS has low sensitivity, but high specificity in diagnosing local recurrences in patients operated on for RC, because it is unable to differentiate perianastomotic surgical changes from recurrent cancer. In this case, EUS-guided FNA increases specificity, but its use in clinical practice has not been standardized. Probably, high resolution images and guided FNA are the best combination for improving EUS accuracy in naive and recurrent RC.

Technological improvements, like elastography, contrast medium administration, high ultrasonographic frequencies and 3D, will certainly improve EUS accuracy and broaden its clinic use; however there is a need for further studies which should confirm the potential of these new technologies.

In conclusion, accurate EUS staging is crucial for the best treatment of each single patient with RC and especially LARC, because patients can be understaged or overstaged, with subsequent mistreatments.

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REVIEW

Endotherapy of leaks and fistula

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Abstract

Perforations, leaks and fistula involving gastrointestinal (GI) tract are increasing encountered in clinical practice. There is a changing paradigm for their management with surgical approach being replaced by conservative approach including endoscopic therapy. Clips (through the scope and over the scope) and covered stent are front runners for endotherapy for GI leaks and fistula. Over the scope clips introduced recently, can treat larger defects compared to through the scope clips. Covered stents are suited for larger defects and those associated with luminal narrowing. However cervical esophagus, gastro-esophageal junction, stomach and right colonic lesions may be better for clip therapy rather than stenting. Recent developments in this field include use of endovac therapy which consists of a sponge with suction device, biodegradable stent, use of fibrin glue and some endo-suturing device. Conservative therapy with no surgical or endoscopic intervention, may be suitable for a small subset of patients. An algorithm based on location, size of defect, associated stricture, infection and available expertise needs to be developed to reduce the mortality and morbidity of this difficult clinical problem.

Key words: Fistula; Leak; Perforation; Post operative; Endoscopy; Endoscopic; Surgery; Stent; Suture; Endoclip; Clip

Core tip: Gastrointestinal (GI) leaks and fistula are increasingly recognized in our day to day practice. While these patients were earlier managed by surgical interventions, more and more such patients are now considered for endoscopic therapy. Endotherapy for GI leaks include endoclips (through the scope and over the scope), covered stents, fibrin glue, suture devices and more recently introduced endoscopic vacuum therapy using bioactive sponge. Since the experience with these modalities is limited, there are hardly any clear guidelines to treat these difficult patients. This review article deals with endotherapy of GI leaks and fistula and presents an updated experience as well some guidance to select appropriate modality.

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INTRODUCTION

Gastrointestinal (GI) leaks and fistula constitute disruption of GI wall. GI leaks and fistula can be either spontaneous due to GI pathology or may be iatrogenic. There seems to be increase in prevalence of GI leaks and this seems primarily due to increasing complexity of GI surgery and endoscopic interventions. There is a changing paradigm in management strategy of GI leaks and fistula. While majority of these complicated patients were managed by surgery 15-20 years back, non-operative treatment including endoscopy presently constitute the primary modality of therapy[1]. There is evidence to suggest that this changing paradigm in form of endoscopic therapy is associated with improved outcome and shortened length of hospital stay[1]. This review deals with endoscopic techniques and their present status in the management of GI leaks and fistula.

Management of pancreatic and bile ductal leaks is however, not discussed.

DEFINITION AND ETIOLOGY

Perforation, fistula and leaks are terms, which are often used interchangeably. However in strict terms, they are somewhat different. Perforation refers to acute full thickness defect in GI tract. Leaks are defined as disruption of surgical anastomosis resulting in a fluid collection[2]. The term fistula usually means an abnormal communication between two epithelialized surfaces[2]. Table 1 enumerates the causes of GI leaks and fistula[3-17], while Table 2 distinguishes the underlying etiology for leaks and fistula. Table 3 details the endoscopic procedures associated with increased risk of perforation[18].

Table 1 Etiology of gastrointestinal leaks and fistula

Diagnostic endoscopy including endoscopic ultrasound
Dilation: bougie, balloon, achalasia
Polypectomy/EMR/ESD
Foreign body
Endoscopic variceal therapy including ligation
POEM
Anastomotic dehiscence
Boerhaave's syndrome
Diverticulitis
Laser
PEG
Endoscopic sphincterotomy
Biliary stent migration
Ampullectomy
Appendicular abscess
Empyema

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; POEM: Peroral endoscopic myotomy; PEG: Percutaneous endoscopic gastrotomy.

Table 2 Causes of leaks and fistula

Leaks	Fistula
Iatrogenic (60%)	Malignant (50%)
Endoscopy	Benign
EVL	Stents
Dilatation	Tuberculosis
ESD/EMR	Crohn's
POEM	Iatrogenic
Spontaneous	Trauma
Boerhaave's	Surgical
Foreign body	AIDS
Surgical	
Trauma	

EVL: Endoscopic variceal ligation; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; POEM: Peroral endoscopic myotomy; AIDS: Acquired immune deficiency syndrome.

TOOLS AND TECHNIQUES

The two options for managing GI leaks and fistula include surgery and endotherapy. The choice between two is decided by size of disruption, location and accessibility of lesion, presence of contamination, time of diagnosis and availability of expertise. Whatever be the choiced option for repairing the disruption, the management needs to include bowel rest, institution of appropriate antibiotics, drainage of associated collection, pneumoperitoneum, pneumothorax and maintenance of nutrition. Proton pump inhibitors are instituted, if leaks are located in upper GI tract. As highlighted in a recently published Position Statement of European Society of Gastrointestinal Endoscopy, it is important to have a systematic approach for diagnosis and treatment of GI perforations[18]. Endoscopist must record details of findings, attending physician must evaluate the clinical profile, necessary investigations which may include a CT scan and a blood picture should be carried out, a decision should then be taken whether to perform endotherapy or surgery and finally post endotherapy monitoring must be done to evaluate success or failure of the endotherapy[18]. Table 4 lists the endoscopic modalities, which can be used for closure of GI leaks and fistula. Of these, endoclips and covered stents are the two modalities, which are most commonly used and have most consistent results.

Endoclips

Endoclips, which are more frequently used for arresting GI hemorrhage can also be used for closing the GI wall disruptions and work like surgical sutures or staples[3,4,19]. First report of endoclipping for closure of GI perforation came from Germany[20]. This report discussed successful endotherapy of a perforation after endoscopic removal of gastric leiomyoma[20]. Endoclips can either be through the scope (TTS) clips, where clip applicator with loaded clip is introduced through the biopsy channel of the endoscope or recently available over the scope (OTS) clips, which are mounted over the scope tip like variceal band ligator device and released by a similar technique. TTS clips (Figure 1) are available in various designs and sizes: Quick clip

Table 3 Endoscopic procedures in different parts of gastrointestinal tract associated with increased risk of iatrogenic perforation

Esophagus and stomach	
Dilatation	ESD
EMR	Foreign body removal
POEM	EVL
Small bowel	
Altered anatomy	DBE in altered anatomy
Dilatation in Crohn's	ESD
Dilatation of GJ stricture after gastric bypass	
Colon	
EMR	Balloon dilatation
ESD	Old age, co-morbidity
Inexperience	Inflammatory colonic disease

ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; POEM: Peroral endoscopic myotomy; EVL: Endoscopic variceal ligation; DBE: Double-balloon; GJ: Gastrojejunostomy.

Table 4 Modalities for endotherapy of leaks/fistula

Closure
Endoclips
Suture
Sealant: Fibrin, cyanoacrylate
Diversion
Covered stents

(Olympus, America Inc., Center Valley PA, United States), Resolution clip (Boston Scientific Inc., Natick, United States) and Instinct clip (Cook Medical Inc.; Bloomington, IN, United States). Some of these are rotatable and re-openable, making them convenient to appropriately align the disrupted tissue. Figure 2 shows an esophageal tear treated by TTS clips.

OTS clips (Figure 3) from Ovesco Endoscopy GmbH (Tuebingen, Germany) are nitinol, super elastic, biocompatible clips with teeth designed in the shape of a bear trap and can produce a full thickness closure. OTS clips are available in various shapes and sizes and selection of a particular size depends upon the size of the defect. For larger defect, one can use accessories like anchor and twin grasper, which can pull the defective mucosa into the OTS cylinder or reduce the gap of the defect respectively (Figure 3). One should carefully avoid capturing twin grasper or anchor while releasing the clip. Figure 4 illustrates the use of OTS clips in a patient with two defects in gastric wall located diagonally opposite one another following a Whipple's surgery. Two OTS clips were placed with the help of anchor and twin grasper through a double channel endoscope. Follow-up CT scan confirmed the complete closure of defects.

In general, it is believed that OTS clips cover a larger defect and one OTS clip can be compared with results obtained with 5 TTS clips. In large defects, such as after Endoscopic Submucosal Dissection (ESD), multiple TTS clips can be used to fix an endoloop at the margin of the defect and then pulling the loop and closing it can obliterate the defect. There are case reports of OTS clips

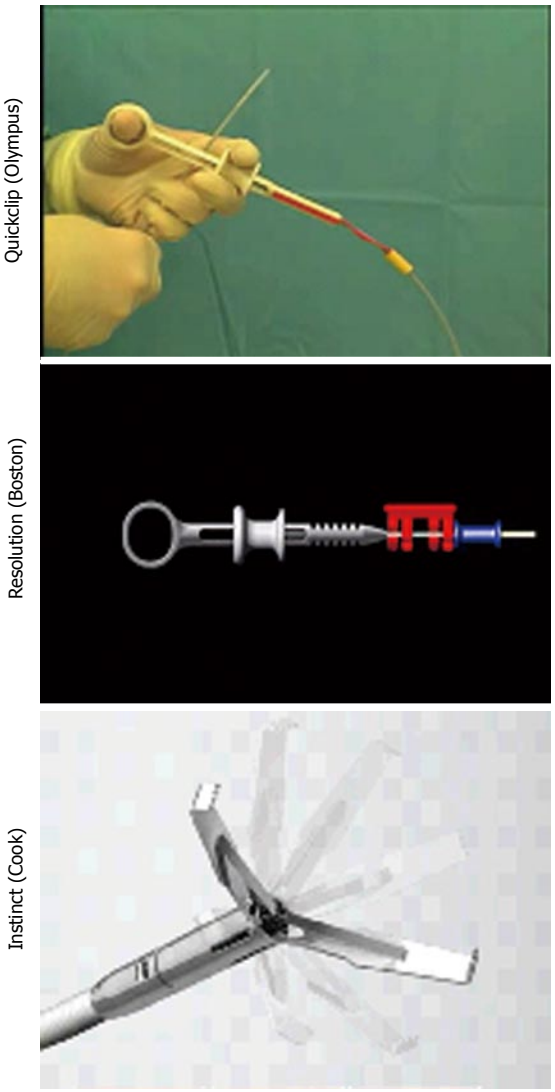

Figure 1 Through the scope clips.

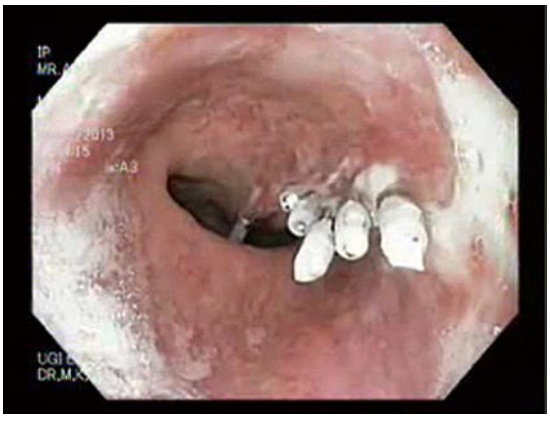

Figure 2 Endo clips (Through the scope) used to close an esophageal defect due to Boerhaave's syndrome.

applied under laparoscopic control in order to achieve greater success[21].

Both TTS and OTS clips have been used to close fistula and leaks located in esophagus, stomach as

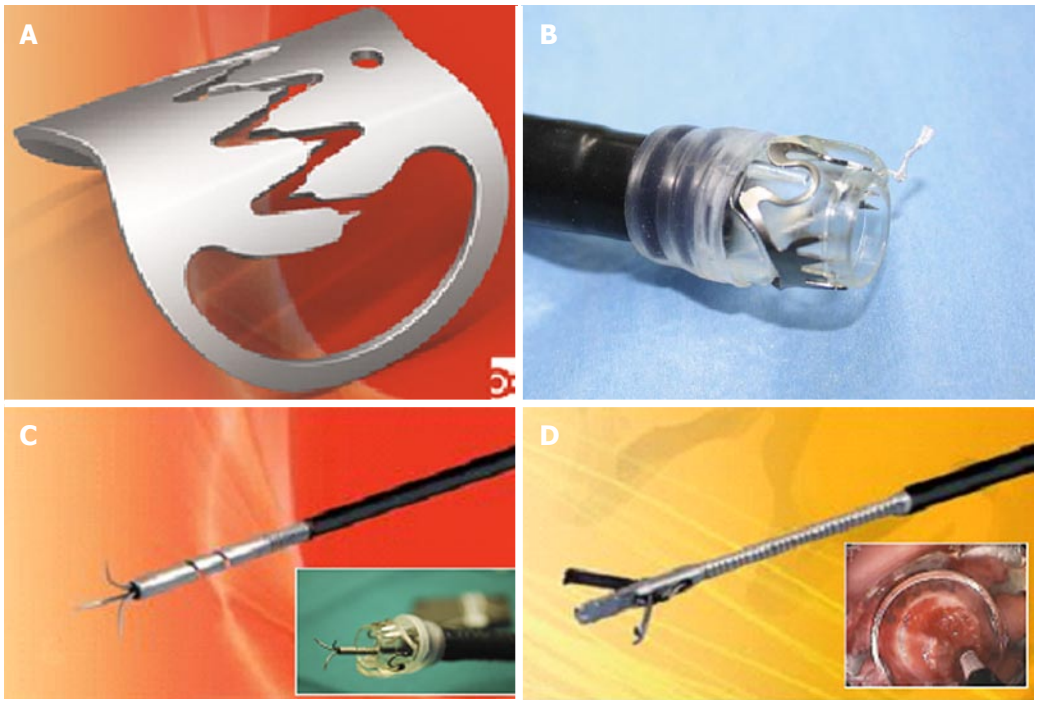

Figure 3 Over the scope clips (ovesco) (A) clip, (B) clip mounted on the endoscope, (C) anchor, (D) twin grasper.

well as colon[20,22-30]. While most of these studies involve small number of patients, large series have reported results of clips to close leaks following ESD and endoscopic mucosal resection (EMR)[23,31]. Minami *et al*[23], in a series of 117 patients with gastric leak following EMR, demonstrated a success rate of 98.3% with TTS clips. Interestingly, they found a similar recovery rate for patients with perforation treated by clips and non perforated patients[23]. Of the 39 patients with perforations following ESD reported by Jeon *et al*[32] managed by endoclip, there was no failure. Overall success rate is higher for esophagus and stomach and somewhat moderate for colonic leaks. Voermans *et al*[22] reported their experience of OTS clips in 36 patients with iatrogenic perforations (esophageal: 5, gastric: 6, duodenal: 12, colonic: 13). Overall success rate of OTS clips was 89% with only one patient having endotherapy related complications. A large muti-center retrospective study by Chavez *et al*[33] involved 188 patients with GI leaks and fistula treated with OTS clips. 27 patients were lost during follow-up. Of the remaining patients, OTS was used as primary treatment in 97 patients and as rescue therapy in 64 patients. The success rate was 75% in first group and 47% in second group. Overall success rate was 64% (103 out of 161 patients). The result was better for perforation (95%) and leaks (80%), compared to fistula (45%).

In general clips are preferred over stents, if the leak is located in proximal esophagus or in distal most esophagus as well as for stomach and right colon[34]. While TTS clips are effective for leaks smaller than 10 mm[35], OTS clips are preferred if defect is larger than 20-30 mm. Prior ablation at edges of defect to make it raw, may help in clip placement[36]. While closing a large leak, it may be worthwhile to attempt to include adjacent omental patch within the clip, akin to surgical practice[37]. Because of possibility of leakage of air during the procedure, it may be a good idea to use CO_2 insufflation during endotherapy of leaks and fistula[18]. In order to get best results, it is important to apply endoclips early after detection of leaks and perforations[35]. There is no reported risk of peritoneal dissemination or tumor recurrence after endoclips used for perforations following ESD or EMR performed for early cancers[38,39].

Luminal stenting

A large variety of stents are available to close luminal defects (Figure 5). These stents are covered (at least partially), so as to seal the defect and avoid contamination of the disrupted area. Mostly these stents are self - expanding metallic stent except for a single design of plastic stent (Polyflex, Boston). Fully covered stents, because of their ease at removability, are generally preferred particularly in the setting of benign disease. Figure 6 shows a patient with leak following gastrojejunostomy done for distal duodenal obstruction. One of the major issues with use of covered stent for closing of the GI defects is the risk of migration in absence of any obstructive pathology. This can be reduced by using large sized stents (Mega stents by Niti or Danis stent by Ella Figure 7), modified stents designs with extra covering in the shaft of stent (Figure 8) or by anchoring the stent by using endoclips or externalised threads (Figure 9)[40].

Stents have been used mostly in esophagus, duodenum and colon. Van Boeckel *et al*[41] reported the

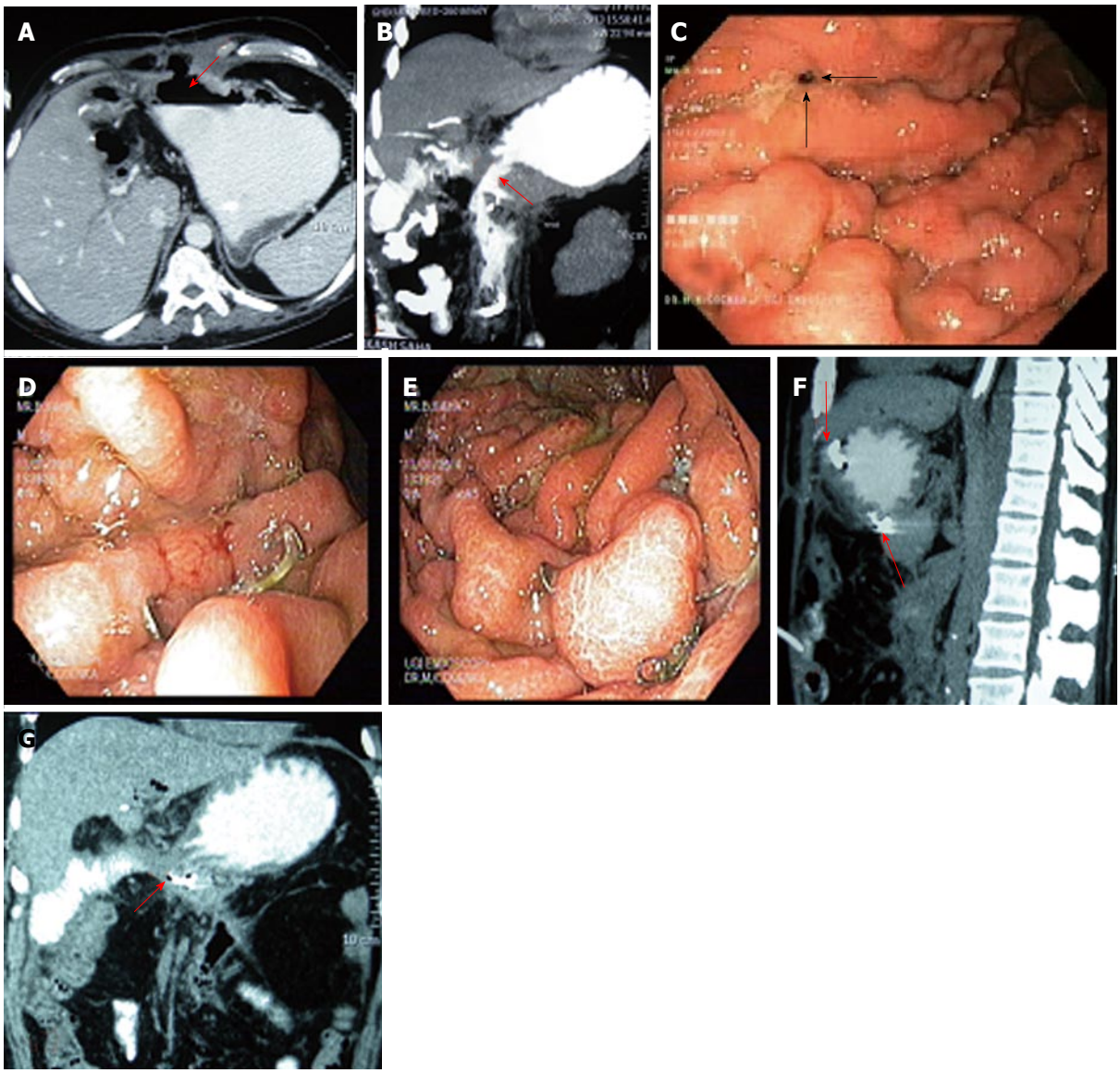

Figure 4 Dual gastric leak following Whipple's Surgery treated by over the scope clips. A and B: Anterior and posterior defects (arrows); C: Endoscopic view showing leak on anterior gastric wall (arrows); D and E: The OTS clips placed on anterior and posterior defects respectively; F and G: Follow-up CT scan showing the clips (arrows) with demonstration of closure of leaks. OTS: Over the scope.

results of 25 studies with luminal stent for iatrogenic esophageal leaks. In the cumulative data involving 267 patients, they reported a clinical success of 85% for closure of leak with no difference between plastic stent, fully covered or partially covered metal stents (84%, 85% and 86% respectively P = 0.097). Overall complication rate was 34%. Migration rate was somewhat higher for plastic stents compared to fully covered and partially covered stents (31% *vs* 26% *vs* 12% respectively). There was however, no difference in other complications such as tumor in-growth or over-growth. Freeman *et al*[42] recently reported that factors associated with failure of leak closure with stent placement include leak at cervical esophagus and esophagogastric junction, injury greater than 6 cm and additional distal leak. Tables 5 and 6 gives details of results of case series with endotherapy in esophageal and gastric iatrogenic perforation respectively[22-24,39,43-56]. As shown most of the series with gastric perforation have used clips, while both clips and stents have been used for esophageal perforation.

Bariatric surgery is not uncommonly complicated by leaks and fistula. In a retrospective study, over a period of 6 years involving 1499 bariatric surgery, Spyropoulos *et al*[57] reported a 2% incidence of luminal leak. Leaks were noted in sleeve itself, at staple line or at anastomosis site (gastrojejunostomy or enteroenteral). Of the 30 patients with leak, stents were used in 9, while surgery was performed in 3 patients and conservative approach was followed in 18 patients. Another recent study by EI Mourad *et al*[58] reported success of stent to close leaks following bariatric surgery in 41 out of 47 patients. Mega stents with a diameter of 30 mm are best suited for these indications.

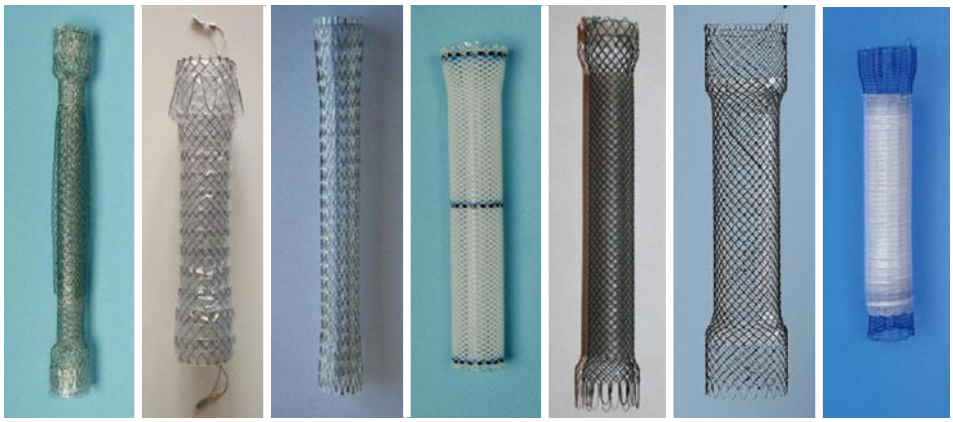

Figure 5 Stents for gastrointestinal leaks/fistula.

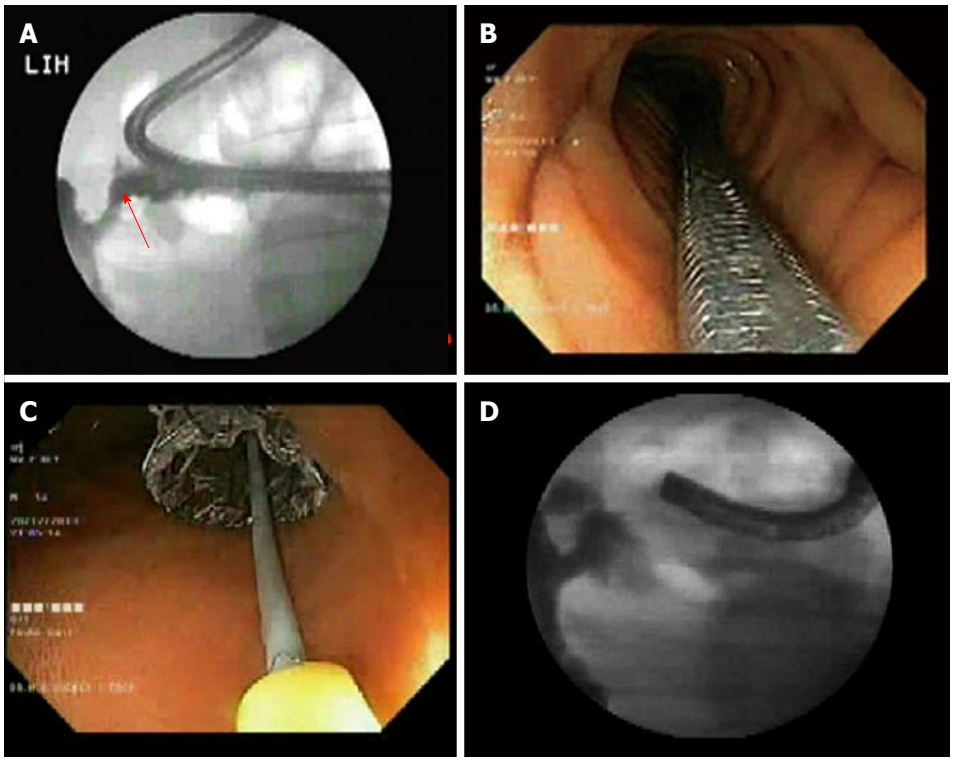

Figure 6 Leak after duodeno-jejunostomy managed by luminal stenting. A: Contrast introduced through the surgical drain site shows the leak (arrow); B: Stent being deployed; C: Fully deployed covered stent; D: Contrast through the surgical drain shows the closure of the leak.

Suturing and sealants

While suturing and use of sealants have been used to close GI leaks and fistula, results are mixed and experience is limited. Some of the suturing devices include EndoCinch suturing device (C.R. Bard, Inc, Boston, Mass, United States) Sefestitch (Safestitch, Medical Inc, Miami, Florida), Medical Power System (Power Medical Interventions, Longtrome, Pennsylvania), ESD Flexible Endoscopic Suturing devices by Wilson-Cook Medical (Winston- Salem, North Carolina) and Eagle Claw (Olympus Corporation, Tokyo, Japan)[59]. All these devices are either being still investigated or have not stood the test of time. Apollo Overstitch system (Figure 10) introduced recently, has been shown to have encouraging results[60,61]. This device is front-loaded onto a double - channel endoscope and allows continuous or interrupted stitches to be made with a cinching device. The merits of this approved device include the ability to reload the device inside the body eliminating the need to remove it between stitches as well as predictability of tissue needle penetration due to it being not suction based. Moreover, the device allows one endoscopic channel to be free to allow passage of grasping forcep for better tissue apposition[61].

Sealants which have been used to obliterate GI leaks and fistula include Cyanoacryate and Fibrin glue[62,63].

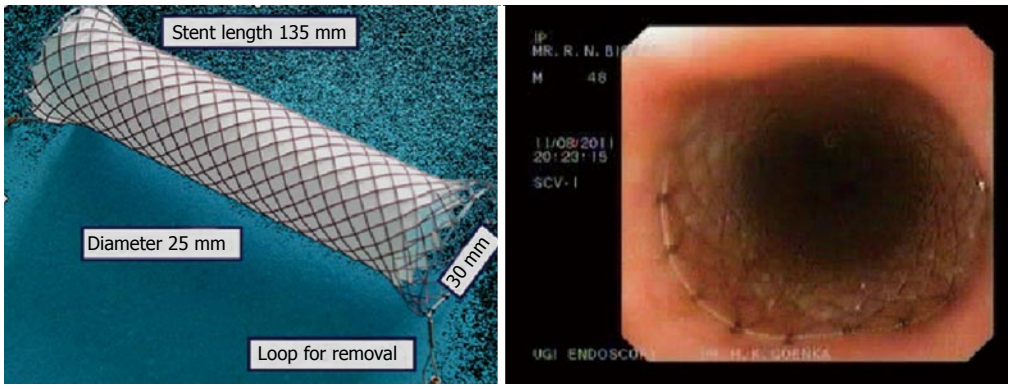

Figure 7 Danis stent.

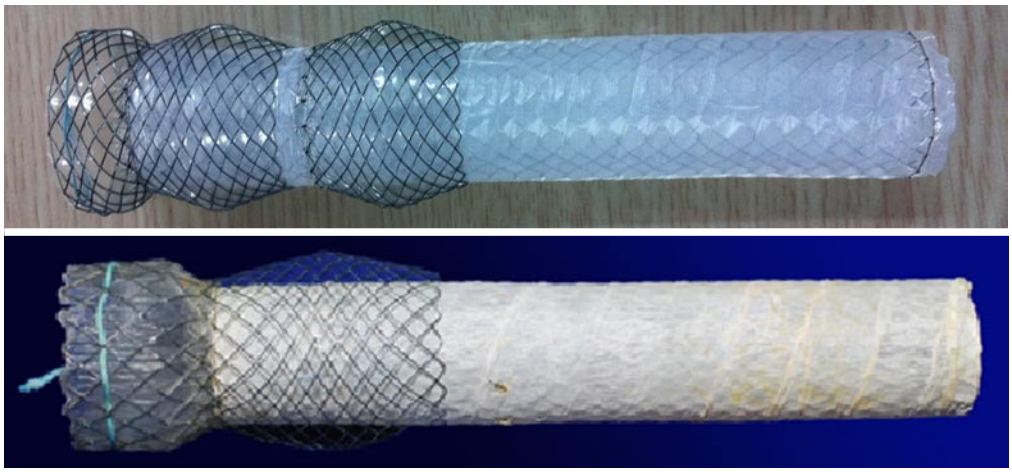

Figure 8 Modified stent design to prevent stent migration.

In a study by Rábago *et al*[62], 15 patients with post operative GI fistula were treated with Fibrin glue (combination of thrombin with fibrinogen). Complete sealing was obtained in 86.6% with a mean 2.5 sessions (range: 1 to 5) and a mean healing time of 16 d (range 5-40 d). Cyanoacrylate has been successfully used to close an esophagojejunal anastomotic leak after failed conservative therapy[63].

LIMITATIONS AND COMPLICATIONS

While endotherapy is exciting and results are encouraging, it has limitations in situations such as large perforation, difficult endoscopic position, fibrosis at the edge of the defect, evidence of abscess or fecal contamination *etc*[64]. Additional procedures or surgical alternatives should be considered in these circumstances. It is important to identify patients with failed clip closure as surgery should be promptly instituted in these patients in order to avoid sepsis and its consequences[65]. Monitoring should therefore be done by clinical profile and repeated blood counts. While endotherapy is safe if performed judiciously, complications such as perforation and bleeding are known. In particular, one must be careful while introducing endoscopes loaded with OTS clips, since the bigger insertion diameter can lead to iatrogenic perforations[22].

RECENT DEVELOPMENTS

Some of the recent techniques used to close GI leaks and fistula include Endovac therapy, Plugs and grafts, Biodegradable stents and Cardiac septal occluder. Endoscopic vacuum assisted closure sponge or Endovac therapy has been used in setting of leaks associated with infections (Figure 11)[66-69]. Ahrens *et al*[68] reported 5 patients with post esophageal surgery anastomotic leaks treated by endovac therapy. Polyurethane sponges with a drainage tube fixed to it allowing continuous suction was positioned endoscopically in the wound cavity and sponge was changed at regular interval. All 5 patients had closure of leak after a median of 9 sponge changes, median duration of drainage being 28 d. Two patients did require bougie dilatation for esophageal stenosis and one of them had fatal outcome due to aortoanastomotic fistula after dilatation. Loske *et al*[67] reported success in 13 out of 14 patients with esophageal leak treated by Endovac therapy with sponge being placed in the esophageal lumen (intraluminal method) or in the extraluminal

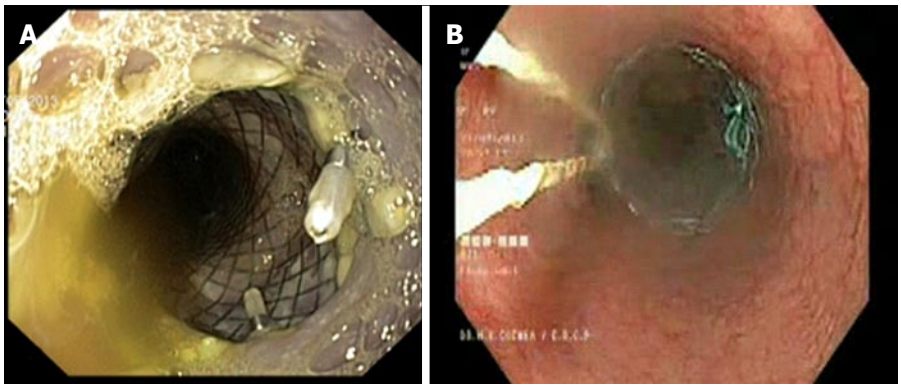

Figure 9 Anchoring of stent using (A) clip and (B) externalized thread.

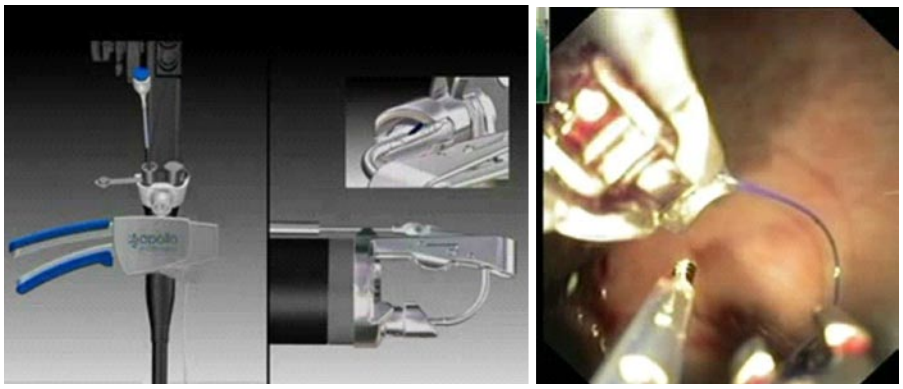

Figure 10 Apollo overstitch device.

Table 5 Result of endotherapy for iatrogenic esophageal perforation[1]

Ref.	Type of treatment	Patients (*n*)	Technical success (%)	Complications (%)
[2]Freeman *et al*[43]	SEPS	19	100	24
Vallböhmer *et al*[44]	SEMS	12	100	8
[2]van Heel *et al*[45]	SEMS/ SEPS	31	100	33
Schimdt *et al*[46]	SEMS ± clip (1)	22	100	NA
Swinnen *et al*[47]	SEMS	23	100	NA
D'Cunha *et al*[48]	SEMS/ SEPS	15	95	13
Biancari *et al*[49],	Stents ± clip (1)	12	100	25
Schweigert *et al*[50]	SEMS/ SEPS	13	100	85
[2]Heits *et al*[51]	Vaccum therapy	10	100	20
Biancari *et al*[52]	SEMS/clip	67	100	34

[1]Only studies with 10 or more patients have been included; [2]Study design was prospective, rest were all retrospective. NA: Not available; OTSC: Over-the-scope clip; SEMS: Self-expandable metal stent; SEPS: Self expandable plastic stent.

Table 6 Result of endotherapy for iatrogenic gastric perforation

Ref.	*n*	Additional procedures	Success rate (%)
TTS			
Tsunada *et al*[53]	7	Omental patch (1 case)	100
Fujishiro *et al*[39]	11	-	100
Minami *et al*[23]	121	> 1 cm: omental patch	98.3
Shi *et al*[54]	20	Endoloop	100
Zhong *et al*[55]	14	Endoloop	100
OTS			
Kirschniak *et al*[24]	7[2]	-	100
[1]Voermans *et al*[22]	6	-	100
Nishiyama *et al*[56]	7	-	86

Only studies with 5 or more patients are included. [1]All studies were retrospective except Voermans *et al*[22]; [2]13 OTS clips were placed in 7 patients.

wound cavity (intracavitary method). Similar technique has also been used for colonic anastomotic leaks with success in 28 out of 29 patients.

Plugs and grafts used include Vicryl plug and Surgisis. Surgisis soft tissue graft (Cook Biotech Inc, West Latayette, Ind) is an acellular bioactive prosthetic biomatrix produced from sheep intestinal submucosa[70]. In contrast to synthetic prosthetic material which has inherent risk of foreign body reaction, sepsis and secondary fistula formation, surgisis has been shown

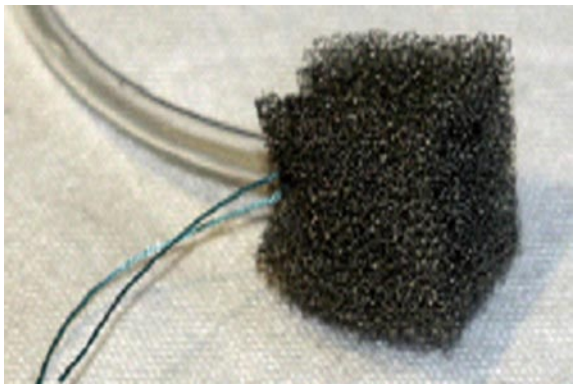

Figure 11 Endoscopic vacuum-assisted closure sponge (Endovac Therapy).

to be safe in contaminated tissues. It has been used successfully to treat complicated infected fistula after surgical resections including bariatric surgeries[71-73]. Vicryl mesh in combination with fibrin glue (covering the mesh as well as injected into the submucosa at the edge of the defect) used by Böhm *et al*[74] has also shown success in 13 out of 15 patients with leaks or fistula in upper GI tract following surgery for cancer. One to four sessions were used for this purpose.

Biodegradable stents have been used in a small series of 5 patients with esophageal leaks[75]. Four out of these 5 patients responded, inspite of 3 stents migrating during follow up. Cardiac septal occluder (Amplatzer Occluder, AGA Medical Corp, Plymouth, MN) used for cardiac septal defects have been used successfully by Repici *et al*[76] to close esophago - tracheal fistula. More data is however, required with these modalities before they are included in routine clinical practice.

CONSERVATIVE TREATMENT

While majority of patient with GI wall disruptions are candidates for either surgery or endotherapy, a small selected group of patients with iatrogenic perforation can be managed by conservative approach[18]. This subset includes stable patients who have perforations in cervical esophagus or a small number of patients with gastric or duodenal perforation, which are diagnosed late (> 12 h), are asymptomatic, have no signs of peritonitis and do not show free fluid or contrast extravasation at CT scan[18]. Somatostatin and its analogue octreotide, which decrease intestinal secretions, have also been used to improve the results of this conservative approach both in adults as well as children[77-79]. However, their role has been primarily considered for post-operative dehiscence, particularly after pancreatic surgery[78,79].

In conclusion, leaks and fistula involving GI tract are increasingly encountered in our routine practice. In a small select group of patients, there is a scope for conservative treatment of perforation and leaks. However, majority of patients are treated by surgery or endoscopic therapy. Techniques such as Endoclips (TTS and OTS) and covered metal stents have made endotherapy a preferred method to treat GI leaks and fistula. In general small leaks (< 10 mm) can be managed by traditional TTS clips, larger leaks require covered stents or OTS clips. Leaks and fistula associated with luminal strictures should be managed by luminal stenting. Recent developments with use of Endovac, Plugs and Graft and Biodegradable stents are encouraging. In particular, use of Endovac in the setting of sepsis seems promising. In view of multiple endoscopic modalities available with us, an algorithm based on location, size and associated features need to be developed to use these techniques judiciously.

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MINIREVIEWS

Current status of laparoendoscopic rendezvous in the treatment of cholelithiasis with concomitant choledocholithiasis

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Abstract

The current evidence in favor of the laparoendoscopic rendezvous is promising and demonstrates the main advantages of this technique in regard to shorter hospital stay and selective cannulation of the common bile duct (CBD), avoiding thus the inadvertent cannulation of the pancreatic duct. In addition, in the rendezvous technique the contrast medium is not injected retrogradely as during the traditional endoscopic retrograde cholangiopancreatography (ERCP), when the medium accidentally could be injected under pressure into the pancreatic duct. The RV technique minimizes that risk. Both these main advantages of the RV technique over the classic ERCP, are related with a significant lower incidence of hyperamylasemia and post-ERCP pancreatitis, compared with the traditional two stage procedure. Choledocholithiasis is present in 10% to 15% of patients undergoing cholecystectomy. To date, the ideal management of CBD stones remains controversial. Prospective randomized trials have shown that laparoscopic management of the CBD stones, as a single stage procedure, is the most efficient and cost effective method of treatment. Laparoendoscopic rendezvous has been proposed as an alternative single stage approach. Several studies have shown the effective use of this technique in the treatment of CBD stones by improving patient compliance and clinical results including shorter hospital stay, higher success rate and less cost. The current evidence about the use of this technique presented in this review article is promising and demonstrates the main advantages of the procedure.

Key words: Common bile duct stones; Laparoendoscopic rendezvous; Endoscopic retrograde cholangiopancreatography; Cholecysto-choledocholithiasis; Laparoscopic cholecystectomy

Core tip: This is a review article for the laparoendoscopic rendezvous technique - a promising single stage procedure in the treatment of patients with cholecysto-

choledocholithiasis. In this article we highlight the main advantages of the procedure compared to the traditional two stage approach [preoperative endoscopic retrograde cholangiopancreatography (ERCP) followed by laparoscopic cholecystectomy]. These advantages include the selective cannulation of the common bile duct and the avoidance of high pressure injection of the contrast medium into the pancreatic duct. Both factors are directly related with the pathogenesis of post-ERCP pancreatitis. The current evidence demonstrated in this paper is in favor of the laparoendoscopic rendezvous, however, this technique is still not widely accepted.

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INTRODUCTION

Choledocholithiasis is present in 10%-15% between patients undergoing cholecystectomy. The overall incidence of unsuspected common bile duct (CBD) stones is approximately 4%[1,2]. Once discovered, CBD stones should be removed in order to prevent several complications, such as acute pancreatitis, jaundice and acute ascending cholangitis and hepatic abscess. The obvious aim in the treatment of patients with choledocholithiasis is to achieve ductal clearance with the less number of interventions and least morbidity[3].

Over the past few decades, there have been significant improvements in both the diagnosis and treatment of patients with gallstone disease and CBD stones. Before the introduction of laparoscopic cholecystectomy, patients with cCBD stones underwent CBD exploration by open surgery. Although a high success rate of CBD clearance was achieved, the significant morbidity and mortality of a major abdominal surgery remained. Since then, many alternative treatment modalities have been developed. Especially, the introduction and evolution of endoscopic retrograde cholangiopancreatography with endoscopic sphincterotomy, which gradually became the gold standard for the treatment of biliary duct stones[1,4].

Nowadays, laparoscopic cholecystectomy (LC) is the treatment of choice for patients with symptomatic cholelithiasis. The introduction of LC as a minimal invasive procedure, has also changed the therapeutic strategies for the management of choledocholithiasis. To preserve the minimal invasive concept of management, a number of options have been proposed, including two and single step management. Thus, the therapeutic approaches today vary, depending on availability experience and expertise and include open or laparoscopic CBD exploration, various combinations of LC and endoscopic retrograde cholangiopancreatography (ERCP) and combined laparo-endosopic procedures[5].

Due to this wide variation of treatment options the ideal management of cholelithiasis and concomitant choledocholitthiasis remains controversial. In the open surgery era, prospective studies compared the use of ERCP and endoscopic sphincterotomy (ES) before open cholecystectomy to open cholecystectomy with surgical exploration of the CBD. In these trials, a shorter hospital stay for patients underwent preoperative ES was reported, as well as, lower mortality and morbidity rates in patients over 60 years of age after ES[6,7]. In the era of LC, the combination of preoperative ERCP and LC is considered the treatment of choice for concomitant cholecysto-choledocholithiasis and remains the most frequently applied strategy at most hospital centers[8].

LAPAROSCOPIC CBD EXPLORATION

Since its introduction, ERCP has mainly been used preoperatively for the diagnosis of choledocholithiasis. However, a high incidence of negative ERCPs was recorded, raising the fear of major complications in patients who do not actually need the procedure. In addition to morbidity many patients were dissatisfied because of the need to have two procedures, an endoscopic for the clearance of CBD and a laparoscopic one for the removal of gallbladder. Thus, there was a desire from many surgeons to provide a single stage approach for the treatment of choledocholithiasis[4,9]. The evolution of laparoscopic surgery stimulated the application of laparoscopic approach for the management of CBD stones. Skilled laparoscopic surgeons proposed LCBD exploration as an effective alternative for the treatment of choledocholithiasis.

Prospective randomized trials comparing LCBD exploration with two stage procedures, have shown that laparoscopic management of the CBD stones, as a single stage procedure, is associated with equivalent success rate and patient morbidity but shorter hospital stay and lower cost[10,11].

Two, recently published meta-analyses, included studies comparing one stage vs two stage management of CBD stones. One stage procedures included LC and LCBDE or intraoperative ERCP, while two stage procedures included LC preceded of followed by ERCP. These meta-analyses showed that both clinical practices have similar clinical outcomes[12,13]. Two studies in the meta-analysis published by Alexakis *et al*[12] reported cost analysis. Both found a significantly higher costs for the two stage management.

Laparoscopic CBD exploration is a logical extension of LC. However it has not gained popularity amongst the surgical community. LCBDE, either through the transcystic route or through choledochotomy, is a technically demanding procedure and requires clinical experience in the open technique and advanced laparoscopic skills[2,10]. Thus, it has remained a procedure for experienced and/or enthusiastic laparo-

scopic surgeons. Apparently, scientific data from centers of excellence cannot not always be extrapolated into everyday clinical practice.

LAPAROENDOSCOPIC RENDEZVOUS FOR THE TREATMENT OF CHOLEDOCHOLITHIASIS

Despite the evidence from prospective randomized trials suggesting the superiority of the so-called one-stage management of cholecysto-choledocholithiasis in regards to the hospital stay and cost effectiveness, two-stage techniques, mainly preoperative ERCP followed by LC, are currently being used by most clinicians in their daily practice[10,11].

ERCP is associated with a failure rate to cannulate the ampula of Vater ranging from 4%-18% of cases while post ERCP pancreatitis is a major complication which can follow inadvertent pancreatic cannulation and contrast injection[14-16]. The laparoendoscopic rendezvous (LERV) procedure, which is a single stage combined laparoscopic and endoscopic approach to CBD stone treatment, represents an effective alternative to the sequential treatment which, in addition, minimizes the risk of inadvertent pancreatic duct cannulation and subsequently the risk of pancreatitis. Several studies during the past decades have shown the effectiveness of this technique as a single stage procedure in the treatment of CBD stones by improving patient compliance and leading to shorter hospital stay, higher success rate and lower cost. However, organization and technical problems have not facilitated the diffusion of this method[5,9,17,18].

The combined laparoendoscopic treatment was first described by Deslandres *et al*[19] in 1993. However, the method didn't encountered wide interest immediately. After the years, many authors used this approach in their practice. In 2009, La Greca *et al*[20] published the first review of original papers and case reports including a total number of some 800 patients, describing the results and comparing the LERV treatment with the other two main available treatment options. The overall effectiveness of the LERV technique was 92.3%. The duration of the endoscopic part of the procedure ranged from 8 to 82 min (mean 35 min), while the time of the whole LERV procedure was 40 to 360 min with a mean time of 104 min. The conversion rate to open surgery was 4.7%. The overall mortality and morbidity rates were 0.37% and 5.1% respectively. The mean hospital stay of patients treated with the LERV procedure was 3.9 d (range from 2 to 51 d)[20].

The advantages of the LERV approach were outlined by most authors of the reviewed studies. The most important suggested advantages compared with the LCBD exploration, which represents the single stage management rival, were the reduced operation time and lower technical difficulties. On the other hand, the main clinical advantages in comparison with the more popular two stage treatment (ERCP followed by LC) is the lower incidence of complications (especially pancreatitis), the higher success rate and the reduced hospital stay[20].

LAPAROENDOSCOPIC RENDEZVOUS AND POST-ERCP PANCREATITIS

The incidence of the post-ERCP pancreatitis ranges between 1% to 14%[21,22]. Multiple cannulation attempts have been described as an iatrogenic risk factor for post-ERCP pancreatitis. One of the most important technical factors in the concept of the LERV technique is that it facilitates the endoscopic procedure by the insertion of a guide-wire through the cystic duct and CBD into the duodenum ensuring thus elective CBD cannulation and avoiding the inadvertent cannulation of the pancreatic duct. This technical advantage provided by laparoendoscopic RV is of paramount importance, especially in cases with anatomical variations and difficult papilla cannulation[1,8].

Another important mechanical factor related to the pathogenesis of post-ERCP pancreatitis is the volume and high pressure of contrast medium injected by the endoscopist inadvertently into the pancreatic duct, during canulation of the papilla of Vater. Using the LERV technique the contrast medium is injected by the surgeon through the cystic duct avoiding thus the direct injection into the pancreatic duct[15,16].

In a recent study, LERV has been compared with standard ERCP at the same stage after the completion of LC. In this prospective randomized trial no case of post-ERCP pancreatitis was reported in either arm. However, during standard ERCP the risk of inadvertent pancreatic duct cannulation still exists, since selective cannulation of the bile duct is not ensured by the insertion of the guide-wire, as in the case of LERV[23].

Two CRTs in which LERV compared with the traditional two stage procedure reported lower serum amylase levels in patients treated with the LERV technique[8,24]. A statistically significant higher medium amylase value recorded by Tzovaras *et al*[24] in their study for the group of patients who underwent therapeutic ERCP followed by LC. La Greca *et al*[25] recorded a statistically significant reduction in serum amylase levels, in patients treated with rendezvous technique compared to ERCP/ES treatment. The authors concluded that the effectiveness and safety of the RV technique is mostly depended on the antegrade injection of the contrast medium by the surgeon through the cystic duct[25].

A statistically significant lower incidence of acute post-ERCP pancreatitis was recorded in two controlled randomized trials comparing the laparoendoscopic technique with the traditional two stage treatment[1,26]. All three meta-analyses, published to date confirmed the statistical significance of the lower post-ERCP pancreatitis rates in favor of the LERV technique[27-29]. The assessment of the overall ERCP/ES related complications in two of three meta-analyses, also confirmed

a statistically significant difference favoring the RV approach. However, when these complications were separately assessed in a subgroup analysis, no differences were found in the incidences of bleeding, perforation, cholangitis, cholecystitis and gastric ulcer.

EFFECTIVENESS OF THE LAPAROENDOSCOPIC RENDEZVOUS TECHNIQUE

It has been demonstrated that the LERV technique is an attractive option for the treatment of patients with CBD stones. It offers an advantage in selective cannulation of the CBD especially in cases of difficult papilla cannulation and where ERCP has already failed to provide a reliable therapeutic solution.

Tzovaras *et al*[30] used the LERV technique for the treatment of 22 patients who had at least one failed attempt of ERCP because of the presence of anatomic variations, mainly papillary diverticula or deemed unable to cooperate for a classic ERCP. Selective CBD cannulation achieved in all but two in whom the guidewire could not advance through cystic duct, however, the procedure completed using the classic retrograde way of ERCP intraoperatively[30].

In their controlled randomized study, Morino *et al*[8], proceeded with the rendezvous technique in 9 patients, initially randomized to the two stage approach, in whom ERCP failed to be performed. The treatment completed successfully in 8 patients using the laparo-endoscopic approach, indicating the use of the LERV technique as a safe and relatively easy way to cannulate selectively the CBD in patients in whom ERCP has failed[8].

La Greca *et al*[20] reported a higher overall effectiveness of the LERV technique regarding the CBD clearance compared to either preoperative ERCP or laparoscopic CBD exploration[20]. In controlled randomized trials comparing the LERV technique with the two stage treatment, the success rates of CBD stones clearance were similar for both treatment approaches[1,8,24,26]. However, as reported by Wang *et al*[29] in their meta-analysis, the success rate of CBD cannulation was significant higher for the rendezvous technique than the sequential treatment (RR = 2.54, 95 %CI: 1.23-5.26; $P = 0.01$)[29].

LAPAROENDOSCOPIC RENDEZVOUS TECHNIQUE AND TOTAL HOSPITAL STAY

Obviously, the laparoendosopic rendezvous as a single stage procedure is related with shorter hospital stay, comparing with the traditional two stage treatment. Four RCTs recorded statistically significant reduced hospital stay for patients treated with the LERV technique, comparing with the two stage approach[1,8,24,26]. Two meta-analyses confirmed the total hospital stay was significantly shorter with the RV technique compared with the sequential treatment[27,29]. This is mainly because a minimum of 24-48 h waiting period is required to ensure that no post-ERCP complication has occurred, before proceeding to LC in the two stage approach. It is difficult if not impossible this time interval to be reduced and this is a clear disadvantage of the two stage approach.

DISCUSSION

The LERV technique is a combined surgical and endoscopic procedure and it has been proposed as an alternative, single stage approach, for the treatment of patients with cholecysto-choledocholithiasis. This technique, did not reach wide acceptance immediately, because it requires the availability of surgical and endoscopic teams in the operating room. La Greca *et al*[20] presented the main disadvantage of the LERV technique to be logistics and organizational problems for an operation requiring the presence of two teams. Lella *et al*[1] considered this technique even more difficult to perform in the emergency setting. However, Tzovaras *et al*[24] concluded that the LERV could be effective and safe even in the urgent setting, including emergency cases in their study[24]. Obviously, in the era of minimal invasive surgery, any possible logistic problems should be resolved making the LERV technique available in the treatment of cholecysto-choledocholithiasis and its complications improving clinical results and patient's discomfort.

In comparing the laparoendoscopic approach with the sequential treatment, it should be mentioned that this technique ensures elective CBD cannulation, avoiding thus the inadvertent cannulation of the pancreatic duct. In addition, in the LERV technique the contrast medium is not injected retrogradely as during the traditional ERCP, when the medium accidentally could be injected under pressure into the pancreatic duct. The LERV technique minimizes that risk. Both these main advantages of the LERV technique over the classic ERCP, are related with a significant lower incidence of hyperamylasemia and post-ERCP pancreatitis, compared with the traditional two stage procedure[27-29].

The CBD clearance rate is an important outcome for the treatment of patients with CBD stones, leading in reduction of conversion rates to open surgery, which is associated with higher morbidity. The LERV technique is associated with at least equally high rates regarding overall CBD clearance compared to the traditional two stage approach, although it is associated with significantly higher success rate of CBD cannulation and lower number of procedures required for complete clearance. This technical advantage could be applied in clinical practice, especially in difficult papilla cannulation making it much easier for the endoscopist.

LERV is related with an additional operating time of approximately 30-45 min to be performed compared with the single laparoscopic cholecystectomy stage of

the sequential treatment. However, it saves more or less similar time in the endoscopic suite, where ERCP is performed as a separate procedure in a sedated but usually not anesthetized patient. Moreover, the extra time which represents the additional time needed for the performance of cholangiography and insertion/advancement of the guide wire into the duodenum would be balanced in case that intraoperative cholangiography is routinely used during LC[24].

Despite the aforementioned advantages of LERV there is some concern about the distention due to insufflation of the stomach and small intestine during the endoscopic part of the procedure. The use of a special bowel desufflator to decrease bowel distention or a laparoscopic small bowel clump placement across the first loop of jejunum, have been proposed to overcome this problem. It has been also suggested to perform as much as possible dissection of the gallbladder during the laparoscopic part before the beginning of the endoscopic part of the procedure[8,24].

Laparoendoscopic rendezvous is an attractive alternative for the treatment of patients with cholecysto-choledocholithiasis. The current evidence in favor of the LERV is promising and demonstrates the main advantages in regard to shorter hospital stay and selective cannulation of the CBD. The concept of the RV technique contributes in avoiding the main mechanisms of iatrogenic pancreatic damage, leading in lower incidence of post-ERCP pancreatitis. LERV requires basic laparoscopic equipment and skills; The only additional laparoscopic skill is the ability to perform an intraoperative cholangiogram, however, at an extra cost of increased operating time[24]. Despite the general improvement of skills in the last years, LERV is still considered as the least invasive approach for the treatment of cholecysto-choledocholithiasis[31]. However, the availability of the LERV nowadays is limited in most hospital centers, where the choice of the best approach for the treatment of patients with CBD stones is based on the institutional availability and expertise of their surgical and endoscopy teams. It seems that the lack of cooperation between the two teams, still does not facilitate the diffusion of the LERV procedure.

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Endoscopic mucosal resection and endoscopic submucosal dissection in the treatment of sporadic nonampullary duodenal adenomatous polyps

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Abstract

Although uncommon, sporadic nonampullary duodenal adenomas have a growing detection due to the widespread of endoscopy. Endoscopic therapy is being increasingly used for these lesions, since surgery, considered the standard treatment, carries significant morbidity and mortality. However, the knowledge about its risks and benefits is limited, which contributes to the current absence of standardized recommendations. This review aims to discuss the efficacy and safety of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) in the treatment of these lesions. A literature review was performed, using the Pubmed database with the query: "(duodenum or duodenal) (endoscopy or endoscopic) adenoma resection", in the human species and in English. Of the 189 retrieved articles, and after reading their abstracts, 19 were selected due to their scientific interest. The analysis of their references, led to the inclusion of 23 more articles for their relevance in this subject. The increased use of EMR in the duodenum has shown good results with complete resection rates exceeding 80% and low complication risk (delayed bleeding in less than 12% of the procedures). Although rarely used in the duodenum, ESD achieves close to 100% complete resection rates, but is associated with perforation and bleeding risk in up to one third of the cases. Even though literature is insufficient to draw definitive conclusions, studies suggest that EMR and ESD are valid options for the treatment of nonampullary adenomas. Thus, strategies to improve these techniques, and consequently increase the effectiveness and safety of the resection of these lesions, should be developed.

Key words: Polyps; Duodenum; Adenoma; Resection; Endoscopy

Core tip: Widespread use of endoscopy leads to increase detection of sporadic nonampullary duodenal adenomas. Due to significant morbidity and mortality of surgical treatment in this setting, endoscopic treatment with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), has been progressively used for the resection of these lesions. This extensive and detailed review discusses the efficacy and safety of EMR and ESD in this context. We conclude that EMR and ESD are valid options for the treatment of sporadic nonampullary duodenal adenomas. Strategies to improve these techniques, and consequently increase their effectiveness and safety should be developed.

Marques J, Baldaque-Silva F, Pereira P, Arnelo U, Yahagi N, Macedo G. Endoscopic mucosal resection and endoscopic submucosal dissection in the treatment of sporadic nonampullary duodenal adenomatous polyps. *World J Gastrointest Endosc* 2015; 7(7): 720-727 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i7/720.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i7.720

INTRODUCTION

We searched Medline (PubMed) for all published manuscript up to 2014. The search terms used were "(duodenum OR duodenal) (endoscopy OR endoscopic) adenoma resection". The search was restricted to English language and was extended by carefully reviewing the bibliographies of the pertinent manuscripts on this subject. Of the 189 retrieved articles, and after reading their abstracts, 19 were selected due to their scientific interest. The analysis of their references, led to the inclusion of 23 more articles for their relevance in this subject.

Duodenal adenomatous polyps are a rare disease in the general population, reported as incidental findings in up to 0.1%-0.34% of the patients undergoing upper gastrointestinal endoscopy[1,2]. The evolution and widespread of this exam contributed to the increase in smaller sized polyps early diagnosis[3-5]. Adenomas are the histologic subtype that constitutes the majority of the duodenal lesions that need resection[2,6]. For this reason, they must be distinguished from non-adenomatous polyps, namely the ones that originate in the mucosa (gastric metaplasia) or submucosa (carcinoid tumors, leiomyomas, lipomas, inflammatory fibroid polyps and gastrointestinal stromal tumors), hamartomatous polyps (Brunner glands hyperplasia and Peutz-Jegher polyps, among others), and metastatic polyps[1,5,6]. One of the goals of the treatment, common to all duodenal adenomas, is the elimination of the tumoral progression risk, which correlates with the size of the lesion and is similar to that of colorectal adenomas[6,7].

These lesions are classified, according to its location, in ampullary (if they involve the duodenal bulb major - ampulla of Vater - or minor) or not ampullary. In both circumstances, they may occur as part of a genetic syndrome associated with the development of polyps, as the Familial Adenomatous Polyposis, or sporadically[8,9].

Sporadic nonampullary adenomatous polyps have similar incidence in both sexes and are mostly diagnosed accidentally between the sixth and eighth decades of life[5,6]. Typically, these lesions are solitary, with sessile or flat morphology, more than 10 mm, located in the second portion of the duodenum and asymptomatic[9-14]. However, depending on their size, location and histological characteristics, they can cause dyspepsia, abdominal pain, bleeding and bowel obstruction[5].

The traditional therapeutic approach for duodenal polyps is local surgical excision or radical surgery, respectively characterized by high rates of recurrence and significant morbidity and mortality[15,16]. In 1973, Haubrich described the first endoscopic excision of a duodenal adenoma, which, since then, has been pointed out by several publications as a safe and effective alternative to surgery[3,4,10,11,17-19]. In a retrospective analysis of 62 patients with duodenal nonampullary polyps, the morbidity of the surgical therapy was significantly superior to the one of the endoscopic resection (33% *vs* 2%)[20].

The use of endoscopic techniques in the duodenum is still controversial, since it represents a diagnostic and technical challenge[3,6]. The duodenum has several peculiarities that make the endoscopic resection complications risk higher than the one described elsewhere in the gastrointestinal tract[21]. Indeed, its narrow lumen and retroperitoneal fixation hampers the maintenance of an adequate vision field during the procedure[22]. On the other hand, this organ has the thinnest wall of the digestive tract and shows a thick fibrous submucosa, even in a non-pathological situation, which can limit the protrusion of the mucosa achieved by the submucosal saline injection[22].

The scientific evidence of the risks and benefits of the endoscopic treatment and its long-term outcomes in the resection of nonampullary polyps, both sporadic and associated with genetic syndromes, is limited[23,24]. This reality contributes, along with the fact that this type of lesions is infrequent and has a natural history and clinical importance that is not fully understood, to the absence of a specific set of criteria for clinical guidance[5,24,25]. Consequently, the therapeutic strategies are usually considered taking into account the patient's condition, the characteristics of the lesion and the experience of who performs the endoscopic technique[5,7,24].

In 2010, a review published by the National Institute of Clinical Excellence highlighted the lack of published material that addressed this topic[23]. Although the number of clinical trials has increased since then, the best treatment of nonampullary adenomas remains

subject of discussion[9]. The purpose of this work is to review the scientific literature regarding endoscopic resection of sporadic duodenal nonampullary adenomatous polyps, highlighting the benefits and drawbacks of EMR and ESD based on the analysis of different outcomes obtained with their practice.

INITIAL ASSESSMENT

Before endoscopic resection, it is essential to characterize the size of the polyp, duodenal folds and lumen extension involvement[6]. It should be ensured that it doesn't involve the ampulla of Vater (which would imply a different diagnostic and therapeutic approach) with a side-viewing endoscope or with endoscopic ultrasound[5,6,25].

The endoscopic appearance of duodenal adenomas cannot always distinguish them safely from non-adenomatous polyps and thus, all lesions considered suspicious should be biopsied[25]. It is also important to determine the resectability of the lesion and detect any signs that suggest submucosal invasion, and that influence the treatment, such as tumors with depression (IIc in the Paris Classification), type Ⅴ pit pattern classification described by Kudo, presence of bleeding, induration, ulceration or irregularities on the surface of the polyp and non-lifting sign after submucosal saline injection[5,6,26,27].

The exact role of endoscopic ultrasound in the evaluation of nonampullary adenomas remains uncertain[24]. When it's impossible to establish the relationship of the polyp with the pancreaticobiliary tree with a forward and side-viewing endoscopy, endoscopic ultrasound is an alternative technique, obviating the need of an endoscopic retrograde cholangiopancreatography[5]. Some researchers advocate its use in the evaluation of the depth of duodenal polyps larger than 20 mm[7,24]. However, according to Al-Kawas, the routinely use of endoscopic ultrasound, apart from not bringing great benefit, would have a considerable cost[7].

Newer techniques such as magnification endoscopy, endoscopy with narrowbanding imaging or chromoendoscopy (with a non absorbable dye such as indigo carmine) allow better delineation of the margins of the lesion and can be used in the initial evaluation of duodenal adenomas, potentially reducing incomplete resection rates[6,21]. Although there is little information regarding the use of magnification chromoendoscopy in the duodenum, this technique showed a reduction of local neoplastic recurrence from 8.7% to 0.5% when associated with EMR of flat colonic lesions bigger than 2 cm[28]. Shinoda *et al*[29] found that magnification endoscopy with narrowbanding imaging or indigo carmine is more accurate than endoscopic ultrasound in the evaluation of the gastric and oesophageal mucosal cancer depth. Future research will be essential for the determination of these techniques' role in the duodenum[13].

EMR

This technique was developed to remove sessile or flat tumors that are confined to the superficial layers (mucosa and submucosa) of the GI tract wall. Classically, it's used for *en bloc* or piecemeal resection, if the diameter is less or more than 2 cm, respectively[30]. The lesion is initially elevated by the injection of a saline substance into the submucosa that causes its protrusion into the duodenal lumen. Depending on the size of the polyp, the volume of injected solution can vary between 5 and 50 mL, and it may be necessary to repeat this procedure if the cushion created by the injected fluid dissipates before the resection is complete[30]. There are several solutions currently available, but isotonic saline (0.9% NaCl) is the most frequently used[30]. However, scientific evidence suggests that hypertonic solutions originate a better and longer-lasting elevation[6,31]. This procedure allows the isolation of the mucosa involved, facilitating its resection with an endoscopic snare, and reduces the risk of thermal and mechanical injury of the deepest layers. The non-lifting sign enables the identification of polyps that are likely to have submucosal invasion, and that don't usually have an indication for endoscopic treatment[6,19,31]. The inclusion of adrenaline in the injected solution reduces the haemorrhagic risk and provides better visibility[6]. As a diagnostic tool, and differently from ablative therapy, it holds an important role in obtaining samples for histological analysis[31]. When compared to snare or forceps polypectomy, EMR allows resection of a larger area, as well as access to deeper levels, through the excision of the medium or deep submucosal layer[31]. It thus facilitates histological assessment of the entire lesion and thereby identifies foci of malignancy that cannot be included in the surface sample obtained by forceps or snare biopsy[18] (Figure 1).

Efficacy

The predominantly retrospective published clinical trials report an EMR complete resection rate of nonampullary adenomas of 79%-100%[4,10-14,18,19,32,33]. In the studies that indicate the type of resection, it appears that in 64% of the cases it was possible to remove the polyp *en bloc*, having the remaining been excised with piecemeal resection[4,10,12,13,18,32-35]. The latter is more frequent in lesions larger than 20 mm, hardly removed safely *en bloc*, and seems to be associated with higher rates of recurrence and residual lesion[13,18,19,33]. The execution of the technique is a critical factor in minimizing these potential risks[19].

Kedia *et al*[12] studied the relationship between the adenomatous polyp size, the extent of duodenal lumen involved, and the efficacy of EMR. He concluded that although there is a significant association between the proportion of duodenal lumen involved and complete endoscopic resection, the same doesn't happen between the latter and the size of the lesion. The complete resection rate achieved in tumors involving less than

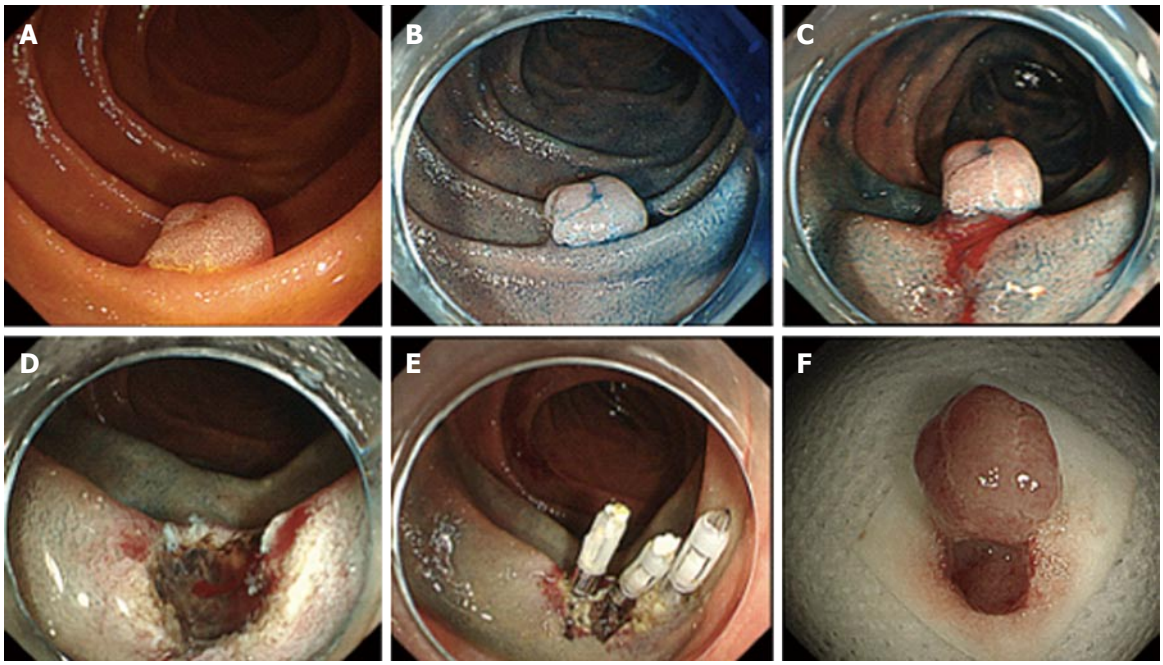

Figure 1 Endoscopic resection of a sporadic neoplastic lesion in the duodenum using endoscopic mucosal resection technique. A: Sessile lesion in the descending duodenum seen with white light (type 0 - Isp of the Paris classifi-cation); B: Same lesion after chromoendoscopy with indigo carmine; C: Same lesion after subepithelial injection of diluted adrenalin; D: Resected area after endoscopic mucosal resection; E: Closure of the resected area with clips; F: Lesion resected *en bloc*. Histology revealed a well-differentiated tubular adenocarcinoma limited to the mucosa, with 7 mm × 8 mm, without lymphatic or vascular invasion.

one quarter of the luminal circumference was 94.7%, compared to 45.5% in those involving one quarter to half of the circumference. In lesions where more than half of the luminal circumference was involved no lesion was resected successfully. Thus, this author suggests that the strongest clinical predictor of a successful polyp excision is the luminal extension that it involves. The American Society for Gastrointestinal Endoscopy (ASGE) guidelines indicate that surgery should be considered in adenomas involving more than 33% of the circumference of the lumen[24].

In the studies that report the number of sessions required to achieve complete resection, 80% of the cases it was possible with one session, 17% with two sessions and only 3% in three sessions[6]. In all situations, the purpose of who performs the EMR should be to remove the entire polyp in one session, without compromise of security[21]. Areas with residual adenoma and fibrosis are more difficult to resect during subsequent interventions, which are associated with increased risk of complications[6,9,21].

The recurrence rate varies widely between 0% and 36%, and all described recurrent lesions were treated with polypectomy snare or ablative therapy[6,9,13,18,19,36]. This high rate reinforces the need of a detailed resection of all adenomatous tissue, possibly with use of adjuvant therapy, and a rigorous follow-up period, especially in larger adenomas or with piecemeal resection[6,12,19].

Safety

Bleeding, which is associated with duodenal abundant vascularization, occurs during EMR (immediate bleeding) in 9% of procedures[6]. As there is no standardized definition of immediate haemorrhage, it's hard to know whether the reported cases were clinically significant or had comparable gravity. However, Lepilliez *et al*[18] does not consider it a true complication, since it can often be controlled by application of endoscopic clips, using ablative therapy or adrenaline injection adrenaline. None of the described cases needed blood transfusion[3,4,6,10,11,18,19].

Late bleeding rate ranges from 0 to 12%[1,4,10,12,13,18,19,33]. A recent study, that included 50 nonampullary adenomas, showed that the risk of delayed haemorrhage is significantly higher in lesions which diameter was bigger than 30 mm[35]. In all cases, bleeding occurred within the first 48 h after resection and was mostly approached conservatively or with endoscopic mono or bipolar electrocautery, epinephrine injection, haemostatic clips or a combination of these[1,4,10,12,13,18,19,33].

The proceeding method regarding the presence of visible non-bleeding vessels and the closure of the resected area as a preventive measure of late haemorrhage, are questions that don't gather a consensus answer[35]. Kim *et al*[13] defends that primary closure with clips is preferable to ablative therapy, since it does not increase the risk of tissue injury. Although closure of primary defects smaller than 2 cm is usually possible, it will probably be unnecessary, except in cases where there is potential risk of late bleeding[35]. On the other hand, areas bigger than 2 cm cannot be safely closed because of the difficulty in opposing margins of the defect[13,18,35]. In the study of Lépilliez *et al*[18], the difference found between late haemorrhage rate of the

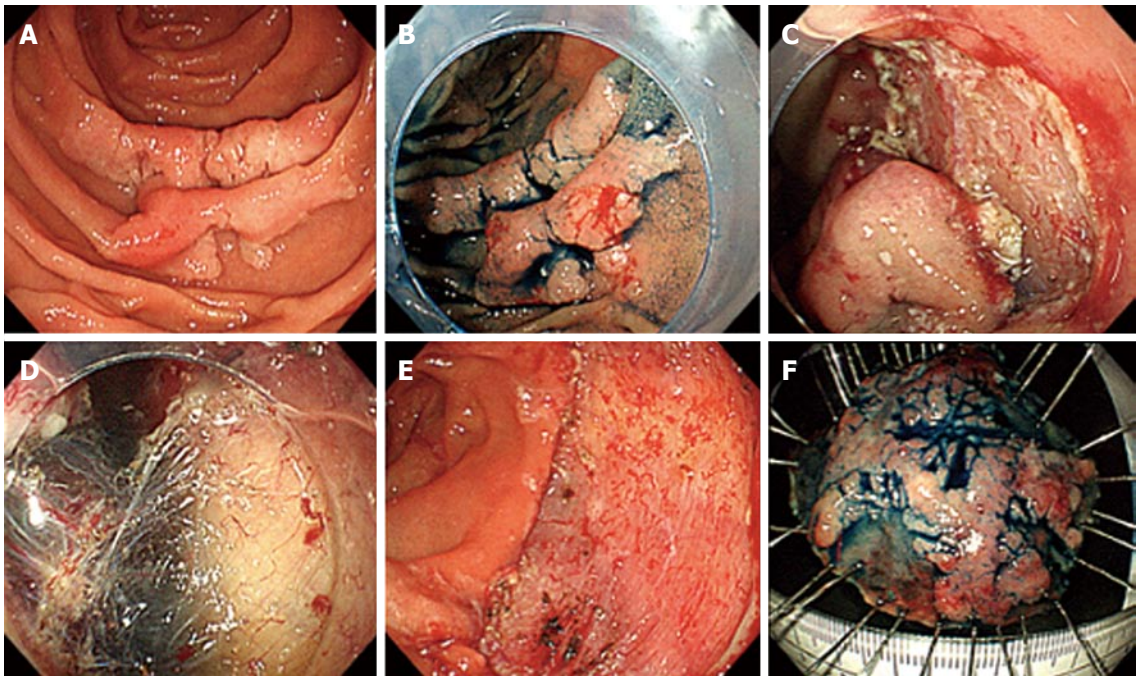

Figure 2 Endoscopic resection of a sporadic neoplastic lesion in the duode-num using endoscopic submucosal dissection technique. A: Flat lesion in the descending duodenum seen with white light (type 0-IIa of the Paris classi-fication); B: Same lesion after chromoendoscopy with indigo carmine; C: Partial dissection with endoscopic submucosal dissection; D: Dissection plan where the submucosal layer and the partially dissected lesion can be seen; E: Dissected area; F: *En bloc* dissected lesion. Histology revealed a well-differentiated adenocarcinoma limited to the mucosa, 40 mm × 32 mm, without lymphatic or vascular invasion.

cases that had haemorrhagic prevention systematically done (with ablative therapy or clips) or bleeding treatment was required during the procedure, and cases that didn't have bleeding prevention or immediate haemorrhage occurred, was statistically significant. In the first group, consisting of 14 patients, there was no late haemorrhage, while in the second 5 bleedings occurred in 23 patients (22%).

EMR has a perforation risk of the duodenal wall of 0.6%[6,35]. Registered perforations were managed with endoscopy or surgery conversion[18,35]. Resection limited to the adenomas that lifted after the submucosal injection may be a way of preventing this complication[36].

ESD

This technique is widely used for *en bloc* resection of gastrointestinal lesions[5]. Despite its growing use in the stomach, colon and oesophagus, its use in the duodenum is less frequent[37]. This fact is probably due to its retroperitoneal fixation, thin wall and narrow lumen, which make the intervention at this location technically difficult[14,29]. The low prevalence of duodenal lesions may be one of reasons that can explain the ESD long learning curve in the duodenum[14]. The published studies that performed this technique are few and include a small number of patients with short follow-up periods[14,29,33,38,39].

ESD is generally performed in several stages. After marking the margins of the lesion, by electrocauterization, and lifting it by submucosal injection, a circumferential incision is made in this layer, and the lesion is dissected from the underlying layers by using dissection knives[30] (Figure 2).

Efficacy

Complete resection rate of sporadic adenomatous nonampullary polyps by ESD ranges from 86% to 100%[14,22,29,33,38,39]. No recurrence was described[14,22,33,38,39]. The choice of ESD instead of piecemeal EMR may be a way of reducing the recurrence associated with this last technique[13].

In a study by Honda *et al*[14], in which 15 non ampullary adenomas were resected by endoscopy (9 by ESD and the rest by EMR), found that the average diameter of the lesions removed by ESD was 24 mm (the largest lesion had 39 mm), and that those removed by EMR had an average size of 8 mm. The mean time of the interventions was also registered. ESD and EMR procedures took respectively 85 and 16 min in average. The inclusion of larger and more challenging lesions, as well as duodenal more difficult haemostasis in duodenum, are possible explanations given by the author for the time consumed by ESD.

Obtaining en bloc resection with negative margins is a well-known ESD advantage[40]. According to Endo *et al*[33], ESD should be the procedure of choice for lesions larger than 10 mm, and when it is desirable to obtain en bloc resection (including lesions whose biopsy or magnification endoscopy are suggestive of carcinoma). In their study, all adenomas larger than 10 mm resected by EMR revealed positive margins. All adenomas resected by ESD had negative margins (the

biggest lesion diameter was 30 mm).

Safety

In three clinical trials, ESD was associated with a bleeding rate between 8% and 22%[14,22,41]. All cases were managed with endoscopic haemostatic clips, without requiring blood transfusion. The reported duodenal perforation rate is 31%[14,22,33,38,39]. This percentage is higher than the one obtained in the oesophagus, stomach and colon, and is associated to the anatomical peculiarities of the duodenum[22]. Duodenal perforation may have a difficult approach and contribute to increased morbidity and mortality of the patient, hospitalization period and health care costs[40].

Late perforation is a very serious complication that, according to a retrospective study published in 2013, is significantly associated with the endoscopic technique that was used and the location of the lesion[41]. In this study, that included lesions resected by EMR or ESD, all late perforations occurred after ESD or piecemeal EMR, which according to the authors, may be due to electrocautery overloading. It was also found that all perforations were distal to the ampulla of Vater, which seems to happen because of the proteolysis or chemical irritation caused by exposure of the duodenal wall to the pancreatic juice and bile enzymes, which can be decreased with the administration of protease inhibitors[14,39]. Given that there are several factors that may be associated with perforations, it is difficult to clarify which ones are more likely to relate to their origin[22]. Jung suggests that ESD is itself a perforation risk factor and, therefore, it should be performed only in selected patients[39]. The most appropriate prophylactic intervention and approach to late perforation in the duodenum have not been established yet[41].

FOLLOW-UP

The guidelines published by the ASGE emphasize that all patients who have undergone endoscopic resection of a sporadic duodenal adenoma should be considered for a follow-up program for the detection and treatment of any recurrence[24]. However, because of the lack of information, formal recommendations regarding surveillance intervals have not been defined. These should be applied on a patient-basis adjusted on the characteristics of the polyp, adequacy of the initial resection, eventual occurrence of complications and comorbidities of the patient[22]. According to a review article, most authors recommended a follow-up endoscopy 3-6 mo after resection, followed by surveillance endoscopies each 6 to 12 mo[6].

CONCLUSION

Analysis of the literature on this topic reveals a reduced number of reviews and studies, that generally include a small sample of patients and short follow-up periods, which hinders drawing consistent conclusions about the endoscopic resection long-term effectiveness of sporadic nonampullary adenomas[13,19,26,34]. Some of the results obtained in clinical trials exhibit considerable variability, which doesn't have a clear justification, but may be associated, for example, to inconsistencies in outcome definitions by different authors, as well as the length of the follow-up period[7]. Moreover, most studies have a retrospective character, which can introduce selection bias and underestimate the complication rate[34].

Although most of the analysed studies and endoscopic techniques mentioned in this review were predominantly developed in Asian countries, it is important to note that this reality may not reflect the Western context[6]. After comparing these two populations, Min *et al*[34] states that Western studies show a lower complete resection rate, and suggests that this discrepancy can be clarified by the smaller sized lesions included in Asian studies, since the diagnosis of smaller adenomas has increased in these countries due to gastric cancer screening programs and subsequent widespread of the endoscopy[12,18,19,34]. Local recurrence rates are higher in Western countries, which again may be explained not only by the difference in the lesions size, but also by the follow-up period after resection, that seems to be shorter in Asia (6-29 mo *vs* 13-71 mo)[34]. Authors, however, rarely address this divergence.

EMR is an alternative to surgery in patients with less invasive superficial duodenal adenomas, entailing shorter hospital in-stay, lower costs, and providing a reasonable complication rate that can usually be controlled by endoscopy[13]. Resection is most likely to be complete in adenomas involving less than half of the luminal circumference[12]. It requires a tight monitoring period, especially after big adenomas or piecemeal resection, so that early detection and treatment of residual or recurrent lesions is possible[6,13]. ESD, although potentially providing en bloc resection with negative margins, has higher haemorrhagic and perforation risks in the duodenum when compared to EMR[9]. Therefore, when choosing the appropriate endoscopic technique, the risks of the procedure must be balanced against its benefits[40].

Although the scientific evidence level in this area is limited, the results obtained in these last years are encouraging. However, prospective studies with larger samples and extended follow-up periods will be necessary. Future development of techniques and tools that contribute to the prevention and early detection of recurrence, and increase the efficacy and safety of endoscopic resection in the duodenum, will be essential for a better therapeutic approach to these patients.

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ORIGINAL ARTICLE

Basic Study

Feasibility and safety of endoscopic cryoablation at the duodenal papilla: Porcine model

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Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at mihir.wagh@medicine.ufl.edu. No additional data is available.

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Abstract

AIM: To assess the feasibility and safety of liquid nitrogen spray cryoablation at the duodenal papilla in a porcine model.

METHODS: This prospective study protocol was approved by the University of Florida Institutional Animal Care and Use Committee. Six pigs underwent liquid nitrogen spray cryotherapy at the duodenal papilla. Freeze time of 20-s was applied per cycle (4 cycles/session). Survival animals (n = 4) were monitored for adverse events. Hemoglobin, white blood count, liver tests, and lipase were obtained at baseline and post-treatment. EGD was performed on day#7 to evaluate the papilla and for histology. All animals were euthanized and necropsy was performed at the end of the one-week survival period. Feasibility was defined as successful placement of the decompression tube in the duodenum, followed by delivery of spray cryotherapy to the duodenal papilla. Safety was determined by monitoring post-treatment blood tests and clinical course. Treatment effect was defined as endoscopic and histologic changes after cryotherapy. This was established by comparing endoscopic and histologic findings from mucosal biopsies prior to cryotherapy and on post-operative day (POD)#7. Full-thickness specimen was obtained post-mortem to assess depth of injury.

RESULTS: Spray cryotherapy was feasible and successfully performed in all 6/6 (100%) animals. Cryospray with liquid nitrogen (four 20-s freeze-thaw cycles) at the duodenal papilla resulted in white frost formation at and around the target region. The mean procedural

time was 54.5 min (range 50-58 min). All six animals studied had stable blood pressure, heart rate, and pulse oximetry measurements during the procedure. There were no significant intra-procedural adverse events. There were no significant differences in hemoglobin, white cell count, liver tests or lipase from baseline to post-cryotherapy. Survival animals were monitored daily post-operatively without any clinical ill effects from the cryotherapy. There was no bleeding, infection, or perforation on necropsy. Endoscopic on POD#7 showed edema and ulceration at the duodenal papilla. On histology, there was loss of crypt architecture with moderate to severe necrosis and acute mixed inflammatory infiltration in each specimen following cryotherapy. The extent of cryogen-induced tissue necrosis (depth of injury) was limited to the mucosa on full-thickness specimen evaluation.

CONCLUSION: Endoscopic liquid nitrogen spray cryotherapy is feasible and safe for ablation at the duodenal papilla in a porcine model.

Key words: Liquid-nitrogen cryotherapy; Cryoablation; Duodenal adenoma; Ampullectomy; Papillectomy

Core tip: With advances in therapeutic endoscopy, endoscopic resection is commonly performed for the management of ampullary adenomas. However, endoscopic papillectomy can still carry significant morbidity, especially in elderly patients with comorbidities. Hence, less invasive effective endoscopic ablative modalities would be desirable. In this study, we demonstrate that endoscopic liquid nitrogen spray cryotherapy is feasible and safe for ablation at the duodenal papilla in a porcine model. These preliminary findings suggest a potential role of cryotherapy as an adjunct endoscopic treatment for residual/recurrent ampullary lesions or as a primary modality in patients who are not optimal candidates for surgery or endoscopic resection.

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INTRODUCTION

Ampullary adenomas are dysplastic glandular lesions that arise from the major duodenal papilla. These lesions can occur sporadically or arise in the context of genetic syndromes such as familial adenomatous polyposis. If not removed, ampullary adenomas can potentially undergo malignant transformation to ampullary cancer with a reported incidence from 25% to 85%[1-3]. Based on this risk, these lesions have been treated historically with pancreatoduodenectomy, a highly invasive surgical intervention associated with high morbidity and mortality[4,5]. With advances in therapeutic endoscopy, there has been a shift towards endoscopic resection, with consideration of surgery only for locally advanced lesions. While endoscopic approaches for the treatment of ampullary adenomas are less invasive than surgery, adverse events associated with endoscopic papillectomy still carry a reported morbidity and mortality rate of 23% and 0.4% respectively[6]. Hence a less invasive modality for endoscopic ablation of ampullary lesions would be helpful, especially in elderly asymptomatic patients with comorbidities.

There has been a growing interest in endoscopic mucosal ablative techniques for the management of different gastrointestinal pathologies, ranging from adenomatous lesions, dysplasia and/or intramucosal carcinoma, to bleeding mucosal lesions in the GI tract[7]. Currently, the role of endoscopic ablative techniques (argon plasma coagulation, laser therapy, monopolar o bipolar coagulation) for ampullary adenomas is limited to destruction of residual or recurrent adenomatous tissue following resection[8].

Cryotherapy is a mucosal ablative technique that employs non-contact delivery of either low-pressure liquid nitrogen or compressed carbon dioxide (CO_2) gas for tissue destruction.

There are currently two commercially available endoscopic cryotherapy systems for the gastrointestinal tract. One device delivers low-pressure liquid nitrogen (at -196 ℃) (CryosprayAblation, CSA Medical Inc, Baltimore, MD) whereas the other system is based on the Joule-Thompson effect, in which highly compressed CO_2 gas produces cooling upon rapid expansion and decrease in pressure (Polar Wand; GI Supply, Camp Hill, PA)[9]. Most of the current clinical experience with endoscopic cryotherapy as a mucosal ablative technique is primarily related to the data on ablation of Barrett's esophagus, where this method has been shown to be efficacious and well tolerated[10]. The use of cryotherapy in other extra-esophageal sites, besides treatment of bleeding in the stomach and colon[11], has been limited to some degree by the concern of gas expansion and high risk of barotrauma and perforation in other regions of the GI tract. We recently reported preliminary data suggesting that liquid nitrogen cryotherapy is a safe technique even in patients with altered post-surgical gastric anatomy when appropriate measures are taken for cryogen gas decompression[12]. The aim of our study was to investigate the feasibility and safety of endoscopic liquid nitrogen spray cryotherapy at the duodenal papilla in a porcine model.

MATERIALS AND METHODS

Study

This prospective study protocol was approved by the

University of Florida Institutional Animal Care and Use Committee. Six female pigs (sus) weighing 80-100 lbs were obtained from the University of Florida Swine Unit. The aim of this study was to prospectively assess the feasibility and safety of endoscopic liquid nitrogen spray cryotherapy at the duodenal papilla in a porcine model.

Animal care and use

The animal protocol in this study was designed to minimize pain or discomfort to the animals. Pigs were housed and maintained in the University of Florida Animal Care Services unit. The animals were acclimatized to laboratory conditions (23 ℃, 12h/12h light/dark, 50% humidity, *ad libitum* access to food and water) for 7-10 d prior to experimentation. All animals were euthanized by barbiturate overdose (intravenous injection, 150 mg/kg pentobarbital sodium) for necropsy.

Outcomes and definitions

Primary outcomes: (1) feasibility was assessed by the technical success of cryotherapy in this porcine model. Technical success was defined as successful placement of the cryotherapy decompression tube past the papilla in the second portion of the duodenum, followed by delivery of liquid nitrogen spray to the duodenal papilla; and (2) safety was determined by monitoring peri-procedural blood tests and clinical course. Endoscopic adverse events were defined based on previously established criteria[13] and post-operative signs of distress, behavior changes, and/or loss of appetite. Elevation of liver tests and lipase post-cryotherapy to more than 3 times the upper limit of normal was considered abnormal.

Secondary outcome: Treatment effect was defined as endoscopic and histologic changes after cryotherapy. This was established by comparing endoscopic and histological findings from mucosal biopsies prior to cryotherapy and on post-operative day (POD)#7. The degree of intestinal injury was graded as previously described by Park *et al*[14]. Full-thickness specimen was obtained post-mortem to assess depth of injury.

Endoscopes and accessories

A single-channel gastroduodenoscope (GIF-140 Olympus Medical Systems, Tokyo, Japan) was used for the study. A pediatric colonoscope (PCF-140, Olympus Medical Systems, Tokyo, Japan) was used as needed, to overcome the J-shaped porcine gastric anatomy in order to have adequate length of the scope available to access the distal duodenum. Endoscopic biopsy forceps (Boston-Scientific, Natick, MA) were used for endoscopic tissue acquisition.

Cryotherapy

Liquid nitrogen spray cryotherapy (CryoSpray Ablation system, CSA Medical Inc, Baltimore, MD) was used for the study. This cryotherapy system, consists of (1) a console with a liquid nitrogen holding tank and a foot pedal for the release of low-pressure (3 to 6 psi) liquid nitrogen (temperature -196 ℃); (2) a 7-French cryocatheter, which is inserted through the working channel of an endoscope; and (3) a modified orogastric cryode compression tube (CDT) placed alongside the endoscope prior to starting cryotherapy. This special decompression tube has two channels, one for passive venting and another for active suction, attached to a separate suction machine to evacuate the rapidly expanding evaporated cryogenic gas during the procedure.

Freeze time was defined as the time interval from the visualization of white frost (ice formation) along the entire surface of the papilla until the cryospray was stopped. Procedure time was defined as the time from endoscope insertion to withdrawal.

Pre-operative care and anesthesia

Animals were not fed for 24 h prior to the procedure. Animals were pre-anesthesized with intramuscular (IM) injection of 4 mg/kg Telazol, ketamine 2 mg/kg, xylazine 2 mg/kg, and atropine (0.04 mg/kg) or glycopyrrolate (0.001 mg/kg). Induction was performed with isoflurane 3%-5% *via* mask delivered with a precision vaporizer prior to intubation. General endotracheal anesthesia was administered with Isoflurane 1%-3.5%. An intravenous (IV) line was placed in the marginal ear vein. Pigs were intubated and placed on mechanical ventilation.

Blood tests

In survival studies, blood specimens to evaluate hemoglobin (Hb), white blood count (WBC), liver tests (AST, ALT, alkaline phosphatase and bilirubin), and lipase were obtained prior to endoscopic treatment (day 0) and post cryotherapy (day 1 and on day 7).

Endoscopic procedure

The intended treatment site (duodenal papilla) was identified by endoscopic visualization. The pediatric colonoscope (Olympus Medical Systems, Tokyo, Japan) was introduced past the second portion of the duodenum and a 0.035 inch, 350 cm length guide-wire (Jagwire, Boston Scientific, Natick, MA) was placed. The endoscope was exchanged over the guidewire and the CDT was placed distal to the papilla. Adequate positioning of the CDT (tip of tube past the papilla in the second portion of the duodenum) was confirmed by re-inserting the endoscope, and the guide-wire was removed. The CDT was connected to active high suction controlled by a foot pedal during cryotherapy.

For survival animals, two peri-ampullary endoscopic biopsies were obtained as baseline prior to initial cryotherapy. The cryocatheter was introduced through the accessory channel of the endoscope and oriented to directly target the duodenal papilla. The freeze time was established as the period from ice formation along the entire surface of the papilla until the cryospray was stopped. The liquid nitrogen dosimetry of 4 cycles of 20-s freeze time was based on published dosing from previous animal studies[15,16]. There was complete

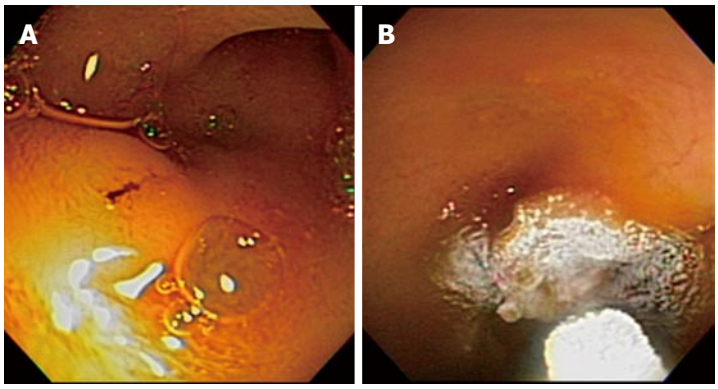

Figure 1 Endoscopic view of porcine duodenal papilla. A: Normal porcine duodenal papilla prior to treatment; B: Frost formation at the porcine duodenal papilla following liquid nitrogen cryotherapy.

thawing of ice between freeze cycles. Expanding liquid nitrogen gas was continuously suctioned via the CDT and through the endoscope between freeze cycles. Continuous monitoring for abdominal distention was performed by anesthesia personnel during the procedure.

Post-operative care, follow up and necropsy

The first two animals were used exclusively to evaluate the feasibility of liquid nitrogen cryotherapy at the duodenal papilla, and thus, were not survived. The animals were euthanized upon completion of the endoscopy, and necropsy performed. At necropsy, the peritoneal cavity and cryotherapy site was visually inspected for perforation, bleeding or damage to surrounding structures.

In survival experiments, pigs were extubated and recovered from general anesthesia. The pigs were monitored daily for any post-treatment adverse events, based on signs of distress, behavior changes, and/or loss of appetite. Oral feedings with standard chow were started the same day after recovering from anesthesia (day 0). Blood specimens were obtained at baseline (day 0), post-cryotherapy day 1 and day 7. Endoscopy was repeated on day 7 after cryotherapy to assess treatment effect at the duodenal papilla and biopsies were obtained at the cryotherapy site. At the end of the procedure, animals were euthanized and necropsy performed to rule out intra-abdominal adverse events associated with cryotherapy, such as transmural injury, bleeding, bowel perforation or abscess formation. Full-thickness duodenal specimen was obtained for histologic examination from one of the survival animals following necropsy.

Histologic examination

Biopsy specimens from all survival animals were obtained at the cryotherapy site on day 7 to assess the degree of intestinal injury. To evaluate the depth of the treatment effect, a full-thickness specimen containing the duodenal papilla was harvested from one of the survival animals following necropsy. All specimens were fixed in 10% neutral buffered formalin for at least 48 h, embedded in paraffin and stained with standard hematoxylin and eosin. The degree and depth of intestinal injury was graded by a single experienced pathologist as previously described in the text.

Statistical analysis

Summary data was expressed as the mean ± SD, and range. One-way analysis of variance (analysis of numerical data) was performed (GraphPad Prism version 6.00 for Windows, GraphPad Software, San Diego California, United States). The statistical methods of this study were reviewed by [Name, division, organization].

RESULTS

Endoscopic liquid nitrogen spray cryotherapy was performed at the duodenal papilla in 6 animals (2 non-survival and 4 survival studies).

Feasibility and safety of liquid nitrogen spray cryotherapy at the duodenal papilla

The duodenal papilla was identified in all 6 cases. The distal end of the CDT was successfully placed past the papilla into the second portion of the duodenum (Figure 1A) in all 6 animals. Cryospray with liquid nitrogen at the duodenal papilla resulted in white frost formation at and around the target region (Figure 1B). Four 20-s freeze-thaw cycles were applied with thawing between each session. Technical success was initially confirmed in the two non-survival animals and also subsequently achieved in all four survival swine studies (6/6; 100%). The mean procedural time was 54.5 min (range 50-58 min). All six animals studied had stable blood pressure, heart rate and pulse oximetry measurements during the procedure and there were no intra-procedural adverse events.

In survival studies, all 4 animals were recovered from general anesthesia and transferred to their housing facility, where they resumed regular feeding the same day of the procedure. The swine were monitored daily without any clinical ill effects from the cryotherapy (no change in activity, feeding habits and bowel and bladder elimination functions). There were no significant changes in Hb, WBC, liver tests or lipase on day 1 and 7 following cryoablation when compared to baseline (Table 1). There was no evidence of bleeding, infection (abscess), or bowel perforation on necropsy in any of

Table 1 Laboratory findings from survival animals (n = 4) at baseline (prior to liquid nitrogen cryospray application), on post-cryotherapy day #1 and #7

Lab	Mean (range)			*P* value
	Baseline	Day 1	Day 7	
Hemogloobin, g/dL	11.2 (10.2-12.3)	11.8 (11.1-12.3)	11 (9.9-11.6)	0.36
White blood count, K/μL	16.6 (12.9-17.4)	19.8 (14.1-22)	17.4 (15-21.9)	0.53
Alkaline phosphatase, U/L	98.8 (90-112)	102 (93-112)	84.5 (72-100)	0.15
Alanine transaminase, U/L	44.3 (32-52)	57.5 (47-80)	53.5 (45-57)	0.25
Aspartate transaminase, U/L	22.8 (16-31)	117.3 (24-385)	22.3 (17-29)	0.37
Total bilirubin, mg/dL	0.2 (0.1-0.3)	0.2 (0.1-0.2)	0.1 (0.1-0.2)	0.53
Lipase, U/L	5.5 (4-8)	9.3 (6-11)	4.8 (2-9)	0.06

Table 2 Histology findings

Swine	Baseline[1]		Day 7[2]	
	Crypt architecture	Inflammation	Crypt Architecture	Inflammation
1	Normal	None	Moderate necrosis	Moderate
2	Normal	None	Moderate necrosis and extensive debris	Moderate to severe
3	Normal	None	Severe necrosis and moderate debris	Severe with dense fibrosis
4	Normal	None	Moderate necrosis and extensive debris	Moderate

[1]Mucosal biopsies of duodenal papilla prior to cryotherapy; [2]Mucosal biopsies obtained from cryotherapy site at duodenal papilla 7 d following liquid nitrogen cryospray application.

the animals.

Liquid nitrogen cryotherapy effects on the duodenal papilla

At 7 days after cryotherapy, survival animals underwent a follow up endoscopy for evaluation of treatment effect on the duodenal papilla. Edema, erythema and ulceration of the papilla were seen on endoscopy (Figure 2). Mucosal biopsies from the papilla were obtained and compared to baseline. The histologic findings of each animal are summarized in Table 2. There was loss of crypt architecture with moderate to severe necrosis and acute mixed inflammatory infiltration in each specimen obtained from the duodenal papilla on day 7 following cryotherapy. The extent of cryogen-induced tissue necrosis (depth of injury) was limited to the mucosa, with the application of four 20-s freeze-thaw cycles of liquid nitrogen (Figure 3).

DISCUSSION

Endoscopic papillectomy has been increasingly used for the treatment of ampullary adenomas and early cancers. While this approach is less invasive than surgery, it is still associated with significant risks and is mainly performed by experienced endoscopists. As such, alternative endoscopic ablative therapies would be helpful, especially for the treatment of elderly asymptomatic patients with multiple comorbidities.

Endoscopic cryotherapy has been primarily used for the management of dysplastic Barrett's esophagus and early esophageal cancer. The clinical application of this mucosal ablative technique in extra-esophageal gastrointestinal tract has been limited by the potential risk of perforation from barotrauma. When liquid nitrogen is delivered to the lumen, it undergoes phase transformation into a gaseous state as energy is delivered to the target tissue[16]. If not evacuated properly, the rapidly expanding nitrogen gas can be a risk for gastrointestinal perforation. Previous reports have evaluated the feasibility of liquid nitrogen cryotherapy in the stomach[17]; however, its application in the small intestine has not been evaluated.

The present study demonstrates the feasibility and safety of endoscopic liquid nitrogen spray cryotherapy at the duodenal papilla in a porcine model. The commercially available CDT could be successfully placed, with the tip of the tube in the second portion of the duodenum in all 6 animals in this study. This step was crucial as it allowed for adequate suction of the nitrogen gas during cryospray application at the duodenal papilla. There were no apparent adverse effects associated with the cryotherapy based on daily post-treatment monitoring, lab data and necropsy 7 d following treatment. There was no evidence of changes in hemoglobin, WBC, liver tests or lipase from ablation at the duodenal papilla.

Our study validated cryogen treatment effect at the duodenal papilla on endoscopy and histology 7 d following treatment. The dosimetry of 4 cycles of 20-s freeze in this study was based on previous reports in animal studies as well as the commonly applied dosimetry for liquid nitrogen spray cryotherapy used in the treatment of BE with high-grade dysplasia or adenocarcinoma[18-20]. Endoscopic appearance of lesions at the duodenal papilla on day 7 ranged from mild erythema and edema to superficial erosions. These results are similar to the endoscopic findings reported by Johnston *et al*[15] in swine esophagus on day 7 following liquid nitrogen cryospray application.

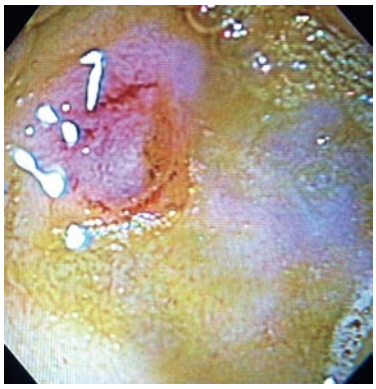

Figure 2 Endoscopic view of duodenal papilla 7 d following liquid nitrogen cryospray application.

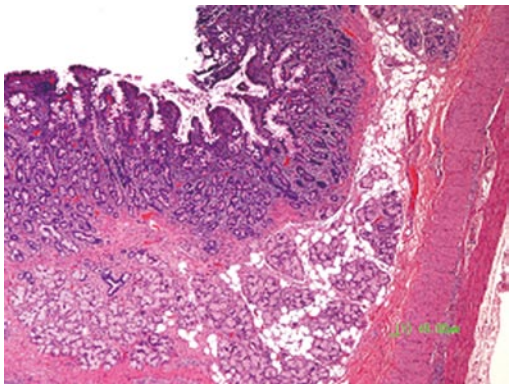

Figure 3 High-power microscopic view (HE x 40) of porcine duodenal papilla 7 d after application of a liquid nitrogen cryospray dose of 20 secfor 4 freeze-thaw cycles. There is severe blunting and loss of villar tips, infiltration of fibrous tissue and influx of mixed inflammatory cells into the lamina propria and loss of crypt architecture extending through the mucosa. The submucosa and muscularis propria are intact.

Our results demonstrate the effect of cryospray on histology based on the mucosal biopsies from the duodenal papilla on day 7. Histology on day 7 (4/4 animals) revealed loss or blunting of villous tissue and tips, crypt architectural distortion with necrosis and debris, and a mixed moderate to severe inflammatory infiltrate. This is a marked change from the normal histology obtained at baseline from the duodenal papilla and confirms treatment effect from the liquid nitrogen cryospray. We also demonstrate from a full-thickness specimen that the depth of injury was reserved to the mucosa, with inflammation and necrosis limited to the lamina propria and intact submucosa and muscularis propria. Previous animal studies have demonstrated dose-dependent injury to the esophagus, with necrosis involving the submucosa and even transmural damage with short exposures (15-30 s)[15,21]. In contrast, Shin and colleagues revealed that average grades of injury in the stomach across various doses were lower when compared with the esophagus[7]. We can speculate that the depth of tissue injury at the duodenal papilla from 4 cycles of 20-s of freeze time followed by thawing was associated with less injury compared to other studies because of differences in anatomical location in the gastrointestinal tract and mode of delivery (liquid nitrogen *vs* carbon dioxide). Further studies are needed to evaluate the relationship of cryogen dosimetry and depth of tissue injury in the small bowel.

We acknowledge the limitations of this study. First, our experiments were performed in a porcine model. While this animal model has been commonly used for experimental endoscopic studies, there are some important differences between human and porcine GI tract anatomy. The distal common bile duct and pancreatic duct in swine are not confluent at the duodenal papilla in pigs. In fact, while the biliary orifice is situated proximally in the duodenum at the papilla the pancreatic duct orifice is located separately several centimeters distal to the site of the biliary orifice. Since the primary aim of this pilot study was to evaluate the feasibility and safety of cryoablation at the duodenal papilla, we did not investigate treatment effect at the separate pancreatic duct orifice. This anatomical difference theoretically confers a decreased risk for pancreatic adverse events, including pancreatitis, when the duodenal papilla or biliary tract is manipulated in the porcine model. Thus, while there were no significant changes in serum lipase levels in our study to suggest pancreatitis following cryotherapy, we cannot definitively assess for this adverse event. Future studies are needed to evaluate the treatment effect and safety of cryotherapy at the pancreatic orifice. For this same reason, a pancreatic stent was also not placed after cryotherapy at the biliary orifice/papilla in this study, though this would need to be placed in human patients as is routinely done after endoscopic ampullectomy.

Second, as opposed to a side-viewing endoscope that is used in humans for endoscopy therapy at the papilla, a forward viewing endoscope (or pediatric colonoscope to overcome the J-shaped porcine gastric anatomy) was used to advance to the distal duodenum for adequate placement of the cryotherapy decompression tube. This technical hurdle may not be an issue with the human anatomy. Interestingly, the side-viewer may pose another challenge not encountered with the forward viewing endoscope used in this study. Use of the elevator of the side-viewing duodenoscope may theoretically kink the cryo catheter and not allow cryotherapy. However, the recently available, second generation of the cryotherapy device (truFreeze G2 spray cryotherapy device, CSA Medical Inc, Baltimore, MD) has a stainless steel reinforced catheter that enables 180 degree retroflexion and this upgrade may overcome the potential problem with the elevator. Additional studies in humans would be needed to evaluate the technical feasibility of placing the decompression tube side-by-side with a duodenoscope and performing cryotherapy with use of the elevator.

Third, in the absence of an animal model for ampullary lesions, cryotherapy was performed on normal porcine tissue. Thus, the extent of cryogen-induced effects may differ in humans with pathology (adenoma/carcinoma) at the duodenal papilla. Furthermore, our

study was limited to small numbers of animals and findings on depth of injury need to be confirmed in larger human protocols. Lastly, the study follow-up was relatively short (7 d); therefore, long term cryo ablative effects at the duodenal papilla were not evaluated.

Despite these shortcomings, our feasibility data shows that there were no adverse events from cryotherapy at the papilla. Specifically, there was no evidence of GI tract perforation, bleeding, cholangitis or bile duct injury despite directly spraying liquid nitrogen (that transforms to gaseous state with major increase in volume) at the open biliary orifice and therefore up the bile duct. Hence it appears that cryotherapy may be a viable option for treating ampullary lesions but further studies are needed to examine optimal dosimetry, effects on the pancreas and ablation of actual neoplastic tissue.

Our preliminary findings suggest that endoscopic liquid nitrogen cryotherapy at the porcine duodenal papilla is both feasible and safe. This data may serve as starting point for assessing the potential role of cryotherapy as an adjunct endoscopic treatment for residual/recurrent ampullary lesions or as a primary modality in patients who are not optimal candidates for surgery or endoscopic resection. Further studies are needed to determine the relationship between dosimetry and tissue injury at the duodenal papilla, with specific testing for effects on the pancreatic duct.

COMMENTS

Background

There is a growing interest in endoscopic mucosal ablative techniques for the management of different gastrointestinal pathologies, ranging from adenomatous lesions, dysplasia and/or intramucosal carcinoma. The role of endoscopic ablative techniques for the management of ampullary adenomas has not been fully elucidated.

Research frontiers

Cryotherapy is an emerging endoscopic mucosal ablative technique. Most of the current clinical experience with endoscopic cryotherapy is primarily related to data on ablation of Barrett's esophagus. The use of cryotherapy in other extra-esophageal sites has been limited to some degree by the concern of gas expansion and high risk of barotrauma and perforation in other regions of the GI tract.

Innovations and breakthroughs

The authors had previously reported preliminary data suggesting that liquid nitrogen cryotherapy is a safe technique even in patients with altered post-surgical gastric anatomy when appropriate measures are taken for cryogen gas decompression. This is the first study that has evaluated the feasibility and safety of endoscopic liquid nitrogen spray cryotherapy at the duodenal papilla in a porcine model.

Applications

This study demonstrates that spray cryotherapy was feasible and successfully performed in all animals. Survival animals thrived without adverse events. Follow-up evaluation one week post-treatment confirmed cryotherapy-induced tissue necrosis limited to the mucosa. These preliminary findings suggest a potential role for cyrotherapy as a primary or adjunct modality for patients who are not optimal candidates for surgery/endoscopic resection or in those with residual/recurrent disease.

Terminology

Endoscopic cryotherapy: mucosal ablative technique that employs non-contact deliver of either low-pressure liquid nitrogen or compressed carbon dioxide gas for tissue destruction. Technical success was defined as the successful placement of the cryotherapy decompression tube past the papilla followed by the delivery of liquid nitrogen spray to the target. Treatment effect was defined as endoscopic and histologic changes after cryotherapy. Freeze time was defined as the time interval from the visualization of white frost (ice formation) along the entire surface of the papilla until the cryospray was stopped.

Peer-review

Well designed, elegant animal study. The primary aim of the study was to assess the safety of a new therapeutic modality. The first acquired data proved the feasibility and safety during the short term follow-up period. The data are important and could be used in human studies.

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ORIGINAL ARTICLE

Retrospective Study

Obtaining research biopsies during pediatric colonoscopy: Safety and adverse events

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Data sharing: Consent for data sharing was not obtained. All data was collected in a de-identified and anonymous manner.

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Abstract

AIM: To investigate the safety profile of acquiring additional intestinal biopsies for research purposes in children undergoing a medically indicated colonoscopy.

METHODS: A retrospective review of 122 pediatric patients who underwent colonoscopy over a 9 mo time period was completed. 38/122 participants consented to a research study in which 4 additional biopsies were obtained, in addition to routine biopsies. The outcomes after colonoscopy were measured in the research participants, and compared to 84 control participants who did not consent for the study. Groups were compared with regard to number of biopsies obtained, underlying diagnosis, and both serious and minor adverse outcomes. Data was collected including: age, gender, race, indication, diagnosis, number of biopsies obtained per case and post procedure adverse events. Medical records were reviewed and a questionnaire was completed by each of the ten gastroenterologists who performed procedures during the study. Physicians were asked about individual patient outcomes to ensure that all adverse events, such as perforation, excessive bleeding, infection, and minor gastrointestinal outcomes, were captured and included.

RESULTS: The research group had more biopsies obtained (mean = 13.58 ± 4.21) compared to controls (mean = 9.33 ± 4.40), $P \leqslant 0.0001$, however there was no difference in adverse events. Serious outcomes, defined as perforation, bleeding and infection, did not occur, in either group. As such, the relationship between serious adverse events and number of biopsies obtained was not determined. Minor gastrointestinal outcomes, such as abdominal pain, diarrhea or vomiting, were reported in 21 patients (8 research participants and 13 control participants) however the incidence of minor gastrointestinal outcomes between the two groups did not vary significantly, $P = 0.45$. Additionally, the mean

number of biopsies obtained in patients who had a minor outcome (mean = 12.1 ± 0.77), compared to those with no adverse outcome (mean = 10.34 ± 0.5), revealed no statistical difference between the groups (P = 0.12), suggesting that number of biopsies is not associated with incidence of minor adverse events.

CONCLUSION: Patients participating in research requiring acquisition of additional biopsies for research purposes alone, are not at an increased risk of adverse outcomes.

Key words: Pediatric colonoscopy; Outcomes; Research; Safety; Intestinal biopsy

Core tip: Acquiring biopsies for research purposes during a colonoscopy may facilitate translational research in the field of gastroenterology. However, the safety profile of acquiring research biopsies has not been established. Our study is the first to conclude that acquiring additional biopsies for research during a colonoscopy does not pose additional risk to the pediatric patient. This manuscript may serve as a reference to researchers applying for IRB approval in biological specimen studies. Additionally, our study is additive to the body of literature on outcomes after pediatric colonoscopy, in that minor gastrointestinal symptoms were the only reported adverse event after colonoscopy.

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INTRODUCTION

Colonoscopy with biopsies is a common procedure in children for the evaluation and diagnosis of gastrointestinal disease. Serious complications, such as perforation and bleeding are routinely discussed during the consent process, however, these events are rare[1-3]. Several adult studies have sought to measure the incidence of adverse outcomes during routine procedures[2,4,5], and this data has largely been applied to the pediatric population[6]. In adults, colorectal perforation is presumed to occur in 0.09% of the general population[7,8], while it remains unclear as to whether patients with pre-existing inflammatory bowel disease (IBD) are at an increased risk for serious outcomes, such as perforation[7,9,10]. The incidence of bleeding after colonoscopy is thought to occur infrequently during routine procedures[8].

There is limited data on serious adverse events in children, such as bleeding. Although one study found that 38.6% (34/86) of all reported complications were related to gastrointestinal bleeding, bleeding was not defined[3]. Other pediatric studies did not include bleeding in their outcome analysis[6]. Infection, similarly regarded as a serious and uncommon outcome after colonoscopy, has not been widely studied in pediatrics[11]. Likewise, minor post-procedure gastrointestinal symptoms, such as bloating and abdominal pain, are not well described in the pediatric literature[12].

The current pediatric studies are limited in number and do not quantify the number of routine biopsies obtained per procedure which may be a risk factor for adverse events. Additionally, these studies have not addressed whether obtaining additional biopsies solely for research purposes imposes additional risk to the patient. To our knowledge, this issue has not been addressed in the pediatric or adult literature. It is critical to establish the safety profile of collecting additional biopsies for research during routine procedures, so that investigators seeking institutional review board (IRB) approval are able to proceed with important research questions. The absence of this risk assessment may explain why studies involving the collection of pediatric biological specimens are difficult to pursue. Such IRB protocols pose a challenge to both author and reviewer, in that the lack of prior safety data serves as an obstacle for IRB approval. To address this gap, we performed a retrospective review for all children undergoing routine medically indicated colonoscopies and measured adverse events. Thirty-one percent of the participants had previously consented for a research study involving the acquisition of four additional intestinal biopsies designated for research purposes. By comparing adverse events in the research study participants to patients who did not consent, the controls, we established that acquiring additional biopsies for research alone is safe.

MATERIALS AND METHODS

We performed a retrospective review of all pediatric patients undergoing a medically indicated routine colonoscopy from June 5, 2013-March 5, 2014. Anesthesia was provided by pediatric anesthesiologists.

Patients who had previously provided written and oral consent for a biological specimens study were identified (n = 38); these participants consented to have four additional intestinal biopsies taken for research purposes alone. This research-consented cohort was then compared to non-study participants (n = 84), who had only routine biopsies obtained during the procedure.

Data was collected including: age, gender, race, indication, diagnosis, number of biopsies obtained per case and post procedure adverse events. Post-procedure adverse events were defined as events occurring within one week of the procedure. Medical records were reviewed for patient phone calls, general practitioner and gastroenterology clinic appointments, emergency department visits and hospital admissions within one week post-procedure. For those patients who were admitted to the hospital prior to their colonoscopy, the

Table 1 Participant demographics

	Research group (n = 38)	Control group (n = 84)	P value[1]
Sex			
Male, n (%)	20 (52.6)	48 (57.1)	0.64
Female, n (%)	18 (47.4)	36 (42.9)	
Age in years, n (%)			
0-5	1 (2.6)	16 (19.0)	0.05
6-12	10 (26.3)	19 (22.6)	
13-21	27 (71.1)	49 (58.3)	
Race			
White, n (%)	5 (13.2)	26 (31)	0.04
Non-white, n (%)	33 (86.8)	58 (69)	
Diagnosis			
IBD[2], n (%)	17 (44.7)	21 (25)	0.03
Normal histology, n (%)	21 (55.3)	63 (75)	
IBD diagnosis			
CD[3], n (%)	11 (28.9)	10 (11.9)	0.23
UC[4], n (%)	5 (13.2)	11 (13)	
IC[5], n (%)	1 (2.6)	0	
History of IBD			
Yes	8	12	0.54
No	9	9	

[1]All P values calculated to significance level of 0.05, [2]Inflammatory Bowel Disease, [3]Crohn's disease, [4]Ulcerative colitis, [5]Indeterminate colitis.

Table 2 Minor gastrointestinal outcomes

	Research group (n = 38)	Control group (n = 84)	P value[1]
Gastrointestinal symptom after Procedure, n (%)			
Yes	8 (21.1)	13 (15.5)	0.45
No	30 (78.9)	71 (84.5)	
Mechanism of reporting			
Phone call	6	6	0.14
PGI[2] clinic visit	0	1	
ED visit	2	1	
Inpatient	0	5	
Management			
Outpatient	5	6	0.81
Admission to hospital	1	1	
Referral to ED	2	1	
Continued admission	0	5	
Gastrointestinal symptom[3] (%)			
Abdominal pain only	2 (5.3)	4 (4.8)	0.82
Abdominal pain + diarrhea and/or vomiting	3 (7.9)	5 (6.0)	
Rectal bleeding	3 (7.9)	2 (2.4)	
Other	2 (5.3)	3 (3.6)	
Number of Biopsies			
Mean ± SD[4]	13.6 ± 4.2	9.3 ± 4.4	< 0.0001

[1]All P values calculated to a significance level of 0.05, [2]pediatric gastroenterology, [3]In research group, 1 patient with both abdominal pain and rectal bleeding, 1 with both rectal bleeding and constipation and in control group, 1 patient with rectal bleeding and diarrhea; [4]standard deviation.

inpatient record was reviewed.

We administered a questionnaire to the ten gastroenterologists who performed procedures during the aforementioned time period regarding individual patient outcomes to ensure that all adverse events, such as perforation, excessive bleeding, infection, and minor gastrointestinal outcomes, were captured and included. This study was approved by the Office of the Human Research Protection Program, Institutional Review Board at Albert Einstein College of Medicine, Bronx, NY.

Statistical analysis

Differences in participant demographics between groups were compared using analysis of variance or t tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables. All analyses were performed using GraphPad Prism version 6 (San Diego, CA). All tests for significance were two-sided, and a value of $P < 0.05$ was considered significant.

RESULTS

A total of 122 colonoscopies were performed during the study period: 38 patients consented to have additional biopsies obtained for research during the medically indicated procedure, compared to 84 non-research related cases. One thousand two hundred and ninety biopsies were obtained, including 136 intestinal biopsies for research alone. The average number of biopsies obtained per case was significantly higher in the research cohort, 13.6 compared to 9.3 in the control group, (P < 0.0001) (Table 1). Participant demographics are detailed in Table 1. Of note, statistical differences in race and age were observed in the research compared to the control groups, P = 0.04 and P = 0.05, respectively. One patient (2.6%), age 0-5, participated in the research study, compared to 16 (19%) who underwent routine colonoscopy alone (P = 0.05). No statistical difference in gender distribution was observed when comparing research to control participants.

The research cohort consisted of 38 patients, 17/38 (44.7%) of whom had IBD, compared to 21/84 (25%) of the patients in the control group (P = 0.03) (Table 1). IBD diagnosis type, such as Crohn's disease (CD) or ulcerative colitis (UC), did not vary significantly between the two groups, P = 0.23.

There were no cases of perforation, infection or hemorrhage in the research or the control group. Given that no serious outcomes occurred in our cohort, the relationship between number of biopsies and serious adverse events was not measured. Minor gastrointestinal outcomes, however, did occur in 8/38 research participants, and 13/84 control participants (Table 2). The incidence of minor gastrointestinal outcomes was not statistically different when comparing the research and control groups, P = 0.45, although the research group had significantly more biopsies obtained per procedure, P < 0.0001. Additionally, the mean number of biopsies obtained in patients who had a minor outcome (mean = 12.1 ± 0.77), compared to those with no adverse outcome (mean = 10.34 ± 0.5), revealed no statistical difference between the groups

Table 3 Indications for colonoscopy

Indication (%)	Research (n = 38)	Control (n = 84)	P value[1]
Abdominal pain	50	50	1
Diarrhea	44.7	36.9	0.41
Rectal bleeding	36.8	34.5	0.8
Weight loss	44.7	20.2	0.01
Loss of appetite	34.2	10.7	0.002
Constipation	18.4	15.5	0.68
Vomiting	15.8	14.3	0.83
Fatigue	23.7	3.57	0.001
Fever	7.89	3.57	0.31
Joint pain	10.5	1.19	0.02
Rash	5.26	0	0.03

[1]All P values calculated to a significance level of 0.05.

(P = 0.12), suggesting that number of biopsies is not associated with incidence of minor adverse events.

When comparing mechanism of reporting and management of adverse minor events no statistical differences were noted when comparing research participants to controls. Likewise, gastrointestinal symptoms reported as minor events were similar between the two groups.

Overall, during this time period, 38 children with IBD underwent colonoscopy: 47.4% (18/38) of this group were newly diagnosed patients, 11 with CD, 6 with UC, and 1 with indeterminate colitis, while 52.6% (20/38) had been previously diagnosed with IBD. Minor outcomes occurred in 21% (8/38) of patients with IBD. The incidence of minor adverse events in IBD versus non-IBD patients, did not vary significantly between the two groups, P = 0.45.

The most common indication for colonoscopy was abdominal pain, occurring in 50% of patients, while diarrhea was the second most common indication (Table 3). Weight loss, loss of appetite, fatigue, joint pain and rash occurred more often in the research group, P = 0.01, P = 0.002, P = 0.001, P = 0.02, and P = 0.03, respectively.

DISCUSSION

To our knowledge, no studies to date have evaluated the safety profile of taking additional intestinal biopsies for research purposes. Obtaining intestinal biopsies for research may facilitate investigations that will further our understanding of pediatric gastrointestinal illnesses. Our study shows that participation in research during a medically indicated colonoscopy does not place the patient at an increased risk for bleeding, perforation, infection, or minor gastrointestinal outcomes, which is in line with prior pediatric studies, as complications during routine colonoscopy are rare[3,6,7,9,11,13], and can be applied to studies involving biological specimens.

Adverse events after pediatric colonoscopy, particularly in regard to IBD, have not been well studied, as subjects with pre-existing disease are often excluded from the cohort[6]. Our data suggests that patients with IBD are not at increased risk for perforation or bleeding, which refutes prior findings[10]. A larger percentage of IBD patients (8/38, 21%) sustained minor adverse outcomes compared to non-IBD patients (13/84, 15.5%), however this difference was not found to be statistically significant. Our findings support a prior study by Tam *et al*[9] that evaluated pain indices in children with IBD, pre and post procedure, and found that patients with functional bowel disease report more pain, compared to children with IBD[9].

Interestingly, our research-consented cohort consisted of a larger percentage of IBD patients, 44.7% compared to 23.8% in the control group. From this, we may conclude that parental concern is greater in children more likely to have IBD, which may explain a greater willingness to participate in studies or to benefit from research. Alternatively, selection bias may impact the recruitment of children most likely to have IBD. In this study, however, all children undergoing colonoscopy during the aforementioned time period were asked to participate.

Given that serious adverse events did not occur in our cohort, we were unable to correlate number of biopsies obtained with incidence of serious adverse events. However, we did observe that of the patients who reported minor gastrointestinal outcomes, most (71.4%) reported the same symptom with which they presented for colonoscopy. Therefore, minor gastrointestinal events occurring after a procedure may be secondary to the primary gastrointestinal complaint, rather than the procedure. In regard to the consent process and clinical practice, clinicians may reassure parents that minor symptoms after a procedure are most commonly related to underlying symptoms on presentation, and not to the colonoscopy itself.

There are few studies in the current pediatric literature that discuss minor adverse outcomes after colonoscopy. Our study found that 17.2% of our population reported minor symptoms after colonoscopy, which is consistent with prior data, for example, Steiner *et al*[12] found that post-procedure symptoms occur in 14%-17% of patients; sore throat, diarrhea and excessive gas occurred in 6% of patients, while abdominal pain occurred in 3%[12]. In our study 1.6% of participants were admitted post procedure for observation, while Steiner et al. admitted 1.1% patients, suggesting that the general concern level regarding minor symptoms is low. Of the 17 patients who reported symptoms, 1 was under the age of 5, suggesting either that minor symptoms are more common in older children, or that underreporting is at play in younger age groups. On a similar note, only 1 patient between the ages 0-5 participated in the research study, compared to 16 children in the control group under the age of 5, suggesting that parents of very young children are less likely to consent for studies requiring the collection of biological specimens. In one study, children 0-5 years of age were the most likely group to have a complication, $P \leqslant 0.001$[3]; this supports the notion that very young

patients may have an increased risk for complications after colonoscopy and that children over the age of 5 may be more suitable candidates for research studies involving acquisition of additional biopsies.

The limitations of our retrospective study include small sample size, limited duration of the study, and selection bias, as underlying gastrointestinal symptoms may have affected study outcome. Additional studies with larger groups of pediatric patients undergoing colonoscopy for medical reasons, while participating in research, are warranted in order to further attest that no additional risk is imposed to the patient. This will allow researchers to pursue questions that will enhance our current knowledge of chronic gastrointestinal problems in children, specifically IBD.

COMMENTS

Background

Colonoscopy with biopsies is a common procedure in children for the evaluation and diagnosis of gastrointestinal disease. There is limited data on serious adverse events in children, such as bleeding, infection and perforation. Likewise, minor post-procedure gastrointestinal symptoms, such as vomiting and abdominal pain, are not well described in the pediatric literature. Current pediatric studies have not addressed whether obtaining additional biopsies solely for research purposes imposes additional risk to the patient. It is critical to establish the safety profile of collecting additional biopsies for research during routine procedures, so that investigators may proceed with studies involving biological specimens. The lack of safety data may explain why studies involving the collection of pediatric biological specimens are difficult to pursue.

Research frontiers

Institutional review board (IRB) protocols involving biological specimen collection pose a challenge to both author and reviewer, in that the lack of prior safety data serves as an obstacle for IRB approval. In order to address key research questions using translational research methods, safety data must be available for reference.

Innovations and breakthroughs

To date, the incidence of adverse events occurring when collecting additional biopsies for research during medically indicated colonoscopies has not been addressed in the pediatric or adult literature.

Applications

The study results suggest that acquiring additional biopsies for research during medically indicated colonoscopies is safe.

Terminology

Serious adverse events after colonoscopy include bleeding, perforation and infection. Minor events after colonoscopy include abdominal pain, diarrhea and vomiting.

Peer-review

This is a small retrospective study in which the authors assessed the safety profile of acquiring additional intestinal biopsies for research purposes during medically indicated colonoscopies. The results indicate that it is safe to acquire such biopsies in children for the purposes of facilitating translational research. The publication of this study may serve as a reference for researchers seeking IRB approval in biological specimen studies, and suggests the need for larger studies in the future.

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ORIGINAL ARTICLE

Retrospective Study

Endoscopic features of early-stage signet-ring-cell carcinoma of the stomach

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Author contributions: All the authors contributed to this work.

Ethics approval: This study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1964, as revised in 2013. Retrospective review of pathologic specimens is exempt from formal approval according to the policies and procedures of the Institutional Review Board (IRB) of Showa University Northern Yokohama Hospital, Yokohama, Japan.
Informed consent: All study participants, or their legal guardian, provided pre-operative informed written consent for the endoscopic or surgical procedures, as well as the collection and analysis of pathologic specimens.
Conflict-of-interest: Dr. Inoue has received fees for serving as an advisory committee member for Olympus Corporation, Tokyo, Japan. The other authors have no conflicts of interest or financial ties to disclose.
Data sharing: Technical appendix and dataset are available from the corresponding author at haruinoue777@yahoo.co.jp. Consent was not obtained but the presented data are anonymized and the risk of identification is low.

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Abstract

AIM: To identify the features of early signet ring cell gastric carcinoma using magnification endoscopy with narrow band imaging (NBI).

METHODS: A retrospective review was conducted of 12 cases of early signet ring cell gastric carcinoma who underwent treatment in a single institution between January 2009 and April 2013. All patients had magnification endoscopy with NBI and indigo carmine contrast to closely examine the mucosal architecture, including the microvasculature and arrangement of gastric pits. Histologic examination of the final endoscopic submucosal dissection or gastrectomy specimen was performed and compared with the endoscopic findings to identify patterns specific to signet ring cell carcinoma.

RESULTS: Twelve patients with early signet ring cell gastric carcinoma were identified; 75% were male, and average age was 61 years. Most of the lesions were stage T1a (83%), while the remainder were T1b (17%). The mean lesion size was 1.4 cm^2. On standard endoscopy, all 12 patients had a pale, flat lesion without any evidence of mucosal abnormality such as ulceration, elevation, or depression. On magnification endoscopy

with NBI, all of the patients had irregularities in the glands and microvasculature consistent with early gastric cancer. In addition, all 12 patients exhibited the "stretch sign", an elongation or expansion of the architectural structure. Histologic examination of the resected specimens demonstrated an expanded and edematous mucosal layer infiltrated with tumor cells.

CONCLUSION: The "stretch sign" appears to be specific for signet ring cell carcinoma and may aid in the early diagnosis and treatment of this aggressive pathology.

Key words: Signet ring cells; Early gastric cancer; Magnification endoscopy; Narrow band imaging; Stretch sign; Endoscopic submucosal dissection

Core tip: With aggressive screening, gastric cancer can be detected in the early stages, leading to the possibility of successful minimally invasive treatments, such as endoscopic submucosal dissection. A rare type of gastric cancer, signet ring cell carcinoma, has aggressive biological features, but patients treated in the early stages may actually fare better than those with adenocarcinoma. Here we present findings specific for signet ring cell carcinoma that can be identified on magnification endoscopy, potentially securing a diagnosis in the early stages of the disease without the need to rely on random biopsies.

Phalanusitthepha C, Grimes KL, Ikeda H, Sato H, Sato C, Hokierti C, Inoue H. Endoscopic features of early-stage signet-ring-cell carcinoma of the stomach. *World J Gastrointest Endosc* 2015; 7(7): 741-746 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i7/741.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i7.741

INTRODUCTION

Gastric cancer can be detected in the early stages by aggressively screening asymptomatic patients. In Japan, where such rigorous screening is conducted, half of gastric cancers are now diagnosed in the early stages of the disease[1]. Early detection affords the opportunity for less invasive treatment options, such as endoscopic submucosal dissection (ESD). However, signet ring cell carcinoma, an unfavorable subtype of gastric cancer that may require more aggressive treatment, has been reported in up to 29% of gastric cancer patients in the United States[2] and over 10% in Japan[3]. If treated early, signet ring cell carcinoma has a better prognosis than other subtypes; however, advanced signet ring cell carcinoma has a prognosis that is even worse than undifferentiated adenocarcinoma[4]. Early diagnosis of signet ring cell carcinoma is therefore critical to guide optimal treatment, but the typical presentation during conventional endoscopy is a pale, flat lesion that can easily be missed even by experienced endoscopists.

Advanced endoscopy using a magnifying endoscope and narrow band imaging (NBI) technology may play an important role. Previous studies have reported fine mucosal patterns of gastric pits and microvasculature that can be identified and classified using magnification endoscopy with NBI[5-7], and that it is possible to predict the depth of invasion of early gastric carcinomas prior to histologic assessment[8,9]. We postulate that magnification endoscopy and NBI can be further applied to the early detection of signet ring cell carcinoma.

The purpose of this study was to review our experience with magnification endoscopy with NBI in 12 cases of early signet cell gastric carcinoma, and to identify specific endoscopic patterns that may predict the final pathologic diagnosis.

MATERIALS AND METHODS

Patient selection

A retrospective chart review was performed to identify patients who underwent endoscopic and/or surgical intervention for signet ring cell gastric carcinoma in a single institution (Showa University Northern Yokohama Hospital). We identified 12 cases of signet ring cell gastric carcinoma during the study period from January 2009 to April 2013.

Magnification endoscopy

Diagnostic procedures were performed following the ingestion of 5 cc of viscous 2% lidocaine and administration of light intravenous sedation. Magnification endoscopy was performed in a single center utilizing high-resolution magnifying upper endoscopes (Olympus Evis Lucera Spectrum, GIF-H260Z, Tokyo, Japan) with 10.8 mm diameter tips and color charge-coupled-device (CCD) optical lenses with a 140 degree field of view. A distal attachment with 3 mm depth (MB-162, Olympus, Tokyo, Japan) was utilized as described by Yao *et al*[10], and images were recorded with NBI both before and after administration of 0.3% indigo carmine dye. Endoscopic images were reviewed by expert endoscopists and assessed for irregularity of the gastric pits and/or microvasculature.

Histopathology

Histologic examination of the final specimen following ESD or laparoscopic-assisted partial or total gastrectomy was performed by pathologists specializing in gastrointestinal pathology, and lesions were classified according to the Japanese classification system[11]. Pathologists did not have access to the endoscopic findings.

Table 1 Demographic data and tumor characteristics of 12 patients with signet ring cell early gastric carcinoma

No.	Age	Sex	Location of tumor	Size (mm)	Depth	Operation	F/U (mo)
1	64	F	Lower body/posterior	10 × 9	T1a	ESD	54
2	77	M	Pyloric/lesser curve	5 × 4	T1a	ESD	45
3	46	M	Mid body/posterior	5 × 5	T1a	LATG	41
4	87	F	Mid body/greater curve	20 × 16	T1b	ESD	38
5	39	M	Lower body/posterior	12 × 6	T1a	ESD	38
6	46	M	Pyloric/greater curve	10 × 8	T1a	ESD	35
7	60	M	Pyloric/greater curve	6 × 6	T1a	ESD	26
8	72	F	Pyloric/greater curve	22 × 19	T1a	ESD	18
9	71	M	Pyloric/greater curve	11 × 10	T1a	ESD	16
10	48	M	Pyloric/lesser curve	20 × 11	T1a	LADG	14
11	82	M	Pyloric/greater curve	20 × 14	T1b	ESD	13
12	44	M	Pyloric/lesser curve	10 × 3	T1a	ESD	10

F/U: Follow-up; ESD: Endoscopic submucosal dissection; LATG: Laparoscopic-assisted total gastrectomy; LADG: Laparoscopic-assisted distal gastrectomy.

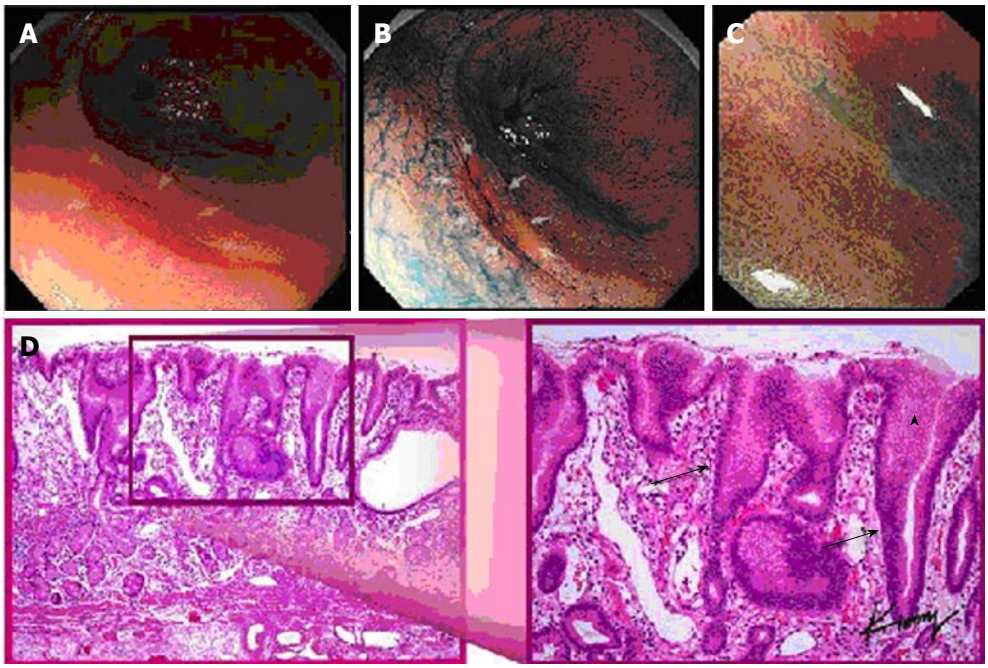

Figure 1 Multiple views of a signet ring cell gastric carcinoma in a single patient: (A) standard white light endoscopy, (B) chromoendoscopy, (C) magnification endoscopy, and (D) histopathology demonstrating elongated gastric glands (arrows) infiltrated with tumor cell (arrowhead).

Biostatistics

The data presented are a qualitative analysis of a single cohort. No statistical tests were performed.

RESULTS

Patient demographics and clinical outcomes

Patient demographic data are summarized in Table 1. Of the 12 patients with signet ring type early gastric cancer, mean age was 61.3 (range 39-87), and 75% were male; the lesions had a maximum dimension of 1.3 cm on average (range 0.5-2.2 cm) with a mean area of 1.4 cm^2 (range 0.2-4.2 cm^2); 83% of lesions were T1a, and 17% were T1b. ESD was performed in 83% of cases; laparoscopic-assisted distal gastrectomy or laparoscopic-assisted total gastrectomy was performed in the remaining 17% due to pre-operative suspicion of lymph node metastases. There was 100% disease-free survival at a median follow-up of 2.5 years.

Endoscopic findings

On standard white light endoscopy, all 12 patients with signet ring early gastric cancer had pale, flat lesions without gross mucosal abnormality such as ulceration, elevation, or depression. On magnification endoscopy, each of the patients had irregularities in the glands and microvasculature, consistent with early gastric cancer; however, in addition, the architecture appeared to be expanded or elongated, as if it had been "stretched", within a portion of the lesion for all 12 patients (Figures 1 and 2).

Pathologic correlation

On histologic examination, patients with signet ring early gastric cancer demonstrated an expanded and edematous mucosal layer infiltrated with tumor cells

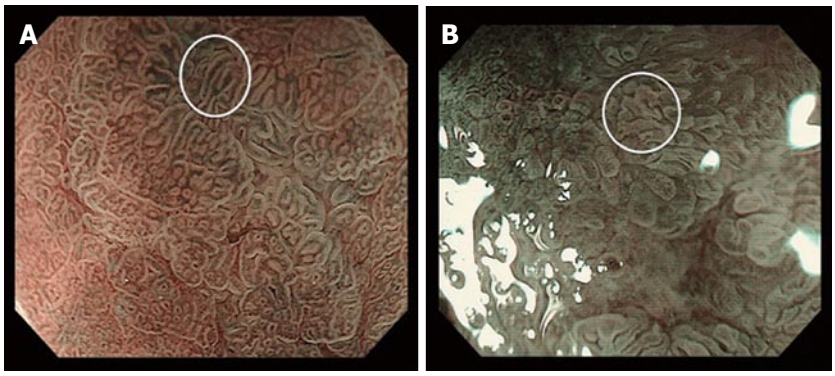

Figure 2 Magnification endoscopy of the stomach: (A) normal polygonal architecture (bottom left, underlying "a") and a signet ring cell gastric carcinoma demonstrating an elongated or "stretched" gastric gland (white circle); (B) a non-signet ring cell adenocarcinoma demonstrating irregular (non-polygonal) but non-elongated glands (white circle).

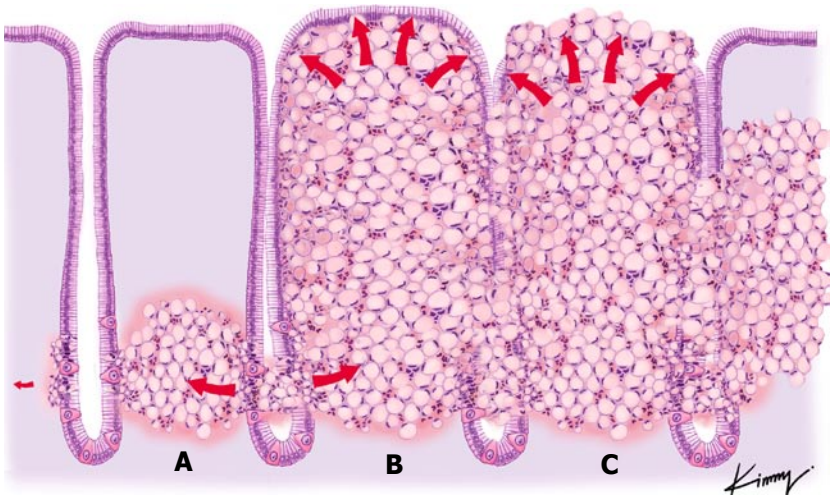

Figure 3 Theoretical view of the pathophysiology of signet ring cell differentiation: (A) tumor cells originating in the neck of the gland and spreading to the submucosal space; (B) an increasing number of tumor cells being packed together, resulting in a barrel shape; and (C) the previously non-exposed tumor becoming exposed through necrosis and formation of an ulcer.

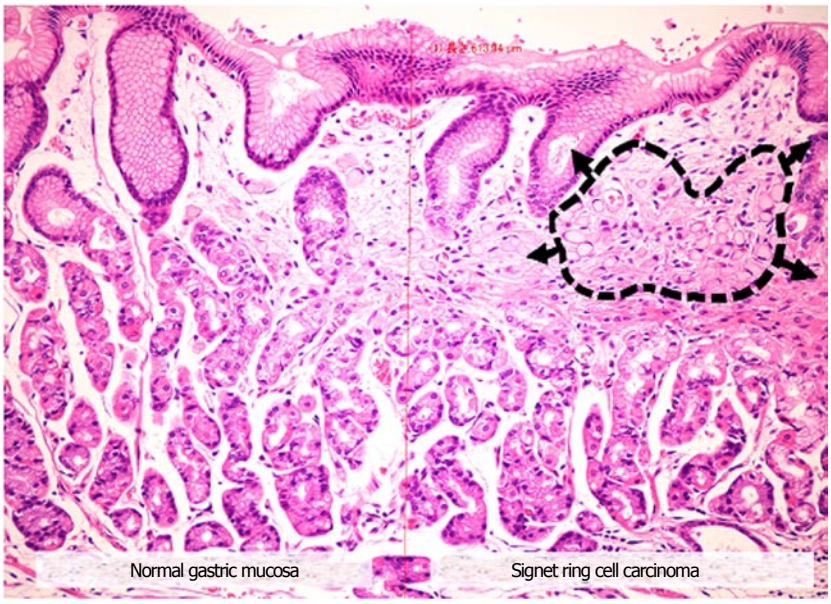

Figure 4 Microscopic view of a signet ring cell gastric carcinoma, demonstrating: (1) normal appearing gastric mucosa (left); and (2) signet ring cells (black dashed circle) causing distortion of the gastric glands (right), consistent with the endoscopic finding of the "stretch sign."

(Figure 1).

DISCUSSION

In all 12 cases of signet ring-type early gastric cancer in our institution, we identified the "stretch" sign - elongation of the architecture of the submucosa. Anecdotally, we do not note any architectural elongation in our non-signet ring early gastric cancer patients.

All 12 of our signet ring early gastric cancer patients underwent either endoscopic or surgical resection and are doing well at 2.5 years median follow-up; however; the optimal treatment for this subgroup of patients has not yet been determined. The current Japanese guidelines recommend ESD for non-ulcerated pT1a undifferentiated gastric cancer with tumor size $\leqslant$ 2 cm, but while some studies have shown only a 4% rate of lymph node metastases for tumors limited to the mucosa (as compared with 92% for tumors with submucosal spread)[12].

In an animal study, signet ring cells originated from the lamina propria at the level of the gland neck and spread through the mucosal[13]. We postulate that this proliferation of signet ring cells along the lamina propria results in clusters of tumor cells, causing the "stretched" appearance of the gastric pits and microvasculature that we observe on magnification endoscopy (Figures 3 and 4).

Our study is limited by its retrospective design and the small numbers associated with the relative rarity of early stage signet ring cell gastric cancer.

Additional studies are needed to further identify unique microendoscopic features of signet ring cell gastric cancer and to more accurately determine the sensitivity and specificity of the "stretch sign". Given that ESD is still considered an investigational treatment in the presence of signet ring cells due to the more aggressive biology and unfavorable prognosis[11,14], the presence of the "stretch sign" may help to identify patients with signet ring cells and perhaps guide more aggressive treatment, such as wider margins during ESD or earlier progression to formal surgical resection.

In conclusion, we found that signet ring cell carcinoma can be identified by the expansion or "stretching" of the gastric pits and microvasculature. This may allow for the diagnosis of signet ring cell carcinoma in the early stages using magnification endoscopy, reducing the impact of sampling error if random biopsies are taken, and perhaps guiding more aggressive treatment.

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COMMENTS

Background

Gastric cancers are aggressive tumors of the stomach that are often asymptomatic in the early stages. By the time patients develop symptoms, the tumors are often advanced and may be incurable. Aggressive screening regimens have been introduced in countries with a high prevalence of gastric cancer, such as Japan, leading to more gastric cancers being diagnosed in the early stages.

Research frontiers

Signet ring cell carcinoma, a rare subtype of gastric cancer, is unique in its biology and progression. Compared to "standard" adenocarcinoma, patients with early stage signet ring cell carcinomas have a better prognosis; meanwhile, patients with later stage signet ring cell carcinomas have a much worse prognosis than those with adenocarcinoma. Identifying and treating signet ring cell carcinoma in its early stages is therefore critical.

Innovations and breakthroughs

Early gastric cancers can be examined with magnification endoscopes using a narrow band imaging to reveal the architecture of the most superficial layers of the stomach, the mucosa and submucosa. This reveals the shapes of the gastric glands and the organization of the tiny submucosal blood vessels. In this study the authors present 12 patients with signet ring cell carcinoma; all of the patients have unique changes to the architecture of the glands and blood vessels (specifically, "stretching") that the authors have only seen when signet ring cells are present.

Applications

Use of the "stretch sign" during magnification endoscopy can potentially be used to identify patients who have signet ring cell carcinoma, allowing their prognosis and treatment to be tailored to the more aggressive biology of their cancer.

Terminology

Magnification endoscopes are upper endoscopes with a special tip and image processing equipment that can zoom in to see the organization of groups of cells. Narrow band imaging uses a small range of light (rather than the full "white light" spectrum) to highlight borders between normal and abnormal areas of the stomach. The "stretch sign" is the authors' term for elongation or "stretching" of the usual architecture of the gastric glands and the tiny submucosal vessels.

Peer-review

It is a concise and easy to read paper which brings a new progress in the field of early gastric cancer diagnosis.

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ORIGINAL ARTICLE

Clinical Trials Study

Management of liver transplantation biliary stricture: Results from a tertiary hospital

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Abstract

AIM: To review results of endoscopic treatment for anastomotic biliary strictures after orthotopic liver transplantation (OLT) during an 8-year period.

METHODS: This is a retrospective review of all endoscopic retrograde cholangiopancreatographys (ERCPs) performed between May 2006 and June 2014 in deceased OLT recipients with anastomotic stricture at a tertiary care hospital. Patients were divided into 2 groups, according to the type of stent used (multiple plastic or covered self-expandable metal stents), which was chose on a case-by-case basis and their characteristics. The primary outcome was anastomotic stricture resolution rate determined if there was no more than a minimum waist at cholangiography and a 10 mm balloon could easily pass through the anastomosis with no need for further intervention after final stent removal. Secondary outcomes were technical success

rate, number or ERCPs required per patient, number of stents placed, stent indwelling, stricture recurrence rate and therapy for recurrent anastomotic biliary stricture (AS). Stricture recurrence was defined as clinical laboratorial and/or imaging evidence of obstruction at the anastomosis level, after it was considered completely treated, requiring subsequent interventional procedure.

RESULTS: A total of 195 post-OLT patients were assessed for eligibility. One hundred and sixty-four (164) patients were diagnosed with anastomotic biliary stricture. ERCP was successfully performed in 157/164 (95.7%) patients with AS, that were treated with either multiple plastic (n = 109) or metallic billiary stents (n = 48). Mean treatment duration, number of procedures and stents required were lower in the metal stent group. Acute pancreatitis was the most common procedure related complication, occurring in 17.1% in the covered self-expandable metal stents (cSEMS) and 4.1% in the multiple plastic stent (MPS) group. Migration was the most frequent stent related complication, observed in 4.3% and 5.5% (cSEMS and MPS respectively). Stricture resolution was achieved in 86.8% in the cSEMS group and in 91% in MPS group. Stricture recurrence after a median follow up of 20 mo was observed in 10 (30.3%) patients in the cSEMS and 7 (7.7%) in the plastic stent group, a statistically significant difference (P = 0.0017). Successful stricture resolution after secondary treatment was achieved in 66.6% and 62.5% of patients respectively in the cSEMS and plastic stents groups.

CONCLUSION: Multiple plastic stents are currently the first treatment option for AS in patients with duct-to-duct anastomosis. cSEMS was associated with increased pancreatitis risk and higher recurrence rate.

Key words: Biliary stricture; Benign; Liver transplant; Endoscopic retrograde cholangiopancreatographys; Endoscopic treatment; Plastic stent; Self-expandable metal stent

Core tip: Endoscopic treatment is effective and safe in the management of post liver transplant biliary complications, mainly for anastomotic strictures. Progressive dilation and multiple plastic stenting have been demonstrated as the best endoscopic therapeutic modality with high success rates and low recurrence. Fully covered stent-expandable metal stents may be an option for endoscopic therapy potentially reducing the number and procedures lowering the costs, however their complication rate needs to be further evaluated.

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INTRODUCTION

Biliary complications have been considered for a long time the "Achilles' heel" of orthotopic liver transplantation (OLT), due to its elevated incidence, need for long-term therapy and major impact on graft survival and quality of life. Despite the advances in surgical techniques, organ selection, preservation and immunosuppression, the biliary tract remains the most common site for postoperative complications[1-4].

The incidence of biliary complications varies from 6% up to 40% of patients and includes strictures, leakages, stones, casts, sludge and sphincter of Oddi dysfunction[1-5].

Among the risk factors enrolled in the development of biliary complications the most important are: type of liver transplant procedure, reconstruction technique, organ preservation, technical factors during surgery, reperfusion injury, infection, prolonged cold and warm ischemia, hepatic artery thrombosis or stenosis, chronic rejection, ABO incompatibility, underlying disease, donation after cardiac death and older age donor[2-4,6-8].

Diagnosis of biliary complications after liver transplantation is challenging. Patients usually present asymptomatic elevations of bilirubin, alkaline phosphatase, gamma-glutamyl transferase and/or liver enzymes. Non-specific symptoms such as anorexia, fever, pruritus, jaundice and rarely pain (due to immunosuppression and hepatic denervation) can be observed.

The evaluation should start with an abdominal ultrasound (US) with Doppler of hepatic vessels. If hepatic artery thrombosis or stenosis is suspected, angiography should be indicated for specific treatment (Figure 1). If bile duct dilation, stones and/or leakage are identified by US the patient should be referred to therapeutic endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous trans-hepatic cholangiography (PTC)[7,9-13]. In case of normal abdominal US, a liver biopsy should be performed to exclude rejection. Finally, in patients with normal US and rejection ruled out by liver histology, a magnetic resonance cholangiopancreatography (MRCP) should precede more invasive procedures (Figure 1)[14]. Those patients who have a stricture or leakage confirmed by MRCP will be referred to therapeutic ERCP or PTC according to the type of biliary reconstruction.

Concerning management, although surgical repair used to be the standard treatment in the past, non-operative therapy of biliary complications has become the first line option in the last two decades[3,6]. Endoscopic approach is well established as the preferred therapeutic modality for patients with duct-to-duct anastomosis[15].

This paper will summarize the results of endoscopic treatment for anastomotic biliary strictures after

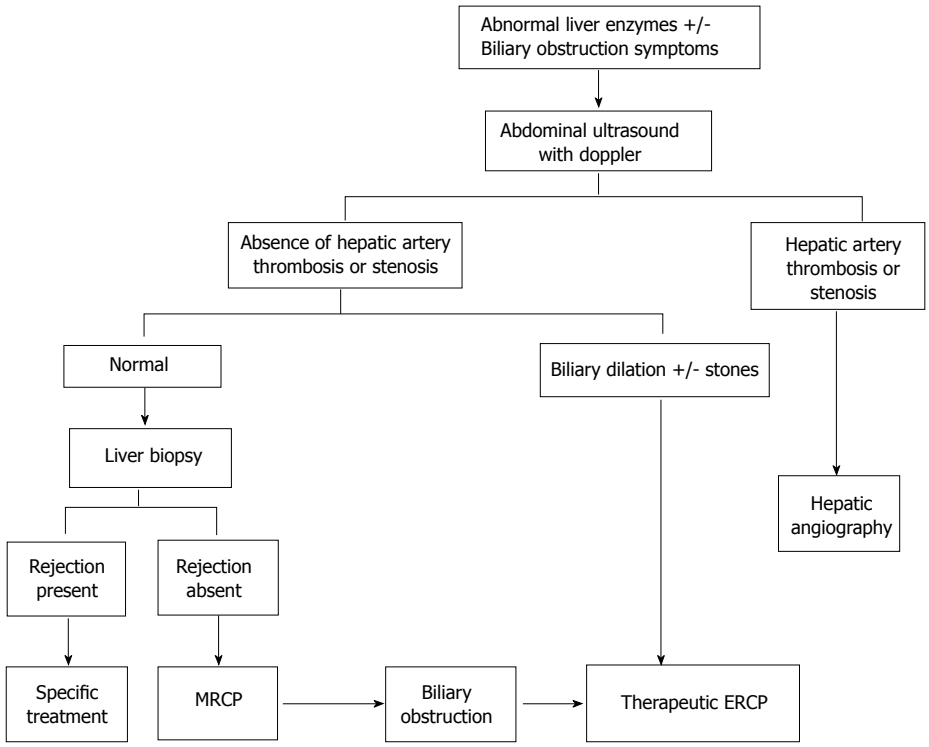

Figure 1 Algorithm for evaluation of suspected biliary obstruction after orthotopic liver transplantation in patients with duct-to-duct reconstruction. MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatographys.

deceased OLT in a tertiary center during an 8-year period and review the literature with future therapy considerations.

MATERIALS AND METHODS

Hospital Israelita Albert Einstein, São Paulo, Brazil, is a tertiary care hospital where around 120 liver transplantations are carried out annually. The study was reviewed and approved by the Hospital Israelita Albert Einstein Institutional Review Board. We retrospectively evaluated all ERCPs performed between May 2006 and June 2014 in deceased orthotopic liver transplant recipients with duct-to-duct anastomosis and suspected biliary complications. This paper reports our overall experience in such patients. All study participants, or their legal guardian, provided informed written consent prior to study enrollment. Procedures were performed under monitored care anesthesia.

Anastomotic biliary stricture (AS) was defined as a dominant short narrowing at the anastomotic site. Patients with AS were individually treated according to standardized protocols either with multiple plastic or single metal stents.

Briefly, plastic stents were initially placed after sphincterotomy and stricture balloon dilation. ERCP was repeated at 3-mo intervals for stent exchange, following a progressive balloon dilation and increasing number of stents protocol at each session, until 12 mo of therapy.

Covered self-expandable metal stents (cSEMS) were deployed with or without sphincterotomy and removed after a 3-mo period if a partially covered metal stent-expandable metal stents (PCSEMS) was used or after 6 mo in case of a fully covered stent-expandable metal stents (FCSEMS). In our early experience, biliary SEMS were placed without sphincterotomy, which we started to perform after recognizing a high rate of pancreatitis in these patients. PCSEMS were also used in our early experience, when fully covered SEMS were not available in Brazil.

Complications after ERCP (pancreatitis, cholangitis, hemorrhage, perforation) were defined by established criteria[16].

Initial technical success was the ability to obtain a cholangiogram and accomplish stent placement at ERCP alone or with a trans-hepatic *rendezvous* procedure. The investigators determined successful stricture resolution if there was no more than a minimum waist at cholangiography and a 10 mm balloon could easily pass through the anastomosis with no need for further intervention after final stent removal. All patients were followed at the institution transplant clinic through a combination of routine laboratory testing and clinical examination protocol. Stricture recurrence was defined as the return of clinical symptoms and/or elevated liver function tests with imaging evidence of obstruction at the anastomosis level causing biliary flow impairment requiring a subsequent interventional procedure in a patient previously considered successfully treated.

The primary outcome was anastomotic stricture resolution rate. Secondary outcomes were technical success rate, number or ERCPs required per patient,

Table 1 Summary of patients characteristics

	Multiple plastic stents	cSEMS
n	109	48
Sex		
Male	76 (69.7%)	36 (75.0%)
Female	33 (30.3%)	12 (25.0%)
Age (yr)		
Mean (± SD)	48.8 (± 14.5)	54.5 (± 12.9)
Median	50	56.8
Range	10-75	17-73
Time of anastomotic stricture after orthotopic liver transplantation (d)		
Mean (± SD)	214.2 (± 411.4)	221.6 (± 263.3)
Median	72	115.5
Range	6-2663	8-1339
Hepatic artery associated lesions		
Stenosis	3 (2.8%)	3 (6.3%)
Thrombosis	8 (7.3%)	1 (2.1%)
Associated biliary lesions		
Anastomotic fistula	5 (4.6%)	2 (4.2%)
Non-anastomotic fistula	1 (0.9%)	0 (0.0%)
Non-anastomotic stricture	1 (0.9%)	0 (0.0%)
Cholangitis	2 (1.8%)	0 (0.0%)
Stones	2 (1.8%)	0 (0.0%)

cSEMS: Covered self-expandable metal stents.

number of stents placed, stent indwelling, follow-up duration, stricture recurrence rate and therapy for recurrent AS.

Descriptive statistics were used to summarize data. Data was reported as the mean, standard deviation and range. Recurrence data was analyzed by the Kaplan-Meier method. Statistical data analysis was performed by the author (Martins FP) and reviewed by Hospital Israelita Albert Einstein Statistics Department.

RESULTS

A total of 195 post-OLT patients were referred to our Endoscopy Unit with a suspected biliary complication between May 2006 and June 2014. One hundred and sixty-four (164) patients were diagnosed with anastomotic biliary stricture (Figure 2).

Patients were divided into 2 groups, according to the type of stent used (multiple plastic or covered self-expandable metal stents), which was chosen on a case-by-case basis (Table 1). Both groups were similar concerning gender, age, time from OLT to anastomotic stricture and associated biliary or hepatic artery lesions.

Among the 164 patients with confirmed post-OLT anastomotic biliary stricture, initial technical success was obtained in 157 (95.7%); 109 individuals being treated with plastic stents and 48 with cSEMS (16 PCSEMS and 32 FCSEMS). Percutaneous trans-hepatic cholangiography was required in 11 (7.0%) patients to achieve access due to high-grade stricture or sharp angulation at the anastomosis. After percutaneous approach cSEMS were used in 7 and plastic stents in 4 cases.

Seven patients failed initial ERCP: 3 were referred to surgery (hepatic-jejunal anastomosis), 2 received external trans-hepatic biliary drainage, one was referred to re-transplantation and one died due to multiple organ failure after an episode of severe acute pancreatitis.

Table 2 Summary of treatment characteristics *n* (%)

	Multiple plastic stents	cSEMS
Total number of ERCP	271	70
Stent treatment duration (d)		
Mean (± SD)	282.7 (± 135.4)	124.2 (± 67.9)
Median	322	107.5
Range	3-767	9-269
Number of ERCP per patient		
Mean (± SD)	3.9 (± 1.5)	2.0
Median	4	2.0
Range	1-7	-
Number of stents per ERCP session		
Mean (± SD)	2.9 (± 1.5)	1
Median	3.0	1
Range	1-10	-
Total number of stents per patient		
Mean (± SD)	10.0 (± 7.2)	1
Median	10	1
Range	1-30	-
Complications	26 (9.6)	17 (24.3)
Acute pancreatitis	11 (4.1)	12 (17.1)
Bleeding	7 (2.6)	0 (0.0)
Perforation	2 (0.7)	0 (0.0)
Cardiorespiratory	2 (0.7)	0 (0.0)
Bacteremia	4 (1.4)	1 (1.4)
Pain	0 (0.0)	4 (5.7)
Stent related complications		
Migration	15 (5.5)	3 (4.3)
Occlusion	5 (1.8)	0 (0.0)

cSEMS: Covered self-expandable metal stents; ERCP: Endoscopic retrograde cholangiopancreatographys.

A total of 341 ERCPs were performed. Ten patients in the cSEMS group and 9 in the plastic stent group still have the stents in place and were excluded from analysis. Mean treatment duration, number of procedures and stents required were lower in the metal stent group (Table 2).

Acute pancreatitis was the most common procedure related complication, occurring in 17.1% in the cSEMS and 4.1% in the plastic stent group (Table 2). Other 4 patients (5.7%) presented abdominal pain without pancreatitis, requiring hospital admission to receive intravenous analgesics. Among stent related complications, migration was the most frequent, observed in 4.3% and 5.5% of patients with metal and plastic stents respectively.

There was one death (0.3%) related to severe acute pancreatitis in one patient who was also a technical failure.

There was no lost of follow-up until the primary outcome. Stricture resolution was achieved in 86.8% in the cSEMS group (Figure 3) and in 91% in the multiple plastic stents group (Figure 4). There were 5 failures in the cSEMS group, two of them presented spontaneous distal stent migration (Figure 5).

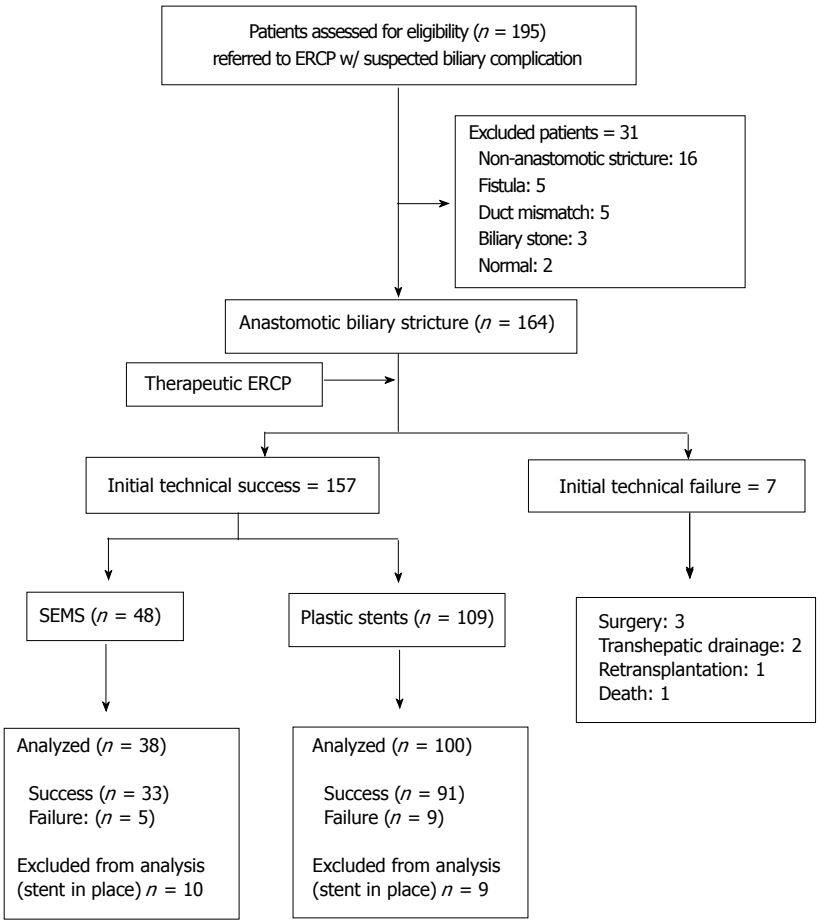

Figure 2 Flow chart of patients in the study. ERCP: Endoscopic retrograde cholangiopancreatographys; SEMS: Stent-expandable metal stents.

Table 3 Summary of the patients outcomes *n* (%)

	Multiple plastic stents	cSEMS
n	100	38
Stricture resolution rate		
Success	91 (91.0)	33 (86.8)
Failure	9 (9.0)	5 (13.2)
Follow-up (d)		
Mean (± SD)	690.8 (± 632.6)	620.3 (± 540.7)
Median	538	479
Range	0-2823	0-1615
Recurrence rate	7 (7.7)	10 (30.3)
Time to recurrent anastomotic stricture (d)		
Mean (± SD)	296.9 (± 259.5)	310.0 (± 348.4)
Median	240	124
Range	73-667	27-975
Re-treatment after failure or recurrent anastomotic stricture		
Success	10 (62.5)	10 (66.6)
Failure	6 (37.5)	1 (6.7)
In treatment	0 (0.0)	3 (20.0)
Lost of follow-up	0 (0.0)	1 (6.7)

cSEMS: Covered self-expandable metal stents.

Late stricture recurrence was observed in 10 (30.3%) patients in the cSEMS and 7 (7.7%) in the plastic stent group (Table 3). A Kaplan-Meier analysis (Figure 6) disclosed a statistically significant difference in the recurrence rate between both groups ($P = 0.0017$).

In the cSEMS group, 8 patients received re-treatment with multiple plastic stents, 2 received another cSEMS, 4 were referred to surgery and 1 lost of follow-up. In the multiple plastic stents group, secondary treatment consisted of cSEMS in 9 patients, multiple plastic stents in 4, surgery in 2 and PTC in 1 (choice of treatment in patients who failed initial treatment was decided by the referring physician). The results are summarized in Table 3.

DISCUSSION

Bile duct strictures after OLT are the most common biliary complication and have been classified according to their location into anastomotic strictures and non-anastomotic. They will be discussed separately in this paper as they differ in pathogenesis, presentation, natural history and response to treatment.

Anastomotic strictures present as a thin, short, localized and isolated narrowing in the area of biliary anastomosis as a result of fibrotic healing arising from ischemia at the end of both the donor and recipient bile duct[4,6,17]. They occur in 5% to 15% of patients after deceased OLT and 19% to 32% after living donor liver transplantation (LDLT)[3,4,6,18,19]. Early presentation

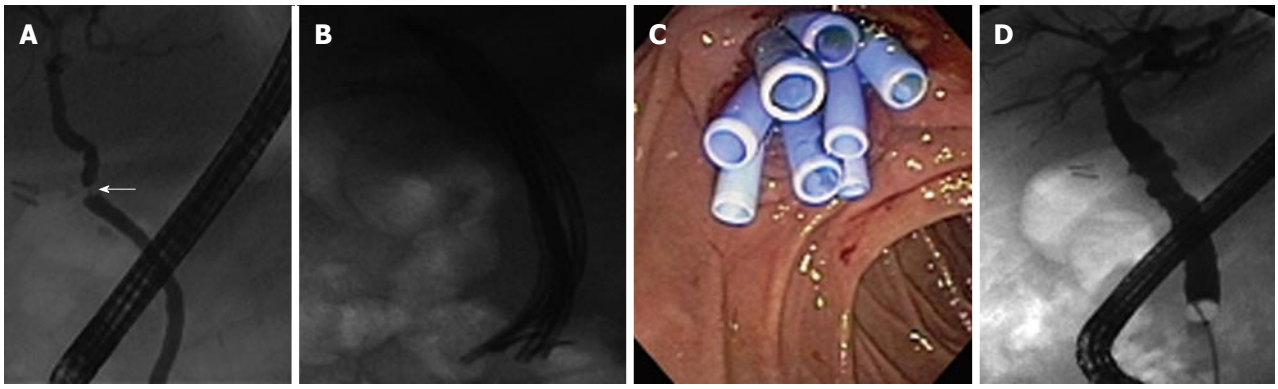

Figure 3 Patient with post-orthotopic liver transplantation anastomotic stricture from index endoscopic retrograde cholangiopancreatographys. A: Retrograde cholangiogram demonstrating post-OLT anastomotic stricture (arrow); B: Patient was treated with progressive multiple plastic stents; C: Patient was treated with progressive multiple plastic stents; D: Final cholangiogram revealing complete stricture resolution. OLT: Orthotopic liver transplantation.

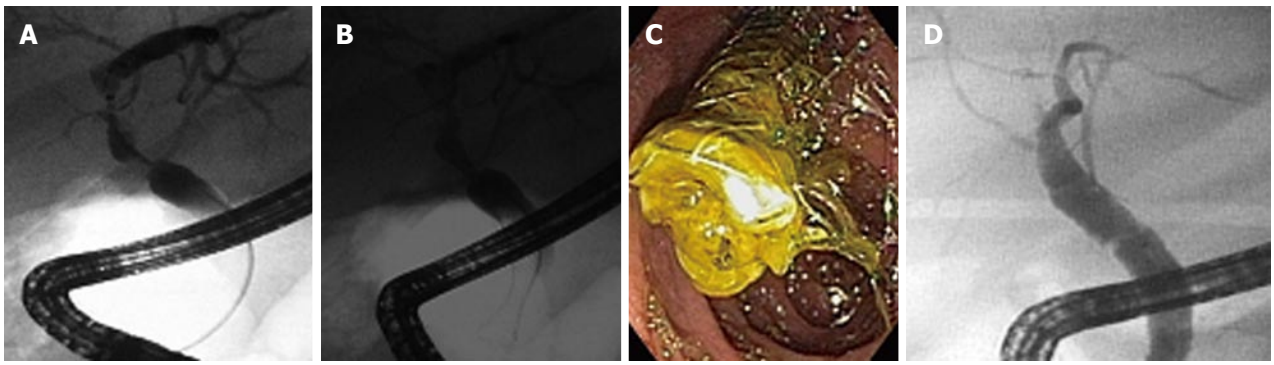

Figure 4 Patient with post-orthotopic liver transplantation anastomotic stricture. A: Post-OLT anastomotic biliary stricture; B: Placement of a fully covered SEMS across the stricture as a primary therapy option; C: Endoscopic view of the FCSEMS after 6 mo in place; D: Fluoroscopic image revealing enlargement of the common hepatic duct after SEMS removal. OLT: Orthotopic liver transplantation; FCSEMS: Fully covered stent-expandable metal stents.

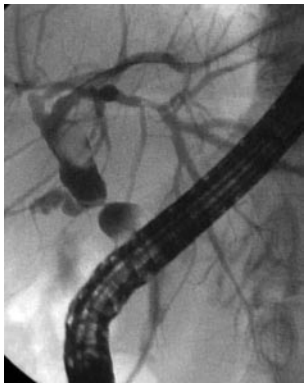

Figure 5 Recurrent anastomotic stricture after fully covered stent-expandable metal stents distal migration.

(within 12 wk) of anastomotic strictures have been related to technical issues, such as, small caliber of bile ducts, mismatch in size between donor and recipient ducts, inappropriate surgical techniques including suture material, tension at the anastomosis and excessive use of electrocautery[20]. The presence of bile leak has been reported as an independent risk factor for the development of AS; the underlying process may be related to the inflammation and subsequent fibrosis as a local effect caused by the bile itself or it may be a marker of poor vascularity in those patients in whom the leak is not originated from the cystic stump[8,21]. Late strictures are mainly due to vascular insufficiency, ischemia and problems with healing and fibrosis[12,22].

The majority of anastomotic stricture develops within the first year after OLT. In our series, the mean time between OLT and biliary stricture presentation was about 7 mo. Patients usually present asymptomatic or may have non-specific symptoms with abnormalities in liver function chemistries. Clinical suspicious must be confirmed by imaging diagnostic tools and patients are then referred to treatment, accordingly to the algorithm presented above.

There has been a transition over the past two decades in the primary management of benign biliary strictures from surgery to minimally invasive *via* ERCP. Endoscopic therapy presents a lower complication rate and shorter hospital stay when compared to surgery, not compromising the option of operation in case of failure[23,24]. Percutaneous therapy is still considered a second line option for patients with duct-to-duct anastomosis, though reserved to failed endoscopic

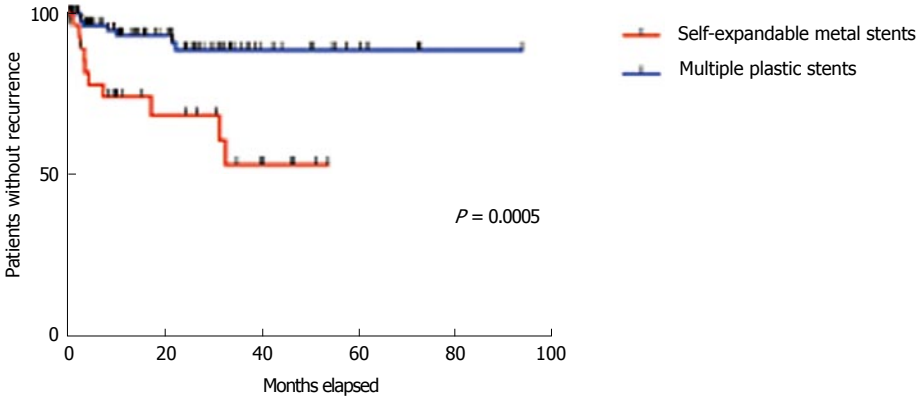

Figure 6 Stricture recurrence after resolution.

access to the anastomotic stricture, and patients with hepaticojejunostomy or choledochojejunostomy reconstruction. Currently surgical revision is confined for patients who have failed endoscopic and percutaneous therapy with re-transplantation being the final option.

Most patients with anastomotic stricture require multiple endoscopic interventions at 3-mo intervals for 12 to 24 mo with balloon dilation and long-term stenting[4,6,7,19,25-29]. The rational for multiple biliary stents placement through the stricture is to maintain the maximal expansion in luminal diameter achieved during balloon dilation, possibly promoting the re-modelation of bile ducts over the stents and preventing duct narrowing when stents are still in place[27,30]. In addition, the use of multiple stents may reduce complications related to stent occlusion, such as obstructive jaundice and cholangitis by adding biliary drainage through interstent channels[27,30,31].

A recent systematic review showed that stricture resolution rates were 78.3% for stent indwelling of less than 12 mo, compared with 97% for those longer than 1 year. The corresponding recurrence rates were 14.2% and 1.5% respectively[32].

In our center, we adopted an aggressive multiple plastic prophylactic stent exchange protocol over 1 year period, achieving a stricture resolution rate of 91%, which compares favorably with literature results. Recurrence rate after a mean follow-up of approximately 2 years is as low as 7.7%, reinforcing the benefits of extending the treatment up to 1 year.

A recent multivariate regression analysis was published assessing the outcome of endoscopic treatment of biliary complications after OLT[5]. Patients who received a graft from living donor or from a donor after cardiac death and those who had a reoperation for a non-biliary indication within the first month after liver transplantation were less likely to respond to endoscopic therapy[5]. Another factor apparently associated to stricture recurrence is the presence of a biliary leakage at initial ERCP[33]. On the other hand, early onset strictures seem to respond better and this finding may be related to the fact that those with late-onset are likely to be more fibrotic and therefore tighter and more resistant to therapy[8,27,33,34]. However, in case of recurrence, patients appear to respond well to repeated endoscopic treatment[8,27,30,35].

The major drawbacks of endoscopic treatment with balloon dilation and multiple plastic stents placement are the need of multiple procedures. Partially or fully covered SEMS were introduced on the market and became a very appealing option for benign biliary strictures due to their removability[36-49].

Post OLT biliary strictures offer an anatomical advantage for the placement of SEMS, which is the presence of the graft duct, permitting enough space above the stenosis to accommodate the metal stent distant from the hepatic confluence. Kahaleh *et al*[44] have been pioneer in the use of SEMS for benign biliary strictures of different etiology. Firstly, by describing metallic stent removability[44] and afterwards testing partially and fully covered SEMS in different clinical and technical settings[42,43,50-52].

Temporary placement of FCSEMS in patients with post-OLT anastomotic strictures refractory to conventional endoscopic therapy reached 87.5% to 100% initial success rate with a 4.5% to 7.4% recurrence. The major drawback of FCSEMS use was migration; occurring in 27.2% to 37.5%, even though with no clinical consequences[36,40,46].

In a systematic review that included 21 studies, multiple plastic stents were compared with metal stents in post liver transplant anastomotic stricture. There was significant heterogeneity in stent protocols, types of SEMS used, the use of balloon dilation or plastic stents before SEMS placement, primary outcome and stent free follow-up. There were no randomized controlled trials or non-randomized studies comparing these two modalities. Two hundred patients treated with SEMS were analyzed and stricture resolution rate was 80% to 94% when stent indwelling was longer than 3 mo, very similar to a 94% to 100% rate seen with multiple plastic stent for at least 12 mo. Moreover SEMS were used as a second line therapy for refractory strictures in 125 of these patients, what can be considered a

selection bias for more difficult strictures. The main problem with SEMS was stent migration, occurring in 16% of cases[32]. The rate of stricture resolution is lower in patients with FCSEMS migration[32,46,48].

In our study, we analyzed 38 post OLT patients with anastomotic stricture treated with cSEMS as a first line approach, reaching a stricture resolution of 86.8% after a mean stent indwelling of 124.2 d. Although the initial success was comparable with the currently standard multiple plastic stent treatment, there was a 30.3% recurrence rate after a mean of 310 d. We wonder if this higher recurrence rate was due to the shorter stent indwelling or the smaller final diameter of a 10 mm (30 French) cSEMS compared with the maximum number of plastic stents (up to 90 French per ERCP session) achieved in the other group.

We presented a mid-term evaluation of our randomized controlled trial comparing cSEMS with multiple plastic stents at DDW 2013. Although success rate was similar between groups, mean treatment duration and number of procedures required were statistically lower in cSEMS group ($P < 0.001$ for both comparisons). Moreover in our prospective trial, the mean total diameter for plastic stent group was 59 French (range 20 to 104.5 French)[47].

In summary, temporary placement of FCSEMS has been demonstrated effective and safe in the treatment of post OLT anastomotic strictures and should be considered for patients with refractory strictures[36,40,42,43,49]. On the basis of the current data, FCSEMS may allow anastomotic biliary stricture resolution with fewer procedure sessions possibly reducing treatment global cost, with the initial high price of a SEMS being compensated by the reduction in the number of ERCPs and the total number of plastic stents used during the 12-mo treatment period[53].

Questions remain about the optimal stenting interval and ideal metal stent. Concerning the first question, FCSEMS may be left in place for longer periods than partially covered ones, but prospective randomized studies with long-term follow-up are necessary to confirm this concept. The pursue for the ideal SEMS is still ongoing, it should be fully covered with an inert and resistant coating and have no fins, which seem to be associated to significant tissue reaction.

Concerning complications rate, in our study, the rate of post procedure acute pancreatitis in the plastic stent group was 4.1%, which compares favorably with the literature reports[54,55]. However, the rate of pancreatitis in the cSEMS group was 17.1%, which is exceedingly high even for a high-risk population.

Biliary sphincterotomy is usually not performed before SEMS placement in malignant biliary obstructions and therefore in the first 16 cases in our study cSEMS were deployed without one. The high incidence of acute pancreatitis (50% in the first 16 cases) came to our attention raising a debate over the impact of the sphincterotomy preceding metal stent deployment in a benign biliary stricture. Moreover, the severity of the event after cSEMS placement without sphincterotomy was also alarming, since 1 case was severe, 5 moderate and 2 mild.

The main hypothesis was that placing a trans-papillary metal stent in a native papilla without prior sphincterotomy was the main reason for the high rate of post procedure pancreatitis. Differently from patients with malignant obstruction that probably have already pancreatic parenchymal atrophy secondary to insidious pancreatic distal obstruction and therefore do not present acute pancreatitis after trans-papillary SEMS[56] Currently in our practice, all cSMES are placed after a biliary sphincterotomy in the post-OLT anastomotic stricture what drastically decreased acute pancreatitis rate to 12.5% (4/32) and all events were mild.

Although advances in surgical technique, organ preservation and selection have been made, biliary complications remain a significant source of morbidity in post liver transplant patients. Endoscopic treatment is already established as standard first line therapy. Progressive balloon dilation and multiple plastic stenting have been considered the first treatment option for biliary stricture in patients with duct-to-duct anastomosis. Our study shows encouraging results regarding placement of biliary cSEMS as the therapeutic endoscopic choice aiming to reduce the number of procedures and thus have a positive impact in cost, morbidity and quality of life of these patients, however their complication rate needs to be further evaluated.

COMMENTS

Background

Biliary complications have been considered for a long time the technical "Achiles heel" of orthotopic liver transplantation (OLT), with biliary strictures incidence up to 40% of patients. The standard strategy for post OLT biliary strictures in patients with duct-to-duct anastomosis has been balloon dilation followed by insertion of multiple plastic stents. Recently, covered self-expandable metal stents (cSEMS) has been increasingly used in the management of benign biliary strictures.

Research frontiers

The major drawback of conventional endoscopic treatment with multiple plastic stents placement is the need of multiple procedures. cSEMS have removability previously demonstrated in published studies and longer patency. In the area of benign biliary lesions, the current research hotspot is to evaluate the effectiveness and adverse events related to cSEMS.

Innovations and breakthroughs

Current evidence does not suggest a clear advantage of SEMS use over multiple plastic sten. In the study although success rates were similar, mean treatment duration and number of procedures required were statistically lower in cSEMS group. On the basis of the current data, fully covered stent- EMS may allow anastomotic biliary stricture resolution with fewer procedure sessions possibly reducing treatment global cost, with the initial high price of a SEMS being compensated by the reduction in the number of endoscopic retrograde cholangiopancreatographys and the total number of plastic stents used during the 12-mo treatment period.

Applications

Conventional endoscopic treatment with progressive balloon dilation and multiple plastic stenting has been considered the first option for post-OLT biliary stricture for decades. The study shows encouraging results regarding placement of biliary cSEMS as the therapeutic endoscopic choice aiming to reduce the number of procedures and thus have a positive impact in cost, morbidity and quality of life of these patients, however the complication rate

needs to be further evaluated.

Terminology

Anastomotic biliary strictures in the post-OLT scenario present as a short narrowing at the area of choledochal anastomosis. Endoscopic therapy can be performed by standardized protocols either with multiple plastic or single metal stents. Multiple plastic stents are placed after sphincterotomy and stricture balloon dilation, exchanged at 3-mo interval, until 12 mo of therapy. cSEMS are deployed at the index procedure and removed after approximately 6 mo.

Peer-review

This is a good descriptive study in which the authors analyzed the effectiveness and safety of endoscopic therapy in the management of post-OLT anastomotic biliary stricture. The results are interesting and suggest that cSEMS is a potential therapeutic option to multiple plastic stents that could be used for reducing the number of procedures and overall costs.

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EDITORIAL

Comprehensive management of full-thickness luminal defects: The next frontier of gastrointestinal endoscopy

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Abstract

Full thickness gastrointestinal defects such as perforations, leaks, and fistulae are a relatively common result of many of the endoscopic and surgical procedures performed in modern health care. As the number of these procedures increases, so too will the number of resultant defects. Historically, these were all treated by open surgical means with the associated morbidity and mortality. With the recent advent of advanced endoscopic techniques, these defects can be treated definitively while avoiding an open surgical procedure. Here we explore the various techniques and tools that are currently available for the treatment of gastrointestinal defects including through the scope clips, endoscopic suturing devices, over the scope clips, sealants, endoluminal stents, endoscopic suction devices, and fistula plugs. As fistulae represent the most recalcitrant of defects, we focus this editorial on a multimodal approach of treatment. This includes optimization of nutrition, treatment of infection, ablation of tracts, removal of foreign bodies, and treatment of distal obstructions. We believe that by addressing all of these factors at the time of attempted closure, the patient is optimized and has the best chance at long-term closure. However, even with all of these factors addressed, failure does occur and in those cases, endoscopic therapies may still play a role in that they allow the patient to avoid a definitive surgical therapy for a time while nutrition is optimized, and infections are addressed.

Key words: Perforation; Fistula; Anastomotic leak; Over the scope clips; Overstitch; Stent; Endoscopic

Core tip: Endoscopic methods are replacing surgical options as the first line therapy for a wide array of gastrointestinal tract defects. Here we will review the available endoscopic modalities, their appropriate applications and their respective success rates. The fusion of standard surgical principles with flexible, intra-luminal modalities is likely to be the key to the successful endoscopic management of these challenging clinical problems.

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INTRODUCTION

Whether in the form acute perforations, acute or sub-acute anastomotic leaks or chronic fistulae, full-thickness gastrointestinal (GI) tract defects remain a challenging and highly morbid healthcare problem. According to the Center for Disease Control (CDC) over 6 million abdominal procedures (including upper and lower endoscopies) were performed in the United States in 2010[1]. As the number of abdominal procedures performed annually in the United States increases, the number of full thickness GI defects that occur as a result will also increase. Historically, full-thickness luminal defects mandated surgical exploration (with its associated high rates of morbidity and mortality)[2,3]. Recent advancements in the comprehensive endoscopic management of GI defects have yielded encouraging results.

In centers of expertise, endoscopic methods have begun to replace surgical options as the first line therapy for a wide array of GI tract defects[4-6]. Here we will review the available endoscopic modalities, their appropriate applications and their respective success rates. The fusion of standard surgical principles with flexible, intra-luminal modalities is likely to be the key to the successful endoscopic management of these challenging clinical problems. Much like polyp resection, gastrostomy tube insertion and GI bleeding, we believe that surgery for full-thickness luminal defects will shortly be relegated only to patients who fail endoscopic therapy in the majority of cases[7].

SCOPE OF THE PROBLEM

GI tract defects include perforations, anastomotic leaks and fistulae and occur with numerous disease states as well as following a wide array of endoscopic, surgical and radiologic procedures. They vary greatly in their presentation and in their associated morbidity and mortality; an acute esophageal perforation from an endoscope and a persistent gastro-cutaneous fistula following gastrostomy tube removal are clearly different clinical entities. Yet until recently, these processes were thought of similar when endoscopic modalities were considered. As the volume of cases within which endoscopic closure could be attempted increases, it becomes increasingly clear that a spectrum of endoscopic therapies is necessary.

Technical limitations are not the only hurdle to overcome in the complete endoscopic management of these conditions. Many surgeons are unaware of or unwilling to permit (and/or not able to perform themselves) the application of novel therapies to patients who have perforations, leaks or fistulae. Many endoscopists with the skill and expertise to manage full thickness perforations do not have access to the patients presenting with these problems (unless they are the result of an iatrogenic endoscopic injury). There is therefore a disconnect between those individuals with the knowledge and skill to manage full thickness perforations and those who are evaluating and caring for the patients. The volume of this patient population is not inconsequential. The spectrum of diseases to which endoscopic methods could be applied includes:

Esophageal

The incidence of acute perforations during esophagogastroduodenoscopy (EGD) is approximately 0.03%[8,9]. One series of 217, 507 EGD procedures had a perforation rate of 0.033% with the esophagus being injured most commonly (51%)[9]. That same series showed a mortality rate of 17% despite intervention. The CDC reported that the total number of upper endoscopies performed in the United States in 2010 (including both diagnostic and therapeutic) was 1.1 million[1]. With an average perforation rate of 0.03%, this would equal 330 perforations.

Anastomotic leaks after esophagectomy ranges from 8%-10%[10,11]. Furthermore, patients with esophageal leaks after surgical resection have an increased mortality rate ranging from 18%-35% compared to patients undergoing similar procedures without leaks[10,12-14].

Gastric

Postoperative gastric leaks range from 1.7%-2.5% after Roux-en-Y gastric bypass (RYGB) and 1.5%-7% after sleeve gastrectomy[5,15-17]. The mortality rate for patients who develop leak ranges from 0.6%-14%[18,19]. The American Society for Metabolic and Bariatric Surgery reported that the number of bariatric surgeries performed in the United States is steadily rising with 158000 cases in 2011 and 179000 cases in 2013.

Iatrogenic gastric perforations during upper endoscopy are rare, but it is the site of injury in 3% of all iatrogenic injuries during both diagnostic and therapeutic EGD[9].

Gastrogastric fistulae occur in patients who underwent Roux-en-Y gastric bypass and develop a fistulous connection between the gastric pouch and the native bypassed stomach that is left *in-situ*. In one series of 1292 patients who underwent Roux-en-Y gastric bypass, 1.2% developed gastrogastric fistulae[20].

Gastrocutaneous (GC) fistulae represent an abnormal connection between the stomach and the skin. GC fistulae can occur at the site of percutaneous endoscopic gastrostomy (PEG) tubes, which are subsequently removed. In the vast majority of cases, these fistulous tracts close spontaneously after the PEG tube is removed. However, in 1.1% of cases these fistulae persist[21,22]. Approximately 216000 PEG tubes

are placed each year[21].

Duodenal and small bowel

Worldwide, peptic ulcer disease affects 4 million people annually[23]. Between 2%-14% of those ulcers will perforate with mortality ranging from 10%-40%[24,25]. In the setting of acute perforation during upper endoscopy, the duodenum is the location of perforation in 32% of cases[9].

Enterocutaneous (EC) fistulae, or tracts from the small bowel to the skin, are a devastating complication of abdominal surgery with mortality rates approaching 20%[26]. Patients with EC fistulae suffer from malnutrition, dehydration, skin excoriation, infection and sepsis. Although the largest percentage of EC fistulae are in patients with Crohn's disease, other inflammatory processes, malignancy, abdominal surgery, trauma, and radiation are all well-known causes[27].

Colon

The incidence of acute colonic perforations during screening colonoscopies ranges from 0.07% to 0.082%[15,28]. These numbers are similar for both screening and therapeutic colonoscopies. In 2010 there were roughly 500000 colonoscopies performed in the United States which would mean that there were approximately 400 perforations[1].

Fistula formation from the colon to other structures or to the skin is most commonly due to diverticular disease, but may also occur in patients after surgical intervention. In one review from the Cleveland Clinic of all patients treated for diverticular disease from 1960 to 1986, 20.4% had internal fistulae with colovesicular fistulae being the most common (65%)[29]. In one series examining colocutaneous fistulae, 88 of 93 patients (94.6%) were following surgery[30].

The incidence of leaks after colorectal resection and anastomosis ranges from 2.6%-26.2%[31]. Many patients who develop an anastomotic leak and require reoperation ultimately receive a permanent stoma[32,33]. Historically, the majority of these cases were treated surgically with the associated morbidity and difficulty of caring for these patients who are often in extremis. The advent of multiple endoscopic techniques and modalities has provided a safe and effective alternative to open surgical management of these complex problems[34].

Other conditions

There are a myriad of other types and combinations of GI tract leaks that are potentially addressable endoscopically including those related to cancer, radiation therapy, urologic procedures and radiologic interventions. Radiation therapy to the abdomen for other reasons can result in abdominal pathology including perforation and fistulae in up to 5% of patients[35]. In one review of fluoroscopically placed intraperitoneal chemotherapy catheters 6 of 750 patients (0.8%) experienced bowel perforation at the time of catheter placement[36].

When one considers the total volume of patients who present with a full thickness GI tract defect, it becomes clear that endoscopic therapies have the ability to change the way we think about managing a wide array of complex disease states.

AVAILABLE ENDOSCOPIC THERAPIES IN THE ACUTE OR CHRONIC SETTING AND THEIR OUTCOMES

The majority of the published literature describing the success of endoscopic management of GI defects consists of small case series and retrospective reviews. To date, there have been no randomized trials to evaluate the efficacy of endoscopic management versus traditional surgical management. The small reported successes of endoscopic management compared to the increased morbidity and mortality associated with surgical management of these disease processes are pushing the use of endoscopic therapies forward and expanding their scope of application. Larger, randomized trials need to be performed to further establish the following endoscopic therapies as both effective and superior to open surgical techniques.

It should be emphasized that the chronicity of the defect has implications about its etiology. Csendes *et al*[37] defined defects appearing 1-4 d as acute, 5-9 d as intermediate, and 10 or more days as late. Leaks presenting less than 2 d from the procedure likely represent a technical error such as stapler misfire or tissue injury while leaks presenting 5-7 d after the procedure more often represent ischemia[38].

Acute GI perforations are those that are identified at the time of injury or immediately afterwards by the sequelae that most commonly accompany perforations including fever, tachycardia, elevated white blood cell count, abdominal pain, peritonitis, systemic inflammatory response syndrome, and sepsis[39]. Early diagnosis and treatment of the defect is essential for improved patient outcomes[37].

Chronic defects are evidenced by contained fluid collections, or established fistulae to the skin or other tubular structures. The success of endoscopic therapies in the setting of longstanding leaks and fistulae has been more limited with fistulae being particularly difficult to manage[40-43]. Our experience has been similar to what has previously been reported. Since 2012 we have endoscopically managed 14 patients with GI fistulae and 6 patients with leaks and achieved a long-term closure rate of 64% and 100% respectively[44]. We believe there are multiple factors affecting the outcome in more chronic GI defects that we will explore in more detail later.

Through the scope clips

Endoscopic clips that are passed through the endoscopic working channel and are deployed within the lumen of the GI tract were initially designed for hemostasis and endoluminal marking (Figure 1). They are also

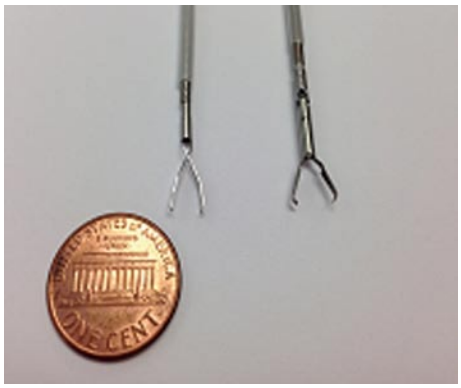

Figure 1 Examples of through the scope clips prior to deployment. Left: QuickClip 2 (Olympus Medical Systems Co., Tokyo, Japan); Right: Resolution Clip (Boston Scientific, Marlborough, MA).

referred to as through the scope clips (TTSC), hemoclips and endoclips. In the late 1990's, reports emerged describing their use as a method to close gastric and colonic perforations[45,46]. Although effective at closing smaller defects, the ability to close larger defects is quite poor due to the small size of the clips, the low grasping force that they generate and the inability to grasp deeper tissues[45]. They are more effective at closing surgically incised tissue with straight regular edges, as opposed to tissue that was bluntly perforated with irregular, striated or gaping edges. Their effectiveness at closing surgically incised mucosal edges has been well documented in the areas of submucosal dissection and POEM (Figure 2)[47-50].

TTSC have been shown to be successful in closing iatrogenic defects in the GI tract with clinical success rates ranging from 59%-83%[51,52]. It is felt that the limitation to their success is their small size, small closing force and mucosa-only tissue apposition, although in the right setting such as small defects that are not gaping, they can be quite effective.

These two factors about endoclip use have introduced bias into the initial clinical experience with acute GI tract perforations. Many acute defects are successfully closed with readily available endoscopic equipment and therefore escape the preview of surgical consultation. Larger defects are more likely to be unsuccessfully managed with TTSC clips and therefore surgeons receive a biased view of the true success rate of the most commonly applied endoscopic therapy.

Endoscopic suturing devices

The endoscopic suturing platform (Overstitch, Apollo Endosurgery, Austin, TX) is a disposable device that is attached to the end of a therapeutic double channel endoscope (Figure 3). It allows for placement of full-thickness absorbable or non-absorbable sutures. The device can be used multiple times without the need to remove the scope from the patient. The sutures can also be applied in a running or interrupted fashion (including simple and figure-of-8 sutures). Since its introduction, it has been successfully used in the closure of GI fistulae, acute perforations and at sites of endoscopic resection[53,54].

Endoscopic suturing devices have been found to provide safe and effective suturing. In one human *in-vivo* study, the Overstitch device was found to place sutures consistently at a subserosal depth in the colon without full thickness penetration or injury to adjacent structures[55]. It has been used successfully in the closure of staple-line leaks after sleeve gastrectomy, anchoring stents to help prevent migration, and closing gastrogastric fistulae[6,54,56,57]. However, the long-term success has been mixed with one study of 95 patients with gastrogastric fistulae achieving a 35% long-term closure rate[58].

Stents

The use of stents as a diversion method in full thickness GI defects is a non-FDA approved use that has been widely accepted by surgeons and endoscopists alike as a method for defect management. Stent deployment at the site of the defect helps by allowing diversion of enteric contents away from the defect. Multiple types of stent have been studied including metallic (partially or completely covered), plastic (covered, expandable), and biodegradable (Figure 4). Stent placement often permits continued enteral nutrition and can be used in cases of larger defect (> 1.5 cm)[59-61]. Although stents have been successful at treating GI defects, they are prone to migration in as much as 20%-30% of cases and require frequent observation with radiographic monitoring[61,62]. This has been addressed with techniques using TTSC and endoscopic suturing devices to anchor the stent in place. Stents also do not create a complete seal within the GI tract and, although variable in its amount, leak around stents is a near universal finding. Percutaneous placement of enteric stents have also been effective in patients with high-output EC fistulas by decreasing the output of the fistula, improving wound care, TPN requirements, and oral diet tolerance[63].

There is a large body of evidence supporting the use of stents in the treatment of GI defects. A recent meta-analysis of 7 studies of stent placement for acute leak after bariatric surgery showed a radiographically confirmed closure rate after stent removal of 87.8% (95%CI: 79.4%-94.2%)[64]. That same analysis showed a migration rate of 16.9% and only 9% of patients undergoing reoperation. Some authors advocate for clip placement to anchor the stents to help prevent migration. One study used 2 to 4 endoscopic clips to anchor the stent in 23 of 44 consecutive patients and found that stent migration occurred in 13% of patients with clips and 34% of patients without[65].

Sealants

Tissue adhesives and hemostatic agents, including fibrin sealant, have been used with varying degrees of success in the management of GI track defects. Fibrin sealant is composed of fibrinogen and thrombin, which are combined to make an acellular clot at the site of

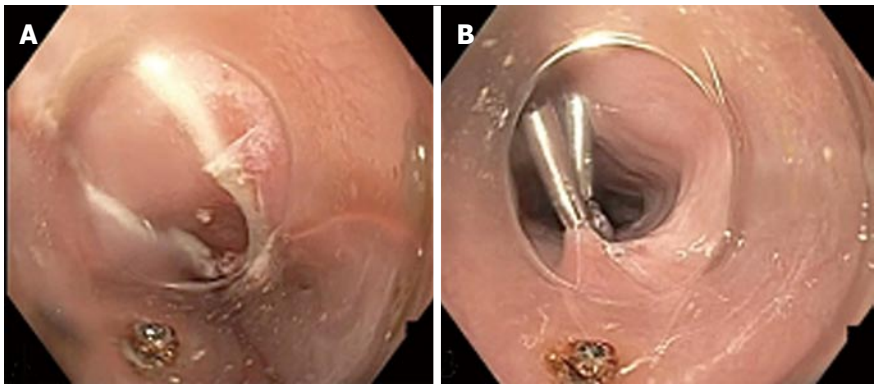

Figure 2 Endoscopic view of mucosotomy during peroral endoscopic myotomy. A: Esophageal mucosal defect after completion of peroral endoscopic myotomy; B: Defect closed with sequentially placed through the scope clips.

Figure 3 Endoscopic suturing device (Overstitch, Apollo Endosurgery, Austin, TX).

Figure 4 Examples of endoscopic stents. From Left: Fully covered plastic stent, fully covered metal stent, partially covered metal stent, larger diameter partially covered metal stent.

application. In one report fibrin glue was injected into the submucosa of a tracheoesophageal fistula causing a wheal and subsequent occlusion of the fistula in a pediatric patient[66]. In another series of 15 patients with persistent fistulae after conservative treatment, fibrin glue was used to occlude the fistula opening and resulted in long-term closure in 86.6% of patients after a mean of 2.5 sessions[67]. Tissue adhesives and sealants will likely be utilized primarily as an adjunct therapy to the definitive closure of leaks with an alternative method (such as a clip or suturing device).

Fistula plugs

SurgiSIS AFP plugs (Cook Biotech, West Lafayette, IN) were developed for the use in anal fistulae and have been used successfully in the treatment of GC fistulae after bariatric surgery[68]. Porcine small intestinal submucosa (SIS) is a bioprosthetic collagen material used in many settings including hernia repair, dressings for venous stasis ulcers, and anal fistulae. One group used SurgiSIS strips to endoscopically occlude GI fistulae in 25 patients with an 80% long-term closure rate[69].

Vacuum-assisted devices

Vacuum-assisted sponge closure has been used in the setting of esophageal and colorectal defects. Porous sponge foam is cut to be just smaller than the defect and sutured to the end of a nasogastric feeding tube (Figure 5). This is then grasped with endoscopic graspers and introduced into the defect. The nasogastric tube is then placed on continuous external suction. This suction minimizes secretions escaping through the defect while increasing blood flow to the area. Furthermore, the sponge induces granulation of the surrounding tissue and promotes healing[70]. Sponges need to be changed every 2-3 d. Small defects with adjacent fluid collections that aren't septated are more amenable to this therapy.

Vacuum-assisted sponge devices have been used successfully in small esophageal defects. In one series of five patients with fluid collections related to a leak at an esophageal anastomosis, all 5 patients resolved their leak with vacuum-assisted sponge therapy. The median length of therapy was 28 d with 9 sponge changes. Two of the patients developed stenosis at the anastomosis and one suffered from a fatal hemorrhage after a dilation procedure revealed an aortoanastomotic fistula[70].

Managing leaks with endoscopically placed tubes

Other strategies for managing leaks from the GI tract

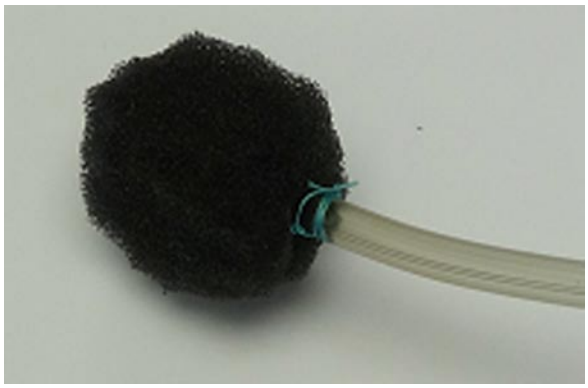

Figure 5 Vacuum-assisted closure device constructed of porous sponge and sutured to a nasogastric feeding tube.

Figure 6 Examples of the over the scope clips (Ovesco Endoscopy, Tubingen, Germany).

without repairing the defect include using the hole for other therapeutic modalities. Such "tube ostomy" formation is a standard surgical maneuver for difficult perforations in retroperitoneal organs like the colon and duodenum. In patients who presented with an acutely dislodged PEG tube and a leaking gastrotomy, the defect can be used to enter the abdominal cavity endoscopically, and replace the tube correctly, a so called "PEG rescue"[71]. We recently published a similar technique in a patient with a dislodged esophagostomy tube. By passing a wire from the cutaneous opening at the skin, securing this wire in the esophagus endoscopically, and drawing the wire out through the patients mouth, a new esophagostomy tube could be placed without any further surgical intervention[72]. Both of these examples illustrate the ability of the endoscopist to use established techniques to endoscopically manage what would traditionally be managed surgically.

Over the scope clips

Over the scope clips (OTSC) (Ovesco Endoscopy, Tubingen, Germany and Padlock, Aponos Medical, Kingston, NH) have gained popularity for the closure of GI track defects. Their ease of use, large capacity caps and short learning curve are the factors responsible for their surge in use.

Ovesco OTSC are made of elastic, biocompatible nitinol and are capable of full thickness closure of defects measuring 2 cm in diameter[73] (Figure 6). Two devices are available to use in conjunction with the OTSC to aid in apposition of the tissues prior to firing: a twin-grasper and a 3-pronged tissue anchor. Either device can be passed through the working channel and is used to secure the edges of the defect and draw them up into the cap prior to deployment of the OTSC. Because of the larger size of OTSC compared to TTSC they are able to close larger defects and take full-thickness bites of the tissue. They also provide a larger closure force due to their design. The Padlock device consists of a nitinol ring and a clear applicator cap that is placed on the end of the endoscope (Figure 7). Once deployed, the ring provides 360-degree tissue compression and approximation.

OTSC has been reported in many case series to be successful in closing acute perforations, leaks, and fistulae with long-term success rates ranging from 71%-100%[74-78]. A recent multi-centered international review examined 188 patients with acute perforations, leaks, and fistulae who were treated with OTSC and found that long-term closure rates were achieved in 90%, 73.3% and 42.9% respectively[79]. Since 2012 we have endoscopically treated 20 patients with the OTSC (6 with leaks and 14 with fistulae) resulting in a 100% and 64% closure rate respectively[44].

FACTORS LEADING TO SUCCESSFUL OUTCOMES

There are multiple factors that influence the ultimate closure rate in any endoscopic therapy, but common themes emerge in the literature in regards to closure rates. Defect size, that is the size of the luminal defect, not the length of the leak or fistula outside the GI tract, seems to play a role with smaller defects being easier to close than larger ones[58]. This is likely due to the technically difficult closure that larger defects present. Also, even though OTSC has been shown to close larger defects measuring up to 3 cm, in *ex-vivo* studies the bursting pressures have been much lower in repairs of larger defects compared to smaller ones[80]. Using the right tool for the type and location of the defect is crucial. Time from perforation to attempted closure certainly plays a role, with longer times being less successful[40-43]. Accurately measuring and appreciated the size of the defect and ensuring closure fluoroscopically at the time of attempted closure also play a role. Furthermore, the type of defect remains important, with acute perforations being more successfully closed than leaks or more chronic fistulae[41].

RECOMMENDATIONS FOR ENDOSCOPIC CLOSURE

When there is clinical suspicion for acute GI perforation, leak, or fistulae, at an area of the GI tract that is reachable by endoscopic means, we recommend prompt

Figure 7 Example of the Padlock over the scope clips (Aponos Medical, Kingston, NH).

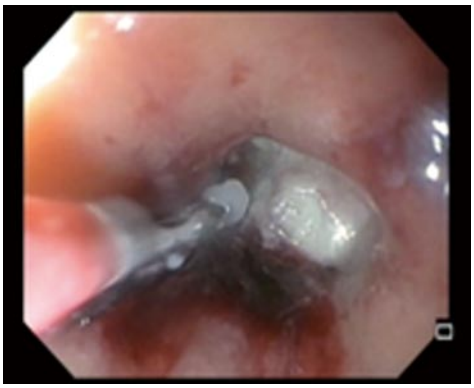

Figure 8 Endoscopic removal of suture foreign body at the opening of a rectal stump fistula.

endoscopic evaluation and treatment. The absolute contraindication to endoscopic therapy is evidence of peritonitis on abdominal exam[73]. Prompt endoscopic intervention provides two major benefits: Firstly, the endoscopist is able to provide a direct evaluation of the location and extent of the defect, and secondly, they are able to provide timely therapeutic attempts at closure for those lesions that are appropriate for endoscopic management.

The method of closure in acute full thickness GI defects will be dictated by three factors: the location, the size, and the operator's proficiency and familiarity with each therapy. Smaller defects may be amenable to TTSC, while larger ones may require one or more deployments of the OTSC. Very proximal perforations may not be amenable to stenting due to the foreign-body sensation that many patients experience with proximal stenting that approaches the upper esophageal sphincter. In many cases of initial failure, multiple attempts with various modalities are often required to ultimately obtain long-term closure[81]. We previously described the use of laparoscopy and endoscopic stent placement for management of leaks following bariatric surgery, but have since moved to definitive endoscopic closure of all leaks with endoscopic suturing or over the scope clips[5]. We now reserve stent use for leaks not amenable to or that have failed previous attempts at definitive closure.

We do not recommend any one type of endoscopic therapy for any specific location in the GI tract. Rather, we recommend that the endoscopist become familiar with all treatment modalities so as to use whichever method he/she deems appropriate based on clinical judgment. We reemphasize that often these defects require multiple attempts with varying modalities to achieve long-term closure, thus familiarity with all types of endoscopic therapies is strongly encouraged.

Because endoscopic closure of fistulae has routinely achieved the lowest long-term success rates, we recommend adopting traditional surgical fistula management techniques jointly with endoscopic attempts at closure[82-85]. Addressing the factors described by the classic acronym FRIENDS (foreign bodies, radiation, infection/inflammation, epithelialization, neoplasm, distal obstruction, and steroids) in the setting of fistula management is imperative to long-term success. It has been our experience that by addressing these issues on a case-by-case basis, we have achieved somewhat higher closure rates in patients with long-term fistulae. Since 2012 we have endoscopically treated 14 patients with GI fistulae with the OTSC resulting in a 64% closure rate[44].

Foreign bodies at the endoluminal opening of any fistula will contribute to its persistence by the foreign body reaction that they perpetuate. We routinely remove any suture, indigestible food matter, or other foreign bodies present within fistulous tract (Figures 8 and 9). Furthermore, once external drains have effectively treated the fluid collection for which they were placed, they should be removed in conjunction with the endoscopic treatment of the fistulous opening.

Infection must be treated with adequate source control in the form of external drainage for infected fluid collections and organism-specific antibiotic coverage. If the patient displays hemodynamic instability or sepsis due to uncontrolled infection, surgical intervention may be warranted as endoscopic management is typically reserved for the more stable patient.

Inflammation at the site of the fistulous opening is a commonly sited factor for failed closure. It is felt that closure rates are lower due to the difficulty in achieving adequate tissue apposition due to the fibrotic and inflamed edges that are present at the fistula opening[86]. Cauterization of the margins of chronic fistulae has been advocated to facilitate subsequent closure with the OTSC[87]. We routinely ablate the margins prior to clip placement in all chronic fistulae.

Epithelialization of the fistula tract can be addressed by both mechanical and ablative techniques. We frequently use argon plasma coagulation to ablate the epithelialized surface of the fistula tract to help prevent recurrence (Figure 10)[88]. Other authors have described mechanical debridement with biopsy forceps or brushes to disrupt the epithelial lining that may be present with more chronic tracts.

Distal obstruction or stenosis may precipitate the

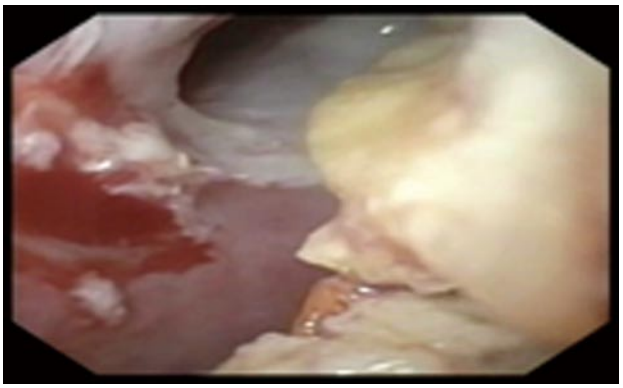

Figure 9 Undigested food within an esophago-cutaneous fistula tract.

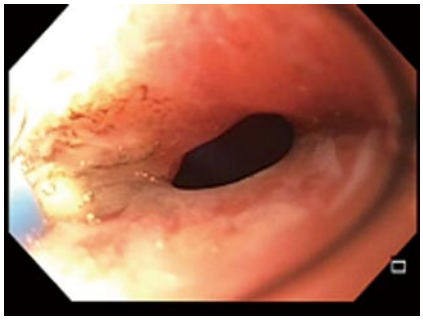

Figure 10 Circumferential argon plasma coagulation catheter ablating epithelialized fistula tract.

failure or breakdown of more proximal anastomoses or staple-lines[89]. When distal stenosis is discovered, this must be addressed concomitantly with any attempt to close proximal fistulae. Stenosis may be adequately treated with serial endoscopic dilations, though more recalcitrant strictures may require stenting (Figure 11)[90].

For the patient who is receiving steroid therapy for unrelated processes, coordination with the provider managing their steroids may provide a window where the steroid load can either be lessened or withheld for a period while endoscopic treatment is attempted. This may not be possible in all cases, but should be addressed on a case-by-case basis.

Maintaining adequate nutrition in these patients is imperative to promote healing. We recommend early enteral feeding in all cases possible. This may be achieved by obtaining feeding tube access distal to the site of the fistula such as a nasojejunal tube, or a percutaneous endoscopic jejunostomy tube. If this is not feasible, total parenteral nutrition may be initiated and continued until enteral feeding is tolerated.

In patients with acute perforations, endoscopic management alone may be sufficient for long-term success. In patients with chronic GI fistulae, all aspects of a patient's care must be optimized in order to achieve long-term success. Similar to the treatment of a patient with acute GI hemorrhage, multimodality endoscopic therapies may be required for more complex or chronic

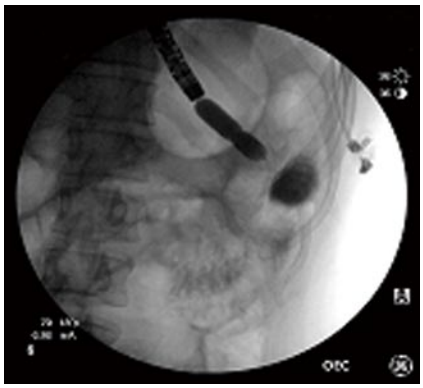

Figure 11 Endoscopic balloon-dilation of a stenotic gastrojejunostomy with adjacent jejunoanastomotic fistula.

GI tract perforation. A large gastro-gastric fistula after RYGB, for example, may require suture foreign body removal, argon plasma ablation of the epithelialized track, endoscopic suture closure of the largest portions of the defect, over the scope clip application to smaller portions and endoscopic dilation of a simultaneous gastro-jejunal anastomotic ulcer. Failure to address all of these issues will likely result in short term endoscopic failure.

Unfortunately, there will be patients who ultimately fail endoscopic therapy and will require surgical intervention. However, even in these patients, early endoscopic management can lessen the symptoms of high-output fistulae, enable patients to leave the hospital if even for a brief period, allow time for nutritional status to be improved, infections to be treated, and time for more in-depth operative planning that would otherwise not be available in the emergent setting.

CONCLUSION

There has been a great deal of advancement in the field of endoscopic treatment of full thickness GI defects with high rates of long-term closure. TTSCs, endoscopic suturing devices, stents, sealants, fistula plugs, vacuum-assisted devices, and OTSC have all been shown to be effective modalities. The treatment of acute perforations is generally more effective than the treatment of chronic fistulae. Because of this, we recommend a marriage of endoscopic therapies with classic fistula management to give the patient the best chance at long-term closure. Ultimately, even in the case of failure, endoscopic therapy can "buy time" for patient optimization prior to definitive surgical management.

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EDITORIAL

Registered nurse-administered sedation for gastrointestinal endoscopic procedure

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Abstract

The rising use of nonanesthesiologist-administered sedation for gastrointestinal endoscopy has clinical significances. Most endoscopic patients require some forms of sedation and/or anesthesia. The goals of this sedation are to guard the patient's safety, minimize physical discomfort, to control behavior and to diminish psychological responses. Generally, moderate sedation for these procedures has been offered by the non-anesthesiologist by using benzodiazepines and/or opioids. Anesthesiologists and non-anesthesiologist personnel will need to work together for these challenges and for safety of the patients. The sedation training courses including clinical skills and knowledge are necessary for the registered nurses to facilitate the patient safety and the successful procedure. However, appropriate patient selection and preparation, adequate monitoring and regular training will ensure that the use of nurse-administered sedation is a feasible and safe technique for gastrointestinal endoscopic procedures.

Key words: Registered nurse; Sedation; Gastrointestinal endoscopy; Safety; Complication

Core tip: The registered nurse-administered sedation for gastrointestinal endoscopy (GIE) procedures has clinical consequences. Generally, moderate (conscious) sedation for these procedures has been offered by the registered nurses by using benzodiazepines and/or opioids. Sedation training courses including clinical skills and knowledge are necessary for the registered nurses to facilitate the patient safety and the successful procedure. However, appropriate patient selection and preparation, adequate monitoring and regular training as well as anesthesiologist consultation in high risk cases and procedures will ensure the use of sedation by registered nurses is a safe and effective technique in GIE procedure.

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INTRODUCTION

Currently, gastrointestinal endoscopy (GIE) procedure is usually performed for diagnosis and treatment of gastrointestinal abnormalities. The need for sedation is depended on the patient physical status, degree of endoscopic difficulty and type of endoscopy, duration of procedure and physicians' preferences. The best methods for sedation during these GIE procedures are still controversial[1]. Endoscopic sedation can be administered by the trained nurse. However, the nurse administering sedation must be skilled to manage the oversedated patients[2,3]. The aim of the report is to present the current knowledge and the clinical application for routine clinical practice concerning the registered nurse-administered sedation for GIE procedures.

DEFINITIONS

Several guidelines created by the American Society of Anesthesiologists (ASA)[4] and the American Academy of Pediatrics[5] created the guidelines and definitions of procedural sedation.

Minimal (mild) sedation

Patient generally responds to the verbal command. Cardiorespiratory functions are unchanged. Minimal sedation does not invoke the monitoring requirements define in this policy. Although minimal sedation does not technically characterize the procedural sedation, the physicians should be aware that sedation can readily develop to the deeper level of sedation depth. The physicians and the registered nurses should be prepared to appropriately care for the patient in the event the level of sedation deepens.

Moderate (conscious) sedation

Patient responds persistently to the verbal command or light tactile stimulation. Additionally, the interventions are not needed to maintain the patent airway and the cardiorespiratory functions are sufficient and also usually preserved.

Deep sedation

Patient responds persistently to repeated or painful stimulation. The capacity to preserve respiratory function may be diminished. In addition, the patient may necessitate support in maintaining the airway and spontaneous respiration may be insufficient. However, the cardiovascular function is generally preserved.

General anesthesia

Patient does not response to the painful stimulus. The cardiorespiratory functions are usually reduced and the patients commonly demand the support in maintaining the airway. In addition, the positive pressure ventilations may be needed.

INDICATIONS

The two primary goals of suitable sedation for GIE procedures are to assist the procedures, and to reduce the anxiety and discomfort[6]. The optimal depth of sedation levels that registered nurses should be aiming for is minimal or moderate sedation depth[7].

LOCATIONS

Currently, endoscopic sedation can be performed in many units. The majority of practical locations of GIE procedures are endoscopy unit and operating room. Physicians who can facilitate the use of GIE sedation include the registered nurses, gastroenterologists, surgeon and anesthesiologists[8].

REQUIREMENTS

Personnel

A physician who continues current advanced life support qualification and who is familiar with endoscopic sedation, must be immediately available during the sedation and after the procedure. Resident and trainee may contribute in the GIE procedures by the supervision of staff physician. The physician is responsible for prescribing the medications including dose and type as well as also understanding pharmacology and the complications related with the sedative drugs. The physician will be in attendance throughout the procedure and will be responsible for managing the patient and must be able to manage the complications that may occur. In addition, the physicians performing the GIE procedure will maintain the responsibility and the competency for providing GIE sedation.

Consequently, an extra person is needed to establish an airway management. The registered nurses with appropriate competency can administer sedative medications with a written physician's order[9]. In addition, the registered nurse must be continuously monitored the patient and must be skilled to recognize clinical signs of hypoventilation and respiratory depression as well as abnormal vital signs and pulse oximetry readings. Importantly, the physician performing a GIE procedure can not be the person monitoring the patient.

Procedure room

The endoscopic room must be large sufficient to contain the operative personnel and monitoring equipments as well as permit an emergency cart to be brought into the room for emergency patient resuscitation. Additionally, the endoscopic room has adequate power outlets and adequate lighting to observe the patient and the monitoring equipments. The cart system with adequate space for the monitors, placed in a position where it is easily visible at all times for the personnel performing the procedural sedation.

Resuscitation equipment

The oxygen source, face mask and bag as well as suction equipments will be available in the endoscopic room. These equipments should be functional and checked before the start of GIE procedure. Moreover, the airway equipments including laryngoscope, endotracheal tubes and airways as well as an emergency cart will be available for the urgent use. This emergency cart must include the equipments for administering the resuscitate drugs and intravenous fluids including blood and blood components, as needed[1].

Monitoring

The patient undergoing sedation will be continuously monitored by the registered nurse with appropriate competency and knowledge. Consequently, vital signs, oxygen saturation and the responsiveness to a verbal stimulus will be documented before administration of sedative medications, 5 min during the endoscopic procedure and at least every 15 min in the recovery room. Electrocardiogram should be established in the high risk patients including elderly patients, patients with cardiac problems and ASA physical status $\geqslant$ Ⅲ[1].

PRE-SEDATION ASSESSMENT

Pre-procedural assessment and preparation part is very important. All patients scheduled for GIE sedation will have a pre-procedural assessment by a physician or registered nurse that includes the patient's medical condition, allergies, previous experience with sedation, drug use, alcohol and tobacco use, past medical history and current medications. A goal of physical exam including airway assessment and the major organ systems will be carried out. ASA physical classes of the patients should be documented before the procedure. A high ASA physical class is at increased risk for developing complications during sedation. Appropriate pre-procedure consultation with the proper specialists including an anesthesiologist is strongly recommended for the patients with severe underlying diseases.

The physician and the registered nurses are responsible for determining and documenting the patient's ASA physical class. If the provider determines that the patient is in an unstable condition or the GIE procedure is more invasive or complicated, sedation should not be considered by the registered nurses and an anesthesiologist consultation is recommended. Furthermore, the patients with ASA physical status IV or V are not the suitable cases in the absence of an anesthesiologist. Routine laboratory testing should not be carried out. However, the laboratory testing ought to depend on patients' physical status and underlying diseases.

Moreover, the informed consent must be completed before sedation is administered or the procedure is performed. All patients will be counseled on the risks, benefits, limitations and methods of sedation and also documented in the medical record before giving sedative drugs. Importantly, the patients can not drive home after sedation. A responsible adult person who will transport the patient should be confirmed before starting the GIE procedure. Fasting should be adhered to the guidelines except for necessary medications. All adult patients should be fasting for at least six hours before the procedural sedation. However, patients with normal gastric emptying time may have clear liquids in moderate amounts three hours prior to sedation. In addition, a time-out will be accomplished before the endoscopic procedure.

AMERICAN SOCIETY OF ASA CLASSIFICATION

The patient physical status is assessed from the ASA classification system. The ASA class should be determined by a person who will be performed GIE sedation: (1) ASA Ⅰ: Healthy patients; (2) ASA Ⅱ: Minimal systemic diseases, controlled on medications such as controlled hypertension, diabetes; (3) ASA Ⅲ: Severe systemic diseases with some limitations such as asthma, heavy smoking, obesity or multiple severe systemic illnesses all well controlled on medications, the patient with history of myocardial infarction or cerebrovascular accident; (4) ASA Ⅳ: Severe systemic diseases with severe limitations and life threatening such as poorly controlled hypertension, diabetes and coronary arterial disease; and (5) ASA Ⅴ: Not predicted to live 24 h regardless of any intervention.

PREPARATION OF SEDATION

The registered nurse who administered the sedative drugs should be considered monitoring equipments and availability of emergency medications and equipments during preparation of the procedure. The registered nurse may take the responsibility to monitor the patient during and after GIE sedation. In addition, the intravenous line must be continued all through the GIE sedation.

SUPPLEMENTAL OXYGEN

Several guidelines advise that oxygen supplementation should be performed during moderate and deep sedation[4]. However, oxygen supplementation will delay the finding of apnea by the pulse oximetry. The capnography can be a role for monitoring ventilation. Clinically, the incidence of desaturation will be reduced during the oxygen supplementation[10].

INTRAPROCEDURAL MANAGEMENT

Monitoring equipments during intraprocedural period should be included pulse oximetry, blood pressure monitor and ECG monitor. Resuscitation equipments and the reversal agents could be immediately accessed. Consequently, patients should receive supplemental

oxygen during the procedure when oxygen saturation reduces a 3% below their baseline saturation. An airway evaluation of the patient is continuously assessed. All evaluation and documentations are also noted. Accordingly, the consciousness should be reviewed frequently whenever sedative drugs are being titrated as well as also documented during sedation. Importantly, the patient is still remained responsive to a verbal stimulus and continued sufficient spontaneous ventilation. Ventilation should be continuously observed by clinical assessment. In patients where verbal response is not possible, search for other indications of consciousness.

A registered nurse experienced in moderate sedation can monitor and sedate the ASA physical status Ⅰ-Ⅱ patients. Generally, anesthesiologist should be consulted for the ASA physical status Ⅳ-Ⅴ patients and the deeply sedated patients as well as the high-risk patients. These patients need special care to make certain adequacy of pulmonary ventilation and to maintain hemodynamic parameters. In addition, the patient's airway must be supported and maintained.

SEDATIVES AND ANALGESIAS

Benzodiazepines

Benzodiazepines are widely used in procedural sedation even in GIE sedation because of their anxiolytic effects and dose-dependent anterograde amnesia[11]. Diazepam is not an ideal agent for short GIE procedures and in the outpatient cases because of its very long elimination half-life. In contrast, midazolam is the commonest premedication and sedative agent because of its pharmacokinetic properties[11]. Midazolam has a synergistic effect with anesthetic drugs. In that way, it can reduce the sedative medications[12]. Respiratory depression is the most important side effect of benzodiazepines when used in combination with opioids and/or sedative drugs. The standard dose is 0.03-0.1 mg/kg intravenously. The registered nurse can be safely used these dugs for GIE sedation.

Opioids

Opioids are usually used for the reduction of procedural pain and positional discomfort. Opioids are often used and carefully titrated with the combination of other sedative drugs[11]. The choice of which opioid should be used significantly depends on patients' physical status, the type and the duration of endoscopic procedure. Fentanyl and pethidine are widely used for GIE procedures. Similar to benzodiazepines, the registered nurses can be safely used the opiods for GIE sedation.

Pethidine

Pethidine (meperidine) is a synthetic opioid. Its onset and duration of action is longer than fentanyl. The standard dose of pethidine is 0.5-2 mg/kg intravenously. Its use in the renal insufficiency patients increases the potential for neurotoxicity. The patients taking monoamine oxidase inhibitors are contraindicated with pethidine[13]. Pethidine is commonly combined with midazolam for GIE procedure in the adult patients[14,15]. Pethidine and fentanyl are equally effective in providing analgesia for pediatric GIE procedures[16,17].

Fentanyl

Fentanyl has a rapid and short duration of action. It is also a synthetic opioid, and is the commonest opioid used for GIE sedation[11]. Normally, the dose of fentanyl is 0.5-2 mcg/kg intravenously. A previous study demonstrated that there were no significant differences in the recovery period, patient satisfaction, time to awake and sedation-related cardiorespiratory complications between the fentanyl-based sedation and the alfentanil-based sedation for esophagogastroduodenoscopy and colonoscopy. However, fentanyl is cheaper than alfentanil in each case[18].

Sufentanil

Sufentanil is also a synthetic opioid and is more potent than fentanyl. The standard dose of sufentanil is 0.1 mcg/kg intravenously[19]. Few studies have been evaluated the clinical efficacy of sufentanil in GIE procedure. In a previous study, the authors compared analgesia and sedation provided by one of four different opioids in combination with midazolam during GIE procedure. Patients were given 1-3 mg midazolam and sufentanil 5-10 mcg, meperidine 50-100 mg, fentanyl 50-100 mcg or alfentanil 150-300 mcg plus additional opioid and/or midazolam if needed. The study was concluded that sedation and analgesia were comparable in the upper gastrointestinal groups. Recovery time was shorter with sufentanil and alfentanil. However, analgesic properties of meperidine were significantly greater than sufentanil[20].

Alfentanil

Alfentanil also has a rapid and short duration of action. However, it is less potent than fentanyl. Donnelly and colleague studied the efficacy and cost of substituting sedation by using alfentanil and midazolam for the existing regimen of diazepam and meperidine in patients underwent upper GIE procedure. Their study demonstrated that the use of alfentanil for sedation in upper GIE procedure was safe and effective, and did not increase the total sedation cost[21]. Moreover, Liu *et al*[22] colleague demonstrated that the patient controlled analgesia with propofol and alfentanil offered greater sedation and patient satisfaction as well as a low complication rate compared with the combination of opioid and benzodiazepine.

Remifentanil

Remifentanil has an ultra-short action. It is a synthetic opioid. Importantly, the clearance of remifentanil is unchanged in the patients with hepatic and renal impairment[11,23]. Generally, remifentanil is given only by a continuous infusion technique. An analgesic dose of

remifentanil is 0.025-0.15 mcg/kg per min[24]. However, remifentanil is not extensively used for GIE procedure. Further studies should to be investigated.

REVERSAL AGENTS

Naloxone

Naloxone is an opioid antagonist. A dose ranges from 1-4 mcg/kg intravenously, and it may be repeated if required. The duration of action of naloxone is about 30-45 min[11]. Because of its short duration of action, an infusion dose of 3-5 mcg/kg per hour could be used after a bolus dose.

Flumazenil

Flumazenil is a benzodiazepine antagonist. It selectively binds to the GABAA receptor complex. The duration of action is approximately 1 h. The standard dose of flumazenil is 0.2 mg intravenously. It can be repeated if necessary. The maximum dose of flumazenil is 1 mg/dose and 3 mg/h[11]. Similar to naloxone, flumazenil can cause acute withdrawal syndrome in the patients who receive benzodiazepines chronically[11].

SAFETY OF NURSE-ADMINISTERED BENZODIAZEPINES AND OPIOIDS

Generally, the registered nurses can administer the benzodiazepines and opioids for moderate sedation in GIE procedures. Additionally, the registered nurse also can be administered the reversal agents by the order of a physician[25]. Consequently, the study of Yang *et al*[26] also investigated the nurse-administered moderate sedation by using the clinical criteria (Ramsay sedation scale, RSS) compared with using Bispectral Index values. They used midazolam and fentanyl or hydromorphone. The authors confirmed that the registered nurses could be safely and effectively performed moderate sedation by using benzodiazepine and opioid for GIE procedures.

However, the registered nurses should not to be sedated in the advanced GIE procedures such as ERCP and EUS procedures[27]. Guimaraes and colleagues assessed a cohort study of 9598 patients underwent ERCP and EUS procedures. The incidence of sedation and endoscopy-related complications as well as serious morbidity and mortality rates were compared. The study demonstrated that the anesthetic management for ERCP and EUS procedures in high-risk patients significantly decreased the incidence of sedation-related complications when compared with the registered-nurse care. However, endoscopy-related complications were unchanged[27].

PROPOFOL

Propofol is a phenol derivative with rapid and short duration of action. It has anxiolytic, hypnotic, anesthetic and antiemetic properties. The onset of action is about 30-60 s. The plasma half-life ranges from 1 to 4 min[28]. However, it does not have an analgesic effect. Propofol is commonly used for sedation in therapeutic GIE procedures[15]. It also potentiates the effects of other sedative drugs. The disadvantages of propofol are related with airway obstruction, apnea and hypotension as well as pain at the injection site.

NURSE-ADMINISTERED PROPOFOL

To date, propofol administration by nonanesthesiologists is controversial. Advocates of nurse-administered propofol sedation are due to the patient safety and the low cost[3,29,30]. American Society of Anesthesiologists guideline on sedation by nonanesthesiologists describes propofol as an anesthetic agent that is commonly related with deep sedation[4]. The use of propofol for routine GIE procedures also is not recommended by American Society of Gastrointestinal Endoscopy[31]. Generally, the registered nurses administered propofol sedation is cost-effective.

Several studies have been demonstrated the safety and efficacy of the registered nurses administered propofol sedation. For example, the study of Rex *et al*[32] demonstrated that the registered nurses and endoscopists could safely administer the propofol for GIE endoscopy[32]. Additionally, several data were also confirmed these in the invasive GIE procedures including ERCP, EUS and balloon endoscopy[33,34].

Moreover, the safety of nurse-administered propofol sedation in an ambulatory center also confirmed by the report of Walker and colleagues[35]. This report described the authors' experience in 9152 GIE procedures. The sedation-related adverse events were observed in seven patients including laryngospasm, apnea and pulmonary aspiration and all related with upper GIE procedures. However, tracheal intubation was not needed in all these cases.

To date, no clinical studies are directly compared between the registered nurse and gastroenterologist or endoscopist-administered sedation for GIE procedures. The administration of propofol by registered nurse is usually performed under direct supervision of the physician. The safety profiles of this sedation technique by the registered nurse for GIE procedures were evaluated in 27500 patients. Among these patients, 6.7% developed hypoxemia (SpO_2 < 90%) and 6.2% required oxygen supplementation. Severe hypoxemia (SpO_2 < 85%) was observed in 0.62% and 0.25% during upper GIE and colonoscopy, respectively. Bag mask ventilation or tracheal intubation was not required. Hypotension was observed in 1.2% and 3.5% during upper GIE and colonoscopy, respectively, and was immediately treated by using intravenous fluid administration. The mean recovery time was 14.6 min. This study demonstrated that propofol administration by the registered nurse was safe and effective[36].

Several studies have been confirmed that gastro-

enterologist or endoscopist can be safely and effectively performed GIE sedation in mild or moderate depth of sedation level. Redondo-Cerezo and colleagues assessed the efficacy and safety of endoscopist-administered propofol for GIE procedures[37]. They studied the propofol administration by gastroenterologist for sedation in EUS procedure. The induction time, duration of procedure, recovery time, patients' comfort and safety, hemodynamic profiles and complications as well as patient and endoscopist satisfaction were analyzed. Their study confirmed that propofol administration by gastroenterologist for EUS procedure in the elderly or the high-risk populations was safe and effective[38].

Recently, a tool for evaluation of the competency of the registered nurse-administered propofol has been developed by Jensen *et al*[39]. The study explored the reliability and validity of the nurse-administered propofol assessment tool. This study demonstrated that the assessment of sedation proficiencies could be performed by using a simulator. However, the video assessment required experienced physicians. Overall, this assessment tool demonstrated a good validity. Further investigations and controlled studies need to be confirmed.

POST-SEDATION CARE

Following the procedure, the registered nurse must continually monitor the patient until the patient ready to discharge. The patient also remains the responsibility of the registered nurse during the recovery period. Generally, the institutions would establish the recovery and discharge criteria for their patients. The recovery unit must have proper monitoring and resuscitation equipments.

The patients' vital parameters and the level of consciousness should be continuously observed in the post-sedation unit. The registered nurse is also required to manage the complications in this unit. The intravenous line and monitors should be utilized until the patient meets specific discharge criteria. If the reversal agents are used, the patients ought to be observed for $\geqslant$ 90 min after the administration of these drugs to assure they do not become re-sedated.

DISCHARGE CRITERIA

The registered nurses working in the post-procedural care use the discharge scoring system to assess the patient before discharge home or move to the ward. The discharge scoring systems such as the Aldrete score and the Post-Anesthesia Discharge Scoring System (PADSS) are commonly used for GIE procedures. The Aldrete and the PADSS scoring systems need continuous re-assessment of the patient. However, all discharge scoring systems have some disadvantages[40]. Importantly, the high-risk patients should be individually assessed. Currently, the reliability of these discharge scoring systems is clearly demonstrated. In the ambulatory setting, patients now accept the idea of going home only a few hours after diagnostic and/or therapeutic GIE procedures. The content and delivery of discharge instructions that outpatients receive from the registered nurse is very important. So far, the role of the registered nurse in providing patient education at the discharge process is becoming increasingly[41].

Importantly, the discharge criteria must be present before a patient can be discharged following GIE sedation. The following criteria suitable for the discharge are patient oriented to time, place and person or at pre-procedure status, vital signs within 20%-30% of pre-procedure values, unobstructed airway and sufficient ventilation, adequate oxygenation, easily and appropriately responsive to verbal commands, no severe pain and nausea/vomiting as well as the Aldrete score should be 9 or 10 in a total of 10. In the author's previous study, the periodic assessment of the home-readiness showed that most patients would complete an acceptable score on or before 1 h after GIE procedure. The time to complete an acceptable score associated with the type of GIE procedures. Consequently, most delayed recovery times after acceptable recovery scores were owing to the non-medical causes[42].

ANESTHESIOLOGIST CONSULTATION

The majority of sedation-related complications during and after GIE procedures are respiratory-related events such as pulmonary aspiration, hypoventilation, airway obstruction and apnea as well as the cardiovascular-related events such as hypotension and bradycardia[43]. Sedation-related adverse events are a risk to the success of the GIE procedure itself. Endoscopic sedation training is a very important issue. The registered nurses can learn about GIE sedation when to call for help and when to join the services of anesthesiologists. To date, the registered nurse should consult anesthesiologists for the patients with ASA physical status IV and V and the patients with known or suspected difficult airway management. In addition, anesthesiologists should be required for emergency or complicated GIE procedures such as ERCP, EUS and small bowel enteroscopy[44]. Moreover, anesthesiologist consultation is advocated for the patients with extremes of age or with significant renal or liver impairment, severe cardiorespiratory diseases, history of difficulty with moderate sedation, patients with previous inadequate response or adverse effect to moderate sedation, alcohol and drug abuse as well as patient or procedure needed at least deep sedation depth.

CONCLUSION

The use of registered nurse-administered sedation for GIE procedures has clinical significances. Most endoscopic patients require some forms of sedation and/or anesthesia. Generally, mild and moderate sedation for GIE procedures has been offered by the

nonanesthesiologist by using benzodiazepines and/or opioids. In contrast, the propofol sedation by the registered nurse is depended on the knowledge, skills and experience of individual nurse as well as the policy and the country guidelines. Importantly, the sedation training courses including clinical skills and knowledge as well as anesthesiologist consultation in high risk cases and procedures are necessary for the registered nurses to facilitate the patient safety and the successful GIE procedure. Additionally, appropriate patient selection and preparation, adequate monitoring and regular training will ensure that the use of registered nurse-administered sedation is also a practicable and safe technique for GIE procedures.

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REVIEW

Current applications of endoscopic suturing

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Abstract

Endoscopic suturing had previously been considered an experimental procedure only performed in a few centers and often by surgeons. Now, however, endoscopic suturing has evolved sufficiently to be easily implemented during procedures and is more commonly used by gastroenterologists. We have employed the Apollo OverStitch suturing device in a variety of ways including closure of perforations, closure of full thickness defects in the gastrointestinal wall created during endoscopic full thickness resection, closure of mucosotomies during peroral endoscopic myotomy, stent fixation, fistula closure, post endoscopic submucosal dissection, endoscopic mucosal resection and Natural Orifice Transluminal Endoscopic Surgery defect closures, post-bariatric surgery gastrojejunal anastomosis revision and primary sleeve gastroplasty.

Key words: Endoscopic suturing; Peroral endoscopic myotomy; Endoscopic full thickness resection; Natural Orifice Transluminal Endoscopic surgery; Endoscopic bariatric surgery; Endoscopic sleeve; Transoral outlet reduction

Core tip: The recent development of an endoscopic suturing platform, the only such device that is currently available in the United States, has led to a rapid expansion of endoscopic suturing applications ranging from simple procedures such as stent fixation to more complex ones such as closure of large full thickness defects and primary and revisional bariatric endoscopic surgery.

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INTRODUCTION

Endoscopic suturing devices have been used in a limited fashion for about a decade. Some of the known devices

Table 1 Advantages and disadvantages of different suturing patterns

Suturing Pattern	Pros	Cons
Interrupted/ simple	Less tissue drag during tightening of the suture compared to a running suture No risk of suture crossing and entanglement as described for running suture Any failure during suturing would only involve the most recently placed interrupted suture rather than the entire suturing work up to that point as is the case with running sutures Suture failure after termination of the procedure would only involve a small segment of the closure without the risk of dehiscence of the entire closure that exists with running sutures	Approximation of the defect edges occurs as soon as the first interrupted suture is tightened and may limit good visualization and grasping of the edges of the nearly closed defect thus making placement of the subsequent interrupted sutures difficult or inaccurate Substantial increase in cost proportionate to the number of sutures used as discussed under running sutures
Figure of 8	Specialized suture used to close small circular defect in a circular fashion with equal circumferential anisotropic compression towards the center of the defect. Thus, it may be the optimal suturing pattern for fistula closure or oversewing an ulcer containing large vessel(s) at risk for bleeding	Technically more challenging than interrupted sutures Risk of suture entanglement Any suture failure (*e.g.*, erosion through tissue, breakage) would result in slack along the entire suture and result in dehiscence of the entire closure
Running	Allows clear visibilty of the defect edges until the suturing is completed Less expensive as it uses only one suture and cinch (in the United States, for the OverStitch platform, each additional suture+cinch adds approximately $100)	Tissue drag caused by the suture going through multiple bites of tissue requires gentle slow careful technique during tightening of the suture prior to cinching Avoiding entanglement of the long suture leading to the start of the suture line during placement of the transverse sutures across the defect requires careful technique and experience Any error such as accidental drop of the needle, fraying and breakage of the suture or device failure results in loss of the entire work up to that point with the need to start the closure from the beginning Similarly, any suture failure after termination of the procedure (*e.g.*, suture eroding through tissue prematurely or breaking) would result in failure of the entire closure

include the Bard Endocinch (MA-US), T-bars (Wilson Cook-NC-US), NDO Plicator (MA-US-no longer available) and GERDX TM (G Surg Seeon, Germany)[1-3]. There are reports on limited preliminary data from experimental or limited-release devices[4-7]. The OverStitch endoscopic suturing system (Apollo Endosurgery, Austin, Texas) evolved from the previously developed Eagle Claw device[8] and is currently the only widely available suturing device, and only Food and Drug Administration approved commercially available device in the United States[9]. Since the other devices briefly mentioned are not available either because they have been withdrawn or because they are at early experimental stages of development, this review will focus on the rapidly emerging widespread applications of suturing enabled by the Overstitch platform. Figure 1 illustrates the use of the endoscopic suturing device. It is a disposable, single-use device that is mounted onto a double-channel gastroscope and it can enable interrupted or continuous suture application[10]. Table 1 and Figure 2 demonstrates the advantages and disadvantages of different suturing patterns. Full thickness suturing is possible for tissue approximation or plication in the gastrointestinal tract *via* use of a tissue anchor, curved suturing arm and a cinch. The current version was approved in 2011 and early use included oversewing a recurrent marginal ulceration, a fundic ulcer, stoma reduction after gastric bypass surgery, and closure of a post-operative rectovaginal fistula[11,12].

PERFORATION CLOSURE

Closure of iatrogenic inadvertent endoscopic perforations not associated with endoscopic submucosal dissection (ESD)/endoscopic mucosal resection (EMR) is largely confined to the animal model. Recently, three patients with iatrogenic esophageal perforation had apparent successful repair with the OverStitch device[13]. The OverStitch device was used to successfully close a full thickness gastric defect in the pig in a two week survival study[14]. An interesting study in humans assessed the depth of endoscopic suture placement in the colon. Test sutures were placed intraoperatively in patients undergoing partial colectomy in the portion of the colon to be resected. Examination of the resected colon demonstrated successful placement of full thickness transmural sutures[15]. Figure 3 demonstrates a case in which we performed successful closure of a very large perforation that occurred during a colonoscopy performed to evaluate Crohn's disease in a 35-year-old patient. The patient had a second perforation at the cecum that was not appreciated by the referring endoscopist and was discovered during surgical exploration performed due to persistent abdominal pain, fever and leukocytosis 24 h after the index colonoscopy. The surgeon discovered a second perforation in the cecum, which he successfully repaired surgically and confirmed successful endoscopic closure of the splenic perforation not requiring surgical intervention. He noted that the endoscopic sutures placed using the OverStitch

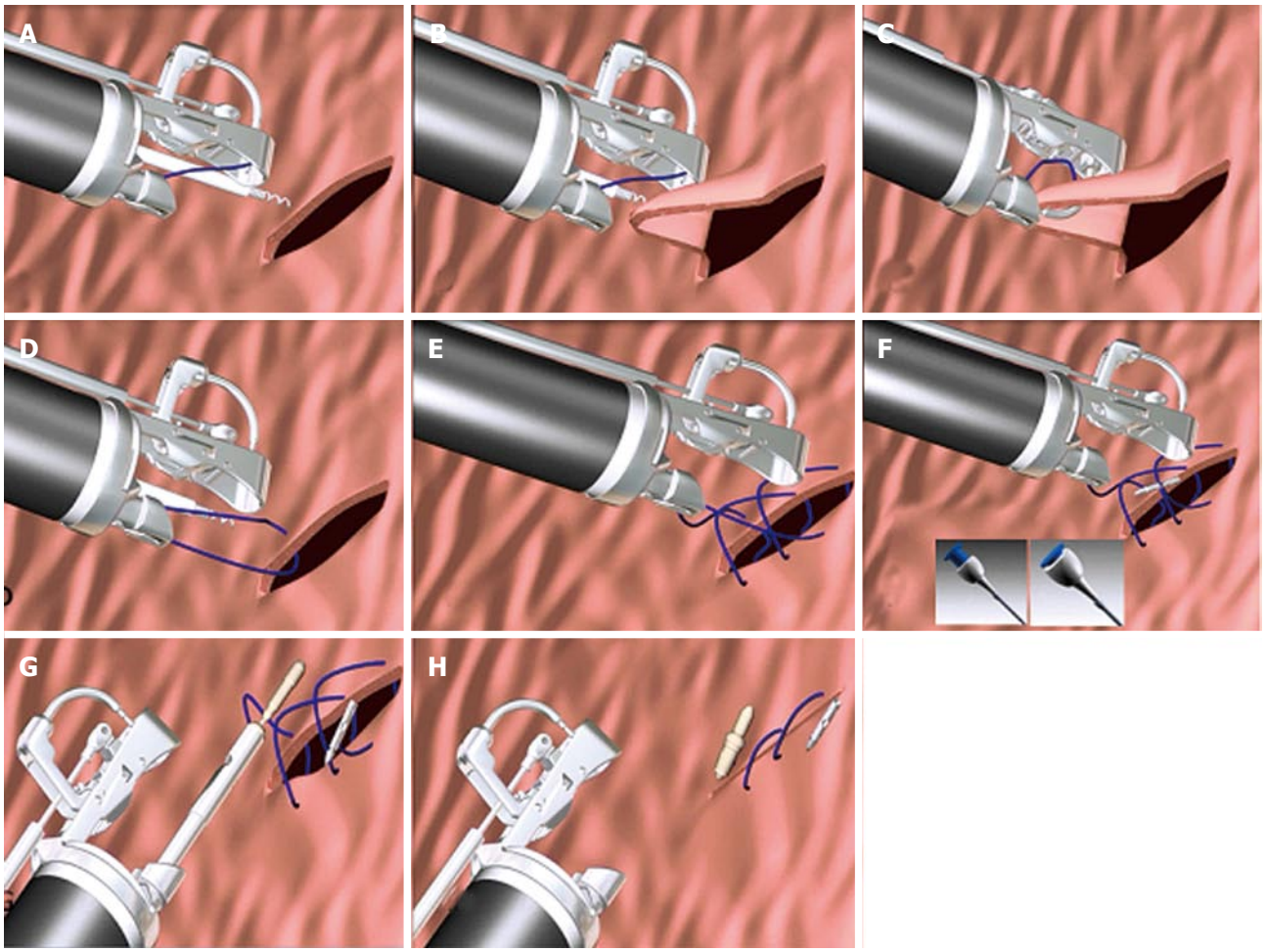

Figure 1 Steps involved in placing endoscopic sutures (Courtesy Apollo endosurgery Austin Texas). A: Grasp the tissue using the tissue helix; B: Retract the tissue into the needle path; C: Drive the needle through the tissue; D: Open the arm and release the tissue; E: Repeat stitched as desired; F: Press the blue button to release the needle (T-fastener); G: Tighten and cinch; H: Repeat as desired.

device had traversed the entire colonic wall, which is in accordance with the results of the colectomy study described above.

STENT FIXATION

Covered self-expanding metal stents have been employed in the treatment of perforations, strictures and fistulae/leaks. The covered feature allows subsequent removal but also predisposes to stent migration. Previously, endoscopic clips have been deployed to prevent stent migration with doubtful efficacy, but there is now an increasing experience with endoscopic suturing for this purpose. A porcine model study comparing clip *vs* suture fixation of esophageal stents favored suturing in terms of migration tendency and force needed to disrupt the stent fixation[16]. A study of esophageal fully covered self-expanding metal stents (FCSEMs) for leaks and strictures compared stenting with and without suturing, and the sutured stents migrated much less.(55% *vs* 35%)[17]. A case series featuring a variety of upper gastrointestinal issues (perforation, leaks, fistulae) necessitating stents had a similar migration of sutured stents (7 of 21 sutured SEM's)[18]. FCSEMs may have a role in treating post-bariatric leak/fistulae and our center and others have employed suturing for stent fixation and occasionally for primary defect closure[19].

FISTULA/LEAK CLOSURE

There is accruing experience with endoscopic suturing use in the treatment of gastrointestinal fistula/leak closure. These can be acute or chronic in nature and often result as complications from surgical anastomoses and stapled tissue divisions such as those of bariatric surgery (especially sleeve gastroplasty). As mentioned, suturing is often used in conjunction with other therapies including stents and glue[20]. The StomaphyX suturing system was used to treat gastric leaks in two bariatric patients[17]. The OverStitch device achieved closure in 3 of 7 patients with gastrogastric fistulae after gastric bypass[8]. This device has been used for a variety of fistulae[21,22]. One study demonstrated the superiority of the full-thickness OverStitch device compared to a superficial suction-based suturing system in the closure of gastrogastric fistulae[23]. The OverStitch device was used to close a persistent esophagopleural fistula[24].

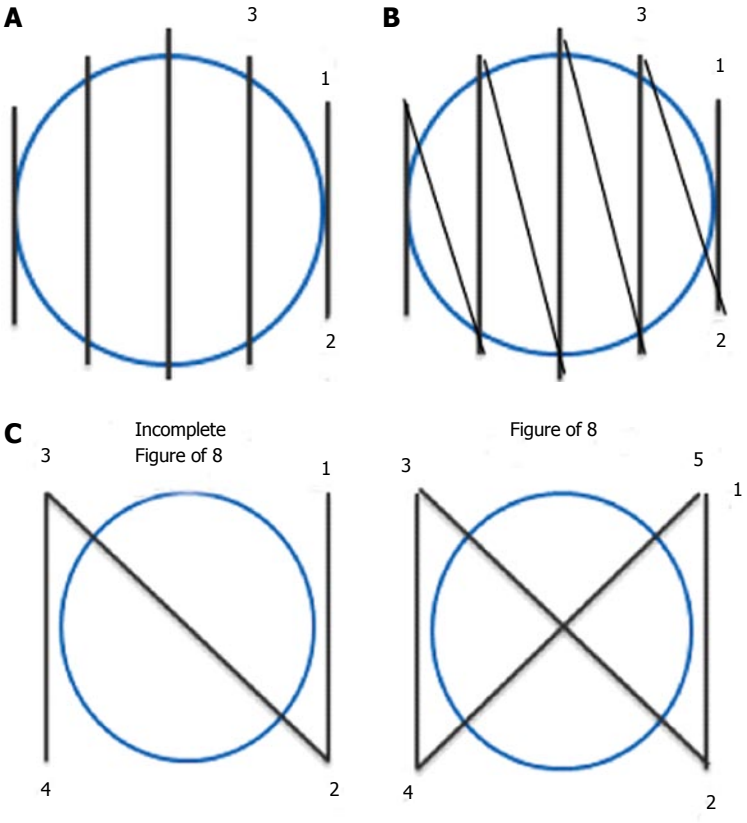

Figure 2 Types of suture pattern. A: Interrupted suture; B: Running suture; C: Figure of 8 suture.

Patients who are fortunate enough to have removal of their feeding tube after gastrostomy usually have wound closure, but occasionally there is a persistent gastrocutaneous fistula. There are a variety of closure techniques and endoscopic suturing may be employed as the sole intervention or in combination with other therapies (glue, clips, percutaneous suturing, *etc.*) Successful closure with the OverStitch device has been described[25,26].

ESD-EMR CLOSURE

There has been a veritable explosion of publications regarding endosurgical resection; predominantly ESD and related offshoots such as submucosal tunnel endoscopic resection (STER) and endoscopic full-thickness resection (EFTR). Endoscopic suturing has ensconced itself as an important if not indispensable component of advanced endoscopic resection. A porcine model study suggested quicker and more complete closure of ESD defects with sutures *vs* clips[27]. However, the efficacy of closure was somewhat subjective (visualization) and this comparison will need to be made in humans. The same group noted in another porcine study that effective suture closure after ESD can be done in a variety of ways and combined with clips[28]. In one study of 12 patients having ESD (4 gastric 8 colon), closure was made successfully with the OverStitch device and the patients were discharged home on the day of the procedure[29].

ESD has evolved such that large submucosal lesions and those with significant extraluminal extension can be resected with the technique known as EFTR. EFTR requires closure of potentially large defects (essentially intentional perforations) and endoscopic suturing is invaluable for this purpose. A porcine two-week survival study demonstrated the feasibility of suturing to close a full-thickness gastric defect (average size of gastric specimen 11 mm) without site ulceration[30]. Three patients with endoscopic perforation avoided surgery *via* OverStitch closure of the defect (all > 2 cm) in conjunction with catheter decompression of pneumoperitoneum, NGT insertion and Ⅳ antibiotics[31]. We employ the device after EFTR for gastric stromal tumors[32]. Without availability of the robust closure achievable with endoscopic suturing, closure of EFTR defects with endoscopic clips often requires specialized adjunctive techniques to achieve secure closure of these large perforations. We have demonstrated use of an omental patch to achieve secure closure with endoscopic clips of a large gastric EFTR one of our early cases prior to OverStitch availability[33]. In Asia, where OverStitch is not yet available, EFTR operators have largely converted to closures of EFTR defects with the endoloop and clips technique further emphasizing the inadequacy of clips for secure closure of these relatively large perforations[33-36]. Figure 4 demonstrates a few cases of EFTR defect closure with OverStitch. Kantsevoy

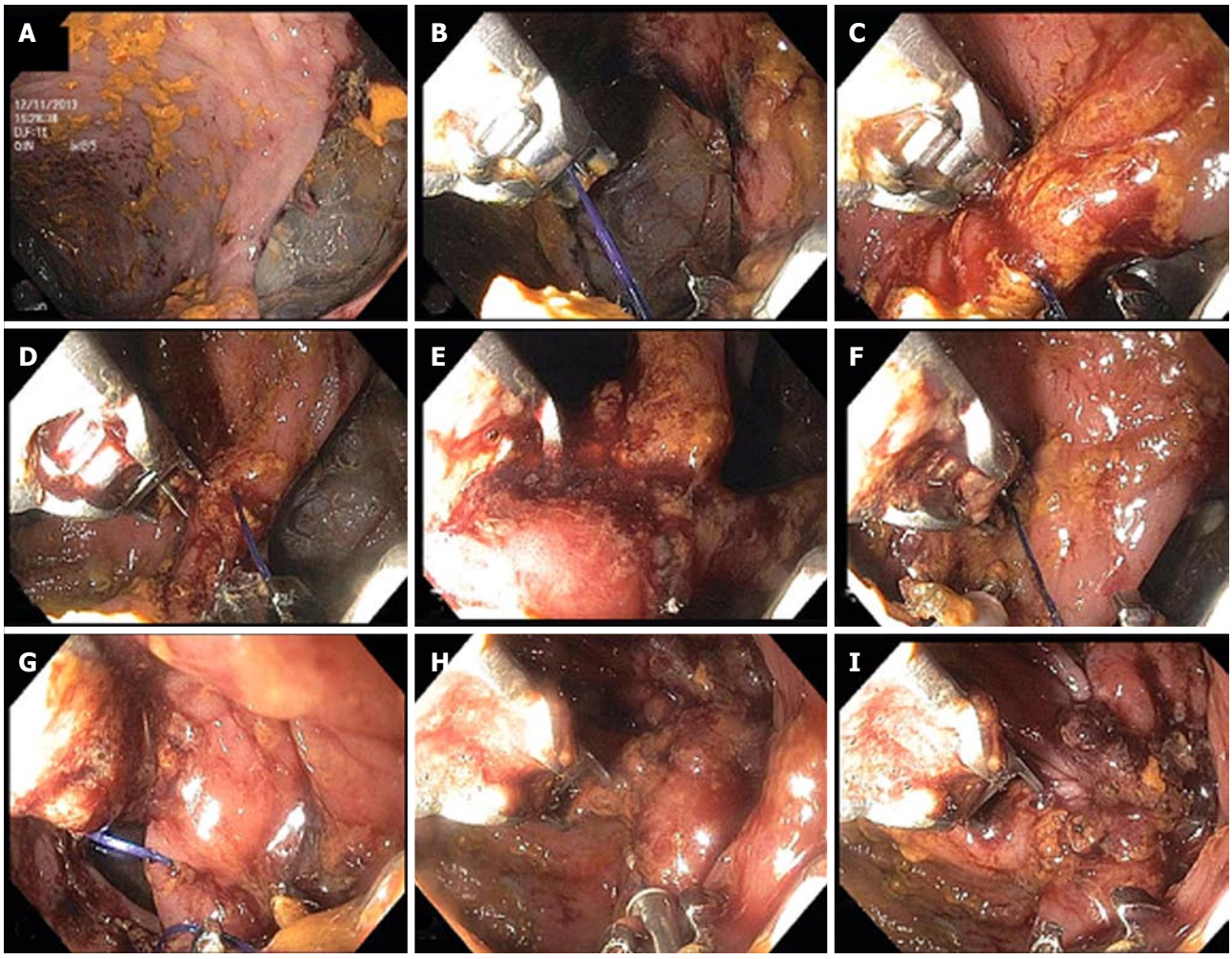

Figure 3 Closure of colonic perforation with endoscopic suturing device. A: Initial tissue bites forming a running suture (B-E) starting at the inferior edge of the perforation and progressing towards the center; F: Tissue helix retractor is used to ensure deep tissue bite along the distal, superior edge of the perforation; G: Suturing has reached the superior edge of the perforation the edges of which are now being pulled together by the sutures; H: After tightening of the sutures closure of the perforation has been achieved and the cinch device is seen being deployed at the 6 o' clock position of the image; I: Immediately after cinch deployment, the complete closure of the perforation is seen. Gastrografin was injected through the scope that confirmed absence of leak (not shown).

had successful OverStitch closure of two patients with one cm colon perforations after more extensive experience with closing two centimeter colon defects in pigs[36].

ESD is challenging for lesions in difficult locations where the endoscope cannot achieve a path tangential to the lesion such as the gastric lesser curvature. For such lesions, ESD can be facilitated by countertraction accomplished *via* use of the OverStitch device to create a "suture-pulley"[37].

A natural extension of EFTR is Natural Orifice Transluminal endoscopic surgery (NOTES) where the endoscopic intervention is done within the peritoneum and the trans-gastric entry site reliably closed. A suturing device was demonstrated to attain durable closure of gastric defects ranging to 18 mm in an animal model[38]. Closure success is similar for both continuous and interrupted suture application[39]. The OverStitch device was used in conjunction with a robotic device to remove a five cm diameter area of the gastric wall in two pigs, solely *via* endoscopic means[40].

PERORAL ENDOSCOPIC MYOTOMY MUCOSOTOMY CLOSURE

Per-oral endoscopic myotomy is a successful clinical application of NOTES. Endoscopic suturing has been utilized for closure of inadvertent mucosotomies and perforations during peroral endoscopic myotomy (POEM)[38-40]. Endoscopic suturing has also been shown to be useful in closing the mucosal entry point after the myotomy is performed (Figure 5)[41-43]. This is now our customary practice in POEM. During the first three years of our POEM experience (2009-2012), prior to the availability of endoscopic suturing, we performed closure of the tunnel entry site with clips. However, when endoscopic suturing with the OverStitch device became available, we converted to closure using suturing hoping for a more predictable and secure closure. We performed a retrospective comparison of clip closure *vs* OverStitch closure in our series of POEM procedures. We compared our initial 62 POEMs closed with a variety of endoscopic clips commonly available

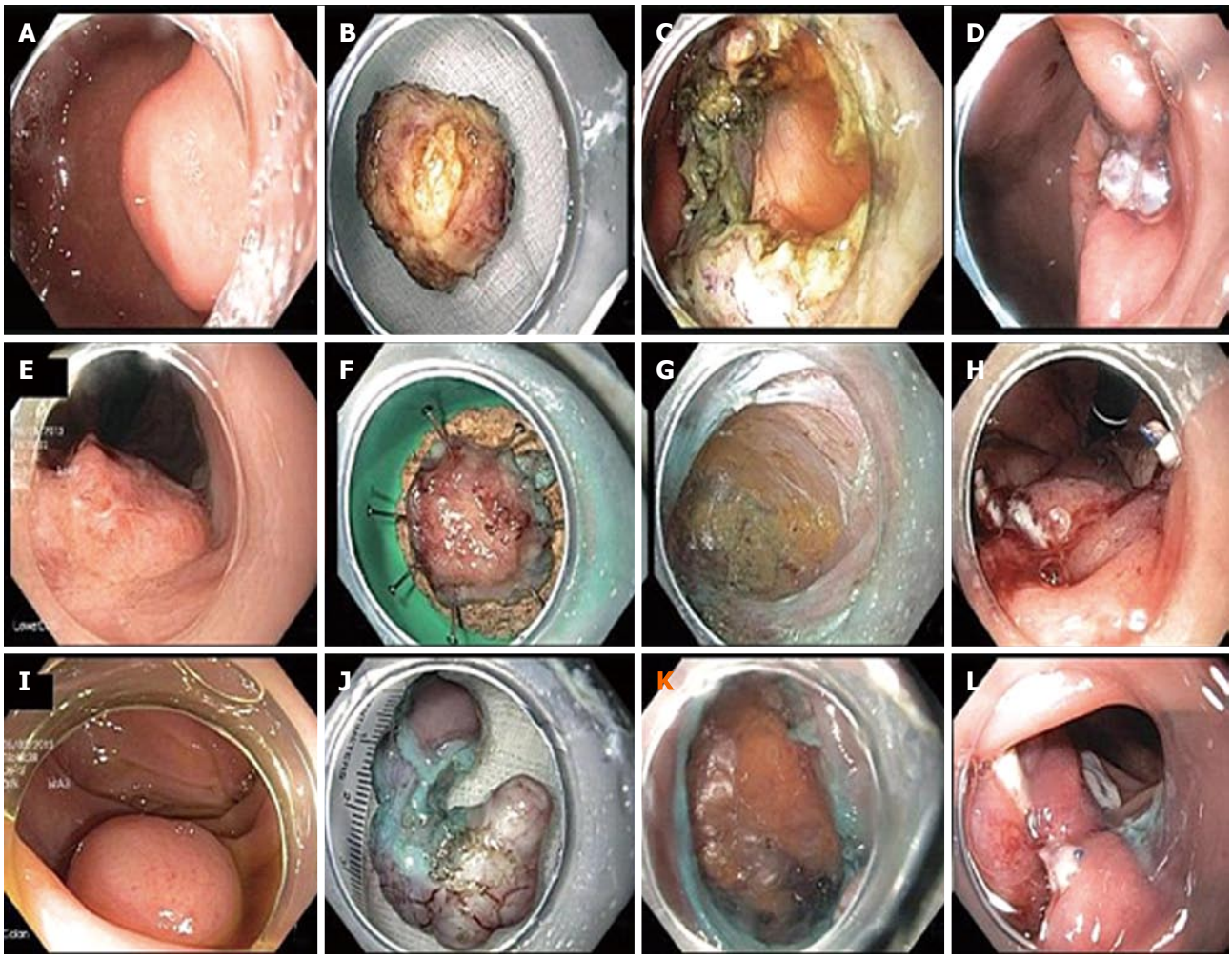

Figure 4 Closure of intentional full thickness perforations after subepithelial tumor removals with endoscopic suturing device. A: Endoscopic image of gastric muscularis propria based subepithelial tumor; B: 2.5 cm schwannoma; C: Resection crater revealing transmural fat; D: Endoscopic sutured closure of defect; E: Endoscopic image of rectal carcinoma superficially extending to muscularis propria; F: 1.3 cm rectal low-grade adenocarcinoma; G: Resection crater demonstrating perirectal fat, circular muscle layer and longitudinal muscle layers; H: Endoscopic sutured closure of defect; I: Endoscopic image of sigmoid muscularis propria based subepithelial tumor; J: 3cm leiomyosarcoma; K: Resection crater demonstrating peritoneal fat; L: Endoscopic sutured closure of defect.

in the United States with the subsequent 61 POEMS closed with endoscopic suturing (Table 2). We did not detect a significant difference in length of stay (1.9 *vs* 1.7 d) or complications (no significant complications in either group). There was one conversion to clips in the suturing group due to a superficial hypopharyngeal mucosal tear caused while attempting to insert the endoscopic suturing device in a patient with very narrow hypopharynx. Closure time and cost per closure was assessed for the most recent 25 cases where clips were used and the most recent 25 cases where suturing was used (after a plateau in the learning curve had been achieved by both techniques) and were found to be similar: mean closure time 8.8 (6-15) *vs* 10.1 (5-16) min and mean cost per closure $916 ($454-$2160) and $818 respectively, (cost based on the cost of these devices to our institution). We should note here, however, that endoscopic suturing device cost varies geographically with relatively small differences within the United States but significantly higher prices in Europe due to distribution costs there.

POST-BARIATRIC SURGERY ENDOSCOPIC STOMA REDUCTION

It is commonplace for patients with Roux-en-Y gastric biopsy to have dilation of both the gastric pouch and the gastrojejunal stoma. Endoscopic suturing lends itself well in reducing the gastric pouch and the stomal diameter, though most work to date centers on the latter. Endoscopic treatment of this condition avoids the need for revisional surgery which is technically challenging and carries significant morbidity. Twenty-five patients with dilated GJ anastomosis (mean 26 mm) had 100% technical success using the OverStitch device with marked reduction of the stoma diameter (mean 6 mm) and mean weight loss of 11 kg[44]. These results are concordant with the results of a multicenter randomized trial[45]. Weight loss was shown to be

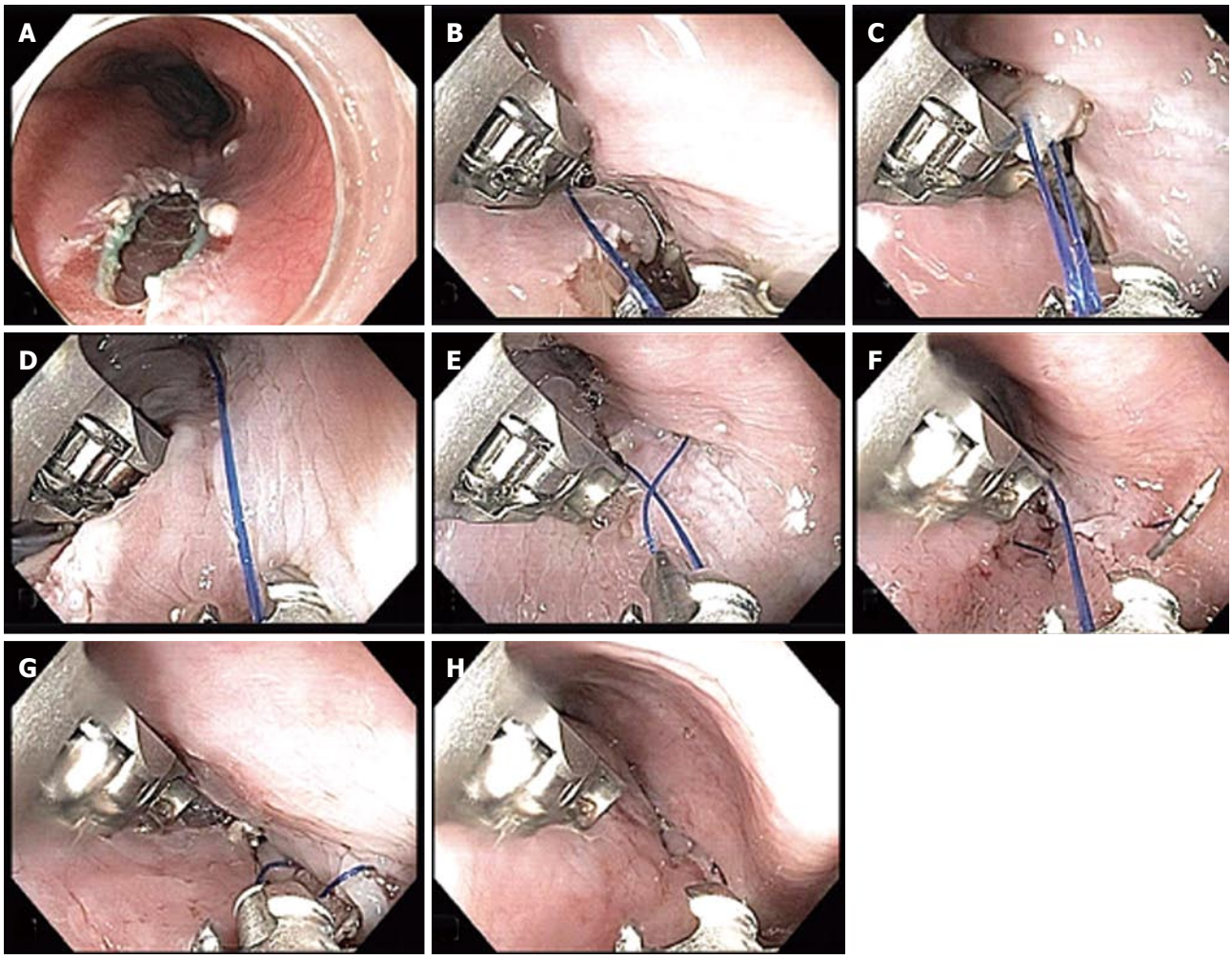

Figure 5 Closure of per oral endoscopic myotomy tunnel orifice with endoscopic suturing device. A: Closure of peroral endoscopic myotomy (POEM) tunnel orifice in a posterior POEM with the tunnel opening at the 5 o' clock position; B, C: We use a single running suture for closure starting at the distal, left margin of the defect as shown here. We attempt to penetrate mucosa and submucosa but not muscularis propria to avoid ischemia and pain or even possible injury to mediastinal structures; D: We proceed with suture placement through the right margin of the defect which is accomplished by torquing the endoscope as shown here; E: It is important to avoid having the running suture (here held by the needle onto the needle transfer catheter prior to loading it onto the needle driver) cross over the long suture leading to the start of the suture line which would then result in inability to properly deploy the cinch to the start or the suture line; F: The single running suture has been completed and has approximated the edges of the defect and the needle has been dropped in order to serve as a T-tag securing the suture at the proximal end of the defect; G, H: The cinch catheter is inserted over the long suture leading to the start of the running suture in the distal end of the defect, the suture is tightened and the cinch is deployed securing the suture at the start of the suture line in the distal end of the defect.

Table 2 Peroral endoscopic myotomy mucosal tunnel closure comparing endoclips and overstitch

	Endoclip	Overstitch
Total number of patients	62 patients	61 patients
Comparison of 25 consecutive closures		
Closure technique (mean number)	8 clips (5-14)	1 suture, 1 cinch, 1 device
Closure duration (mean minutes, $P = 0.1$)	8.8 min (6-15)	10.1 min (5-16)
Cost analysis (mean dollars, $P = 0.2$)	$915.84 ($453.81-$2160)	$818
Hospital Stay (mean days, $P = 0.1$)	1.9 d	1.7 d
Complications	No leaks Increased length of stay (4 d) in one patient with thick mucosal edges approximated with clips and endoloop	No leaks One aborted overstitch closure due to a mucosal tear in the hypopharynx during Overstitch insertion. Had mild sore throat for 4 d

inversely proportionate to stoma diameter[46]. Transoral outlet reduction (TORe) is most effective with a full thickness suturing device as compared to a superficial suturing device, even with similar stoma apertures[47].

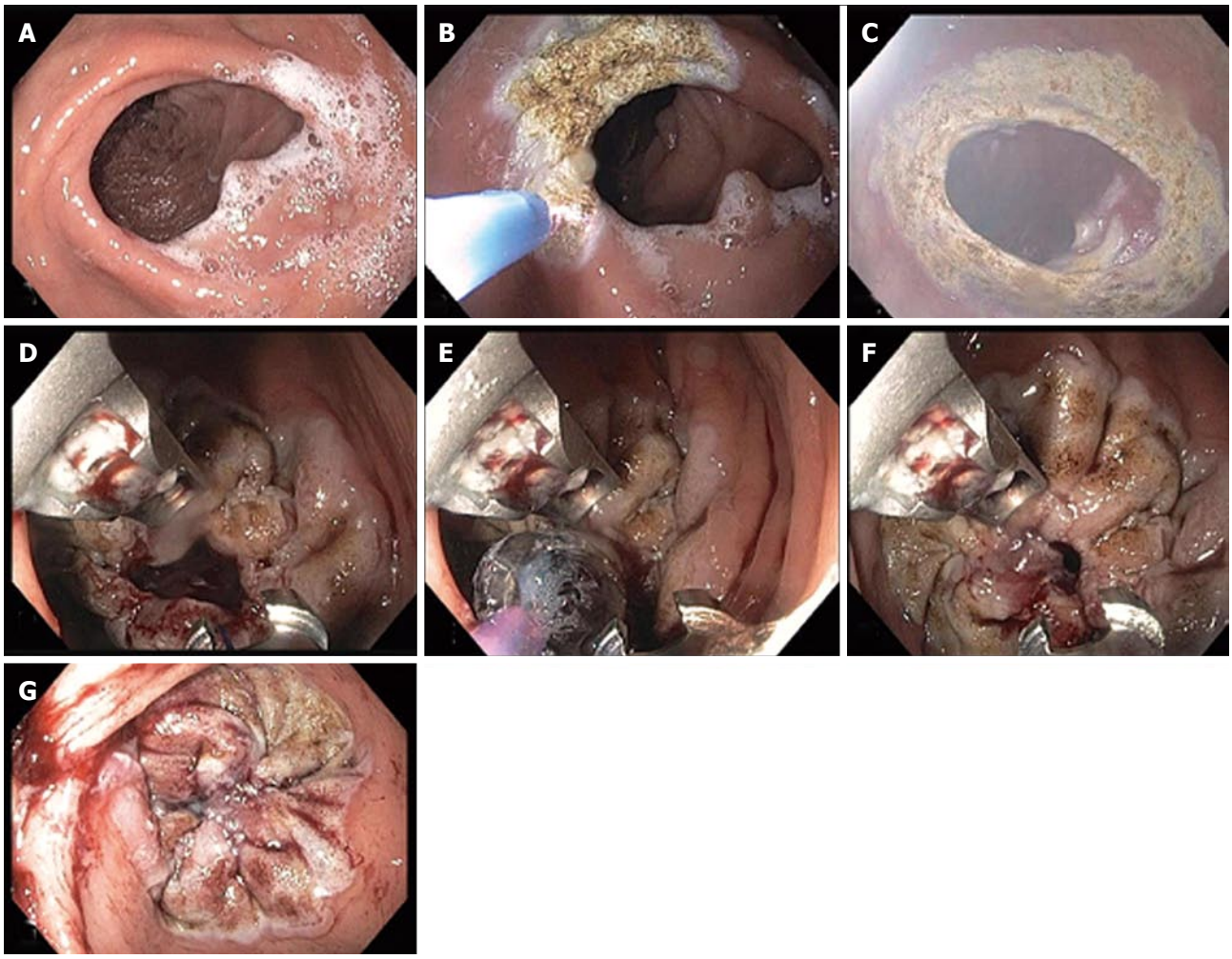

Figure 6 Endoscopic revision of gastrojejunal anastomosis in gastric bypass patient. A: An enlarged gastrojejunal anastomosis is noted; B and C: Argon plasma coagulation was used around the stoma to ablate the mucosa and facilitate tissue fusion during the healing process; D: Two sutures were used obtaining circumferential tissue bites to achieve a purse-like closure of the stoma; E: A 10 mm controlled radial expansion balloon was dilated and placed through the stoma opening via the second channel of the double-channel therapeutic endoscope and then the sutures were tightened so that the final stoma diameter was approximately 10 mm in size; F and G: The balloon was then deflated and removed. A markedly diminished stoma orifice is seen at the end of the procedure.

Preliminary TORe experience at our center in 10 patients is also favorable with mean weight loss of 19 lbs at mean follow-up of 34 wk. Figure 6 demonstrates TORe *via* endoscopic suturing in a 39-year-old woman who had roux en y gastric bypass 14 years ago. Longer term data concerning TORe is being accumulated.

PRIMARY ENDOSCOPIC OBESITY SURGERY

It appears that the restrictive anatomy after surgical sleeve gastroplasty can be duplicated by endoscopic plication of the gastric wall *via* endoscopic suturing. Two groups utilizing an older endoscopic suturing platform (Endocinch) performed gastric restriction in humans with excellent technical success rates and encouraging short term efficacy. Fogel utilized an early generation device of the Endocinch platform to reduce the gastric volume in 64 obese subjects from South America with no reported complications and an impressive 58% excess weight loss at 12 mo that has not been replicated however by other groups[48]. More recently another group used a second generation of the same device used by Fogel to reduce the gastric volume in 18 obese patients from the United States with no complications and a 27% (SD 22%) excess weight loss at 12 mo[49]. Preliminary encouraging data are emerging on endoscopic sleeve gastroplasty performed with the OverStitch device[50]. Under the current protocol followed at the Mayo Clinic, Brigham and Women's, our center and other centers investigating this technique in the United States, sutures are placed approximating the anterior wall, greater curvature and posterior wall of the stomach extending from the antrum to the fundus to achieve restriction similar to that of a surgical sleeve gastroplasty (Figures 7 and 8). The impressive restriction can be seen on the endoscopic images from a patient that underwent the procedure at our institution (Figure 9). Preliminary data indicate no significant morbidity with short-term weight loss similar

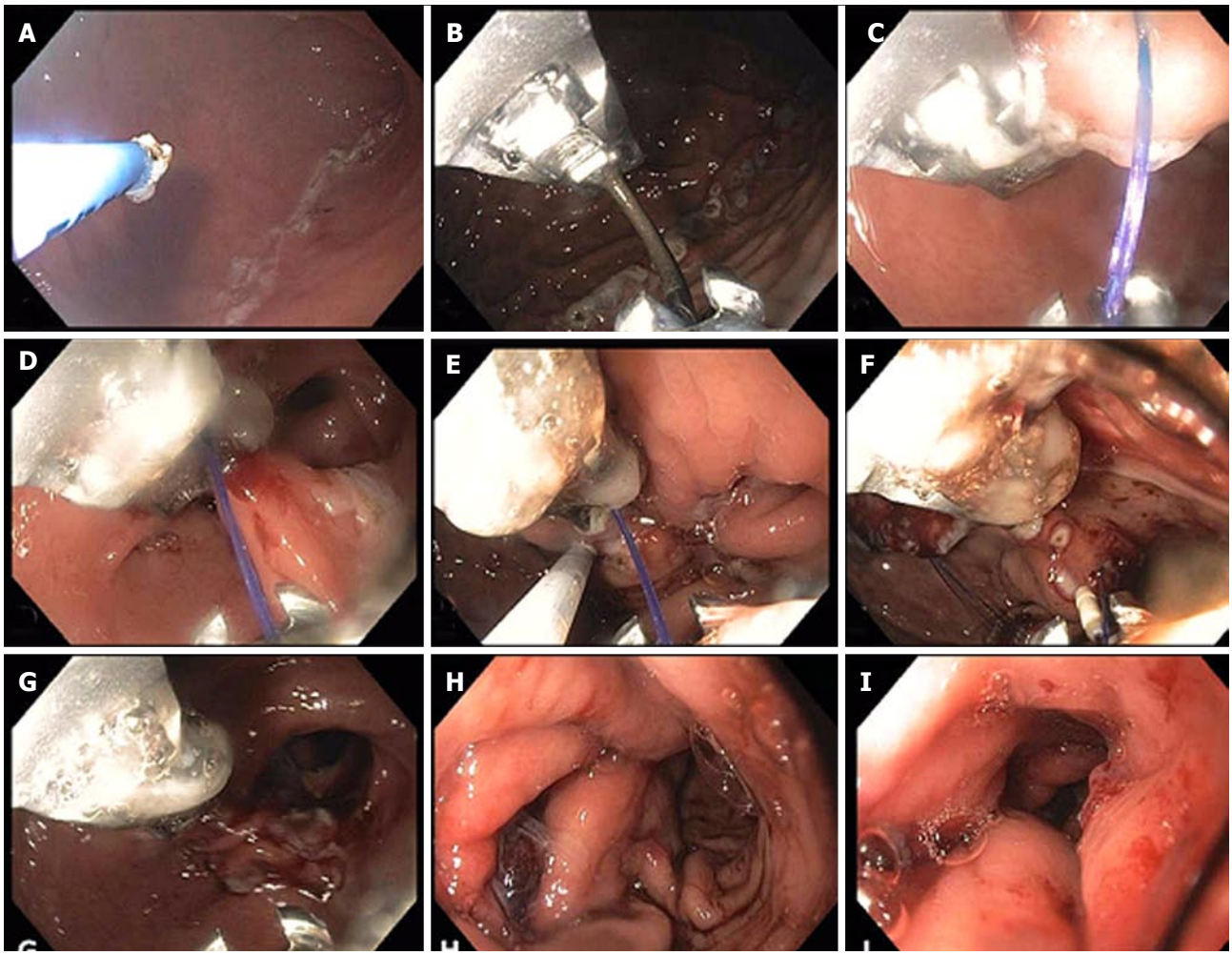

Figure 7 Endoscopic sleeve gastroplasty. A: Initially argon plasma coagulation is used at a setting of 0.8 L 30 W, forced coagulation to mark the anterior and posterior extents of a corridor that will contain the outer sutures to be placed (as shown in the attached schematic (bites along the anterior wall, greater curvature and posterior wall); B: The suturing device is inserted and placement of the first running outer suture is begun as shown in figures C and D reducing the lumen along the greater curvature of the antrum; E: The helical tissue retractor is used through the second channel of the endoscope as seen in figure E to achieve deep, transmural if possible placement of the sutures and to facilitate suture placement in difficult locations; F: Insertion of the cinch device shown at the 6 o'clock position. The running suture can be seen at 7 o' clock prior to tightening; G: After tightening and cinching of the suture the lumen reduction forming the beginning of the endoscopic sleeve can be seen; H: Completion of the outer sutures showing marked lumen reduction; I: Completion of the inner row of sutures with final appearance of the endoscopic sleeve gastroplasty at the end of the procedure. A tight 3-4 cm tunnel is seen which extends from just distal to the fundus to approximately 3 cm proximal to the pylorus.

to that reported for laparoscopic band (Christopher Gostout personal communication). Thus this procedure may find a niche along with other minimally invasive interventions, such as intragastric balloons, in the treatment of patients with moderate obesity (BMI 30-35) for whom traditional bariatric surgery may represent overtreatment. We have entered an era of endoscopic management of obesity, and the huge economic burden associated with this entity will drive further studies and technological development.

WINTHROP ENDOSCOPIC SUTURING EXPERIENCE

At our institution, we employed the Overstitch endoscopic suturing device extensively and in a variety of ways[51] (Table 3). One hundred and seventy-seven procedures incorporated endoscopic suturing. Since this represents one of the 2 or 3 largest volume series worldwide and includes novel applications such as a large number of POEM tunnel closures, we briefly review these data that illustrate the broad range of applications of endoscopic suturing. We typically do not require an overtube for device insertion. The closure success was remarkable with all patients having suturing for POEM, STER, EFTR, ESD, accidental perforations and leak closures having complete closure. Of these 149 closure procedures, there were no episodes of leakage or wound dehiscence; only 2 minor adverse events including one patient with dysphagia due to stricture at site of tunnel closure requiring a single balloon dilation with total resolution of dysphagia and one superficial mucosal tear in the hypopharynx during OverStitch insertion, which was clinically insignificant except for transient sore throat. Table 2 presents comparative data on POEM closure with clips *vs* suturing. We used clips in the

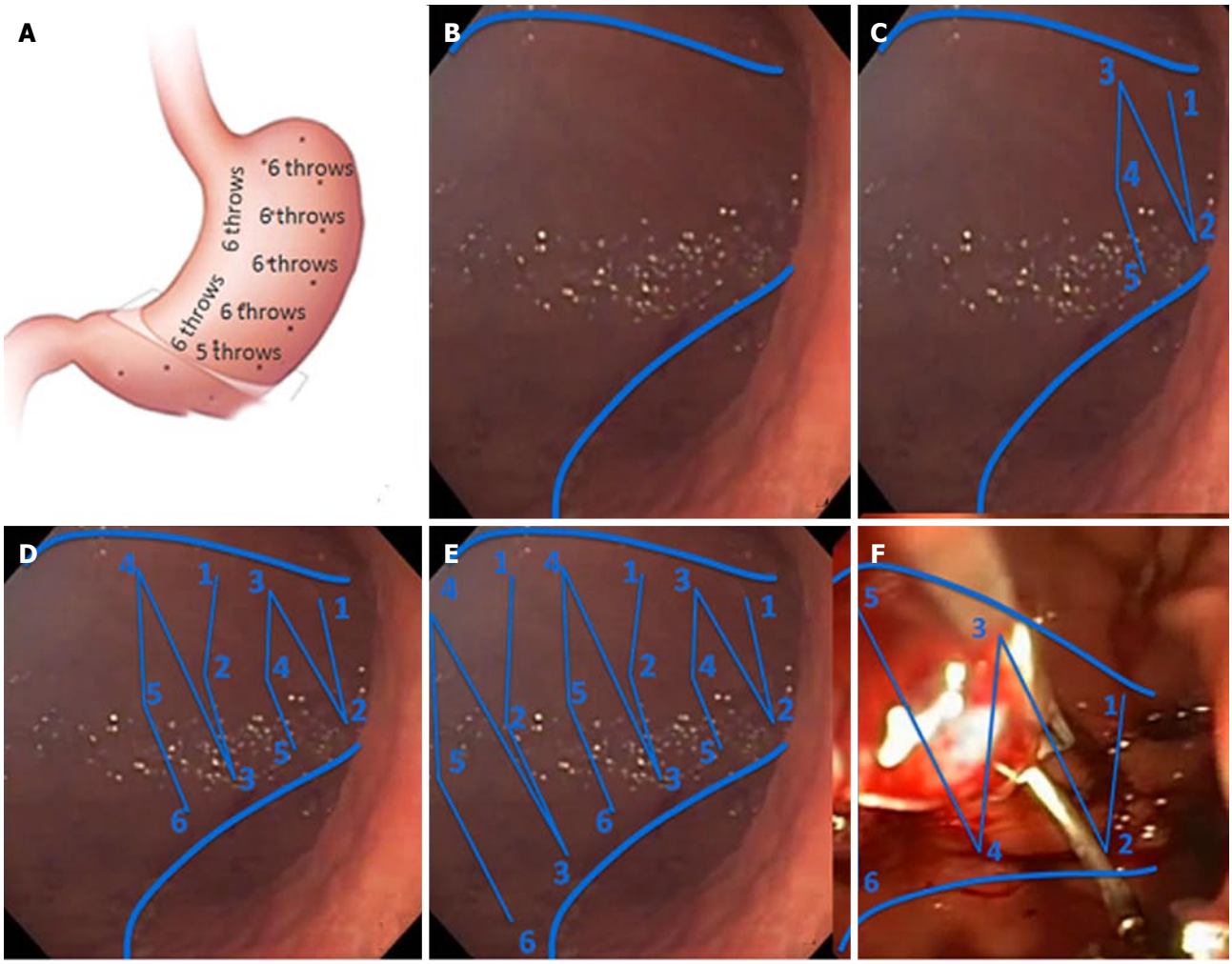

Figure 8 Suture placement needed to achieve endoscopic sleeve gastroplasty. A: Schematic of the configuration of sutures used to achieve endoscopic sleeve gastroplasty. Initially 5 to 8 plication sutures are placed along the greater curvature in a distal to proximal direction, followed by placement of an inner row of 2 to 3 short anterior/posterior "retention sutures" that take some of the tension off the plication sutures; B: Using APC ablation two lines are made along the anterior and posterior wall that mark the outer borders of the plication sutures; C: The first plication suture is placed within 3 cm of the pylorus where due to the narrowing of the lumen results in a modified 5-point suture with the first bites placed on the anterior and posterior wall of the antrum while the 3rd, 4th and 5th bites are placed on the anterior wall, greater curvature and posterior wall; D, E: Subsequent plication sutures all have the same 6 point configuration (anterior wall, greater curvature, posterior wall, anterior wall, greater curvature, posterior wall); F: The inner row of retention sutures consists of sutures of sutures between the anterior and posterior wall a shown (Courtesy Apollo Endosurgery Austin Texas).

Table 3 Winthrop University Hospital endoscopic suturing registry

Indication	Number of Cases	Comment
POEM submucosal tunnel entry closures	100	100% successful closure
EFTR of subepithelial tumor intentional defect closures	24	Mean closure time: POEM/STER -10 min for a mean 2 cm defect
STER submucosal tunnel entry closures	6	EFTR/ESD -13 min for mean 3 cm defect
ESD	22	Perforations/leaks-18 min for mean 1.8 cm defect
Accidental perforation	16	Complications: No episodes of leakage or wound dehiscence 2 minor adverse events
Transoral outlet reduction	7	At mean 34 wk follow-up, mean 19.1 lb weight loss (2-34 lbs)
Primary sleeve gastroplasty	1	At 32 wk follow-up pt lost 40 lbs
Ulcer oversew	1	Required surgical intervention 2 wk post procedure due to lack of response
Leak/fistulae closure	14	2 leaks and 12 fistulas (9 gastric sleeves, 2 roux en y gastric bypass, 1 post- PEG tube removal. 2/2 (100%) leaks and 10/12 (83%) fistulas were successfully closed
Stent anchoring	10	Mean time was 8 min. No episodes of stent migration at mean 8 wk

POEM: Per oral endoscopic myotomy; EFTR: Endoscopic full thickness resection; STER: Submucosal tunnel endoscopic resection; ESD: Endoscopic submucosal dissection.

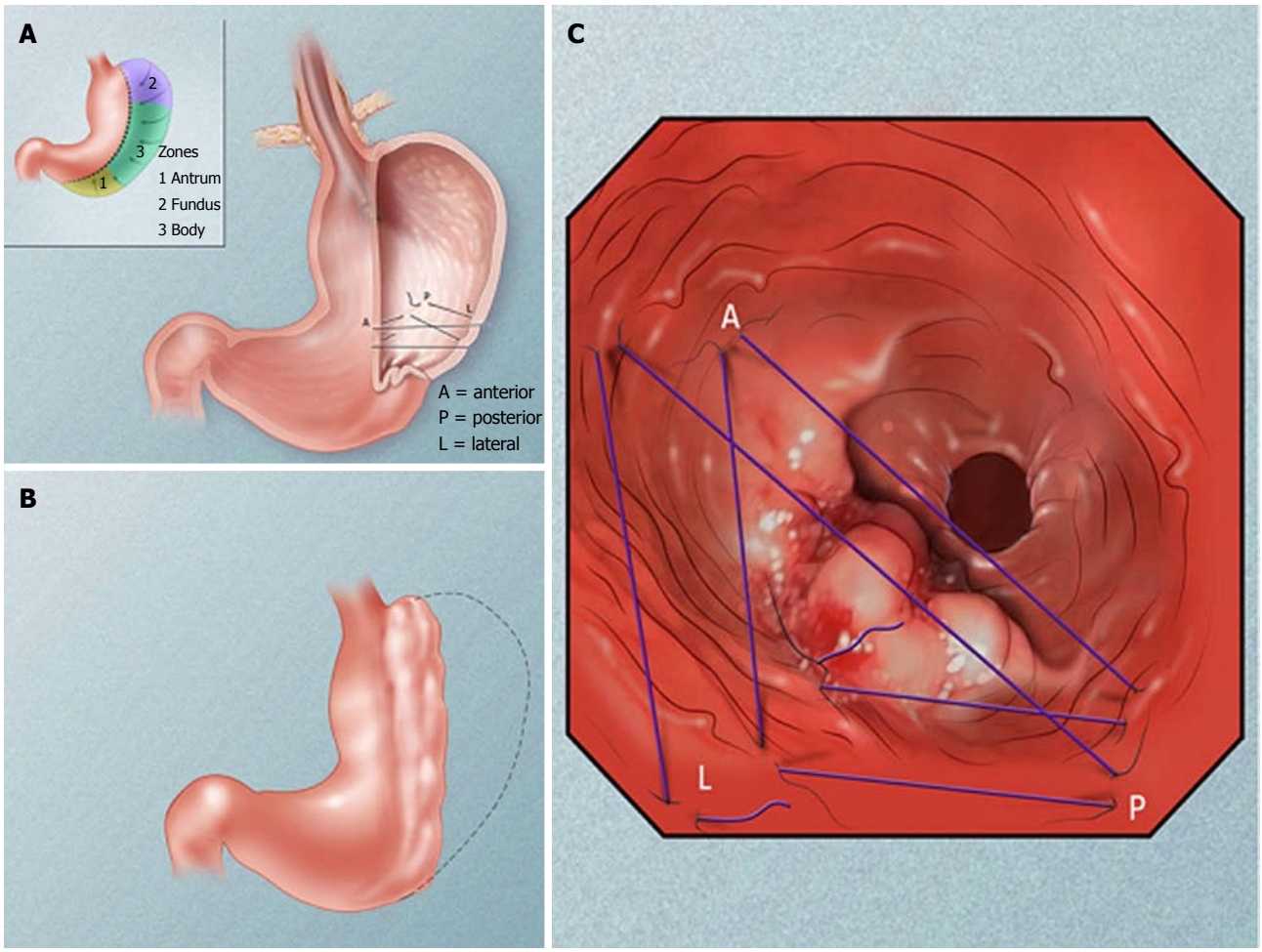

Figure 9 Illustration of the overall sleeve gastroplasty configuration achieved by placement of sutures as to achieve plication of the greater curvature of the stomach. A: Endoscopic gastroplication pattern; B: Plicated stomach; C: Schematic of suture pattern (Courtesy Apollo Endosurgery Austin Texas).

first half of our experience but switched to endoscopic suturing over the past two years. We selected the most recent 25 consecutive cases in each group (to eliminate any learning curve effects) to compare cost, closure time, length of stay and complications. There was no statistically significant difference between clips and suturing for POEM closure (however, regarding cost, it should be noted that this reflects costs of clips and the suturing device in the United States). All 10 sutured stents were in the same place at 8 wk. There was significant weight loss with both gastric outlet stomal reduction and the one primary sleeve gastroplasty. There were two fistula patients that required surgery and the single ulcer oversew patient required surgery for no evident healing at 2 wk.

FUTURE CONSIDERATIONS

The current version of the OverStitch, the dominant endoscopic suturing device requires a double channel gastroscope which limits flexibility and length of insertion thus making suturing in difficult locations such the gastric fundus or duodenum or in deep locations such as the right colon and small bowel difficult or impossible. Newer versions of the device are expected to address these issues. Looking further into the future, it is unclear what the impact of the development of flexible endoscopic staplers might have on endoscopic suturing. One would expect that selection of stapler *vs* suturing device would be guided by similar considerations as guide selection of hand-sewn *vs* stapled closures or anastomoses in surgery. However, unfortunately, this dilemma may not be a consideration for the near future given the expense and technical hurdles involved in developing flexible endoscopic staplers which likely resulted in two prior stapler devices having failed to become commercially viable[52,53]. Another device is in early trials but in its current version is restricted to a single indication, endoscopic fundoplication to treat GERD.

CONCLUSION

There has been a true revolution in gastrointestinal endoscopy with the evolution of endoscopic suturing to now be practically incorporated into clinical practice. As noted, there is a wide gamut of potential applications. There are issues including training and best imple-

mentation, but these should be clarified with time. The current instruments may be replaced or refined with technological developments and experience. Endoscopic suturing is here to stay!

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Endoscopic botox injections in therapy of refractory gastroparesis

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Abstract

Gastroparesis (GP) is a common disease seen in gastroenterology practice particularly in western countries, and it may be underdiagnosed. The available drug therapies for this condition are quite disappointing. Botulinum toxin type A (BT) has been found to be effective therapy in various spastic disorders of smooth muscle of gastrointestinal tract. However, the benefits of BT injections in GP have been unclear. Several retrospective and open label studies have shown clinical advantages of intrapyloric Botulinum toxin type A injections, while two small randomized trials did not show positive results. Therefore, the available published studies yielded conflicting results leading to fading out of botox therapy for GP. We recognize possible clinical benefit of BT injections without any disadvantages of this treatment. We are calling for revisiting the endoscopy guided botox therapy in refractory GP. In this review we discuss important features of these studies pointing out differences in results among them. Differences in patient selection, doses and method of administration of botox toxin in the prior studies may be the cause of conflicting results. The mechanism of action, indications, efficacy and side-effects of BT are reviewed. Finally, we recognize limited evidence to recommend BT in GP and calling attention for future research in this field since no advances in drug management had been made in the last two decades.

Key words: Gastroparesis; Delayed gastric emptying; Botox; Botulinum toxin; Refractory gastroparesis

Core tip: Refractory gastroparesis (GP) has been identified as a chronic debilitating disease. After failure of diet and prokinetic drugs for treatment of refractory GP only surgical options are left. Because of the limited available treatment options and frequent failure of medical therapy, botulinum toxin (BT) injection in the pylorus might offer clinical value in GP. Currently available evidence is not strong enough to support the recommendation of this procedure in all patients with

refractory GP; but promising results have been seen as most patients have noticed symptomatic improvement. Although BT injections were successful in some GP patients, the role of BT remains undetermined. We addressed the position of botulinum toxin in the spectrum of available treatments for refractory GP. Continuing other treatment modalities after BT may improve the results.

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INTRODUCTION

Refractory gastroparesis (GP) constitutes a major therapeutic challenge. Drug therapies are often found to be ineffective for a long term treatment. We found in our practice that some GP patients noticed significant improvement in symptoms and quality of life after botulinum toxin (BT) injections. Therefore, we question if there is a role for intrapyloric BT-A injections for treatment of GP. In this review article, the latest available literature (using Medline) and our own data on this topic will be summarized.

Epidemiology and types of GP

GP has been defined as a chronic disorder of impaired gastric motility in the absence of any mechanical obstruction of the upper gastrointestinal tract. Characteristic symptoms include early satiety, nausea, vomiting, bloating, postprandial fullness and upper abdominal pain[1]. The age adjusted prevalence of GP has been estimated to be 9.6 for men and 37.8 for women per 100000 by a community based study[2]. Most cases of GP have been found to be idiopathic or secondary to autonomic neuropathy associated with diabetes mellitus, surgery, Parkinson disease and collagen vascular diseases[3,4].

Idiopathic GP (IGP), the most common type of GP, is a result of viral or bacterial infection[5]. The underlying etiology of IGP is degeneration of myenteric plexus combined with loss of interstitial cells of Cajal[6]. In diabetic GP (DGP), many mechanisms are responsible for delayed gastric emptying (GE) including neuropathy which affects vagal nerve, reduction in the numbers of intrinsic inhibitory neurons responsible for motor coordination, and reduction in number of pacemaker cells. Acute hyperglycemia with serum glucose levels > 288 mg/dL significantly delays GE in diabetic patients when compared to euglycemia[7]. Post-surgical GP is less common type seen after surgery for peptic ulcer, fundoplication and bariatric surgery, pylorus-sparing pancreatoduodenectomy and heart and lung transplantation[8-10].

Pathophysiology and diagnosis of GP

Delayed GE as the major pathophysiological mechanism of GP is multifactorial, which includes impaired fundal tone, antral hypomotility, antroduodenal discoordination, gastric pacemaker dysrhythmias and excessive inhibitory feedback from the small bowel to the stomach[11]. It has been suggested that increased tone of the pylorus (pylorospasm) may contribute to delayed gastric emptying[12]. Therefore, reduction of pyloric pressure may facilitate improved GE and this can be achieved by botulinum toxin-A (BT-A) injection.

Diagnosis of GP is established based on the presence of clinical symptoms of GP, absence of gastric outlet obstruction or ulceration, and delay in gastric emptying. It is also recommended to document delayed gastric emptying before starting drug therapy of gastroparesis[13].

Treatment of GP

Treatment options for GP include dietary changes, prokinetic drugs, antiemetics, correction of malnutrition and electrolyte disturbances, jejunal feeding, parenteral nutrition, gastric neurostimulation therapy and surgery. In refractory cases of GP, a total gastrectomy has been suggested[14]. Prokinetic agents are the mainstay of treatment in GP after diet failure. However, the side effects and lack of effectiveness limits the long-term use of prokinetics in GP. Because of limited medical options, botulinum toxin-A intrapyloric injections have been offered as a salvage therapy in cases of refractory GP.

Botulinum toxin: Mechanism of action and clinical uses

Botulinum toxin, a bacterial neurotoxin, is one of the most potent paralytic agents of skeletal muscle. In two (2) *in-vivo* studies on piglets evaluating effects of BT-A on smooth muscle, the basal sphincter of Oddi pressure decreased by 50%, and lower esophageal sphincter pressure decreased by 60% with BT-A injection when compared to saline injection[15,16]. An *in vitro* study done on pyloric muscle strips showed that BT-A injection was able to decrease contractions induced by acetylcholine (Ach), substance P and electric field stimulation[17]. Two underlying mechanisms have been proposed for the action of BT-A. At low doses, BT-A inhibits the calcium dependent release of acetylcholine from cholinergic nerve terminals, and at higher doses direct inhibition of smooth muscle contraction has been observed[17]. The effects of BT-A are time and concentration dependent as axonal sprouting and accumulation of extrajunctional Ach lead to slow reversal of denervation[18,19].

BT-A has been found to be effective in the treatment of spastic disorders of smooth muscle in the upper and lower gastrointestinal tract. Case reports and prospective trials have shown positive results with BT-A administration in treatment of diffuse esophageal spasm[20], achalasia[21], oropharyngeal dysphagia[22], anismus[23], anal fissures[24] and anterior rectocele[25]. Administration of BT-A has a very low rate of adverse reactions and complications. Several case reports and

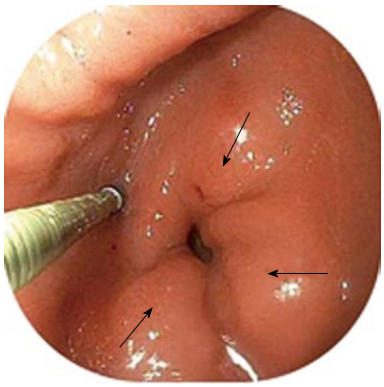

Figure 1 Endoscopic technique for botox injection in the pylorus (4 quadrants - see arrows).

trials of the effects of intrapyloric BT-A injection in GP have been published. Two small prospective studies suggested a limited value of endoscopic intrapyloric BT-A injections in GP[26,27].

There is conflicting data whether BT-A can effectively relieve the symptoms, improve quality of life and improve the rate of gastric emptying in GP patients.

Suggested technique of BT-A injection

The commercial preparation of BT-A in the United States is supplied in vials containing a 50 or 100 U of the lyophilized powder. The powder is diluted in 5 mL of normal saline to yield a solution containing 20-25 U/mL. After diagnostic upper endoscopy, the pyloric sphincter area is identified, and a sclerotherapy needle (23 or 25 gauge) is introduced through the biopsy channel. Aliquots of 1-1.5 mL (20-25 U botulinum toxin/mL) are injected into each of four quadrants of the pylorus, for a total of 100 U (See Figure 1). A total dose between 100 to 200 U can be injected. Patients go home after routine post-sedation criteria are met and they are allowed to eat light meal later on the same day.

CLINICAL STUDIES OF BT-A FOR TREATMENT OF GP

The first data on the intrapyloric application of botulinum toxin in patients with GP was published by Ezzeddine *et al*[28] in 2002. An open label trial included 6 males with diabetic GP, documented by solid phase gastric emptying study, and a mean age of 62 years. All patients had 100 U of botulinum toxin injected in the pyloric sphincter. A solid phase gastric emptying study was done before the BT-A injection, and then repeated at 48 h and 6 wk after the procedure. The mean solid phase gastric emptying at 90 min improved from 27.8% before BT-A injection to 44.4% at 2 wk, and 49% at 6 wk. Baseline clinical symptoms were recorded and the symptoms were reassessed at 2 wk and 6 wk interval after the BT-A injection to document improvement. A mean improvement of 55% was noticed at both 2 and 6 wk. No complications were seen after BT-A therapy. This study was very limited in terms of population and control group but it certainly demonstrated some clinical efficacy and immediate improvement in gastric emptying rate.

In an open label trial[29], eight patients (including 6 women) with type 1 diabetes and GP were studied. Mean age was 41 years. A control group consisted of asymptomatic non-diabetic patients matched for age and gender. A higher dose of BT-A 200 U was used. Clinical symptoms, antro-pyloric manometry, gastric emptying, weight and insulin use were measured at baseline and at 12 wk with follow up completed in 7 patients. Prokinetic drugs were not discontinued during the trial. Significant improvement in symptoms after the BT-A injection was reported in all the patients with the average symptom score reduction to 12 from 27.4 patients had improvement in the solid phase gastric emptying post therapy including 1 case of normal GE study. Three patients had no improvement in GE, and 1 patient had a worse gastric emptying rate when compared to the pre-procedural values. Radiologists reading the gastric emptying study were blinded to the trial protocol. Pylorospasm was demonstrated on antro-pyloric manometry in all patients with GP, but it was not seen in any of the controls. Significant reduction in pylorospasm was found after BT-A when compared to baseline. Insulin requirement was increased in 4 patients at 8 wk and remained increased in 3 of them at 12 wk follow up. Weight gain was noticed in all patients except one. Prokinetic drug use was reduced in 50% of the patients.

A retrospective study by Bromer *et al*[30] included 63 patients (53 women; 10 men) with average age 42 years. Most of the patients (44) received a dose of BT-A 200 U and 13 patients received 100 U. No dose was recorded for 6 cases. The outcomes in this study were assessed on the basis of improvement in major GP symptoms. Forty-three percent patients reported improvement in symptoms, and men had better response to BT-A therapy than women. The mean duration of response to BT-A therapy was 5.1 mo. Treatment with BT-A was repeated based on recurrence of symptoms. Apart from the small study population, the absence of any quantitative measure of improvement and no standardized scale of symptomatic relief limited the quality of this study.

A small retrospective analysis of 21 patients (15 females) with refractory GP was recently published from the United Kingdom[31]. The mean age of patients was 47.8 years and 81% of cases were secondary to DGP. A dose of 200 U of BT-A was used in all the patients. The mean follow up was 2 years. Sixty-two percent patients reported response to treatment compared to 19% non-responders. The mean response duration was 4.2 mo. Weight gain and increased insulin requirement was observed in the diabetic group. Greater effectiveness of BT-A therapy was found in the diabetic population compared to idiopathic GP cases.

In an open label trial[32] of 10 female patients with

IGP, a mean duration of symptoms of 4 years and prokinetics failure, BT-A in doses 80-100 U was used. Response was assessed on the basis of upper GI symptom improvement and 4-h solid phase gastric emptying study at 4 wk after the treatment compared to the baseline. Nine out of 10 patients reported improvement in symptom scores. An improvement in the gastric emptying rate was found in 7 of the 10 patients (70%), while 2 patients had no change and 1 case had worsening of gastric emptying rate. The patients were followed up for at least 6 mo. In 5 out of 10 patients repeat BT-A injections were required due to recurrent symptoms. All the patients reported improvement after the second BT-A injection. This study showed effectiveness of repeat BT-A injection but at the same time raised a question regarding long term outcomes of the procedure.

In another open label study[33], 20 patients with GP (17 women; 17 IGP) received 100 U of BT-A injections in the pylorus. An assessment of solid and liquid gastric emptying, and improvement in intensity of cardinal GP symptoms was performed at 4 wk. Significant improvement was found in solid phase gastric emptying and the symptom score compared to pre procedural numbers, but no improvement in liquid phase emptying was seen. No correlation was found between symptomatic improvement and the change in gastric emptying rate. This study had only a short follow up. The study raised an important question pertaining to the methods of measurement of improvement in GP patients. If we should assess the objective improvement based on the diagnostic test (GE study), a measurable standard, or the subjective improvement should be determined on the basis of their symptom scores as outcome measures.

Those promising results from the open label trials and observational studies prompted researchers to conduct randomized control trials. Two randomized, placebo controlled double blinded studies were published. In a trial by Friedenberg *et al*[26], a total of 32 patients were divided into two groups of 16, and randomized to receive either 200 U of botulinum toxin or saline injection in the pylorus. Each group contained 9 patients with diabetic GP. All patients had a symptom score $\geqslant$ 27. A decrease of 9 points or more in the symptom score at 1-mo follow up was considered as the primary endpoint. Only 6 patients in the botox group showed improvement compared to 9 patients in the saline injection group. Gastric emptying rate improved markedly in the BT-A group, but did not reach statistical significance when compared to the placebo group. Out of the 32 patients, 17 had no symptom improvement including 10 from the BT-A group. The study was based on an assumption of an efficacy of 80% for the BT-A injection which was relatively high and had a small population size and low statistical power. The second randomized controlled study by Arts *et al*[27] included 23 patients with GP (18 women, and 19 IGP). The mean age of the patients was 45 years. The study was double-blinded and patients received either BT-A injection at a dose of 100 U or saline injection in a cross-over pattern. Baseline gastric emptying and GP cardinal symptom index (GCSI) were recorded. In the first session, 12 patients received BT-A injections and 11 had saline injections. Both groups showed considerable improvement in the solid phase gastric emptying after the first injection. But no subsequent improvement was seen in either group after the second injection (cross-over). No statistically significant difference was seen when pooled data was compared from both groups after the two procedures. Both groups showed similar improvement in GCSI. Even though the pooled data analysis showed considerable improvement of post-prandial fullness and bloating in the BT-A group, it was not statistically different from the placebo group.

The largest study published up to date was a retrospective trial of 179 patients including 81 with DGP and 76 IGP cases[4]. The response was measured in terms of symptom improvement and change in body weight within 1 to 4 mo after BT-A injection. Almost 51% patients reported benefit and 32% of them had no benefit from the BT-A therapy. No record was available for the rest of the patients. BT-A was injected in doses ranging between 100-200 U. Patients who received higher doses reported better symptom control. Many patients (87) underwent repeat BT-A injections and received doses of 150 U or 200 U. Similar results were observed on repeat injections among first time responders and non-responders. This study results suggested a better response in women, younger patients (< 50 years old) and those with idiopathic GP.

Recently a case series[34] of 3 patients with diabetic GP and islet cell transplant between ages 42-55 years was published. They were treated with intrapyloric BT-A injections (2 patients received 200 U and one received 150 U). Symptomatic improvement was noticed in all the patients. The response lasted 6-8 wk in 2 patients who had BT-A 200 U injections and 8 mo in the patient who received lower dose 150 U. This result raised a question of the most effective dose to use for intrapyloric BT-A injections in GP.

The data on the use of BT-A in pediatric population with GP is even more scant. Only 1 study[35] has been published on BT-A in refractory GP. A retrospective review of 47 children including 23 girls was conducted with follow up available for 45 of them. The mean age of the patients was 9.8 years and mean follow up was 18 mo. The majority of the patients (66%) had idiopathic GP. Botulinum toxin was injected at a dose of 6 U/kg up to a maximum total dose of 100 U. The outcome was measured based on symptoms index as no response, mild, moderate or complete resolution of symptoms. At least mild improvement in symptoms was seen in 66.7% patients, with only 1 patient reporting worsening of symptoms. Repeat BT-A injections were required in 18 patients, out of which 8 showed response and 7 did not benefit from repeat treatment. Median duration of response to BT-A was 3 mo. The children older than 12

Table 1 Summary of the literature on use of botulinum toxin injection for gastroparesis in adults

Ref.	Number of patients	Study design	Botox dose (units)	Results (% of patients with symptomatic improvement)
Ezzeddine *et al*[28]	6	Prospective non-controlled	100	55
Lacy *et al*[29]	8	Prospective non-controlled	200	100
Bromer *et al*[30]	63	Retrospective	100 (n = 13) 200 (n = 44) Unknown (n = 6)	43
Rameshshanker *et al*[31]	21	Retrospective	200	62
Miller *et al*[32]	10	Prospective non-controlled	80-100	100
Arts *et al*[33]	20	Prospective non-controlled	100	100
Friedenberg *et al*[26]	32	RCT	200	37.5
Arts *et al*[27]	23	RCT	100	100[1]
Coleski *et al*[4]	179	Retrospective	100-200	51

[1]100% improvement was seen on botulinum toxin as well as normal saline so botox was not proved to be better than placebo. RCT: Randomized-controlled trial; n: Number of patients.

years showed better response when compared to those of < 12 years old. This study was important by showing that efficacy rates, duration of response and safety of botox in children were comparable to the results seen in adult population.

In a recent meta-analysis[36] of 15 studies, including single case reports of GP, almost all open label and retrospective studies showed a beneficial effect of BT-A treatment for GP, while 2 randomized control trials have shown no superiority of BT-A in comparison to placebo. Based on the meta-analysis, it has been suggested that the current evidence did not justify the use of BT-A in GP patients, but the analysis consisted of only a small population (186 patients). Across these studies, the 2 randomized control trials included in the meta-analysis were found to be significantly heterogeneous. Because of these limitations, the meta-analysis failed to add any useful knowledge for practical purposes in therapy of GP (Table 1).

DISCUSSION

Botulinum toxin has been widely used in the past as a treatment option for patients with refractory GP with clinically beneficial effects, mainly symptomatic improvement. All the open label trials have reported the intrapyloric BT-A injection to be useful therapy in GP[28-35]. However, two small prospective randomized control trials (RCT)[26,27] did not show positive response to botox injection in regards to symptomatic improvement and rate of gastric emptying. Both studies in different subgroups (DGP *vs* IGP) of patients have not proven BT-A to be superior to normal saline injection, and cast some doubts over its effectiveness. Based on results of those RCTs some GI societies do not recommend routine use of botox injections as a treatment option in GP.

Limitations of therapy for gastorparesis

It has been a major concern that currently available drug therapy for severe GP is very limited. Traditionally prokinetics, metoclopramide, domperidone and cisapride, have been widely used in the treatment of functional dyspepsia and GP[37]. These prokinetic agents work by increasing antral contractility and accelerating gastric emptying[38]. In a systematic analysis, prokinetics have been shown to be more effective than placebo in GP by improving the symptoms of postprandial fullness, nausea and vomiting[39-42]. However, available prokinetic drugs only modestly enhance gastric emptying and the evidence that their symptomatic improvement in GP is related to enhancement of gastric emptying is actually lacking. Serious side effects such as cardiac arrhythmias (QT prolongation) seen with cisapride (Propulsid; Janssen Pharmaceutica, Titusville, NJ) led to withdrawal of the drug from United States market in 2000[43]. Cisapride was also banned in India and Philippines in 2011, and its use in Europe has also been quite limited. Metoclopramide (Reglan; A. H. Robins, Richmond, Va) is the most commonly used drug for the treatment of GP. However, extrapyramidal symptoms and sedative effects of metoclopramide limited its usage in GP. Metoclopramide significantly increases the risk of tardive dyskinesia, drug-induced Parkinsonism, and subjective akathisia[44]. The severity of tardive dyskinesia was greater in diabetics when compared to non-diabetics[44]. A dramatic reduction in prescribing of metoclopramide by clinicians for GP has been seen after a black box warning was placed for the risk of tardive dyskinesia when used for prolonged period[45]. Side effects are a common reason for discontinuation of metoclopramide therapy. Erythromycin is the only other Food and Drug Administration (FDA) approved drug for use in GP. Studies have shown symptom improvement in only 43% of the patients taking

erythromycin[46]. The use of erythromycin is often limited by development of tachyphylaxis as a result of down regulation of motilin receptors, which develops days after initiating the treatment[47]. Other side effects of erythromycin such as nausea, vomiting, and abdominal pain seen more often with higher doses can result in discontinuation of therapy[48,49]. Domperidone (Motilium; Janssen) appears to be effective for treating symptoms of GP. However, it is not available for sale in the United States. Domperidone has not been approved by the FDA because of concerns regarding its cardiotoxicity, mainly QT prolongation seen especially in hypokalemic patients[50]. The hurdles in obtaining the drug have discouraged the physicians in United States regarding its applications in GP. Currently, domperidone can be prescribed in United States for GP patients 12 years of age and older through an expanded access investigational new drug application and local institutional review board (IRB) approval[51].

Hence, there is a clear need for new therapeutic approaches for the treatment of GP. Gastric electric stimulator (GES) has been shown in clinical studies to be effective to control nausea and vomiting in GP patients. Even though patients with refractory symptoms have embraced the availability of this device, the special status and certain requirements used by some third party insurance carriers may deny coverage. The GES device has a humanitarian device status. Therefore, the gastric electrical stimulator cannot be implanted at any center unless its placement has been approved by the local IRB. Candidates for this therapy are patients with diabetes and IGP with relentless nausea and vomiting, who have failed medical therapy. Conversely, patients without nausea and vomiting but with other manifestations such as fullness, early satiety, anorexia, and abdominal pain have not been shown to predictably respond to gastric stimulation[52].

General concerns regarding studies on botox in GP

Most published studies looked only at a total symptom score (GCSI) rather than selected symptoms of nausea and vomiting. From clinical standpoint improvement in symptoms appears to be the most important outcome when treating patients with GP. The most troublesome symptoms for patients are nausea and vomiting, which tremendously limit oral intake and may lead to progressive weight loss and malnutrition. Abdominal pain associated with GP is the most challenging symptom to treat since patients often request pain medications, especially narcotics, and those drugs can lead to further delay in gastric emptying and diffuse GI tract dysmotility. Chronic dependence on narcotics has to be recognized in patients with both IGP and DGP. Those patients are taking opioids for different reasons including abdominal pain, but often not related to GP. Narcotics use makes this condition more difficult to treat. For some patients discontinuation of pain medications is not a viable option because of their quality of life.

In patients with refractory GP, even a partial clinical response may provide significant improvement in quality of life and possibly reduce number of hospitalizations. On the other hand, improvement in GE has not been shown to correlate with symptom improvement in this patient population. Therefore assessing response to BT-A based on GE study only has its own limitations.

Patients with severe refractory GP often require frequent visits to emergency center (ER) and hospitalizations, which is also associated with higher cost of medical care. Because of above limitations and high prevalence of GP, other therapeutic options are needed to improve symptoms and quality of life in GP patients. With the limited availability of medical treatment options, side effects and drug failure, we believe that physicians may need to reconsider botox as a trial therapy before directing patient with refractory GP for more aggressive treatment such as surgical interventions including placement of jejunostomy tube or GES and gastrectomy.

Our limited experience with Botox therapy in GP

In our small retrospective unpublished study of patients with GP (confirmed by solid phase gastric emptying study) treated with intrapyloric BT-A injection, a survey was performed to assess symptoms, the overall improvement after procedure, and the number of visits to ER and hospitalizations[53]. Twenty-five patients (19 females; 6 males) were included in the analysis. The causes of GP were idiopathic 17, diabetes 6, and postsurgical 2. Mean follow up was 31 mo. Seventy-two percent of our patients noticed significant (> 50%) symptom improvement. The patients who benefited the most from BT-A injection were males and those with IGP. Twenty-eight percent of patients (7/25), non-responders to botox therapy underwent laparoscopic GES placement. Reduction in number of ER visits and hospitalizations was reported by 24% of patients.

Role of botox in treatment of GP

The results of available literature are quite controversial to determine the clinical effects of botox therapy in GP. Some patients clearly reported symptomatic improvement with botox therapy. In refractory GP cases it is quite difficult to reject this therapeutic option especially as it is very safe.

For example, there is also controversy on effectiveness of botox in patients with anismus, but it has been often used since no other therapies offer benefits in this condition. We have solid data available on use of botox in achalasia, including safety and need for repeat injections. Despite more effective and permanent solutions available including Heller myotomy and peroral endoscopic myotomy, BT-A injections are still in the armamentarium for achalasia[54,55].

Several questions need to be further addressed regarding botox application in refractory GP. First, it is unclear, which patients with GP benefit the most from botox therapy. Some studies have suggested better results in patients with IGP including our own data[4,53].

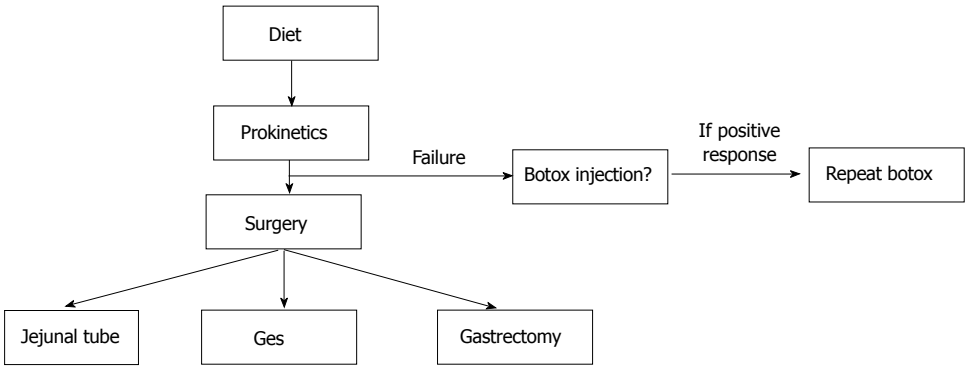

Figure 2 Summary of therapeutic options for gastroparesis. GES: Gastric electric stimulation.

There may be also a sex difference in response to BT-A injections. In a one retrospective study men had superior response[30], while the other large study showed the opposite results[4]. The effects of patient age on outcomes also need to be evaluated further. In pediatric population, older children appeared to have better results to BT-A injection[35]. There is a concern regarding safety of multiple BT-A injections into pylorus which could lead to local scarring as documented for comparison in achalasia patients[56,57].

Another issue that requires further study is to evaluate if the effect of botox injection may be dose dependent? Is a higher dose of botox more beneficial in GP? There is no clear answer to this question. In the RCTs botox was mainly used in two different dosages of 100 U or 200 U, and both showed negative outcomes[26,27]. Question has been raised about the effectiveness of higher dose of botox and the length of the response[34]. For example, in achalasia, no data exist to support that higher dose of botox is more effective and has longer lasting beneficial effect. One of the concerns is rather a short lasting effect of BT-A injections in GP. Based on the available studies the beneficial effects of Botox lasted between 3-8 mo[32,34]. Therefore, patients may require additional BT-A injections. The results on the duration of response to BT-A injection appear to be similar to published data in patients with achalasia. Often retreatment may be needed.

When to repeat BT-A injection? Should botox be used if there is no prior response or only if previously there was a good response to it? Should a higher dose of botox be injected next time if no response is found to the first treatment? Should the dose of botox be selected based on the severity of delayed gastric emptying?

Based on the prior studies, patients who had a positive response to the first dose continued to respond to repeat BT-A injections[4,32]. The studies do not provide an answer in which setting to use repeat botox. In our practice we use a standard dose of 100 U in each case. From personal experience we repeat BT-A injection only if there is an initial symptomatic improvement after first injection. The BT-A injections are repeated based on duration of response typically every 6 mo if needed. In patients with IGP spontaneous improvement in symptoms over time can be expected. Therefore botox injection may be used as a bridging therapy during a period of severe symptoms before the condition can be managed by diet and prokinetic drugs only.

To our knowledge no studies evaluated quality of life in patients with GP after BT-A injections. This issue may also be evaluated in further studies. If lower number of ER visits or hospitalizations can be documented with Botox therapy this could have an impact on cost of care in GP patients. Finally, we recognize that patients after BT-A injection need to continue to follow the diet and drug therapy. Diet and prokinetics adjustments should be done gradually as patients report symptomatic improvement. In only one study a reduction in prokinetic medication use has been addressed as an outcome measure[29].

There may still be a role for Botox use when patients fail diet modification, prokinetics or when the promotility drugs are not available. (See our proposed algorithm (Figure 2). At present there is no clear answer which patients benefit the most from botox injection. In general, patients have no contraindications for BT-A injection unless they face major cardiopulmonary issues not allowing for a safe endoscopy. Studies suggest that GP patients with pylorospasm have the best response to BT-A injections. However, in clinical practice, no easy access to gastroduodenal motility testing is available. Therefore, a decision to use botox has to be individualized in GP. Botox injections should not be used routinely in all GP cases.

CONCLUSION

Pyloric injection with botulinum toxin is an easy to perform procedure with minimal risk and negligible side effects compared to other available treatments for refractory GP. Although, the lack of convincing evidence has limited the use of botox in clinical practice, most uncontrolled studies have shown symptomatic improvement in the GP patients. Other concern regarding botox use is that, the dose and most effective site of BT-A injection for optimal response has not been standardized. Misplaced injections and skills of the endoscopist should also be taken into account

when determining the effectiveness of treatment with botox injection. If botox therapy is effective, the results of this treatment have not been long lasting and repeat procedures may be necessary. The long-term effects with repeat procedures have not been well studied. Further large population randomized studies are required to justify the use of botox for refractory GP. There may be a role for BT-A therapy in properly selected GP patients. With limited treatment options, we believe that botox injections can still be considered as treatment option for refractory GP when drug therapy failed.

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Endoscopic ultrasound in common bile duct dilatation with normal liver enzymes

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Abstract

In recent years, the description of isolated bile duct dilatation has been increasingly observed in subjects with normal liver function tests and nonspecific abdominal symptoms, probably due to the widespread use of high-resolution imaging techniques. However, there is scant literature about the evolution of this condition and the impact of endoscopic ultrasound (EUS) in the diagnostic work up. When noninvasive imaging tests (transabdominal ultrasound, computed tomography or magnetic resonance cholangiopancreatography) fail to identify the cause of dilatation and clinical or biochemical alarm signs are absent, the probability of having biliary disease is considered low. In this setting, using EUS, the presence of pathologic findings (choledocholithiasis, strictures, chronic pancreatitis, ampullary or pancreatic tumors, cholangiocarcinoma), not always with a benign course, has been observed. The aim of this review has been to evaluate the prevalence of disease among non-jaundiced patients without signs of cytolysis and/or cholestasis and the assessment of EUS yield. Data point out to a promising role of EUS in the identification of a potential biliary pathology. EUS is a low invasive technique, with high accuracy, that could play a double cost-effective role: identifying pathologic conditions with dismal prognosis, in asymptomatic patients with negative prior imaging tests, and excluding pathologic conditions and further follow-up in healthy subjects.

Key words: Unexplained common bile duct dilatation; Endoscopic ultrasound; Normal liver enzymes

Core tip: Common bile duct dilatation, often without identified causes, in subjects with normal liver function tests and nonspecific abdominal symptoms, and absence of lesions on prior noninvasive imaging tests, is increasingly found in the clinical practice. Since the clinical suspicion for biliary pathology in that setting is usually low, and there are limited literature data, this condition is ignored. However, recent evidences show the existence of pathologies among these patients, often with a non-benign course. In this scenario, endoscopic

ultrasound may have a role in the identification of the etiology of dilatation.

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INTRODUCTION

The biliary system plays a central role in digestive pathophysiology, since it allows bile sterile flow from hepatocytes, through intra- and extra-hepatic ducts, Oddi's sphincter and Vater's ampulla, to the duodenum determining lipids absorption and excretion of metabolites and toxins in the small bowel[1]. In case of obstruction of these structures (as observed in choledocholithiasis, Mirizzi's syndrome, neoplastic or flogistic papillary strictures, parasitic infection, cholangiocellular or pancreatic adenocarcinoma), liver biochemical abnormalities and jaundice, sometimes in association with fever or abdominal pain, usually appear[1].

In recent years, due to the widespread use of high-resolution imaging techniques in order to investigate the causes of nonspecific abdominal symptoms, isolated bile duct dilatation in non-jaundiced patients with normal liver function tests has been increasingly reported. There is scant literature about the diagnostic impact of endoscopic ultrasound (EUS) in this setting and not much is known about the natural evolution of this condition. The aim of this review has been to analyze EUS accuracy in this scenario.

CAUSES OF BILIARY DILATATION

There are controversies regarding the upper normal diameter of the common bile duct (CBD) but it is conventionally accepted to be 7 mm[2-6]. A variety of factors can influence bile duct size, prominently imaging modality, age[7-10] and prior cholecystectomy. In transabdominal ultrasound (TUS), distal CBD may be difficult to visualize because of bowel gas, thus resulting in underestimation of duct size compared to other imaging techniques as computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC)[11]. On CT and MRCP imaging, bile duct wall is included in the measurement and, because of its oblique course and the difficulty to separate a possible low cystic duct insertion, result on the axial source may be inaccurate[8]. Finally, magnification and duct distension by contrast, used in ERCP and transhepatic cholangiography, may overestimate duct size[8].

Several studies in the last 20 years reported an increase in the CBD diameter in older patients, even if with consistent variability[6,7,9,10,12]. Based on autoptic observations, some authors identified loss of elastic fibers and proximal compensatory dilatation due to distal sclerosis as potential causes of the phenomenon[13]. Moreover, the fragmentation of the longitudinal smooth myocyte bands in elderly subjects and use of drugs such as calcium antagonists and nitroglycerine, may reduce contractility and cause hypotonus of the duct[12,14]. Finally, prior cholecystectomy seems to influence CBD diameter since gallbladder physiologically plays a role in accommodation of pressure fluctuation in biliary system which, after surgery, could be transferred to bile duct causing dilatation[11,15-17].

Among non-obstructive etiologies of CBD dilatation, opioids consumption has been described. Opiates may cause an increase in the basic pressure and in frequency of phasic contractions of the Oddi's sphincter leading to biliary dilatation[18,19]. In a study performed by Farahmand *et al*[20], the authors showed an association between increased biliary diameter, evaluated on TUS, and addiction to opioids in asymptomatic patients, with normal levels of serum bilirubin and alkaline phosphatase tests and absence of obstructive factors on TUS. In a recent study, opium addicts, symptomatic for abdominal pain were subjected to EUS. The authors observed CBD dilatation, especially in the extra hepatic tract, in all 15 patients included and increased surface area of Vater's papilla in 12 of them, after a mean of 20 years of opium addiction[21].

Pathologic conditions are also able to induce isolated bile duct dilatations with non-specific symptoms or biochemical abnormalities. Choledocholithiasis, which develops in about 10%-20% of patients with gallbladder stones, may be asymptomatic in half of cases and CBD stones cannot always be identified by traditional non invasive imaging techniques[22]. Reported sensitivity in detection of CBD stones is 18%-74% for TUS and 50%-90% for CT[23-25]. Recently developed imaging modalities, such as MRCP and helical computed tomographic cholangiography (HCT-C) have shown higher sensitivity than TUS and conventional CT, and remain less invasive than ERCP[26]. However, EUS is considered more accurate in detecting CBD stones, especially if smaller than 5 mm in diameter, which are sometimes not identified by MRCP and HCT-C[26]. When choledocholithiasis is suspected, sensitivity of EUS reaches 90% for the detection of CBD stones[27-29]. In a prospective study, performed by Fernández-Esparrach *et al*[30] on patients with dilatated biliary tree, EUS increased the pretest probability of accurately diagnosing choledocholithiasis as the cause of obstruction from 49% to 84%. On the contrary, this probability decreased from 49% to 0% if EUS ruled out lithiasis as the cause of obstruction[30].

In a meta-analysis published in 2008, on EUS perfor-

mance in detecting choledocholithiasis, the authors proposed EUS as a less low invasive technique to be incorporated into the diagnostic algorithm of patients with suspected CBD stones, in order to confirm the pathological condition before proceeding with therapeutic ERCP, when indicated[31]. Scheiman *et al*[32], in a prospective study and cost analysis performed on a cohort of patients referred to ERCP, defined EUS the preferred initial diagnostic test, compared with MRCP, for the evaluation of biliary system and identification of extrahepatic disease.

After excluding tumors, stones, flogistic strictures, a rare cause of CBD dilatation may be identified in choledochal cysts, a heterogeneous group of congenital focal or multiple anomalous dilatations of the biliary tree, usually diagnosed in childhood but remaining undetected until adulthood in 25% of cases[33,34]. Although abdominal pain is the most frequent symptom in adult patients, non-specific symptoms are also reported and the cyst may be incidentally identified in patients undergoing radiologic evaluation for other clinical suspicions[35,36].

IMPACT OF EUS IN THE DIAGNOSTIC WORK UP OF CBD DILATATION

In the presence of CBD dilatation without symptoms or clinical and laboratory alarm signs, when non-invasive imaging test (TUS, CT or MRCP) fail to indentify the etiology, clinical suspicion for biliary pathology is low, thus making further investigations unwarranted[2,8]. In this setting, despite negative results of previous imaging tests, diagnostic EUS could have a role in the identification of the etiology of dilatation (Figure 1) with a very low complication rate[37]. EUS combines endoscopy with real-time and high-resolution ultrasound providing excellent sonographic visualization of the extrahepatic biliary tree without interference of bowel gas, due to its ability to place the transducer in close proximity to the extrahepatic bile duct. Additionally, EUS permits the accurate and systematic visualization of the wall of the duodenum, including the papillary region[38].

Several authors compared MRCP and EUS in detecting choledocholithiasis showing cost-effectiveness and higher accuracy of EUS in detecting distal small stones in non-dilated ducts[26,32,39]. De Lédinghen *et al*[39] reported a 100% negative predictive value of EUS in the diagnosis of lithiasis, thus excluding the needing for further investigation and limiting unnecessary surgery. In the previously mentioned study by Scheiman *et al*[32], EUS was the most useful test for confirming a normal biliary tree, and the initial EUS strategy had the greatest cost-utility by avoiding unnecessary ERCPs and preventing ERCP-related complications[40].

In 2001, a prospective study performed by Kim *et al*[41] showed the existence of pathological conditions in subjects with dilatated CBD, despite the lack of symptoms, jaundice or causative lesions in TUS. Among the 49 patients who underwent ERCP, a significant prevalence of abnormal findings likely causative of dilatation (periampullary duodenal diverticula, benign strictures, choledochal cysts, anomalous pancreaticobiliary ductal anatomy and distal CBD masses), associated with both normal or altered liver chemistry tests, was found.

In 2007, Malik *et al*[3] retrospectively evaluated a cohort of patients with CBD dilatation and non-diagnostic imaging (TUS, CT or MRCP), previously performed for abdominal pain, weight loss or elevated liver enzymes in serum. These patients underwent EUS, being divided into two groups based on the level of clinical suspicion for biliary pathology (32 patients with normal liver chemistry tests and 15 patients with elevated enzymes)[3]. In the first group, the authors identified two findings on EUS (6%) potentially causative of biliary dilatation, a 7-mm stone of the CBD and a periampullary diverticulum. In the second group, 8 significant findings (53%) were observed: 4 periampullary diverticula, 3 choledocholithiasis and 1 ampullary tumor, not previously detected by TUS and CT.

As expected, the prevalence of biliary pathology is significantly higher in the case of elevated liver chemistry tests; however, despite the lack of pathological findings with non-invasive imaging techniques and normal liver biochemistry, biliary abnormalities may still be present and EUS is recommended for further evaluation.

A study by Carriere *et al*[42] showed a EUS yield of 28.7% in a cohort of 94 patients with unexplained isolated CBD dilatation, although an undetermined number of subjects of the group underwent endoscopy because of abdominal pain and/or abnormal liver function tests, thus suggesting a higher pre-test probability of pathological findings.

In an abstract published in 2009, based on a retrospective study, 30 patients with biliary dilatation and no evident causes on prior imaging underwent EUS[43]. Four patients had normal biliary system on EUS, 15 patients presented a dilatation of unknown etiology while pathology accounting for CBD dilatation was demonstrated in 11 of them (choledocholithiasis, ampullary adenoma, chronic pancreatitis or cholangiocarcinoma). Similarly to other studies, prevalence of abnormal findings during EUS examination was different between the patients with abnormal and those with normal liver chemistry tests (55% and 33% respectively). Conversely, the number of pathological findings in the latter group differed from percentages reported by other authors[2,3], probably because no details were specified in this study, about clinical presentation and previously used imaging techniques. Notably, none of the patients with unexplained CBD dilatation on EUS was found to have causative lesions after a mean follow-up of 16 mo.

Similarly, Bruno *et al*[2] studied 57 patients with normal liver enzymes (aminotransferases, gamma glutamyltranspeptidase and bilirubin) referred to EUS at our centre after prior negative imaging studies, excluding previous

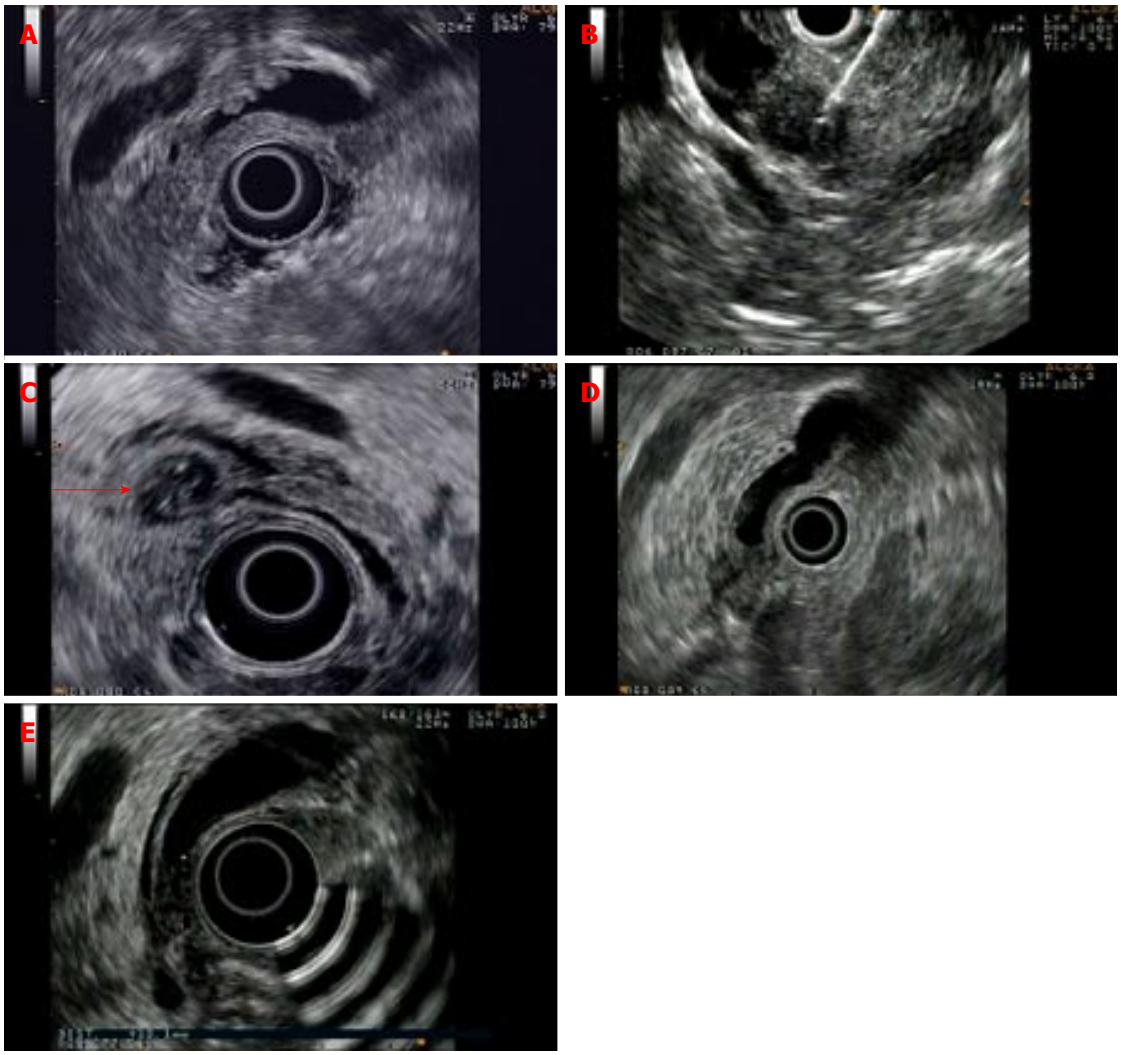

Figure 1 Examples of pathologic findings identified on endoscopic ultrasound in patients with negative prior imaging tests. A: Choledocholithiasis: Small stones in the common bile duct; B: Small pancreatic cancer; C: Small duodenal diverticulum with bile duct indentation (see arrow); D: Ampullary carcinoma with pancreas invasion; E: Inflammatory thickening of the distal common bile duct.

ERCP or history of biliary obstruction, pancreatitis or jaundice. Reasons for initial investigations were unspecific abdominal pain, dyspepsia, weight loss or pancreatic enzymes elevation in 49.2% of patients but in the majority of them biliary dilatation was an incidental finding. Employed imaging techniques, some of which performed in other centers, were TUS (7%), TUS and MRCP (63.1%), TUS and CT (10.5%) or TUS, MRCP and CT (19.3%). Abnormal EUS findings were observed in 12 patients (21%). As already described by other authors, causative identified lesions were periampullary diverticula, although a true compression on the CBD was rare (2/6), 2 ampullary adenoma, chronic pancreatitis according to predefined criteria[44] in 2 cases, a 7-mm biliary stone and one pancreatic cancer; 66.7% of patients were completely asymptomatic while unspecific abdominal pain or dyspepsia had been reported by the others. As suggested by the authors, a 21% prevalence of pathologic findings among patients with the aforementioned features, is probably overestimated since chronic pancreatitis and periampullary diverticula without bile duct indentation are not sure causes of biliary dilatation. Excluding these cases, the percentage is lower (10.5%) and comparable with Malik's findings[3].

Recently, a retrospective study was performed by Rana *et al*[45] about EUS diagnostic accuracy in patients with unexplained dilatation of CBD on MRCP, in order to establish EUS yield in the clinical practice. Among the 40 selected patients, 10 subjects had elevated serum alkaline phosphatase while the others presented normal liver function tests: in the former group, EUS detected a pathological condition causing dilatation of CBD (stones, cholangiocarcinoma, benign strictures) compared to a minority of significant findings identified in patients with normal liver tests (33.3% received diagnosis for stones or chronic pancreatitis). The remnant 20 patients with dilatated biliary system and normal liver function had regular EUS findings. There was no difference in the mean duct diameter in subjects presenting elevated serum alkaline phosphatase compared to patients with normal liver function tests nor between groups with identified pathology or not. The authors concluded, as

reported by previous scientific literature, that abnormal liver function tests are useful to identify patients with high pre-test probability of pathological findings underlying however that normal biochemistry does not exclude the existence of biliary ducts abnormalities.

Finally, Oppong *et al*[46] presented data retrospectively collected from a cohort of patients referred for EUS evaluation to a tertiary center. By excluding subjects with jaundice, liver function tests abnormalities, evidence of mass, stricture or ductal filling defect on pre-EUS imaging or symptoms suggestive of sphincter of Oddi dysfunction or chronic pancreatitis, they selected 40 patients with isolated dilatation of CBD. New findings on EUS were identified in 8 patients (20%). In 7 the following was considered as cause of dilatation: 3 had biliary polyps (not confirmed in 2 patients who later underwent ERCP), 3 had biliary stones and 1 had portal vein compression on the CBD. Microlithiasis, identified in the eighth subject, was assessed as a secondary event. Prior cholecystectomy was significantly more frequent in patients with no new findings on EUS, although CBD diameter did not differ among patients with prior surgery or not.

CONCLUSION

Changes in bile duct anatomy and adaptation of biliary system to normal or pathological processes, impose an accurate analysis of the patient anamnesis, liver biochemical parameters, clinical context in order to differentiate subjects with higher probability of biliary pathology from those with low index of suspicion. In recent years, the availability of a low-invasive modality, without post-procedural risk of pancreatitis, led to an increasing use of EUS in the investigation of biliary dilatation, even when symptoms or signs typically suggestive of obstruction were absent. On the other hand, the use of high-resolution cross-sectional imaging to investigate abdominal symptoms commonly results in increasing findings of dilatated biliary ducts in patients with normal liver tests. Currently, EUS program presents an increasing number of referrals in this setting and evidences in literature suggest a promising role for this technique in the identification of a potential biliary pathology, despite a low pre-test clinical suspicion. Firstly, in a small subset of patients, although asymptomatic or with vague symptoms, it can underlie pathologic conditions with dismal prognosis even with negative prior imaging tests. Secondly, according to the known high negative predictive value of EUS[47,48], if EUS evaluation does not identify the cause of biliary dilatation, the patient should be reassured and no further follow-up is recommended, since no pathologic conditions emerged during follow-up period in the aforementioned studies.

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Endoscopic management of hilar biliary strictures

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Abstract

Hilar biliary strictures are caused by various benign and malignant conditions. It is difficult to differentiate benign and malignant strictures. Postcholecystectomy benign biliary strictures are frequently encountered. Endoscopic management of these strictures is challenging. An endoscopic method has been advocated that involves placement of increasing number of stents at regular intervals to resolve the stricture. Malignant hilar strictures are mostly unresectable at the time of diagnosis and only palliation is possible.Endoscopic palliation is preferred over surgery or radiological intervention. Magnetic resonance cholangiopancreaticography is quite important in the management of these strictures. Metal stents are superior to plastic stents. The opinion is divided over the issue of unilateral or bilateral stenting.Minimal contrast or no contrast technique has been advocated during endoscopic retrograde cholangiopancreatography of these patients. The role of intraluminal brachytherapy, intraductal ablation devices, photodynamic therapy, and endoscopic ultrasound still remains to be defined.

Key words: Biliary strictures; Malignant; Benign; Endoscopy; Endoscopic retrograde cholangiopancreatography

Core tip: Management of benign or malignant hilar biliary strictures is difficult. Surgery is technically demanding for benign hilar biliary strictures and results of endoscopic management are not very satisfactory. Endoscopic palliation is preferred modality of managing malignant hilar strictures. However, it is still controversial to drain unilaterally or bilaterally. Use of contrast during endoscopic retrograde cholangiopancreatography and leaving some ducts undrained is a major problem in these patients. We have reviewed the literature on all these aspects of hilar biliary strictures.

Singh RR, Singh V. Endoscopic management of hilar biliary strictures. *World J Gastrointest Endosc* 2015; 7(8): 806-813 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i8/806.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i8.806

INTRODUCTION

Biliary strictures at hepatic hilum are not uncommon and present a difficult diagnostic and therapeutic

Table 1 Etiology of benign and malignant hilar strictures[1]

Malignant hilar strictures
Primary tumors (cholangiocarcinoma)
Local extension (gallbladder cancer, hepatocellular carcinoma, and pancreatic cancer)
Lymph node metastases (Breast, colon, stomach, ovaries, lymphoma, and melanoma)
Benign hilar strictures
Postoperative injuries (cholecystectomy, liver transplantation, liver resection, and biliodigestive anastomosis)
Primary sclerosing cholangitis
Others (stone disease, follicular cholangitis, parasite infection, granular cell tumor, chronic fibroinflammatory process, compression from portal cavernomatosis, granulomatous process, and lymphoplasmacyticscleros ingpancreatitis/cholangitis)

problem. Hilar strictures can be benign or malignant which are often difficult to differentiate. Various modalities as surgery, endoscopy and radiology have been used in the management of these strictures with variable results. The role of some newer modalities, *e.g.*, intraluminal brachytherapy, intraductal ablation devices, photodynamic therapy (PDT), still remain investigational.

Etiology

Etiologically, these strictures can be divided into benign or malignant causes[1] (Table 1). The differentiation of benign from malignant hilar strictures is difficult.

Diagnosis

The alkaline phosphatase isoenzyme and CA19-9 have been used to discriminate benign from malignant strictures with variable sensitivity and specificity[2-4]. Radiologic evaluation of patients with hilar strictures can be done with ultrasonography, contrast-enhanced computed tomography (CT) scan, magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreaticography (MRCP). These modalities can help to delineate the level of bilary obstruction along with the extent of biliary dilatation. Any mass lesion or distant metastasis can also be detected with these methods[5-9]. Increased alkaline phosphatase and CA19-9 levels, increased thickness of bile duct wall to ⩾ 5 mm and regional lymphadenopathy (> 1 cm) on CT scan, and cholangiographic appearance of abrupt cutoff and separation of biliary ductal system suggest a malignant etiology of hilar obstruction[10]. Another study showed an association of raised bilirubin levels of > 8.4 mg% and CA19-9 level > 100 U/L with malignant etiologies of biliary obstruction[11]. MRI/MRCP performed better than CT to differentiate benign and malignant causes of biliary obstruction[11]. However, in a study of 49 patients with mass lesion at hilum on abdominal ultrasonography or CT scan, raised CEA and CA 19-9 levels, and presence of irregular, eccentric strictures with abrupt cutoff suggesting malignancy on cholangiography, benign diseases was documented in 24% of cases on surgical histopathology[12]. Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) provide a better assessment of the biliary tree. It also enables brush biopsy and cytology studies providing a histological diagnosis in these patients. However, these procedures carry a significant risk of complications[13,14]. Various studies have shown a variable sensitivity (37%-70%) and high specificity (> 95%) for biopsies or brush cytology (Table 2)[15-18].

Table 2 Brush cytology in malignant biliary obstuction

No.	Ref.	No. of patients	Sensitivity (%)	Specificity (%)
1	Venu *et al*[15]	53	70	100
2	Foutch *et al*[16]	24	60	100
3	Ferrari Júnior *et al*[17]	70	56	100
5	Singh *et al*[18]	30	37	100

Table 3 Bismuth-lazorthes Classification of postsurgical benign biliary strictures

Type I: Common hepatic or main bile duct stump ⩾ 2 cm
Type II: Common hepatic duct stump < 2 cm
Type III: Hilar stricture- ceiling of the biliary confluence is intact, right and left ductal system communicate
Type IV: Ceiling of the confluence is destroyed, bile ducts are separated
Type V: Type I, II or III plus stricture of an isolated right duct

Endoscopic ultrasound (EUS) has shown promising results for the diagnosis of hilar strictures. In a study of 24 patients with negative or unsuccessful brush cytology results in cases of proximal bile duct obstruction, EUS revealed a mass lesion in 23 patients (96%)[19]. EUS-FNA in these patients provided a sensitivity of 77% and accuracy of 79%. However, the negative predictive value was quite low (29%). In another study of 44 patients with negative brush cytology in cases of suspected hilarcholangiocarcinoma, EUS-FNA had an accuracy of 91% with 89% sensitivity and 100% specificity[20]. Intraductal ultrasonography enhances the diagnostic accuracy of ERC (88%) as compared to MRC (58%) or ERC alone (76%)[21].

MANAGEMENT

Benign biliary strictures

Benign biliary strictures at the hepatic hilum most commonly result from surgical injuries, most often after cholecystectomy. Post-cholecystectomy strictures develop in 0.2%-0.5% of patients undergoing surgery and account for 80% of benign hilar strictures[22]. Post-liver transplant strictures develop in 5.9% of patients[23].

The management and outcome of postsurgical strictures depends on the type of stricture. Bismuth and Lazorthes classified postsurgical biliary strictures based on the level of healthy biliary mucosa suitable for anastomosis (Table 3)[24,25].

Surgical management of postsurgical benign biliary strictures carries a morbidity of 18%-51%, mortality

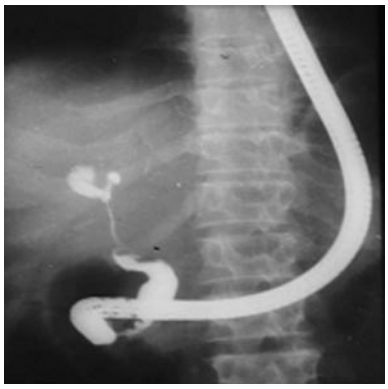

Figure 1 Postoperative type 3 hilarstricture with patent confluence.

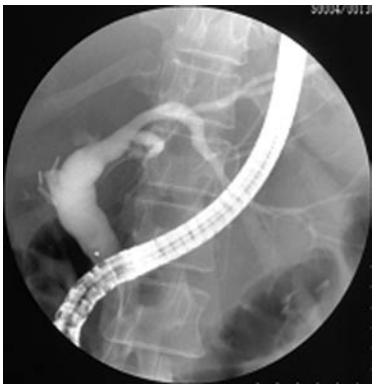

Figure 2 Postoperative type 5 hilarstricture involving right hepatic duct.

Table 4 Bismuth classification of malignant hilar block[31]

Type I: Obstruction within 1 cm of bifurcation but confluence patent
Type II: Obstruction limited to confluence
Type III: Obstruction at confluence with proximal extension to right or left side
Type IV: Obstruction involving bilateral secondary or tertiary branches or multifocal strictures

of 4%-13%, and recurrence rate of 10%-30%[22]. It, therefore, requires specific skills and expertise. The management of hilar postsurgical strictures (types III, IV, and V) is more challenging and results in worse outcomes (Figures 1 and 2)[1]. A retrospective study of 57 patients surgically treated for cicatricial biliary strictures showed a higher rate (14%) of stricture recurrence and cholangitis in patients with hilar obstruction compared to none in patient with lesions below the hilum[26]. A recent study reported the safety and efficacy of right hemihepatectomy with cholangiojejunostomy in patients with strictures involving secondary bile duct branches associated with vascular injuries. The study showed 100% survival without stricture recurrence after a mean follow up of 80 mo. No major postoperative complications were documented[27].

Endoscopic management of postsurgical strictures is more safe and efficacious. Two 10F plastic stents are placed in for a maximum duration of 12 mo. Stent exchange is done at 3 mo interval to reduce the risk of stent blockage and cholangitis (classical approach)[28,29]. Endoscopic management is feasible in 80% of cases. Stricture recurrence occurs in 20% of patients after stent removal over a period of 9.1 years. All the instances of restenosis were noted within 2 years of stent removal. Mean time from stent removal to symptom onset was 2.6 mo (range 1 wk–2 year)[29].

An aggressive approach involves insertion of an increasing number of plastic stents until resolution of stricture, with stent exchange performed at 3-5 mo interval[30]. In a study of 40 patients with 18 hilar strictures, overall success rate with this approach was 89%. Recurrence occurred in only one patient after a mean follow up of 48.8 mo (range 2-11.3 years). Mean number of stents used was 3.2 ± 1.3 (range 1-6) over a period of 12.1 ± 5.3 mo (range 2-24 mo)[30].

Malignant biliary strictures

Cholangiocarcinoma, carcinoma gall bladder (GB) and secondaries account for majority of malignant hilar biliary strictures. Malignant hilar biliary strictures are classified as per the Bismuth Classification (Table 4)[31]. It carries a poor prognosis with 5 year survival of < 10%. Curative resection is feasible in < 10%. Palliation remains the mainstay of therapy. However, surgical palliation is associated with an unacceptable 33% mortality[31,32].

Current options for palliation include surgical bypass, percutaneous drainage and endoscopic stenting.Endoscopic drainage is safer and more successful with a lower propensity to bile leak, infection and haemorrhage. However, a recent randomized controlled study of 54 patients with unresectable carcinoma GB with Bismuth type 2 (Figure 3) or 3 hilar block showed better drainage (89% *vs* 41%) and lower complication rate (cholangitis 48% *vs* 11%) with percutaneous approach[33]. Both the groups had similar procedure-related mortality (4% *vs* 8%), 30-d mortality (4% *vs* 8%) and median survival (60 d in both; P = 0.71). Percutaneous drainage resulted in a significantly better quality of life, as assessed at 3 mo after the procedure[33]. This study used plastic stents instead of metal stents in unresectable carcinoma GB with Bismuth type 2 or 3 hilar block and biliary ducts were left opacified and undrained after contrast injection which could be responsible for higher rates of complication with endoscopic approach. Hence, the results need to be interpreted with caution.

Endoscopic stenting in hilar obstructions can be done with plastic or metal stents (Figures 4-7). Plastic stents are less expensive, have technically easy insertion with relatively easy removal and exchange. But, they have limited stent patency. Metal stents have prolonged stent patency, do not occlude side branches and have easier passage across biliary strictures due to relatively smaller delivery system. But, greater cost and difficulty

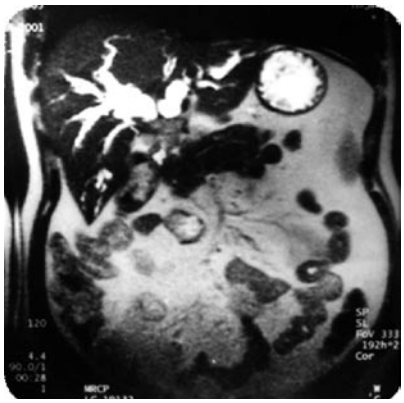

Figure 3 Magnetic resonance cholangiopancreaticography showing type 2 malignant hilarstricture.

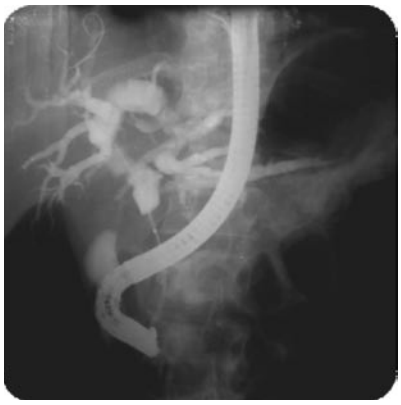

Figure 4 Type 1 malignant hilar stricture.

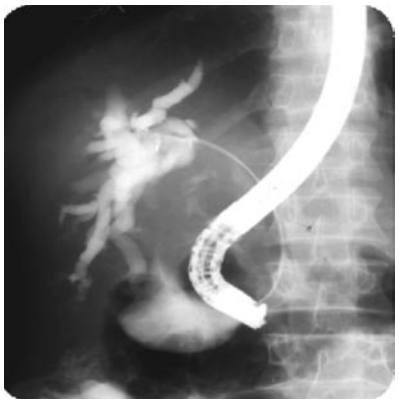

Figure 5 Type 2 malignant hilarstricture.

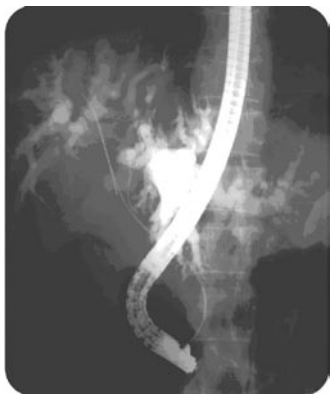

Figure 6 Type 2 malignant hilarstricture with bilateral guide wires.

in removal once blocked are the limitations[34].

Metal stents have been shown to perform better than even large bore plastic endoprostheses. A prospective randomized trial of 20 patients with Bismuth type Ⅱ-Ⅳ hilar obstruction compared 14 French plastic stents with 24 French metal endoprostheses in the management of malignant hilar obstructions with obstructive jaundice[35]. Metal stents insertion was associated with greater success as well as patency rates compared to placement of plastic stent. It was also cost-effective due to lower number of re-interventions required in these patients. Another randomized controlled trial of 108 patients with Bismuth type Ⅱ-Ⅳ unresectable hilarcholangiocarcinoma demonstrated better drainage and more prolonged survival with self-expandable metal stents compared to plastic stents[36]. A meta-analysis of 10 trials showed a significantly higher successful drainage rate [odds ratio (OR) = 0.26; 95%CI: 0.16-0.42; I^2 = 40.3%], lower early complication rate (OR = 2.92; 95%CI: 1.65-5.17; I^2 = 0%), longer stent patency [hazard ratio (HR) 0.43; 95%CI: 0.30-0.61; I^2 = 57.6%], and longer patient survival (HR = 0.73; 95%CI: 0.56-0.96; I^2 = 56.9%) with metal stents in comparison with plastic stents[37].

There is much controversy regarding the placement of unilateral or bilateral stents for hilar strictures. In a study of 190 patients with Bismuth type Ⅰ-Ⅲ hilar strictures, successful drainage after single stent was achieved in 80% of patients[38]. The placement of a second stent was considered only in patients with new onset cholangitis or incomplete resolution of cholestatic symptoms. Early complications were observed in 7%, 14% and 31% patients with type Ⅰ, Ⅱ and Ⅲ strictures, respectively. De Palma *et al*[39,40] showed that unilateral stenting is feasible, safe and effective. In a prospective study of 61 patients with hilar malignancy, the placement of a single metal stent across the stricture into duct easier to access achieved successful stent insertion in 96.7% and successful drainage in 96.7% patients. Median survival of these patients was 140 d with median stent patency of 169 d. Stent malfunction was seen in 4.9%[40]. A recent meta-analysis also revealed that unilateral and bilateral biliary drainage may have equivalent efficacy in hilar biliary obstruction with a higher success rate for unilateral stent placement[37]. A case series of 151 patients with unresectable Bismuth type Ⅱ and Ⅲ hilar biliary obstruction revealed similar successful drainage rate, complications, 30-d mortality, number of re-interventions and survival based on whether right or left biliary ductal system was drained[41]. However, in patients with bilobar opacification of biliary ductal system, bilateral drainage should be obtained to reduce the risk of cholangitis[42].

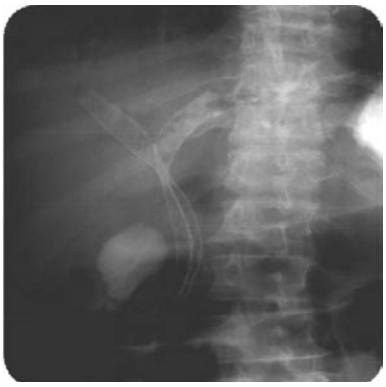

Figure 7 Bilateral metal stents in type 2 malignant hilar stricture.

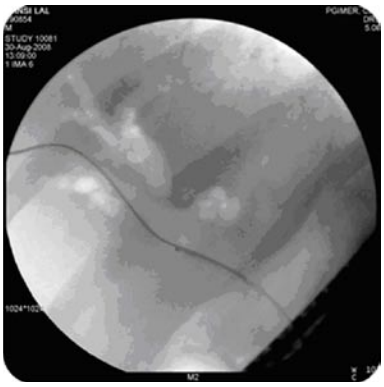

Figure 8 Air cholangiogram showing type 2 malignant hilar stricture.

It was widely held that draining 25% of liver volume provides adequate palliation of obstructive jaundice with biochemical improvement in these patients[43]. However, a recent study of 107 patients with Bismuth type Ⅱ-Ⅳ hilar strictures concluded that drainage of more than 50% of liver volume predicts efficacy of drainage and translates into longer survival (119 d *vs* 59 d, P = 0.005),especially in Bismuth type Ⅲ hilar strictures[44]. Bilateral stent insertion is often required to achieve more than 50% drainage. The study, however, has several drawbacks. The study had a retrospective design, most of the patients underwent plastic instead of metal stenting in hilar biliary obstruction and majority of the patients had cholangiocarcinoma which has relatively prolonged survival and can confound the results.

Failure to drain the hepatic lobes or segments after contrast injection is responsible for most of the cases of post procedure early cholangitis and mortality[42]. It brought to the fore the concept of contrast free stenting[45,46]. To avoid bilateral contrast injection and stent placement in Bismuth-type III and IV Klatskin tumors, Hintze *et al*[47] used MRCP in 35 patients for ERC and unilateral stent insertion. The placement of stents under MRCP guidance reduced incidence of post-ERC bacterial cholangitis. A prospective study of 18 patients with Bismuth type Ⅱ malignant hilar biliary obstruction demonstrated successful endoscopic drainage in all the patients and no cholangitis or 30-d mortality with MRCP guided contrast-free unilateral metal stenting[45]. Another study of 15 patients with Bismuth type Ⅱ malignant hilar strictures used contrast-free balloon-assisted unilateral plastic stenting with 100% successful drainage and no cholangitis or 30-d mortality[48]. Comparison of air and iodine contrast cholangiography in hilar strictures in a retrospective study showed less cholangitis with air contrast in Bismuth type Ⅱ-Ⅳ strictures[49]. Subsequently, two studies showed 100% successful stent placement and drainage with no cholangitis and 30 d mortality with contrast-free air cholangiography-assisted (Figure 8) unilateral stent deployment[50,51]. A recent randomized controlled study compared CO_2 cholangiography with iodine contrast cholangiography in 36 patients with Bismuth type Ⅱ-Ⅳ malignant hilar obstruction and revealed lower incidence of cholangitis in CO_2 group (5.6% *vs* 33.3%, P = 0.04)[52].

NEWER APPROACHES

Novel approaches including drug eluting stents, EUS guided biliary drainage, intraluminal brachytherapy, intraductal ablation devices and PDT have recently been used with variable results.

External beam irradiation therapy in malignant biliary strictures is limited by radiation tolerance of liver, bowel and kidneys. Intraluminal brachytherapy allows greater radiation dose locally administered to predefined volume of tissue. It can be administered *via* endoscopic or percutaneous route. A few recent studies have documented the safety and efficacy of intraluminal brachytherapy in association with stent placement in unresectable, malignant hilar strictures. This new method resulted in prolonged survival in these patients[53-56].

PDT is a promising mode of therapy for unresectable cholangiocarcinoma. It uses a combination of photosensitising chemical and light of appropriate wavelength to generate cytotoxic reactive oxygen species culminating in tumour cell death by necrosis or apoptosis. Continuous biliary drainage is achieved by stent implantation after the procedure. A randomized controlled study of 39 patients with histologically confirmed unresectable cholangiocarcinoma was terminated prematurely due to prolongation of survival (median 493 d *vs* 98 d; P < 0.0001), more effective biliary drainage and improved quality of life with stenting and PDT in comparison with stenting alone[57]. In a recent retrospective study of 184 patients with hilar cholangiocarcinoma managed with either surgery (60), stenting (56) or stenting with PDT (68); PDT had a longer survival compared to stenting (12.0 mo *vs* 6.4 mo, P < 0.01) and comparable survival to R1/R2 resection (12.2 mo)[58]. In conclusion,management of hilar biliary strictures is a difficult problem. Surgical, endoscopic and percutaneous approaches have been

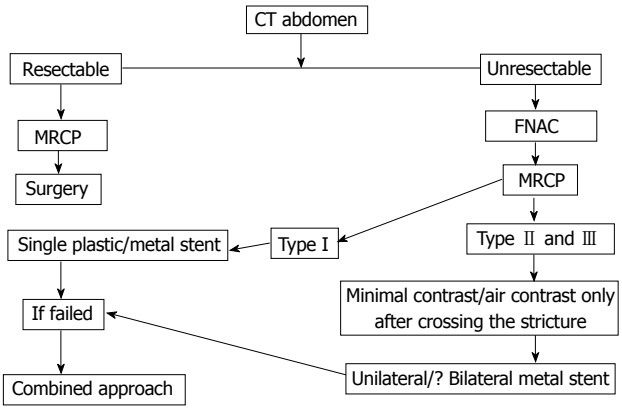

Figure 9 Approach to malignant hilar biliary strictures. CT: Computed tomography; MRCP: Magnetic resonance cholangiopancreaticography; FNAC: Fine needle aspiration cytology.

used in the management of these strictures with variable results. However, the appropriate management also depends on expertise available at that centre. Endoscopic management with increasing number of plastic stents and surgery for failed cases in benign biliary strictures is a reasonable approach. Appropriate management algorithm for malignant hilar strictures is given in Figure 9.

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MINIREVIEWS

Towards the Holy Grail: What can we do for truly scarless surgery?

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Abstract

The work of Muhe and Mouret in the late 1980s, paved the way for mainstream laparoscopic procedures and it rapidly became the mainstream method for many intra-abdominal procedures. Natural orifice transluminal surgery (NOTES) and Laparo-endoscopic single-site surgery (LESS) are very exciting new modalities in the field of minimally invasive surgery which work for further reducing the scars of standard laparoscopy and towards scarless surgery. However, according to objective assessment of the literatures, there is no clearly demonstrated benefit of NOTES (LESS), even cosmesis is poorly supported and had mixed results in the available data. NOTES (LESS) is far from the truly scarless surgery. Towards the Holy Grail, we have developed several techniques of creating nonvisible scar and named them as "Scar-hidden Endoscopic Surgery". With the rapid development of science and technology, we believe that minimally invasive surgery over the next 2 decades will continue to bring remarkable change and realize truly scarless surgery even we may not be able to imagine what lies ahead.

Key words: Minimally invasive surgery; Scarless surgery; Laparo-endoscopic single-site surgery; Natural orifice transluminal endoscopic surgery; Scar-hidden endoscopic surgery

Core tip: Natural orifice transluminal surgery (NOTES) and Laparo-endoscopic single-site surgery (LESS) are very exciting new modalities in the field of minimally invasive surgery which towards scarless surgery. However, according to objective assessment, NOTES (LESS) is far from the truly scarless surgery. Towards the Holy Grail, we have developed several techniques of creating nonvisible scar and named them as "Scar-hidden endoscopic surgery". With the rapid development of science and technology, we believe that minimally invasive surgery over the next 2 decades will continue to bring remarkable change and realize truly scarless surgery.

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INTRODUCTION

The past thirty years has witnessed the infancy and rapid development of minimally invasive surgery (MIS). From the early multiple small incisions laparoscopic surgery to the single incision laparoscopic surgery nowadays, minimally invasive surgery has come a long way from its initial stage and scarless surgery has been the Holy Grail.

EVOLUTION OF SCARLESS SURGERY

Phillipe Mouret performed the first laparoscopic cholecystectomy in 1987[1]. Since then, laparoscopic approach has been used to many disease processes and gradually become the mainstream procedure for many intra-abdominal surgeries. Compared with open procedures, laparoscopic surgery has shown to decrease postoperative morbidity, shorten hospitalization and convalescence, and improve cosmesis for many applications[2,3]. Therefore laparoscopic surgery has been a well-established and commonplace technique worldwide in the past century. However, there were still 3-6 small incisions post-operation, which not only cosmetically unappealing, but also increase the wound pain and potential wound morbidity, such as abdominal wall bleeding and hernia, and intra-abdominal organ damage[4].

The quest for scar reduction and the increasing recognition of patient's satisfaction has led to the innovation of conventional laparoscopic surgery. In the last decade, natural orifice transluminal surgery (NOTES) and Laparo-endoscopic single-site surgery (LESS) have been considered as the most advanced representative "evolution" of minimally invasive surgery. NOTES was first descripted by Kalloo *et al*[5] in 2004 and developed towards the scarless surgery, but did not gain popularity due to a variety of reasons including difficulty in accessing anatomical sites, lack of appropriate devices and sterility. The lack of success of NOTES has prompted the interest in LESS which also aimed to "scarless" effect. Compared with NOTES, LESS offers an advantage to surgeons with its similar performance used in traditional laparoscopy. However, LESS is also more technically difficult than traditional laparoscopic surgery, due to the challenges included loss of triangulation, external an internal conflict[6]. What's more is that while laparoscopic literature sought to demonstrate superiority of the technique over that of open surgery, the publications on LESS generally seem to seek to demonstrate equivalence with laparoscopy, with the major focus being on cosmesis[7]. LESS still has far a long way to go before becomes the mainstream approach for truly scarless surgery as it remains an evolving technique.

WHAT'S TRULY SCARLESS SURGERY?

With the rapid development of science and technology, scarless surgery has been the Holy Grail of MIS. However, what's MIS? Indeed, the term "minimally invasive surgery" has often been bastardized to imply a specific access strategy such as laparoscopy, robotic surgery or endoscopy, but the true definition of minimally invasive surgery may have been created by Sir William Osler over a century ago when he said that, "Diseases that harm call for treatments that harm less". More specifically, minimally invasive surgery should meet the following factors. The first and foremost factor is curing the pathology[8]. When approach and technique are considered, the most important question that mandates answer is will the pathology be appropriately treated with the absolute best safety profile possible. Secondary to surgical efficacy is decrease blood loss, postoperative pain, postoperative complications, surgical time (not by itself an absolute goal), convalescence and length of hospital stay. Thirdly, and the least important are surgical cosmesis and cost-effectiveness ratios. Based on the above, when define the truly scarless surgery, not only do these procedures should provide equivalent outcomes to traditional laparoscopic surgery, but also offer significant benefits as quicker recovery, shorter hospital stays, less scarring, less pain, lower morbidity and less surgical time (not an absolute goal).

Towards to the scarless surgery, NOTES and LESS have been developed and aimed to reducing the incisions of conventional laparoscopy. Surgeon's interest was focused on reducing or eliminating the incisions caused by the procedure. The hope is that reduced access points will ultimately decrease pain, morbidity, convalescence, and improve cosmesis. However, according to objective assessment of the literature which compared current standard laparoscopic techniques with NOTES (LESS), there is no clearly demonstrated benefit of NOTES (LESS), even cosmesis is poorly supported and had mixed results in the available data[9,10]. In patient polls, surgical success, risk, pain, convalescence and cost all ranked higher than cosmesis. NOTES and LESS were far from the truly scarless surgery.

WHAT WE HAVE DONE FOR SCARLESS SURGERY?

As already mentioned, scarless surgery has been the Holy Grail of minimally invasive surgery. However, as it is difficult, if not impossible, to achieve truly scarless in current days, several techniques of creating nonvisible scar have been developed, which we named as "Scar-hidden endoscopic surgery (SHES)". SHES include 2 broad categories of those techniques performed by obtaining new access to peritoneal cavity and those by hiding scar in the anterior abdominal wall.

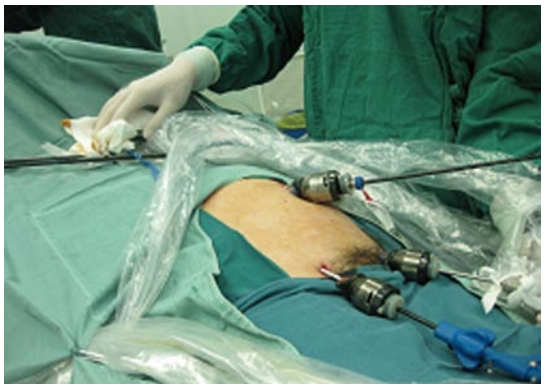

Figure 1 Ports position of approach 1.

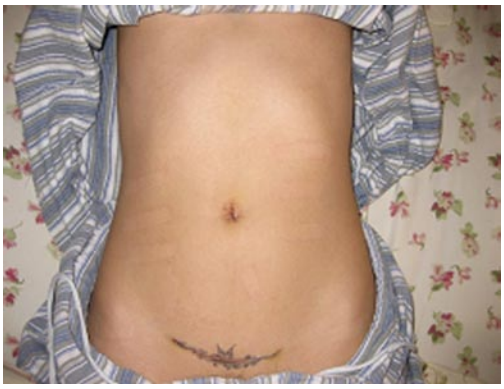

Figure 2 Scars are hidden in the tattoo.

Obtain new access to peritoneal cavity

The use of first category was represented by NOTES. In its purest form, NOTES does not use any transabdominal ports therefore decreased pain and eliminated the abdominal wound morbidity. However, NOTES was hampered by difficulty in accessing anatomical sites, lack of appropriate devices and sterility, thus far been successfully performed in patients and not a truly scarless surgery.

Hide the scar in the anterior abdominal wall

The limitations of NOTES led to the concept of LESS which also produced nonvisible scar as it hidden easily in umbilical plica. However, LESS is also more technically difficult than traditional laparoscopic surgery, due to the inherent challenges. As techniques mentioned above were fraught with problems, we attempted other approaches.

Approach 1: Transfer the incision to the superior margin of suprapubic hair

Surgical technique: A10-mm trocar was placed through an umbilical incision. After establishment of a pneumo-peritoneum, a 5-mm 30° laparoscope was introduced through the trocar. Two 5-mm suprapubic trocars were placed near the right and left ends of the superior margin of suprapubic hair under the guidance of the laparoscope. The laparoscope was then moved to the left side trocar. The instruments were introduced through the umbilical and the right side ports (Figure 1).

Advantages: Our research indicated that, compared with LESS, this approach characterized by no visible scar, a shorter operation time, minimal bleeding, *etc.*, but longer instruments should be used[11].

Approach 2: Transfer the incision to the tattoo (Figure 2) or previous operation scar (Figure 3)

The surgical technique and advantages of this approach were the same as described in approach above. What' s different is that the two 5-mm trocars were placed near the right and left ends of the tattoo or previous operation scar.

Approach 3: Transfer the incision to the linea alba (the transxiphoid-umbilical laparoscopic approach)

Surgical technique: A 15-mm incision was made at the right side of the umbilicus; a 10-mm trocar for the optic unit and another 5-mm trocar for the grasper were inserted side by side into the incision; a 5-mm trocar for instruments (ultrasonic scalpel, grasper, electrosurgical hook knife and hem-o-lok clips) was placed 20 mm inferior to the xiphoid (Figure 4).

Advantages: In our opinion, the transxiphoid-umbilical laparoscopic approach for laparoscopic cholecystectomy is as comfortable as the conventional techniques for laparoscopic cholecystectomy and allows the use of normal laparoscopic instruments. It has an advantage over conventional three-port laparoscopic cholecystectomy in both postoperative pain and, more importantly, cosmetic outcome, without a significant learning curve or increase in operative time. It offers a realistic better approach to conventional LC for chronic benign gallbladder disease.

Approach 4: Reduce the size of incision.

According to a previous study of us, the Optimized two-trocar LESS technique (a 2-mm trocar inserted for a grasper in the right upper abdomen) was found to be faster and less painful than the LESS approach and the 2-mm incision was almost nonvisible post-operation[12]. Under the guidance of this technique, we proposed another novel SHES as described below.

Surgical technique: A 15-mm incision was made at the right side of the umbilicus; a 10-mm trocar for the optic unit and another 5-mm trocar for an ultrasonic scalpel or clips were inserted side by side into the incision. Under laparoscopy, a 2-mm needle-shape grasper was placed direct through the abdominal wall in the midclavicular line 20 mm inferior to the costal margin, and electrocautery placed 20 mm inferior toxiphoid (Figure 5).

Advantages: Using the 2-mm needle-shape instruments, the new technique has following advantages: (1)

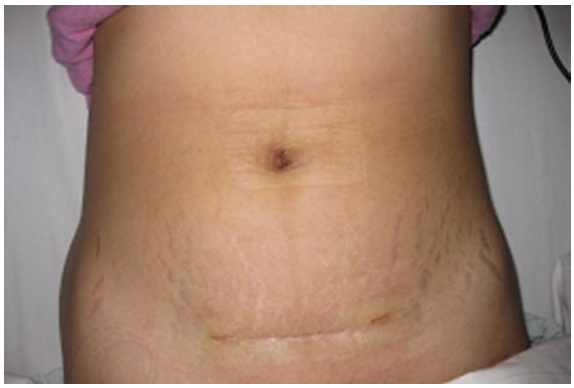

Figure 3 Scars are hidden in previous operation scar.

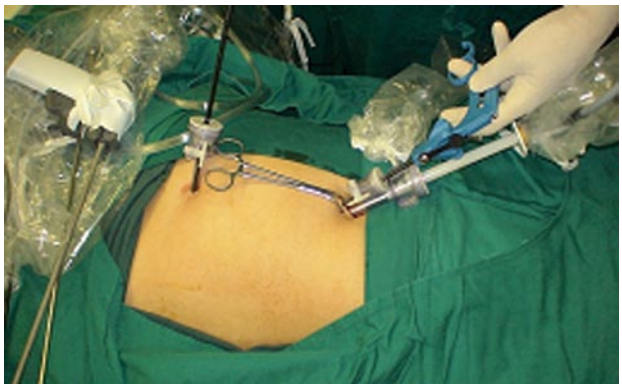

Figure 4 Ports position of the transxiphoid-umbilical laparoscopic approach.

The 2-mm grasper and electrocautery are at the normal location as the same as the traditional laparoscopic surgery. It helps to regain manipulate triangulation which not only enable performing sufficient traction of the gallbladder but also allow good mobilization of the gallbladder in order to dissect the calot's triangle safely; (2) compared with LESS, the novel SHES was performed more feasibly and safely, with significantly shorter operation time and higher satisfactory score. Cosmesis, safety, and economy were balanced better in this new technique; and (3) the scars of the new technique were hidden in the natural folds of the skin around the navel and were too small to affect cosmesis when the 2-mm puncture hole on the upper abdomen healing. Compared with conventional laparoscopic surgery, it produced better cosmetic results while the operative time was almost equal according to our data[13].

WAY TO TRULY SCARLESS SURGERY

According to the above analysis, NOTES or LESS is far from the truly scarless surgery as there were no longer follow-up, controlled and randomized studies which supported the touted benefits. There is no doubt that NOTES or LESS will be spurred on by rapid advances in technology and better instrumentation. However,

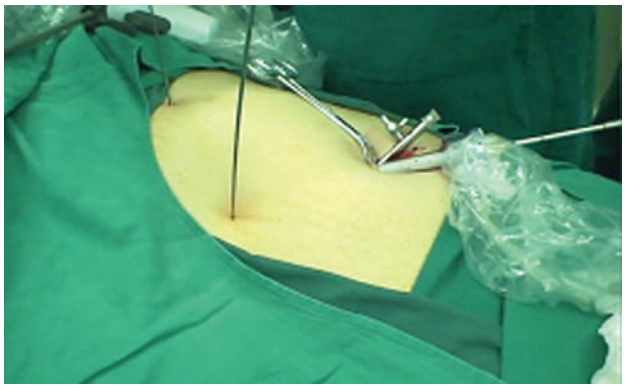

Figure 5 Laparoscopic cholecystectomy by using 2-mm needle-shape instruments without trocar.

when offering conventional *vs* investigational treatment options for patients, surgeons should be honest and balanced the safety and efficacy in their decision making.

In a word, what we believe is that, with the rapid development of science and technology, such as the use of da Vinci Surgical System, minimally invasive surgery in the nearly future will continue to bring remarkable changes and realize the truly scarless surgery.

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Management of iatrogenic colorectal perforation: From surgery to endoscopy

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Abstract

Iatrogenic colon perforation is one the most pernicious complications for patients undergoing endoscopic screening or therapy. It is a serious but rare complication of colonoscopy. However, with the expansion of the indications for endoscopic therapies for gastrointestinal diseases, the frequency of colorectal perforation has increased. The management of iatrogenic colorectal perforation is still a challenge for many endoscopists. The methods for treating this complication vary, including conservative treatment, surgical treatment, laparoscopy and endoscopy. In this review, we highlight the etiology, recognition and treatment of colorectal iatrogenic perforation. Specifically, we shed light on the endoscopic management of this rare complication.

Key words: Iatrogenic perforation; Colorectum; Surgery; Laparoscopy; Endoscopy

Core tip: Iatrogenic colorectal perforation is one of the most pernicious complications for patients who undergo endoscopic screening or therapy. In this review, we highlight the etiology, recognition and treatment of colorectal iatrogenic perforation, including conservative treatment, surgical treatment and laparoscopy. The flying development of the endoscope and its surgical assistant accessories have improved the endoscopic clip closure procedure. It can remarkably decrease the rate of surgical reparation following iatrogenic perforation of the colon.

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INTRODUCTION

Iatrogenic perforation of the colon and rectum is an avoidable complication of diagnostic tests or an unavoidable procedure of endoscopic treatment. In the past, the causes of iatrogenic perforation were

barium enema and diagnostic endoscopy. Recently, due to the expanded indications for endoscopic resection lesions, more colon perforation occurs after colonoscopy therapy. As a major cause, it is estimated that the frequency of iatrogenic perforation is 0.019%-0.8% and 0.10%-3% for diagnostic and therapeutic colonoscopy, respectively[1-4]. Perforation located at the colon can rapidly cause peritonitis and even sepsis. These complications imply high morbidity and mortality. Therefore, all endoscopists should pay more attention to prevent this kind of perforation and immediate treatment is needed once colon perforations occur. In this review, we highlight the etiology, recognition and treatment of colorectal iatrogenic perforation. Specifically, we shed light on the endoscopic management of this rare complication.

ETIOLOGY

Colonoscopy is widely used during diagnosis and therapy in endoscopy. There has been an increasing number of patients undergoing this procedure. Consequently, the number of associated complications has also risen. In addition, older and less appropriate patients are receiving colonoscopies who are more vulnerable to iatrogenic colonoscopic injury. In the Iqbal *et al*[5] study, the perforation rates were higher at the rectosigmoid junction and the sigmoid colon (52%). The perforation rates in other sites of the colon were 17% (cecum), 14% (ascending colon), 7% (transverse colon), 8% (descending colon) and 1% (rectum), respectively. The perforation size was between 0.1 and 6.0 cm (average, 1.7 cm). Mechanical injury leads to the largest perforations, while electrocautery injury causes the smallest perforations. The patient risk factors were state of anticoagulation, extensive contamination, active malignancy, prior hospitalization history, delayed diagnosis and steroid usage. Electrocautery, polypectomy and mechanical injury caused the postoperative morbidity. Other factors which pose difficulty in colonoscopy and likely cause perforations include the existence of dense or wide-mouthed diverticula, incomplete bowel preparation, active hemorrhage and, the most important, the experience of endoscopists.

DIAGNOSIS

With the different causes, sizes and sites of perforation, there are various complaints from patients, including non-pain, only localized instantaneous pain which happens suddenly, severe cramp-like pain and distension of the abdomen[5,6]. If there was a tiny perforation caused by snaring or the endoscopic knife application, the patient would not have symptoms or only local pain. In general, the frequency of these kinds of abdominal pain is remarkably higher in perforation caused by diagnostic endoscopy than surgical endoscopy. Abdominal roentgenogram provides a quick sign. Cho *et al*[3] reported a lot of subdiaphragmatic free air in all cases of perforation caused by diagnostic endoscopy and in almost 45% of therapeutic perforation cases. Thus, abdominal roentgenogram is a cost-effective and useful method to detect the presence of subdiaphragmatic free air, with a positive predictive value of 92%[5]. However, sometimes subdiaphragmatic free air cannot be detected by abdominal roentgenogram. In this setting, computed tomography can offer great help in diagnosing the free air, micro-perforations and/or abscess. Patients who are clinically unstable or who exhibit peritonitis on physical examination warrant immediate exploration.

MANAGEMENT

Conservative management

If a patient presents as subdiaphragmatic free air alone, it is not an indication for surgical reparation. Most patients who do not show signs of peritoneal irritation or abdominal sepsis have an ideal prognosis after being given intravenous antibiotic therapy, bowel rest and serial abdominal examinations[7]. Conservative management in appropriate patients results in a shorter length of hospitalization and lower morbidity. Iqbal *et al*[5] reported only one death among patients undergoing conservative treatment, a patient in the intensive care unit whose family refused surgery.

Surgical management

Prompt abdominal surgery is usually recommended once perforation has occurred[8,9]. Immediate surgical intervention is not compulsory. Intraoperative findings determine the surgical management. Surgery may be primary closure or resection with primary anastomosis in cases of intra-abdominal contamination accompanied by normal tissues in order to limit the comorbidity. Due to the extensive contamination, poor tissue situation and a higher complication rate, stoma or fecal diversion after reparation is chosen. Iqbal *et al*[5] indicated that only two preoperative factors determined the type of procedure, the time after the perforation and mechanical injuries. Comparing patients who were diagnosed with perforation after 24 h, those within 24 h were more suitable for a primary closure because the latter was more likely to have extensive fecal contamination. Moreover, mechanical injury always induced larger perforations (average, 1.9 cm) which needs fecal diversion after resection. However, this type of injury cannot always be ascertained before surgery.

Laparoscopic management

With the emergence and development of minimally invasive surgery over the last few decades, laparoscopic colonic repair has been increasingly adopted for colorectal perforation repair[10-12]. In the past, laparotomy was usually selected as the treatment approach for iatrogenic colon perforation and most patients under-

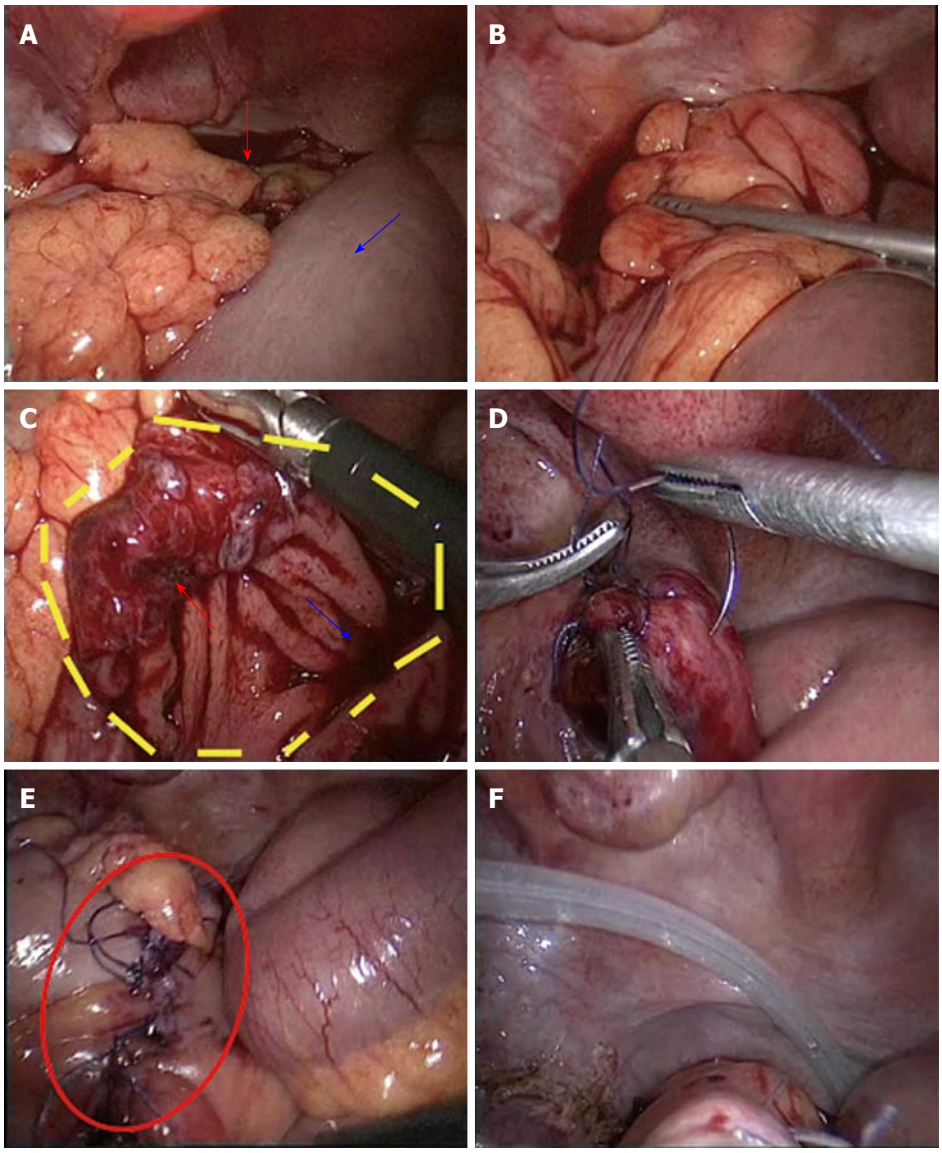

Figure 1 Laparoscopic management of iatrogenic colorectal perforation with endoscopic assistance. A: Laparoscopic examination of iatrogenic colorectal perforation: blue arrow, small bowel dilation; red arrow, perforation location; B: Explore and make sure of the perforation location; C: Expose the perforation: blue arrow, anal side; red arrow, opposite side; D: Suture the perforation; E: Effective closure of the perforation; F: Place a drainage tube.

went colostomy[13,14]. Unfortunately, ileostomy and colostomy are associated with a significant decrease in patient quality of life and require another operation to restore intestinal continuity[15]. Several doctors have therefore proposed either a primary repair of the colorectal perforation or a segmental colectomy with primary anastomosis. The improvement of laparoscopic techniques boosts the practice of laparoscopic repair for colon perforations more widely[16]. In the Zhang *et al*[4] study, their experience in laparoscopic direct suturing of colon perforations indicated that laparoscopic primary perforation repair was a safe and feasible repair method. Compared to an open method, patients who underwent laparoscopic repair had a significantly shorter total incision length (16 ± 15 mm *vs* 163 ± 54 mm), shorter overall length of stay (5.1 ± 1.7 d *vs* 9.2 ± 3.1 d) and fewer perioperative complications (two *vs* five)[17]. Thus, their data suggest it is rational to regard laparoscopic therapy as the initial approach for repairing iatrogenic colorectal perforation.

Endoscopic management

Despite the fact that laparoscopy is effective in resolving colorectal iatrogenic perforation, recent advances of endoscopic techniques have made it possible to handle iatrogenic perforations by applying mini-invasive procedures. Endoscopy can assist laparoscopy to close the perforation (Figure 1). Repairing the perforation alone with endoclips has been well described in related studies since 1997[18]. In addition, large or difficult intestinal perforations can be treated with a combined application of endoclips and endoloops[19]. In the recent study by Kim *et al*[20], 115285 diagnostic colonoscopies were performed with a total of 27 iatrogenic colon

perforations (incidence of 0.02%). Endoscopic closure of the perforation site was attempted in 16 patients, with success in 13 patients. This suggests that immediate endoscopic closure with clips can be performed for diagnostic perforations as well as therapeutic colonoscopy-associated perforations.

Jovanovic *et al*[21] reported that endoscopic closure of colonic perforations could be performed when the perforation is < 1 cm. Few authors[22,23] have used the endoclips to treat perforations > 1 cm. Trecca *et al*[22] reported 2 perforations > 3 cm that were managed by using endoclips successfully. In the Velchuru *et al*[24] case report, the perforation was 3 cm in size and 7 clips were used to close the defect. The patient was discharged on the second day. The number of clips used depends on the size of the perforation. Endoscopic closure of an iatrogenic colonic perforation at colonoscopy is feasible as the prepped colon contains minimal contamination. Considering the technical challenge of endoclip application, an experienced endoscopist is the most important factor, as well as the site and size of the perforation. Clip closure was reported to be successful in 69.2% to 92.6% of cases[25,26].

However, there have also been some limitations in the treatment of colorectal perforation by endoscopic clips. It is hard to evaluate the degree of closure after an endoscopic clip reparation. If the endoscopic clip closure is incomplete, it would develop to limited leakage, which may result in the abdominal symptoms again. In these cases, minor symptoms make it difficult to decide whether or not to operate. The proper management may be delayed until the optimal period. Moreover, delayed complications can develop due to extra-luminal contaminants or intermittent minor leakage. The Cho *et al*[3] study indicates that peritoneal abscess formation developed in 50% of cases after a large perforation repaired by endoscopic clips. After colorectal perforation, the decision to perform surgery or endoscopic closure should be made promptly, within 24 h. The high risk clinical factors within 24 h after a colon perforation include a large perforation, leukocytosis, fever, severe abdominal pain and large peritoneal free gas and these should also be identified within 24 h.

CONCLUSION

In conclusion, iatrogenic colorectal perforation is one of the most pernicious complications for patients undergoing endoscopic screening or therapy. Its management is still a challenge for many endoscopists. The methods of treating this complication are varied and include conservative treatment, surgical treatment and laparoscopy. With the development of endoscopy and its assistant accessories, using endoscopic clips to repair the iatrogenic perforation could remarkably decrease the possibility of undergoing additional surgery. For patients with a high risk of complications after endoscopic clip reparation, an early decision regarding additional surgery such as laparoscopy is also significant.

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ORIGINAL ARTICLE

Retrospective Study

Accuracy of endoscopists' estimate of polyp size: A continuous dilemma

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Author contributions: Izzy M and Virk MA contributed equally to this article; Izzy M made substantial contributions to conception and design of the study, drafting the article, making critical revisions related to important intellectual content of the manuscript, and final approval of the version of the article to be published; Virk MA made substantial contributions to conception and design of the study, making critical revisions related to important intellectual content of the manuscript, and final approval of the version of the article to be published; Saund A contributed to acquisition of the data and drafting the article; Tejada J contributed to acquisition of the data and making critical revisions related to important intellectual content of the manuscript; Kargoli F contributed to data analysis and interpretation; Anand S contributed to critical revisions related to important intellectual content of the manuscript and final approval of the version of the article to be published.

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Abstract

AIM: To examine the discrepancy, if any, between the endoscopist's estimate and pathologist's measurement of colonic polyp size.

METHODS: We retrospectively studied 88 patients who underwent colonoscopy with a clear unequivocal documentation of polyp size by both endoscopist and pathologist. Endoscopist measurements were based on the visual estimate of polyp size seen on high definition screens. The measurement was done by our pathologists after formalin fixation. We compared the endoscopist estimate of the polyp size to the pathologist measurement in order to explore the discordance between the two readings. Data regarding demographics and method of polypectomy (snare polypectomy *vs* excisional biopsy) was collected, as well. Statistical analysis software (SAS) was used to analyze the data.

RESULTS: Our cohort included 88 patients from which 111 polyps were removed. Fifty-two (46.8%) of the 111 polyps were excised using biopsy forceps and fifty-nine (53.2%) were removed by snare. In the biopsy forceps group, the mean polyp size documented by the pathologist was 0.38 ± 0.19 cm and the mean polyp size documented by the endoscopist was 0.54 ± 0.16

cm. The mean difference was 0.16 cm (P < 0.001). In the snare group, the mean polyp size documented by the pathologist was 0.54 ± 0.24 cm and the mean polyp size documented by the endoscopist 0.97 ± 0.34 cm. The mean difference was 0.43 cm (P < 0.001). Combining both groups, the mean size documented by pathologist was 0.46 ± 0.23 cm compared to 0.76 ± 0.35 cm documented by the endoscopist. The mean difference was 0.3 cm (95%CI: 0.23-0.36).

CONCLUSION: Post polypectomy measurement by the pathologist are generally smaller than the endoscopist's estimate.

Key words: Polyp size estimate; Colonic polyps; Endoscopist estimate

Core tip: Our results suggest wide variance in polyp size documentation. Neither endoscopist estimate nor pathologist measurement accurately reflects colonic polyp size. Inaccurate determination of polyp size can negatively impact advanced adenoma detection. Using a screen cursor like that used in ultrasound and computed tomography scanners may serve as a standardized, accurate technique to solve this issue.

Izzy M, Virk MA, Saund A, Tejada J, Kargoli F, Anand S. Accuracy of endoscopists' estimate of polyp size: A continuous dilemma. *World J Gastrointest Endosc* 2015; 7(8): 824-829 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i8/824.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i8.824

INTRODUCTION

The incidence of colorectal cancer continues to rise to make it the fourth most common cancer in men and third most common cancer in women[1]. The concept of adenoma-carcinoma sequence has been already established by several studies[2-4]. The various characteristics that need to be considered upon evaluating the malignant potential of an adenomatous polyp are size, villous components and dysplasia[2,5]. These factors significantly impact the decision regarding follow up surveillance studies. While an experienced pathologist can precisely recognize the villous component or dysplastic changes in the polyp, achieving an accurate estimate of the polyp actual size remains challenging for the endoscopist as well as the pathologist.

With the growing importance of early detection of premalignant colonic polyps, accurate determination of polyp size becomes critical to recognize patients with potential to develop colon cancer. National and international guidelines consider polyp size as a key factor in determining follow up intervals with 10 mm cutoff as an important threshold for closer monitoring and surveillance[6,7]. Polyps less than 5 mm rarely show pre malignant histological features while a size over 10 mm has a 33% potential of pre malignant characteristics[8-10]. Polyp size is visually estimated during endoscopy. This is an approximate determination with variability between observers. Pathological measurements are made after excision using the untreated sample or after treatment with formaldehyde[11]. There is a possibility of incomplete estimation because some polyps are submitted piecemeal or fragmented. In addition, visual estimation is 2 dimensional while pathologic measurement is 3 dimensional[12]. Accurate estimation of polyp size also appears to be critical based on its location. Gupta *et al*[13] have reported advanced adenomas are more likely with a smaller size estimate on the right side of the colon. In this study, we aim to investigate the inconsistency, if any, between the endoscopist's estimate and pathologist's measurement of polyp size hoping to find a way to standardize the polyp size measurement.

MATERIALS AND METHODS

Eighty-eight subjects who underwent endoscopic polypectomy over a two-year period were studied retrospectively. Data was collected on 111 excised polyps. Visual estimation by the endoscopist was rounded to the nearest millimeter. Pathological estimation after fixation with formaldehyde was obtained from biopsy pathology reports. Data regarding the method of polypectomy being biopsy forceps *vs* snare was collected from each procedure report and analyzed accordingly. Demographic data was collected, as well. We only included patients with clear numerical documentation of the polyp size by the pathologist and the endoscopist and clear documentation of method of polypectomy in the endoscopy report. Subjects with incomplete data or missing parameters were not included. Only cases that were cared for by the teaching consult service were included. From the entire cohort, a random selection of 88 cases that fulfill these criteria was made by our GI pathologist. In order to get a wide representation of all endoscopists and fellows rotating through our service, an average of 3-4 cases from each month over the course of 2 years was maintained.

Visual estimates were obtained using Olympus Evis Exera 111 (CF-HQ190L/I and PCF-HQ190L/I) colonovideoscopes with dual focus optical system and Narrow Band Imaging. Visual estimation was done by the endoscopists for snared polyps and in reference to open forceps for excisional biopsies. The method of polypectomy was determined based on the size of the polyp and type of its attachment, *i.e.*, sessile or pedunculated. All study colonoscopies were performed by our 9 gastroenterology fellows under the supervision of 4 experienced faculty members. The documented

Table 1 Discrepancy in reporting polyp size between endoscopists and pathologists based on the method of excision

Method of excision	Number of polyps	Mean endoscopist's estimate	Mean pathologist's measurement	Mean difference	Overestimate	*P* value
Biopsy excision	52	0.54 (± 0.16) cm	0.38 (± 0.19) cm	0.16 cm	39%	< 0.001
Snare polypectomy	59	0.97 (± 0.34) cm	0.54 (± 0.24) cm	0.43 cm	77%	< 0.001
Total	111	0.76 (± 0.35) cm	0.46 (± 0.23) cm	0.3 cm	65%	< 0.001

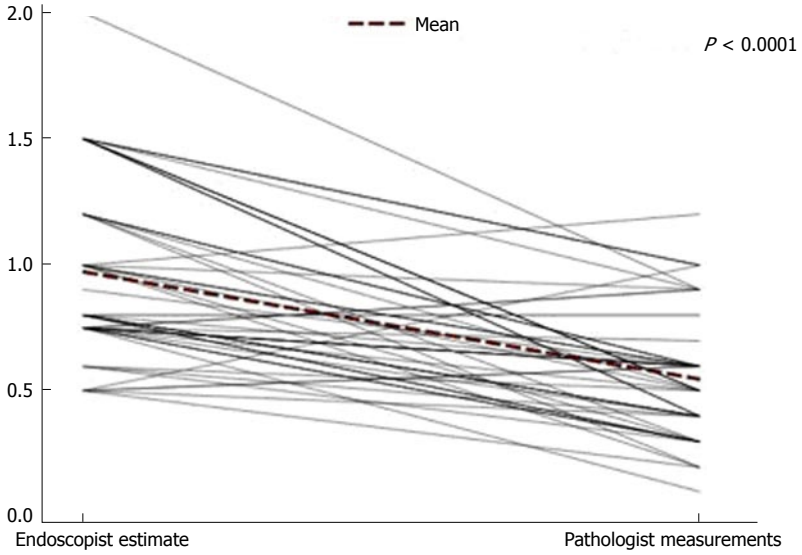

Figure 1 Snared polyp overestimate by endoscopist. Dotted line is the mean difference (Measurements in centimeters).

size was agreed upon by the performing fellow and supervising faculty.

The pathologist was blinded to the visual estimate. The macroscopic measurement was done at the cut-up bench.

Statistical analysis

Retrospective analysis was performed comparing endoscopist visual estimate of polyp size and pathologist measurement. Continuous and categorical data were presented using means (± SD) and frequencies, respectively. Student *t* test was used to measure the difference of the means between different polypectomy techniques (snare *vs* excisional biopsy). Paired *t* test was used to estimate the difference of the means between the endoscopist and pathologist size determinations. Linear regression model was used to determine the predictors of the difference of the means between the two determinations (endoscopist *vs* pathologist). All statistical analysis was done using statistical analysis software (9.2, South Carolina).

RESULTS

In our cohort, 37% were men and 63% were women with 75% African American, 21% Hispanic, 3% Caucasian and 1% Asian American. Fifty-two (46.8%) of the polyps were excised using biopsy forceps and 59 (53.2%) of the polyps were removed by snare polypectomy. In the biopsy excision group the mean visual size reported by the endoscopist was 0.54 ± 0.16 cm *vs* a mean polyp size of 0.38 ± 0.19 reported during pathological exam. The mean difference was 0.16 (95%CI: 0.09-0.215) (Figure 1). The location of the polyp did not have any impact on the reported measurements. In the snare polypectomy group the mean visual size reported by the endoscopist was 0.97 ± 0.34 cm *vs* a mean polyp size of 0.54 ± 0.24 reported during pathologist exam. The mean difference was 0.43 cm (95%CI: 0.33-0.52) (Figure 2). Visual overestimation in the biopsy excision group was 39% in comparison 77% in the snare polypectomy group (Table 1).

Combining both groups, the mean visual size was 0.76 ± 0.35 cm compared to 0.46 ± 0.23 cm by the pathologist. The mean difference was 0.3 cm (95%CI: 0.23-0.36). Visual estimates during endoscopy were within 1 mm of the pathologist measurement in 28 polyps (25%) and were within 2 mm in 52 polyps (46%) (Figure 3).

DISCUSSION

To date, our study is the largest in the field with special emphasis on the method of polypectomy as a factor affecting the endoscopist visual estimate. It also clearly shows that endoscopists tend to overestimate the polyp size; a fact that was previously considered a controversial concept. This study showed that endoscopists tend to overestimate the polyp size by 65% in comparison to the measurements reported

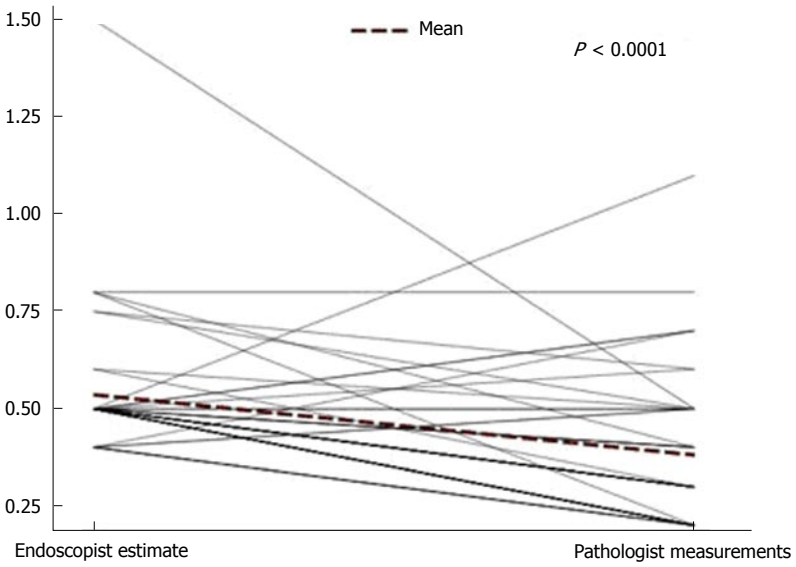

Figure 2 Forceps-excised polyp overestimate by the endoscopist. Dotted line is the mean difference (Measurements in centimeters).

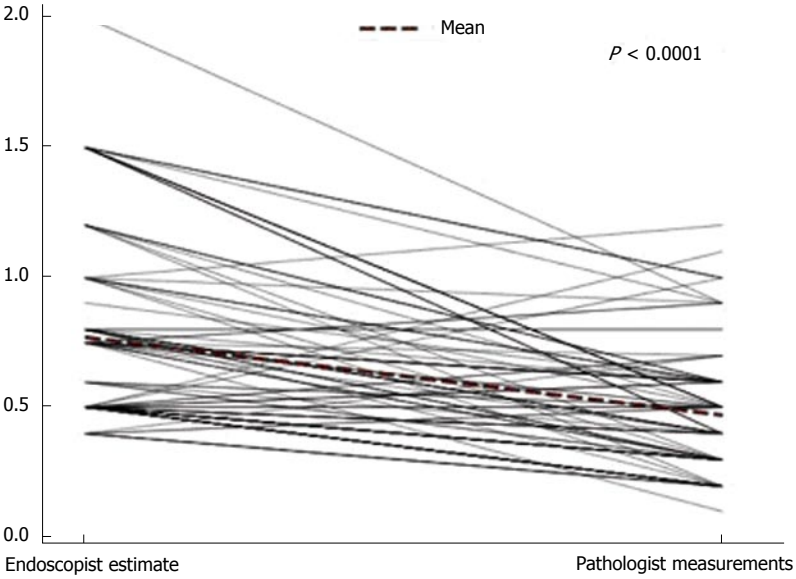

Figure 3 All polyps overestimate by endoscopist. Dotted line is the mean difference (Measurements in centimeters).

by pathologists. This difference between polyp size measurement that was noted between the endoscopists and pathologists may be attributed to the physical damage of the specimen. The polyp may be damaged in situ during excision or the endoscopist may not remove the polyp in its entirety. This will result in a specimen being sent to the pathologist that is actually smaller than it was *in situ*. Another factor that could be considered is the formalin fixation effect on size shrinkage. However, previous studies have shown that there was no significant difference between post excision polyp size and post fixation measurement, which strongly argues against formalin impact on polyp size[14,15]. Piecemeal submission of polyp tissue for pathological exam can be a factor that results in discrepancies in size too. Furthermore, a study by Schoen *et al*[14] determined that the type of polyp had an impact on the estimated size. In their measurement of 61 polyps, of which, 44 were pedunculated, the size was overestimated by the endoscopist 55% of the time. The stalk on pedunculated polyps may cause the polyp to sit on an angle which makes it more difficult for the endoscopist to accurately estimate its size. In our study, no such observation was noted.

In the current study, only 46% of the endoscopists estimations were within 2 mm of the pathologic measurements. There appears to be a wide variance in the remaining 54% of the measurements. Several published studies support our conclusion that endoscopists overestimate polyp size. A study of 61 polyps concluded that endoscopists overestimated polyp size by greater than 3 mm in 20% of the cases[14]. Morales *et al*[15] determined that in a sample of 31 polyps the endoscopists' estimates were on average 1.6 mm

greater than the postpolypectomy measurement. Other studies contradict our findings by asserting that endoscopists underestimate polyp size. A study of 107 polyps conducted by Turner *et al*[16] concluded that on average both colonoscopists and pathologists significantly underestimate polyp size in comparison to the prefixation measurement. Another recent study on 35 polyps also concluded that colonoscopists underestimate polyp size in 74% of the cases[11]. However, this study of 35 polyps presents a potential bias due to its small sample size.

It is noteworthy that, in our study, endoscopists showed greater overestimation of size in the polyps that were removed by snare biopsy *vs* removal using biopsy forceps (77% *vs* 39%). This can suggest that larger polyps are likely to be overestimated than smaller ones.

One possible limitation of this study is the retrospective model rather than a prospective one. This makes the study rely on the merit of record keeping by the endoscopists and pathologists. Moreover, we also looked only at post fixation size and did not have adequate data on prefixation measurements. However, the latter factor is unlikely to impact our findings in view of previously published studies about the effect of formalin fixation.

In conclusion, this study determined that endoscopists tend to overestimate the size of colonic polyps. This was more pronounced in case of snared polyps in comparison to polyps excised by forceps. Considering the major importance of accurate polyp size estimation on detecting advanced adenoma, visual estimates provided in a non-standardized manner can result in significant inter-observer (endoscopist) variations. Pathology reports for the size are not reliable either considering that most polyps get some degree of physical damage upon removal, which directly affects the size. Use of measurement cursors is a standard practice during imaging studies such as sonography. We suggest that the addition of a measurement cursor to video endoscopes can standardize the visual estimates and provide accurate information to determine appropriate surveillance intervals allowing for better management and ultimately a decreased mortality rate from colon cancer.

COMMENTS

Background

Colonic polyp size is critical in determining the significance of the polyp and thus the colonoscopy surveillance interval. The inaccuracy in determining the size can have remarkable consequences represented by repeating colonoscopy earlier than needed in case of overestimating the actual polyp size or delaying a necessary procedure which might result in development of colorectal cancer in case of underestimating the polyp size.

Research frontiers

There have been only few small studies that attempted to address the issue of estimating polyp size by the endoscopists. Those studies have shown inconsistent results in terms of endoscopists' tendency to overestimate *vs* underestimate polyp size.

Innovations and breakthroughs

This study is, to date, the largest of its kind and it clearly shows that endoscopists tend to generally overestimate polyp size with wide variance in the overestimate. On the other hand, the pathologist's measurement cannot be considered reliable given the possibility of physical damage or shrinkage of the polyp.

Applications

This study highlights the desperate need for an accurate standardized method of measuring colonic polyp size. To solve this issue, the authors suggest using cursors for colonoscopy screens like those used in ultrasound and computed tomography scanners.

Peer-review

This is a well-written manuscript. The retrospective nature of the study may actually be a plus as it gives a true representation of the endoscopists estimation of size as they would normally do in their routine practice.

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Toward an easier indigocarmine chromoendoscopy

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Author contributions: Barret M drafted the manuscript; Camus M, Leblanc S and Coriat R performed the endoscopic procedures; Prat F corrected the manuscript; Chaussade S performed the endoscopic procedures and designed the study; all authors approved the final version of the manuscript.

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Abstract

Indigocarmine chromoendoscopy has been proven to improve the detection of colonic lesions during screening colonoscopy, and is associated with increased adenoma detection rates. Furthermore, it is commonly used to help in the delineation and characterization of colorectal neoplasms. However, it usually requires the use of a spraying catheter that decreases the suction capacity of the endoscope, and is time- consuming. Herein, we report on the feasibility of indigo carmine chromoendoscopy during colonoscopy without using a spraying catheter, with the dye being administered through the air/water channel of the endoscope. Since the suction channel remains free, the air can be exsufflated and the staining then applies uniformly onto the colonic walls with the excess indigocarmine dye being immediately eliminated. In our experience with various types of colonoscopes and cap-assisted colonoscopy, this procedure makes indigocarmine chromoendoscopy much easier and quicker to perform, and might save the use of a spray catheter.

Key words: Indigocarmine; Chromoendoscopy; Colonoscopy; Adenoma detection rate; Colorectal cancer screening

Core tip: We report on the feasibility of indigocarmine chromoendoscopy during colonoscopy without using a spraying catheter, with the dye being administered through the air/water channel of the endoscope.

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TO THE EDITOR

Indigocarmine chromoendoscopy has proven useful in increasing the overall diagnostic yield of colonoscopy and the adenoma detection rate[1]. This technique is currently recommended in routine colorectal cancer

Figure 1 0.2% indigocarmine solution prepared in the water bottle.

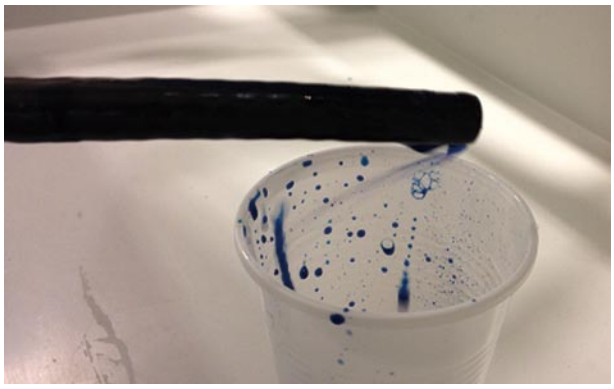

Figure 2 Indigocarmine dye application through the air/water channel of the endoscope.

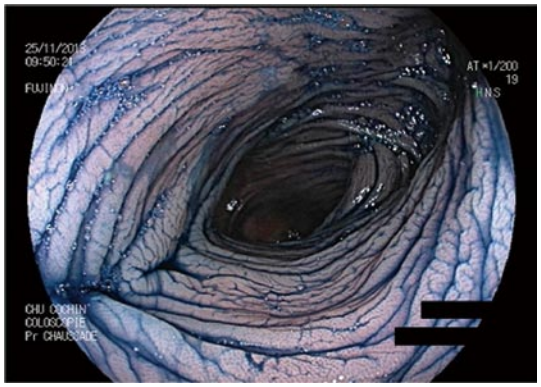

Figure 3 Endoscopic view of the colonic mucosa after indigocarmine staining using a Fujifilm® colonoscope.

screening in patients with long-standing inflammatory colitis or hereditary nonpolyposis colorectal cancer[2]. The standard technique implies pancolonic spraying with 0.2% indigocarmine delivered through a spraying catheter inserted in the accessory channel of the colonoscope. Spraying is performed segmentally during withdrawal of the endoscope and excess dye is suctioned before mucosal examination.

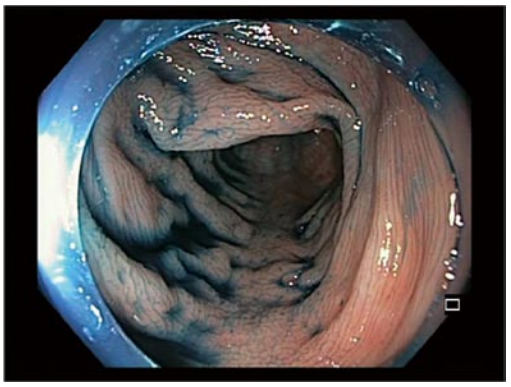

Figure 4 Endoscopic view of the colonic mucosa after indigocarmine staining using an Olympus® colonoscope and a cap.

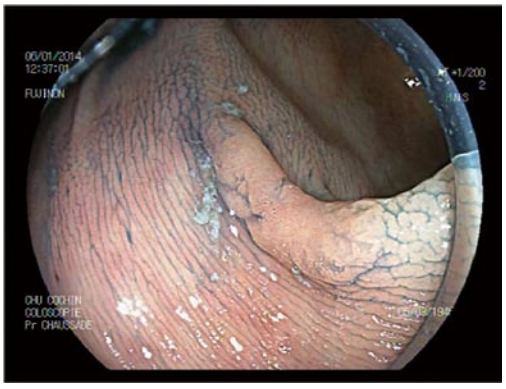

Figure 5 Endoscopic view of a sessile serrated adenoma after indigocarmine staining.

However, the use of a spray catheter has a certain cost, limits the suction capacity of the endoscope and often requires several passages with the endoscope, which can sometimes be difficult in some patients. We report on the feasibility of the indigocarmine dye application directly through the colonoscope air/water channel. Upon cecal intubation, the indigo carmine solution is prepared in the water bottle, using two 10 mL vials of 1% indigocarmine diluted in 80 mL of water, in order to obtain the 0.2% concentration (Figure 1). The indigo carmine dye is delivered by pressing on the air/water valve while orienting the head of the endoscope against the colonic walls and withdrawing the colonoscope. The indigocamine dye application is shown on Figure 2. It should be noted that the indigocarmine stained water does not remain on the objective lens of the endoscope rendering clear water unnecessary for the cleaning of the tip of the endoscope during the chromoendoscopy procedure. Once the end of a colonic segment has been reached, suction of the air allows uniform application of the dye on the mucosa and elimination of excess fluid. New air insufflation is then needed for the colonic mucosal examination.

Immediately after the procedure, the air/water channel of the endoscope is flushed with water from another water bottle until the outflow is clear, to make sure that no indigocarmine dye remains inside the channel. After standard washing, we did not observe any residual staining in the water bottles. Our preliminary experience with 15 patients suggests that this simplified indigocarmine chromoendoscopic technique is feasible with Olympus® or Fujifilm® colonoscopes, with or without a cap (Figures 3-5) and with a median withdrawal time of 21 ± 12 min.

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EDITORIAL

Methods and outcomes of screening for pancreatic adenocarcinoma in high-risk individuals

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is a lethal neoplasia, for which secondary prevention (*i.e.*, screening) is advisable for high-risk individuals with "familiar pancreatic cancer" and with other specific genetic syndromes (Peutz-Jeghers, p16, BRCA2, PALB and mismatch repair gene mutation carriers). There is limited evidence regarding the accuracy of screening tests, their acceptability, costs and availability, and agreement on whom to treat. Successful target of screening are small resectable PDAC, intraductal papillary mucinous neoplasms with high-grade dysplasia and advanced pancreatic intraepithelial neoplasia. Both magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) are employed for screening, and the overall yield for pre-malignant or malignant pancreatic lesions is of about 20% with EUS and 14% with MRI/magnetic resonance colangiopancreatography. EUS performs better for solid and MRI for cystic lesions. However, only 2% of these detected lesions can be considered a successful target, and there are insufficient data demonstrating that resection of benign or low grade lesions improves survival. Many patients in the published studies therefore seemed to have received an overtreatment by undergoing surgery. It is crucial to better stratify the risk of malignancy individually, and to better define optimal screening intervals and methods either with computerized tools or molecular biomarkers, possibly in large multicentre studies. At the moment, screening should be carefully performed within research protocols at experienced centres, offering involved individuals medical and psychological advice.

Key words: Endoscopic ultrasound; Pancreatic cancer; Screening; High-risk individuals; Magnetic resonance

Core tip: Screening for pancreatic cancer is advisable for high-risk individuals. There is limited evidence regarding the accuracy of screening tests, their acceptability, costs and availability, and agreement on whom to treat. Successful target of screening are small resectable pancreatic ductal adenocarcinoma, intraductal papillary mucinous neoplasms with high-grade dysplasia and advanced pancreatic intraepithelial neoplasia. Both magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) are employed for screening, and the overall yield for pre-malignant or malignant pancreatic lesions is of about 20% with EUS and 14% with MRI/magnetic resonance colangiopancreatography. However, only 2% of these detected lesions can be considered a successful target. It is crucial to better stratify the risk of malignancy individually, and to better define optimal screening intervals and methods.

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INDICATION FOR SCREENING FOR PANCREATIC ADENOCARCINOMA: WHICH PATIENTS SHOULD RECEIVE SCREENING AND WHICH LESIONS ARE WE LOOKING FOR?

Pancreatic ductal adenocarcinoma (PDAC) is the most common and lethal type of neoplasia occurring in the pancreas. Its incidence has progressively increased in Western countries, possibly due to changes in lifestyle[1]. The prognosis of PDAC is dismal, due to delayed diagnosis, biological aggressiveness and poor response to medical treatment[1,2]. PDAC is going to become the second cause of cancer-related death in the United States by 2030[2].

Prevention, therefore, seems one of the few reasonable approaches to tackle this deadly disease. Primary prevention, consisting of policies aimed at reducing the risk related with modifiable factors, such as cigarette smoking or overweight, is of paramount importance and might reduce substantially the incidence of PDAC[3].

On the other hand, secondary prevention (*i.e.*, screening) is not advisable for the general population, as the overall lifetime risk of developing PDAC is relatively low, being close to 1%. PDAC, indeed, does not meet some of the criteria set by the World Health Organization for considering a population screening worthwhile[4], such as being the target disease a common form of cancer, although it does have a high associated morbidity or mortality. Moreover, screening for cancer is justified if a there is an acceptable, safe and relatively inexpensive test procedure and if an effective treatment, capable of reducing morbidity and mortality, is available.

With regards to PDAC, there is limited evidence regarding the accuracy of screening tests, their acceptability, costs and availability, and agreement on whom to treat on the basis of screening results. Furthermore, as the accuracy of a given test also relies on the prevalence of the disease (pre-test probability), it is clear that screening is only advisable for specific population groups with a significantly increased risk of developing PDAC.

With regards to which individuals should undergo screening for early diagnosis of PDAC there is good general agreement among experts. The members of the International Cancer of the Pancreas Screening Consortium (CAPS)[5] have recently stated that screening is indicated for: (1) Individuals with "Familiar pancreatic cancer" (FPC), without a defined genetic syndrome, but with two or more blood relatives affected by PDAC, of whom at least one first degree relative (FDR); and (2) As far as regards known genetic syndromes, screening is indicated for all patients with Peutz–Jeghers syndrome regardless of family history of PDAC, while for p16 [familial atypical multiple mole melanoma syndrome (FAMMM syndrome)], BRCA2, PALB and hereditary non-polyposis colorectal cancer mutation carriers, screening is indicated only if one FDR or two family members are affected by PDAC.

It is more difficult to agree on which lesions should be considered the target of screening examinations. Ideally small cancerous lesions (T1) amenable for surgery should be diagnosed in due time and receive appropriate treatment, and individuals with clear macroscopic preneoplastic lesions, such as intraductal papillary mucinous neoplasms (IPMNs), might also be considered for surgery depending on size and other cyst features. However, there is no evidence suggesting that cystic lesions should be treated differently than in sporadic cases[6-8]. The possibility to recognize and the need to treat microscopic preneoplastic lesions such as pancreatic intraepithelial neoplasia (PanIN), whose presence might be indirectly suspected at screening examinations by signs of chronic pancreatitis, is less clear. Advanced PanINs (grade 3) might be considered an appropriate target for screening, while PanIN1 and 2 are extremely common findings in healthy subjects, with their prevalence increasing with age. The yield of "successful" screening examinations should therefore be considered in terms of detection and indication for surgery of lesions such as small, resectable PDAC, PanIN3 and IPMN with high grade dysplasia[5].

Finally, no imaging modalities gained a univocal evidence-based consensus for screening high-risk indivi-

duals (HRI) for pancreatic cancer, and both magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) have been proposed to be the first line modalities in terms of accuracy.

The present review article will discuss critically the rationale for the use, and the yield of EUS and MRI for detecting solid malignant and premalignant (solid or cystic) pancreatic lesions, and the outcome of surgery in this setting, in order to try to highlight the clinical impact of the screening policies.

EUS

EUS has emerged as an accurate imaging modality for the study of the pancreatic diseases providing high-resolution images of the pancreas without the risk of radiation exposure.

The CAPS Consortium suggests that initial screening of the HRIs should include EUS examination, with an agreement exceeding 83%[5].

EUS is, indeed, an extremely powerful diagnostic method, and is considered the most sensitive technique for the detection and diagnosis of PDAC. The sensitivity of EUS for solid lesions smaller than 2 cm is 93% compared to 53% and 67% of computed tomography (CT) scan and MRI respectively[9]. Moreover, the high negative predictive value (100%) of EUS for tumor detection suggests that the absence of a focal mass reliably excludes pancreatic cancer[10].

In the setting of cystic lesions, EUS obtains a good definition of their morphological characteristics, useful for the differential diagnosis and to identify features (mural nodules, wall thickness) associated with an increased risk of malignancy[11]. It has also been demonstrated that EUS performs better than MRI regarding the early detection of malignancy in patients with IPMN[12].

Finally, the possibility to perform guided fine needle aspiration (FNA) permits to obtain tissue samples for histopathological characterization of the lesion with low risk of complication[13]. However, although the sensitivity, specificity and accuracy of EUS-FNA in solid pancreatic masses was found to be high (84.3%, 97%, 84% respectively) the relatively low negative predictive value (64%) does not allow to exclude the diagnosis of PDAC if it is suspected[14]. The routine use of EUS – FNA in a screening program is therefore questionable.

On the other hand, microscopic precursor lesions of PDAC, such as PanINs cannot be reliably detected with current imaging methods. Some data, however, suggest that EUS might be able to detect parenchymal changes caused by these lesions. In HRIs PanINs are multifocal and might be associated with lobular atrophy of the surrounding parenchyma, but these features are not associated with the grade of dysplasia. The parenchymal changes caused by multifocal PanINs might be visualized at the EUS as chronic pancreatitis-like features (ectasia, irregularity of the duct and/or parenchyma heterogeneity and lobularity) that cannot be differentiated from non-neoplastic alterations[15].

For all these reasons, EUS has been used in several studies as the baseline screening test for PDAC in HRIs, alone or in combination with other abdominal imaging techniques. The diagnostic yield of this procedure in detecting any lesions - morphologically suspicious or histologically proven to be malignant or pre-malignant - ranged from 2.6% to 46% at baseline evaluation or during the follow-up. However, the actual rate of detected and resected lesions, for which screening might be considered successful, is much lower, as many patients undergoing surgery in these studies had PanIN 1 or 2, or IPMNs without dysplasia or even benign lesions such as serous cystoadenomas, and few others were diagnosed with unresectable PDAC (Table 1).

A screening programme based on EUS was first proposed by Brentnall *et al*[16] in 1999. A small prospective cohort of 14 patients (kindreds that had two or more members in the last two generations with pancreatic cancer) were evaluated with both EUS and endoscopic retrograde cholangiopancreatography (ERCP) and compared to CT results. The EUS findings were available for 13 of 14 patients and resulted abnormal in 10 (ranging from minimal to marked signs of chronic pancreatitis) at the first examination. Seven patients were treated with total pancreatectomy, with findings of signs of widespread dysplasia, although the grade of such lesions was not clarified in the paper. The diagnostic yield of EUS in this study was very high (46%) but whether resecting such target lesions might be considered a success is unclear given the associated morbidity of total pancreatectomy. Kimmey *et al*[17] reported the experience of the same centre, with a similar protocol, a few years later on 46 patients with more than two first or second-degree relatives with PDAC. This second paper seems to include also the patients reported in their pivotal study. Cross-sectional imaging did not detect abnormalities in those patients, while EUS showed signs of chronic pancreatitis in 24 patients, most of them also reporting symptoms such as diarrhoea and diabetes. Twelve patients (including the seven subjects of their first paper) underwent surgery and the histological examination showed widespread dysplasia in all of them. The diagnostic yield of EUS was equal to 26%, yet it is not clear if the operated patients had PanIN3 or lower grades of dysplasia. Notably, these pivotal papers employed ERCP in all screened individuals, and this might have caused some false positive findings, with the addition of possible procedure-related risks.

The pilot study of Johns Hopkins Hospital[18] enrolled 38 patients with $\geqslant$ 2 FDR with PDAC or affected by PJS. EUS was performed as a baseline screening method and in case of abnormalities CT scan and ERCP were carried out. Twenty-nine patients had abnormalities at EUS (12 pancreatic lesions and 17 EUS changes of chronic pancreatitis). FNA was performed in 21 and 3 alterations were found at cytological examinations (1 atypical neoplastic and 2 atypical reactive pancreatic cells). Seven patients underwent surgery, but only one was diagnosed with a T2N1 PDAC and another with multiple PanINs

Table 1 Summary of diagnostic yields of endoscopic ultrasound based protocols for familiar pancreatic cancer screening in high risk individuals

Ref.	Patients and syndrome	Diagnostic Yield[1] of EUS	No. of solid lesions (mass or nodule)	No. of cystic lesions	No. with chronic pancreatitis features	No. with pre/malignant lesions suspected at baseline or FU	Number with histologically confirmed target lesions for which treatment can be considered a success[2]
Brentnall *et al*[16]	13 (FPC)	46.2%	-	-	10 (77%)	6 (46.2%)	?
Kimmey *et al*[17]	46 (FPC)	26%	-	-	24 (52.2%)	12 (26%)	?
Canto *et al*[18]	38 (FPC, PJS)	10.5%	12 (31.5%)	-	17 (44.7%)	6 (15.7%)	2/7 patients who underwent resection (1 PDAC, 1 PanIN3)
Canto *et al*[19]	78 (FPC, PJS)	10.2%	8 (10.2%)	9 (11.8%)	61 (78.2%)	8 (10.2%)	3/7 patients who underwent resection (1 IPMN+ca *in situ*, 1 IPMN + PanIN3, 1 PanIN3)
Poley *et al*[20]	44 (FPC, PJS, FAMM, FBOC, HP, LFS)	22.7%	3 (6.8%)	7 (16%)	3 (6.8%)	10 (22.7%)	3/3 patients who underwent resection (3 PDAC)
Langer *et al*[21]	76 (FPC, FAMM)	2.6%	7 (9.2%)	3 (3.9%)	17 (22.3%)	7 (11.8%)	0/7 patients who underwent resection
Verna *et al*[23]	31 (FPC, FBOC)	22.5%	2 (6.4)	12 (38.7)	9 (29%)	7 (22.6%)	1/5 who underwent surgery (1 PDAC)
Canto *et al*[24]	216 (FPC, FBOC, PJS)	37%	3 (1.4%)	79 (36%)	54 (25%)	79 (37%)	3/5 who underwent surgery (2 MD-IPMN, 1 BD-IPMN + panIN3)
Total	542	22.2%	35 (6.5%)	110 (20.3%)	195 (36%)	135 (25%)	12/542 (2.2%) of total

[1]Endoscopic yield is defined as EUS detection of any lesions morphologically suspicious for BD-IPMN or histologically proven (pre) malignant lesion (PanIN $\geqslant$ 2, IPMN and pancreatic adenocarcinoma) at baseline evaluation and, when performed, during the follow up; [2]Treatment is considered a success if any of the following lesions is found at surgery: resectable PDAC, MD-IPMN or IPMN with dysplasia, PanIN3. EUS: Endoscopic ultrasonography; FNA: Fine-needle aspiration; FPC: Familial pancreatic cancer; BD: Branch duct; MD: Main duct; IPMN: Intraductal papillary mucinous neoplasm; PDAC: Pancreatic ductal adenocarcinoma; PJS: Peutz–Jeghers syndrome; PanIN: Pancreatic intraepithelial neoplasia; FAMMM: Familial atypical multiple mole melanoma; FBOC: Familial breast ovarian cancer; HP: Hereditary pancreatitis; LFS: Li fraumeni syndrome.

ranging 1-3. The other 5 resected patients had either a borderline IPMN, PanIN2 or benign lesions (serous cystoadenoma). The diagnostic yield of EUS was 10.5%, if one considers borderline IPMN and PanIN2 appropriate targets for screening. The subsequent prospective study conducted by Canto *et al*[19] screened 78 consecutive HRIs with EUS. In case of abnormal findings at EUS, further evaluations with EUS- FNA/ERCP were performed. In four patients pancreatic malignancy was suspected at baseline screening. The surgical findings were of IPMN with carcinoma in situ in one case, and of IPMN with numerous foci of PanIN3 in another, while the other two patients had IPMN with diffuse and multiple PAnIN1-2, or diffuse PanIN1-2. During the follow-up, within 1 year, further 4 patients were diagnosed having suspected pancreatic neoplasia, and while 1 had an advanced unresectable adenocarcinoma, the others underwent surgery with findings of PanIN3 in one case, and either IPMN with/without PanIN1-2 in the other cases. Therefore, although EUS diagnosed 7 of 8 pathologically confirmed pancreatic neoplasms (yield of 10.2%), one might discuss that a large part of the resected patients did not have significant lesions, and that, despite the screening process, one lesion was diagnosed at mestastatic stage.

Poley *et al*[20] reported their data of a first-time EUS screening on a prospective study of 44 patients (with a relatively large proportion of carriers of a clearly defined genetic syndrome associated with an increased risk to develop PDAC). In case of EUS abnormalities, CT or MRI were performed, as well as a multidisciplinary discussion of all the findings. A total of 7 cystic lesions were diagnosed. Their morphological features at EUS examination were typical of IPMN without signs of malignancy (diameter between 4 and 15 mm without solid component or intramural nodules). In this study this was not considered an indication for surgery. Three asymptomatic solid lesions were detected by EUS and, after resection, the histological examination indeed showed adenocarcinoma. The stage of the tumour was T3N1M0 in two patients and T1N0M0 in the other, but even in this case distant metastases were found 16 mo after surgery. The diagnostic yield of EUS in detecting neoplasms in HRIs in this study was 22.7%.

No malignant lesion was diagnosed in the German surveillance program[21]. This prospective screening study was carried out in 76 HRIs. The imaging procedures performed at baseline were MRI combined with magnetic resonance colangiopancreatography (MRCP) and EUS. A total of 7 suspected lesions were further evaluated with FNA, but none showed cytological alterations. Surgical exploration of the pancreas was performed in 7 individuals, but the histological diagnoses were 3 serous cystoadenomas, 1 PanIN1, 1 PanIN2 and 1 IPMN. The diagnostics yield of EUS in this study was 2.6%, considering as a "successful" target precancerous lesions also the histologically presence of PanIN2 in the pancreatic parenchyma. This low yield compared to the other previous studies could be correlated to a

selection bias of the patients (the study included a large number of patients at moderate risk). The subsequent German study[22] evaluated 5-year of prospective screening in the HRIs from this same series, showing a higher yield in detection of pre-malignant lesions using EUS and MRI/MRCP as follow-up methods. Further 9 patients underwent surgical resection, with diagnosis of 1 advanced PDAC and 1 PanIN3, with the other lesions being either serous cysts (n = 3) or lower grade PanIN or IPMN.

Verna *et al*[23] screened a total of 51 HRIs, 31 of them with EUS. The most common abnormal findings, as expected, were parenchymal changes seen in chronic pancreatitis: two patients had a mass lesion confirmed to be PDAC after FNA, one was resectable (2 cm moderately differentiated adenocarcinoma arising from main duct IPMN), and one metastatic to the liver. Five BD (branch-duct) IPMN were diagnosed and in 4 of them surgery was carried out (all of these had BD IPMN with moderate dysplasia and multifocal PanIN2 lesions on pathology). In this cohort study the diagnostic yield was 22.5%, although only one of these lesions might be considered a successfully detected target.

The multicentre prospective cohort CAPS 3 study[24] enrolled three groups of asymptomatic HRIs (FPC, BRCA and PJS). It is the first blinded study that compared standardized protocol CT, gadolinium and secretin-enhanced MRCP and EUS. Of 226 patients, EUS diagnosed parenchymal and ductal abnormalities (chronic pancreatitis features) in 25%. Surgery was performed in 5 HRIs, and three of 5 them had IPMN with main duct involvement, high-grade dysplasia and/or associated PanIN3. The diagnostic yield in detecting precursor lesions was considered equal to 37%, but the number of significant lesions was relatively low, with few cases with indication for surgery as compared with previous studies.

MRI

MRI is a widely available technique, and when compared to EUS, has the advantages of being non-invasive, less operator-dependent, easier to be compared and reviewed over time by different specialists taking care of the patients. MRI also offers the opportunity to image the entire abdomen and pelvis. This latter aspect is noteworthy, as it might help diagnosing extra-pancreatic neoplasms, which are fairly common in some specific groups of HRI[25]. Moreover, MRCP provides excellent visualization of the pancreatic and biliary tree and is particularly useful for characterizing cystic lesions such as IPMNs that are the most common precursor lesions diagnosed in HRI[6,20,26].

Seven papers investigated the use of MRI for the screening of individuals at high risk for developing a pancreatic cancer. The employed methods are extremely heterogeneous in terms of employed MR scanner, acquisition phases, use of contrast agents and use of secretin. The diagnostic yield for the detection of pancreatic lesions also varies among the different studies (Table 2), ranging from 3.3% to 57.4%[21,23-25,27-29].

Secretin-enhanced sequences have been used in three of these seven papers[21,24,29], but its use has not been univocally validated to improve the diagnostic yield of MRCP in this setting. Nevertheless, a recently published paper on patients with a strong family history of pancreatic cancer undergoing a multicenter Cancer of the Pancreas Screening-3 trial (CAPS 3), proved evidences that the use of secretin can improve the visualization of ductal communication of cystic pancreatic lesions[30].

Some authors decided to use non-contrast MRI protocol for screening, basing on the hypothesis that changes in pancreatic duct and/or focal drop in pancreatic signal would be detectable even without contrast and that these alterations would have triggered further investigations[28]. Other authors indeed used a contrast-enhanced MRI protocol. The former argued against this latter position because, even if using a contrast enhanced protocol, all pancreatic cancers individuated in screening programmes were advanced and/or metastatic and due to patient's death[27,28].

The diagnostic yield of MRI varies sensibly among the different studies with a wide range, between 3% and 50%, probably due to the heterogeneity both of investigated populations and screening protocols[23,25]. The rate of solid lesions found at MRI seems to be low, ranging between 0.4% and 9%[24,27]. Similar results have been reported for the detection of chronic pancreatitis-like changes, duct ectasia and PanIn lesions, while pancreatic cystic lesions are diagnosed in a higher percentages of patients (2.6%-35.3%)[21,24,29]. In two series, a percentage of about 3% of patients with non-reproducible alterations has been reported[21,28].

Recently a series of 40 high risk individuals undergoing a MRI based screening protocol has been published. Patients underwent a baseline secretin-enhanced MRCP and then a yearly MRI imaging in case of negative result or a EUS with FNA/additional CT scan imaging protocol in case of suspicious result. An overall 40% MRI yield was reported (35% IPMNs, 5% PDAC) at a median 1 year follow up. An additional, synchronous PDAC was found during the IPMN follow up. Five patients underwent a surgical resection, all of them with a successful surgical treatment (3 PDAC, 2 IPMNs with indeterminate grade dysplasia)[30].

COMPARISON OF EUS AND MRI

There are few studies comparing the diagnostic yield of MRI and EUS in screening HRIs, and it is therefore still unclear which is the best method in detecting early stage PDAC and premalignant lesions in these subjects. The CAPS 3[24] study evaluated, in a blinded fashion, the ability of these two screening methods in detecting pancreatic lesions in HRIs. This study showed a high concordance between the two diagnostic examinations for the detection of any pancreatic lesion (91%). In

Table 2 Summary of diagnostic yield of magnetic resonance imaging based protocols for familiar pancreatic cancer screening in high risk individuals

Ref.	Patients and syndrome	Diagnostic Yield[1] of MRI	No. of solid lesions (mass or nodule)	No. of cystic lesions	No. with chronic pancreatitis features	No. with pre/ malignant lesions suspected at baseline or FU	Number with histologically target lesions for which treatment has to be considered a success[2]
Langer *et al*[21]	76 (FAMMM, MPCS, FBOC)	23.3%	6 (7.8%)	2 (2.6%)	1 (1.3%)	12 (15%)	1/7 who underwent surgery (1 PDAC)
Vasen *et al*[27]	77 (FAMMM)	20.7%	7 (9%)	Not specified	9 (11.6%)	7 (9%)	4/5 who underwent surgery (4 R0 PDAC)
Ludwig *et al*[28]	109 (FPC)	16.5%	1 (0.9%)	Not specified	2 (1.8%)	18 (17.4%)	4/6 who underwent surgery (2 MD-IPMN, 1 PDAC, 1 PanIn3)
Canto *et al*[24]	216 (PJG, FPC, FBOC)	33.7%	1 (0.4%)	71 (32.8%)	-	45 (20.8%)	3/5 who underwent surgery (1 MD-IPMN + HGD, 1MD IPMN, 1 BD IPMN + PNET + HGD)
Al-Sukhni *et al*[25]	226 (PJG, FPC, FBOC, FAMMM, HP)	50.4%	2 (0.8%)	80 (35.3%)	25 (11%)	5 (2%)	1/4 who underwent surgery (1 PDAC)
Verna *et al*[23]	33 (FPC, FAMMM, FBOC, HNPCC)	3.3%	3 (9%)	7 (21.2%)	1 (3%)	5 (15%)	Not specified how may pathological reports had been previously described in MRI
Del Chiaro *et al*[30]	40 (FPC, BRAC 2, BRAC 1, FAMMM)	40%	3 (7.5%)	14 (35%)	-	4 (10%)	5/5 (3 PDAC: 1 of them T1N0M0, 1 developed on a synchronous BD-IPMN in FU; 2 intermediate grade dysplasia IPMN of which one mixed type and one branch duct)
Total	777	26.8%	23 (2.9%)	174 (22.39%)	38 (4.8%)	96 (12.35%)	18/777 (2.3%) of total

[1]MRI yield is defined as detection of any lesions morphologically suspicious for BD-IPMN or histologically proven (pre) malignant lesion (PanIN $\geqslant$ 2, IPMN and pancreatic adenocarcinoma) at baseline evaluation and, when performed, during the follow up; [2]Treatment is considered a success if any of the following lesions is found at surgery: resectable PDAC, MD-IPMN or IPMN with dysplasia, PanIN3. FPC: Familial pancreatic cancer; BD: Branch duct; MD: Main duct; IPMN: Intraductal papillary mucinous neoplasm; PDAC: Pancreatic ductal adenocarcinoma; PJS: Peutz–Jeghers syndrome; PanIN: Pancreatic intraepithelial neoplasia; FAMMM: Familial atypical multiple mole melanoma; FBOC: Familial breast ovarian cancer; HP: Hereditary pancreatitis.

particular, a strong positive correlation was found for the size of the lesions, and a moderate agreement for the number of pancreatic cystic lesion/solid mass was described. MRI better assessed communication of the cyst with the main pancreatic duct, being superior to EUS (53% *vs* 27%). EUS missed five patients with a cystic lesion seen by MRI (2 of which BD-IPMN) but diagnosed 12 patients with cystic lesions not reported by MRI (3 of which BD IPMN).

A prospective blinded comparison study was conducted by the Rotterdam group and has recently been submitted for publication. A total of 139 high-risk patients were enrolled and screened with both MRI and EUS. There was high agreement regarding location and size of all lesions. Instead, only a moderate agreement (55%) was reached for the detection of the 11 clinically relevant described lesions. MRI was very sensitive for the diagnosis of cystic lesions, while EUS detected two solid lesions that were not found by MRI (one of these was shown to be PDAC). The results of this study suggest that both techniques are useful, and that they might be complementary rather than interchangeable in screening HRIs, with MRI being able to detect cystic lesions better than EUS, but EUS being more accurate for the diagnosis of small solid lesions, which are the primary target of screening.

Thus, even taken for granted the major sensitivity of EUS in detecting small solid pancreatic lesions, one might argue that there are no solid data suggesting that such ability has a beneficial effect on the disease outcome in this setting. On the other hand, MRI with MRCP protocols have reasonably a good accuracy for the detection of IPMNs, which represent a precancerous lesion, that potentially progress towards pancreatic cancer. Future studies should compare the ability of these methods in a randomized designed study, and their impact on the long-term outcome of screened subjects.

USE OF SERUM CARBOHYDRATE ANTIGEN 19-9 AS A SCREENING TEST

Serum carbohydrate antigen (CA) 19.9 is the most widely used biomarker for pancreatic cancer, and its use is recommended to monitor the response to treatment[31] in patients who had elevated level before treatment (between 5% and 10% of the general population are unable to express CA-19-9).

However, the dosage of Ca 19.9 in screening asymptomatic population is not recommended. A number of 70940 asymptomatic patients were screened by Kim *et al*[32] using Ca 19.9 (cut off > 37 U/mL)[32]. Although it showed an high sensitivity (the CA 19-9 level was increased in all four patients diagnosed with pancreatic cancer), in screening pancreatic cancer in the general population it showed a very poor predictive positive value (0.9%). Similar results were obtained by Chang *et al*[33] that found high sensitivity and specificity of this biomarker in predicting pancreatic cancer (100% and 92% respectively) but a 0.5% of positive predictive value.

Slightly better results were obtained in screening symptomatic patients (with high prevalence of pancreatic cancer equal to 49%) where it was found an high positive predictive value (71%) using a cut off Ca 19.9

> 40 U/mL[34].

The diagnostic role of Ca 19.9 in screening HRIs patients was poorly investigated. The serum dosage of Ca 19.9 was carried out in 8 of 14 patient screened by Brentnall *et al*[16] and found to be normal in all these patients. Between the patients enrolled by Verna *et al*[23] only one had elevated Ca 19.9. This patient was found to have a pancreatic cyst without dysplasia, and Ca 19.9 remained elevated after surgery. In the german study by Langer *et al*[21] all but one patient showed a normal Ca 19.9. The imaging examinations did not show any abnormality of the pancreas at the first evaluation and during the subsequent 28 mo of follow up, and after further investigations the cause of elevation of this biomarker remained unclear. Therefore, although data are limited, the dosage of Ca 19.9 doesn't seem helpful during the screening of HRIs.

SURGICAL INDICATIONS AND OUCTOME

Although screening policies for the prevention or early detection of pancreatic cancer have been initiated about 15 years ago, there are still not enough data to generate evidence-based guidelines regarding the role of pancreatic surgery in this setting. In many of the initial studies screening HRIs, indication for surgery was possibly too wide, and many patients undergoing surgery were diagnosed with benign or borderline findings[16-19]. As discussed above, what makes the current picture more complicated is the definition of the targets for surgery, as reasonable goals of the screening programme are early invasive or resectable pancreatic cancer, high grade dysplasia IPMNs, and PanIN3 lesions, while the significance of other lesions is less clear. The different approaches to screening and treatment of HRIs is reflected in the results from different surveillance programmes. In this view, not surprisingly, the more recent studies, and personal viewpoints now point toward a less aggressive surgical approach, both in terms of timing for surgery and in extent of pancreatic resection[35].

PanIN lesions are considered detectable by EUS, by some Centers[19]. Those lesions may appear as parenchymal changes resulting from a lobulocentric atrophy (LCA) that is present in chronic pancreatitis. However, recent studies showed that this association between PanIN and LCA is not clear and for this reason the use of LCA as a target for early detection of pancreatic cancer should be considered with extreme caution. First, PanIN might not be the cause of LCA; second, LCA can be found in other conditions (as aged pancreas); third, the value of low grade dysplasia at FNA can't exclude another area of high grade dysplasia in a distinct area, sometimes distant from the biopsy site, but not associated with LCA, and not visible at EUS[36]. Furthemore, while the agreement among different operators for the interpretation of EUS findings when a frank solid or cystic lesion is diagnosed is generally good, this is not the case for the diagnosis of chronic pancreatitis features, where the agreement remains disappointing even after a consensus process[37].

For all these reasons there is no consensus on surgical treatment of PanIN lesions, and it is questionable whether finding of PanIN1-2 should be considered a success. However, one can assume that histological confirmed PanIN3 lesions should be resected. The extent of pancreatectomy for those patients is not defined, but a radical partial pancreatectomy seems to be the adequate option.

IPMNs are the most frequent finding detected during the screening of HRIs[35]. Even if the natural history of IPMNs in individuals with family history is not well defined, some data[38] suggest that the risk to progress to cancer is not higher than that of sporadic cases. However, the IAP guidelines for treatment and follow-up of cystic pancreatic lesions[8] suggest to shorten follow-up intervals in patients with BD-IPMN and FPC, and more recently the Italian guidelines[7] have suggested to consider surgery for all IPMNs in the setting of FPC in fit patients. Which surgical procedure should be performed in such cases is also unclear. Notably, it has been reported that in the setting of HRIs, BD-IPMNs are often associated with distant foci of PanIN3[36], and IPMNs are also frequently multifocal, thus a radical surgical treatment might be a total pancreatectomy. On the other hand, this may often result in an overtreatment. At any rate, such patients should be discussed in highly specialized centers and the indications should also take in consideration patient age and perception of the problem.

The surgical treatment of solid tumors of the pancreas (suspected pancreatic adenocarcinoma) in HRIs, should follow the rules of oncologic surgery[26]. The initial approach to these patients in Seattle was total pancreatectomy[16], but this is not supported by evidence and might only be considered in cases with diffuse multiple lesions in the pancreas (for example a solid tumor in the head and IPMN in the tail). Data on post-operative follow-up of HRIs are extremely scanty. It seems reasonable to follow-up HRIs diagnosed with cancer and resected as other sporadic cases. For patients operated for pre-malignant lesions, the pancreas remnant should be followed-up according to the surveillance program for HRIs[5].

AREAS FOR IMPROVEMENT

Screening for pancreatic cancer or its precursors has an indication in research settings only. As compared with other screening policies for cancers indeed, there are a number of issues that need to be clarified in order to consider screening worthwhile.

The overall yield of screening methods for pre-neoplastic or neoplastic pancreatic lesions in HRIs is of about 20% with EUS and 14% with MRI/MRCP. However, only 2% of the detected lesions might be considered a successful target of screening (Tables 1 and 2), and there are insufficient data demonstrating that resection

of benign or low grade lesions improves survival. Many patients in the published studies, indeed, seemed to have received an overtreatment by undergoing surgery.

In this view, it is crucial to better stratify the risk of malignancy individually, and to better define optimal screening intervals and methods. The use of a computerized risk assessment tool named PancPRO has been proposed and tested in incident cases of PDAC[39]; similar tools taking into account the role of family history and possibly other factors such as smoking, might help selecting patients at a substantially higher risk. In the future, application of novel methods of molecular analysis might help better select patients for screening, and provide the indication for surgical treatment. Eshleman *et al*[40] recently investigated the possible role of KRAS and GNAS mutations in the duodenal juice of PDAC patients and HRIs undergoing screening EUS. As expected, a high percentage of PDAC patients had KRAS mutations, but among screened individuals the presence of KRAS mutations did not discriminate between these with or without lesions. This is most likely due to the fact that KRAS mutations are an early event, already present in PanIN1, which is extremely common in HRIs and does not represent a target lesion for resection. Crnogorac-Jurcevic *et al*[41] analysed the gene expression profile of precursor lesions, PanIN2/3 obtained from prophylactic pancreatectomy specimens of FPC from the Seattle-Washington screening program. They found that transcriptomic changes occur during the progression of PanIN to PDAC, not only in the epithelium but also in the surrounding stroma. These findings support the view that early changes in familial cases are similar to those seen in sporadic cases, and might serve as a tool to predict the behaviour of pre-neoplastic changes in HRIs. The possible role of microRNAs, and other biomarkers, has been investigated by Slater *et al*[42]. They reported that serum levels of miR-196a and miR-196b were significantly higher in patients with PDAC as compared to controls, but notably, the serum levels of such miRs were also higher in HRIs screened for PDAC with PanIN2/3 lesions than in screened subjects without lesions or with PanIN1 lesions only. These results, if confirmed, might suggest that a panel of miRs might help selecting patients at higher risk of significant findings among screened individuals.

It is also uncertain whether EUS or MRI, or both, should be employed as screening tests, as few studies compared these two methods. It seems that the two techniques might be considered somehow complementary, with EUS being more accurate for solid lesions and MRI for cystic ones. Future studies should also take into account different subgroups of HRIs when establishing screening intervals and modalities. As an example, it has been reported that in individuals with FAMMM (p16 mutation carriers), cystic lesions are less frequent than in FPC, but solid lesions diagnosed as PDAC are far more frequent[43]. Thus, in p16 mutation carriers a screening with EUS and not with MRI, with closer intervals, might be preferred.

Another intriguing issue regards the diagnosis of other pancreatic lesions at screening. Pancreatic neuroendocrine tumours (PNETs) have been diagnosed in HRIs receiving screening for PDAC, with a prevalence apparently exceeding the expectations[24,25,27]. It is unclear whether these findings are just occasional, or if PNETs may represent a part of FPC phenotype, as possibly suggested by findings of similar risk factors for the occurrence of PNETs and exocrine neoplasms[44].

Finally, it also needs to be determined whether screening for pancreatic cancer in HRIs is really cost-effective. In a simulation considering a 20% prevalence of pancreatic "dysplasia" and 90% sensitivity of EUS and ERCP, endoscopic screening was calculated to be cost-effective, but this analysis most likely considered an excess of lesions now considered as successful targets of screening[45].

Future large collaborative studies are likely to give the answer to many of these open questions but, until then, screening for pancreatic neoplasms in HRI should be carefully performed within research protocols at experienced centres, offering involved individuals medical and psychological advice.

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EDITORIAL

Staple-line leak after sleve gastrectomy in obese patients: A hot topic in bariatric surgery

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Abstract

Laparoscopic sleeve gastrectomy is a surgical procedure that is being increasingly performed on obese patients. Among its complications, leaks are the most serious and life threatening. The placement of esophageal, covered, self-expandable metal stents in these cases has been performed by many authors but reports on the outcome of this procedure are limited and the technical aspects are not well defined. Stent migration is the main complication of the procedure and poses a challenge to the surgeon, with a limited number of options. Here we evaluate the technical and clinical outcome of a new, dedicated, self-expanding metal stent, comparing the advantages of this stent to those traditionally used to treat staple-line leak after sleeve gastrectomy. While published data are limited, they seem support the use of this kind of new stent as the best option for the stenting treatment of a staple-line leak after sleeve gastrectomy, over other kinds of stents. Further studies based on larger series are needed to better evaluate patient outcome.

Key words: Bariatric surgery; Leak; Obesity; Sleeve gastrectomy; Endoscopic stent; Therapy

Core tip: Laparoscopic sleeve gastrectomy (LSG) is a surgical procedure increasingly performed on obese patients with convincing outcomes. Among its complications, leaks are the most serious. The use of esophageal self-expandable metal stents in these cases has been performed by many authors but reports are limited and stent migration is the main complication of the procedure. Megastent®, a new stent dedicated to the treatment of leaks after LSG, seems to resolve most of the problems of the esophageal stents. While published data are limited, they seem support the use of Megastent® as the best option for the stenting treatment

of a staple-line leak after sleeve gastrectomy. Further studies on larger series are needed to better evaluate definitive outcomes.

Galloro G, Ruggiero S, Russo T, Telesca DA, Musella M, Milone M, Manta R. Staple-line leak after sleve gastrectomy in obese patients: A hot topic in bariatric surgery. *World J Gastrointest Endosc* 2015; 7(9): 843-846 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i9/843.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i9.843

A HOT TOPIC IN BARIATRIC SURGERY: NEW DEDICATED STENTS TO IMPROVE TREATMENT

Laparoscopic sleeve gastrectomy (LSG), first described by Gagner[1] in 2003, has become a well standardized therapeutic option for the surgical treatment of different degrees of obesity[2-6]. Since its introduction, LSG has gained acceptance due to its technical simplicity and the convincing outcomes[7,8]. While specific complications have been reported, including staple-line bleeding and stricture, staple-line leaks are the most serious as they are associated with the greatest morbidity. The incidence of this type of leak after LSG varies in different series[9-11] and its management has been attempted using several different therapeutic approaches[7,10,12-21].

Staple-line leak after LSG reportedly develops in 2.5% of patients undergoing primary sleeve gastrectomies, with a range between 0.5% and 7% in the different series of dedicated bariatric surgeons[6,7,10,16,22,23]. Recently Gagner[24] reported that the incidence of staple-line leak after LSG is decreasing from a generally accepted rate of 2.5% initially to a now 1.1% leak rate in 2013 as reported in a large cohort of 46.133 sleeve gastrectomies, with more than 50% decreased incidence.

Nevertheless, in our opinion, the true rate is probably underestimated. A detailed review by the American Society for Bariatric and Metabolic Surgery reported an overall complication rate after LSG of 0%-24%, with the leakage occurring in 16%-20% of the cases in several series of different experienced surgeons[16] and in patients requiring re-operation after a previous gastric operation performed in no-dedicated to bariatric surgery centers[25].

The gastro-esophageal junction and the proximal stomach near the angle of His are, according to the literature, the most frequent origins of leaks[6,9,11,15], but the reason for this predominance is still unknown. Baker[26] suggested that staple-line leaks are secondary to an impaired healing process and may have multiple risk factors (impaired suture-line healing, poor blood flow, infection, poor oxygenation with subsequent ischemia), but these can be divided into two main categories: mechanical-tissue causes and ischemic causes.

A mechanical mechanism can be invoked when the intraluminal pressure, in association with a low compliance of the gastric tube, exceeds the strength of the staple line. This situation is more likely in patients with difficulties in gastric emptying due to a middle or a distal stenosis of the sleeve[27,28]. In order to reduce the possibility of mechanical failure, the use of buttress material associated with the stapler has been advised, but there is no statistical evidence to support this solution[29].

On the other hand, some Authors claim that most fistulas are not due to staple failure and dehiscence but to ischemia in the gastric wall next to the staple line, likely reflecting devascularization of the gastro-esophageal junction during liberation of the greater curvature or dissection of the greater curvature when electrocautery, Ultracision®, or the LigaSure® system is used[30,31].

Moreover, regardless of the mechanism (mechanical or ischemic) the physiology of the normal sleeve must be considered as well. Studies assessing volume and pressure after LSG[28,32] clearly demonstrated that the removed portion of the stomach (fundus and corpus) is indeed the most expandable, with an important reservoir function. The volume of the sleeve is less than 10% of the volume of the whole stomach and the mean pressure in the sleeve is higher (43 ± 8 mmHg *vs* 34 ± 6 mmHg, $P < 0.005$). Furthermore, the valve function of the cardia and pylorus persists in the gastric sleeve as does the pumping function of the antrum, both of which may further increase the intraluminal pressure.

For these reasons, in obese patients undergoing LSG, although the high intraluminal pressure resulting from the small volume and reduced distensibility of the sleeve confers early satiety, it is also a risk factor for dehiscence of the staple line.

The use of covered, esophageal, self-expandable metal stents (C-SEMS) in the treatment of staple-line leak after LSG has been supported by many authors in recent years[15,17,18,31] even if this is not a widely accepted treatment. C-SEMS permit the comfortable management of this complication, as the temporary fistula-bypass enables enteral nutrition (liquid hyperprotein diet progressing to a soft diet as tolerated) and, if the clinical situation is appropriate, allows the patient to return home temporarily[15]. Nevertheless, reports on the outcome of this procedure are limited and the technical aspects are not well defined.

To select candidates for this form of treatment, the following criteria should be observed: (1) Any abscess or intra-abdominal collection should be previously drained prior to stent placement[31]; (2) Leaks located at the proximal and mid part of the sleeve are the only ones amenable to stent treatment[10,11,17,18,21]; (3) The size of the leak should not exceed 2 cm[17]; (4) The stent should be chosen based on an evaluation of the gastric sleeve diameter, using a larger size in case of doubt, to prevent migration[17,18]; and (5) Late leaks (persisting for more than 4 wk) have the best outcome[15,33,34].

Most authors recommend leaving the stent in place

for a period of 6-8 wk.

In the literature, a highly variable success rate has been reported for this technique[21]. However, most of the published papers have been case reports or small surveys; statistically reliable data are, at this point, lacking.

Stent migration is the main complication of the procedure and it occurs in 30% of the cases in some series[14,17,18,33] and in as many as 42%-50% in others[15,20,35]. The highly variable stent migration rate can be explained by the following: (1) These stents are designed for use in esophageal stenosis and have therefore been adapted in a different site and to a different target; (2) The "abnormal" placement of the stent along the last portion of the esophagus and the gastric sleeve does not ensure proper containment of the stent; and (3) The coating of the stents prevents its integration into the stomach wall but reduces the grip on the wall and therefore allows migration along the gastric tube.

Regardless of the cause, failure of C-SEMS treatment poses a challenge to the surgeon, as successful management of the fistula is then very difficult, with a limited number of options.

Recently, Taewoong Medical Industries developed and marketed Megastent®, a new, fully covered stent dedicated to the treatment of leaks after LSG. Its features resolve some of the above-mentioned problems. The proximal and distal ends of the stent are slightly flared, with a high edge profile permitting good anchorage. The body of the stent is longer than that of other esophageal stents (15, 18 and 23 cm) thus allowing the distal end (with the same shape as the proximal one) to open into the duodenal bulb. The large diameter (24 or 28 mm) ensures optimal adherence of the stent to the sleeve wall, even in the antral segment, conferring adequate radial strength to dilate a possible stenosis. The entire stent is coated, which prevents its integration into the stomach wall due to a granulomatous reaction while the flexibility of the stent nets is sufficient to allow adaptation of the stent to the post-operative anatomy of the gastric sleeve.

In our experience[36], stents 230 cm long and 24 mm in diameter were chosen. The shape of the proximal end of the stent and its angle with respect to the stent body allowed complete coverage of the leak, thus promoting healing. Moreover, the total length of the stent facilitated delivery of the proximal end into the distal esophagus and the distal end into the duodenal bulb, such that the stent body extended through the entire sleeve. In our opinion, this is the main advantage of the Megastent®, as this feature eliminates the pressure gradient in the gastric sleeve. Thus, by establishing a communication with the esophagus and the duodenum, the Megastent® completely resolved the high-pressure condition that had developed in the gastric sleeve, thus promoting healing of the leak hole. The absence of stent migration was likely due to the fact that the length and diameter of the stent allow it to firmly grip the entire gastric sleeve, despite its full-length coating.

In our patients one week after the stent placement a liquid high protein diet was started, followed by a soft diet and discharge 3 d later. The stent was removed after 8 or 9 wk and an upper endoscopy documented complete healing of the leak.

While the procedure described herein was successful, two problems arose during and after stent placement. The first was biliary vomiting, which the patient experienced during the treatment. Pharmacologic therapy with domperidone was mandatory, to reduce the symptoms, which were due to esophageal biliary reflux. The second problem occurred after stent removal: a decubitus lesion in the duodenal bulb that arose, in our opinion, from the decubitus of the free edge of the distal end of the stent, strained by the radial strength of the net.

In conclusion, we recommend that the complicated multi-disciplinary management of patients with gastric leakage treated by stent graft should be confined to specialized centers. Stent placement, in appropriately selected patients, is a safe and effective treatment for staple-line leaks after LSG. This minimally invasive technique has an acceptable complication rate and causes little discomfort to the patient, who avoids the need for more invasive procedures or even total gastrectomy.

Published data about Megastent® are limited but very interesting and encouraging. I like to close this article citing the words by Gagner[24] on a his recent editorial: "I project that staple line leaks will continue to decrease. However, it may never be eliminated completely and nonoperative treatment with endoscopic fully covered metallic stent placement will continue to be the best method in leaks < 12 wk. If the long stents advoked by Galloro *et al*[36] will solve the migration problem seen in earlier series, as well as take care of the mid-body stricture often associated, then we might see less fistula-jejunostomies in the near future".

Obviously, further studies based on larger series are needed to better evaluate patients outcome.

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REVIEW

Endoscopic therapy for weight loss: Gastroplasty, duodenal sleeves, intragastric balloons, and aspiration

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Abstract

A new paradigm in the treatment of obesity and metabolic disease is developing. The global obesity epidemic continues to expand despite the availability of diet and lifestyle counseling, pharmacologic therapy, and weight loss surgery. Endoscopic procedures have the potential to bridge the gap between medical therapy and surgery. Current primary endoscopic bariatric therapies can be classified as restrictive, bypass, space-occupying, or aspiration therapy. Restrictive procedures include the USGI Primary Obesity Surgery Endolumenal procedure, endoscopic sleeve gastroplasty using Apollo OverStitch, TransOral GAstroplasty, gastric volume reduction using the ACE stapler, and insertion of the TERIS restrictive device. Intestinal bypass has been reported using the EndoBarrier duodenal-jejunal bypass liner. A number of space-occupying devices have been studied or are in use, including intragastric balloons (Orbera, Reshape Duo, Heliosphere BAG, Obalon), Transpyloric Shuttle, and SatiSphere. The AspireAssist aspiration system has demonstrated efficacy. Finally, endoscopic revision of gastric bypass to address weight regain has been studied using Apollo OverStitch, the USGI Incisionless Operating Platform Revision Obesity Surgery Endolumenal procedure, Stomaphyx, and endoscopic sclerotherapy. Endoscopic therapies for weight loss are potentially reversible, repeatable, less invasive, and lower cost than various medical and surgical alternatives. Given the variety of devices under development, in clinical trials, and currently in use, patients will have multiple endoscopic options with greater efficacy than medical therapy, and with lower invasiveness and greater accessibility than surgery.

Key words: Weight loss; OverStitch; Aspire; Transoral outlet reduction; Gastric balloon; Orbera; EndoBarrier; Apollo; Primary Obesity Surgery Endolumenal; Gastric bypass; Duodenal sleeve; Intragastric

Core tip: A broad array of endoscopic procedures and

devices will be approved to treat obesity and its metabolic comorbidities in the coming years. A robust body of safety, efficacy, and cost effectiveness data will continue to develop. Endoscopists should have familiarity with target population, benefits, contraindications, and adverse events for each device or procedure. Furthermore, the use of these devices and procedures in the context of a diet and lifestyle management program will be important to ensure success.

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INTRODUCTION

A new paradigm is developing in the treatment of obesity and metabolic disease. Endoscopic procedures in development, in trials, and in use have the potential to bridge the gap between medical therapy and weight loss surgery. Obesity and its comorbidities - diabetes, hypertension, hyperlipidemia, and nonalcoholic fatty liver disease, have become a global epidemic[1]. Dietary modification, exercise, and pharmacologic therapy have been ineffective in arresting the spread of obesity at the population level. Bariatric surgery, which is effective and is utilized by hundreds of thousands of patients each year, can only be performed on a fraction of eligible patients given the current number of practicing surgeons[2]. Endoscopic therapies for weight loss are potentially less invasive, reversible, and lower cost; they may also be repeatable as necessary. These characteristics mean that various endoscopic procedures may play a role as primary therapy, as a bridge to bariatric surgery, or as a revisional procedure after bariatric surgery. Current primary endoscopic bariatric therapies can be classified as restrictive, bypass, space-occupying, or aspiration therapy. These procedures, as well as endoscopic revision of gastric bypass, are discussed herein.

RESTRICTIVE PROCEDURES AND DEVICES

Restrictive procedures remodel the stomach *via* suturing, stapling, or tissue anchor placement to reduce gastric volume.

Incisionless Operating Platform for Primary Obesity Surgery Endolumenal

The Incisionless Operating Platform (IOP) [USGI Medical, San Clemente, California (CA)] can perform full-thickness tissue plication. The platform of the IOP is the four-channel TransPort, which is steerable in four directions and has a 73 cm insertion length. A 4.9-mm endoscope is passed through one channel for endoscopic visualization. The g-Prox, which is capable of 360-degree rotation, has 33-mm stainless steel jaws at its tip to grasp tissue. A helix, called g-Lix, is passed through one channel to grasp tissue and pull it into the jaws of the g-Prox. The g-Cath is advanced through the g-Prox and used to deploy suture anchors. The g-Prox is able to cut suture. The device can be reloaded *in vivo*.

The device has been used to perform the Primary Obesity Surgery Endolumenal (POSE) procedure. To perform POSE, eight to ten plications are created in the gastric fundus (in retroflexion) in two parallel ridges until the fundic apex is brought down to the level of the gastroesophageal junction. The device is then straightened so that the distal gastric body is visualized. A tissue ridge is created with three or four plications in the distal gastric body across from the incisura. Care should be taken to avoid deep g-Lix insertion in this area, in order to avoid injury of adjacent viscera. After the procedure, patients advance from a clear liquid diet to soft pureed diet during the first month, and then to solid food by six weeks. A study of 45 patients with average body mass index (BMI) 36.7 ± 3.8 kg/m^2 reported six-month weight loss of 16.3 ± 7.1 kg or 15.5% ± 6.1%[3]. BMI decreased by 5.8 ± 2.5 kg/m^2 over six months. Adverse events associated with the procedure included one case of low-grade fever and one case of chest pain. POSE is currently being studied in the ongoing randomized sham-controlled ESSENTIAL trial.

OverStitch for endoscopic sleeve gastroplasty

The Apollo OverStitch (Apollo Endosurgery, Austin, TX) can place full-thickness stitches in a variety of interrupted or running patterns. Sutures can be reloaded without endoscope removal. The OverStitch includes a curved needle driver attached to the tip of the endoscope, a catheter-based suture anchor, and an actuating handle attached near the endoscope controls. A double-channel endoscope is necessary.

The OverStitch can be used to perform endoscopic sleeve gastroplasty (Figure 1). Initial human cases were performed in a three-center study: a pilot study of five patients to establish procedure technique, safety, and feasibility followed by 23 cases to study efficacy[4]. Gastroplasty was performed by placing running stitches in a triangular configuration starting in the antrum and working proximally. Each suture was used to create two conjoined triangles. Between 8 and 14 sutures were placed in this fashion. The procedure included fundic reduction in retroflexion. The sleeve was reinforced with interrupted stitches. BMI in the 23 patients studied for efficacy decreased from 34.2 ± 1.1 kg/m^2 to 29.4 kg/m^2. Gastroplasty using a different method was studied in a single-center pilot trial including four patients with average BMI of 35.9 ± 1.2 kg/m$^{2[5]}$. This technique employed two parallel rows of interrupted plications to create a gastric sleeve. The trial established technical feasibility. The multicenter Primary Obesity Multicenter

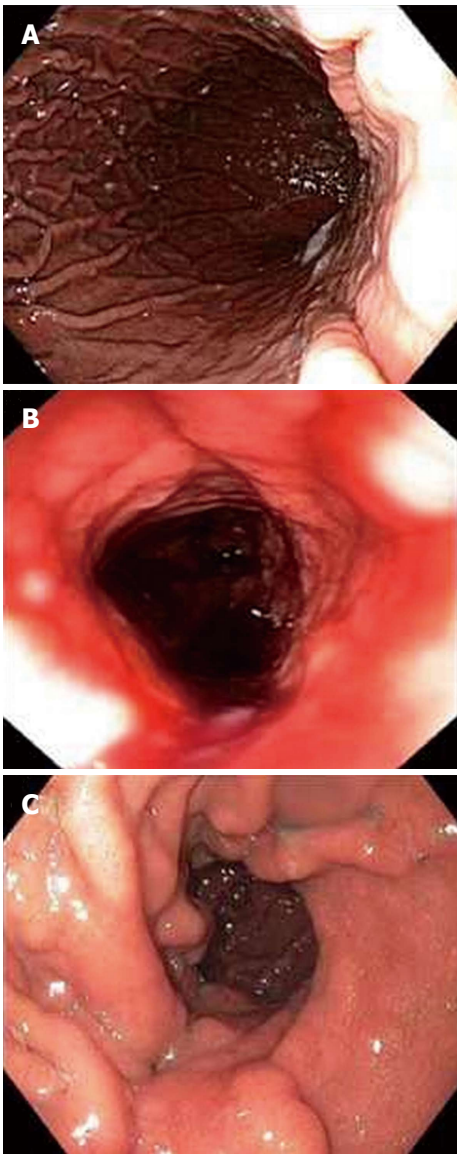

Figure 1 Endoscopic sleeve gastroplasty using Apollo OverStitch: before (A), after (B), and at three months (C)[5].

Incisionless Suturing Evaluation trial to study efficacy of endoscopic sleeve gastroplasty using OverStitch is ongoing in the United States.

EndoCinch for endoscopic gastroplasty

The EndoCinch [Davol, Murray Hill, New Jersey (NJ)] is a superficial-thickness endoscopic suturing system. EndoCinch uses suction to acquire tissue in a hollow capsule, and then passes a needle through the tissue. EndoCinch has been studied for endoscopic gastroplasty in adolescents and adults. A study of gastroplasty in 64 patients with average BMI of 39.9 kg/m^2 reported no serious adverse events[6]. Weight loss of 58.1% ± 19.9% Excess Weight Loss (EWL) was reported after one year. A study of the same procedure in 21 adolescents (age 13-17) with average BMI of 36.2 kg/m^2 reported 67.3% EWL after one year and 61.5% EWL after 18 mo[7]. The device was then modified and named the RESTORe (Davol, Murray Hill, NJ), and was capable of both full-thickness suturing and suture reloading *in vivo*. This device was studied in a two-site trial including 18 patients[8]. There were no significant adverse events. One-year mean weight loss was 11.0 ± 10 kg, or 27.7% ± 21.9% EWL. Half of the patients lost more than 30% of excess weight. Average waist circumference declined by 12.6 ± 9.5 cm. Blood pressure decreased significantly (systolic -15.2 mmHg, diastolic -9.7 mmHg). However, follow-up endoscopy revealed partial or complete release of plications in 13 of 18 patients.

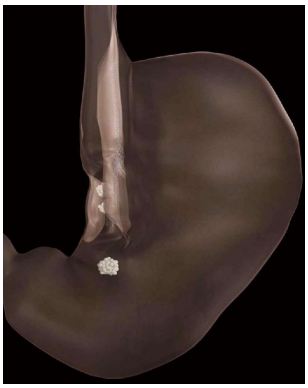

Figure 2 Creation of sleeve using TransOral GAstroplasty[9].

TransOral GAstroplasty

The TransOral GAstroplasty device (TOGA; Satiety Inc, Palo Alto, CA) is a flexible endoscopic stapler capable of full-thickness tissue apposition. The device comprises a stapler and a restrictor. The sleeve stapler comprises a handle and a long but flexible shaft. It also has a short rigid capsule with stapler assembly, two vacuum pods, and a septum at the end. An 8.6 mm endoscope can be passed through the device and retroflexed to visualize the procedure. The stapler creates a vertical sleeve approximately 8 cm long and 2 cm in diameter along the lesser curvature. The restrictor has a long flexible shaft and a short rigid capsule with stapler. It reduces the sleeve outlet to 10-15 mm in diameter. The procedure begins with dilation of the esophagus to 60F with a Savary dilator[9]. The device is inserted into the stomach over a guidewire. Once in position, vacuum apposes the gastric walls, acquiring tissue into the device. Firing the stapler creates a 4.5 cm sleeve around the stapler using titanium staples. The device has to be removed for reloading, and the firing process is repeated once more distally, overlapping the first sleeve. The restrictor is inserted over the guidewire, with the endoscope adjacent to the device. Vacuum acquires tissue into the device at the distal sleeve, and firing the restrictor creates a 2.5 cm long stapled narrowing at the outlet of the sleeve.

TOGA has been studied for endoscopic gastroplasty (Figure 2). A study of 21 patients (average BMI 43.3 kg/m^2) used the first-generation device[10]. There were no serious adverse events, although pain, nausea, vomiting, and temporary dysphagia were reported. Average 6-mo weight loss was 12 kg (24.4% EWL). Endoscopy at that

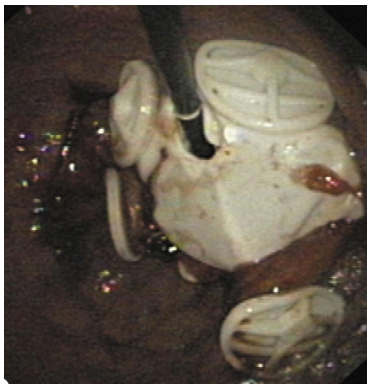

Figure 3 Transoral Endoscopic Restrictive Implant System restrictive diaphragm[14].

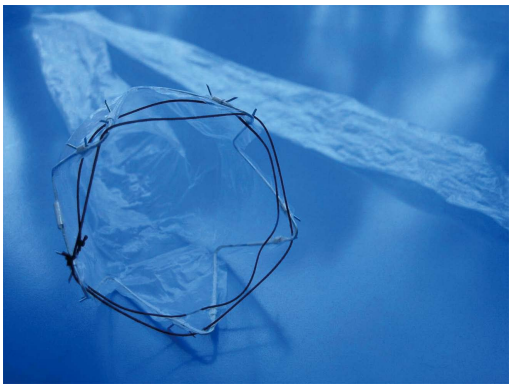

Figure 4 EndoBarrier duodenal-jejunal liner[16].

time found staple line gaps in 13 patients, although every patient had at least a partial sleeve. The second-generation device was studied in 11 patients[11]. In this study, additional distal restrictions were created during retreatment if necessary. No significant adverse events were reported. Six-month weight loss was an average 24.0 kg, and average BMI decreased from 41.6 to 33.1 kg/m^2. A multicenter study of 67 patients reported adverse events including respiratory insufficiency in one case and asymptomatic pneumoperitoneum in another[9]. At one year, patients with BMI $\geqslant$ 40 had 52.2% EWL and patients with BMI < 40 had 41.3% EWL. There were significant improvements in hemoglobin A1c (decline from 7.0% to 5.7%), HDL and triglycerides. A single-center study of 29 patients reported mean BMI decline from 41.7 kg/m^2 to 35.5 kg/m^2 over two years[12]. Average weight loss was 16.8 kg, or 14.9% total body weight loss.

ACE stapler

The ACE stapler (Boston Scientific Corporation, Natick, MA) is an endoscopic stapler with a head capable of both 360-degree rotation and complete retroflexion. A 5-mm endoscope enables visualization; the device is 16 mm in diameter. The stapler head acquires gastric tissue using vacuum suction; firing the stapler creates a full-thickness plication using a 10-mm plastic ring with 8 titanium staples. For gastric volume reduction, up to 8 plications are made in the fundus. Two plications are created in the antrum, which may delay gastric emptying. A prospective safety and feasibility study of gastric volume reduction in 17 patients (median BMI 40.2 kg/m^2) reported median procedure time of 123 min[13]. The most common adverse event was abdominal pain (7 patients); sore throat, diarrhea, nausea, constipation, and vomiting were also reported. All were self-limited. Median EWL was 34.9% (interquartile range 17.8-46.6). Endoscopy performed at 12 mo (in 11/17 patients) revealed 6-9 plications in all participants, as well as durability of gastric volume reduction.

Transoral Endoscopic Restrictive Implant System

Unlike the aforementioned devices, Transoral Endoscopic Restrictive Implant System (TERIS) (Barosense, Menlo Park, CA) is an implanted device. A gastric pouch is created by implanting a diaphragm with a 10-mm orifice. This is attached to the cardia (Figure 3). For implantation, a 22-mm endogastric tube is inserted. A gastroscope with a stapling device is retroflexed, and a full-thickness plication is created in the cardia. An anchor is attached to the plication. This is repeated until five anchors have been implanted. The restrictive diaphragm is then attached to the anchors. A study of TERIS in 13 patients reported three adverse events: One gastric perforation and two cases of pneumoperitoneum[14]. The procedure was modified after these events, and no further adverse events occurred. In total, 12 of 13 implantation procedures were successful. Procedure time was 142 min on average. Weight loss at three-month follow-up was 16.9 kg or 22.2% EWL; median BMI fell from 42.1 to 37.9 kg/m^2.

BYPASS DEVICES AND PROCEDURES

Bypass of the small intestine is thought to have a significant role in the weight loss and metabolic benefits experienced after certain bariatric surgeries. Animal models suggest that duodenal exclusion and accelerated arrival of partially-digested meals to mid-jejunum and ileum are partially responsible for the salutary effects of gastric bypass in diabetes and obesity. Endoscopically implanted devices have been developed to reproduce this effect.

EndoBarrier duodenal-jejunal bypass liner

The EndoBarrier duodenal-jejunal bypass device (GI Dynamics, Lexington, MA) comprises a nickel-titanium implant attached to a 60 cm polymer sleeve (Figure 4). The sleeve extends from the duodenal bulb into the jejunum. It prevents food from contacting the mucosa of the small intestine, but allows pancreaticobiliary secretions to move along the outside of the device to the jejunum. Additionally, it allows food to reach the mid-jejunum earlier. The device is placed endoscopically, with fluoroscopic guidance, under general anesthesia. A guidewire is advanced into the duodenum. The sleeve

and anchor are enclosed in a capsule, which is advanced over the guidewire. The sleeve is deployed in the intestine; once it is fully extended, the anchor is deployed in the duodenal bulb approximately 5 mm distal to the pylorus. Device removal is also performed under general anesthesia. A foreign body hood is placed at the tip of the endoscope, and the device is removed by securing the anchor with a procedure-specific grasping device.

A multicenter randomized trial compared 30 EndoBarrier patients (BMI 48.9 kg/m^2) with 11 controls (BMI 47.4 kg/m^2)[15]. No serious adverse events were reported. However, four of 30 EndoBarrier patients required removal due to migration, obstruction, pain, or anchor dislocation. The EndoBarrier group had significantly higher weight loss at three months, with BMI decrease of 5.5 kg/m^2 *vs* 1.9 kg/m^2 in control patients. Notably, 7 of 8 diabetics in the EndoBarrier group had improvement in diabetes.

A multicenter randomized trial including 25 patients reported successful EndoBarrier implantation in 21 patients, with implantation failure in patients with small duodenal bulb[16]. Adverse events resulted in device explantation in seven of 21 implanted patients, including three cases of bleeding that presented as hematemesis. There was significantly more weight loss in the EndoBarrier group: (8.2 ± 1.3 kg *vs* 2.0 ± 1.1 kg).

A randomized trial of 39 patients assigned 25 patients to EndoBarrier and 14 patients to the control group[17]. At 3 mo, the EndoBarrier group had 22% EWL *vs* 5% EWL in controls. The adverse event rate, including bleeding, migration, and obstruction, was 20%.

A multicenter randomized controlled trial including 77 patients with obesity and type Ⅱ diabetes included 31 patients who completed EndoBarrier therapy and 35 controls who completed dietary intervention[18]. The EndoBarrier group experienced 32.0% EWL *vs* 16.4% in the control group; the EndoBarrier group also had a significantly larger improvement in hemoglobin A1c (P < 0.05 for both). After the EndoBarrier had been removed for 6 mo, EWL was 19.8% *vs* 11.7% in controls (P < 0.05).

A one-year prospective open-label trial of 42 patients reported that 39 patients were successfully implanted[19]. Premature explantation was necessary in 15 patients due to anchor movement in 8 patients, device obstruction in 3 patients, abdominal pain in 2 patients, acute cholecystitis in 1 patient, and one patient request. Initial average BMI was 43.7 ± 5.9 kg/m^2. At 1 year, the 24 patients with EndoBarrier in place experienced weight loss of 22.1 ± 2.1 kg or 47.0% ± 4.4% EWL, and BMI decline of 9.1 ± 0.9 kg/m^2. Waist circumference decreased significantly, from 120.5 ± 6.8 cm to 96.0 ± 2.6 cm. Statistically significant improvements were also reported in blood pressure, hemoglobin A1c, cholesterol, low-density lipoprotein, triglycerides, and prevalence of metabolic syndrome.

A modified EndoBarrier with a 4-mm flow-restriction orifice was implanted in 10 patients with average BMI of 40.8 kg/m^2[20]. Eight of 10 patients in the trial developed abdominal pain, nausea, and vomiting; they required balloon dilation of the restrictive orifice. Weight loss at three months was 16.7 ± 1.4 kg.

SPACE-OCCUPYING DEVICES

Space-occupying devices displace volume and induce gastric distention, but may also alter gastrointestinal motility, nutrient transit, and hormone levels[21]. One space-occupying device, the intragastric balloon, was described in 1982 and approved for American use in 1985[22]. In the intervening decades, balloons have built a track record of safety and efficacy in Europe, and are likely to reappear in the United States. The intragastric balloon has found a role as a bridge to bariatric surgery in patients with high risk for anesthesia, temporary use in patients eligible for bariatric surgery but unwilling to undergo it, and temporary use in patients not eligible for bariatric surgery as part of an integrated medical weight loss program[23]. Space-occupying devices other than balloons are in clinical trials.

Orbera intragastric balloon

The Orbera (formerly BioEnterics) intragastric balloon (Apollo Endosurgery, Austin, TX) is an endoscopically implanted spherical silicone elastomer device. The balloon is placed in the stomach and then filled with saline (and where allowed, methylene blue dye, which alters urine color in case of balloon perforation). The balloon is resistant to gastric acid, and is indicated for insertion for up to six months. The device is inflated in the gastric fundus during endoscopic visualization using 500-750 mL saline and 10 mL methylene blue.

Orbera balloon placement was studied in a meta-analysis of 3698 patients[24]. Early device removal was required in 4.2% of patients; reported adverse events included nausea, vomiting, bowel obstruction (0.8%), and gastric perforation (0.1%). Average weight loss after six months was 14.7 kg or 32.1% EWL, with drop in BMI of 5.7 kg/m^2. The largest study in the meta-analysis, which included 2515 patients, reported average decrease in BMI of 9.0 kg/m^2 over six months[25]. Notably, statistically significant improvement was reported in blood pressure, fasting glucose, and lipid profile. Significant decrease in or normalization of hemoglobin A1c was reported in 87.2% of the 488 diabetic patients in the study. Two instances of mortality were reported, both in patients with prior gastric surgery.

The long-term weight loss trend after removal of the Orbera balloon was studied in 500 patients[26]. Average BMI before therapy was 43.7 kg/m^2. Success was defined as ⩾ 20% EWL. At the time of balloon removal, 83% of patients had reached this threshold, with average loss of 23.9 ± 9.1 kg and BMI loss of 8.3 kg/m^2. In the 41% of patients available five years after balloon removal, the successful group had average loss of 7.3 ± 5.4 kg and average BMI loss of 2.5 kg/m^2.

The effectiveness of a second Orbera balloon place-

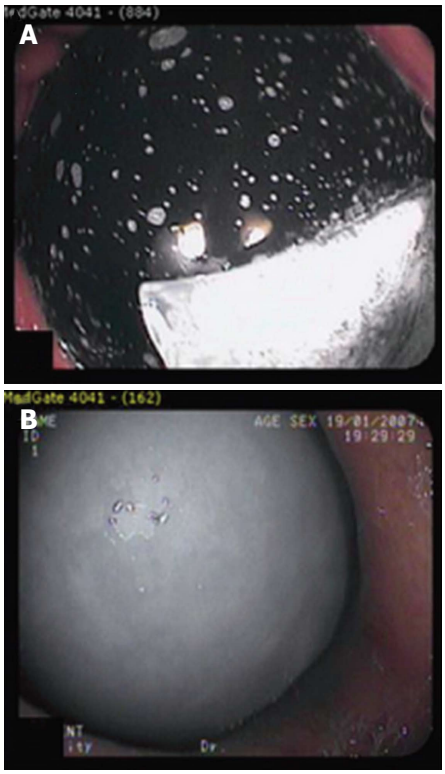

Figure 5 The Orbera intragastric balloon (A) and Heliosphere BAG (B)[34].

ment was studied in a prospective trial of 118 patients[27]. The balloon was replaced immediately in 8 patients, replaced after a balloon-free interval in 11 patients, and not replaced in 99 patients. Those patients undergoing a second balloon placement with a balloon-free interval regained 13.6 kg on average during that interval. The second balloon therapy did result in weight loss, although its magnitude was smaller than that of the initial therapy (9.0 kg *vs* 14.6 kg, or 18.2% EWL *vs* 49.3% EWL). The effect of second balloon placement dissipated by the third year of follow-up. A study of 112 patients undergoing a second Orbera balloon placement within one month of removing the first balloon found average BMI loss of 2.5 kg/m^2 with the second balloon in addition to BMI loss of 6.5 kg/m^2 with the first balloon[23].

The utility of the Orbera balloon as a bridge to gastric bypass was studied in 60 consecutive super-super obese subjects with average BMI of 66.5 ± 3.4 kg/m^2[28]. The balloon was placed in 23 patients, while 37 patients went to surgery without prior balloon therapy. In the Orbera group, the balloon was in place for 155 ± 62 d. The balloon group achieved BMI loss of 5.5 ± 1.3 kg/m^2 at the time of gastric bypass, as well as statistically significant decreases in systolic blood pressure and gamma-glutamyl transpeptidase. The operative time for performance of gastric bypass was shorter in the Orbera group (146 ± 47 *vs* 201 ± 81 min). The Orbera group also experienced significantly fewer major adverse events (defined as conversion to laparotomy, ICU stay longer than 2 d, and total hospital stay longer 2 wk): 2 events *vs* 13 in patients who did not have balloon placement. Weight loss was similar between groups one year after gastric bypass.

The metabolic effects of Orbera balloon placement were examined in a prospective trial including 130 patients (average BMI 43.1 kg/m^2)[29]. Premature balloon explantation was required in ten patients due to intolerance, abdominal pain, or vomiting. Patients were maintained on a 1000-1200 daily kilocalorie diet during the 6-mo balloon therapy period. Average weight loss was 13.1 kg, with decrease in prevalence of class Ⅳ obesity from 23% to 8%. Metabolic effects included decrease in the prevalence of hyperglycemia from 50% to 12%, and hypertriglyceridemia from 58% to 19%. Patients with decrease in BMI of greater than 3.5 kg/m^2 experienced a significant decrease in the prevalence of severe hepatic steatosis from 52% to 4%. Weight regain occurred in 50% of the patients in the follow-up period (median 22 mo) after balloon removal.

Dietary counseling during Orbera balloon therapy was been found to be beneficial in a study of 28 patients[30]. Patients saw a dietitian weekly for two weeks, every two weeks for one month, and then monthly while the balloon was in place. BMI declined from 32.4 ± 3.7 kg/m^2 to 28.5 ± 3.7 kg/m^2 with therapy. Of the patients who achieved at least 20% EWL, 85% had attended at least half of dietitian appointments. Of patients failing to reach 20% EWL, 75% had missed at least half of dietitian appointments.

Orbera balloon therapy is associated with mental health benefits in patients with depression[31]. In this study, 100 consecutive female patients were characterized as depressed (65 patients) or non-depressed (35 patients) using the Beck Depression Inventory score. Other characteristics were similar between groups. Weight loss was similar between groups (39.3% EWL in depressed patients *vs* 36.1% EWL in non-depressed patients). The Depression Inventory score improved from 20.3 ± 8.5 to 7.9 ± 5.6 during balloon therapy. Resolution of depression occurred in 70.8% of the depressed patients, with a decrease in the prevalence of severe depression (27.7% to 1.5%).

Heliosphere BAG

The Heliosphere BAG is filled with 950 mL of air rather than fluid. The Heliosphere BAG has been compared with the Orbera balloon (Figure 5)[32]. Sixty patients with average BMI of 46.3 kg/m^2 were randomly assigned. The Heliosphere group achieved BMI decrease of 4.2 kg/m^2, *vs* 5.7 kg/m^2 in the Orbera group. The Heliosphere group had significantly longer extraction procedure time and significantly more discomfort during extraction.

A prospective study of 91 patients compared the Orbera balloon (73 patients) with Heliosphere BAG (18 patients, mean BMI 45.2 kg/m^2)[33]. Balloons were implanted for six months, and 13.2% were removed early due to intolerance. Average weight reduction at six months was 13.3 kg, and BMI reduction was 5 kg/m^2; 88% of weight reduction occurred in the first three

months. Weight loss was similar between balloon types. The Heliosphere BAG deflated and passed spontaneously in 2 cases. Balloon extraction was difficult in 8 cases, and a rigid esophagoscope as required in 4 cases; laparoscopic surgery was required to remove BAG in 1 case. BAG was significantly more likely to result in retrieval complications.

A nonrandomized study compared Heliosphere BAG with the Orbera balloon in patients who failed six months of medical and dietary weight loss therapy[34]. The Orbera balloon was placed in 19 patients (BMI 45.6 ± 9 kg/m^2), and the Heliosphere BAG was placed in 13 patients (BMI 45.0 ± 8 kg/m^2). The Orbera balloon was more effective, with weight loss of 19.0 kg *vs* 13.0 kg for Heliosphere BAG. One patient with the Orbera balloon required removal for persistent nausea and vomiting at one month. There was one mortality in the Orbera group 13 d after placement.

Reshape Duo intragastric balloon

The Duo intragastric balloon (Reshape, San Clemente, CA) contains two silicone spheres filled with a total of 900 mL of saline, which prevents migration if one balloon deflates. A prospective trial of Duo included 30 patients at three centers (21 Duo *vs* 9 controls)[35]. Both groups received diet and exercise counseling. Four of the 21 Duo patients were readmitted for nausea, and two patients were found to have gastritis at the time of balloon removal. After 48 wk, 30% of the Duo patients achieved 25% EWL, *vs* 25% of the control patients.

Obalon intragastric balloon

The Obalon intragastric balloon (Obalon Therapeutics, Carlsbad, CA) is a 250-mL gas-filled balloon which is swallowed under fluoroscopic visualization rather than inserted endoscopically. The balloon is enclosed in a capsule. A catheter, which extends through the esophagus and outside the mouth, is used to fill the balloon with gas. The balloon is removed endoscopically; it is punctured and then grasped with forceps for extraction. If the balloon is tolerated and induces weight loss, a second balloon can be swallowed at 4 wk and a third balloon at 8 wk. A study including 17 patients with BMI ranging from 27 to 35 kg/m^2 reported that 98% of balloons were swallowed successfully[36]. Abdominal pain (in 76%) and nausea (in 41%) were the most frequent adverse events. All balloons were removed endoscopically, under conscious sedation, at 12 wk.

Transpyloric Shuttle

The Transpyloric Shuttle (BAROnova, Goleta, CA) is made of a large spherical bulb attached to a smaller cylindrical bulb by a flexible tether. The cylinder is small enough to enter the duodenal bulb with peristalsis, and pulls the spherical bulb to the pylorus. The spherical bulb is too large to traverse the pylorus, but occludes it intermittently to reduce gastric emptying. The device is delivered transorally *via* catheter and removed endoscopically. A single-center nonblinded prospective trial of 20 patients with average BMI of 36.0 kg/m^2 reported loss of 8.9 ± 5.2 kg, or 31.3% ± 15.7% EWL, at 3 mo[37]. Six-month weight loss was 14.6 ± 5.7 kg, or 50.0% ± 26.4% EWL. Two patients required early removal due to persistent ulcer.

SatiSphere

The SatiSphere (Endosphere, Columbus, OH) is made from a preformed memory wire with curled ends that conforms to the shape of the duodenum. The device anchors itself in the distal stomach and in the duodenum. Several mesh spheres are mounted along the wire. SatiSphere slows duodenal transit of food, which may alter satiety hormones levels and glucose metabolism. A trial of 31 patients with average BMI of 41.3 kg/m^2 compared 21 SatiSphere patients with 10 controls[38]. Device migration was reported in 10 of 21 implanted patients. Emergency surgery was necessary in two patients. Of patients completing the trial, three-month weight loss was 6.7 kg in the SatiSphere group *vs* 2.2 kg in controls. SatiSphere was associated with delayed glucose absorption, delayed insulin secretion, and altered glucagon-like peptide-1 kinetics.

ASPIRATION THERAPY

AspireAssist

The AspireAssist (Aspire Bariatrics, King of Prussia, PA) is a modified percutaneous endoscopic gastrostomy tube with an external accessory capable of aspirating a portion of ingested caloric intake. The device includes a large-bore gastrostomy tube with holes in the intragastric portion; this is attached to a skin port with a connector and valve placed at the skin (Figure 6). A 600-mL reservoir allows for flushing and aspiration of gastric contents after meals.

A randomized trial of 18 patients assigned 11 to AspireAssist and 7 to the control group; all patients underwent a 15-session diet and behavioral education program[39]. At one year, 10/11 Aspire patients and 4/7 control patients remained in the trial. Weight loss was 18.6% ± 2.3% of total body weight in Aspire patients *vs* 5.9% ± 5.0% in controls. Of the ten Aspire patients in the trial at one year, seven chose to continue for another year; this group reached 20.1% ± 3.5% total body weight loss. Notably, there was no evidence of increased food intake to compensate for the aspirated food. Reported adverse events included abdominal pain at the aspiration tube site, which improved after the device was redesigned; infection in three patients requiring topical medication or oral antibiotics; and persistent gastrocutaneous fistula (which eventually closed spontaneously) in one of the four patients who underwent aspiration tube removal. A prospective multicenter clinical trial, PATHWAY, is ongoing.

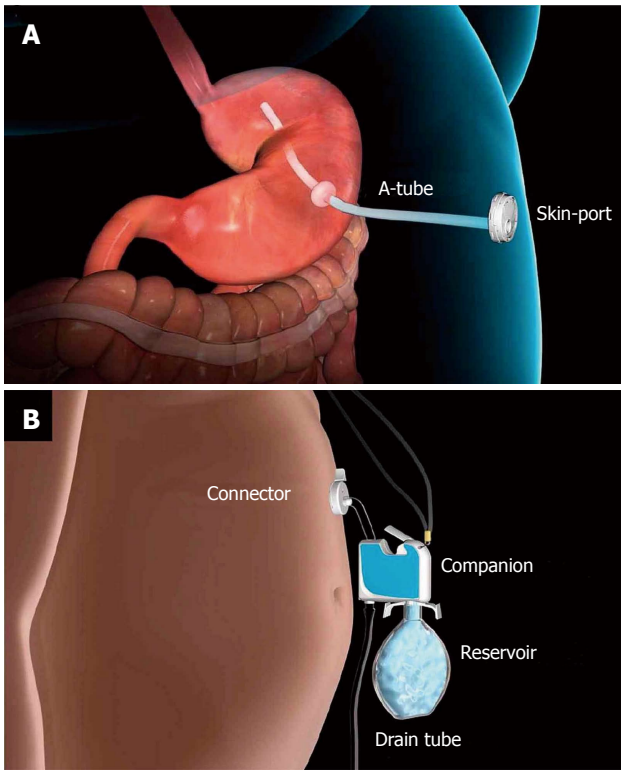

Figure 6 The Aspire aspiration tube (A) and AspireAssist (B)[39].

ENDOSCOPIC REVISION OF GASTRIC BYPASS

Roux-en-Y gastric bypass can induce 56.7%-66.5% EWL during the two years after surgery[40]. Comorbidities associated with obesity, including hypertension, diabetes, obstructive sleep apnea, and hyperlipidemia, often improve or resolve. It is postulated that small gastric pouch size and gastrojejunal anastomosis aperture create a restrictive effect. A weight plateau typically occurs as equilibrium in energy balance is reached 12 to 18 mo after gastric bypass[41]. However, approximately 20% of patients fail to achieve 50% EWL in the first year after gastric bypass. Additionally, 30% of patients regain weight by 18 to 24 mo after bypass; average regain of 18 kg has been reported at 2 years[42,43]. The long-term outcome of gastric bypass is affected by a number of factors, including preoperative BMI and postoperative diet and lifestyle[44]. Weight regain may be induced by neuroendocrine-metabolic dysregulation resulting in a starvation-like response[45,46]. Anatomic factors may also play a role: increased gastrojejunal anastomotic aperture may result in loss of restriction, and has been associated with weight regain in a linear fashion[5,47,48].

Surgical procedures, including reconstruction of the gastrojejunal anastomosis, placement of an adjustable gastric band over the gastric pouch, surgical revision of the pouch, and distal gastric bypass, are available to treat weight regain; however, few patients undergo surgical revision. Revision surgery is challenging in the context of older patients, altered anatomy, scarring, and adhesions; complication and mortality rates are higher than that of primary gastric bypass[49,50]. Endolumenal revision is an attractive option in this patient set. Endoscopic suturing, plication, and sclerotherapy are discussed here.

EndoCinch for transoral outlet reduction

The EndoCinch (Bard Davol, Murray Hill, NJ), as described above for endoscopic gastroplasty, is a superficial-thickness suturing device which uses suction to acquire tissue. The EndoCinch has been used to perform transoral outlet reduction (TORe), or endoscopic revision of gastric bypass. First, the entire gastric margin of the gastrojejunal anastomosis is ablated with argon plasma coagulation. The aperture of the gastrojejunal anastomosis is then reduced by placing interrupted stitches at the anastomotic margin, across the anastomotic opening. Cinching the sutures apposes the anastomotic margin, reducing the diameter of the anastomosis. The volume of the gastric pouch can be reduced by creating ridges and suturing them together.

Use of the EndoCinch for TORe was first reported in 2004[51]. The device was used in RESTORe, a randomized sham-controlled double-blinded multicenter trial which resulted in level 1 evidence for the effectiveness of endoscopic suturing in revision of gastric bypass[52]. Seventy-seven patients with gastrojejunal anastomosis aperture larger than 20 mm were randomized to TORe or to sham endoscopy. Average BMI was 47.6 kg/m^2. Anastomotic aperture of < 10 mm was achieved in 89% of TORe patients. There was no difference in the adverse event rate between groups, and no perforations occurred. In the intent-to-treat analysis, total body weight loss was 3.8% in TORe patients *vs* 0.3% in the sham group (P = 0.02). Weight stabilization or weight loss was achieved in 96% of TORe patients during the 6-mo follow-up period.

OverStitch for TORe

Apollo OverStitch, as described in detail above for endoscopic sleeve gastroplasty, is reloadable *in vivo* and is capable of placing full-thickness sutures in a variety of stitch patterns. After TORe is performed to reduce the aperture of the gastrojejunal anastomosis, gastric pouch size can be reduced and fistulas can be closed during the procedure. TORe should be performed using general anesthesia, endotracheal intubation, and carbon dioxide insufflation. An overtube should be placed. Upper endoscopy is performed to ablate the margin of the gastrojejunal anastomosis. This can be performed using end-firing argon plasma coagulation (at 30 watts) to create a ring 5-10 mm thick around the margin of the anastomosis, or performance of endoscopic mucosal resection around the anastomosis. Anastomotic reduction can be performed using an interrupted technique, in which stitches are placed across the anastomosis and then cinched to appose its margins. Alternatively, a pursestring suture technique can be used (Figure 7). The pursestring technique potentially confers a number of benefits compared with the interrupted technique. It

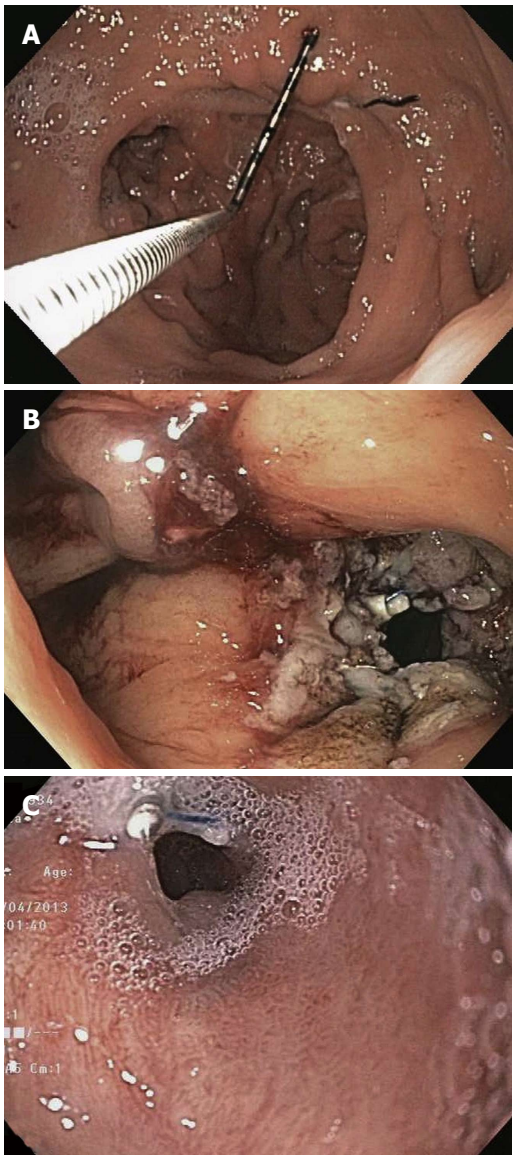

Figure 7 Gastrojejunal anastomosis before (A), immediately after (B), and six months after (C) TORe using Apollo OverStitch[54].

allows the use of a sizing balloon, which ensures precise control of final anastomosis aperture. It reinforces the entire circumference of the anastomosis against future dilation, and against transient compliant dilation during meals. In contrast, the interrupted technique closes part of the lumen entirely, but does not reinforce the remaining anastomotic margin, and the final anastomotic diameter cannot be precisely controlled. To perform anastomotic reduction using the pursestring technique, a running pursestring suture is placed around the anastomosis. A controlled radial expansion balloon is passed through the second channel of the endoscope and inflated to 8-10 mm. The pursestring is tightened around the balloon, and the suture is cinched. A second pursestring can be placed around the anastomosis for reinforcement.

Endoscopic revision of gastric bypass using OverStitch proved effective in a study of 25 patients[53]. Gastrojejunal anastomosis aperture was reduced from 26.4 mm to 6 mm on average. No significant adverse events were reported. Patients lost an average 11.7 kg during the 6-mo follow-up period, or 69.5% of regained weight. Endoscopic revision of gastric bypass using the superficial-thickness EndoCinch and full-thickness OverStitch were directly compared in a matched cohort study[54]. The interrupted stitch technique was used in both groups, and the technique used in the EndoCinch patients was the same technique used in the RESTORe trial. One hundred eighteen patients (59 in each group) were sequentially matched by gastrojejunal anastomosis aperture, then BMI, and then age. Average weight loss at six months was significantly higher in patients undergoing full-thickness suturing (4.4 ± 0.8 kg with EndoCinch *vs* 10.6 ± 1.8 kg with OverStitch, $P < 0.01$). One-year weight loss was also significantly higher in the OverStitch group (2.9 ± 1.0 kg with EndoCinch *vs* 8.6 ± 2.5 kg with OverStitch, $P < 0.01$).

IOP for Revision Obesity Surgery Endolumenal

The IOP (USGI Medical, San Clemente, CA), as described in detail above for the POSE procedure, is capable of performing full-thickness tissue plication by placement of tissue anchors. The platform has been optimized specifically for endoscopic revision of gastric bypass, called Revision Obesity Surgery Endolumenal (ROSE). ROSE entails reduction of dilated gastric pouch and gastrojejunal anastomosis aperture. A prospective study included 20 patients with weight regain[55]. The procedure was technically successful in 85%, with reduction of anastomotic aperture by an average of 65% and reduction of gastric pouch length by 36%. Anastomotic aperture was reduced to an average of 16 mm. Average weight loss was 8.8 kg after 3 mo. A subsequent iteration of the device was studied in five patients, with all five patients losing weight (average weight loss was 7.8 kg)[56]. A prospective multicenter trial of 116 patients with dilated gastrojejunal anastomosis and gastric pouch achieved technical success in 97%[57]. Gastrojejunal anastomosis aperture was reduced by an average of 50%, and the gastric pouch was shortened by an average of 44%. No significant procedural complications occurred; three patients had superficial esophageal tears, one of which required placement of an endoscopic clip. Pharyngitis was reported in 41% of patients, nausea and vomiting in 12%, and abdominal pain in 11%. During the 6-mo follow-up period, patients lost 32% of the weight regained after Roux-en-Y gastric bypass. Patients with anastomotic aperture of less than 10 mm at the end of the procedure experienced 24% EWL. The device has since been further optimized for revision of gastric bypass.

StomaphyX

StomaphyX (EndoGastric Solutions, Redmond, Washington) is a full-thickness tissue plication platform capable of endoscopic revision of gastric bypass. It uses vacuum to acquire a fold of the gastric pouch.

Polypropylene H-fasteners are passed through the tissue to create full-thickness plications. Without removal of the device, 3 to 4 rows with 4 to 6 plications each (a total of 12-24) are created circumferentially around the margin of the anastomosis.

A study of StomaphyX in 39 patients with average BMI of 39.8 kg/m^2 reported no adverse events[58]. EWL was 13.1% after 3 mo and 19.5% after 1 year. A subsequent study of 64 patients with average BMI of 39.5 kg/m^2 reported placement of an average 23 plications, resulting in reduction of anastomotic diameter from 22 mm to 9 mm[59]. One patient had bleeding that did not require transfusion; no other significant adverse events were reported. During follow up (average 5.8 mo), patients lost an average 7.6 kg. A retrospective study of 59 patients with mean BMI of 36.1 kg/m^2 reported mean weight loss of 3.8 kg and 11.5% EWL after 6 mo[60]. However, endoscopy in 12 patients at an average of 18 mo after revision showed no sustained reduction in pouch or anastomosis size. Mean follow-up duration was 41 mo, with average loss of 1.7 kg; 35.8% of patients had actually gained weight by this point. A randomized sham-controlled single-blind trial of StomaphyX revision with SerosFuse fasteners was terminated prematurely due to failure to reach preliminary efficacy targets. There was one adverse event in the StomaphyX group, and laparoscopic exploration and repair were necessary. A total of 45 StomaphyX patients and 29 sham patients completed 1-year follow-up. Of these, 22.2% of the StomaphyX patients and 3.4% of the sham patients achieved 15% excess BMI loss ($P < 0.01$). The StomaphyX group had significantly more weight loss at 6 and 12 mo ($P \leqslant 0.05$).

Endoscopic sclerotherapy

Endoscopic sclerotherapy entails injection of a sclerosant, such as sodium morrhuate, around the gastrojejunal anastomosis to reduce compliance and aperture. The procedure can be performed under conscious sedation in many patients. The anastomotic aperture should be measured prior to injection, as measurement afterwards will be inaccurate due to transient edema. A test dose of the sclerosing agent should be injected at the rim of the anastomosis, and the patient should be monitored for an adverse reaction before further injection. Approximately 2 mL should be injected into the submucosa at the margin of the gastrojejunal anastomosis until a bleb forms. Several such injections are performed around the anastomotic margin, for a total of 10-25 mL[61]. Overinjection is indicated by dark red or black discoloration and subsequent overt bleeding. Intravenous ciprofloxacin should be given as prophylaxis prior to the procedure, followed by a five-day course of liquid ciprofloxacin or trimethoprim-sulfamethoxazole. The patient should can start a liquid diet the day after the procedure and advance to a regular diet during the month after the procedure. Sclerotherapy can be repeated every 3-6 mo until the anastomosis aperture has reached a target of 12 mm; two or three sessions are often necessary[62]. The development of scar tissue after each sclerotherapy session can eventually make submucosal injection difficult.

Endoscopic sclerotherapy has proven effective in arresting weight regain after gastric bypass. One study including 28 patients reported that most patients (64%) lost more than 75% of regained weight[62]. An average of 2.3 sessions was required. Notably, patients with anastomotic aperture larger than 15 mm did not benefit. A study of 32 patients reported arrest or reversal of weight regain in 91.6% of patients at 1 year[61]. A study of 71 patients reported arrest or reversal of weight regain in 72% of patients after 1 year[63]. A recent study of 48 patients undergoing sclerotherapy reported average loss of 1.45 kg during a follow-up period averaging 22 mo[64]. Although weight regain was arrested, weight loss after sclerotherapy was not significant. The largest published series included 231 consecutive patients with mean anastomosis diameter of 19 mm undergoing 575 sclerotherapy sessions[65]. Weight regain was arrested in 78% of patients at one year after sclerotherapy. Average weight loss at six months was 4.5 kg. Bleeding occurred in 2.4%, with 57% of those requiring endoscopic clip placement. Transient elevation in blood pressure was observed in 15%, and was associated with higher injection volume. Small ulcerations were found on follow-up endoscopy in 1%.

CONCLUSION

The global obesity epidemic has continued to expand despite the availability of diet and lifestyle counseling, pharmacologic therapy, and bariatric surgery. Endoscopic therapies for weight loss have the potential to transform the treatment of obesity. Given the variety of devices under development, in clinical trials, and in use, patients will have multiple options with greater efficacy than medical therapy, and with lower invasiveness and greater accessibility than bariatric surgery. Endoscopic therapies have also proven safe and effective for revision of bariatric surgery. As data for safety, efficacy, and cost effectiveness of endoscopic therapies accumulates over the coming years, endoscopists will play a leading role in the management of obesity and metabolic disease.

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REVIEW

Serrated polyps of the colon and rectum: Endoscopic features including image enhanced endoscopy

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Abstract

In this review, I outline the characteristic endoscopic findings of serrated lesions of the colorectum based on image enhanced endoscopy (IEE). Histopathologically, lesions with serrated structures are typically classified into the following three types based: hyperplastic polyps (HPs), traditional serrated adenomas (TSAs), and sessile serrated adenoma/polyps (SSA/Ps). Both HP and SSA/P often present as dark-green colors on auto fluorescence imaging (AFI) colonoscopy that are similar to the normal surrounding mucosa. In contrast, TSAs often have elevated shapes and present as magenta colors that are similar to the tubular adenomas. The superficial type of TSA also includes many lesions that present as magenta colors. When SSA/Ps are associated with cytological dysplasia, many lesions present with magenta colors, whereas lesions that are not associated with cytological dysplasia present with dark-green colors. When observed *via* narrow band imaging (NBI), many SSA/P include lesions with strong mucous adhesions. Because these lesions are observed with reddish mucous adhesions, we refer to them as "red cap sign" and place such signs among the typical findings of SSA/P. Because the dilatation of the pit in SSA/P is observed as a round/oval black dot on magnified observations, we refer to this finding as Ⅱ-dilatation pit (Ⅱ-D pit) and also positioned it as a characteristic finding of SSA/P. In contrast, dilatations of the capillary vessels surrounding the glands, such as those that occur in tubular adenoma, are not considered to be useful for differentiating HPs from SSA/Ps. However, in cases in which SSA/P is associated with cytological dysplasia, the dilatation of capillary vessels is observed in the same area. When submucosal layer invasion occurs in the same area, the blood flow presents with irregularities that are similar to those of common colorectal cancer at an early stage and disappears as the invasion proceeds deeply. The surface pattern of invasive cancer that is observed at the tumor surface is also likely to disappear. Based on the above results, we considered that the differentiations between HP and TSA, between TSA and SSA/P, and between HP and SSA/P might become easier due to the concomitant use of white light observation and IEE. We

also concluded that AFI and NBI can be useful modalities for SSA/P lesions associated with cytological dysplasia.

Key words: Image enhanced endoscopy; Hyperplastic polyp; Early colon cancer; Traditional serrated adenoma; Sessile serrated adenoma/polyp

Core tip: Histopathologically, "serrated lesions" are categorized by the World Health Organization into three groups: (1) hyperplastic polyp; (2) traditional serrated adenoma; and (3) sessile serrated adenoma/polyp (SSA/P). I have discussed the findings associated with each lesion type as observed on image enhanced endoscopy. Regarding HPs and SSA/Ps, it is easy to differentiate both lesions. Especially, dilatations of the gland orifices are frequently observed in SSA/P and appear as blackish dotted orifices. And a thick mucous adhesion referred to as a "mucous cap" can be confirmed as red mucus on narrow band imaging observation and can be recognized when it adheres to the surface of a "red cap" polyp in SSA/P.

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INTRODUCTION

Among colon polyps, hyperplastic polyps (HPs) have previously been defined as non-neoplastic lesions and are not considered to be lesions that are indicated for endoscopic treatment[1]. However, since the mid-1980's, reports on HP lesions associated with neoplastic changes have become more common[2,3] and it has been suggested in 1990 that the serrated lesions that are associated with neoplastic changes be referred to as serrated adenomas[4] to differentiate them from HPs. Later, in 2003, there was a report of a lesion with a gland structure that was an extremely similar to that of HP, and this lesion invaded into the submucosal layer (SM) primarily in the right colon[5].

Therefore, several guidelines for colon polyps have been published regarding the indications for the endoscopic treatment of sessile serrated lesion in the past several years[6-9]. However, the details of the endoscopic characteristics of sessile serrated lesions (SSLs) have obviously never been described in terms of guidelines. Particularly, the macroscopic appearances of SSLs present as flat elevations in the proximal colon, and it has been suggested that proximal serrated lesions, which can be more difficult to find than lesions in the distal portion due to the fold, might have an important role in this limitation[10-13]. Thus, Butterly *et al*[14] recommended that more time should be taken to withdraw to enable the detection of SSLs in the proximal colon.

Here, we would like to illustrate the characteristic endoscopic findings from these serrated lesions of the colorectum, particularly as observed with image enhanced endoscopy (IEE). These endoscopic images are observed with a Lucera Elite system® (Olympus Medical Science, Tokyo Japan).

ENDOSCOPIC FEATURES WITH PATHOLOGICAL FINDINGS

Histopathologically, "serrated polyps" can be categorized into the following three types according to the World Health Organization (WHO) classification[15] (Table 1): (1) HPs; (2) traditional serrated adenomas (TSAs); and (3) sessile serrated adenoma/polyps (SSA/Ps). All of these lesions have serrated structures within the crypts from the histological perspective: however, the extent to which these tissue diagnostic standards have become widespread and commonly understood among gastroenterological pathologists across the world remain unclear[16]. Especially, the definition of all sessile serrated adenomas and sessile serrated polyps are not as neoplastic changed lesions despite of the usage of "adenoma". Therefore there is a strong possibility to confuse whether neoplastic or non-neoplastic lesions for SSA/Ps.

Here, the conventional endoscopic features, including those from magnified examinations, related to SSLs are reviewed based on previous reports[9,17-19].

HP (Figure 1)

HPs can be categorized into the following three subtypes based on histological findings: (1) microvesicular HPs: MVHPs (Figure 1A); (2) goblet-cell rich HPs: GCHPs (Figure 1B); and (3) mucin-poor HPs: MPHPs (Figure 1C). Of these, MVHPs are thought to often be found often in the right side of the colon, and GCHPs are often found in the left side of the colon. The incidence of MPHPs is low[20-23]. All of these lesions are small in diameter and treated as non-neoplastic lesions[24].

The characteristic endoscopic findings of these HPs are that they generally present with pale colors and the boundaries with the normal surrounding mucosa are occasionally obscure. Adhesions of the mucus are also commonly observed on the surface. Large tumors are often found in the right side of the colon and differentiation between the above-mentioned MVHPs and SSA/Ps can be necessary. HPs characteristically presents with primarily asteroid shaped pits (type Ⅱ pits) on magnifying endoscopy (ME).

SSA/P (Figures 2-4)

Prior to the proposal of a definition of SSA/Ps based on pathological criteria, SSA/Ps were termed "large HPs[25]", "giant HPs[26]", *etc.* Therefore, these sessile serrated lesions thought to be defined as a single entity.

SSA/Ps are primarily located in the right side of the colon and account for 3%-9% of all of the colorectal

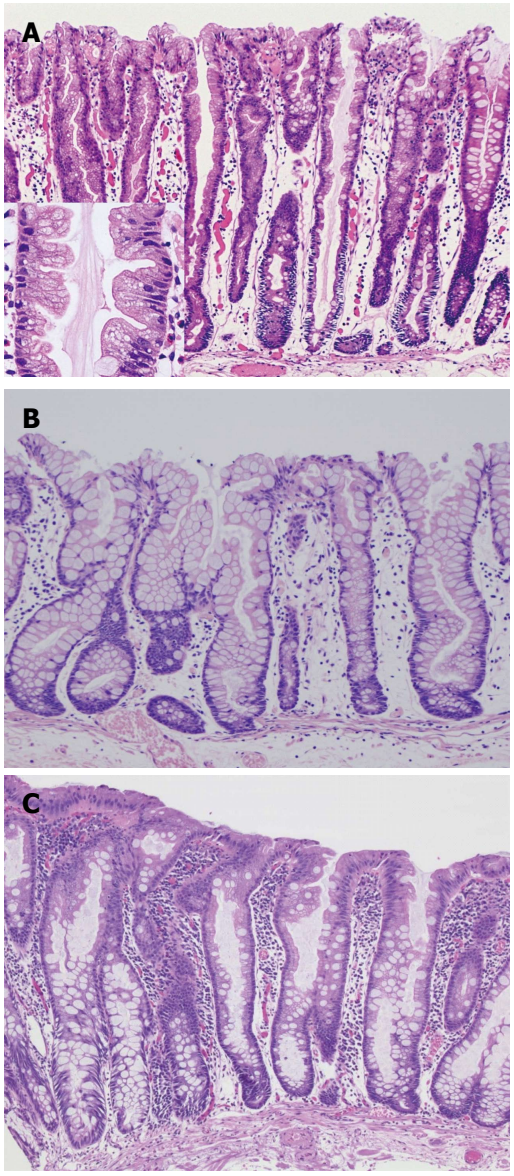


Figure 1 Histological findings of hyperplastic polyps. A: Microvesicular hyperplastic polyp (MVHP): The crypts and surface epithelium showing a serrated appearance with micro-goblet cells increased. High power view is shown at left side bottom. Many small droplet (microvesicular) mucin within the cytoplasm at the epithelial layer is specific findings as shown the picture; B: Goblet-cell rich HP: In contrast to MVHP, this type polyp is showing a much less serrated appearance inside the surface epithelium of crypts. And showing a preponderance of goblet cells without microvesicular mucin; C: Mucin-poor HP (MPHP): MPHP is rare, and little is known about their molecular features and natural history. The histological features are showing no cytoplasmic mucin with a luminal serration pattern. And also showing increased nuclear atypia without pseudostratification.

polyps[10,15,21,23,27]. The most important histological findings of SSA/Ps are characterized by the shapes of the growth pattern within the serrated glands as follows: (1) crypt dilatation; (2) irregularly branching crypts; and (3) horizontally arranged crypts in the basal portion that have boot-like shapes (*i.e.*, inverted T- and/or L-shaped crypts) (Figure 2H and I, 3H, 4J)[5,15,28-30].

The histological characteristics of SSA/Ps can be differentiated from those of HPs based on the histological criteria advocated by the WHO. SSA/Ps are also sub-

Table 1 Classification of serrated lesion World Health Organization (2010)

Hyperplastic polyp
Microvesicular hyperplastic polyp
Goblet cell rich hyperplastic polyp
Mucin poor
Sessile serrated adenoma/polyp
Without cytological dysplasia
With cytological dysplasia
Traditional serrated adenoma

categorized into the following two types based on cellular dysplasia (Table 1); *i.e.*, those without and with cytological dysplasia (Figures 2-4). As shown in the Figure 3 and 4, SSA/Ps with cytological dysplasia comprise two types of lesion; the first is confined within the mucosa (Figure 3), and the second invades further into the SM layer (Figure 4).

Conventional SSA/P endoscopic findings have revealed superficial types of lesions with a pale color that is similar to that of HPs. Notably, the characteristic tumor sizes of such lesions are greater than 10 mm and these lesions adhered with a yellowish thick mucus. Some studies have termed this mucus a "mucous cap"[19,31,32]. When observed with crystal violet staining under magnification, the orifices can be seen to be widely opened and are referred to as Ⅱ-open pit[19,32,33]. However, these findings are often also found in associated with HPs and thus not suitable for differentiation at present.

Traditional serrated adenoma (Figure 5)

Traditional serrated adenoma (TSA) is an additional name for "serrated adenoma" that was previously advocated and is currently user to differentiate TSAs from SSA/Ps as further discussed below. Although this type of lesions is primarily observed on left side of the colon[17,18] and these lesions are primarily of the protruded type (Figure 5), there are also some superficial types of lesion. The characteristic pathological findings as a serrated adenoma are the following: (1) the presence of goblet cell; (2) upper zone mitoses; (3) prominent of nucleoli; and (4) the absence of a thickened collagen table[4]. Based on the above observations, the characteristic pathological findings of SSA/Ps are not observed among the above-mentioned four findings.

The characteristic endoscopic findings of TSAs reveal that the protruded type is composed of enhanced-reddish villous lesions that are often associated with a type Ⅱ pit pattern at the base[17]. The macroscopic gross type is characterized as "pine cone-shaped" or "coral-shaped" *via* conventional observation[34]. Magnifying endoscopic findings also reveal that the type Ⅳ pit pattern is often present and that differentiation from traditional adenomas is easy. In contrast, differentiation of superficial type lesions from SSA/Ps based on endoscopy is considered difficult due to the similar pit patterns. Some endoscopists have used the terms types ⅢH and ⅣH pits or type Ⅳ-serrated pit pattern to differentiate

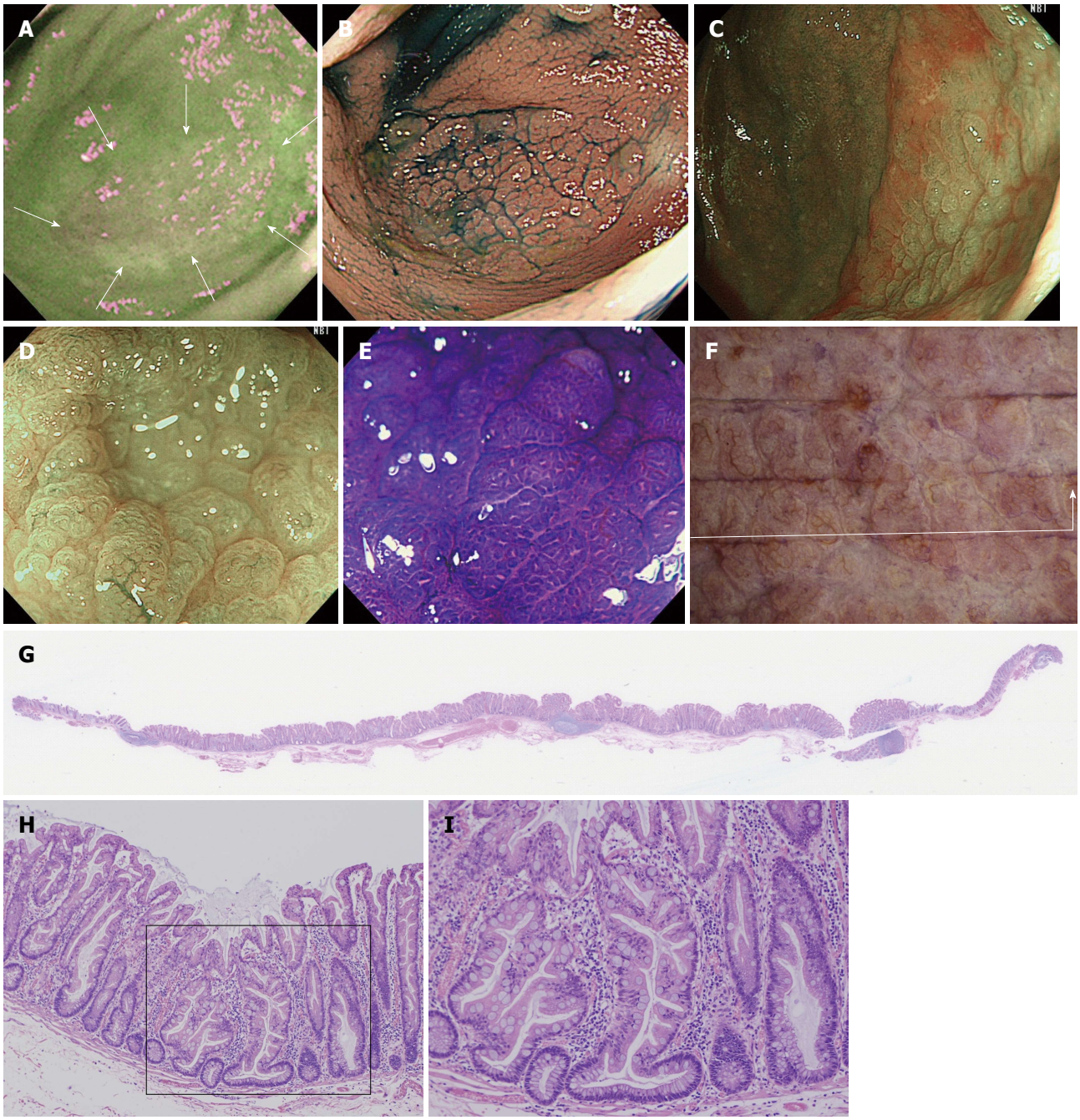


Figure 2 A case of sessile serrated adenoma/polyp without cytological dysplasia (scope: CF: FH260AZI). A: AFI imaging. The flat elevated polyp is approximately 37 mm in diameter as is located in cecum. No change to magenta of the tumor relative to the surrounding normal mucosa can be observed (inside white arrows); B: Indigocarmine spraying endoscopic finding. The structure of the granular surface is clearly revealed by chromoendoscopy; C: NBI observation, non-magnified. A red cap is covering the surface of the tumor; D: NBI observation, magnified. Small black dots can be observed in the tumor. This finding indicates that this tumor possesses the characteristic of SSA/P; E: Crystal violet staining under magnified observation. Type Ⅱ open pits (Ⅱ-O pits) containing T normal type Ⅱ pits are shown in the tumor; F: Stereoscopic finding. The tumor was excised by the ESD method. The tumor was cut into12 pieces; G: HE staining, whole specimen findings from section #4; H: Low power view of the HE staining findings. The tumor contains serrated glands in the mucosal layer; I: High power view of the HE staining findings. Typical histological findings for SSA/P. The crypt exhibits an "inverted T" type. NBI: Narrow band imaging; SSA/P: Sessile serrated adenoma/polyp; AFI: Auto fluorescence imaging.

conventional villous adenomas (Figure 4E and F)[18,19,33,34].

ENDOSCOPIC FEATURES ON IEE

According to the endoscopic imaging-object-oriented classification[35,36], IEE can be classified into three major categories: auto fluorescence imaging (AFI); narrow band imaging (NBI); and infra-red imaging. In this review, I will describe the characteristic endoscopic findings of AFI and NBI observations in details.

HP

Most of HPs are visualized as dark-green colors on AFI that are similar to the normal surrounding mucosa. We

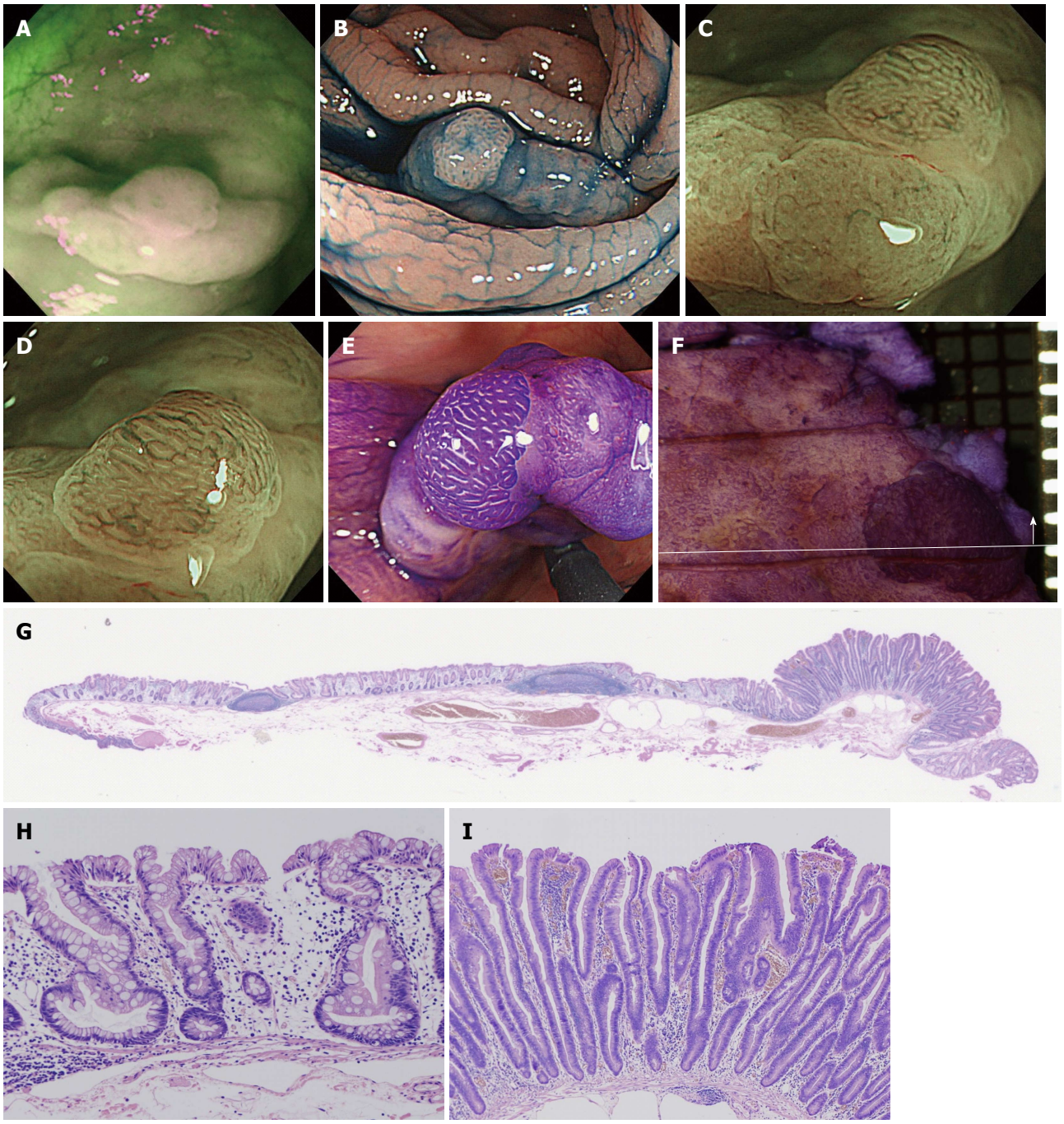
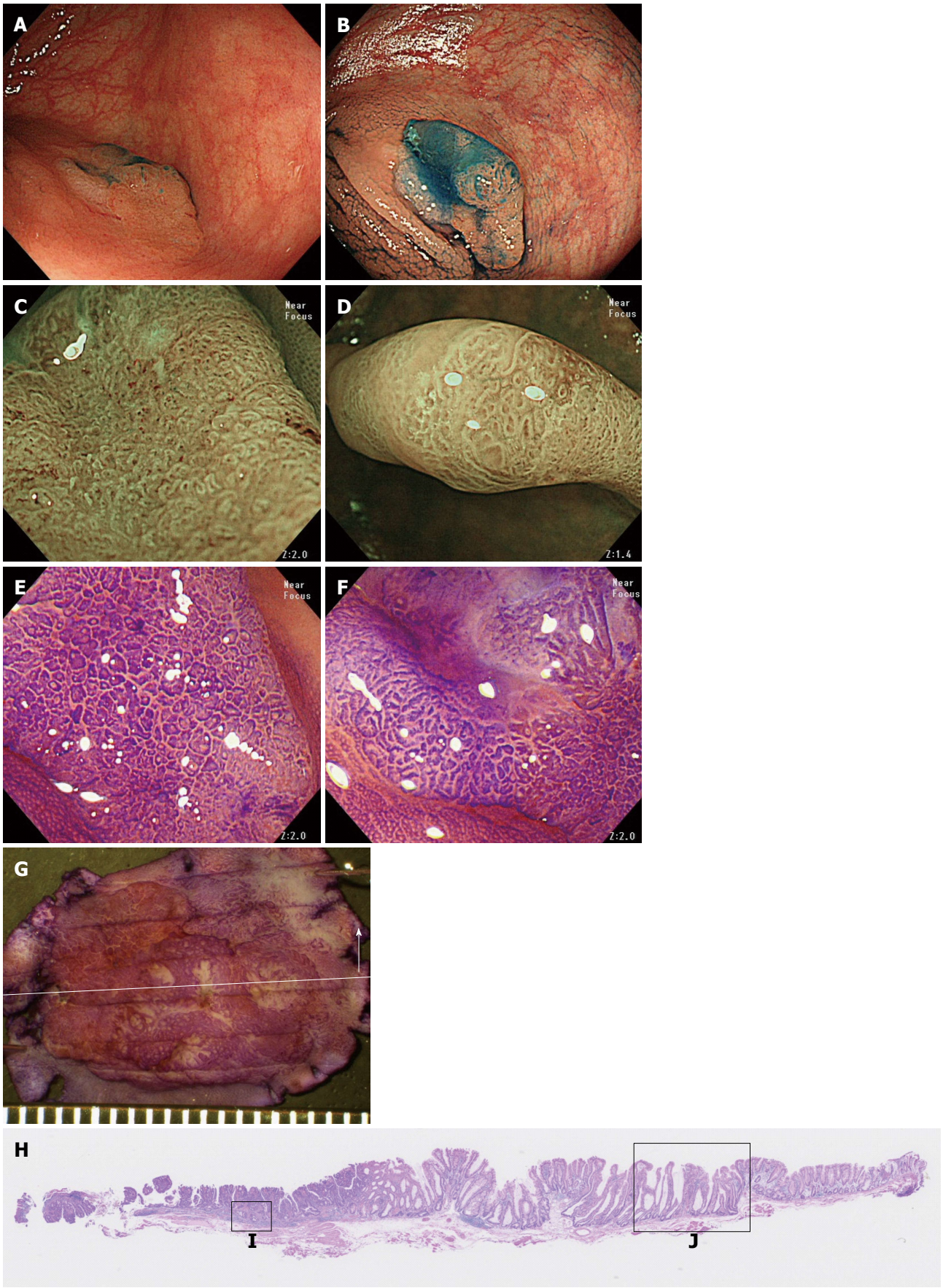


Figure 3 A case of sessile serrated adenoma/polyp with cytological dysplasia (scope: CF: FH260AZI). A: AFI imaging. The polyp is shown as a flat elevated lesion with a small nodule and is located in the ascending colon. A slightly change to a magenta color can be seen localized to a small elevated lesion in the tumor; B: Indigocarmine spraying endoscopic finding. The small elevated nodule in the tumor can be seen observed following dye spraying; C: Magnified NBI observation. In the tumor lesion, whitish mucosa with II-D pits can be observed. The microcapillary vessels are not dilated in the tumor; D: Magnified NBI observation. In contrast, the microcapillary vessels are dilated surrounding the tumor pits at the small elevated nodule. Moreover, a III$_L$ pit (white line) can be indirectly observed; E: Magnified crystal violet staining observation. Type II open pits (II-O pits) containing normal type II pits are shown in the tumor; F: Stereoscopic finding. The tumor was excised by the ESD method. The tumor was cut eight pieces; G: HE staining, whole specimen findings from section #4 including a small nodule; H: High power view of the HE staining finding. A part of an SSA/P is shown in the picture; I: High power view of the HE staining finding. The small elevated lesion is shown as a neoplastic change. Low grade cytologic dysplasia is present with nuclear hyperchromasia and pseudostratification. NBI: Narrow band imaging; SSA/P: Sessile serrated adenoma/polyp; AFI: Auto fluorescence imaging.

have previously reported that HPs can also be observed to exhibit dark-green colors[36,37]. Unlike neoplastic lesions, dilatation of the capillary vessels surrounding the glands cannot be observed *via* NBI magnifying endoscopy (NBI-ME)[38-42], and the type Ⅱ pit pattern can be indirectly observed. Basically, as visualized by IEE, HPs appear to be similar to the normal colon mucosa.

SSA/P (Figure 6)

Currently, satisfactory analysis based on AFI has not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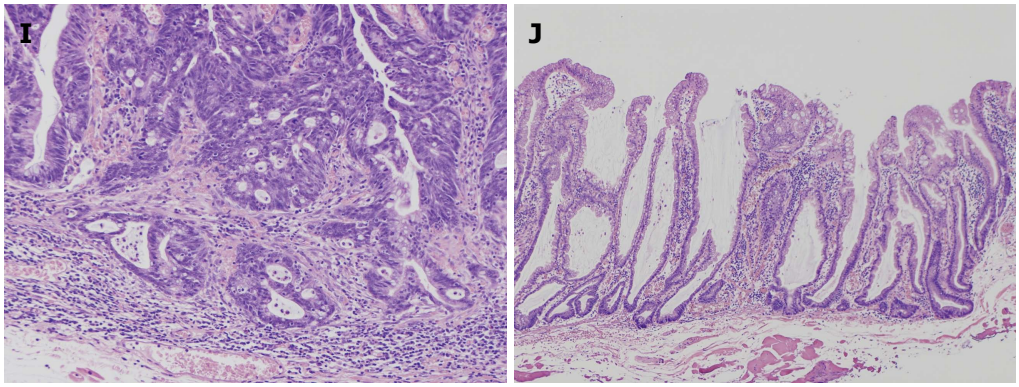

Figure 4 A case of an sessile serrated adenoma/polyp that has invaded the submucosal layer (scope: CF: HQ290I). A: Conventional white light observation. A flat elevated polyp of approximately 20 mm with a reddish depressed area can be observed in the ascending colon; B: Indigocarmine spraying endoscopic finding. Chromoendoscopy revealed this lesion, which is clearly composed of lesions. One edge area is covered with thick mucus; C: Magnified NBI observation. Firmly attached mucus can be observed on the tumor. A II-D pit that is indicative are markedly dilated crypts can be seen in this area; D: Magnified NBI observation. A granular surface pattern with dilated microcapillary vessels can be observed on this tumor in the absence of a thick mucous adhesion; E and F: Magnified crystal violet staining observation; G: Stereoscopic finding. The tumor was excised by the EMR method. The tumor was cut into seven pieces; H: HE staining, whole specimen finding from #4; I: High power view of the HE staining. The neoplastic glands have invaded into the SM layer to a depth of approximately 400 μm. The glands exhibit high grade dysplastic change; J: Low power view of the HE staining. This polyp is composed of SSA/P glands with markedly dilated crypts. NBI: Narrow band imaging; SSA/P: Sessile serrated adenoma/polyp.

been achieved[43,44]. However, in a single study from our group, we identified substantial difference between SSA/Ps with and without cytological dysplasia based on further prospective study prior to resection.

Specifically, the frequency with which the color changed to magenta color in SSA/Ps with dysplasia was higher than that of the SSA/Ps without dysplasia (Figures 2A and 3A). Moreover, the frequency of color changes among SSA/Ps is also higher than that among HPs[43]. Specifically, highly dysplastic lesions were strongly visualized. In contrast, 26 out of 46 SSA/P lesions (56.5%) presented with dark-green colors. Additionally, 17 out of 25 HP lesions (68.0%) presented with dark-green colors. Based on the above results, AFI observations can be considered useful for diagnoses in terms of whether SSA/Ps are associated with neoplastic changes.

When the above-mentioned "mucous cap" is observed on NBI, the bile is visualized in a red color tone; therefore, we reported this observation as the "red cap sign" (Figure 6A) and considered it to be useful in the differentiation of SSA/Ps. Additionally, because the orifices of the glands are frequently found to be wide open on magnified NBI observation, such orifices are referred to as type Ⅱ dilatation pits (Ⅱ-D pits) to differentiate them from Ⅱ-open pits[19,33] (Figure 6B).

Also in this study, Ⅱ-D pits were observed in 37 of 46 SSA/Ps without dysplasia lesions (80.4%), and HPs were found in approximately half of the lesions (7/25, 28.0%). Regarding SSA/Ps with dysplasia, only 4 of the 15 lesions presented type Ⅱ pits or Ⅱ-D pits, and 11 of these lesions presented with type Ⅲ to Ⅴ pits (Figure 4D). Based on the above results, differentiation can be considered to the possible based on observation of magenta color on AFI and the neoplastic pit pattern (with the exception of type Ⅱ pits) on magnified NBI observations when SSA/Ps are mixed with neoplastic changes.

Additionally, one, study has also reported that the presence of varicose microvascular vessels is useful for the differentiation of HPs based on magnified NBI observations of SSA/P lesions[45]. Unlike the blood vessels around the glands of the superficial mucosal layer, this finding is characterized by the observation of blood vessels running throughout the deep mucosal layer.

Dilatations and irregularities of the capillary vessels that are similar to those that develop from conventional adenomas are observed in polyp sites of SSA/Ps with dysplasia, but the disappearance of blood vessels and the superficial structures have been confirmed in invasive lesions that are deep into the SM layer (Figure 4D).

TSA (*Figure 5*)

Unlike HPs, TSAs can be visualized as magenta colors when observed on AFI, and this change is indicative of a neoplastic lesion. Protruded type TSAs primarily present with villous structures[17,18] and can be visualized as a color that is a mix of magenta and dark-green (Figure 5A). In contrast, superficial type TSAs can be identified although the intensity of the visualization of the magenta color varies depending on the degree of histological dysplasia.

In contrast, lesions that present with red color under white light observation can be observed to exhibit brownish color on NBI. Regarding the protruded type, the orifices of the glands and the interstitial capillaries can be observed in whitish and in blackish-brown color, respectively, on NBI magnifying observations; thus, their appearances are similar to those of normal villous tumors (Figure 5D). The superficial type of TSA can also be indirectly observed to exhibit a relatively villous

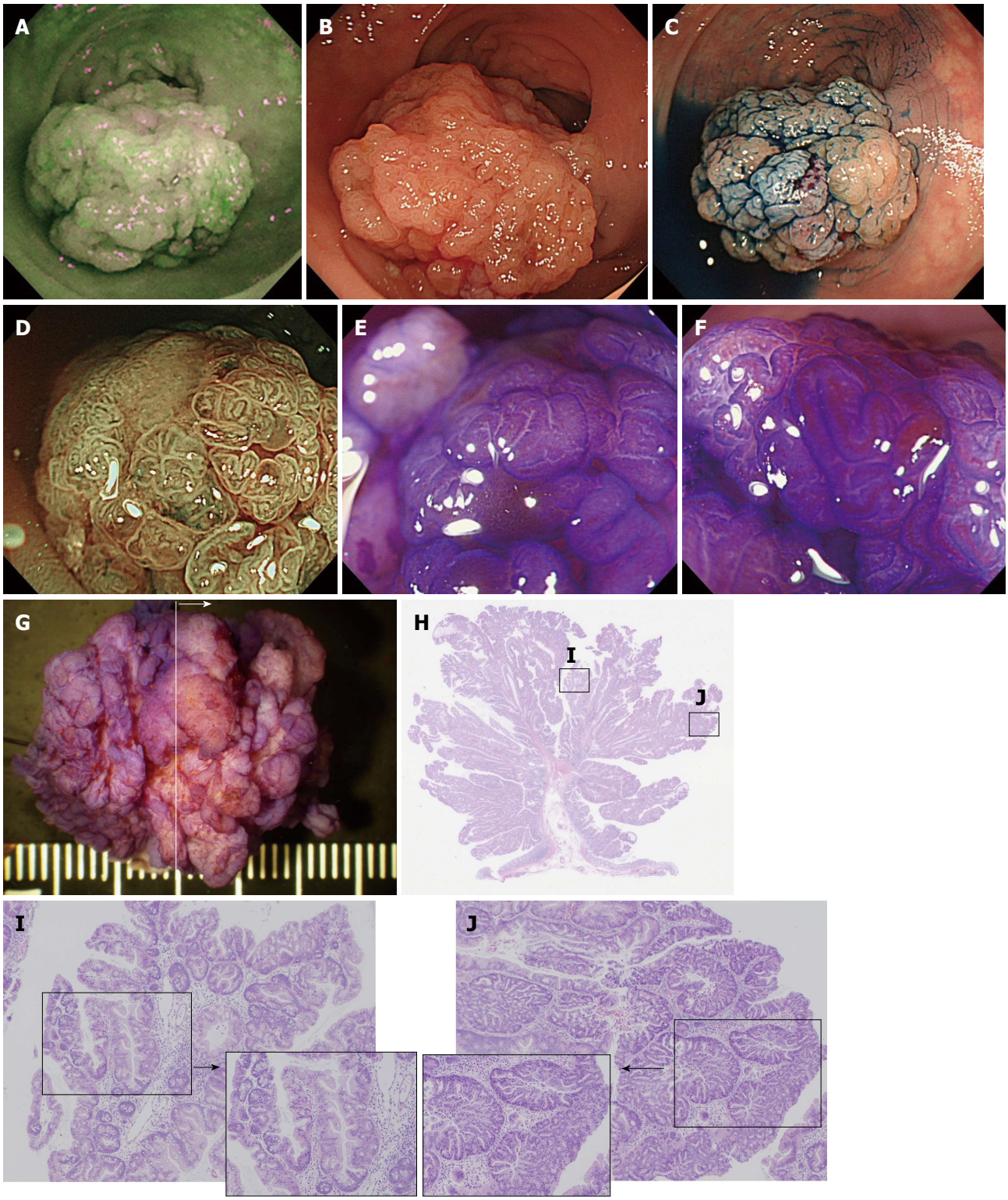

Figure 5 A case of a traditional serrated adenoma with conventional dysplasia (scope: CF: FH260AZI). A: AFI imaging. A dark green tone that is nearly the same as the surrounding normal colon mucosa can be observed in the tumor; B: Conventional white light observation. A large (approximately 30 mm) semipedunculated polyp exhibiting a slightly reddish change can be observed at the rect-sigmoid junction. There are no findings suggestive of submucosal invasion of the cancer; C: Indigocarmine spraying endoscopic findings. The structure of the nodular surface pattern is clearly revealed; D: NBI observation, magnified. A granular surface pattern with dilated microcapillary vessels can be observed in the tumor; E and F: Magnified crystal violet staining with observation. A type III_{H} or IV_{H} pit pattern is shown in the tumor; G: Stereoscopic finding. The tumor was excised by the EMR method. The tumor was cut into 4 pieces; H: HE staining, whole specimen finding from section #2; I: Histological findings from the HE staining. The tumor contains serrated glands in the mucosal layer. Dysplastic change is not observed; J: Histological findings of the HE staining. At several points, TSAs with conventional epithelial dysplasia exhibiting enlarged crowding and pseudostratification of the nuclei with crypt structure dysplastic changes can be observed. TSA: Traditional serrated adenoma; NBI: Narrow band imaging; AFI: Auto fluorescence imaging.

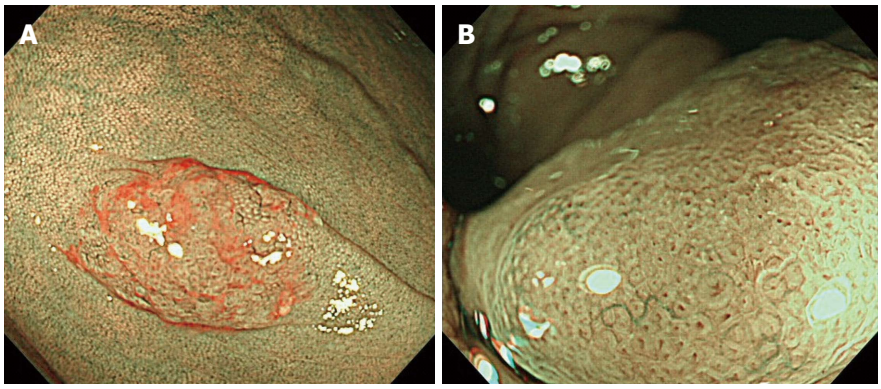

Figure 6 Endoscopic characteristics on narrow band imaging observation. A: Red cap sign – positive case; B: A finding of showing Ⅱ-D pit.

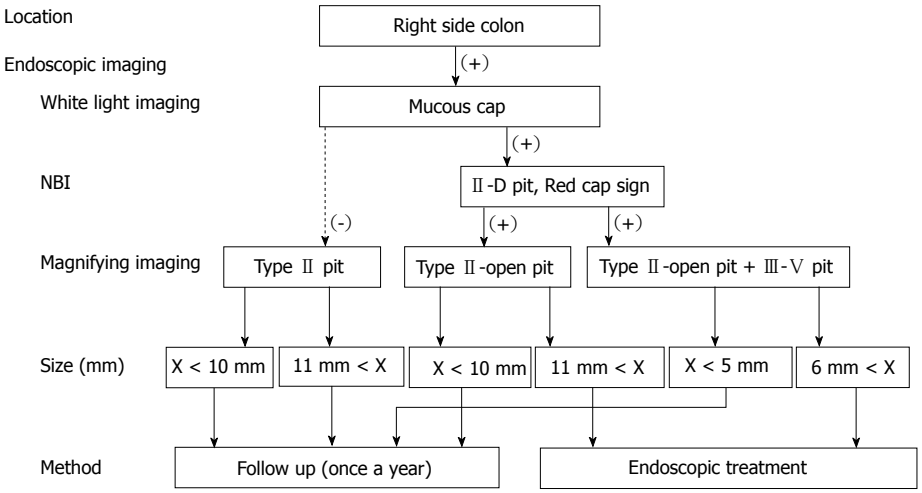

Figure 7 Flow chart for endoscopic treatment about sessile serrated adenoma/polyp. NBI: Narrow band imaging.

structure that is characteristic of a lack of associated with vasodilatation in contrast to the protruded type. However, within the lesion, a blackish dotted orifice of the crypt that is similar to that of SSA/Ps is often observed as discussed later (Figure 2B); this similarity makes, differentiation difficult.

INDICATIONS FOR ENDOSCOPIC TREATMENT

Currently, there is no established indication for endoscopic treatment about serrated polyps. However, according to the guidelines of management published by the ASGE[6,11,31] or ESGE[46], a five-year follow-up period is recommended for SSA/Ps without dysplasia that are 10 mm or less in size, and a follow-up with a three-year intervals is recommended for SSA/Ps with dysplasia of that are 10 mm or more in size. Notably, a biennial follow-up is recommended for serrated polyposis.

However, we summarized about the indication for endoscopic treatment of serrated polyps as a flow chart in Figure 7. Especially, the indication of endoscopic treatment for SSA/Ps is complicated. As we mentioned above, it is recommended to use the ME with NBI method and chromoendoscopy for diagnosis of characterized findings. At first, it is recommended to do the endoscopic treatment for greater than 6 mm sized polyps with Ⅱ-D pit and neoplastic changes (type Ⅲ-Ⅴ pit pattern) on right side colon. In contrast, small sized polyps smaller than 10 mm are should be follow up, even if shown to the mucous cap and Ⅱ-D pit. And also most of small sized HPs at sigmoid colon and/or rectum are not indication for endoscopic treatment. However TSAs, which are shown to type Ⅲ-Ⅳ pit pattern in left side colon are indication for endoscopic treatment.

In terms of numbers of lesions, once every-five-year follow-ups are recommended when SSA/Ps and TSAs greater than 10 mm are found at three or more sites, and once every-three-year follow-ups are similarly recommended for SSA/Ps and TSAs greater than 10 mm according to guideline. In contrast, once every-three-year follow-ups are recommended when SSA/Ps and TSAs of 10 mm or less are found at three or fewer sites, and one to three year follow-ups are recommended when lesions of 10 mm or more are found at two or more sites. The same follow-up schedule is recommended when associated cytological dysplasia is found.

Although the above mentioned guidelines recommend

a once every-three-year follow-ups for lesions that are associated with dysplasia and are 10 mm or more in size (regardless whether they are SSA/Ps or TSAs), we recommend endoscopic resection such conditions in our department. We made this recommendation because some lesions will develop SM invasion even if they are less than 10 mm sized polyp. Lesions with tumors that are 20 mm or greater are particularly recommended for endoscopic resection even when endoscopic findings of obvious dysplasia are absent.

CONCLUSION

Histopathologically, "serrated lesions" are categorized by the WHO into three groups[15]: (1) HPs; (2) TSAs; and (3) SSA/Ps. I have discussed the findings associated with each lesion type as observed on IEE and provided a particular focus on such associated findings on magnified, AFI and NBI[43]. The differentiation between HP and TSA or SSA/P based on AFI is possible to some extent based on changes in color tone. However, similarly to HPs, more than half of SSA/Ps exhibit no change in color. In contrast, 90% lesions of SSA/P with cytological dysplasia changed in magenta color tone; therefore, AFI might be a useful method for determining the presence of neoplastic characteristic of SSA/Ps.

Regarding HPs and SSA/Ps, differentiation is impossible based only on the presence or absence of dilated microcapillary vessels because such dilatation is not observed around the glands on magnified NBI observation. However, dilatations of the gland orifices are frequently observed in SSA/P and appear as blackish dotted orifices (Figure 6B). Additionally, a thick mucus adhesion referred to as a "mucous cap" can be confirmed as red mucus on NBI observation and can be recognized when it adheres to the surface of a "red cap" polyp (Figure 6A). According to our data, it is concluded to possible to differentiate between SSA/Ps and another serrated polyps. When AFI color changes were used to differentiate from HPs and SSA/Ps, the sensitivity, specificity, PPV, NPV, and diagnostic accuracy of SSA/P diagnosis were 43%, 68%, 71%, 40%, and 52%, respectively. In contrast, NBI method with using magnifying observation is also usefulness. When the red cap sign was used to differentiate between HPs and SSA/Ps, the sensitivity, specificity, PPV, NPV, and diagnostic accuracy of SSA/P diagnosis were 94%, 40%, 74%, 77%, and 75%, respectively. And the existence of Ⅱ-D pit in magnifying observation is also important. When the Ⅱ-D pit was used to differentiate between HPs and SSA/Ps, the sensitivity, specificity, PPV, NPV, and diagnostic accuracy of SSA/P diagnosis were 80%, 72%, 84%, 67%, and 78%, respectively.

Based on the above findings, the differentiation of HPs and SSA/Ps is likely possible. In contrast, the superficial type of TSA is considered to be difficult to differentiate from SSA/Ps. However, further studies should be conducted because the histopathological diagnoses of both HPs and SSA/Ps have ambiguities that have yet to be resolved.

Additionally, SSA/Ps with dysplasia are observed to be associated with dilatation of the microcapillary vessels at the tumor site, and the same finding as been observed to be associated with traditional neoplastic change (Figure 4D).

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REVIEW

Recent development of optical coherence tomography for preoperative diagnosis of esophageal malignancies

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Abstract

Endoscopic diagnosis with histological evidence is necessary to decide the best strategy for treating esophageal squamous cell carcinoma and Barrett's-associated neoplasia, and the recent development of endoscopic technologies have made possible real-time information of malignant hallmarks. We focused on the development of optical coherence tomography (OCT), the only technology that can depict real-time cross-sectional images with high resolution. With the improvements in image resolution, acquisition rate and demonstrable area of three-dimensional devices with Doppler capability, OCT imaging was shown to enable visualization of structural/functional alterations in the mucosal/submucosal tissue of the esophagus, resulting in more accurate preoperative diagnosis of such malignancies. Moreover, it approved to be useful for targeting malignant areas for biopsy and treatment as well as for predicting the treatment effects. Therefore, further development of this technology is expected to overcome the current clinical issues in management strategies of esophageal malignancies.

Key words: Optical coherence tomography; Barrett's esophagus; Esophageal squamous cell carcinoma

Core tip: Optical coherence tomography (OCT) provides real-time cross-sectional images with extremely high resolution. We previously reported that OCT provided significantly more accurate preoperative staging of esophageal squamous carcinoma (ESCC) than endosonography. With remarkable improvements in this technology, such as three-dimensional devices with Doppler capability, for the detection of Barrett's-associated neoplasia, the diagnostic accuracy gradually became better through enhanced visualization of structural/functional alterations in mucosal/submucosal tissue. Recent reports suggested its usefulness for targeting malignant lesions for endoscopic intervention and for predicting treatment effects. Therefore, further development of OCT should promote improved management strategies for esophageal malignancies, including ESCC.

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INTRODUCTION

Both endoscopic assessment and histological evidence of gastrointestinal malignancies are necessary to decide the best treatment strategy. Notably, image-enhanced endoscopic technologies have been developed to provide real-time information on malignant hallmarks. In this review, we focused on the development of optical coherence tomography (OCT), the only technology that can depict real-time cross-sectional images of biological tissue at a near-microscopic level without contrast agents[1].

OCT IMAGING

Mechanism of OCT imaging and its advantage

OCT images by near infrared light in the wavelength range of 700-1500 nm are similar to the B-mode images of ultrasonography. To construct an image, optical interferometry measures the delay between the emission of an invisible beam and the detection of its reflection to determine the distance from the emitter to the site. Its axial resolution is determined by coherence length of the light source. Most of the OCT devices reported in previous studies were first-generation probe-types [Light Lab Imaging (Boston, United States)] that used a super-luminescent diode light source with a center wavelength of 1300 nm, a bandwidth of 50 nm, and power output of 10 mW[2-7]. They had 10-20 μm of axial resolution, 5-25 times higher than that of high-frequency endosonography, which was another cross-sectional imaging device. Although its image acquisition rate was gradually improved from 1 frame/s to 9.8 frames/s with a lower signal-to-noise ratio, 4.0 frames/s could be used for the easy interpretation of images (Table 1)[8-10]. As a result, detailed OCT images can be constructed in gray-scale.

These mechanical characteristics provides several advantages to OCT in comparison with other advanced endoscopic technologies, as follows. First, it provides high-resolution cross-sectional images in real-time. OCT shows tissue structures in the mucosal/sub-mucosal layers at a microscopic scale, such as "pit and gland" morphology, revealing crypts/villi/vessels[4,6,7,11,12], as well as intracellular strictures, such as nuclei and other organelles, based on their different intensity of signal scattering[13]. Second, OCT does not always need tissue contact or coupling, although a biocompatible chemical agent was reported to possibly enhance its signal penetration depth[14]. Actually, we used a probe-type OCT [HOYA (Tokyo, Japan)] to depict detailed structures of the esophageal wall components, regardless of the location, while EUS-based imaging required acoustic coupling with a water preparation or a water-filled balloon, resulting in some difficulty in avoiding artifacts[2]. Third, a prototype OCT has a through-the-endoscope design, which may be easier to handle during endoscopic examination. In the next section, we will describe the technique for acquiring high-quality images using the OCT.

Best technique and indication for OCT imaging

Nowadays, two types of OCT probe-devices, such as a radial-probe/linear-probe, and one balloon-type device are available but only for research[10,11,13]. While linear scanning is able to sample only a small area, radial scanning creates an image similar to that of radial EUS with the potential for assessing larger areas, due to its easier identification of the scanning orientation compared with the linear scanning. Therefore, radial-type probes have been applied in most of the previous studies.

The OCT devices are inserted through the accessory channel of an endoscope and maneuvered under direct endoscopic observation so that the imaging plane is perpendicular to the gastrointestinal wall. Its position when scanning across the tissue surface is monitored using visible light. A series of tomograms are obtained, while its spot diameter is selected for maintaining the appropriate depth of focus, while the distance above the surface is controlled by endoscopic maneuvers. In fact, the distance between the device and the site may affect the penetration depth of its signal. While mucosal structures were well-focused when the probe was held about 1 mm above the surface, the structures in the deeper submucosa (SM) could be revealed when the wall was compressed or collapsed around the probe. Using such a technique, the penetration depth of the OCT signal and consequent image quality in the stomach, duodenum, and colon were reported to be inadequate compared with those in the esophagus, suggesting that the OCT device was most suitable for the esophagus[11].

Previous studies demonstrated close correspondences between the clear, five-layered morphologies in the OCT images and those of a normal esophageal wall in the histological findings[4,15]. It was shown that the first relatively less reflective layer corresponded to stratified squamous epithelium (EP); the second more reflective layer to the lamina propria mucosa (LPM); the third less reflective layer to the muscularis mucosa (MM); fourth more reflective layer to the SM; and fifth less reflective layer to the muscularis propria (MP) with deeper structures of the esophageal wall. Subsequent studies based on such findings promoted the development of OCT devices for the management of Barrett's-associated neoplasia and esophageal squamous cell carcinoma (ESCC). Originally, the studies aimed to improve the quality of "optical biopsies" of OCT devices for Barrett's-associated neoplasia and remarkable advances were achieved in the West from the first-generation conventional probe-type OCT to the second-generation OCT (Table 1). In the East, we demonstrated the usefulness of the first-

Table 1 Specification of optical coherence tomography devices

Manuscript	OCT device			Diameter (mm)	Image acquisition rate (frame/s)
	Type	Resolution			
		Axial (μm)	Transverse (μm)		
4	Probe	10	25		4
5	Probe	10	25	2.4	-
6, 7	Probe	10	-	2.5	2
2	Probe	11	30	1.5	4
3					
33	Probe	5	-	1.8	4
34	Probe	Approximately 2	5.6	-	-
39	Probe	5	14	-	60
41	Probe-3D	5	15	-	60
10	Balloon (OFDI)	7	30	18	4
46	Balloon (VLE)	7	-	20	10

OCT: Optical coherence tomography; OFDI: Optical frequency-domain imaging; VLE: Volumetric laser endomicrography.

generation OCT in the preoperative staging of superficial ESCCs (SESCCs) (Table 1). Therefore, we review these achievements, and propose future roles for OCT in the management of esophageal disease.

OCT-BASED DIAGNOSIS OF BARRETT'S-ASSOCIATED NEOPLASM

Significance of OCT in Barrett's esophagus

Barrett's esophagus (BE) is a precursor lesion with a 30-40-fold increased risk of cancer occurrence, *i.e.*, from specialized intestinal metaplasia (SIM) to low grade dysplasia (LGD) and high grade dysplasia (HGD) and, finally, to adenocarcinoma[16]. Based on knowledge of the multi-step transformation, a surveillance program with regular endoscopic examination is recommended, but the prognosis for adenocarcinoma remains poor, with an overall 5-year survival of less than 20%[17]. Previous studies suggested that some dysplasia and intramucosal adenocarcinoma might be overlooked until the advanced stage in the current clinical setting[18]. Most of them were shown to be minute with a patchy distribution in a wide-ranging BE, and subsquamous SIM (SSIM) was found in 71.4% of pre-treatment dysplastic BE when 0.4-6.8 mm of oral extension was observed, although the sampling area and depth by random biopsy were limited[18-22]. Therefore, there still remain controversies about sampling errors and costs/time of endoscopic biopsies in the current surveillance system[18,20,21]. Moreover, several studies have pointed out the low inter- or intra-observer agreement of their histological diagnoses[23-29]. Likewise, cutting-edge endoscopic technologies have difficulties in reaching a consensus on the recognition or interpretation of abnormal patterns, which can limit their clinical usefulness[30]. However, real-time visualization of high-resolution cross-sectional architectural information, even in the SM, analogous to the loupe image, is an important advantage of the OCT imaging. In this section, we list previous achievements by OCT devices employed for endoscopic "optical biopsies" of Barrett's-associated neoplasm.

First-generation of probe-type OCT

Previous studies demonstrated that *in vivo* or *ex vivo* use of probe-type OCT devices could provide characteristic images of normal human esophagus, gastric mucosa, BE, dysplastic BE and adenocarcinoma, although subsequent studies showed that the differences in OCT images between non-dysplastic BE and dysplastic BE were subtle. Bouma *et al*[13] first reported the ability of *in vivo* OCT to provide detailed images of structures in Barrett's-associated neoplasia by investigating biopsy-correlated OCT images, and proposed OCT-based grading criteria for characterizing dysplastic BE, as follows: (1) normal squamous epithelium: homogenous layered structures; (2) BE: absence of the layered-structure of normal esophagus in addition to abnormal/disorganized glandular structure of low reflectance within/under the mucosa; (3) dysplastic BE: highly reflective intensity of the background correlated with increased architectural disorder and heterogeneity; and (4) Barrett's adenocarcinoma: abnormal configuration of neoplastic epithelium containing large pockets and surrounded by cellular stroma.

In 2001, using 288 biopsy-correlated OCT images of 121 patients, Poneros *et al*[4] demonstrated that *in vivo* OCT had sensitivity of 97% and specificities of 92% for the diagnosis of BE. In 2005, Isenberg *et al*[5] conducted a prospective study to evaluate diagnostic accuracy of *in vivo* OCT for dysplastic/non-dysplastic BE in comparison with the histological diagnosis of jumbo biopsy specimens. They used a 2.4 mm-diameter probe under a two-channel endoscope fitted with a cap attachment, which might stabilize the OCT device on the mucosal surface during the procedure. Using a total of 314 biopsy-correlated OCT images of 33 patients, they reported sensitivity of 68%, specificity of 82%, and positive predictive value of 53%, negative predictive value of 89%, and diagnostic accuracy of 78% for the

diagnosis of BE. When the analysis was restricted to the diagnosis of HGD/ adenocarcinoma based on findings, such as: (1) lack of epithelial surface maturation; (2) gland architecture disarray; and (3) cytologic atypia[31,32], its sensitivity and specificity was 54% and 72%, respectively. Although such a negative predictive value may be advantageous for directing the examiners' attention to malignant areas for the biopsy target, there remained limitations, such as large variability in the endoscopists' accuracy rates, 56%-98%. Therefore, more refined criteria for differentiating dysplastic BE from non-dysplastic BE were required. In 2006, in a prospective study, Evans *et al*[6] investigated the relationship between a new scoring system, a "dysplasia index", based on both the OCT findings of surface maturation and gland architecture, and biopsy-proven histology of HGD/adenocarcinoma in BE subjects. Using a total of 177 biopsy-correlated OCT images, the threshold of > 2 in the scoring system had sensitivity of 83% and specificity of 75% for the diagnosis of HGD/adenocarcinoma. Accordingly, these studies demonstrated that discrimination between non-dysplastic BE and dysplastic BE using OCT devices with standard resolution still remained a challenging issue.

Then, Chen *et al*[33] developed an ultra-high resolution OCT (UHR-OCT) with 5-μm axial resolution and compared its image quality and diagnostic accuracy with those of a standard OCT with 12-μm axial resolution. Using a total of 233 biopsy-correlated OCT images of 50 patients, the accuracy of UHR-OCT for making a diagnosis of normal squamous epithelium, non-dysplastic BE, HGD and adenocarcinoma was 100%, 98.1%, 83.3% and 100%, respectively. Actually, UHR-OCT depicted smaller/finer structures and sharper layered structures, resulting in improved discrimination and more detailed features of dysplastic BE. In 2010, Cobb *et al*[34] reported that UHR-OCT detected clearly SSIM as well as abnormal structures of non-dysplastic BE/HGD/adenocarcinoma in 14 post-surgical specimens. Accordingly, these studies suggested that higher-resolution OCT with the developed criteria might be more useful for targeting biopsies to differentiate between BE and normal esophagus, or between dysplastic/cancerous BE and non-dysplastic BE. However, some studies pointed out that the point-sampling nature of a probe-type OCT, similar to those of biopsy, might miss dysplastic lesions in large surface areas of BE[10].

Second generation of OCT

These drawbacks of the probe-type OCT might have been mainly caused by the relatively slow image-acquisition rate, while recent improvements in OCT technology have enabled dramatic increases in imaging speed[35-38]. As a result, three-dimensional balloon-type OCT, referred to optical frequency-domain imaging (OFDI) and three-dimensional probe-type OCT (Light-Lab Imaging, Massachusetts, United States), could be developed with a combination of high-resolution at a near-microscopic level, large field of view, and rapid data acquisition[10].

Three-dimensional probe-type OCT: Volumetric data of a 10-mm circumference and 20-mm length could be acquired in 20 s by the helical scan of a prototype three-dimensional OCT, and each of data set provided comprehensive imaging of the glandular structure over a sampling area of 200 mm^2, which was 30-60 times as large as those of approximately 6 mm^2 by jumbo biopsy forceps and those of approximately 2.5 mm^2 by conventional biopsy forceps[39]. Additionally, the imaging depths of 3D-OCT and biopsy were 1.5-mm and < 1 mm, respectively. Using data of biopsy-correlated OCT images of 3 patients, Adler *et al*[39] demonstrated the usefulness of a three-dimensional OCT system for the detection of large areas of a normal esophagus, non-dysplastic BE and post-ablative BE. The increase in the data volume of three-dimensional OCT improved the clear detection of SSIM at 300-500 μm depth beneath neosquamous epithelium, and they therefore proposed its use to guide decisions concerning additional treatment sessions or biopsy points with a reduction of sampling error[39]. Subsequent studies demonstrated that the pre-treatment thickness of Barrett's mucosa and the presence of residual glandular structures immediately after focal radiofrequency ablation (RFA) in the three-dimensional OCT images were correlated with the treatment response determined by surveillance endoscopy with biopsy 6-8 wk after the latest session[40,41]. Accordingly, the three-dimensional OCT findings might be used as a promising real-time predictor of successful ablative therapy for BE.

Use of OFDI/volumetric laser endomicrography: OFDI can provide more than 100-fold faster imaging, compared with the conventional probe-type OCT[42]. The optical components in the inner sheath, positioned at the center of a 1.8 mm-diameter balloon catheter, are rotated helically, and cross-sectional images of the esophageal wall are revealed when the balloon is in contact with the mucosal surface, whose demonstrable area in the circumferential lumen might be affected by the degree of contact. All raw data are simultaneously stored and displayed in real-time. The OFDI/volumetric laser endomicrography (VLE) image with balloon-compression has four advantage, as follows: (1) the acquirement of microstructural data over large areas; (2) increased contrast of anatomical architecture; (3) increased signal penetration depth; and (4) reduced artifacts during imaging process.

Originally, volumetric OFDI images of the mucosa extended to the outer layer of the MP, with clear delineation of each layer, obtained for 4.5-cm-long segments in less than 6 min. In 2008, in a single-center study, complete acquisition of the OFDI data was successfully performed in 8 of 12 patients, and their images were consistent with the histological findings obtained by target/random biopsy specimens[10]. The loss of

an appropriate image due to inadequate contact of the balloon was observed in 0.37% ± 0.79% of the total tubular esophageal surface area/patient. More recently, the Nvision Volumetric laser endomicrography Imaging System (Nine Point Medical, Cambridge, MA) was developed as a commercially available device. It is derived from OFDI and provides real-time three-dimensional images of mucosa/SM over a 6-cm length of the esophagus in 90 s. Baron *et al*[43] demonstrated that *in vivo* use of VLE clearly depicted SSIM proven by random endoscopic biopsy in 3 post-RFA BE patients, and Leggett *et al*[44] revealed that *ex vivo* use of VLE clearly detected subsquamous adenocarcinoma of endoscopic mucosal resection specimens, which could not be seen by conventional endoscopy or confocal laser endomicroscopy (CLE). In a multicenter prospective feasibility study, 4 lesions of HGD/adenocarcinoma were detected by VLE in 74 BE patients[45].

However, there still remain two drawbacks. First, previous studies pointed out that inadequate contact of the balloon, due to the interference of blood/mucus, existing motion artifacts, or excessive compression of the balloon on the mucosal surface, might still reduce the image quality. Especially, in some parts of the esophagus, such as in large hiatal hernias, tissue contact with the balloon surface was not maintained throughout the imaging window. Second, it is impossible to make one-to-one correlations between OFDI/VLE images and the histological evidence, because the balloon-centering system is not suitable for the subsequent biopsy procedure, nor is the technology to localize the region of interest in the three-dimensional data. Unfortunately, unreliable correlations between them may make it difficult to determine whether the possible discrepancies are caused by either a sampling error or misdiagnosis of the images, so we cannot assess abnormal findings detected in only one session of OFDI/VLE. Actually, the true biological significance of SSIM has not been clarified by the current OFDI/VLE system without histological evidence. To overcome this issue, a biopsy guidance platform that provides endoscopically visible laser markings at VLE-determined sites was developed, and its feasibility was demonstrated in a pilot study[46]. During the examination of VLE, the marks were made in 2 s at 410 mW of electric current, with the thermal-damage predominantly limited to the mucosa[47]. The accuracies of endoscopy, VLE intent-to-biopsy, and corrected VLE post-marking images for diagnosing tissue between the marks were 67%, 93%, and 100%, respectively. The transverse and longitudinal targeting error was 1.2 ± 1.3 mm and 0.5 ± 0.9 mm, respectively, while there were no longitudinal targeting errors in 21 of 30 cases. Henceforth, larger trials by VLE-guided biopsy can be expected to evaluate its practical usefulness.

Doppler OCT: Doppler OCT can directly visualize the intensity of the blood-flow data derived from moving erythrocytes, and its velocity resolution was reported to be 10-100-times as high as that of Doppler EUS[48]. Previous studies demonstrated that it could depict dramatic alterations in the functional microvascular network, which might provide additional clues for improved identification of the layer structure, during the sequential development of Barrett's carcinogenesis[42,49]: (1) Normal esophagus: Distinct layers with small vessels in the LPM and medium vessels in the SM; (2) BE: Absence of the distinct layers with diffuse/small vessels and glandular structure; and (3) Esophageal Adenocarcinoma: Absence of distinct layers with diffuse/small vessels.

Recently, Tsai *et al*[50] developed OCT-angiography with an ultrahigh-speed (more than 10 times than that of conventional systems) and minimal motion artifacts, enabling imaging of the finer/denser microvascular architecture in BE. With an image acquisition of 400 frames/s, the total area of its image acquisition was improved to > 100 mm^2 in 8 s. Because of these technological advances, the OCT-angiography could reveal more detailed structural/functional changes in the subsurface vasculature/glandular structure for early identification of Barrett's carcinogenesis.

OCT-BASED TUMOR STAGING OF SUPERFICIAL ESOPHAGEAL SQUAMOUS CELL CARCINOMA

Significance of OCT-based staging

In the East, ESCC is the most predominant type of esophageal carcinoma, and its mortality rate remains still high. With the development of endoscopic technologies, the indication for endoscopic treatment for SESCCs has been expanded, since it is a minimally invasive procedure with few complications and after-effects. According to the esophageal cancer treatment guidelines of the Japanese Society of Esophageal Diseases, the definitive indication for endoscopic resection (ER) is limited to carcinoma *in situ* and tumors invading the LPM, regardless of tumor size[51]. Although more precise preoperative staging has been required for curative treatment, the accuracy of EUS has not yet been satisfactory, due to its limited visualization[52,53].

Establishment of staging criteria of SESCCs

Second, we established the criteria of OCT-based staging for SESCCs in a phase I study. We used a probe-type OCT system under endoscopic observation in order to detect every part of a key finding for tumor staging[2]. After we investigated correlation the between OCT-based staging and histological staging of *en bloc* ESD specimens, the criteria of OCT-based staging for SESCCs were established. The criteria were classified into 3 categories based on the treatment guidelines: clinical EP/LPM, clinical MM, and clinical SM: (1) Clinical EP/LPM: the thick or normal layer Ⅰ with regular interfacial signal of layer Ⅱ or involvement of the tumor signal

into layer Ⅱ without involvement of layer Ⅲ; (2) Clinical MM: involvement of the tumor signal into layer Ⅲ with regular interfacial signal of layer Ⅳ; and (3) Clinical SM: Destruction of layers Ⅰ to Ⅲ and irregular interfacial signal of layer Ⅳ or loss of layer Ⅴ architecture by high backscattering.

Thereafter, in a prospective phase Ⅱ study, we investigated the accuracy based on the criteria in 62 consecutive patients[2]. The overall accuracy was 92.7%, and the accuracy of EP/LPM, MM, and SM cancer was 94.7%, 85.0%, and 90.9%, respectively. Although the staging accuracy was not significantly different among tumor locations (P = 0.79), the 0.46 (range 0.10-1.5) mm thickness of the lesion in the images without deep attenuation was significantly thinner than the 2.5 (1.2-5.0) mm images with deep attenuation. Conversely, this study uncovered the following limitations of this modality: (1) the limited depth of OCT signal penetration; (2) the inability to distinguish between cancer cell invasion and inflammatory cell infiltration; and (3) the inability to distinguish between intraepithelial cancer and normal tissue. Still, this phase-Ⅱ study suggested that the criteria might be applicable for clinical use with high accuracy of tumor staging for SESCCs.

Comparison of tumor staging accuracy between OCT and EUS

Finally, we investigated the clinical usefulness of OCT-based staging of SESCCs in a single-center prospective study by comparing the staging accuracy of OCT with that of 20-MHz probe-type EUS (UM-3R; Olympus, Tokyo) without a water-filled balloon for a total of 131 SESCCs in 123 consecutive patients[3]. The histological staging was confirmed by specimens obtained by *en bloc* ESD or surgical resection. As the primary endpoint, the accuracy for EP/LPM, a definitive indication for ER, by OCT was significantly higher than that by EUS (94.6% *vs* 80.6%, respectively, $P < 0.05$). The overall accuracy of OCT and EUS was 90.1% and 77.1%, respectively (P = 0.0046). Although there were no significant differences in the accuracy of OCT among tumor locations, the accuracy of EUS in the distal esophagus was significantly lower than that in the middle esophagus (P = 0.023). Further, due to the inferiority of EUS in image resolution, we found that the accuracy rate in 33.6% of the cases, which had less than 9-layer visualization in the EUS finding, was significantly lower than that in the remaining cases, which showed a clear discrimination of the 9-layer structure (P = 0.015). This study demonstrated that, because of mechanical advantage of OCT compared to EUS, the accuracy of OCT was significantly superior to that of EUS for the preoperative staging of EP/LPM in the clinical management of SESCCs. However, we noted 3 drawbacks of OCT: (1) a limitation in the penetration depth; (2) the limited width of the depiction area (limited to 4 mm); and (3) the inability to distinguish between cancer invasion and inflammatory cell infiltration. Accordingly, since the first-generation OCT-device still had limited usefulness in the management of SESCCs, further development of the OCT devices will be needed.

PERSPECTIVE

From the point of view that OCT may have advantages in the real-time visualization of the mucosal/submucosal architecture with/without functional alterations, we review promising research data on OCT-devices for providing "optical biopsies" for early detection of neoplastic changes during Barrett's carcinogenesis or for accurate staging of SESCCs to improve treatment curability. However, to apply this technology in the clinical setting, the following issues will needed to be addressed, *i.e.*: (1) easy interpretation with low inter-observer variability; (2) real-time image acquisition for large-areas; and (3) cost effectiveness.

As for the first issue, more refined criteria for easy interpretation with less variability are needed for effective and stable stratification during surveillance. Although accurate interpretation is necessary for both well-trained endoscopists and well-trained pathologists, Qi *et al*[54] demonstrated 82% sensitivity, and 74% specificity in a computer-aided algorithm for the diagnosis of dysplastic BE based on the current criteria. Hence, future computer-aided algorithms can be realized by easy-to-identify criteria.

For the next two issues, OFDI/VLE may provide great cues toward real-time imaging of structural/functional alterations in the 6 cm-length circumferential esophageal mucosa during cancer development and the after-effects of endotherapies. Although no study has demonstrated a close correspondence between the OFDI/VLE imaging and histological evidence, a monitoring system for occult lesions, such as SSIM and tiny dysplastic Barrett's mucosa, with a laser marking platform at VLE-determined sites for biopsy-guidance might unmask their true malignant potential during surveillance. Actually, there has been no study of them using conventional endoscopic imaging, CLE or the first-generation OCT, due to the limited sampling width/depth[55]. Instead, recent studies have proposed that OCT devices might be used to guide the biopsy target for enhanced detection of malignant Barrett's mucosa or to assist in predicting the treatment effect[39,40,49]. Future monitoring by biopsy-correlated OFDI/VLE imaging might yield more effective management strategy with a risk-stratification, which could have the greatest impact on cost-effectiveness and clinical risk-management.

Regarding this point, we also emphasize that the second-generation OCT-devices with marking equipment may have a great impact on the development of new management strategies for SESCCs. In fact, there remain two difficulties in the current strategy for SESCCs. First, accurate staging for large-sized SESCCs by the detection of tiny abnormalities of superficial microvascular structure in the magnifying endoscopic findings with point-sampling characteristics is more difficult than that for small-sized SESCCs[56]. Second, another well-known

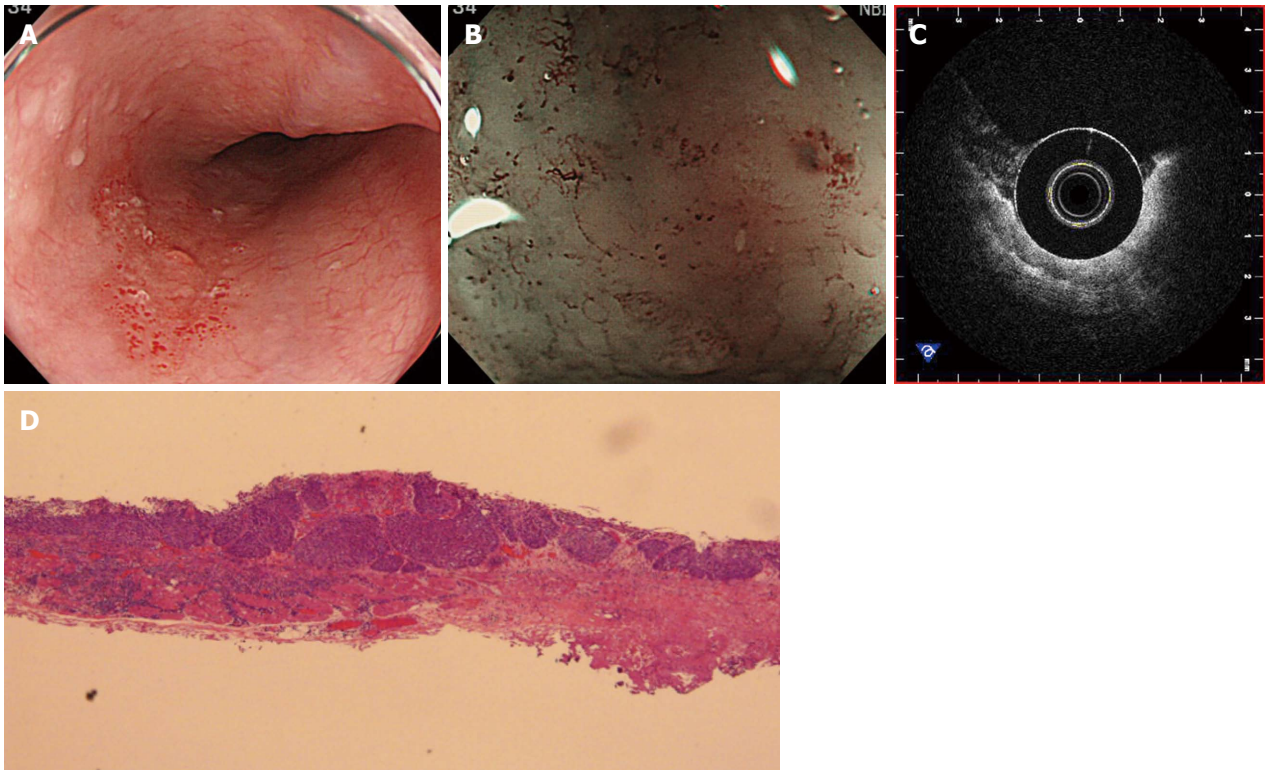

Figure 1 Representative images of superficial esophageal squamous cell carcinoma (0-IIc) with the recurrence after chemo-radiation therapy. A 71-year-old patient suffered from the recurrence of esophageal squamous cell carcinoma after chemo-radiation therapy. A: Irregular reddish lesion in the middle-esophagus in a non-magnifying white light endoscopic finding; B: Avascular area with irregular microvessels was observed in narrow-band imaging magnifying endoscopic finding; C: The involvement of the tumor signal into layer II without involvement of layer III in the OCT-imaging; D: A representative photo of *en bloc* ESD specimen demonstrated pT1a-LPM of histological diagnosis (× 10). OCT: Optical coherence tomography; LPM: Lamina propria mucosa.

difficulty is achieving early detection of the subepithelial recurrence of SESCCs after chemo-radiation therapy (Figure 1). However, the newly advanced OCT-devices can help with early detection by revealing tiny and invasive spots in large lesions and small subepithelial lesions[57]. Accordingly, real-time inspection with the OCT devices, after further technologic innovation, may play a central role in the histological diagnosis and choice of management strategies for esophageal malignancies.

CONCLUSION

In this review, we described previous achievements by which endoscopic OCT enhanced the visualization of structural/functional alterations in mucosal/submucosal tissue of the esophagus, and suggested that it might be useful for guiding/monitoring the area to be targeted for biopsy and treatment as well as to predict the treatment effect. Basically, it is important that the examiner/reviewer have familiarity and expertise in both histopathology and OCT imaging in order to achieve high accuracy in the diagnostic process. However, if reliable criteria of OCT imaging can be developed with computer-aid algorisms, the general use of OCT-related devices may provide "optical biopsies" or "optical staging" of Barrett's-associated neoplasia and SESCCs. Therefore, further development of OCT technology is required for the future progress of management strategies of the esophageal malignancies.

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ORIGINAL ARTICLE

Retrospective Study

For "difficult" benign colorectal lesions referred to surgical resection a second opinion by an experienced endoscopist is mandatory: A single centre experience

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Author contributions: Luigiano C and Iabichino G designed research and wrote the text; Luigiano C performed the endoscopic resection; Iabichino G, Miraglia S and Judica A managed the medical record and extracted all the results from the endoscopy and surgical database for analysis; Pagano N and Eusebi LH were involved in editing the manuscript and literature research; Alibrandi A performed data analysis; Virgilio C reviewed the paper for important intellectual content.

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Abstract

AIM: To assess how many patients with benign "difficult" colorectal lesions (DCRLs) referred to surgical resection, may be treated with endoscopic resection (ER) rather than surgical resection.

METHODS: The prospectively collected colonoscopy database of our Endoscopic Unit was reviewed to identify all consecutive patients who, between July 2011 and August 2013, underwent an endoscopic re-evaluation before surgical resection due to the presence of DCRLs with a histological confirmation of benignancy on forceps biopsy. ER was attempted when the lesion

did not have definite features of deeply invasive cancer. The "nonlifting sign" excluded ER only in naive lesions without a prior attempted resection. Lesions were classified, using the Kyoto-Paris classification for mucosal neoplasia. For sessile and non-polypoid lesions the "inject and cut" resection technique was used. Pedunculated and semi-pedunculated lesions were transected at the stalk just below the polyps head and before or after resection, metal clips or a loop were applied on the stalk to prevent bleeding. The lesions were histologically classified according to the Vienna criteria and for the pedunculated lesions the Haggitt classification was used.

RESULTS: Eighty-two patients (42 females, mean age 62 years) with 82 lesions (mean size 37 mm) were included in the study. Sixty-nine (84%) lesions were endoscopically resected, while 13 underwent surgical resection since ER was deemed unsuitable. On histology, cancer was found in 21/69 lesions (14 intra-mucosal, 7 sub-mucosal) and was associated with the size ($P < 0.001$) and with type 0-Ⅱa + Ⅰs ($P = 0.011$) and 0-Ⅱa + Ⅱc ($P < 0.001$) lesions. All patients with sub-mucosal cancer, underwent surgical resection. Complications occurred in 11/69 patients (7 bleedings, 2 transmural burn syndromes, 2 perforations), all managed endoscopically or conservatively, and were associated with presence of invasive cancer ($P = 0.021$). During follow-up recurrence/residual tissue was found in 14/51 sessile or non-polypoid lesions (13 treated endoscopically, 1 underwent surgical resection) and was associated with type 0-Ⅱa + Ⅰs lesions ($P = 0.001$), piecemeal resections ($P = 0.01$) and with lesion size ($P = 0.004$). Overall, 74% of patients avoided surgery. Surgical resection was significantly associated with type 0-Ⅱa + Ⅰs ($P = 0.01$) and 0-Ⅱa + Ⅱc ($P = 0.001$) lesions, with sub-mucosal invasion on histology ($P < 0.001$), with presence of the "nonlifting sign" ($P < 0.001$), and related to the dimension of the lesions ($P = 0.001$). In the logistic regression analysis, the only independent predictor for surgical resection was the dimension of the lesions ($P = 0.002$).

CONCLUSION: Before submitting patients to surgical resection for a benign DCRL, a second opinion by an experienced endoscopist is mandatory to avoid unnecessary surgery.

Key words: Difficult colorectal lesion; Complications; Endoscopic resection; Non-polypoid lesions; Polypoid lesions; Recurrence

Core tip: A "difficult" colorectal lesion (DCRL) is defined as any lesion that due to its size, shape and location or due to fibrosis as a consequence of previous attempts of endoscopic resection (ER), makes it difficult to remove. Patients with DCRLs are often referred to surgeons for surgical colorectal resection. In our institution, for all patients referred for colorectal surgical resection for DCRLs, the surgeons request an endoscopic re-evaluation and if possible an ER of the lesions. The purpose of this study was to review our results with this approach.

Luigiano C, Iabichino G, Pagano N, Eusebi LH, Miraglia S, Judica A, Alibrandi A, Virgilio C. For "difficult" benign colorectal lesions referred to surgical resection a second opinion by an experienced endoscopist is mandatory: A single centre experience. *World J Gastrointest Endosc* 2015; 7(9): 881-888 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i9/881.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i9.881

INTRODUCTION

A "difficult" colorectal lesion (DCRL) is defined as any lesion who's endoscopic resection (ER) is technically challenging due to the size, the shape or the location, or due to the presence of fibrosis as a consequence of previous attempts of ER[1].

For these reasons, patients with DCRLs are often referred to surgeons for colorectal surgical resection[2,3].

However, surgery is associated with significant morbidity and mortality, especially in older patients with comorbid illnesses, as well as higher costs of the procedures[4-6].

In our institution, patients referred for surgical colorectal resection of DCRLs, with a histological confirmation of benignancy on forceps biopsy, are advised by surgeons to undergo an endoscopic re-evaluation and, if possible, an ER of the lesions.

The aims of this study were to estimate how many patients referred to our unit with DCRLs really needed surgical resection, and to evaluate the outcomes of ER of the lesions in whom it was possible.

MATERIALS AND METHODS

Patients

The prospectively collected colonoscopy database of our Endoscopic Unit was reviewed to identify all consecutive patients who, between July 2011 and August 2013, underwent an endoscopic re-evaluation before surgical resection due to the presence of DCRLs with a histological confirmation of benignancy on forceps biopsy.

All patients underwent a colonoscopy to confirm the presence and location of the lesions, to exclude synchronous lesions, and if possible to endoscopically resect the lesion.

ER was attempted when the lesion did not have definite features of deeply invasive cancer, such as surface ulceration, converging folds, firm consistency with a surface pit pattern suggestive of invasion.

The "nonlifting sign" excluded ER only in naive lesions without a prior attempted resection, whereas it was

not considered an exclusion criteria in case of recurrent lesions or that had undergone a previous partial resection.

Lesion classification

Lesions were classified, using the Kyoto-Paris classification for mucosal neoplasia[7,8]. Polypoid types rise > 2.5 mm above the surrounding mucosa, including lesions with a clear stalk, pedunculated (0-Ip) and semi-pedunculated (0-Isp) types, and lesions without clear stalk, defined as sessile (0-Is) type. Non-polypoid types rise < 2.5 mm above the surrounding mucosa and include elevated (0-Ⅱa), barely perceptible elevated or flat (0-Ⅱb) and slightly depressed (0–Ⅱc) types. Mixed types are lesions with mixed pattern of both a polypoid sessile and a non-polypoid morphology in distinct sectors and include 0-Ⅱa + Is and 0-Ⅱa + Ⅱc types.

ER procedure

All endoscopic procedures were performed by one expert interventional endoscopist (Carmelo Luigiano)[9-12].

For sessile and non-polypoid lesions the "inject and cut" resection technique was used; *en bloc* resection was attempted for lesions ⩽ 30 mm, while for lesions > 30 mm piecemeal resection was performed, taking care to include 1-3 mm of normal tissue in the lateral margins of the resection[9,10].

Pedunculated and semi-pedunculated lesions were transected at the stalk just below the polyps head, complete ensnarement of the head portion with a single application of the snare was first attempted; if this failed, the lesion was trimmed with piecemeal technique until the snare could be placed around the lesion. Before or after resection, metal clips or a loop were applied on the stalk to prevent bleeding[11,12].

Patients were prepared with a fiber- and residue-free diet within 72 h and 4000 mL of a polyethylene glycol electrolytic lavage solution 18 h before colonoscopy.

The procedures were performed with a high-definition colonoscope (Pentax EC-3490L: Pentax, Hamburg, Germany), with a paediatric colonoscope or with an operative or diagnostic video gastroscope (Pentax, Hamburg, Germany), with a high-definition processor (Pentax EPK-i HD).

Submucosal injections were performed with variceal injection needles (Olympus). The injection solution contained only saline, saline with epinephrine (1:10000) or saline and epinephrine with methylene blue mixture (1:10000). The snares used were standard, jumbo or stiff (US Endoscopy, Mentor, Ohio).

Electrosurgery was performed using a combination of cutting (120 W) and coagulation current (60 W), using an ERBE-ICC 200 (Erbe Elektromedizin GmbH, Tübingen, Germany). For sessile or non-polypoid lesions argon plasma coagulation (APC) at a power of 40-60 W and gas flow of 2 L/min using an ERBE APC 300 (Erbe Elektromedizin) was used to ablate any residual tissue at the edge of the resection area.

If localization of the ER site during colonoscopic follow-up was likely to be difficult, the site was marked with a submucosal injection of sterile carbon particle suspension (Spot, GI Supply, Camp Hill, Penn) in the adjacent normal mucosa.

ER procedures were performed on outpatients in the morning. After ER, patients remained in a second-stage recovery area for 4 to 6 h until medically cleared for discharge by the endoscopist. If the case of clinical concerns, the patient was admitted for observation. On discharge, dietary instructions, written contact information and instructions regarding symptoms and potential problems were provided to patients.

Assessment of lesions size and histopathology

The size of the lesions was estimated by comparison with open biopsy forceps and, when possible, also after retrieval. All removed tissue was retrieved using a basket or through the suction channel. All specimens were stained with hematoxylin and eosin for histopathological assessment, and two experienced pathologists examined the resected material. Based on the histological configuration of the crypts, adenomas were classified into tubular, villous, and tubulo-villous. The lesions were histologically classified according to the Vienna criteria and for the pedunculated lesions the Haggitt classification was used[13,14].

Complications

ER induced bleeding was defined as procedural (occurring during resection), early (within 24 h) or delayed (after 24 h). The diagnosis of early and delayed bleeding was based on the presence of rectorrhagia or melena. Transmural burn syndrome, caused by thermal injury, with resultant serosal inflammation, was characterized by localized abdominal pain, leucocytosis and, occasionally, fever. Perforation was diagnosed either by endoscopy during the resection or by the presence of free air on plain abdominal film or abdominal computed tomography scan.

Clinical and endoscopic follow-up

Clinical follow-up was performed after 3 wk from the ER, when the histological results were communicated to the referring specialists and patients.

In patients with pedunculated and semi-pedunculated lesions, surveillance colonoscopy was performed at 12 and 24 mo for lesions with high and low-grade dysplasia, respectively, while for lesions harbouring cancer at 6 and 12 mo, and annually thereafter.

In patients with sessile, non-polypoid and mixed type lesions surveillance colonoscopy was performed after 3, 6 and 12 mo, and then annually after the initial ER.

In patients with sessile, non-polypoid and mixed types lesions, recurrence was defined as the presence of tissue on a follow-up endoscopy. If visible tissue was seen on follow-up examinations, it was snare resected when

Table 1 Characteristics of patients and colorectal lesions recruited

No. of patients	82
Age (mm ± SD) (range)	62 ± 10 (38-81)
Sex (M/F)	40/42
Associated extra-intestinal diseases (%)	
Hypertension	6 (7.5)
Cardiac diseases	3 (3.5)
Chronic renal failure	1 (1.5)
Neoplasms	1 (1.5)
Diabetes mellitus	1 (1.5)
Associated intestinal diseases (%)	
Diverticula	15 (18)
Others colorectal lesions	10 (12)
Left hemicolectomy	3 (3.5)
Number of lesions	82
Size (mm ± SD) (range)	37 ± 18 (20-100)
Indication for surgical resection (%)	
Location	36 (44)
Size	32 (39)
Shape	10 (12)
Recurrence	4 (5)
Shape (%)	
0-Ip	11 (13)
0-Isp	1 (1.5)
0-Is	17 (21)
0-Ⅱa	19 (23)
0-Ⅱa + Is	18 (22)
0-Ⅱa + Ⅱc	12 (14.5)
0-Ⅱb	4 (5)
Location (%)	
Anorectal junction	4 (5)
Rectal	7 (8.5)
Rectosigmoid junction	14 (17)
Sigmoid	16 (19)
Descending colon	3 (4)
Splenic flexure	4 (5)
Transverse	3 (3.5)
Hepatic flexure	10 (12)
Ascending colon	8 (10)
Caecum only	9 (11)
Cecum with ileocecal valve involvement	3 (3.5)
Cecum with appendix orifice involved	1 (1.5)
Biopsy results at the first colonoscopy (%)	
Low-grade dysplasia	18 (22)
High-grade dysplasia	64 (78)
Successful endoscopic resection (%)	69 (84)
Aborted endoscopic resection (%)	13 (16)
Non-lifting sign	6
Frankly malignant lesions	3
Difficult position	2
Very large lesions with difficult position	2

mm: Millimeters; M: Male; F: Female; 0-Ip: Pedunculated lesions; 0-Isp: Semi-pedunculated lesions; 0-Is: Sessile lesions; 0-Ⅱa: Elevated non-polypoid lesions; 0-Ⅱb: Barely perceptible elevated non-polypoid lesions; 0-Ⅱc: Slightly depressed non-polypoid lesions.

feasible and submitted for histopathological examination. The edges of the resection site were typically cauterized with the argon plasma coagulator. Lesions that were too small for snare resection were removed with forceps and then fulgurated with an argon plasma coagulator. During the endoscopic follow-up, any alterations of the mucosa in the area of the previous resection (ulceration, scarring, retraction of mucosa, *etc.*) underwent biopsies.

Outcomes of the study

The parameters evaluated in the study were: age, sex, associated intestinal or extra-intestinal diseases, lesions size, shape and location, reason for surgical resection, successful of ER, reason of aborted ER, technique of ER, complications, technique of treatment of complications, histology, grade of dysplasia and cancer, and recurrence.

Statistical analysis

Continuous data are described by mean, standard deviation and range, according to distribution. Categorical data are presented as numbers and percentages. Relationships between numerical variables were examined by the Spearman correlation coefficient, between categorical and numerical variables by the Biserial correlation, and between categorical variables by the Log-likelihood Ratio test. Results were analyzed in relation to lesion size (divided in two groups: group A lesions < 35 mm and group B lesions ⩾ 35 mm) and were also compared for the technique of resection used (*en bloc vs* piecemeal; APC *vs* no APC). Logistic regression was used to assess the independent predictors of outcomes. A *P*-value of less than 0.05 was considered statistically significant. The software packages applied were SPSS for Windows 11.0. Data analysis of the study was performed by a biomedical statistician (Angela Alibrandi).

RESULTS

During the study period, 82 patients (42 female; mean age 62 years) underwent an endoscopic re-evaluation before surgical resection of a DCRLs with a histological confirmation of benignancy on forceps biopsy. Demographic and clinical data of the included patients are summarised in Table 1.

The reason for referral was the location of the lesion in 36 cases, the size in 32 cases, the type in 10 and recurrence in 4 cases.

The mean (± SD) lesion size was 37 ± 18 mm (range 20-100 mm). The most frequent type was the mixed types in 30 cases (18 type Ⅱa + Is and 12 type Ⅱa + Ⅱc) and the most frequent location was the sigmoid colon in 16 cases.

Among the included lesions, 44 (54%) were < 35 mm, while 38 (46%) were ⩾ 35 mm in diameter.

Of the 82 lesions, 69 (84%) were successfully resected endoscopically, while 13 cases were referred for surgical resection since ER was considered unsuitable due to the following reasons: presence of the "nonlifting sign" in 6 patients, endoscopic appearance of invasive cancer in 3 cases, very large size with difficult location in 2 cases (one patient with a sessile lesion occupying more than 60% of the lumen in the rectosigmoid junction and one patient with a type Ⅱa lesion involving more than half of the cecum and more than half of the circumference of the proximal ascending colon) and in 2 cases due to difficult location (1 with ileocecal valve and 1 with appendiceal orifice involvement).

Table 2 Characteristics of colorectal lesions resected

No. of lesions	69
Size (mm ± SD) (range)	33 ± 12 (20-80)
Shape (%)	
0-Ip	11 (16)
0-Isp	1 (1.5)
0-Is	15 (22)
0-Ⅱa	16 (23)
0-Ⅱa + Is	15 (22)
0-Ⅱa + Ⅱc	8 (11.5)
0-Ⅱb	3 (4)
Location (%)	
Anorectal junction	4 (6)
Rectal	6 (8.5)
Rectosigmoid junction	13 (19)
Sigmoid	15 (22)
Descending colon	2 (3)
Splenic flexure	3 (4)
Transverse	1 (1.5)
Hepatic flexure	9 (13)
Ascending colon	6 (8.5)
Caecum only	8 (11.5)
Cecum with ileocecal valve involvement	2 (3)
Technique of endoscopic resection for the 57 sessile and non-polypoid lesions	
En-bloc endoscopic mucosal resection	23
Piecemeal endoscopic mucosal resection	34
Resection with argon plasma coaugulation	15
Technique of endoscopic resection for the 12 pedunculated and semipedunculated lesions	
Clips	9
Endoloop	3
Complications (%)	11 (16)
Bleeding	7
Perforation	2
Transmural burn syndrome	2
Histology (%)	
Tubular adenoma	13 (19)
Villous adenoma	22 (32)
Tubulovillous adenoma	33 (47.5)
Serrated adenoma	1 (1.5)
Low-grade dysplasia	3 (4)
High-grade dysplasia	45 (65.5)
Intramucosal cancer	14 (20.5)
Invasive cancer	7 (10)

mm: Millimeters; 0-Ip: Pedunculated lesions; 0-Isp: Semi-pedunculated lesions; 0-Is: Sessile lesions; 0-Ⅱa: Elevated non-polypoid lesions; 0-Ⅱb: Barely perceptible elevated non-polypoid lesions; 0-Ⅱc: Slightly depressed non-polypoid lesions.

The characteristics of the 69 resected lesions are presented in Table 2. All lesions were resected in a single session and the resection was evaluated as endoscopically complete in all procedures.

Of the resected lesions, 42 (61%) were < 35 mm, while 27 (39%) were ⩾ 35 mm in diameter. In 12 pedunculated and semi-pedunculated lesions, bleeding prophylaxis was performed with the application of clips to the stalk in 9 cases and with endoloop in the 3 remaining cases.

In the 57 sessile and non-polypoid lesions, *en-bloc* resection was performed in 23 cases while piecemeal resection was used in the other 34 cases. Argon plasma coagulation was applied to the margins of the lesions in 15 of the 57 lesions (all piecemeal resections).

Histological diagnosis of the resected lesions showed 47.5% tubulo-villous, 32% villous, 19% tubular and 1.5% serrated adenomas. Carcinoma was found in 30% of patients (21 cases), out of which 14 showed intra-mucosal and 7 sub-mucosal invasion. All patients with lesions showing sub-mucosal invasion on histology underwent surgery.

Of the 7 invasive lesions, one was located at the rectum, one at the rectosigmoid junction and the remaining 5 lesions in the colon.

The presence of cancer on histology was significantly associated with type 0-Ⅱa + Is (P = 0.011) and 0-Ⅱa + Ⅱc (P < 0.001), and was also related to the size (P < 0.001) of the lesions.

Procedural bleeding occurred in 5/69 (7%) resected lesions; one early (within 10 h) and one delayed (after 72 h) bleeding occurred, both requiring blood units transfusion. The procedural bleeding was always managed endoscopically by applying clips.

Transmural burn syndrome occurred in 2 patients (3%) and was successfully managed conservatively.

Two patients had a perforation that occurred during the final resection of a 40 mm 0-Ⅱa lesion of the ascending colon and during a resection of a 30 mm 0-Is recurred lesion of the rectum. In both patients, successful closure of the perforation with clips was achieved and no further intervention was required.

Endoscopic complications were significantly associated with the presence of invasive cancer on histology (P = 0.021), and in the logistic regression analysis, the only independent predictor of a complication was the dimension of the lesions (P = 0.002).

Among the 69 cases of successful ER, 62 (90%) patients have undergone colonoscopy follow-up for a mean (± SD) time of 16 ± 6 mo (range 6-24).

Among the sessile and non-polypoid lesions (51 cases), during the endoscopic follow-up residual/recurrence tissue was found in 14 (27%) cases; 13 were successfully treated endoscopically, while one patient underwent surgical resection due to 2 recurrence during the endoscopic follow-ups.

Recurrence of the lesion after ER was significantly associated to type 0-Ⅱa + Is (P = 0.001) lesions, to piecemeal resection (P = 0.01) and to the dimension (P = 0.004) of the lesions.

Overall, 74% of patients avoided surgery. Surgical resection was significantly associated with type 0-Ⅱa + Is (P = 0.01) and 0-Ⅱa + Ⅱc (P = 0.001) lesions, with sub-mucosal invasion on histology (P < 0.001), with presence of the "nonlifting sign" (P < 0.001), and related to the dimension (P = 0.001) of the lesions.

In the logistic regression analysis, the only independent predictor for surgical resection was the dimension of the lesions (P = 0.002).

DISCUSSION

This report describes a single-center experience in the endoscopic treatment of a cohort of patients with

DCRLs, showing that three quarters of the patients referred for surgical resection were successfully treated endoscopically.

Data of an European regional FOBT-based colorectal cancer screening program, suggest that up to 10% of patients with benign adenomas detected by screening colonoscopy after a positive fecal occult blood test will be treated surgically[15].

Indeed, a proportion of colorectal lesions, due to their location, size, or shape are considered technically more challenging to be removed endoscopically or are associated with an increased risk of complications (such as bleeding or perforation). Thus, these lesions are not routinely endoscopically resected and are often referred to surgeons for surgical resection[1-3].

Our study confirms these findings since, in our series, failure of ER was associated with the large size and the type of the lesions, as well as the lack of the lifting sign.

However, considering all the patients evaluated, 69 (84%) of them were successfully treated endoscopically, and 61 (74%) have so far avoided an unnecessary surgical procedure.

Our results are in agreement with other studies in whom, in referral centers surgical resection was avoided in the majority of patients with DCRLs (range 58%-90%)[2,16-18].

Therefore, it is possible that endoscopists who are inexperienced or are not used to treat technically challenging lesions, choose to refer patients for surgical resection.

Compared to the 20.1% morbidity and 1.3% mortality rates for surgery of colorectal tumors, general data on ER show much lower morbidity rates (0.7% to 3.7% for perforation and 0.4% to 3.8% for bleeding) and no mortality[19].

The Munich Polypectomy Study showed a correlation between large size, non-pedunculated shape and right-sided location of colorectal lesions and the occurrence of post-procedural complications[20].

Considering only the studies on DCRLs resection, these findings were evident, indeed the mean morbidity rate was 18% (the majority treated endoscopically), however without mortality[2,16-18,21,22].

In accordance with previous studies[2,16-18,21,22], also in our series, ER for DCRLs was performed without mortality and with an acceptable rate of morbidity (16%); moreover, all the complications that occurred were successfully managed endoscopically or conservatively. Procedural bleedings were controlled endoscopically in all cases and all the perforations were detected during the procedure and closed endoscopically with good clinical outcomes.

Furthermore, the complications of ER seem to depend on the lesions characteristics as well as on the experience and skills of the endoscopist.

The present study confirms that ER of DCRLs can be performed with satisfactory safety and that high-risk ERs should be performed by experts at a high-volume center.

Residual/recurrent disease can occur after ER of non-pedunculated colorectal lesions, with a mean rate of 15%[23].

For DCRLs, the mean rate of residual/recurrence is doubled, approximately 30%[2,16-18,21,22]. In our study the local residual/recurrence was detected in 27% of cases in accordance with the results of previous studies on the ER of DCRLs. Moreover, our results confirmed that the piecemeal technique is associated with a higher rate of residual/recurrent neoplasia, as stated by the Italian Colorectal ER Study Group in a recent published paper[24], and was similar despite the use or not of APC after resection.

Our results show also a correlation with the size of the lesions, in accordance with a recent systematic review[23]. The review also confirmed that the pooled estimate risk of recurrence was significantly higher for piecemeal (20%; 95%CI: 16%-25%) than for en bloc resections (3%; 95%CI: 2%-5%; Cochran's Q test $P < 0.0001$)[23].

To reduce residual/recurrence rates, endoscopic submucosal dissection (ESD) has been proposed as a superior technique compared to the "inject and cut" piecemeal ER, since it allows an *en bloc* excision of large colorectal neoplastic tissue, thus allowing a more accurate pathological diagnosis[19].

However, ESD in the colon is technically demanding, with a long learning curve and increased procedures duration; moreover, it requires the use of specialized accessories, increasing the costs of the procedures and has a high perforation rate, making it unlikely to be adopted into therapeutic colonoscopy practice in western countries[19].

Hypothetically, applying ESD to our series, at the best of the performance of the technique, we would have achieved an *en-bloc* resection rate of 80% (45 out of 57 patients). This could have allowed a better evaluation of the submucosal invasion in the 7 patients in which it was found to be present, virtually avoiding surgery to 2 or 3 more patients. The lower recurrence rate (about 1%-2%) could allow a reduction of the number of treatments needed to achieve complete clearance of the lesion, but the higher costs of the procedures counterbalance the reduction of the number of sessions. Moreover, ESD has higher complication rates, requiring the mandatory admission of the patient to be treated. About 1% to 2% of these complications need surgical intervention, reducing the beneficial effect of the better *en-bloc* resection rate.

Furthermore, if the piecemeal ER is performed acquiring as bigger and fewer pieces as possible, including at least 1-3 mm of normal tissue surrounding the lesions, and all fragments of the lesion are retrieved, the risk of missing neoplastic invasion seems negligible, and the recurrence rate is acceptable.

Our results also show that the endoscopic treatment of residual/recurrent tissue was easy and effective (successful in 93%), in accordance with the systematic review by Belderbos *et al*[23], in which after a mean of 1.2 endoscopic re-treatments, successful eradication was

achieved in 91.4% of recurrences.

The main limitations of our study are the relatively small number of reported lesions and the non-prospective, randomized design of the study. Thus, the superiority of ER over surgical treatment cannot be proven, however, such a trial would probably be unethical to perform.

In conclusion, before submitting patients to surgical resection of a benign colorectal lesion, a second opinion by an examiner who is experienced in ER of such lesions is worthwhile and mandatory to avoid unnecessary surgery.

COMMENTS

Background

A "difficult" colorectal lesion (DCRL) is defined as any lesion who's endoscopic resection (ER) is technically challenging. In less experienced endoscopic centres, benign DCRLs are often referred to surgical resection.

Research frontiers

This study aimed to assess how many patients with benign DCRLs referred to surgical resection, may be treated with ER rather than surgical resection.

Innovations and breakthroughs

In these research results, 74% of patients with DCRLs referred to surgeons for colorectal resection, after an endoscopic re-evaluation were successfully treated with ER and avoided surgery.

Applications

Before submitting patients to surgical resection for a benign DCRL, a second opinion by an experienced endoscopist is mandatory to avoid unnecessary surgery.

Terminology

A DCRL is defined as any lesion who's ER is technically challenging due to the size, the shape or the location, or due to the presence of fibrosis as a consequence of previous attempts of ER.

Peer-review

It is an good article.

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ORIGINAL ARTICLE

Retrospective Study

Comparison of endoscopic stenting for malignant biliary obstruction: A single-center study

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Abstract

AIM: To evaluate the efficacy and safety of single-step endoscopic placement of self-expandable metallic stents (SEMS) for treatment of obstructive jaundice.

METHODS: A retrospective study was performed among 90 patients who underwent transpapillary biliary metallic stent placement for malignant biliary obstruction (MBO) between April 2005 and October 2012. The diagnosis of primary disease and MBO was based on abdominal ultrasound, computed tomography, magnetic resonance imaging, endoscopic ultrasound, endoscopic retrograde cholangiopancreatography with brush cytology, biopsy, and/or a combination of these modalities. The type of SEMS (covered or non-covered, 8 mm or 10 mm in diameter) was determined by the endoscopist. Ninety patients were divided into two groups: group 1 (49 patients) who underwent a single-step SEMS placement and group 2 (41 patients) who underwent a two-step SEMS placement. The technical success rate, complication rate, stent patency, and patient survival rate were compared between the groups. In addition, to identify the clinical prognostic factors associated with patient survival, the following variables were evaluated in Cox-regression analysis: gender, age, etiology of MBO (pancreatic cancer or non-pancreatic cancer), clinical stage (Ⅳb; with distant

metastases or Ⅳa >; without distant metastases), chemotherapy (with or without), patency of the stent, and the use of single-step or two-step SEMS.

RESULTS: Immediate technical success was achieved in 93.9% (46/49) in group 1 and in 95.1% (39/41) in group 2, with no significant difference (P = 1.0). Similarly, there was no difference in the complication rates between the groups (group 1, 4.1% and group 2, 4.9%; P = 0.62). Stent failure was observed in 10 cases in group 1 (20.4%) and in 16 cases in group 2 (39.0%). The patency of stent and patient survival revealed no difference between the two groups with Kaplan-Meier analysis, with a mean patency of 111 ± 17 d in group 1 and 137 ± 19 d in group 2 (P = 0.91), and a mean survival of 178 ± 35 d in group 1 and 222 ± 23 d in group 2 (P = 0.57). On the contrary, the number of days of hospitalization associated with first-time SEMS placement in group 1 was shorter when compared with that number in group 2 (28 *vs* 39 d; P < 0.05). Multivariate analysis revealed that a clinical stage of Ⅳa > (P = 0.0055), chemotherapy (P = 0.0048), and no patency of the stent (P = 0.011) were independent prognostic factors associated with patient survival.

CONCLUSION: Our results showed that single-step endoscopic metal stent placement was safe and effective for treating obstructive jaundice secondary to various inoperable malignancies.

Key words: Endoscopic stenting; Single-step; Malignant biliary obstruction; Self-expandable metallic stents; Two-step

Core tip: Single-step placement of expandable metallic stents for treating malignant biliary obstruction is useful for shortening hospitalization. To maximize symptomatic relief and cost benefits, stent placement should not be delayed after deciding on metal stent palliation.

Yamamoto R, Takahashi M, Osafune Y, Chinen K, Kato S, Nagoshi S, Yakabi K. Comparison of endoscopic stenting for malignant biliary obstruction: A single-center study. *World J Gastrointest Endosc* 2015; 7(9): 889-894 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i9/889.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i9.889

INTRODUCTION

Because of improvements in operative procedures and diagnostic techniques, both the incidence of biliary pancreatic malignancies and resection rates have increased. Nevertheless, partly due to the high incidence obstructive jaundice in affected patients, some cases remain inoperable with a poor prognosis. Presently, the preferred treatment for jaundice due to malignant biliary pancreatic obstruction is biliary stent placement. Such stenting was initially performed using polyethylene plastic stents; however, expanding metal stents have been available for several years[1,2]. These expandable metallic stents have several advantages over plastic stents: (1) they can be introduced by a smaller delivery catheter; (2) they have a large inner diameter; and (3) they can remain fixed in position after release[3-6]. In this study, we assessed the safety and efficacy of single-step endoscopic placement for self-expandable metallic stents (SEMS) for treating obstructive jaundice secondary to various inoperable malignancies.

MATERIALS AND METHODS

This study included 90 patients who underwent transpapillary biliary metallic stent placement for malignant biliary obstruction (MBO) between April 2005 and October 2012 at the Saitama Medical Center of Saitama Medical University. For these 90 patients (72 men and 18 women), the diagnoses of primary disease and MBO were based on abdominal ultrasound, computed tomography, magnetic resonance imaging, endoscopic ultrasound, endoscopic retrograde cholangiopancreatography with brush cytology, biopsy, and/or a combination of these modalities. Before cholangiography, all patients were diagnosed with obstructive jaundice caused by an unresectable malignancy because of either very advanced carcinoma or old age. The type of SEMS (covered or noncovered, 8 mm or 10 mm in diameter) was determined by the endoscopist. Ninety patients were divided into two groups: group 1 (49 patients) who underwent a single-step SEMS placement and group 2 (41 patients) who underwent a two-step SEMS placement, depending on the severity of cholangitis. The flowchart for the single-step and two-step SEMS placements for distal MBO is shown in Figure 1.

The technical success rate, complication rate, length of hospital stay, stent patency, and patient survival rate were compared between the groups. Techinical success was defined as successful endoscopic deployment of the stent at the appropriate position resulting in a smooth drainage of the stented bile ducts. Complication rate was defined as the pancreatitis, bleeding and cholangitis arising from stent placement for malignant bile duct obstruction. And, length of hospital stay was defined as the period between hospital admission and discharge. In addition, to identify the clinical prognostic factors associated with patient survival, the following variables were evaluated with a Cox-regression analysis: gender, age, etiology of MBO (pancreatic cancer or nonpancreatic cancer), clinical stage (Ⅳb with distant metastasis or Ⅳa > without distant metastasis), chemotherapy (with or without), patency of the stent, and the use of single-step SEMS or two-step SEMS. This study was performed according to the principles of the Declaration of Helsinki, and informed consent was obtained from the patients and/or their families.

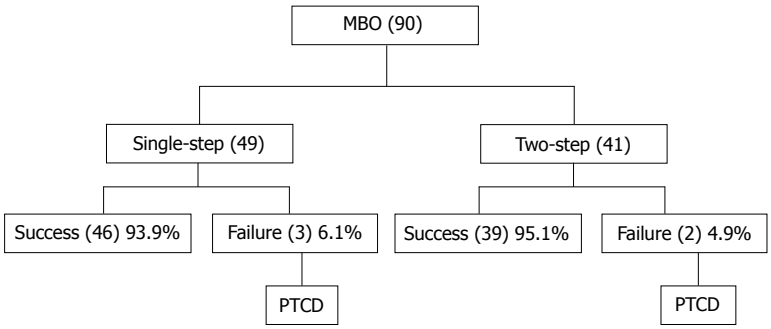

Figure 1 Flowchart showing one-step and two-step self-expandable metal stent placement for distal malignant biliary obstruction. MBO: Malignant biliary obstruction; PTCD: Percutaneous transhepatic cholangiodrainage.

Table 1 Patients characteristics in the two groups

Variable	Single-step (n = 49)	Two-step (n = 41)	P
Mean age (yr)	70.1 ± 12.6	74.3 ± 9.9	NS
Gender (n)			
Male	49	23	< 0.01
Female	0	18	
Etiology of MBO: pancratic cancer (%)	59.2	31.7	0.016
MPD tumor involvement present (%)	36.7	24.4	NS
Spincterotomy (%)	2.0	22.0	0.003
Hilar biliary obstruction (%)	22.4	46.3	0.03
Clinical stage			
Ⅳa > (%)	40.8	61	NS
Ⅳb (%)	59.2	39	NS
Bilateral drainage (%)	4.1	12.2	NS
Technical success rate (%)	93.9	95.1	NS
Complication rate (%)	4.1	4.8	NS
Chemotherapy (%)	55.1	51.2	NS
Length of hospital stay (d)	28.1 ± 28.6	39.6 ± 25.7	< 0.05

MBO: Malignant biliary obstruction; MPD: Main pancreatic duct.

Statistical analysis

We reviewed medical records and radiological images of all patients undergoing stent placement. We then assessed the following variables using univariate analyses (χ^2 test or Fisher's exact test) to identify patient survival: sex, age, etiology of MBO (pancreatic cancer or nonpancreatic cancer), clinical stage (Ⅳb with distant metastasis or > Ⅳa without distant metastasis), chemotherapy (with or without), stent patency, and the use of single-step SEMS or two-step SEMS. We estimated survival times with the Kaplan–Meier method and compared them using the log-rank test. We also calculated odds ratios with 95%CIs for all variables. These statistical tests were two-sided, and statistical significance was set at P value < 0.05 for all analyses. The statistical evaluation was performed using SPSS (IBM, JAPAN) 21.0 for Windows.

RESULTS

The clinical characteristics of the study participants are summarized in Table 1. The single-step group (group 1) included only 49 men (percentage of men = 100%) with a mean age of 70.1 years. The two-step group (group 2) included 23 men (56.1%, P < 0.01) and 18 women (43.9%) with a mean age of 74.3 years. The incidence of pancreatic cancer was higher in group 1 than in group 2 (59.2% *vs* 31.7%, P = 0.016) (Table 1). The information concerning stricture location and endoscopic sphincterotomy (EST) performance before stenting is shown in Table 1. The number of ESTs performed before stenting was statistically significantly higher in group 1 than in group 2 (2.0% *vs* 22%, P < 0.01). The patient characteristics in the two groups categorized by treatment are summarized in Table 1. Although hilar obstruction was significantly less frequent in group 1 than in group 2 (22.4% *vs* 46.3%, P = 0.03), there was no difference in bilateral drainage rate between the two groups (group 1, 4.1% and group 2, 12.2%; P = 0.24). Immediate technical success was achieved in 93.9% (46/49) patients in group 1 and 95.1% (39/41) patients in group 2; there was no significant difference (P = 1.0). Serum total bilirubin levels were within normal limits within two weeks after placement of the stent in all patients who underwent successful procedures. Likewise, there was no difference in the occurrence of complication between the groups (group 1, 4.1% and group 2, 4.9%; P = 0.62).

We observed stent failure in 10 cases in group 1 (20.4%) and 16 cases in group 2 (39.0%). The stent was patent in all 26 cases. There was no difference in the stent patency or patient survival between both groups using the Kaplan–Meier analysis, with a mean patency of 111 ± 17 d in group 1 and 137 ± 19 d in group 2 (P = 0.91, Figure 2), and a mean survival of 178 ± 35 d in group 1 and 222 ± 23 d in group 2 (P = 0.57, Figure 3). In contrast, the number of hospitalization days associated with first-time SEMS placement in group 1 was shorter than in group 2 (28 *vs* 39 d; P < 0.05). Multivariate analysis found that a clinical stage of Ⅳa > (P = 0.0055), chemotherapy (P = 0.0048), and no patency of the stent (P = 0.011) were independently associated prognostic factors for patient survival (Table 2).

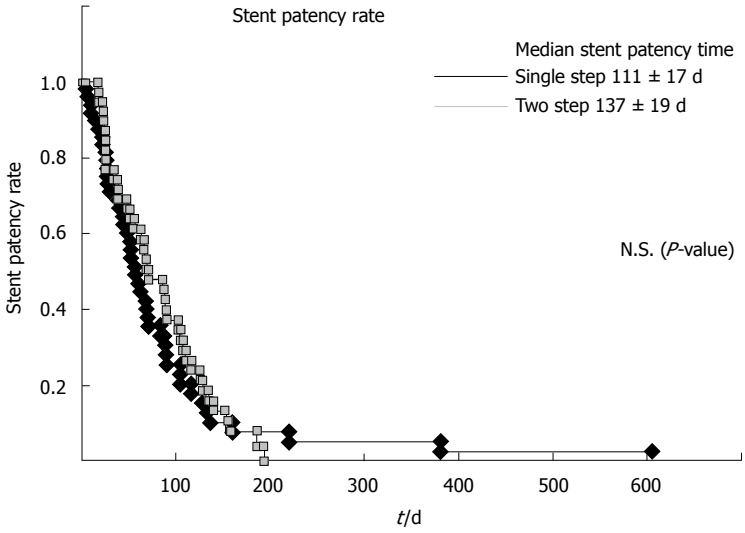

Figure 2 Kaplan-Meier curves showing the patency time of the stent in the single-step and two-step groups.

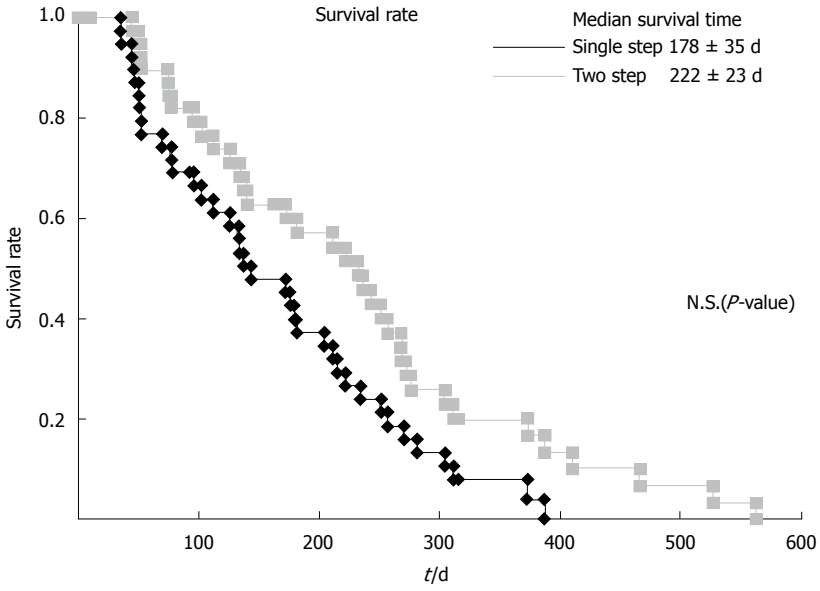

Figure 3 Kaplan-Meier curves showing the survival time of the patient in the single-step and two-step groups.

DISCUSSION

Patients with malignant bile duct obstruction have poor long-term survival and are not candidates for surgical resection. The goals of palliation using a biliary stent placement are symptomatic relief of obstructive jaundice, prevention of cholangitis, and prolongation of survival. Stenting has also been found to improve quality of life of these patients. To maximize the symptomatic relief and cost benefits, the stent should be placed as soon as the decision for metal stent palliation has been made. However, a recent study[7,8] that compared the single-step and two-step procedures found that procedure-related complication rate improved with single-step procedures with no increase in early complications. However, Hamada *et al*[8] reported that single-step SEMS placement for distal MBO was associated with a shorter time to dysfunction and a higher rate of stent migration than two-step SEMS placement. In addition, single-step procedure caused minimal patient discomfort, and avoided both the second intervention and drainage catheter dislocation risk before the deployment of the stent. The single-step placement procedure has two goals: (1) reducing the number of interventions and hence the procedural expenses; and (2) eliminating the need for bile-collecting bags or bottles, thus resulting in an improvement in quality of life as well as reduction in hospitalizations.

In this study, we evaluated the efficacy and safety of the single-step endoscopic placement of SEMS for treating obstructive jaundice that can be caused by various inoperable malignancies. There was no difference in stent patency and patient survival between the two groups in the Kaplan–Meier analysis. In contrast, the

Table 2 Multivariate analysis to identify the clinical prognostic factors for patient survival

Variables	OR	95%CI	*P*
Step (single *vs* two)	0.81	0.49-1.36	0.42
Gender (male *vs* female)	1.05	0.66-1.67	0.83
Age (69 ≥ *vs* 70 <)	1.02	0.59-1.76	0.96
Pancratic cancer (yes *vs* no)	1.01	0.21-1.61	0.98
Clinical stage (ⅣA ≥ *vs* ⅣB)	2.03	1.23-3.34	0.006
Chemotherapy (with *vs* without)	2.18	1.27-3.76	0.005
Patency of the stent (no *vs* yes)	2.21	1.20-4.07	0.011

number of hospitalization days associated with first-time SEMS placement in group 1 was lower than in group 2 (28 *vs* 39 d, $P < 0.05$). The multivariate analysis revealed that a clinical stage of ⅣA > ($P = 0.0055$), chemotherapy ($P = 0.0048$), and no patency of the stent ($P = 0.011$) were independently associated prognostic factors of patient survival. Patients with inoperable malignant strictures generally receive only palliative radiotherapy or chemotherapy and have a limited life expectancy. One possible reason for poor outcomes may be the delay between the diagnostic cholangiography and the placement of the metallic stent[9]. McDougall *et al*[9] determined that 25 (78%) patients had a plastic stent placed before placement of the metallic stent, leading to a mean delay of 123 d, and that 7 (22%) patients had > 1 metallic stent placed. This clearly suggests that if a metallic stent is placed earlier in the course of the disease, the stent patency can be prolonged.

The strategies for self-expandable metal stent placement can depend on the primary cancer types because of the differences in their biological behavior. However, the survival times were not significantly different between patients with pancreatic cancer and those with other primary cancers in our study population. Therefore, this factor may not have any effects on the results of the analyses.

The limitations of our study were as follows. Firstly, our study population was not large enough for a meaningful analysis regarding the efficacy of single-step endoscopic metal stent placement. Secondly, because this was not a prospective study, selection biases regarding the type of SEMS and the procedure adopted for cannulation of the ampulla were present. We propose the implementation of initial stenting for partial drainage of malignant hilar bile duct strictures, rendering contralateral drainage as a last resort for cases with severe cholangitis or insufficient reduction of jaundice.

To conclude, single-step placement of expandable metallic stents for MBO cases that are inoperable is a useful method to shorten hospitalization. Once the decision about metal stent palliation has been made, the stent should be placed as soon as possible to maximize symptomatic relief and cost benefits.

In conclusion, our results showed that single-step endoscopic metal stent placement was safe and effective for treating obstructive jaundice secondary to various inoperable malignancies.

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COMMENTS

Background

Although self-expandable metal stent (SEMS) placement has been widely performed for treating malignant biliary obstruction (MBO), few studies have compared single-step SEMS (direct placement without a prior plastic stent) and two-step SEMS (stent placement at second session following temporary plastic stent placement).

Research frontiers

The objective of this study was the evaluation of the safety and efficacy of single-step endoscopic placement of SEMS for treating obstructive jaundice caused by various inoperable malignancies.

Innovations and breakthroughs

This was a retrospective single-center study of 90 consecutive patients who had undergone endoscopic retrograde cholangiopancreatography-guided transpapillary biliary metallic stent placement for MBO during a 7.5-year-period. The patients of this study were divided into two groups: a single-step SEMS placement group ($n = 49$) and a two-step SEMS placement group ($n = 41$). MBO etiologies were similar between both groups, with pancreatic cancer accounting for 46.7% cases. No significant differences in the patency rate of stents and patient survival were observed between the single-and two-step groups. In contrast, the number of hospitalization days associated with first-time SEMS placement in the single-step group was lower compared with that in the other group (28 *vs* 39 d). Multivariate analysis identified that ⅣA > clinical stage ($P = 0.0055$), chemotherapy ($P = 0.0048$), and no patency of the stent ($P = 0.011$) were independently associated prognostic factors for patient survival.

Applications

These findings will be particularly interesting to the readership of World Journal of Gastrointestinal Endoscopy as they demonstrate that single-step endoscopic metal stent placement is effective and safe for treating obstructive jaundice caused by various inoperable malignancies.

Peer-review

This is a manuscript about an interesting issue that has not been published extensively. It is written in fluent, simple English, easy to comprehend.

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Review on sedation for gastrointestinal tract endoscopy in children by non-anesthesiologists

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Abstract

AIM: To present evidence and formulate recommendations for sedation in pediatric gastrointestinal (GI) endoscopy by non-anesthesiologists.

METHODS: The databases MEDLINE, Cochrane and EMBASE were searched for the following keywords "endoscopy, GI", "endoscopy, digestive system" AND "sedation", "conscious sedation", "moderate sedation", "deep sedation" and "hypnotics and sedatives" for publications in English restricted to the pediatric age. We searched additional information published between

January 2011 and January 2014. Searches for (upper) GI endoscopy sedation in pediatrics and sedation guidelines by non-anesthesiologists for the adult population were performed.

RESULTS: From the available studies three sedation protocols are highlighted. Propofol, which seems to offer the best balance between efficacy and safety is rarely used by non-anesthesiologists mainly because of legal restrictions. Ketamine and a combination of a benzodiazepine and an opioid are more frequently used. Data regarding other sedatives, anesthetics and adjuvant medications used for pediatric GI endoscopy are also presented.

CONCLUSION: General anesthesia by a multidisciplinary team led by an anesthesiologist is preferred. The creation of sedation teams led by non-anesthesiologists and a careful selection of anesthetic drugs may offer an alternative, but should be in line with national legislation and institutional regulations.

Key words: Gastro-intestinal endoscopy; Gastroscopy; Colonoscopy; Sedatives; Pediatric ages; Anesthetics; Analgesics

Core tip: Sedation for pediatric gastro-intestinal endoscopy is preferably performed by pediatric anesthesiologists, as part of a multidisciplinary team. However, in many hospitals pediatric anesthesiology is insufficiently developed. The creation of sedation teams led by non-anesthesiologists and a careful selection of anesthetic drugs may offer an effective and safe alternative. These teams should be in line with national legislation and institutional regulations. This paper will help non-anesthesiologists to provide as good-as-possible sedation for children undergoing endoscopy. Practical protocols were developed providing up-to-date information on the most effective and most safe options.

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INTRODUCTION

Esophago-gastro-duodenoscopy in children needs almost always to be performed under anesthesia or deep sedation. Procedural analgesia and sedation for procedures performed in ambulatory care are changing. The authors reviewed the literature on sedation and for endoscopy by non-anesthesiologists and to propose practical algorithms.

In order to obtain the greatest yield from a pediatric gastrointestinal (GI) endoscopic procedure and to perform these with the highest quality and with the maximum level of safety, some prerequisites must be fulfilled. A pediatric gastroenterologist or dedicated pediatrician must have judged the necessity of the procedure to optimize patient management. The procedure must be performed by a skilled endoscopic team with appropriate equipment in a suitable environment. The patient and parents or guardians must be informed as much and good as possible.

General anesthesia is only possible in a limited number of centers because of shortness of anesthesiologists. The aim of this review is to present and discuss different sedation protocols for non-anesthesiologists for pediatric GI endoscopies. Several protocols for procedural sedation by non-anesthesiologists have been produced by different professional bodies and organizations. However, practical algorithms for these procedures have not been published[1].

MATERIALS AND METHODS

The search for studies on pediatric sedation for GI endoscopy was an update of van Beek and Leroy[2]'s search strategy for the period between January 2011 (when their search was finished) and January 2014 and utilized the following databases: MEDLINE, Cochrane, and EMBASE[2]. These were searched for the keywords "endoscopy, GI", "endoscopy, digestive system" and "sedation", "conscious sedation", "moderate sedation", "deep sedation", and "hypnotics and sedatives" for publications in English restricted to the pediatric age group, which was defined as 0 to 18 years. Subsequently a search for pediatric GI endoscopy sedation guidelines for the same keywords as above for the last 20 years with the same limits (publications in English, pediatric population) was undertaken. The search was expanded to include guidelines for GI endoscopy sedation by non-anesthesiologists for the adult population for the last 10 years. Furthermore a search for guidelines for pediatric procedural sedation published in the last 10 years was made.

RESULTS

The first search revealed 12 studies of which 8 are listed in Table 1[3-10]. Four of them were not relevant: Liu *et al*[11] analyzed anesthesia for outpatient gastroscopies and colonoscopies in adults only, Yen *et al*[12] studied sex differences in sedation with midazolam and alfentanil for gastroscopy only in adults, too[3,4]. The aim of the study of Vadlamudi *et al*[13] was evaluation of ileoscopy *via* stoma and not a sedation[13]. And finally, Siwiec *et al*[14] tested transnasal gastroscopy with ultrathin endoscope in non-sedated healthy volunteers or patients with the signs or symptoms of gastro-esophageal reflux disease.

We found one guideline for pediatric GI endoscopy in

Table 1 Publications from the first search ("endoscopy, gastrointestinal", "endoscopy, digestive system" AND "sedation", "conscious sedation", "moderate sedation", "deep sedation", and "hypnotics and sedatives"; limits: publications in English, paediatric population

Ref.	Methodology	Results	Limitations	Conclusions
Bedirli *et al*[3]	Study type: prospective, randomised, double-blinded Patients: *N* = 80; 1–16 yr; ASA Ⅰ, Ⅱ Procedure: upper GI endoscopy Drugs: baseline: propofol (1 mg/kg; additional 0.5–1 mg/kg as needed); intervention: fentanyl (2 μg/kg) *vs* tramadol (2 mg/kg) Intended sedation level: deep sedation Additional interventions: spray of lidocaine 10%; infusion of 10 lactated Ringer's solution (10 mL/kg per hour); supplemental oxygen 3–4 L/min) Administered by: anesthesiologist Outcome measures: Adverse events: HR (change for 20% from the baseline), BP (change for 20% from the baseline), SpO2 (< 90% for more than 15 s), respiratory rate, agitation score Effectiveness: Ramsey sedation score, duration of endoscopy, Steward recovery score, endoscopist's rating of ease of procedure, total propofol consumption	Adverse events: self-limited bradycardia and transient desaturation in age group 0–2 yr, more in the fentanyl group Effectiveness: lower sedation scores in tramadol group; no difference of gastroenterologist rating	Only one dosage of drugs instead of titrating them	Propofol with tramadol or propofol provided efficient sedation; significantly less adverse effects in the tramadol group
Brecelj *et al*[4]	Study type: randomized, controlled, single-blinded Patients: *N* = 201; 1–18 yr Procedure: gastroscopy, colonoscopy Drugs: ketamine (0.75 mg/kg with additions of 0.25 mg/kg up max. to 1.5 mg/kg; repeated after 10–15 min at 0.5 mg/kg as needed) Intervention: midazolam (0.1 mg/kg; max 2.5 mg; repeated after 30–60 min at 0.05 mg/kg as needed) *vs* no premedication Intended sedation level: deep sedation Additional interventions: none Administered by: dedicated nurse under supervision of endoscopist Outcome measures: Adverse events: respiration rate, HR, BP, SaO2 (any drop below 92%), adverse reactions Effectiveness: ease of procedure, total ketamine consumption	Adverse events: mild self-limited laryngospasm in 3%, high rate of desaturations (approx. in 40%), vomiting in 17%, regardless of study group; more emergence reactions in ketamine group during recovery (10 *vs* 2) Effectiveness: high rate of sedation adequacy	Study was not double-blinded	Ketamine starting dose should be at least 1 mg/kg; more emergence reactions without midazolam premedication; same frequency of other adverse reactions
Miqdady *et al*[5]	Study type: retrospective cohort study Patients: *N* = 301; 1 (more than 10 kg) –18 yr; ASA Ⅰ, Ⅱ Procedure: upper, lower or combined GI endoscopy Drugs: atropine (0.01–0.02 mg/kg per minute. 0.1 mg, max. 0.4 mg); midazolam (0.05–0.2 mg/kg); ketamine (0.5–1 mg/kg) Intended sedation level: deep sedation Additional interventions: none Administered by: endoscopist Outcome measures: Adverse events: respiration rate, HR, BP, SaO2 (any drop below 94%), side effects Effectiveness: the adequacy of sedation	Adverse events: desaturation in 12.3%, in 1.2% disruption of examination due to persistent desaturation; in 1.2% respiratory distress after examination Effectiveness: effective and uneventful sedation in 79.4%	Retrospective study	Midazolam and ketamine sedation is safe and effective for diagnostic GI endoscopies in children older than 1 yr weighting more than 10 kg without comorbidities

Motamed *et al*[6]	Study type: prospective, randomised, double-blinded Patients: *N* = 150; 1–18 yr; ASA Ⅰ, Ⅱ Procedure: upper GI endoscopy Drugs: main sedative: midazolam (0.1 mg/kg; if needed repeated doses up to 5 mg or 0.3 mg/kg); premedication 45 min before the procedure with oral placebo (normal saline), oral ketamin (5 mg/kg), or oral fentanyl (2 μg/kg) Additional interventions: spray of lidocaine 10%; additional oxygen trough nasal cannula at 2 L/min Administered by: registered nurse supervised by anaesthesiologist Outcome measures: Adverse events: respiration rate, HR (decrease by 30% from baseline), BP (decrease or increase by 20%), SaO2 (any drop below 90%) Effectiveness: total midazolam dose, modified Ramsey sedation score, procedure time, discharge time, ease of *iv* catheter placement, separation from parents agitation, the adequacy of sedation	Adverse events: in total in 26% of patients (hypoxia in 7.3%, hypotension in 6.7%, dizziness in 20%, nausea in 10%, vomiting in 17.6%); mild, easily managed Effectiveness: the total recovery and procedure duration time was shorter in the ketamine-midazolam group, inadequate sedation in 10.2% in placebo-midazolam and in 8% in fentanyl-midazolam *vs* in 3.9% in ketamine-midazolam group; the mean administered dose of midazolam was the lowest in ketamine-midazolam group; the *iv* line placement and separation from parents was easier in ketamine-midazolam group; only 27.4% of patients did not remember the procedure		Sedation with oral ketamine-iv midazolam is better than placebo-midazolam or oral fentanyl-iv midazolam
Chiaretti *et al*[7]	Study type: retrospective (12 yr), multicentric Patients: N = 36516; 1 to > 10 yr; ASA Ⅰ, Ⅱ, Ⅲ Procedure: different painful procedures Drugs: main sedative: propofol 2 mg/kg in children from 1 to 8 yr of age and 1 mg/kg in older children and in children younger than 1 yr; further doses of 0.5–1.0 mg/kg in the case of agitation or complain; premedication: atropine 0.010–0.015 mg/kg, ketamine (0.5 mg/kg) to avoid infusion pain in 2 centres (not in gastroscopy); additional oxygen trough nasal cannula at 6 L/min Intended sedation level: deep sedation Administered by: paediatrician (anaesthesiologist available in case of need) Outcome measures: mean arterial pressure, heart rate and SatO2, incidence, type and timing of adverse events (major and minor) and number of calls to the emergency team Effectiveness: total dosage of the sedative agents, level of sedation (Ramsay scale)	Adverse events: in 6 patients (0.02%) emergency team intervention (prolonged laryngospasm in 3 patients, bleeding in 1, intestinal perforation in 1, and 1 during lumbar puncture); milder adverse events: hypotension in 19 patients (0.05%), ventilation by face mask and additional oxygen in 128 patients (0.4%), laryngospasm in 78 patients (0.2%), bronchospasm in 15 patients (0.04%); minor complications more often in children who underwent gastroscopy; none of the children experienced severe side effects or prolonged hospitalisation.	Retrospective study	Propofol is safe and effective for paediatrician-administered procedural sedation in children; appropriate training for paediatricians is important
Gül *et al*[8]	Study type: randomized, controlled, double-blinded Patients: *N* = 64; 3-14 yr; ASA I Procedure: esophagogastroduodenoscopy Drugs: main sedative: propofol 2 mg/kg; analgesic: group R: remifentanil 0.25 μg/kg, group F: fentanyl 0.5 μg/kg; additional oxygen trough nasal cannula at 4 L/min Intended sedation level: deep sedation Administered by: anesthesiologist Outcome measures: MAP, HR, RR, and SpO_2 Effectiveness: ease of gastroscopy, patient's movements during procedure, additional doses of drugs; level of sedation (Ramsay scale); duration of PACU stay	Adverse events: prolonged apnoea in 14 (43.8%) children in group R and in 11 (33.3%) children in group F; none required endotracheal intubation; Effectiveness intraoperative respiratory rate, time to eye opening, opioid consumption, and duration of recovery were significantly shorter in group R duration of PACU stay were significantly shorter in group R than in group F		Remifentanil (combined with propofol) is an efficient and as safe as fentanyl propofol combination for esophagogastroduodenoscopy in children
Long *et al*[9]	Study type: retrospective analysis of prospectively collected data Patients: *N* = 4904; 15-90 yr; ASA Ⅰ-Ⅳ Procedure: esophagogastroduodenoscopy Drugs propofol 1-100 mg and/or midazolam 1-3 mg^2 mg/kg Administered by: endoscopist Outcome measures: influence of pre-existing disease and ASA score on oxygen desaturation (SpO_2) < 90%	Adverse events: hypoxemia in 245 patients (5%); risk factors: high BMI (30 kg/m^2), hypertension, diabetes, gastrointestinal disease, heart disease ASA score was not predictive for hypoxemia	Retrospective study	Independent risk factors for hypoxemia were high BMI, hypertension, diabetes, gastrointestinal and heart diseases and combined gastro and colonoscopy

Agostoni *et al*[10]	Study type: retrospective analysis of prospectively collected data Patients: *N* = 17999 (17524 in older than 12 yr, 457 in < 12 yr); 4-74 yr; ASA I-IV Procedure: esophagogastroduodenoscopy and in some cases different procedures (mucosectomy, hemostatic clip, percutaneous endoscopic gastrostomy, …) Drugs: propofol induction (in children 1-2 mg/kg BW) then in continous infusion Intended sedation level: deep sedation Administered by: anesthesiologist Outcome measures: adverse events (hypotension, desaturation, bradycardia, hypertension, arrhythmia, aspiration, respiratory depression, vomiting, cardiac arrest, respiratory arrest, angina, hypoglycemia, and/or allergic reaction)	Adverse events: rare in children (2.6%) and in adults (4.5%), in children were more often only bradycardia (2.1%) and hypotension (0.44%) 3 adult patients died; no death case in children	Retrospective analysis, single centre data	Deep sedation with intravenous propofol for endoscopic procedures is safe in children and adults

ASA: American Society for Anesthesiology; BP: Blood pressure; GI: Gastrointestinal; HR: Heart rate; SpO2: Oxygen saturation; BMI: Body mass index; RR: Respiratory rate.

English which addressed different aspects including sedation[15].

We expanded the search to guidelines for sedation for GI endoscopy performed by non-anesthesiologists in adult patients during the last 10 years. The search revealed 9 publications which are listed in Table 2[16-24].

The search for guidelines for pediatric procedural sedation published in English during the last 10 years revealed 10 publications. Two are general guidelines for sedation in children[25,26]. Another one, followed by an update published 7 years later, addresses specifically ketamine sedation for emergency departments[27,28]. Others are specifically developed for sedation for dental procedures in children. They are listed in Table 3[15,25,26,28-33].

Pre-requisites for safe and effective sedation by non-anesthesiologists

GI endoscopy must be discussed with the child if emotionally and intellectually competent enough and parent(s)/guardian(s). The pre-sedation assessment is listed in Table 4. Patients should be classified by physical status assessment as developed by the American Society for Anesthesiology (ASA) (Table 5). If the child's ASA classification conforms to class Ⅰ or Ⅱ, sedation can be performed safely. If the child fits in ASA class Ⅲ classification, the benefits of sedation must be carefully weighed against the risks and in the vast majority of cases anesthesiology will be preferable. Patients in ASA class Ⅳ and Ⅴ must be anesthetized by anesthesiologists[28,34].

The depth of sedation is influenced by the procedure. If analgesia is needed together with sedation, as in the case of endoscopic-therapeutic procedures, the patient has to be anesthetized. The same is valid for emergency GI endoscopies such as removal of a foreign body from the upper GI tract and GI bleeding. Sedation necessitates that a team member assigned for observing the vital signs of the patient, since monitoring of pulse oximetry, heart rate and preferably also capnography are insufficient[8,12].

Equipment for resuscitation must be present in the endoscopy room. The team has to be trained in pediatric advanced live support techniques and has to be familiar with measures needed in any scenario of complications[1].

Sedatives and their combinations

Legislation and regulation regarding limitations of administration of different medications, such as inhalation anesthetics, differ from country to country. Therefore, limitations caused by local legislation should be carefully checked. In most countries, the administration of inhalation anesthetics is only authorized by anesthesiologists.

Premedication

Premedication with midazolam (oral or intra-nasal) lessens the stress for an intravenous (*iv*) catheter placement and other preparations for GI endoscopy before sedation or anesthesia. This procedure is effective and safe although intranasal administration may cause local discomfort. In order to decrease the stress and pain caused by a venepuncture, an eutectic mixture of the topical anesthetics lidocaine and prilocaine provides local anesthesia when applied with an occlusive dressing 30-60 min before venipuncture[35].

An *iv* catheter provides the most effective way of delivering agents needed for sedation and analgesia. Inhalation, intramuscular or other sedation regimens are less well

Table 2 Gastrointestinal endoscopy sedation guidelines for adults

Organisation Ref.	Title	Year of publication
American Association for the Study of Liver Diseases; American College of Gastroenterology; American Gastroenterological Association Institute; American Society for Gastrointestinal Endoscopy; Society for Gastroenterology Nurses and Associates Vargo *et al*[16]	Multisociety sedation curriculum for GI endoscopy	2012
Task Force Members. European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anaesthesiology Dumonceau *et al*[17]	Guideline: Non-anesthesiologist administration of propofol for GI endoscopy	2010
Society of American Gastrointestinal Endoscopic Surgeons Heneghan *et al*[18]	Surgeons. Society of American Gastrointestinal Endoscopic Surgeons guidelines for office endoscopic services	2009
Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy Lichtenstein *et al*[19]	Sedation and anesthesia in GI endoscopy	2008
Training Committee of the American Society for Gastrointestinal Endoscopy Vargo *et al*[20]	Training in patient monitoring and sedation and analgesia	2007
Working Group on Endoscopy, Austrian Society of Gastroenterology and Hepatology (OGGH) Schreiber[21]	Austrian Society of Gastroenterology and Hepatology (OGGH)-guidelines on sedation and monitoring during GI endoscopy	2007
Training Committee American Society for Gastrointestinal Endoscopy[22]	Training guideline for use of propofol in gastrointestinal endoscopy	2004
American Society for Gastrointestinal Endoscopy, Standards of Practice Committee Waring *et al*[23]	Guidelines for conscious sedation and monitoring during GI endoscopy	2003
Standards Practice Committe American Society for Gastrointestinal Endoscopy Faigel *et al*[24]	Guidelines for the use of deep sedation and anesthesia for GI endoscopy	2002

GI: Gastrointestinal.

Table 3 Paediatric procedural sedation guidelines

Organisation Ref.	Title	Year of publication
Green *et al*[28]	Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update	2011
National Clinical Guideline Centre (United Kingdom)[26]	Sedation in children and young people: Sedation for diagnostic and therapeutic procedures in children and young people	2010
American Academy on Pediatric Dentistry Clinical Affairs Committee-Sedation and General Anesthesia Subcommittee; American Academy on Pediatric Dentistry Council on Clinical Affairs[29]	Guideline on use of anesthesia personnel in the administration of office-based sedation/general anesthesia to the pediatric dental patient	2009
American Academy on Pediatrics; American Academy on Pediatric Dentistry[30]	Guideline for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures	2009
American Academy of Pediatrics; American Academy of Pediatric Dentistry Coté *et al*[25]	Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update	2006
American Academy on Pediatric Dentistry Clinical Affairs Committee-Sedation and General Anesthesia Subcommittee; American Academy on Pediatric Dentistry Council on Clinical Affairs[31]	Guideline on use of anesthesia care providers in the administration of in-office deep sedation/general anesthesia to the pediatric dental patient	2005
American Academy of Pediatric Dentistry American Academy of Pediatric Dentistry Committee on Sedation and Anesthesia[15]	Guideline on the elective use of minimal, moderate, and deep sedation and general anesthesia for pediatric dental patients	2005
American Academy of Pediatric Dentistry[32]	Clinical guideline on the elective use of minimal, moderate, and deep sedation and general anesthesia for pediatric dental patients	2004
Green *et al*[27,28]	Clinical practice guideline for emergency department ketamine dissociative sedation in children	2004
UK National Clinical Guidelines in Pediatric Dentistry Hosey[33]	UK National Clinical Guidelines in Paediatric Dentistry. Managing anxious children: the use of conscious sedation in paediatric dentistry	2002

Table 4 Preparation of a child for sedation for gastrointestinal endoscopy

	Preparation of the patient	Comments
Planning of the investigation /procedure	Understanding of the investigation	Explanation of the examination:
		Aims of investigation
		Possible risks
	Informed consent	Signed by parents and/or the child (depending on the age and legislation)
	Presedation assessment	Co-morbidity
		ASA score (Table 5)
		Medicines
		Bleeding tendency
		Previous undesirable effects of sedation/anesthesia
		Specific contraindications for the planned sedation
		Previous complications of investigations
		Allergies
		The need for antibiotic prophylaxis
		Laboratory investigation/consultation before the investigation/procedure (*e.g.*, tests of hemostasis in case of bleeding tendency)
		Additional important data
Preparation	Exact instructions (fasting time, colon cleansing *etc.*)	
On the day of examination	Focused history:	
	Current health state	
	Infectious diseases	
	Epidemiologic situation	
	Fasting	
	Allergy	
	Specific contraindications for the planned sedation	
	Physical examination	Complete physical examination with the focus on respiratory and cardiovascular system
	Measurement of vital signs	Arterial blood pressure
		Heart rate
		Arterial oxygen saturation
	Laboratory investigations	If needed

ASA: American Society for Anesthesiology.

Table 5 American Society of Anesthesiologists physical status classification[24]

Class	Description	Suitability for sedation
Class Ⅰ	A normally healthy patient	Excellent
Class Ⅱ	A patient with mild systemic disease (*e.g.*, controlled asthma)	Generally good
Class Ⅲ	A patient with severe systemic disease (*e.g.*, a child who is actively wheezing)	Intermediate to poor
Class Ⅳ	A patient with severe systemic disease that is a constant threat to life (*e.g.*, a child with status asthmaticus)	Poor
Class Ⅴ	A moribund patient who is not expected to survive without the operation (*e.g.*, a patient with severe cardiomyopathy requiring heart transplantation	Extremely poor

documented. An *iv* catheter is also important for emergency access in the case of adverse events occurring during sedation or the endoscopic procedure[25,36,37].

Mechanisms of action and the main undesirable effects of sedatives and adjuvant medicines are listed in Table 6[8,38-49]. Usual dosage regimens and the main contraindications are listed in Table 7.

Propofol

Propofol is a rapid onset and short acting anesthetic without analgesic properties and with a narrow therapeutic range. Its sedative properties result from agonistic action on gamma-aminobutyric acid (GABA) receptors. Propofol is contraindicated in infants younger than 1 mo bacasue of missing data on safety according to a Cochrane review[50]. The main undesirable effects include pain on injection, respiratory depression, bradycardia and hypotension[38,46].

van Beek and Leroy[2] reported failure to conduct a procedure due to incomplete sedation in only 0.0%–0.4% of cases, despite the fact that the sedation was performed in 88.1% by non-anesthesiologists[2]. The recovery time after propofol administration was shorter than after midazolam/meperidine[2]. Major respiratory complications occurred in 11/3883 propofol sedations (0.3%), but no I intubation and no sequelae were reported. The incidence of undesirable effects (*e.g.*, temporary desaturation due to hypoventilation, laryngospasm) was comparable to other protocols and was more frequent in younger children, especially infants[2].

A randomized study in 90 adults undergoing colonoscopy showed that the satisfaction of patients was greater

Table 6 Sedatives and adjuvant medicines for paediatric gastrointestinal endoscopy sedation

Generic name	Mechanism(s) of action	Main undesirable effects	Comments	Ref.
Sedatives				
Fentanyl	Opioid receptors agonist; analgesia and sedation	Respiratory depression, hypotension	Due to analgesic effect only it should be combined with benzodiazepine; antagonist naloxone	[38-40]
Ketamine	Binds to the Nmethyl-Daspartate (NMDA) receptors; anesthesia, analgesia, amnesia, sedation, immobilisation	Laryngospasm, hypertension, tachycardia, hypersalivation, vomiting, random movements, increase in intraocular pressure, emergence phenomena (floating sensations, vivid dreams, blurred vision, hallucinations, and delirium)	Beneficial respiratory properties and analgesic potency S(+) isomer has less adverse effects	[40-42]
Meperidine	Opioid receptors agonist; analgesia and sedation	Respiratory depression, pruritus, vomiting	Interaction with monoamine oxidase inhibitors	[38,43,44]
Midazolam	GABA receptor agonist; anterograde amnesia, anxiolysis, sedation, hypnosis	Respiratory depression, hypotension, paradoxical agitation	Without analgesic effect; should be combined with analgesic (usually opioids) Concomitant use with opioid increases the risk of respiratory depression antagonist flumazenil	[38-40]
Nitrous oxide	Inhalation anaesthetic	Vomiting, dizziness, voice change, euphoria, laughter	The need of scavenging system Use mostly limited to anaesthesiologists	[38,40,45]
Propofol	GABA receptor agonist; sedation, hypnosis, amnesia	Respiratory depression, apnoea, hypotension, painful injection		[38,40,46]
Sevoflurane	Inhalation anaesthetic	Recovery agitation, bradycardia, hypotension, cough, vomiting, seizures	The need of scavenging system Use limited to anaesthesiologists	[47-49]
Antagonists				
Flumazenil	Benzodiazepine antagonist	Nausea, vomiting	Contraindicated in benzodiazepine dependence, seizure disorder, cyclic antidepressant overdose, elevated intracranial pressure in patients, and in patients taking medicines known to lower the seizure threshold	[40]
Naloxone	Opioid antagonist	Nausea, vomiting, tachycardia		[40]

and there were less undesirable effects when they were sedated by an endoscopist than by an anesthesiologist[51]. A Scandinavian study tested a 6-wk educational program for registered nurses with excellent safety results[52].

The largest multicenter prospective study of propofol sedation for different pediatric procedures outside an operating theatre was published by the international (United States and Canada) Pediatric Sedation Research Consortium. They analysed the data of 49836 propofol sedation episodes and showed that propofol-based sedation is amongst the safest sedation practice for children[53]. Cardio-respiratory resuscitation was necessary in two cases. Pulmonary aspiration of gastric fluid secondary to vomiting during sedation occurred in four patients. Less serious respiratory adverse events were: desaturation in 154/10000 procedures; central apnea or upper airway obstruction in 124/10000; stridor in 10/10000; laryngospasm in 20/10000; excessive salivation in 73/10000; and vomiting in 10/10000 cases. The authors of this report estimate propofol sedation safe in children. Interestingly there were no differences in adverse effects between anesthesiologists and non-anesthesiologist. However, it should be pointed out that this report did not focus on upper GI endoscopy specifically, in which a shared airway is an important consideration, especially as attempting esophageal intubation may have the potential for induction of laryngospasm. However, it is stressed by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Endoscopy Working Group that the advice of the Pediatric Sedation Research Consortium, including institutions with highly motivated and well organized sedation/anesthesia teams, is only to be considered when anesthetic teams are not available, and that priority should go to actions to obtain these anesthetic teams.

Chiaretti *et al*[7] published a retrospective study on pediatric procedural sedation with propofol over a 12-year period in three Italian hospitals[7]. They analyzed 36516 procedural sedations for different painful procedures. Deep sedation was achieved in all patients. None of the children experienced severe side effects or needed a prolonged hospitalization. In six patients (0.02%) emergency team had to intervene (prolonged laryngospasm in three patients, bleeding in one, intestinal perforation in one, and one during lumbar puncture). But milder adverse events were more often: hypotension in 19 patients (0.05%), ventilation by face mask and additional oxygen in 128 patients (0.4%), laryngospasm in 78 patients (0.2%), bronchospasm in 15 patients (0.04%). Minor complications were more often in children who underwent gastroscopy.

The usual loading dose of propofol is 2 mg/kg in infants and young children (younger than 3 years) and 1 mg/kg in older children and teenagers. Subsequent

Table 7 The list of sedatives/analgesic, adjuvant medicines and antagonists with usual dosage regimens, and main contraindications

Medicine generic name	Route	Dose	Time to start sedation/ analgesia (after *iv* application)	Sedation/ analgesia duration	Repeating time and dose	Contraindications	Comments	Ref.
Sedative/ analgesic								
Fentanyl	*iv*	1–2 μg/kg (up to 50 μg)	0.5 s	20–40 min (30–60 min)	3 min 1–1.25 μg/kg		Due to higher clearance younger children need frequent dosing	[38,40]
Ketamine	*iv* slowly over 1 min; other routes have less predictive effects and different dosing – see the discussion	1–1.5 mg/kg	1–5 min	15 min	10 min 0.5 mg/kg	Severe cardiovascular disease, malignant hypertension, CSF obstructive states (controversial), intraocular pressure pathology; previous psychotic illness, hyperthyroidism or thyroid medicine use; porphyria	A single enantiomer S(+); the anesthetic management of seriously ill hypovolemic patients, it may be the agent of choice for managing children and burned patients; low cost	[8,40-42]
Meperidine	*iv* slowly over 1–2 min	0.3–2 mg/kg	3–6 min	60–180 min		Simultaneous treatment with monoamine oxidase inhibitors		[38,43,44]
Midazolam	*iv* slowly over 2–3 min; other routes have less predictive effects and different dosing	0.05–0.1 mg/kg in < 5 yr (max. 0.6 mg/kg); in 6–12 yr 0.025–0.05 mg/kg (max.0.4 mg/kg); in older than 12 yr 2–2.5 mg (in total not per kg BW)	2–3 min	45–60 min	Repeating doses every 2–5 min until desired effect; in children 6 mo–5 yr total dose up to 0.6 mg/kg or max. 6 mg; in 6–12 yr total dose up to 0.4 mg/kg or max. 10 mg; in older than 12 yr additional boluses of 1 mg until desired sedation	Respiratory depression, hypotension	Rarely used as a sole sedative; might be used to sedate the frightened child before iv catheter placement; mostly combined with opioids; paradoxical irritation in 1%–5% of patients	[38-40]
Nitrous oxide	Inhalation	Mostly the mixture of nitrous oxide (50%) and oxygen	0.5–1 min	5 min	Continuously or "on demand"	Pneumothorax, bowel obstruction, head injury, pregnancy	Its use limited to anaesthesiologists	[38,40,45]
Propofol	*iv*	2 mg/kg in infants and young children (younger than 3 yr); 1 mg/kg in children older than 3 yr	1–2 min	5–15 min	1 mg/kg (infants and children up to 3 yr); 0.5 mg/kg (children older than 3 yr) to reach the desired sedation; may be continuously infused at 100 μg/kg per min and increasing the speed of infusion by 50 μg/kg per min for prolonged procedures	Egg or soy allergy	For additional medication to alleviate infusion pain see text; alfentanil but not fentanyl increases propofol blood level; in many countries the use is limited to anaesthesiologists	[38,40,46]
Sevoflurane	Inhalation	Different concentrations according to the age				Duchenne's muscular dystrophy, moderate to severe liver disease of unknown aetiology, history of malignant hyperthermia	Its use limited to anaesthesiologists	[47-49]
Antagonists								
Flumazenil	*iv*	0.02 mg/kg (max. 1 mg)	1–3 min	30 min	1 min; same dose	Chronic benzodiazepine use; ingestion of drugs that increase the risk for seizures development (*e.g.*, cyclic antidepressants, cyclosporine, and others)	Due to its shorter duration of action than most of benzodiazepines (*e.g.*, midazolam) repeated doses may be needed	[38,40]
Naloxone	*iv* or *i.m.*	0.1 mg/kg (max. 2 mg)	2 min	20–40 min	2 min; same dose	Hypersensitivity only	Due to its shorter duration of action than most of opioids (*e.g.*, fentanyl) repeated doses may be needed	[38,40]

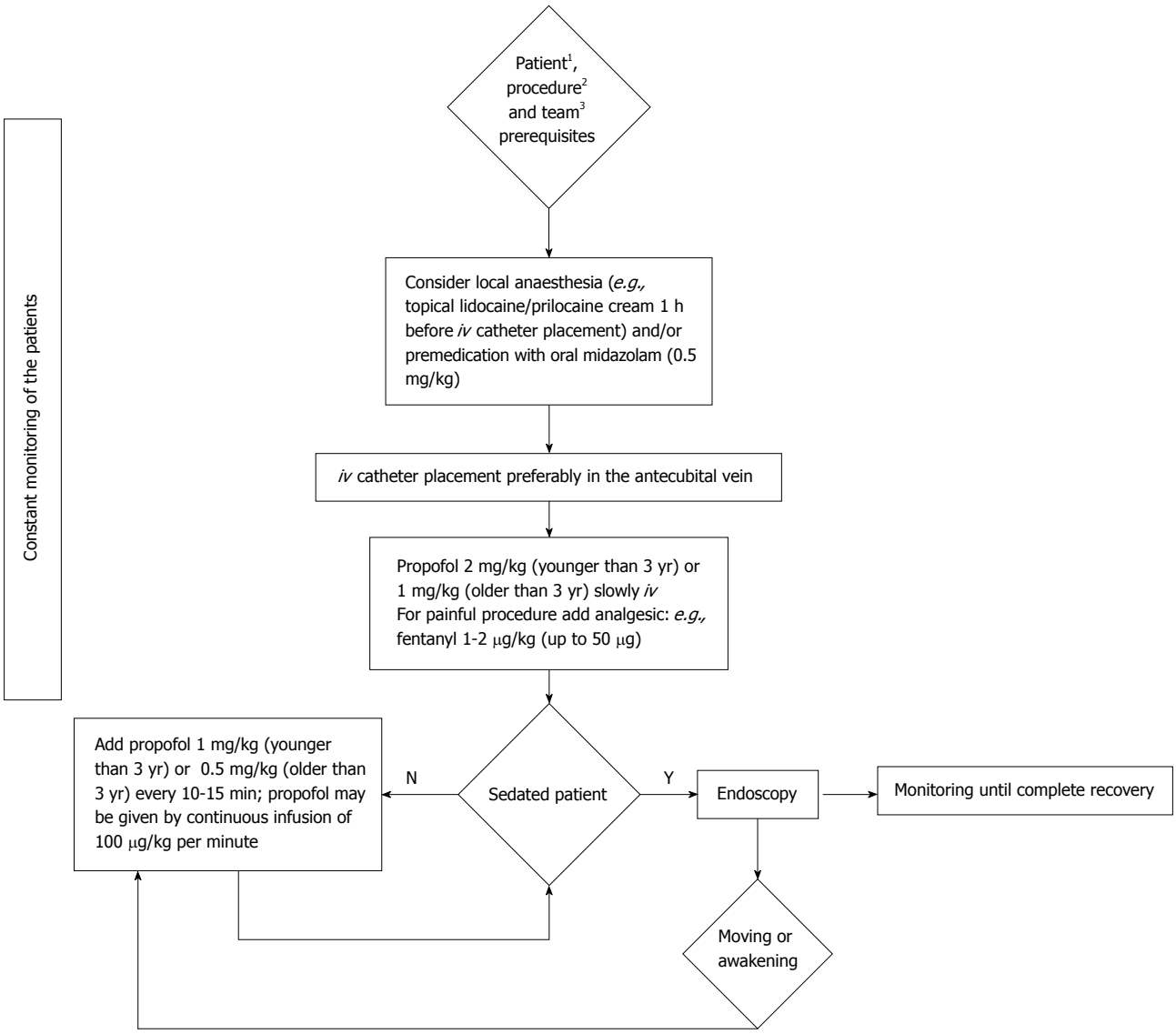

Figure 1 Flow chart of propofol sedation protocol for paediatric gastrointestinal endoscopy. [1]Older than 1 mo, without contraindications (egg or soy allergy); [2]Diagnostic endoscopy or procedure for which no endotracheal intubation is needed; [3]The team qualified for paediatric sedation for gastrointestinal endoscopy.

boluses of 1 mg/kg for younger, or 0.5 mg/kg for older children, may be added to ensure the appropriate level of sedation. For longer procedures propofol may be administered in a continuous infusion[38].

For painful procedures an analgesic must be added as propofol has no analgesic properties[38]. Bedirli *et al*[3] showed that the addition of tramadol or fentanyl to propofol provided efficient sedation, with less adverse events in the tramadol group (less desaturation, hypotension, and bradycardia; but more vomiting in fentanyl group)[3]. According to Gül *et al*[8] there was no difference in safety and efficacy between remifentanil and fentanyl co-administration with propofol.

The pain of propofol injection can be reduced by choosing a larger vein such as the antecubital site, or alternatively the injection of lidocaine[54]. A possible flow chart of propofol sedation for pediatric GI endoscopy is presented in Figure 1.

Generally, one cannot extrapolate data from adult practice to children. However, four different European Societies (of Gastrointestinal Endoscopy, of Gastroenterology, of Endoscopy Nurses and Associates, and of Anesthesiology) jointly issued guidelines for propofol sedation of adults for GI endoscopy by non-anaesthesiologists[16]. It is interesting that although the Board of Directors of the European Society of Anesthesiology (ESA) decided unanimously to endorse these guidelines, a majority of the national societies of the ESA did not support them. Consequently ESA retracted the endorsement[55]. The Danish training program for nurses includes training on how to administer propofol for GI endoscopic procedures in adults[52].

Ketamine

Ketamine is a dissociative anesthetic and analgesic. It is an N-methyl-D-aspartate channel antagonist and

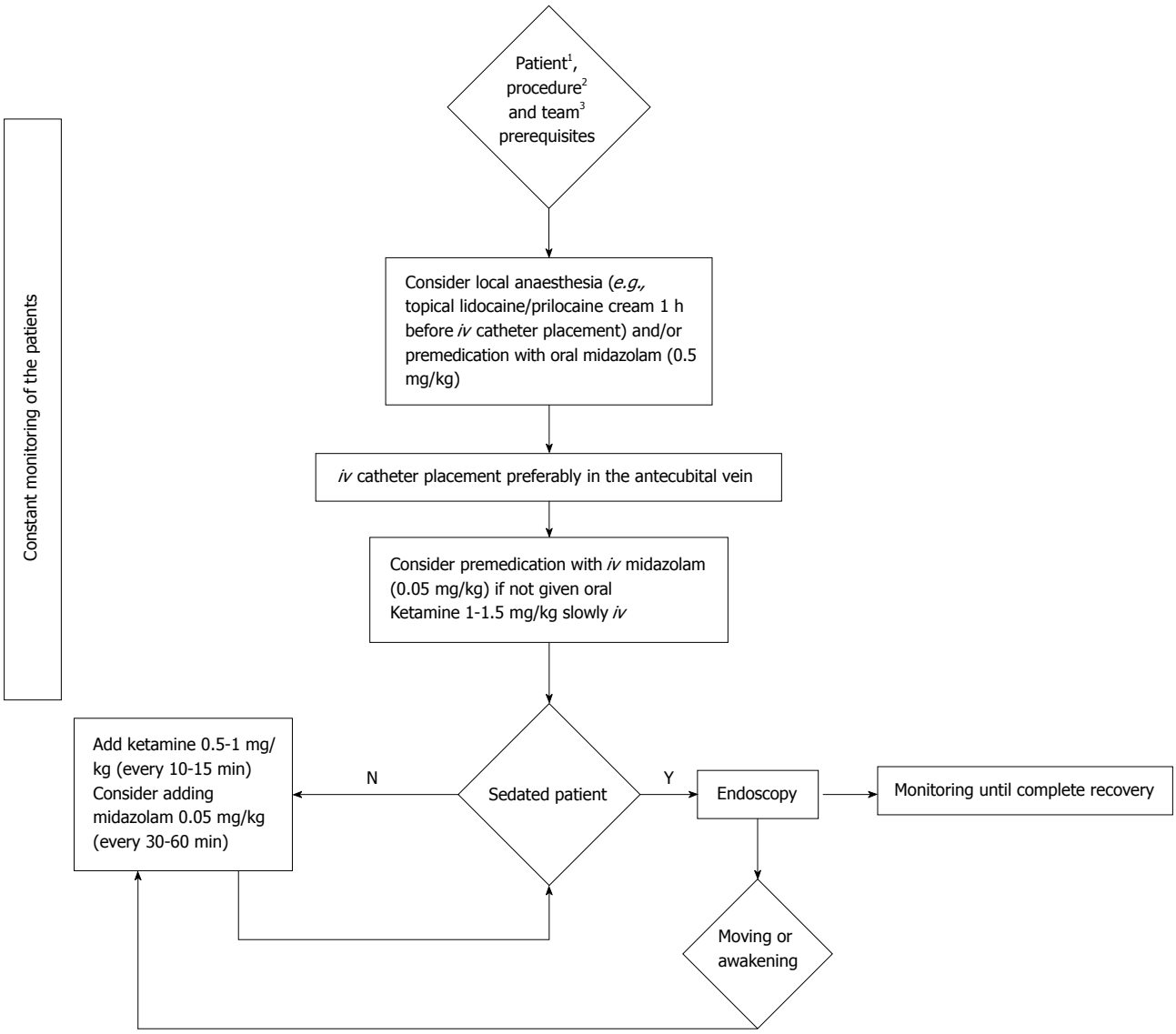

Figure 2 Flow chart of ketamine sedation protocol for paediatric gastrointestinal endoscopy. [1]Older than 3 mo, without contraindications (severe cardiovascular disease, malignant hypertension, CSF obstructive states, intraocular pressure pathology, psychotic illness, hyperthyroidism or thyroid medicines use, and porphyria); [2]Diagnostic endoscopy or procedure for which no endotracheal intubation is needed; [3]The team qualified for paediatric sedation for gastrointestinal endoscopy.

depresses sensory association areas of the cortex, limbic system and thalamus. It has been used for a long time for sedation and analgesia in emergency pediatrics due to its association with a preserve gag reflex and lack of respiration depression and hypotension[41]. Despite its good safety profile, the significant association with laryngospasm (especially with gastroscopy), emergence phenomena such as hallucinations, excitation, nightmares, delirium, recurrent illusions or "flashbacks", vomiting, and hypersalivation limit ketamine's broader use[27,38,41].

When used as a sedative, ketamine must be administered by slow *iv* injection at a dosage of 1-2 mg/kg initially. The sedative effect lasts 10-15 min. Repeated doses of 0.5 mg/kg prolong its action (Figure 2)[27,38].

The most frequent undesirable effects are vomiting, hypersalivation, nystagmus, hypertension, tachycardia, skin erythema, and emergence phenomena. Laryngospasm, which is potentially of greatest danger, is uncommon. The use of ketamine is contraindicated in infants younger than 3 mo, patients with psychosis, uncontrollable hypertension or hyperthyroidism, and as it increases intracranial and intraocular pressure. Ketamine should not be used after a head or eye trauma, or surgery, although some data advocate against these precautions[27,38].

The concomitant use of midazolam with ketamine decreases the frequency of emergence phenomena, although this remains controversial[56]. Two randomized double-blind studies performed in pediatric emergency departments did not find sufficient evidence to support the addition of midazolam for this purpose[57,58]. However, a randomized study using midazolam in co-administration with ketamine for pediatric sedation for GI endoscopy

suggests that midazolam does prevent emergence phenomena[4]. Other co-administered medicines might lessen some undesirable effects of ketamine but their use is not supported by sufficient evidence. Anticholinergics may prevent hypersalivation[59], but this has also been contradicted[60]. The anti-emetic ondansetron prevents vomiting in some patients[61].

Benzodiazepines and opioids

Midazolam is a short-acting benzodiazepine which is widely used for sedation but is generally considered to be insufficient as a monotherapy. It has anxiolytic, amnesic, sedative, hypnotic, muscle relaxant, and anticonvulsant properties which result from GABA receptor activation[38,39]. The major undesirable effects are respiratory depression and hypotension, which are avoidable with appropriate dosing and are reversed by the antagonist flumazenil[38]. Other undesirable effects such as paradoxical agitation are reported in up to 15% of children[38].

Midazolam may be administered orally as an anxiolytic before the placement of an *iv* cannula but its effect is less predictive orally than when administered *iv* The usual starting dose is 0.1 mg/kg *iv* as a pre-medication but may be titrated to the desired effect by incremental doses of 0.05 mg/kg[39].

Opioids are potent analgesics which express their activity *via* different opioid receptors. The most suitable for sedation is fentanyl due to its rapid onset and short action. As it has no sedation properties it must be combined with benzodiazepines but the combination increases the risk of respiratory depression[38]. Other undesirable effects are itching, hypotension and vomiting but those are less pronounced than in histamine-releasing opioids such as morphine and meperidine[38]. Naloxone is an opioid receptor antagonist and is administered intravenously at 0.1 mg/kg[38].

Meperidine was the first synthetic opioid agent. It acts mainly as an antagonist of μ and κ receptors and has an analgesic potency ten times greater than that of morphine[62]. Like other opioid drugs, meperidine causes nausea, vomiting, urinary retention and respiratory depression. Its property of acting on nerve fibers, similar to those of local anesthetics, allows its use as an alternative for anesthetic blockade and differentiates it from other opioids. An *iv* route has been used for treating moderate to severe pain, for regional anaesthesia, for pre-medication and for analgesia during anesthesia. The combination of midazolam and meperidine can be used to achieve sedation and analgesia during colonoscopy[63]. There are few studies that have compared the efficacy of midazolam alone to midazolam and meperidine. According to Ozel *et al*[64], there were no significant differences in oxygen saturation/blood pressure but a better patient compliance was observed in the combined sedation group[64]. Cinar *et al*[65] showed that in respect of the recovery and procedure time there were no significant differences between the midazolam and the midazolam/meperidine group[65]. In a randomized trial comparing the efficacy and recovery time of two sedation regimens consisting of midazolam in combination with either meperidine or fentanyl, it was found that the fentanyl combination with midazolam resulted in a significantly faster recovery, without any apparent loss of analgesic effect[66]. Again, these are adult studies, and extrapolation to pediatrics is not necessarily appropriate.

Meperidine is administered intravenously at 1 mg/kg[64]. A possible flow chart of benzodiazepine and opioid sedation for pediatric GI endoscopy is presented in Figure 3.

Fentanyl is usually administered at 1–2 μg/kg. The analgesic effect lasts 20-40 min[38].

van Beek and Leroy[2]'s analysis found opioid and benzodiazepine sedation protocols suboptimal. These protocols were inferior in comparison to general anaesthesia. The comparison of midazolam/fentanyl with propofol sedation by Lightdale *et al*[67] addressed mainly procedure duration and discharge times which were similar for both groups, but the endpoint of this study was not to compare safety or efficacy.

Inhalation anesthetics

In most countries, legislation limits the administration of inhalation anesthetics to anesthesiologists.

Sevoflurane: Sevoflurane is an inhalational anesthetic with a very good safety profile (low incidence of airway hypersecretion, respiratory depression or cardiovascular events)[47]. When used for paediatric sedation for endoscopies it was characterized by a shorter recovery time and earlier discharge. Sevoflurane can only be administered by an anesthesiologist. The insertion of an *iv* catheter may not be needed. The use of inhaled anesthetics requires waste gas scavenging to prevent anesthetic gases being released into the ambient air[47].

There are no recently published studies on sevoflurane sedation for pediatric GI endoscopies.

Nitrous oxide: Nitrous oxide is an inert gas which has analgesic, sedative and amnesic properties of short duration. Michaud *et al*[68] reported a good experience with 50% nitrous oxide for gastroscopies and procto-sigmoidoscopies in children. They did not evaluate it for ileo-colonoscopy nor compare this type of sedation to other protocols[68]. There are no newer studies on nitrous oxide sedation for GI endoscopy in children.

In adults nitrous oxide has been used successfully for proctoscopies and colonoscopies. In a systematic review Welchman *et al*[45] analyzed in a systematic review 11 studies including 623 patients. Continuous nitrous oxide inhalation provided comparable analgesia to *iv* sedation for colonoscopies. There was no difference in procedural pain between on-demand nitrous oxide and no sedation for colonoscopies. The recovery time was shorter in the nitrous oxide groups[45].

Nitrous oxide is often more used as an anxiolytic before *iv* catheter placement if the face mask does not agitate the patient. However, most anesthesiologists

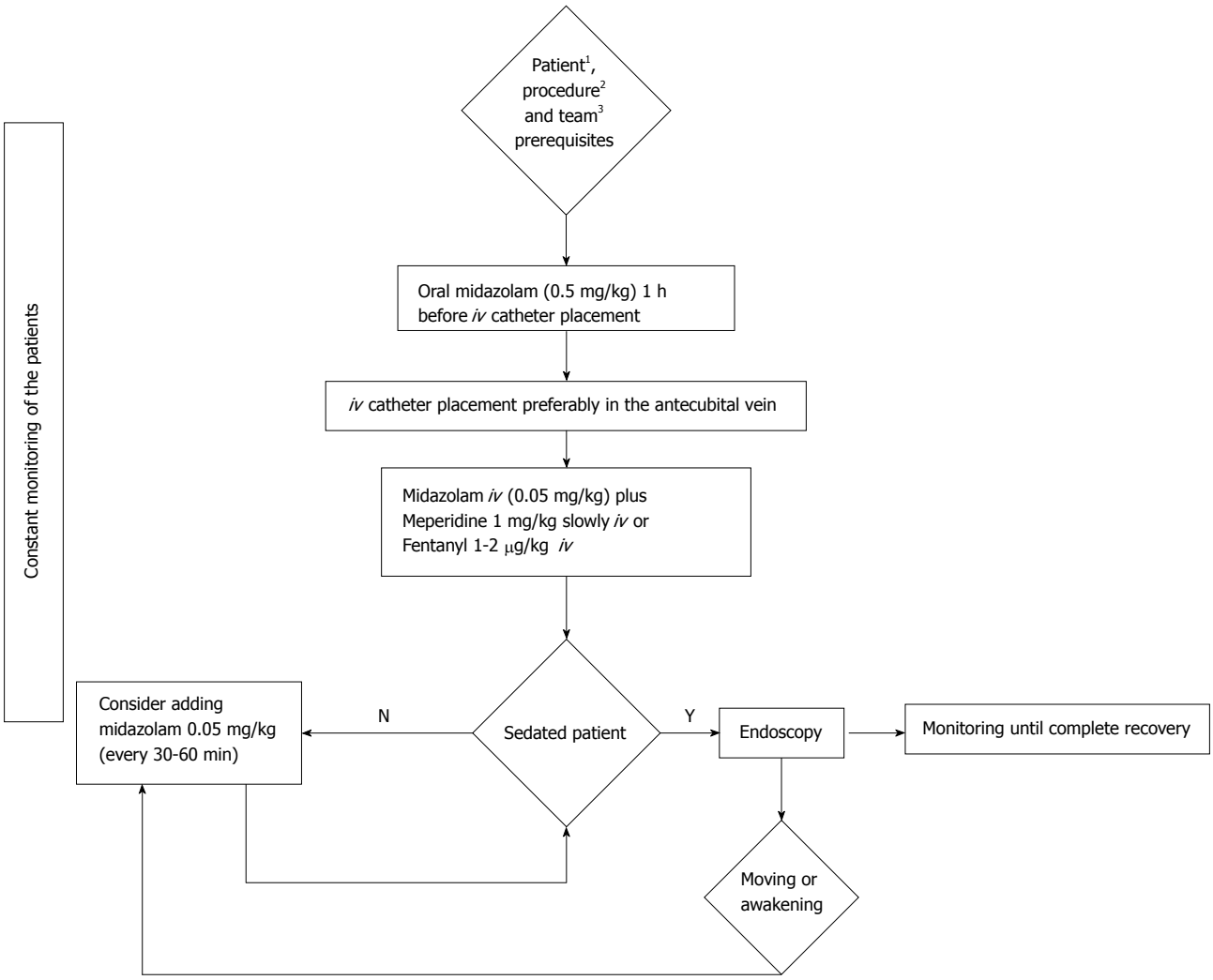

Figure 3 Flow chart of opioid and benzodiazepine sedation protocol for paediatric endoscopy. [1]Patient without contraindications (not being simultaneously treated with monoamine oxidase inhibitors); [2]Diagnostic endoscopy or procedure for which no endotracheal intubation is needed; [3]The team qualified for paediatric sedation for gastrointestinal endoscopy.

would suggest that age-appropriate calming of a patient by engagement would have a similar result. Vomiting occurs in up to 10%. It is contraindicated in bowel obstruction and should not be administered if any of the team members is pregnant[38]. Its routine use in pediatric GI endoscopy is not ratified.

Adjuvant medicines and antagonists

Anti-cholinergics: As discussed in the section on ketamine, anti-cholinergics (*e.g.*, atropine or glycopirolate) decrease the hypersalivatory effect which may influence airway patency[59]. However, importantly, it should be noted that available evidence does not support this practice and anti-cholinergics are no longer routinely recommended[26,60].

Anti-emetics: Many sedative/analgesic agents (*e.g.*, ketamin, fentanyl), with the exception of propofol, provoke vomiting[50]. Ondansetron reduced the incidence of vomiting in a double-blind, randomized, placebo-controlled study in 255 children in an emergency department sedated by ketamine[61].

Flumazenil: Flumazenil is an antagonist used to reverse the undesirable effects of benzodiazepines such as respiratory depression. It is delivered *iv* at 0.1 mg/kg up to a maximum of 2 mg and has a rapid onset of action in 1-3 min. The half-life of flumazenil is shorter than that of other benzodiazepines (*e.g.*, midazolam) making close monitoring essential and reapplication sometimes needed[38,40].

Naloxone: Naloxone reverses opioid effects and results in normal respiration within 1-2 min of application of 0.1 mg/kg (up to 2 mg) *iv* or intramuscular. Its duration of action is around 20-40 min hence repeated doses might be needed as the duration of action of most opioids (*e.g.*, fentanyl) is longer[38,40].

DISCUSSION

Effective and safe sedation for pediatric endoscopic proce-

dures is a non-negotiable pre-requisite and an important factor for lowering patient distress. In principle, total *iv* anesthesia should be performed by anesthesiologists. However, it has to be recognized that in many countries, including a majority of European countries and in parts of the United States, the limited availability of anesthesiology teams and limited organizational considerations represents a medical dilemma. In many European countries anesthesia departments cannot cope with the increasing demands[37]. Therefore, a shortage of anesthetic teams may force pediatric endoscopists to conduct sedation without anesthetic teams applying guidelines adapted according to national regulations and institutional practices[4]. However, this situation is not optimal and requires consequent actions to increase the number of anesthesiologists.

In this situation, the intention of the authors is not to encourage such practice. This paper summarizes the evidence for sedation schemes which could be safely and efficiently performed by non-anesthesiologists. Sedation protocols have to be adapted to international, national and local legislation and institutional practice. The national institutions must organize multidisciplinary teams for education, licensing and supervision of non-anesthesiologists and registered nurses involved in sedation practices as long as there is a shortness of anesthesiologists. An efficient system of quality control is a paramount.

The choice of medicines for procedural sedation is wide, but none has the properties of an ideal sedative, which are: predictable dose dependent level of sedation with rapid onset; broad therapeutic window; anxiolytic effect with anterograde amnesia for the duration of the procedure; absence of respiratory, cardiovascular and other undesirable effects; and a smooth post-procedural recovery without side effects[34]. Another important problem in pediatrics is the off-label use of many medicines, which was recently addressed for medicines prescribed for outpatients in pediatric gastroenterology[69]. The investigators found that in 33.2% of the prescriptions, medicines were used "off-label" and that 47.3% of the patients had at least 1 medicine described as an "off-label" medication. Sedatives and other *iv* medicines were not covered by this study. The legal risk of a prescribing doctor is greater when using "off-label" medicines or indications. Parents should be informed of the "off-label" use. A solution of this problem is to motivate the pharmaceutical companies to register medicines for pediatric use, as has happened in the majority of the EU Countries under the jurisdiction of the European Medical Agency for new medicines.

Propofol is probably the most promising and controversial sedative/anesthetic at present. It is stated that only those trained in anesthesia should use it, a position that anesthesiologists and their societies strongly defend[70]. On the other hand, there are studies of safe and efficient use of propofol for sedation for GI endoscopic investigations in pediatric and adult gastroenterology[2,3,7,8,51,71]. The administration of propofol by non-anesthesiologists is "off-label" in most cases and, therefore, every adverse event might have medico-legal consequences.

Therefore, these data could not be simply extrapolated to every sedation/analgesia practice. According to the review by Havidich *et al*[72] the evidence of the safety of sedation by non-anesthesiologists for procedures outside operating theatres is growing, especially for propofol. Despite the drawbacks listed above, published data justify propofol use in certain circumstances[2].

Ketamine-based sedation is safe and effective in otherwise healthy infants older than 3 mo[27]. Ketamine has dissociative anesthetic and analgesic properties with a wide safety margin and is frequently used in pediatric emergency departments[27,28]. Emergence reactions are observed in adults in up to 28%, but seem less prevalent in paediatric studies and not influenced by the addition of midazolam to ketamine[56-58]. Guidelines advised against routine benzodiazepine pre-medication[27,28]. Data from larger studies are needed as one recent study found less emergence reactions when midazolam was routinely administered as a pre-medication[4]. Another major limitation of ketamine-based sedation for endoscopy is laryngospasm. In general, the laryngospasm resolves without consequences rapidly after removal of the endoscope and administration of oxygen[73]. Another study reports transient laryngospasm manageable with simple measures in 3% of gastroscopies[4]. Therefore, the ketamine-based sedation regime for GI endoscopy is an acceptable option when sedation with propofol is not feasible.

Midazolam is most likely the most widely used drug for sedation in everyday endoscopic work. The duration of action of midazolam is dependent on the duration of its administration. The sedative and amnestic effects of benzodiazepines sometimes do not provide adequate patient comfort during colonoscopic procedures[74]. Opioids are often added and meperidine is commonly used[75]. The value of adding analgesics to sedatives has well evaluated in large number of prospective, randomized and placebo-controlled studies[76]. Sedation with midazolam/meperidine is safely and can be administrated under adequate monitoring[77].

These recommendations review and discuss sedation practices for pediatric GI endoscopy which can be safely and efficiently performed by non-anesthesiologists, but only when the necessary pre-requisites regarding patient assessment, team composition and experience, medicines and equipment are met.

ACKNOWLEDGMENTS

The authors reviewed the literature and made practical recommendations for effective and safe sedation for endoscopic procedures in children. However, the authors decline every legal responsibility for the proposed algorithms. Legislation and regulation regarding limitations of administration of different medications, such as inhalation anesthetics, differ from country to country.

Therefore, limitations caused by local legislation should be carefully checked.

COMMENTS

Background

Anesthesia is by preference performed by anesthesiologists.

Research frontiers

The creation of sedation teams led by non-anesthesiologists and a careful selection of anesthetic drugs may offer an alternative, but should be in line with national legislation and institutional regulations.

Innovations and breakthroughs

The intention of this review is to offer effective and safe alternatives for non-anesthesiologists.

Peer-review

The present paper was well organized and well investigated. This paper will give us important information about the anesthesia during endoscopy especially in children.

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CASE REPORT

Carcinoma *in situ* in a 7 mm gallbladder polyp: Time to change current practice?

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Institutional review board statement: This study was considered exempt by the Bronx-Lebanon Institutional Review Board.

Informed consent statement: Informed consent was obtained from the patient for publication in this case report.

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Abstract

Detection of polypoid lesions of the gallbladder is increasing in conjunction with better imaging modalities. Accepted management of these lesions depends on their size and symptomatology. Polyps that are symptomatic and/or greater than 10 mm are generally removed, while smaller, asymptomatic polyps simply monitored. Here, a case of carcinoma-*in-situ* is presented in a 7 mm gallbladder polyp. A 25-year-old woman, who had undergone a routine cholecystectomy, was found to have an incidental 7 mm polyp containing carcinoma *in situ*. She had few to no risk factors to alert to her condition. There are few reported cases of cancer transformation in gallbladder polyps smaller than 10 mm reported in the literature. The overwhelming consensus, barring significant risk factors for cancer being present, is that such lesions should be monitored until they become symptomatic or develop signs suspicious for malignancy. In our patient's case this could have led to the possibility of missing a neoplastic lesion, which could then have gone on to develop invasive cancer. As gallbladder carcinoma is an aggressive cancer, this may have led to a tragic outcome.

Key words: Gallbladder; Polyp; Cholecystectomy; Size; Carcinoma

Core tip: Current guidelines for management of gallbladder polyps recommend cholecystectomy for

polyps with size > 10 mm and/or presence of symptoms. Considering some cases of carcinoma in polyps with size less than 10 mm have been seen, consideration of a cholecystectomy for smaller size polyps is warranted.

Kasle D, Rahnemai-Azar AA, Bibi S, Gaduputi V, Gilchrist BF, Farkas DT. Carcinoma *in situ* in a 7 mm gallbladder polyp: Time to change current practice? *World J Gastrointest Endosc* 2015; 7(9): 912-915 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i9/912.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i9.912

INTRODUCTION

Detection of polypoid lesions of the gallbladder (PLG) has become increasingly more frequent over the last thirty years primarily due to an increase in the use of ultrasound and other imaging modalities in evaluation of patients with abdominal complaints. In the adult population, 0.03%-9.5% of people are estimated to have PLG[1]. Due to the malignant potential of these lesions their management has been well documented[2,3].

In current practice, symptomatic lesions or polyps greater than 10 mm warrant cholecystectomies, while asymptomatic polyps less than 10 mm are followed with routine ultrasound every 3-6 mo for one to two years[3]. Here, we present a case of a 25-year-old woman who presented with a 7 mm PLG which was found, after cholecystectomy, to contain carcinoma-*in-situ*. Our goal is to add to existing literature of PLG and to caution physicians that delaying polyp removal simply due to lack of a lesion's symptoms or significant size may be harmful.

CASE REPORT

A 25-year-old female presented to the emergency room with right upper quadrant abdominal pain for duration of 2 d. On physical examination she had mild tenderness in right upper quadrant. Laboratory work up revealed: WBC 7500/mL, ALT 148, AST 254, ALP 119, Total Bilirubin 0.5 and direct bilirubin 0.3. Ultrasound examination showed multiple gallstones and a common bile duct (CBD) of 12 mm. She underwent an endoscopic retrograde cholangiopancreaticography at which time her CBD was cleared of stones, and subsequently a laparoscopic cholecystectomy was performed. The postoperative period was uneventful and the patient was discharged home.

The final pathology report revealed acute and chronic cholecystitis with multiple small gallstones. An incidental 7 mm pedunculated tubular adenoma was seen in the fundus of the gallbladder, with a segment of carcinoma *in situ*.

The patient was informed, and an appointment for oncology was arranged, but the patient chose not to go. Current guidelines do not recommend further treatment for T1a tumors, and certainly not for Tis disease[4,5]. Even aggressive surveillance is not recommended according to the National Comprehensive Cancer Network[6]. The patient next presented to our hospital system for an unrelated problem three years later, and was showing no signs of disease.

DISCUSSION

Approximately 4% of the adult population is estimated to have gallbladder polyps, the majority of which are benign cholesterol lesions[1,2]. Adenomas comprise the second most common PLG, 3% to 8% of which are reported to have malignant potential[1,2].There is no correlation between symptomatology and the probability of a malignant lesion. As such, there is no reliable way of differentiating a benign polyp from a malignant one outside of pathologic examination of the polyp[1,3].

The consensus regarding resecting a patient's gallbladder or leaving it in place has been widely documented. A search including PubMed, Embase, and Web of Science was done to locate relevant literature on the subject. Keywords included gallbladder, polyps, carcinoma or neoplasms, and gallbladder neoplasms were used.

Boulton *et al*[7] published the basic algorithm utilized today which differentiates lesions primarily based on size and symptoms but also included "complicating factors," or risks, in ultimately making a decision[8]. These risk factors include age greater than 50 and the presence of gallstones. Cha *et al*[9] include diabetes mellitus as a significant risk, while Myers *et al*[1] include polyp growth and a solitary lesion among these complicating factors, but state that no "consistent profile" exists among patients. Polyps > 10 mm (or some say > 9 mm) are resected regardless of a person's symptoms or risk factors, as are symptomatic PLG[7,10]. All asymptomatic lesions < 10 mm in patients with limited/no risk factors are monitored by ultrasound[7]. The duration of monitoring is inconclusive with some sources quoting every 3-6 mo for 1-2 years, while others state that lesions less than 6 mm do not need monitoring at all[3,7,10,11].

A number of studies have been done in an attempt to ascertain the appropriate size that gallbladder polyps should be removed due to their risk of malignant potential. Corwin *et al*[10] published a study in 2011 describing 346 patients with PLG. Following these patients with cholecystectomy and serial ultrasound, no neoplastic lesions were found in polyps < 6 mm, one neoplastic polyp was noted in polyps 7-9 mm, and two polyps greater than 10 mm were neoplastic[10]. Their conclusion was that PLG's < 6 mm require no follow up, but regarding lesions > 7 mm no conclusion could be made and further studies were recommended[10]. Another study published in 2010 by Matos *et al*[12] followed 93 patients, 91 of whom had benign polyps and two who had malignant ones. Of the two, which were found to be malignant, the average size in diameter was 18.8

mm and they concluded that polyp diameters greater than 10 mm were required to induce surgery, assuming no known risk factors existed[12]. Several other studies of asymptomatic patients with PLG have been reported in the literature, with case series ranging between 161 and 417 patients. These have all come to the conclusion that 10 mm or greater was the appropriate cutoff in asymptomatic patients with no risk factors to require surgery[13-15].

In our patient, a 7 mm polyp was incidentally identified after a cholecystectomy performed due to symptomatic gallstones. Upon pathological examination carcinoma *in situ* was discovered within the lesion. In a less fortunate person with a PLG and no symptomatic gallstones, current management would have resulted in missing a precancerous lesion. Considering that gallbladder carcinoma usually presents late, with a five-year survival from 5%-13%[16], this may have led to a detrimental outcome in our patient. This is a drastic difference in survival outcome compared to gallbladder cancers that are removed early, which has up to a 95% to 99% survival if extracted prior to muscularis and mucosal invasion, respectively[17].

Our patient demonstrates the care that must be taken regarding the management of polyps even smaller than 10 mm. This is especially true considering the significant benefit of avoiding a serious cancer relative to the small risk of surgical complications. Perhaps we should consider removing gallbladders with asymptomatic PLG that are between 5 mm-10 mm in size even in the absence of known risk factors. While this paper adds to the growing literature on these smaller size polyps, larger studies with more cases are necessary before formal recommendations can be made.

COMMENTS

Case characteristics

A 25-year-old woman presented with right upper quadrant abdominal pain for two days.

Clinical diagnosis

There was mild right upper quadrant tenderness on exam, with no jaundice.

Differential diagnosis

Differential diagnosis included acute cholecystitis or biliary colic, with choledocholithiasis less likely at this point.

Laboratory diagnosis

White blood cell count was normal, with elevation of transaminases, minimal elevation of alkaline phosphatase and normal bilirubin.

Imaging diagnosis

Ultrasound showed gallstones and a significantly dilated common bile duct of 12 mm.

Pathological diagnosis

Acute and chronic cholecystitis with gallstones, and an incidental finding of a 7 mm gallbladder polyp with carcinoma *in situ*.

Treatment

Patient underwent endoscopic retrograde cholangiopancreaticography and then laparoscopic cholecystectomy, which is sufficient for her carcinoma *in situ*.

Related reports

Other reports have suggested observation for polypoid lesions of gallbladder less than 10 mm.

Term explanation

Polypoid lesions of the gallbladder refer to lesions seen on imaging that look like a polyp, as opposed to stones which are mobile and layer in the dependent region of the gallbladder.

Experiences and lessons

The important lesson from this case is that malignant degeneration can develop in polyps less than 10 mm in size.

Peer-review

This adds to the literature of polyps less than 10 mm, and can suggest lowering the threshold for recommending cholecystectomy, but more research with larger numbers is necessary.

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CASE REPORT

Unusual complication of amebic liver abscess: Hepatogastric fistula

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Abstract

Amebic liver abscess is a parasitic disease which is often encountered in tropical countries. A hepatogastric fistula secondary to an amebic liver abscess is a rare complication of this disease and there are only a handful of reported cases in literature. Here we present a case of an amebic liver abscess which was complicated with the development of a hepatogastric fistula. The patient presented with the Jaundice, pain and distension of abdomen. The Jaundice and pain improved partially after he had an episode of brownish black colored increase in frequency of stools for 5 to 6 d. Patient also had ascites and anemia. He was a chronic alcohol drinker. Esophagogastroduodenoscopy performed in view of the above findings. It showed a fistulous opening with bilious secretions along the lesser curvature of the stomach. On imaging multiple liver abscesses seen including one in sub capsular location. The patient was managed conservatively with antiamebic medications along with proton pump inhibitors. The pigtail drainage of the sub capsular abscess was done. The patient improved significantly. The repeat endoscopy performed after about two months showed reduction in fistula size. A review of the literature shows that hepatogastric fistulas can be managed conservatively with medications and drainage, endoscopically with biliary stenting or with surgical excision.

Key words: Amebic liver abscess; Hepatogastric fistula; Esophagogastroduodenoscopy; Entaameba histolytica; Ultrasonography; Computed tomography

Core tip: Hepatogastric fistula is a rare complication of the amebic liver abscess. High index of suspicion is required for its diagnosis. The presenting complaints may be brownish black vomitus or stool. It can be managed conservatively, endoscopically or surgically depending on case. Hence in cases of amebic liver abscess developing brownish black stools or vomiting we should always rule out hepatogastric fistula formation especially when it is associated with improvement of symptoms.

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INTRODUCTION

Amebic liver abscess is a parasitic disease which is commonly encountered in tropical countries[1]. A hepatogastric fistula secondary to an amebic liver abscess is a rare complication and only a handful of cases have been reported in literature[2,3]. A patient presenting with an anchovy sauce like vomitus or stool along with a simultaneous decrease in a preexisting pain in the abdomen should alert a clinician to the possibility of a hepatogastric fistula due to an abscess. There are a few other causes of this clinical entity. This condition can be managed conservatively with antibiotics and proton pump inhibitors, failing which surgery is the treatment of choice. Surgery involves excision of the fistulous tract with anastomosis. Here we report a case which presented with an anchovy sauce like stool and was successfully managed conservatively.

CASE REPORT

A 47-year-old male, with a history of regular alcohol intake presented with a history of pain and swelling in right upper abdomen which was mild to moderate in intensity, dull aching in character with occasional throbbing sensation with no radiation to any other site. The pain lasted a month and a half and was followed by generalized distension of the abdomen. This was accompanied with high color urine and jaundice. There was no fever. The patient then developed an increased frequency of stool which was liquid brownish-black and went on for 6 d. This was associated with a marked improvement in the abdominal pain and a decrease in the swelling over right upper abdomen. On examination there was tender hepatomegaly with ascites. The patient's hemoglobin was 9.3 g/dL and leucocyte count was 16700/mcl. There was reversal of albumin and globulin ratio, increase in aspartate transaminase was more than alanine transaminase and increased total and direct bilirubin. Ascitic routine microscopy revealed a high serum ascites albumin gradient. Patient's ultrasonography showed hepatomegaly with multiple heterogeneous solid cystic lesions with thickened walls, the largest measured 13.7 cm × 7.5 cm. In view of a history of daily alcohol intake with recent onset of black stool and a physical finding of ascites an esophagogastroduodenoscopy was performed. The study revealed a 2 cm × 2 cm deep ulcer with bilious discharge just above incisura on lesser curvature of the stomach (Figure 1). There were no varices. On further evaluation computed tomography (CT) suggested multiple large hepatic abscesses in both lobes of liver, the largest measuring 12.8 cm × 8.6 cm × 3.4 cm in the right lobe of liver. One of the abscesses in right lobe was sub capsular. The left lobe of liver had a hepatic abscess in segment 3 which had an exophytic extension and was indenting the lesser curvature of stomach. Air pockets were seen in the abscess cavity suggesting the probability of a fistulous opening within the stomach (Figure 2). His blood antibodies [enzyme linked immunosorbent assay (ELISA)] for entaamoeba histolytica came positive. An ultrasonography guided pigtail catheter was placed in right sub capsular abscess. The abscess content was anchovy sauce like. Pus culture was negative for bacteria. He was started on metronidazole and other supporting medications. He was also started on diloxanide furoate for luminal clearance of cysts. The patient improved clinically and at 4 wk a repeat endoscopy was performed. It showed a significant decrease in the size of the fistulous tract. A surgical option was explained to the patient and his relatives but they opted for medical line of management in view of risk associated Child Pugh C status. He was continued with close monitoring with proton pump inhibitors. The patient has been in regular follow up since the past 6 mo. The patient had American society of anesthesiologists' classification of physical status of 4 on presentation, 3 at the time of discharge and 2 at 6 mo follow up.

DISCUSSION

The prevalence of E. histolytica infections in India has been shown to range from 3.6% to 47.4% in different areas[1]. Amebic liver abscess occurs in less than 1% of entaameba histolytica infested patients[2]. Liver abscess rupturing into the pleural and peritoneal cavities is a relatively common phenomenon[3]. Only a handful of case reports of hepatogastric fistula have been published till now as it is a rare complication[3]. Hepatogastric fistulas have also been reported in cases of hepatocellular carcinoma intruding into stomach and presenting as an upper gastrointestinal bleed[4], post embolization for hepatocellular carcinoma leading to the formation of an abscess[5], as a complication of placing a pig tail in a liver abscess and also in cases of post hepatic surgeries. An iatrogenic hepatogastric fistula can be done for biliary drainage in infants with congenital obstructive jaundice.

The presentations of hepatogastric fistula secondary

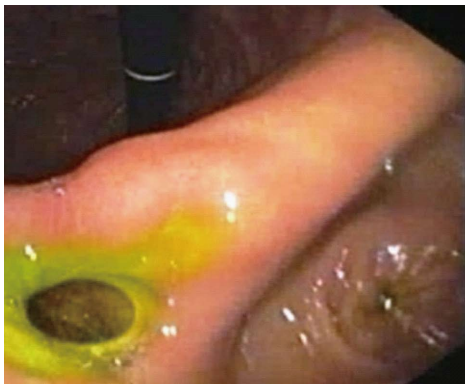

Figure 1 On retroflexon in stomach fistula with bile seen.

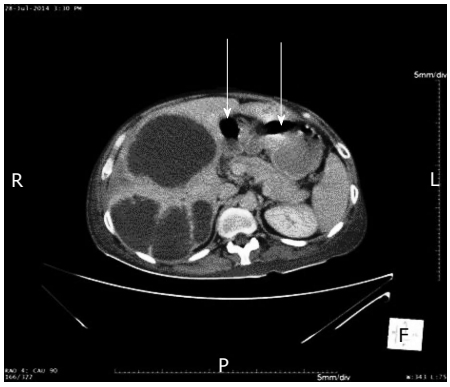

Figure 2 Multiple liver abscess with air pocket seen in the abscess in left lobe. (White arrows).

to amebic liver abscess can be as an anchovy sauce color vomitus or stool, hematemesis or malena[6]. In our patient decompression of the abscess into the stomach probably lead to the anchovy sauce color of stool and subsequent improvement of pain. Diagnosis was made based on the imaging and endoscopic findings. ELISA test for detecting antibodies was done for confirming entaameba histolytica as the causative agent. On the CT scan images the abscess seen with air pocket in continuation with the stomach was also a clue to the presence of the fistula (if it was performed before the endoscopy). On esophagogastroduodenoscopy the fistulous opening was seen as deep ulcer with (as in our case) or without bilious discharge[3]. In our case the diagnosis was confirmed taking into account the serology, CT finding and endoscopic findings. Rupture of an amebic liver abscess into an adjacent structure such as pleural and peritoneal cavity is a life threatening condition but rupture into stomach is not a dreaded complication.

Definitive management is surgical but if the patient's general condition does not permit surgery (as in our case) conservative management has also showed improvement[7]. Conservative treatment includes metronidazole for clearance in extraintestinal site and diloxanide furoate or paromomycin for luminal clearance. In certain cases of impending rupture of sub capsular abscess, pigtail drainage of the liver abscess has to be done to avoid complications. Biliary stenting has been found to hasten the recovery due to selective drainage of bile through common bile duct[8]. Nutrition can be given through per oral, nasojejunal tube, or feeding jejunostomy. Spontaneous closure of fistula can be seen within 5 wk of conservative management which was observed in our case[9]. If no improvement is observed on conservative management or if there is clinical worsening then surgical excision of the fistulous tract with gastric anastomosis is an option. Complications of hepatogastric fistulas include sepsis, debilitation and electrolyte imbalance[10].

In conclusion, hepatogastric fistula is a very unusual complication of liver abscess. One has to have a high index of suspicion for it to be diagnosed early. Management can either be conservative, endoscopic or surgical. We have managed this patient conservatively as patient was Child Pugh C status and high risk for surgery.

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COMMENTS

Case characteristics

A 47-year-old male, chronic alcoholic presented with pain and distention of abdomen along with jaundice followed by brownish black diarrhea for 5 to 6 d.

Clinical diagnosis

Patient was having symptoms of chronic liver disease along with hepatomegaly and pain specifically in right upper quadrant.

Differential diagnosis

This is a case of chronic liver disease with either hepatocellular carcinoma or liver abscess or spontaneous bacterial peritonitis causing decompensation of liver disease.

Laboratory diagnosis

Patient had anemia and high leucocyte count along with inversion of albumin and globulin ratio and presence of antibodies to entaameba suggestive of chronic liver disease along with infection.

Imaging diagnosis

Ultrasonography and computed tomography suggestive of liver abscess with air in left lobe abscess probably fistulous opening which is confirmed on esophagogastroduodenoscopy.

Treatment

Patient was managed conservatively with metronidazole, diloxanide furoate.

Related reports

Very few case reports were published related to hepatogastric fistula due to hepatocellular carcinoma, iatrogenic and abscess.

Term explanation

Hepatogastric fistula is communication of liver with stomach due to various etiologies.

Experiences and lessons

High index of suspicion is required for diagnosis of hepatogastric fistula. Patient had marked improvement in pain and upper right quadrant swelling once he had brownish black stools for 5 to 6 d. Though rare, knowledge of this complication leads to early diagnosis and prompt treatment.

Peer-review

This is a well prepared and detailed case report referring to a rare complication of amebic liver abscess, a hepatogastric fistula. The manuscript is well organized with a comprehensive discussion section.

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EDITORIAL

What is the current role of endoscopy in primary sclerosing cholangitis?

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Abstract

Endoscopy has important roles in the management of primary sclerosing cholangitis (PSC), ranging from narrowing down the differential diagnoses, screening for complications, determining prognosis and therapy. While the need for a diagnostic endoscopic retrograde cholangiopancreatography (ERCP) may be obviated by a positive magnetic resonance cholangiopancreatography (MRCP), a negative MRCP does not exclude PSC and may therefore necessitate an ERCP, which is traditionally regarded as the gold standard. In this editorial we have not covered the endoscopic management of inflammatory bowel disease in the context of PSC nor of endoscopic surveillance and treatment of portal hypertension complicating PSC.

Key words: Sclerosing cholangitis; Endoscopic retrograde cholangiopancreatography; Endosonography; Cholangiocarcinoma; Stents; Fluorescence *in situ* hybridization technique; Biochemical markers

Core tip: Primary sclerosing cholangitis is a cholestatic disease of unclear etiopathogenesis, often seen in association with inflammatory bowel disease. It is characterized by fibrosis of the intra and extra hepatic bile ducts, resulting in stricturing disease, predisposing to cholangiocarcinoma. Diagnosis requires a high index of clinical suspicion and is often made by magnetic resonance cholangiopancreatography in the appropriate clinical context, although endoscopic retrograde cholangiopancreatography remains the gold standard. The latter being invasive is seldom used as a diagnostic modality and is reserved for management of complications including dilatation and stenting of dominant and anastomotic strictures, brush cytology and for SpyGlass Cholangioscopy.

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease characterized by inflammation and fibrosis that may involve the entire biliary tree. Inflammation and fibrosis results in diffuse narrowing of the intra and extra hepatic bile ducts causing persistent biliary stasis eventually leading to secondary biliary cirrhosis. It usually presents in the fourth decade of life with a variable disease progression[1].

Laboratory tests do not play a significant role as there is no definite test to confirm PSC. Non-invasive imaging modalities like trans abdominal ultrasound may pick up nonspecific abnormalities such as bile duct thickening, gall bladder enlargement or wall thickening. Contrast computed tomography (CT) scan and magnetic resonance cholangiopancreatography (MRCP) may detect inflammation, intrahepatic dilations as well as varices and splenomegaly indicative of portal hypertension. CT detects intraabdominal lymphadenopathy, suggestive of underlying cholangiocarcinoma. Even invasive tests like percutaneous transhepatic cholangiography have been used in the past. However none is confirmatory.

PSC recurs in about 10% of patients post orthotopic liver transplantation (OLT), with acute cellular rejection, need for maintenance steroids, HLA-DRB1*08 being positive predictors and pan colectomy being a negative predictor[2,3]. The diagnostic modalities for recurrent PSC (r-PSC) remain the same, with low threshold for biopsy to rule out rejection, which needs to be managed aggressively to prevent decompensation of the liver[2].

It is important to distinguish immunoglobulin (Ig) G4-associated cholangitis (IAC), also called IgG4-related sclerosing cholangitis, a recently described chronic cholangiopathy from PSC and other secondary sclerosing cholangitis, due to the excellent response of the former to steroid treatment. About 10% to 15% of patients with PSC also have elevated IgG4 levels. There is some evidence that the incorporation of IgG4/IgG1 ratio may be used in clinical practice to distinguish PSC from IAC[3,4]. Liver biopsy is rarely used these days, thought, might still be needed in the diagnosis of small duct PSC and when diagnosis is unclear.

Biliary IgG antineutrophilic cytoplasmic antibody and IgA against biliary epithelial cells correlates with the severity of bile duct strictures and may serve in the future as a diagnostic and prognostic marker of the disease progression and biliary complications[5,6]. Biliary protein biomarkers might help in distinguishing benign from malignant strictures, though further studies are warranted[7]. Novel biliary biomarkers like extracellular vesicles containing Micro-RNA's (miRs), U2 small nuclear RNA fragments (RNU2-1f) and oxidized phosphatidyl cholines (ON-PC and S-PC) have been proposed for the early diagnosis of cholangiocarcinoma in PSC, that is stable, reproducible, and has potential clinical utility[7-9].

ENDOSCOPIC DIAGNOSIS

Endoscopic retrograde cholangiopancreatography

Endoscopic retrograde cholangiopancreatography (ERCP) is the mainstay for accurate assessment of the hepatobiliary tree to establish a diagnosis of PSC. Typical cholangiographic findings include multifocal annular biliary strictures interspersed between dilated intra and extrahepatic bile ducts with alternating normal segments, creating the characteristic beaded pattern of PSC.

Even though MRCP is the preferred cholangiographic modality given the high sensitivity, non-invasive nature and lack of exposure to radiation, it has limited accuracy in early PSC, cirrhosis and in the differentiation of Caroli's disease, secondary sclerosing cholangitis and cholangiocarcinoma (CCA)[10]. A retrospective study by Moff *et al*[11] demonstrated that ERCP and MRCP were comparable for diagnosis of PSC. They recommended that MRCP be employed as the initial diagnostic modality given the safety profile as well as sensitivity and specificity of approximately 90% and 88% respectively, although ERCP with its higher specificity of nearly 96% would be necessary for confirmation[11].

Complications occur in about 4% to 16% of patients with PSC undergoing ERCP[12,13]. The complication risk was often dependent on the ease of cannulation, with post ERCP pancreatitis (PEP) reported in up to 7% of procedures[14]. Hence, we recommend routine sphincterotomy, especially in those who are likely to need further procedures, to minimise the risk of PEP[14]. PSC patients undergoing ERCP are routinely given antibiotic prophylaxis to reduce the risk of cholangitis, which is more so in the presence of strictures[12,14,15]. An extra attempt is made to clear the bile duct of all contrast by suctioning or irrigation. Overall, benefits of doing an ERCP outweighed the risks in PSC, when the indications were appropriate[14,15].

A confirmatory ERCP is warranted when clinical suspicion of PSC is moderately high, also in cases with inconclusive MRCP results and or cases being evaluated at centres where the technical expertise with MRCP is not well established[16]. A cost effectiveness analysis comparing ERCP with MRCP by Meagher *et al*[17] in the face of competing technologies revealed that initial MRCP, when negative, followed by subsequent ERCP was the most economic initial approach in the work-up of patients with suspected PSC.

It is crucial to distinguish dominant strictures (DS) in PSC from cholangiocarcinoma, which remains a challenge given that the former predisposes to CCA, which could be found in upto 25% of DS as per some studies[18]. The American Association for the Study of Liver Diseases (AASLD) guidelines recommend those with dominant strictures be assessed with CA 19-9, MRCP and ERCP for tissue acquisition. CCA is one of the major causes of mortality in PSC and

may be detected concurrently at the time of or within months of its diagnosis. However, cholangiocarcinoma related mortality does not diminish with early liver transplantation[19]. Due to the unpredictable natural history and lack of early predictors of cancer, there is no set guideline for surveillance of patients with PSC. Biliary tissue acquisition can be achieved by brush cytology and or intraductal biopsy (for histology using pediatric forceps) to distinguish benign from malignant strictures. Brush cytology being technically easy, safe and less time consuming is more commonly used[20]. The AASLD guidelines recommend performing the above to exclude superimposed malignancy prior to endoscopic therapy for dominant bile duct strictures[21]. A meta analysis by Navaneethan *et al*[7] demonstrated that biliary brush cytology has high specificity (97%) for the diagnosis of CCA, however the low sensitivity limited its role in detecting early CCA[22]. Most cases of malignant DS occur in the perihilar region and accessible to brush cytology[23]. Repeated brush cytology aids early detection of high grade dysplasia before manifest CCA, enabling pre-emptive liver transplantation[24]. A weighted scoring system, proposed by Witt *et al*[25], termed the Atypical Biliary Brushing Score (ABBS) helps to risk stratify the individuals with atypical brush cytology to identify those at high risk of CCA[25]. ABBS considers seven variables including age over 60, pancreatic mass as an indication, distal biliary stricture, CA 19-9 over 300 U/mL scoring one each, endoscopic impression of malignancy, common hepatic duct stricture and a definite diagnosis of PSC with the last three scoring two each. Patients with a score over 4 are considered to be at high risk of harboring malignancy despite atypical results on a biliary brush cytology[25].

There are now advanced techniques in cytology such as digital image analysis (DIA) and fluorescence in situ hybridization (FISH) that enhance the sensitivity and improves diagnostic yield of brush cytology, compared with routine cytology[26-28]. DIA is a method by which microscopic images of a cell are quantified by digital conversion and computer analysis of the image feature[29]. FISH allows fluorescent labeling of DNA probes to target chromosomal regions to detect numerical or structural chromosomal abnormalities, such as trisomy or polysomy which suggest malignant process. The ability of FISH to detect polysomic cells from pancreatobiliary brushings puts it ahead of other pathological or imaging modalities in detecting CCA[30]. FISH of the cytologic specimen has significantly greater sensitivity than conventional cytology for the identification of CCA in patients with PSC, however it has lower specificity compared to biliary brushings[26,31]. Combining FISH with routine cytology can markedly improve the odds of detecting CCA at an early stage[30,32]. By identifying chromosomal abnormalities, DIA and FISH highly improve sensitivity while maintaining specificity. A prospective study from Mayo clinic revealed that composite DIA and FISH yielded 100% specificity and improved sensitivity by fivefold in indeterminate biliary strictures[27]. Many of these techniques once widely available should be used routinely.

Cholangioscopy

In recent years, peroral cholangioscopy as an adjunct to ERCP has gained popularity as it helps overcome diagnostic inaccuracies in biliary diseases, initially described by Chen and Pleskow[33]. In the management of challenging indeterminate biliary strictures, cholangioscopy permits direct intra luminal view of the biliary tree, targeted tissue acquisition and allows endoscopic guidance for therapeutic interventions[34]. The dual operated cholangioscope, "mother-baby" system was the first to be introduced, however the "two scope system" was time consuming, expensive, had limited manoeuvrability, poor irrigation capacity, required two endoscopists, and was easily damaged[35,36] it is therefore seldom used in clinical practise. The single-operator peroral cholangioscopy using SpyGlass direct visualization system appears to have overcome some of the limitations of the conventional peroral cholangioscopy. In addition to having two independent irrigation channels, this provides a 70-degree field of view, though the single use SpyBite forceps has only a maximum jaw separation of 4.1 mm. Hence, negative findings on the mini-forceps biopsy cannot exclude CCA owing to small sample obtained[37]. SpyGlass system was shown to have a lower complication rate, with a potential to become a diagnostic standard for the assessment of indeterminate biliary lesions with further refinements[38]. In a single center prospective study of thirty six patients with indeterminate biliary stricture, Ramchandani *et al*[36] from the Hyderabad group, showed that SpyBite had an overall accuracy of 82% in differentiating malignant from benign ductal lesions on an intention-to-treat analysis. The sensitivity of SpyGlass to obtain adequate tissue from indeterminate strictures could be upto 88%, especially when atleast 3 bites are taken. Sensitivity of diagnosing CCA by visual impression is 78% and by biopsy alone is 49%[39].

Endoscopic ultrasound scan

Endoscopic ultrasound scan (EUS) is a safe, accurate and technically feasible approach for diagnosing extrahepatic PSC. Lutz *et al*[40] demonstrated it to be an efficient tool for confirming suspected PSC, which has eluded diagnosis by ERCP or other modalities. Sensitivity and specificity of EUS-FNA for evaluation of biliary strictures ranges from 43% to 86% and 95% to 100% respectively[40-42]. The specific sonographic features include duct wall thickening greater than 1.5 mm, irregular CBD wall/caliber (change of wall thickness by $\geqslant$ 1 mm over 5 mm and caliber $\geqslant$ 2 mm over 5 mm ductal length) and the presence of perihilar lymph nodes at least 1 cm diameter, with an EUS diagnosis of PSC when two or more of above

criteria positive[43]. EUS enables refinement in disease detection and diminishes need for high risk invasive procedures[40]. In patients with a high index of suspicion of PSC with an inconclusive MRCP and EUS, core biopsy of the liver could be done safely in the same sitting (less than 1% risk of major complication), to look for small duct PSC and also to rule out cirrhosis, which would have prognostic implications[44-47]. Tumour seeding has been rarely reported with the FNA and hence some authorities advocate FNA of only suspicious lymph nodes[48]. Hence, we do not advocate EUS-FNA of the bile duct in a patient with suspected cholangiocarcinoma, who is a possible OLT candidate, until discussion at the tumor meeting with transplant surgeons. Direct biopsy using a cholangioscope would certainly be the preferred modality of tissue acquisition. EUS guided FNA has a significant role in diagnosing CCA when standard modalities are inconclusive, as it allows assessment and aspiration of malignant appearing lymph nodes[49,50].

Intraductal ultrasound

Intraductal ultrasound (IDUS) utilises a standard duodenoscope to insert a high frequency ultrasound transducer over a wire into the biliary system under fluoroscopic guidance. IDUS allows visualisation of the wall layers of the biliary strictures thereby providing an estimate of the extend of potentially cancerous infiltration[51]. This information is valuable in deciding treatment options. IDUS as an adjunct to ERCP guided tissue sampling significantly enhances the ability to distinguish malignant from benign strictures, it however is not an efficient modality assessing lymph nodes associated with malignant strictures[52]. Biliary cannulation with IDUS can be performed with ease, thereby avoiding the need for sphincterotomy; it provides detailed images of ductal and peri ductal tissues with high resolution. Additionally, when CCA is identified, IDUS may be employed for local staging in candidates prior to surgical resection[53].

Confocal laser endomicroscopy

Probe-based confocal laser endomicroscopy (pCLE) is a novel diagnostic technique that provides a virtual biopsy to facilitate subepithelial evaluation of the pancreatobiliary mucosa. It delivers microscopic information in real time and also provides dynamic information such as blood flow, cellular architecture, contrast uptake and leakage[54].

In a small single centre study of pCLE, Heif *et al*[55], showed a high technical success rate in patients with PSC and DS. Sufficient visualization was achieved in 95%, with sensitivity, specificity, positive predictive value and negative predictive values of 100%, 61.1%, 22.2% and 100% respectively, in detecting neoplasia. If verified in larger prospective studies, this could be potentially utilized for risk stratification of dominant strictures in patients with PSC[55].

ENDOSCOPIC THERAPY

PSC is characterized by inflammation and fibrosis leading to bile duct strictures. DS is defined as stenosis with a diameter of 1.5 mm in the common bile duct or 1 mm in the hepatic duct[21,56]. They develop in about forty percent of patients with PSC leading to significant biliary obstruction[57]. These predispose to stone formation, recurrent cholangitis and secondary biliary cirrhosis; also it may be a marker for underlying malignancy.

Traditionally ERCP has been employed for the stone removal that is the main indication for biliary sphincterotomy in PSC; balloon dilation *via* ERCP reduces stenosis thereby improving biliary flow and potentially preventing recurrent cholangitis[58,59]. Current therapy for stricture in PSC including balloon dilation, biliary stent placement and often a combination of both have become the mainstay of treatment, at least as a first line intervention[43,60]. Studies have established that repeated endoscopic therapy in patients with PSC is safe, the prognosis however worse in the subgroup of patients with dominant strictures at increased risk for development of cholangiocarcinoma[56].

An average of 3.46 ERCP's were needed per patient over a 8 year follow up study, with an improved observed survival rate of 82.8% at 4 years compared to 71.3% predicted survival (as per the Mayo Clinic natural history model)[58]. Endoscopic dilatation with short-term stenting is effective in benign dominant strictures and does not have predilection for malignant transformation or complications after transplantation[23]. Gotthardt *et al*[61] in a 20 year follow up of 171 patients have shown that repeated endoscopic therapy helps preserve a functioning common bile duct for many years, improving transplant free survival to 81% at 5 years and 52% at 10 years after initial endoscopic therapy. In a small subset of patients with DS in the extra hepatic duct without signs of cirrhosis, resection or bypass surgery may be performed, especially when endoscopic treatment fails[62].

Biliary sphincterotomy done in PSC is often a limited one, to minimize the reflux of enteric contents and ascending cholangitis[63]. Sphincterotomy prior to stent placement minimizes the chance of post ERCP pancreatitis (PEP)[64]. Stricture dilation could also be done using tapered-tip dilators (Cotton graded dilator) over a guide wire as a stand-alone or in combination with balloon dilatation[65]. In difficult cases, where only the wire could be passed through, a screw-tip dilator (Soehendra screw) could be employed[66]. In high grade stenosis, a Terumo guide wire could be used, since it has the added advantage of a very flexible tip[63]. Following this, stiff dilatation upto 7F facilitates balloon dilatation upto a target of 24F in the common duct and 18F in the hepatic ducts. Stiehl *et al*[57,67] have shown that even long segment stenosis (over 2 cm) of the common bile duct and shorter-segment intrahepatic stenosis within 2 cm of the hilum could be successfully

treated endoscopically.

Although controversial, there are interventional endoscopists, who advocate routine placement of one or more stents with frequent stent exchanges (every 6 to 8 wk), after dilatation with any of the above modalities, to prevent the stricture from reforming immediately due to the underlying fibrosis and elasticity[43]. International bodies like AASLD however, do not endorse this above practice, since there is no strong evidence demonstrating additional benefit of stenting over endoscopic dilatation[68]. Though results have been conflicting, there is evidence from a recent study in favour of additional stenting when clinically appropriate[68]. In cases of hilar strictures, it is preferable to gain access into both ducts first, as dilatation of one system somehow makes access to the other side more challenging[69].

Stents used in PSC could be either plastic or self-expandable metallic stents (SEMS). Teflon (PTFE) stents are the most commonly used ones, with longer patency[70]. However, fully/partially covered SEMS (CSEMS) have also been used for management of dominant strictures, though there are no randomized trials to support this[71-73]. The possible reasons why SEMS has not become standard of care of dominant strictures in PSC, is the theoretical risk of ascending cholangitis in this high risk group due to the larger caliber of the metal stent, in addition to not being cost effective compared to plastic stents in this situation. This is in addition to the potential risk of cholecystitis from obstruction of the cystic duct (in individuals who have not undergone cholecystectomy) and of obstruction of bile flow from the other lobe of the liver in case of hilar lesions.

Uncovered SEMS has been successfully used for palliation of inoperable CCA[56,74,75]. SEMS is preferred over plastic stents for patients with life expectancy over 3 mo[76]. For hilar strictures, stenting of one or both lobes and use of plastic stent or metallic stents continues to be debated, with ongoing research into the design of specifically tailored stents including cross wired stents and new plastic inside stent with thread (IT) stent[77-79].

EUS-guided palliation of malignant obstructive jaundice, when ERCP access fails has been gaining grounds and when expertise available replacing percutaneous drainage, since the latter is less appealing cosmetically with the external bag and inconvenient. This is mostly used for drainage of the obstructed left system (though there have been initial attempts to drain the right duct) using EUS-guided hepaticogastrostomy and of the main duct by a choledochoduodenostomy. Although technically feasible, the challenge is in the controlled deployment of the fully CSEMS, preferably in a single step, to minimize the risk of perforation, biliary peritonitis and stent migration[80-85]. These risks are minimized by the availability of lumen apposing metal stents. Endoscopic placement of nasobiliary drains to decompress the non-atrophic lobe has been done in some centers especially in Japan, to bridge the gap to surgery[79].

Biliary complications can occur in as many as 10% to 35% of patients after orthotopic liver transplantation with PSC recurrence in around 10%[86-88]. The most common biliary complications after OLT include biliary strictures (anastomotic or ischemic), bile duct leaks, common bile duct stones, and biliary casts, sphincter of Oddi/ampullary muscle dysfunction/spasm and r-PSC. With the advances in biliary endoscopy, majority of the complications could be managed with ERCP using regular techniques and tools. ERCP directed brachytherapy for locoregional disease control in cholangiocarcinoma, using photodynamic therapy or radiofrequency ablation, is promising, though still in its early stages[89,90]. They have comparable efficacy for local disease control and safety profile.

APPROACH TO THE PATIENT WITH SUSPECTED PSC

We recommend MRCP to be done as the initial diagnostic modality in suspected patients with PSC. ERCP with brush cytology and or biopsy, to date, continues to be the gold standard for diagnosis especially if the former is inconclusive, due to the surveillance and prognostic implications of making a correct and early diagnosis. EUS, IDUS and cholangioscopy could be utilized in the evaluation of patients, especially those with indeterminate dominant strictures, to get better cytologic yields to exclude early biliary dysplasia and cholangiocarcinoma. With further evidence and validation of EUS criteria for PSC, it might be done before ERCP in the diagnostic algorithm, especially considering its safety profile. Advancements in cytology including DIA and FISH should be considered to improve the yield, when ever available. The role of molecular markers and proteomics in diagnosis is still evolving. ERCP with repeated biliary dilatation with or without stenting is our current practice in management of benign strictures, in addition to routine use of antibiotic prophylaxis, as per BSG and ASGE recommendations. EUS guided biliary drainage procedures could be attempted in cases of failed SEMS deployment by ERCP for palliation of CCA. There is some evidence that endoscopic therapy could delay the need for orthotopic liver transplantation in patients with PSC.

CONCLUSION

Endoscopy has a pivotal role in the diagnosis and management of the condition, both pre and post orthotopic liver transplantation. Advances in endoscopy (complimented by cross sectional imaging) and ancillary cytologic testing would enhance earlier diagnosis, facilitating a surveillance protocol that could be used, to improve survival rates by timely curative therapy.

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REVIEW

Rare gastrointestinal lymphomas: The endoscopic investigation

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Abstract

Gastrointestinal lymphomas represent up to 10% of gastrointestinal malignancies and about one third of non-Hodgkin lymphomas. The most prominent histologies are mucosa-associated lymphoid tissue lymphoma and diffuse large B-cell lymphoma. However, the gastrointestinal tract can be the site of rarer lymphoma subtypes as a primary or secondary localization. Due to their rarity and the multifaceted histology, an endoscopic classification has not been validated yet. This review aims to analyze the endoscopic presentation of rare gastrointestinal lymphomas from disease diagnosis to follow-up, according to the involved site and lymphoma subtype. Existing, new and emerging endoscopic technologies have been examined. In particular, we investigated the diagnostic, prognostic and follow-up endoscopic features of T-cell and natural killer lymphomas, lymphomatous polyposis and mantle cell lymphoma, follicular lymphoma, plasma cell related disease, gastrointestinal lymphomas in immunodeficiency and Hodgkin's lymphoma of the gastrointestinal tract. Contrarily to more frequent gastrointestinal lymphomas, data about rare lymphomas are mostly extracted from case series and case reports. Due to the data paucity, a synergism between gastroenterologists and hematologists is required in

order to better manage the disease. Indeed, clinical and prognostic features are different from nodal and extranodal or the bone marrow (in case of plasma cell disease) counterpart. Therefore, the approach should be based on the knowledge of the peculiar behavior and natural history of disease.

Key words: Endoscopy; Lymphoma; Endosonography; Stomach; Intestine

Core tip: The gastrointestinal tract can be the site of rare lymphomas as a primary or secondary localization. Their endoscopic behavior has been scantily evaluated but is emerging as a useful tool with prognostic and therapeutic implications. T-cell lymphomas present mainly with ulcerative lesions, while B-cell lymphomas (follicular or mantle cell lymphomas) present as a duodenal mass or multiple polyposis. Plasma cell-related disorders localize to the gastrointestinal tract, either as a neoplastic mass or as an amyloid deposition. Immunodeficits (primary or secondary) can lead to gastrointestinal localization of rare and seldom fatal high-grade lymphomas. More rarely, Hodgkin's lymphoma localizes to the gastrointestinal tract with an uncertain impact on prognosis.

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INTRODUCTION AND MAIN SECTION OF THE WORK

Gastrointestinal (GI) lymphomas represent 5%-10% of primary GI malignancies and almost two third of extranodal non Hodgkin's lymphomas (NHL), that in turn account for 24%-49% of all NHL[1,2]. The most common lymphomas are mucosa-associated lymphoid tissue (MALT) and diffuse large B-cell lymphoma (DLBCL), accounting for 70%-95% of GI lymphomas[3,4]. Apart from MALT and DLBCL, the GI tract can be the site of other lymphomas, either as a primary or secondary localization[5], and these lymphomas will be the subject of this report. The knowledge of their clinical and echo-endoscopic features would help in addressing clinical questions[3,6-8], sparing inappropriate evaluations[9-13]. Nonetheless, histology, together with immunohistochemistry and molecular biology, are mandatory for diagnosis[14].

While the endoscopic classification for MALT and DLBCL has been already validated[15,16], such an analysis on rare GI lymphomas is still under debate. In 2001 and 2003, the Taiwanese[17] and the South Korean group[18] respectively published a 3/5 item classification of ileocolonic GI lymphomas. Table 1 shows patterns analyzed in both classifications. Basically, the endoscopic appearance is classified according to the presence and depth of ulcerations and of fungating lesions. To date, these were the only attempts to classify rare GI lymphomas. After that, Kim *et al*[19] investigated the endoscopic differences between B- and T-cell lymphomas of the colon and they observed that B-cell lymphomas occur more often as fungating or ulcerofungating lesions, while T-cell lymphomas more frequently have an ulcerative or ulceroinfiltrative pattern (Figure 1). Notwithstanding, a clear prognostic implication based on the endoscopic pattern has not been validated yet.

Table 1 Endoscopic features of rare gastrointestinal lymphomas according to two classification systems

Ref.	Wang *et al*[18]		Myung *et al*[17]	
No. of patients	13		32	
Endoscopic pattern	Mucosal - ulcerative	30.7%	Fungating	39%
	Mucosal - erosive	15.3%	Ulcerative	6%
	Polypoid	23%	Infiltrative	14%
	Massive	31%	Ulcerofungating	31%
			Ulceroinfiltrative	11%

Newer techniques, *i.e.,* capsule endoscopy (CE) and double-balloon enteroscopy (DBE), are emerging as useful tools in detecting small bowel tumors (15% of them represented by lymphomas)[3,20-22]. Surely both techniques can augment the endoscopic diagnostic field (especially for follicular lymphomas[21]). Moreover, spiral enteroscopy has been also evaluated as a tool for revealing GI lymphomas of the small intestine. Boudiaf *et al*[23] reported that 4 out of 14 patients affected by refractory celiac sprue developed a small bowel mass that was confirmed to be an enteropathy-associated T-cell lymphoma (EATL) by histological evaluation. Although less widespread, single-balloon enteroscopy has been used in the definition of small bowel lesions and recently it has been implemented with the water exchange method in order to improve the visualization of the lumen to better define and sample the lesion[24]. However, such deep diagnostic tools have not been validated for routine use in GI lymphoma staging and follow-up since they do not induce a treatment change. Thus, their application in gastric or colonic lymphomas has not been fully validated[25]. Differently, faced with T-cell lymphomas with a jejunal tropism, DBE can lead to a definitive diagnosis coupling the endoscopic investigation with the bioptic evaluation[26,27]. However, not many publications related to the usage of these techniques are available to date.

A particular consideration should be given to the role of endoscopic ultrasonography (EUS). Its role has gained more and more importance in MALT lymphomas since the locoregional staging of the disease has a great

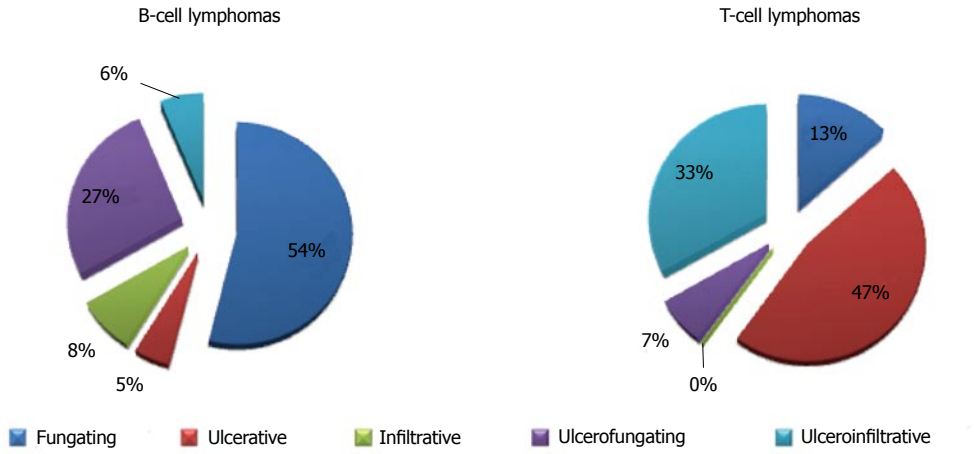

Figure 1 Differences in endoscopic pattern between B-cell and T-cell lymphomas of the gastrointestinal tract. Data extrapolated from Kim *et al*[19] 2005.

impact on the treatment approach[6]. Regarding DLBCL, the locoregional extension has significant prognostic implications, although its role in treatment definition is still under discussion[3]. In contrast, few data are available in rare GI lymphomas. In particular, they are more frequently regarded as general diseases so that the locoregional extension is not always evaluated, with some reports indicating just the EUS pattern without any clinical implication. Exceptional cases have indicated the role of EUS in defining the limited extension of the disease, thus leading to an endoscopic resection of the mass [see the paragraph "Extramedullary Plasmacytoma (EMP) and Plasma Cell-related Diseases"]. That notwithstanding, EUS information is gathered only for describing the behavior of these lesions in most cases without any significant clinical impact.

Definitively, a proper staging for GI lymphomas will include[28]: (1) physical examination: evaluation of superficial lymph nodes and Waldeyer ring inspection; abdomen palpation in order to detect liver enlargement, splenomegaly and abdominal masses; (2) endoscopic ultrasonography that is the golden standard in defining the locoregional GI involvement since it is able to distinguish the involvement of a specific layer and also of regional lymph nodes. However, as stated above, its role is under study and it is not strictly recommended in this setting; (3) computed tomography of the neck, chest and abdomen in order to detect involvement of nodes above and below the diaphragm and also other extranodal involvement not pertaining to the GI tract. In some cases, computed tomography can be of great help in defining the extension of a large bulky mass departing from the GI tract but exteriorizing outside the GI tract (see the paragraph "Plasma-cell related diseases"); (4) positron emission tomography is not generally indicated as a staging procedure, especially in MALT lymphomas, but it retains a role in defining the pre-treatment lymphomatous involvement and response to treatment; and (5) bone marrow biopsy: notwithstanding the low-grade, indolent diseases that tend to remain localized at the GI tract, bone marrow biopsy should be performed in order to exclude a marrow involvement that could influence treatment and follow-up management. However, the level of evidence on its utility is poor. A recent update of the staging recommendation in nodal lymphomas does not encourage the performance of bone marrow biopsy facing diffuse large B-cell lymphoma and Hodgkin's lymphoma, but this strategy has not been evaluated specifically for GI lymphomas[29].

However, these are general guidelines adopted from MALT lymphoma since in more rare GI lymphomas these guidelines have not been fully validated.

The aim of the present review is to highlight macroscopic features of rare GI lymphomas using endoscopy and related techniques. In particular, we will focus on T-cell lymphomas, lymphomatous polyposis (LP) and mantle cell lymphoma (MCL), follicular lymphoma (FL), plasma cell-related diseases, gastrointestinal lymphomas in immunodeficiency and Hodgkin's lymphoma (HL). An outline on the endoscopic presentation will be given for the diagnostic aspect and follow-up assessment. As a whole, Table 2 summarizes the clinical and molecular characteristics and prognostic features of these lymphomas.

T-cell and natural killer lymphomas

GI T-cell lymphomas are rare, representing about 5% of GI lymphomas[14,30,31]. However, the incidence varies according to the geographical zones. European studies reported that 1.3% of primary GI lymphomas are of T-cell origin[32], while groups from eastern countries reported 7%-15%[33,34], reaching 41% in other series of intestinal lymphomas[35].

Ulcerated lesions are the main endoscopic features[30,36-38]. The first definition of this disease was "ulcerative jejunitis" by Isaacson and Du, given the always present ulcerative pattern[14]. Usually, symptoms are related to malabsorption[14], although perforation[39] or intestinal bleeding[40] can occur. Incidentally, GI perforation or bleeding can occur in cases of nodal T-cell lymphomas independently from GI localization and are an infective etiology, reflecting the immune impairment that characterizes these lymphomas[41,42].

Table 2 Table listing gastro-intestinal lymphoma with main gastro-intestinal organ involvement, typical presenting characteristics, typical immunophenotype and genotype and prognosis

Lymphoma histotype		Presenting characteristics	Main GI involvement	Main endoscopic pattern	Typical immunophenotype	Typical genotype	Prognosis
T and NK lymphomas	EATL	Celiac patients with abdominal pain and small intestine obstruction/ perforation	Duodenum and jejunum	Multiple erosions and ulcers	$CD3^+$, $CD4^-$, $CD8^{+/-}$, $CD7^+$, $CD5^-$, $CD2^+$, TIA^+, $GrBPer^+$, $CD30^{-/+}$, $CD25^{-/+}$, $CD56^{-/+}$, $CD16^-$, $CD57^-$, $BCL6^-$, $CD10^-$, EBV^-, $EMA^{-/+}$	TRB and TRG clonally rearranged +9q31.3 -16q12.1 +1q32.2-q41 +5q34-q35.2 +8q24 (MYC)	Poor
	PTCL	Poor performance status	Stomach and duodenum	Ulcerative	$CD3^+$, $CD4^+$, $CD8^-$, $CD7^+$, $CD5^+$, $CD2^+$, TIA^-, $GrBPer^-$, $CD30^{-/+}$, $CD25^-$, $CD56^-$, $CD16^-$, $CD57^-$, $BCL6^-$, $CD10^-$, EBV^-, EMA^-	[1]TCR clonally rearranged +7q/+8q/+17q/ +22q/-4q -5q/-6q/-9p/-10q/-12q/-13q	54% survival at five year Poor in case of high IPI score and stage III-IV disease
	Extranodal NK/T-cell lymphoma	Gastrointestinal bleeding and B symptoms	Small intestine	Multiple erosions and ulcers	$cyCD3^+$, $CD4^-$, $CD8^{-/+}$, $CD7^-$, $CD5^-$, $CD2^+$, TIA^+, $GrBPer^+$, $CD30^-$, $CD25^-$, $CD56^+$, $CD16^-$, $CD57^-$, $BCL6^-$, $CD10^-$, EBV^+, EMA^-	TCR in germinal configuration No specific cytogenetic studies on this specific subtype	Poor especially if perforation occurs
	Adult T-cell leukemia/ lymphoma	Abdominal pain, diarrhea, general fatigue, weight loss	No site preferences	Ulcers	$CD3^+$, $CD4^+$, $CD8^-$, $CD7^-$, $CD5^+$, $CD2^+$, TIA^-, $GrBPer^-$, $CD30^{-/+}$, $CD25^{++}$, $CD56^-$, $CD16^-$, $CD57^-$, $BCL6^-$, $CD10^-$, EBV^-, EMA^-	TCR clonally rearranged Monoclonal integration of HTLV-1	Poor[2] Good[3]
	Indolent lympho-prolipherative diseases of GI tract: T-LPD	Dyspepsia and mild diarrhea	Small intestine and colon	Unremarkable/ friable or erythematous mucosa	$CD3^+$, $CD4^-$, $CD8^+$, $CD7^{+/-}$, $CD5^{+/-}$, $CD2^+$, $TIA^{+/-}$, $GrBPer^{-/+}$, $CD30^-$, $CD56^-$, EBV^-	TCR-γ monoclonal	Indolent course
	NK-cell enteropathy	Vague symptoms (dyspepsia)	Stomach and small intestine	Lesions exhibit superficial ulceration, flat elevations with central depression and are associated with edema and local hemorrhage	$cCD3^+$, $CD4^-$, $CD8^-$, $CD7^+$, $CD5^-$, TIA^+, $GrBPer^+$, $CD56^+$, EBV^-	TRC polyclonal or oligoclonal	Indolent course
Mantle cell lymphoma		Vague symptoms (dyspepsia)	Colon	Multiple polyposis, seldom with ulcerations	$CD19^+$, $CD20^+$, $CD5^+$, $CD10^-$, $CD43^+$, sIg^+, $BCL6^-$, $IRF4/MUM1^-$, $Cyclin\ D1^+$	BCR rearranged t(11;14)(q13;q32)	Negative impact on prognosis
Follicular lymphoma		Vague symptoms (dyspepsia)	Second part of duodenum	Whitish polyps	$CD19^+$, $CD20^+$, $CD5^-$, $CD10^+$, $CD43^-$, sIg^+, $BCL6^+$, $IRF4/MUM1^{-/+}$, $Cyclin\ D1^-$, $\alpha4\beta7^+$	BCR rearranged t(14:18)(q32:q2 1)	Good
Extramedullary plasmacytoma		Alarm symptoms and obstruction	Stomach	Infiltrating mass	Plasmacells expressing $CD79a^+$, $CD38^+$, $CD19^-$, $CD138^+$, $CD56^+$, usually $CD20^-$	BCR rearranged t(11;14)(q32;q13)	Poor
PTLD		Alarm symptoms	Colon	Rubbery erythematous or ulcerated	Similar to DLBCL and Burkitt's lymphoma $CD19^+$, $CD20^+$, $CD5^{-/+}$, $CD10^{-/+}$, $CD43^{-/+}$, $sIg^{+/-}$, $BCL6^{-/+}$, $IRF4/MUM1^{-/+}$, $Cyclin\ D1^-$	Monoclonal BCR	Poor median survival 6 mo
Plasmablastic lymphoma		Alarm symptoms	Stomach	Large masses and exophitic processes	$CD79a^+$, $CD138^+$, $CD38^+$, $IRF4/MUM1$, $CD45^-$, $CD20$, $PAX5^-$, $CD56^-$	Clonal IgH chain gene rearranqement	Poor
Hodgkin's lymphoma		Obstruction	Colon	Protruding mass	$CD30^+$, $CD15^+$, $CD45^-$, $CD20^-$, $CD79a^-$, $PAX5^+$, Ig^-, $OCT2^-$, $BOB1^-$, $CD3^-$, $CD2^-$, $CD5^-$, ALK^-	Clonal immunoglobulin gene rearrangements	Prognostic impact not known

[1]Estrapolated from nodal counterpart but not explored in Primary GI lymphoma; [2]ATLL acute and lymphoma types; [3]ATLL chronic and smoldering types. TCR: T-cell receptor; BCR: B-cell receptor; EATL: Entheropathy–associated T-cell lymphoma; PTCL: Perypheral T-cell lymphoma; T-LPD: T-cell lymph-prolipferative disease; NK: Natural killer; DLBCL: Diffuse Large B-cell lymphoma; PTLD: Post-transplantation lymph-proliferative disease; GI: Gastro-intestinal.

Guidelines suggest that diagnostic work-up and follow-up should be done in synergism between hematologists and gastroenterologists in order to better define the staging and the treatment needed and to ensure the best nutritional guidance (evidence level Ⅲ grade B)[43].

In a study from the German group, the most frequent histotype of intestinal lymphoma was T-cell lymphomas[44]. The most commonly involved organs are the duodenum and jejunum, followed by the ileum and colon. Less frequent is the involvement of the stomach[45], also as part of composite lymphoma[46], *i.e.,* lymphoma with B- and T-cells origin. Regarding gastric involvement, in 30% of cases there is localization in the upper part of the stomach, in 20% the localization is in the middle part and diffuse in 40% of cases[47]. Due to the fact that the prognosis and treatment strategy depends on the lymphoma histotype, bioptic evaluation is a mandatory step. In addition, each subtype presents peculiar endoscopic behaviors that can drive diagnosis and treatment. GI T-cell lymphomas typically have a mature phenotype, while acute types of T-cell neoplasms do not classically involve the GI tract[48].

According to the 2008 WHO classification of hematological malignancies, the most prevalent histotypes are[48,49]: (1) enteropathy-associated T-cell lymphomas (EATL) (distinguished in type Ⅰ and Ⅱ); (2) peripheral T-cell lymphomas and extranodal natural killer (NK)/T-cell lymphoma; and (3) adult T-cell leukemia/lymphoma (ATLL).

In addition, very rare cases have been reported (mostly as singular events) of colorectal T-cell prolymphocytic leukemia/lymphoma[50] or anaplastic T-cell lymphoma (ALCL) ALK$^+$[51] or ALK$^-$[52]. Distinct entities not described in the WHO classification are indolent T-cell/NK diseases that will also be taken into account.

Although EUS findings are not usually reported except in peculiar cases, submucosal hypoechogenic lesions destroying the involved layer would be the main pattern[53]. Another proof of the sub-mucosal origin of the tumor is given by narrow band imaging that is able to show intact gastric pits elevated from the underlying mass[51]. Very rare and unusual is the GI involvement in Sezary syndrome where, despite unremarkable gastric mucosa, EUS can show the hyperechogenic submucosa layer at giant fold level[54].

Enteropathy-associated T-cell lymphoma

EATL can be divided into two forms[14]. The first variant is characterized by features of celiac disease with abdominal pain and small intestine obstruction/perforation. Usually there is a large mass with massive necrosis, while the neighboring mucosa shows villous atrophy and crypt hyperplasia as in typical enteropathy. Type II exhibits villous atrophy in the context of tumor mass with normal intestinal mucosa in uninvolved sites. Contrarily to type I EATL, type Ⅱ EATL does not progress from undiagnosed or refractory celiac disease[14,55]. Prognosis is poor with a median overall survival of 7-10 mo[56].

The exact incidence and lymphoma risk in celiac patients is still a debated issue[57]. Some studies indicate a 200-fold increased risk of developing EATL compared to the general population[58,59]. According to other studies, the risk of developing non-Hodgkin's lymphomas in celiac patients appears to be 6-fold higher than in the general population and this risk assumes a downward trend over years[60]. Nonetheless, it appears clear that the occurrence of complications in celiac patients, although infrequent, is an event that negatively impacts on patient survival[61]. In fact, the occurrence of intestinal perforation in a patient affected by celiac disease should lead to suspicion of lymphoma.

Usually, EATL patients tend to have a poorer performance status than B-cell lymphomas (even though tends to be localized), independent of the stage. Fever and diarrhea are the most frequent symptoms[44]. The duodenum and jejunum are the most involved sites, with secondary involvement of the gross intestine in 14% of cases[44]. The diagnosis of the disease in some cases is difficult since neoplastic lymphocytes can be present in a context of an inflammatory background.

Endoscopic features are aspecific, with multiple erosions and ulcers[31]. Nodularity and thickened folds can be seen at DBE[26,27]. Strictures and masses are less common[62]. In some cases, macroscopic findings together with the occurrence of an intense inflammatory reaction can lead to a mistaken diagnosis of Crohn's disease (CD)[31,63]. However, although it is not a general rule, CD ulcers are transversal, while, in the presence of T-cell lymphoma, ulcers are longitudinal[63].

Peripheral T-cell lymphomas and extranodal NK/T-cell lymphoma

Peripheral T-cell lymphomas (PTCL) and NK lymphomas are more frequent in South America and Asia. These entities are distinct from other GI T-cell lymphomas by morphological and immunohistochemistry criteria[62] and should be diagnosed when other more frequent T-cell lymphomas are excluded[48]. Korean and Japanese series indicated that these are the most frequent GI T-cell lymphoma subtype, accounting for 40% of primary T-cell GI lymphomas HTLV-1 negative[64]. PTCL arises frequently in extranodal sites, especially at the skin. However, the involvement of the gastrointestinal tract is a severe prognostic factor[65,66]. The stomach and duodenum accounts for 60% of GI localizations[52]. The most frequent findings are ulcerative (46% of cases), infiltrative (9%), ulceroinfiltrative (18%), ulcerofungating (18%) and erosive (9%)[52]. Multiple polyposis can also be detected[67]. In the literature, there are two reports indicating the involvement by T-cell lymphomas in the ileocolonic anastomosis for a previously resected right colon, presenting with polypoid lesions[68] or ulcerative lesions[69].

Extranodal NK/T-cell lymphoma usually arises in nasal cavities and rarely affects the GI tract. A strict relationship exists between ENKTCL and EBV infection,

with almost 70% of cases positive for Epstein–Barr virus-encoded small RNAs (EBER) detection[70]. The small intestine is the most involved organ, while the stomach is rarely involved[71]. The endoscopic pattern in the majority of cases is given by multifocal ulcers[72-75] and infiltrative lesions[52]. Sometimes the ulceration leads to intestine perforation and acute peritonitis (60% of the total complications)[52]. Additionally, perforation is more frequent in the infiltrative pattern compared to the non-infiltrative. Fungating lesions are not usually reported[76]. The most involved organ is the small intestine[77,78] and/or colon[72,76] (depending on the case series), followed by the small intestine, rectum and stomach[72]. However, the location at the GI tract does not seem to affect the prognosis[77]. Interestingly, since the perforation usually leads to the development of peritonitis, the Lugano staging system has been applied, resulting in the advanced stage of the disease being a prognostic factor at multivariate analysis[72]. Due to the high risk of perforation, many patients undergo surgery as a pre-emptive or curative strategy, rarely for diagnosis[79]. However, according to Kim *et al*[77], patients undergoing surgery followed by chemo/radiotherapy would show a better OS. However, as the authors themselves stated, this benefit would be ascribed to the fact that patients undergoing surgery had a better performance status and more limited disease which would have affected the outcome. Similarly, as Hong *et al*[78] reported in a multivariate analysis, surgery ensures a better survival compared to chemotherapy. Therefore, an appropriate locoregional staging is also useful to tailor treatment.

Adult T-cell leukemia/lymphoma

As for EATL, ATLL tends to present with ulcers with aggressive behavior. This is a specific variant of peripheral T-cell lymphoma that recognizes the HTLV-1 virus as an etiological agent[48]. This variant is mainly found in endemic areas of Japan[64]. In about one third of ATLL cases, GI involvement is secondary to a systemic disease[49]. According to the first data by Suzumiya, the stomach is involved in 40% of cases and the small and large intestine in 38% and 34% respectively[80]. Although four types of ATLL have been depicted (*i.e.,* smoldering, chronic, lymphoma, acute), no endoscopic pattern has been related to a peculiar histotype. HTLV-1 infection has no role in determining the macroscopic features[47]. Noteworthy, the detection of GI involvement has a prognostic impact[49], representing the aggressiveness of the disease[43]. In fact, smoldering or chronic ATLL subtypes do not typically show GI involvement[81]. However, primary GI smoldering ATLL have been described and show long term disease-free survival after chemotherapy[82]. Gastric involvement can be enhanced by *Helicobacter pylori* infection that creates an inflammatory state able to lead lymphocytes (also malignant) to migrate into gastric wall through the expression of specific adhesion molecules[83].

An ulcerative pattern is present in more than half of cases of gastric involvement[47]. Single or multiple yellow-whitish polyposis of the first or second loop are more frequent in the duodenum[49] and multiple polyposis is the recurrent lesion in cases of colon involvement[84]. Although a single or multiple polyps are the most frequent lesions, flat ulcerations/erosions can also be present[84]. Red flat or elevated lesions in the rectum have been also documented[85,86]. Rarely, there is the involvement of the ileum, where polyps are the main features[87]. It should be underlined that GI lesions are not always monotone but can be variegated. For examples, case reports indicate the occurrence of protruding masses with normal or eroded mucosa at the stomach and the occurrence of flat granular, friable lesions that bled on contact with mucosa at the colon[88] or reddish irregular flat lesions at the esophagus[89].

Narrow band imaging is able to document irregular microvascular architecture, dilated and destroyed gastric pits and dense aggregations between the pits with variegated irregular nuclei without interglandular infiltration (reflecting the absence of lymphoepithelial lesions)[90].

Indolent lymph-proliferative diseases of the GI tract

A new category of T-cell GI lymphoproliferative disease, namely T-cell lymphoproliferative disease (T-LPD), has been recently introduced[91]. The indolent course is the main clinical hallmark while this entity has been previously treated and managed as PTCL. Noteworthy, the etiology of the disease is unknown, although many patients present with a history of inflammatory bowel disease (IBD). Basically, the clinical picture is dyspepsia and mild diarrhea, while endoscopic features can vary from unremarkable mucosa to erythema. The small intestine and colon are the most frequently involved sites, followed by the oral cavity, stomach and esophagus. Usually, the gastric mucosa is normal despite a disease localization, while the duodenum can show thickened folds and an irregular pattern. In the colon, the occurrence of friable mucosa, erythematous mucosa and small polyps can be seen. Ulcerations are not described. At immunohistochemistry, lymphoid cells have a cytotoxic phenotype ($CD8^+$; $CD4^-$; TIA^+), clonal T-cell receptor (*TCR*) gene rearrangements, do not form masses, do not invade the intestinal crypts and do not cover the full thickness of the bowel[91]. Additionally, the lymphoid infiltrate is limited to the mucosa and sub-mucosa. The molecular study for TCR can show a monoclonal rearrangement of TCR-γ chain[91]. The recognition of this disease has many therapeutic implications since aggressive chemotherapy is excessive and an immunosuppressive treatment is virtually sufficient.

Indolent $CD4^+$ T-cell lymphoma has also been described and shows a good outcome and survival despite a persistence after immunomodulatory drug-based treatment[92]. Rarely, gastric mucosa can show multiple nodularities[93]. However, a clinical and endoscopic follow-up of these lesions is always

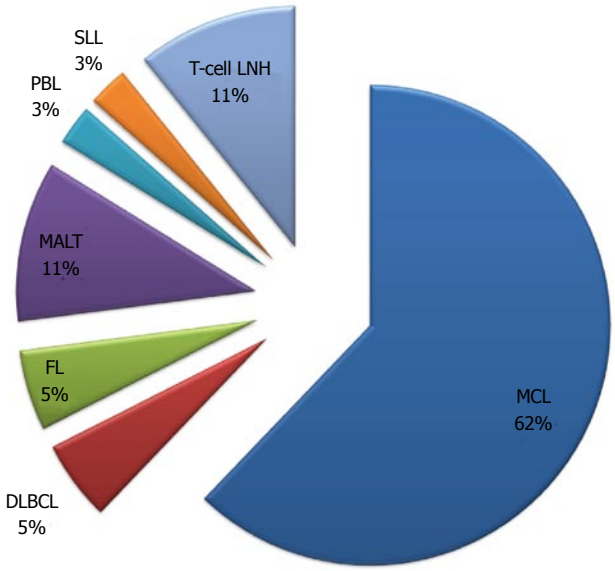

Figure 2 Pie chart describing the distribution of lymphomatous polyposis as a presenting gastrointestinal feature in gastrointestinal non-Hodgkin's lymphomas according to histotype. SLL: Small lymphocytic lymphoma; PBL: Plasmablastic B-cell lymphoma; DLBCL: Diffuse large B-cell lymphoma; MCL: Mantle cell lymphoma.

advisable[93], also for the risk of progression in the long term[92].

Similarly to T-LPD, NK cells can also give rise to an indolent form of lymphoid infiltrate in the context of the GI tract, *i.e.,* NK-cell enteropathy[94]. Usually the symptoms are vague and the GI lesions can be present in the stomach (more frequently), duodenum, small intestine and colon. At endoscopy, these lesions exhibit superficial ulceration, flat elevations with central depression and are associated with edema and local hemorrhage. Usually these ulcers are 1 cm in diameter and the surrounding mucosa is not abnormal. This disease is distinct from ENKTL since gastric involvement in the latter is really infrequent (and if present, the localization is not limited to the stomach) and EBER is positive. In addition, in the presence of NK-enteropathy, the epithelium can be invaded, showing a lymphoepithelial-like lesion[95]. Moreover, contrarily to T-LPD, the TCR rearrangement is polyclonal or oligoclonal[94].

Lymphomatous polyposis and mantle cell lymphoma

The pioneering study by Cornes *et al*[96] in 1961 first reported the term "lymphomatous polyposis (LP)". It is defined as the presence of diffuse proliferation of monotonous small-to-intermediate sized lymphocytes presenting as multiple polypoid tumors from 2 mm to several centimeters in different GI sites. Although the preferred site is the small intestine[14], other sites can be involved alone or at the same time[97-104]. Actually, LP is present in 4%-9% of all GI lymphomas[14], more frequently in western than eastern countries[105]. B-cell lymphomas are more frequent than T-cell lymphomas and this is due to the fact that histologically these polyps originate from the mantle zone of the lymphoid follicle of the mucosa-associated lymphoid tissue[106]. Additionally, this fact justifies the augmented frequency in the small intestine (rich in lymphatic tissue) compared to other GI tract sites. Additionally, multiple tumors or different kinds of lymphomas can be simultaneously present in a context of LP[107]. Therefore, the biopsy of more than one polyp and of different types of lesions is always advisable[108,109]. Additionally, it must be underlined that although the occurrence of multiple polyposis in a patient with nodal lymphoma is not a criterion to absolutely define the involvement of the GI tract, the histological evaluation is always mandatory[110].

Typical lymphoma presenting with LP is MCL[14,111], although other tumors can show this feature[98-100,112-114]. Among 37 case reports of LP since 2000[67,84,98-100,103,112-142], MCL was indeed the most frequent disease (more than 50% of cases) (Figure 2). The most involved site was the colon (Figure 3). In the case series by Saito *et al*[143], regarding patients affected by MALT lymphomas or MCL at the ileal site, it was underlined that LP was the most frequent presentation of MCL and the least common lesion in MALT lymphomas (Figure 4).

MCL can locate at the GI tract secondary to the generalized disease[102] and, although only 25% of patients with nodal mantle cell lymphoma suffer GI symptoms, 77%-88% have a localization at the gross intestine and 43%-77% in the upper GI tract, also in the absence of macroscopic lesions[14] (Figure 5). LP is the most frequent endoscopic pattern although other endoscopic features can be present[144], for example, a granular pattern associated with polyps (Figure 6) or ulcerated polyps[145] or masses[146]. In addition, the endoscopic pattern varies according to the part of the GI tract involved (Figure 7). EUS has been applied in this setting, giving the possibility of identifying submucosal lesions[115]. MCL appears echo-poor, usually departing from the second layer and remaining confined to the GI wall (Figure 8)[115,147,148]. In some cases, the diagnosis of MCL could be incidental during the endoscopic definition of gastric bleeding caused by gastric ulcers[149].

Contrarily to GI follicular lymphoma (discussed below), the GI tract involvement by MCL assumes a great prognostic implication and is useful to monitor patients after the treatment[14,101]. Indeed, the occurrence of LP designates a median survival of 3-4 years[14,101]. Due to the fact that the small intestine can be also involved by the tumor, the performance of CE or DBE would be advisable in order to correctly stage the patient and assess the follow-up evaluations[116,117].

Although the disease presentation has been well studied, there are no data about the management of LP during follow-up assessment. Our opinion is that endoscopic evaluation with mapping biopsies should be performed in these patients since in some cases the presence of aspecific abnormalities during follow-up can lead to the finding of lymphoma reappearance[146], sometimes many years after complete remission[103,119].

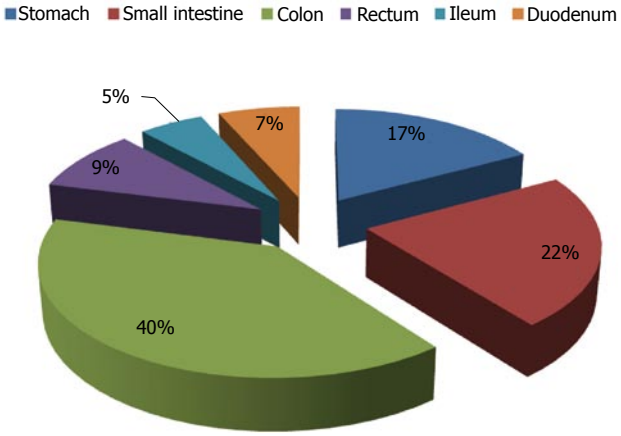

Figure 3 Pie chart describing the most involved gastrointestinal site in lymphomatous polyposis.

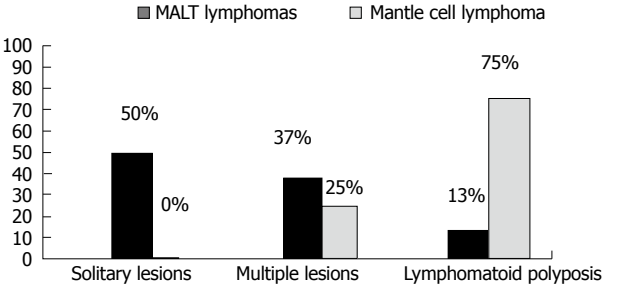

Figure 4 Frequency of lymphomatous polyposis at ileum in mucosa-associated lymphoid tissue lymphoma and mantle cell lymphoma. Adapted from Saito *et al*[143], 2005.

Follicular Lymphoma

GI FL is a rare entity, representing up to 3.6% of all GI NHL[150,151]. Primary GI FL was recognized as an histological variant of FL in the 2008 WHO classification of hematopoietic tumors[152]. Sites most frequently involved are the duodenum (55.6% of cases)[101], in particular the second part[152], and the terminal ileum (33.3% of cases)[151,153]. Since positron emission tomography and computed tomography have low sensitivity and specificity[154] in catching small intestine involvement, CE and DBE have acquired more and more importance[155,156]. Indeed, these techniques have shown that the small bowel can be involved in 70%-83% of cases[157,158], even in cases of duodenal lymphoma[152].

To date, a clear endoscopic classification of GI-FL has not been done, as for GI MALT lymphomas. However, Yamamoto *et al*[151], reviewing 249 GI-FL cases, reported a reliable endoscopic classification of the disease. Whitish polyps usually up to 2 mm[151,153] and/or white granules-nodular aggregates, with or without ulceration of the mucosa layer (Figure 9), are the typical endoscopic pattern[150,159,160]. This can be unifocal or multifocal and is mainly present in intestinal FL. A large mass with or without ulceration is less frequent and in half of cases can be associated with multifocal whitish polyps. The latter is the most frequent endoscopic pattern of primary gastric FL. Multiple lymphomatous polyposis can also be

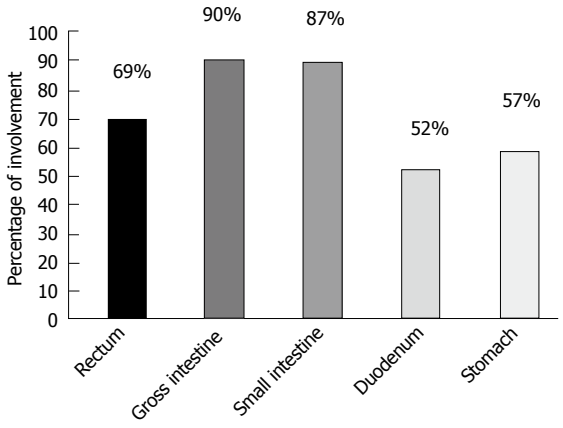

Figure 5 Frequency of the sites involved in mantle cell lymphoma. Adapted from Ruskoné-Fourmestraux *et al*[101], 2010.

found[30,101,150,158,161,162]. Interestingly, in the series of 48 patients with GI FL reported by Yanai *et al*[163], it was found that the LP was the most frequent endoscopic feature (more than 50% of cases), followed by polypoid or ulcerative lesions (Figure 10).

Recently, high-definition endoscopy, as well as magnifying endoscopy (ME), has been used to describe the surface microstructures of GI FL, such as enlarged whitish villi and tiny whitish depositions and an irregular microvascular pattern[164,165]. This fact indicates that the tumor is of non-epithelial origin and usually reflects the formation of lymphoid follicles[164,166-169]. EUS has not been widely applied. A few reports have indicated that the echoendoscopic pattern is given by second and third layer thickening, dotted by hypoechogenic nodules[170].

Capsule endoscopy and double-balloon enteroscopy are useful in the definition of small intestine involvement in a non-invasive way. The typical picture is a whitish submucosal elevation presenting as nodules or polyps[21], usually multifocal[171,172]. However, the limitation is the inability to perform a biopsy that is postponed until the enteroscopy and the risk of retention in cases of stenosis (unusual in cases of GI-FL).

Nodal spread is rare and GI FL tends to be localized in the gastrointestinal tract (stage IE according to Ann Arbor staging system)[173] and to have an indolent course[152,174]. However, transformation to aggressive lymphoma has been documented[175]. Different from other form of lymphomas, the GI involvement is not an adverse prognostic factor[176]. Lymphoma grading is low in the majority of cases, while in the nodal counterpart grade I-II FL is documented in 1 case out of 10[173]. Furthermore, in contrast to nodal FL, these cells do not acquire additional mutations and this justifies the absence of grade 3 GI FL and the very low rate of transformation[173,175].

Treatment strategies are not uniform, although GI FL are treated more frequently compared to the nodal counterpart[177]. Different case series have demonstrated that a watch and wait approach is as useful as the pharmacological approach, except for relieving clinical symptoms[163,178-180]. However, case series differ greatly

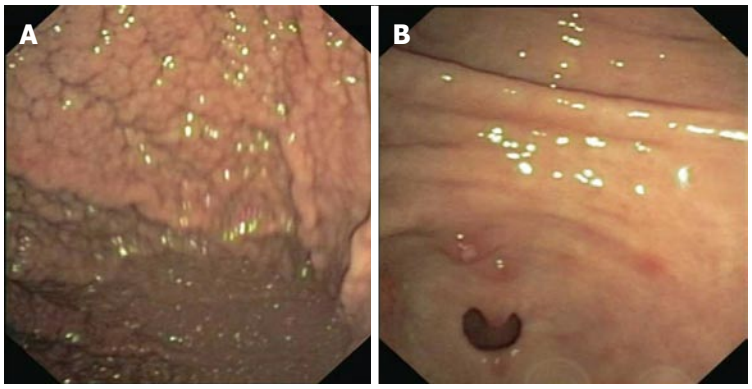

Figure 6 Endoscopy stomach: Granular pattern of the fundus and body of the stomach (A) and polyps in the antrum (B).

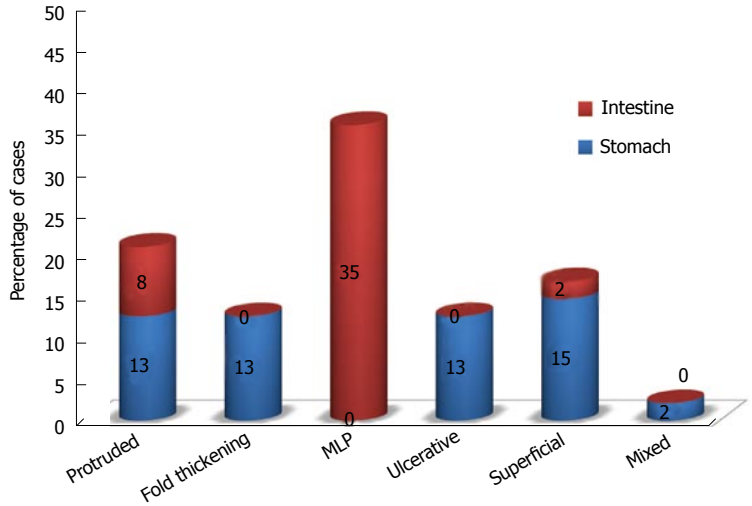

Figure 7 Endoscopic lesions in mantle cell lymphomas according to the gastric and intestinal localization. Adapted from Iwamuro *et al*[144], 2010.

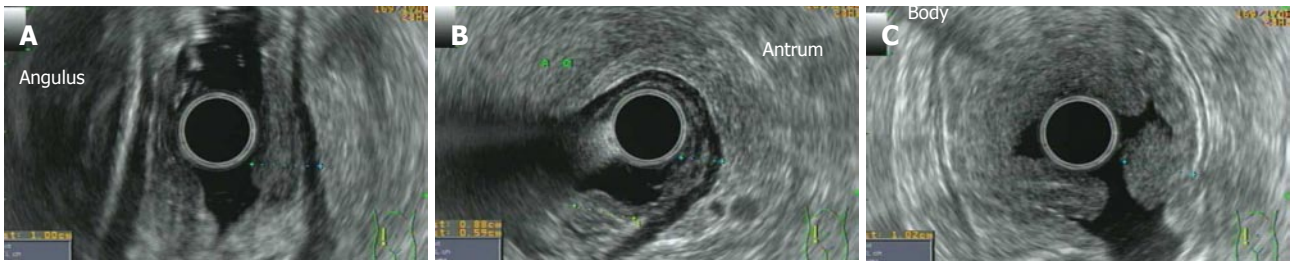

Figure 8 Endoscopic ultrasonography (radial scanning): Marked thickening of the muscularis propria and increased wall thickness (12 mm) in the angulus (A); antrum (B); body (C).

in identifying the correct treatment approach to be applied. Surgical resection is not recommended and chemoimmunotherapy is preferred[151,171]. It must also be considered that the introduction of anti CD20 antibodies has augmented the survival rate and in some series localized/low-grade GI FL have been treated with anti CD20 monoclonal antibody alone, without chemotherapy[151].

It is debatable whether CE and/or DBE are truly useful. Indeed, no studies have demonstrated that the detection of small bowel involvement (especially if duodenal lymphoma is present) would have changed the treatment needed. Surely, these procedures would change the treatment strategy in cases of radiation or surgical treatment and are needed in cases of obscure gastrointestinal bleeding[172,181]. Apart from these occurrences, the effectiveness of chemoimmunotherapy or immunotherapy alone would render these procedures less practical in patient management. However, since no clear data exists regarding survival and quality of life in dependence of small bowel involvement, clinician choice is the only way to proceed.

That notwithstanding, the diagnostic suspicion based on the endoscopic features, together with the patient history, is fundamental in addressing the pathological diagnosis. Indeed, in almost 20% of cases, FL can be misdiagnosed by endoscopic biopsy evaluation[182]. Therefore, multiple biopsies would be necessary. In particular, biopsies of the peripheral mucosa would be more informative than biopsies from the erosion/ulceration since the probability of catching necrotic tissue decreases significantly.

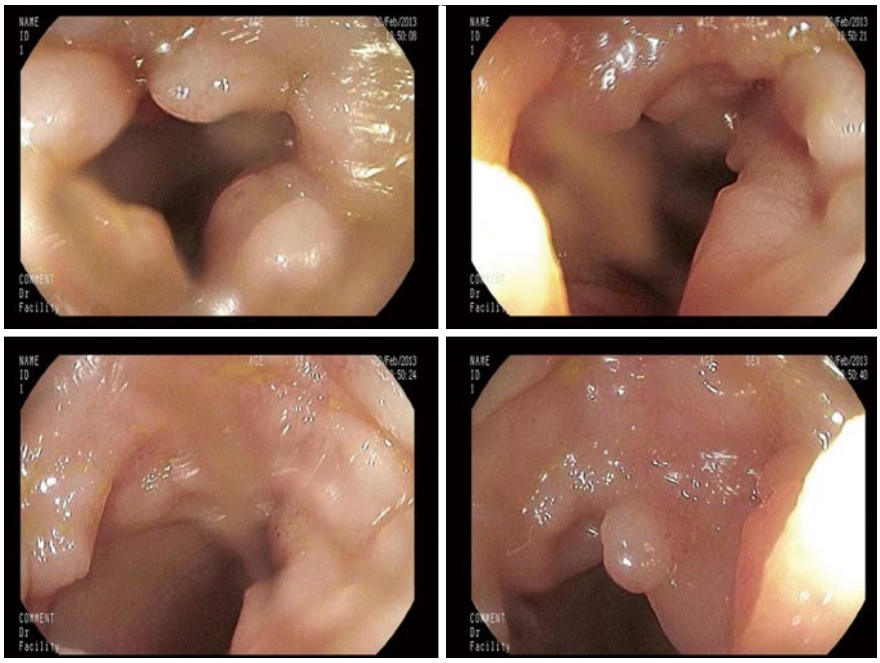

Figure 9 Ileoscopy revealing the presence of hyperemic mucosa with whitish polypoid nodularity. The subsequent diagnosis was a grade 2A follicular lymphoma.

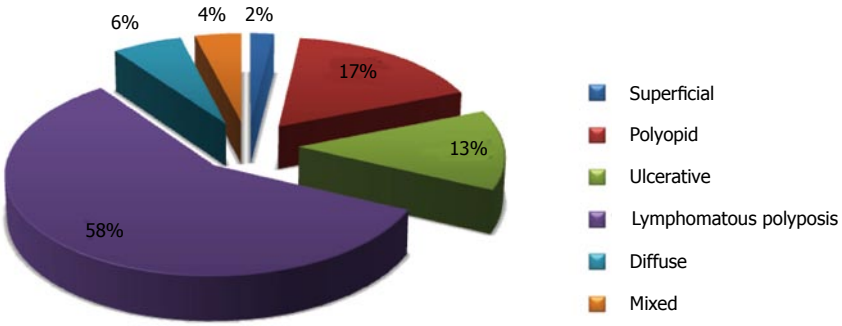

Figure 10 Endoscopic features of follicular gastrointestinal lymphomas. Adapted from Yanai *et al*[163], 2011.

EMP and plasma cell-related diseases

EMP belongs to a precise type of lymphoid malignancies, *i.e.,* plasma cell neoplasms, representing 3%-4% of cases[183]. It is important to distinguish this subtype from lymphomas with plasmacytic differentiation, particularly MALT lymphomas[48]. The upper respiratory tract is the most involved organ (almost 80% of cases), while GI localization is rare[48]. Among these cases, the stomach is the most involved site, followed by the liver, colon and the small intestine (duodenum, jejunum and ileum)[184].

Usually, gastric localization is secondary to a plasma cell myeloma (PCM) and often emerges through a clone selection process. Indeed, multiple myeloma treatment itself can select a particular chemoresistant PC clone able to migrate at extra-nodal organs. In these cases, an accurate endoscopic investigation is critical for the diagnostic assessment and disease monitoring[185]. Due to the strict relationship with plasma cell myeloma, the clinical course is poor. The most frequent endoscopic finding consists of an infiltrating mass or masses in the stomach and/or the duodenum[186,187] or well-demarcated, flat, yellow-whitish mucosal changes[188] or nodular lesion with central umbilication[189]. Endoscopic appearance as diffusely thickened mucosal folds simulating linitis plastica is rare[190]. Sometimes, large ulcerations can be seen[191,192]. However, the gastric mucosa can appear normal, while the extramural growth is incredibly vast (Figure 11). EUS could be of great help in defining the disease extension that appears as a large echo-poor mass infiltrating surrounding organs[186]. However, sometimes EUS can be useful to detect limited gastric wall involvement and in these cases, an endoscopic resection of the mass can be performed, resulting in safety for the patient and effective in the treatment of the disease[188,193,194]. Alternatively, patients with localized disease can be treated with radiation treatment[190,195].

Small intestine involvement is generally primary with a benign course. These lesions can be explored by enteroscopy and/or capsule endoscopy[196], paying attention to the cases in which obstructions or retention are expected. Differential diagnosis is other cases of

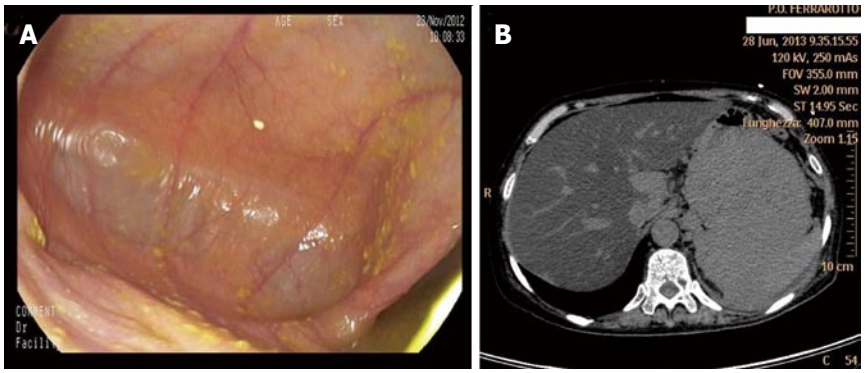

Figure 11 Extra-medullary plasmacytoma with gastric localization arising after treatment for multiple myeloma. A: Gastroscopy resulted negative for tumor detection; B: CT scan analysis of the upper abdomen showing a bulky mass departing from the stomach.

sub-mucosal masses in the small intestine, as reported by Lopes da Silva[196]. Colon involvement appears more frequently as stricture[197,198], in some cases difficult to differentiate from colon adenocarcinoma[199], returning to the differential diagnosis of sub-mucosal tumors[193]. Rarely it can determine rectal bleeding[200]. The localization at the rectum appears as a mild granularity as well as a reddish, protruded lesion[201]. Usually these lesions disappear after treatment and this is a confirmation of treatment efficacy[186], although mucosal atrophy and non-specific inflammation can be reinstated[195].

Apart from EMP, other plasma cell-related disorders can involve the GI tract. This is due to the production of amyloid protein in AL amyloidosis (light chain amyloidosis)[187]. The most involved organ is the small intestine. In some cases the amyloid deposition is synchronous with EMP[187,193,195] or other GI lymphomas[202]. Usually, the amyloid protein in AL amyloidosis involves the submucosa and the muscularis mucosae, resulting in thickened folds and valvulae conniventes and polypoid lesions in the GI tract. The typical deposition of AL amyloid proteins result in pseudo-obstruction, constipation and mechanical obstruction as the main symptoms[203]. Intestinal bleeding can also occur[204] and if this event occurs in a patient with multiple myeloma, the occurrence of aspecific elevated lesions at the endoscopic evaluations should lead to suspicion of systemic amyloidosis. More rarely, submucosal hematoma, ulcers and hemorrhagic bullous colitis can be seen[205]. On the other hand, nodularity, fine granular appearance and mucosal friability are more frequent in other types of amyloidosis, *i.e.,* AA amyloidosis (amyloidosis secondary to systemic disorders). This is due to the deposit of amyloid proteins into the lamina propria with impaired absorption and subsequent diarrhea[203].

Immunodeficiency and GI lymphomas

Immunodeficiency is defined as a state of impaired function of the immune system that can be congenital, acquired or iatrogenic. The reduced immune-surveillance can determine an augmented rate of lymphomas. Two conditions mainly determine the arising of lymphomas: human immunodeficiency virus (HIV) infection with the correlated acquired immunodeficiency syndrome (AIDS) and post-transplant immunosuppression. In both conditions, the GI tract is the most involved site[206]. Apart from HIV and PTLD, common variable immunodeficiency (CVID) has been associated with the development of gastrointestinal NHL, although this is a very rare finding[207,208].

In HIV patients, the rate of GI lymphomas was higher in the pre-HAART era before 1996[209] and the risk of gastric NHL was 353-fold compared with normal subjects, with aggressive lymphomas the most prevalent feature[59]. In cases of AIDS-related lymphoma, the GI tract is involved in 20% to 50% of cases[206,210]. However, the decrease of GI lymphoma incidence has not been as high as in central nervous system lymphomas[209]. A recent analysis of 243 HIV patients performed at the University of Sao Paolo revealed an incidence of gastric NHL of 2.5%[211]. Co-infection with EBV and/or CMV would complicate the prognosis[212], although the occurrence of viral infection is less pathogenetically important compared to PTLD[206]. The main histologies are B-cell lymphomas (67%) (DLBCL, Burkitt lymphoma, MALT lymphoma)[213], while T-cell lymphomas are less frequent (33%)[209] and other types of hematological malignancies are anecdotal[214,215]. In 5%-10% of cases, cMyc rearrangement is present and confers a poor prognosis[212]. Additionally, the prompt recognition of this lymphoma subtype has a great impact in patient management since the presenting symptoms are usually alarm symptoms in about half of patients. However, in the majority of patients, the lymphoma is diagnosed at Ann Arbor stage Ⅲ-Ⅳ[206]. The most frequent endoscopic features are multifocal ulcerations, followed by polypoid or a bulky mass together with bloody spots[206,212]. The most involved sites are the stomach and duodenum[216], followed by the small bowel and colon-rectum (Figure 12)[211]. However, unusual presentations can be seen more commonly than in immunocompetent patients[206]. At narrow-band, a honeycomb-like pattern is present without irregularity in the microvasculature[212]. The localization can also be perirectal and in these cases,

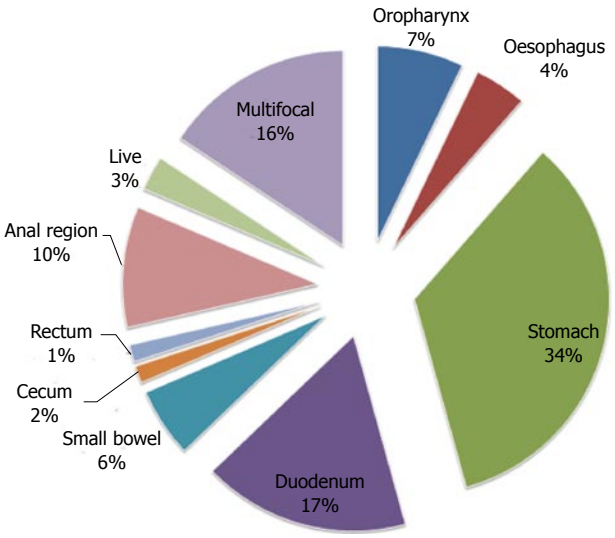

Figure 12 Frequency of the involved gastrointestinal tract in human immunodeficiency virus-related gastrointestinal lymphomas. Adapted from Heise[206], 2010.

EUS-guided fine needle biopsy would be a valid tool for diagnosis given the high grade nature of this kind of lymphomas[217]. Noteworthy, EUS appearance is of a hypoechoic poorly defined mass[217] and is important for the locoregional staging[206]. Prognosis is poor with a median survival of 6 mo and a rate of complete remission less than 40%[211]. Prognosis is also impaired by the occurrence of opportunistic infections[210]. Extremely suggestive is the development of EBV-related DLBCL in patients suffering other types of lymphomas that induce a state of immunosuppression, such as AITL[218]. In these peculiar cases, the outcome is really poor and alarm symptoms and perforation can occur with fatal implications[218].

GI lymphomas are also more frequent in solid organ transplant recipients, particularly after renal, heart and small bowel transplantation, encompassing the spectrum of PTLD (Table 3). The pathogenetic events seem to be different compared to HIV-related lymphomas since in this kind of lymphomas, Epstein-Barr virus reactivation due to immunosuppressants plays a pivotal role[219]. Apart from negative EBV serology prior to transplantation, length of immunosuppression is an overt risk factor[220,221]. EBV-positive lymphomas arise earlier than EBV-negative lymphomas[221]. In adults, the majority of cases arises over 12 mo from transplantation[222], at a median of 36 mo[223]. A second peak is after 5-10 years[206]. Median overall survival is 8 years and the principal histotype is B-cell lymphoma, although lymphomas of T-cell origin can also be present. Noteworthy, the GI tract is involved in one third of cases. Endoscopy is of great help in establishing the diagnosis. Especially in small bowel transplantation, endoscopic follow-up has gained a pivotal role in defining the transplant-related complications, including the onset of PTLD[224]. Typically, lesions are raised, rubbery, erythematous or ulcerated[222,225,226]. The most involved organ is the colon, followed by the small intestine and stomach[223]. However, the recognition of symptoms together with the patient history is of great help in driving the diagnosis. Additionally, endoscopic procedures are essential in order to follow the course of disease[225], also valid in the long-term[226]. Interestingly, early stage PTLD can be safely removed endoscopically and this would be a valid approach in the treatment of localized PTLD[224].

Table 3 Prevalence of gastrointestinal lymphomas among transplant recipients according to transplanted organ

Transplant	Prevalence
Bone marrow	0.50%
Liver	1%-2%
Kidney	0.7%-4%
Heart	2%-10%
Small bowel	up to 30%

The data extracted from Heise[206], 2010.

Plasmablastic lymphoma (PBL) is a rare and aggressive type of lymphoma characterized at histological evaluation by the presence of large immunoblasts with plasmacytic differentiation with an high replication index[227]. Usually, this lymphoma arises in the oral cavity in HIV-infected patients and in the literature there are few cases of GI localization (Table 4)[228-237]. The stomach is the most involved site (about 50% of cases), followed by the small intestine, anal region, cecum, colon and esophagus[237]. Large masses and exophytic processes are the main endoscopic appearance in the stomach and anal region. Intestinal localization is extremely rare and when present, the endoscopic appearance is of multiple nodularity[227]. Moreover, PBL can also arise in immunocompetent patients with ulcerated lesions at the stomach[236]. These patients are normally older than HIV^+ patients, tend to present with GI localizations more that HIV^+ patients and have a worse overall survival[236,237].

Additionally, CD has also been linked to the development of lymphomas of the gastrointestinal tract. Most of them are of B origin, comprising DLBCL and HL, although T-cell lymphomas can also arise. In the recent report by Kappelman *et al*[238], patients with CD showed a greater risk of developing hematological malignancies compared to the general population. This study confirmed the previous report by Askling *et al*[239], also showing an augmented rate of hematological malignancies compared to the general population and 10% of developed lymphomas were T-type. Probably, it would be related to the state of immunosuppression leading to infection of lymphotropic and oncogenic viruses, but the specific mechanism is still to be clarified. This predisposition seems to be unrelated to immunosuppressive treatment. In this setting, anti-TNFα treatment has been related to development of hepatosplenic T-cell lymphoma[240]. However, two years later, a meta-analysis by Siegel *et al*[241] indicated that

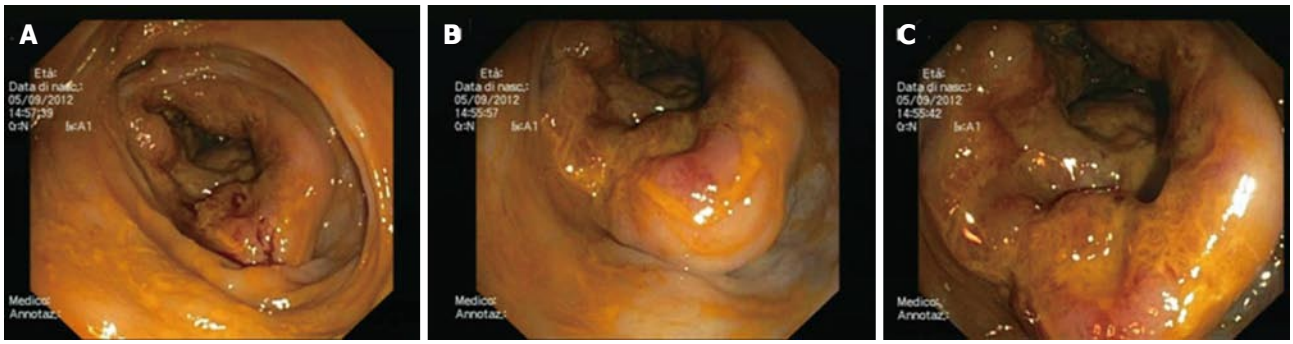

Figure 13 Exophytic erythematous circumferential non-ulcerated mass determining a stenosis of the ileocecal region. The mass arises from the deep layer and the mucosa presents reddish areas suggestive for lymphomatous infiltration of the cecum.

Table 4 Reports of gastrointestinal plasmablastic lymphoma from 1998

Manuscript	Year	localization	Endoscopic appearance	HIV
Pruneri *et al*[230]	1998	Stomach	Large polypoid mass	-
Colomo *et al*[231]	2004	Anal region	Mass	+
Dong *et al*[232]	2005	GI tract	Not reported	+
		Small Intestine	Not reported	+
Tavora *et al*[228]	2006	Anal region	Not reported	+
		Anal region	Exophytic mass	+
Taddesse-Heath *et al*[233]	2010	Small intestine/colon (2 cases)	Not reported	+
Brahmania *et al*[234]	2011	Ano-rectal junction	Hypervascular cauliflower-like mass	-
Mihaljevic *et al*[235]	2012	Stomach	Not reported	-
Hashimoto *et al*[236]	2012	Stomach	Not reported	-
Chapman-Fredricks *et al*[229]	2012	Stomach	Not reported	+
Luria *et al*[237]	2014	Anal region	Mass	+
		Sigma	Mass	-
		Small bowel	Not reported	-
		Ileum	Not reported	-

HIV: Human immunodeficiency virus; GI: Gastrointestinal.

immunosuppressive treatment is not a risk factor for the development of NHL in CD patients. However, it is still a matter of discussion since the augmented incidence of GI lymphomas in these patients is related to the more intensive examinations. Moreover, the histological evaluation is a crucial point since the inflammatory background can lead to a false positive result. That notwithstanding, anti-TNFα treatment seems to be safe regarding the incidence of NHL and should not be regarded as a risk factor. Therefore, more epidemiological studies will be needed in order to better define the link between CD and GI lymphomas.

Hodgkin's lymphoma

Lymphomatous GI involvement in HL appears as a stricture (Figure 13) or ulceration[242-245]. The abundant lymphoid tissue present at this site renders it one of the most involved regions[246]. HL rarely presents as a colonic localization (almost 1%-3% of extra-nodal HL cases[247] and less than 5% of gastrointestinal lymphomas[243]) and the prognostic impact is still obscure. Mixed-cellularity subtype is the most common feature[248]. As for the nodal counterpart, the inflammatory background is a key feature of HL[249]. In some cases, the endoscopic and histological presentation can resemble IBD, that in turn is seldom associated with colonic HL[244,250]. Additionally, immunodeficiency is a risk factor[251], although this type of lymphoma can also arise in immunocompetent patients[247].

Recently, a new entity has been proposed, *i.e.*, "EBV-associated mucocutaneous ulcer" (EBVMCU)[252]. This disease subtype resembles HL but there are peculiar clinical and histological differences. Indeed, the presence of "plasmacytoid" apoptotic cells and the confinement to mucosa and sub-mucosal layers are the histological hallmark that can lead to a differential diagnosis from cHL. However, EBV infection is always present, as in GI-HL.

CONCLUSION

Endoscopic features of GI lymphomas are variegated encompassing ulcers, erosions, polyps and so on. It is a fascinating matter of study for both hematologists and gastroenterologists. As stated in guidelines, a synergism between these two figures is fundamental. This is due to the lack of data and the fact that information regarding rare GI lymphomas are extrapolated from case series or

case reports. Actually, the scientific community is gaining more and more knowledge about the recognition and management of these lymphomas, with the creation of proper guidelines for specific lymphoma subtypes. In this setting, the collection of different case series and their analysis will assume a pivotal role in drawing general guidance on disease characterization. Certainly, as has emerged in the manuscript, the management of these lymphomas is different from the nodal or medullary counterparts and a proper understanding of the endoscopic features together with clinical and histological characteristics is crucial for better management of patients, with the ultimate goal of improving clinical outcome and quality of life for patients.

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REVIEW

Duodenal adenoma surveillance in patients with familial adenomatous polyposis

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Abstract

Familial adenomatous polyposis (FAP) is a hereditary disorder caused by Adenomatous Polyposis Gene mutations that lead to the development of colorectal polyps with great malignant risk throughout life. Moreover, numerous extracolonic manifestations incorporate different clinical features to produce varied individual phenotypes. Among them, the occurrence of duodenal adenomatous polyps is considered an almost inevitable event, and their incidence rates increase as a patient's age advances. Although the majority of patients exhibit different grades of duodenal adenomatosis as they age, only a small proportion (1%-5%) of patients will ultimately develop duodenal carcinoma. Within this context, the aim of the present study was to review the data regarding the epidemiology, classification, genetic features, endoscopic features, carcinogenesis, surveillance and management of duodenal polyps in patients with FAP.

Key words: Familial adenomatous polyposis; Adenoma; Duodenum; Surveillance; Endoscopy; Digestive system

Core tip: The development of duodenal adenomas is considered a very common and important extracolonic manifestation in patients with familial adenomatous polyposis. Results from recently published studies have indicated the need for life-long surveillance of patients presenting with this condition due to a risk of malignization, especially in patients with severe adenomatosis. The present study discusses the incidence, endoscopic features and management of duodenal adenomas and reviews the published data regarding cancer prevention and surveillance.

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Duodenal adenoma surveillance in patients with familial adenomatous polyposis. *World J Gastrointest Endosc* 2015; 7(10): 950-959 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i10/950.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i10.950

INTRODUCTION

Familial adenomatous polyposis (FAP) is an inherited autosomal dominant syndrome that is caused by germline mutations in one copy of the adenomatous polyposis coli (*APC*) gene. These mutations lead to the development of a variable number of colorectal polyps during the second and third decade of life[1,2]. *APC* is a tumor suppressor gene that is located on the long arm of chromosome 5 (5q21-22) and is composed of 15 exons. Exons 1-14 are small compared to the large exon 15, which has 6571 base pairs and accounts for over 70% of the coding portion of the gene[3,4].

As the disease is associated with an almost 100% risk of developing colorectal cancer (CRC) in untreated patients, prophylactic colectomy is considered the cornerstone of FAP management[1,5]. Performing a proctocolectomy before a patient reaches adulthood is associated with a substantial reduction in the incidence of CRC and a better prognosis. Consequently, the extracolonic manifestations (ECM) of the disease have been reported to lead to a relative increase in death[6]. Survival effects associated with screening and prophylactic surgery, life expectancy remains lower than that observed in the general population[7,8].

The majority of ECM have little clinical significance, but some of them may cause serious complications and even lead to death[9-11]. The majority of FAP patients (over 70%) present with some level of ECM during the course of the disease, such as cutaneous lesions (lipomas, fibromas, sebaceous and epidermoid cysts), desmoids tumors, osteomas, dental abnormalities, congenital hypertrophy of retinal pigment epithelium lesions (CHRPE) or upper-gastrointestinal polyps[1]. Moreover, patients with PAF are also at an increased risk for several malignancies, including hepatoblastoma, pancreatic, thyroid, biliary-tree, brain and duodenal cancers[12].

Gastric fundic gland polyps, gastric adenomas, duodenal adenomas and carcinoma represent the most common upper digestive lesions that are diagnosed in FAP patients (Figure 1)[13,14]. As they are an important potential cause of morbidity in FAP patients, duodenal polyps require diagnosis, follow-up and preventive measures to avoid carcinogenesis. Thus, the aim of the present study was to review the data regarding the epidemiology, classification, genetic features, endoscopic features, carcinogenesis, surveillance and management of duodenal polyps in patients with FAP.

CHARACTERIZATION OF DUODENAL POLYPS IN FAP

Historical aspects

After the colon and rectum, the duodenum is the second most common site of polyp development in patients with FAP[12-14]. The existence of gastric and duodenal polyps in these patients was established more than a century ago, and Cabot described the first case of duodenal cancer in 1935[12-17]. In a different study, it was found that a considerable number of stomach and duodenum polyps develop at an early age in the majority of pediatric patients, which led to the recommendation of periodic screening of the upper gastrointestinal in the 1960s[18]. The malignant potential of duodenal lesions was gradually established over the next decade, primarily following the introduction of flexible endoscopes during the 1970s[18-21]. During the 1970s and 1980s, numerous additional studies described high numbers of gastroduodenal polyps being identified during endoscopic screenings, providing definitive support for the inclusion of upper digestive endoscopy during routine evaluation and surveillance of FAP patients[22,23].

Epidemiology

Duodenal adenomas tend to occur approximately 15 years after the appearance of colonic adenomas[20,21,24]. Duodenal adenomas have been found in 30%-92% of FAP patients, with a lifetime risk approaching 100%[7,14,22-24]. The frequency of detecting duodenal adenomas in FAP patients may vary depending on endoscopic technique and the method of tissue sampling[7,23-27]. Employing side-viewing endoscopes and random biopsies, exceptional detection rates of 70% and above may be achieved for duodenal and periampullary adenomas[22,26,28]. Biopsies of periampullary regions and duodenal papilla revealed numerous microadenomas that were not detected in normal duodenal mucosa[22,26,27].

Polyp distribution and histology

The macroscopic appearance of duodenal adenomas in patients with FAP varies widely[21,29-31]. These lesions are usually white, numerous and sessile flat. Due to their small size, they may easily be missed or even entirely overlooked during upper endoscopy. With the aid of chromoscopic techniques, such as sprinkling indigo-carmine or methylene blue over the mucosa, the number of detected polyps may increase considerably. In any given patient, using such techniques can identify anywhere from no visible microadenomas to the existence of over 100 microadenomas of varying diameters (1-10 mm)[7,21,22]. The use of side-viewing endoscopes may eventually enable the detection of a prominent papilla of Vater within a solitary adenoma (Figure 2).

The distribution pattern throughout the duodenum

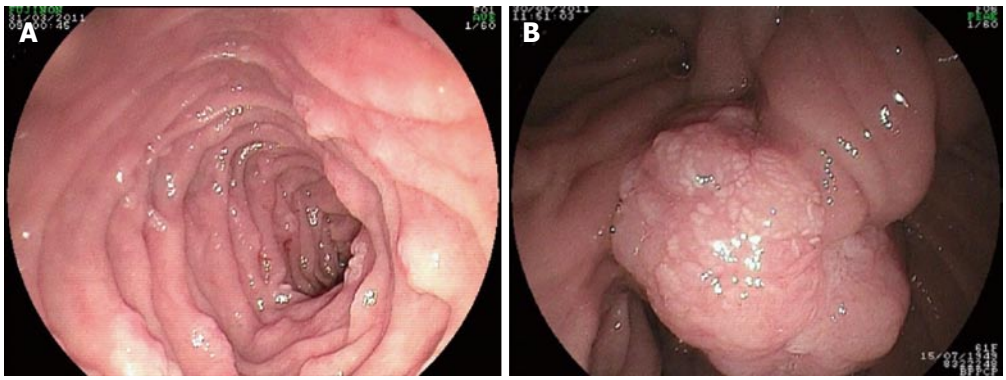

Figure 1 Endoscopic view showing a stage II disease (10-20 small duodenal adenomas with tubular histology) in A, and a large papilla lesion which biopsy revealed a well-moderated carcinoma in B.

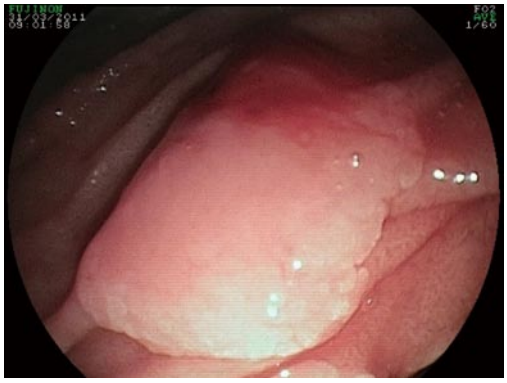

Figure 2 Detection of a prominent papilla of Vater with a solitary adenoma with the help of a side-viewing endoscope.

and the upper part of the small bowel reveals that the majority of polyps are found in clusters around and mainly distal to the ampulla of Vater (second and third part of the duodenum)[32,33].

In 1989, Spigelman *et al*[22] proposed a five-stage classification (0-IV) system to evaluate polyp severity that has become widely adopted. Classification is based on points that are accumulated according to the number, size, histology and dysplasia of polyps. Following this, disease stages are categorized as mild (I), moderate (II), or severe (III and IV) (Table 1).

Previous reports have indicated that approximately 70%-80% of FAP patients have stage II or III duodenal disease and 20%-30% have stage I or IV disease[22,33] (Figure 3). In a retrospective Swedish study that evaluated 180 patients with FAP, 134 (74%) of the patients exhibited duodenal adenomas, of which only 14 (7.8%) were classified as stage IV periampullary adenomas. The authors estimated a time course of 7.1 (range: 5.3-9.8) years for the development of stage IV periampullary adenomas from normal duodenum. Periampullary adenocarcinomas were diagnosed in 5 (2.7%) patients, of whom 3 had a previous diagnosis of stage IV disease based on endoscopic screening and 2 had less severe periampullary adenomatosis[34].

In an interesting, large multicentric study that analyzed 368 upper endoscopies, Bülow *et al*[14] detected duodenal polyps in 228 (61.9%) patients, with adenomas in 209 (91%) and normal mucosa in 19 (9%). Moreover, random duodenal biopsies revealed adenomatous tissue in 28 patients who did not have visible polyps at endoscopy. Based on Spigelman classification, 34%, 15%, 27%, 17% and 7% of patients had stage I, II, III, IV and V disease, respectively. Two of the patients in this series presented with duodenal carcinoma during screening. The estimated cumulative lifetime risks were 88% for duodenal adenomatosis and 35% for stage IV disease. The authors also measured a cumulative cancer incidence of 18% at 75 years of age. Groves *et al*[33] followed 99 patients over a course of 10 years and reported a progression in the incidence of stage IV disease from 9.6% to 14% in patients with a mean age of 42 years. These prospective studies showed that adenomas progress slowly in the duodenum and that adenomatosis is usually diagnosed at a premalignant stage.

In addition to the above, it must be emphasized that although Spigelman classification correlates well with duodenal cancer risk, it focuses primarily on non-ampullary duodenal disease. Therefore, a separate evaluation of ampullary disease is required to establish an accurate individual risk assessment[35].

Duodenal carcinogenesis and cancer risk

The distribution of adenomas within the duodenum probably reflects the exposure of duodenal mucosa to bile acids, suggesting a role for these compounds in duodenal carcinogenesis[22]. Duodenal cancer is one of the two leading causes of death (the other being desmoid tumors) in patients with FAP after they receive prophylactic colectomy[10,12]. When compared to the general population (in whom duodenal carcinoma is rare), the relative risks of developing duodenal adenocarcinoma and ampullary carcinoma were respectively 331 and 124 times higher in FAP patients[36]. Similarly, another study estimated these risks as being 100- to 330-fold higher[27]. The absolute lifetime risk was estimated to be approximately 3%-5%[32-35].

In contrast to colorectal polyps, duodenal polyps

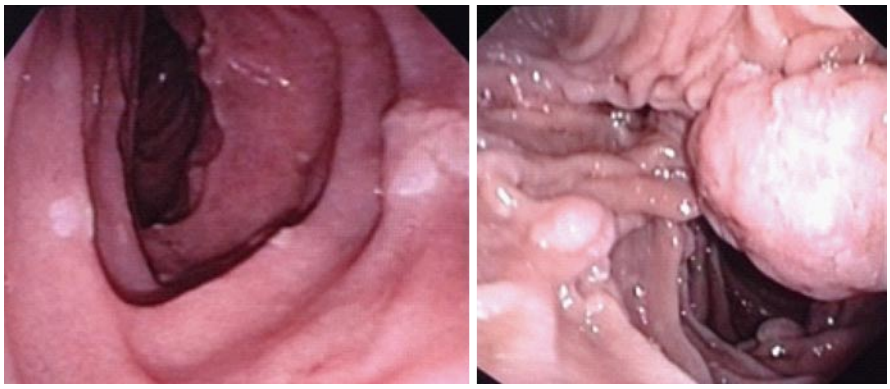

Figure 3 Endoscopic aspect of a stage Ⅰ patient exhibiting 3 adenomatous-tubular polyps with low-grade dysplasia (left); on the right, one may observe a 6 mm tubulo-villous polyp with severe dysplasia, along with other smaller adenomas diagnosed in another patient (stage Ⅳ disease).

do not inevitably transform into cancer[14]. Dysplastic duodenal polyps in FAP patients generally occur 10-20 years after the development of colorectal polyps, and the risk of malignant transformation ranges from 1% to 5%[14,33,37,38].

Stage Ⅳ patients have the greatest risk of developing duodenal cancer, with rates of 7%-36% having been described in 7.6- to 10-year follow-up periods[14,33]. Alternatively, this risk is low (0.7%) among stage 0 to stage Ⅲ patients[12] . Mortality rates from duodenal cancer vary from 1.7% to 8.2%[10,39-43].

Genotype-phenotype correlation

Several genotype-phenotype correlations have been described for colonic polyposis and ECM in FAP patients, including those related to CHRPE and desmoids[44-46]. Aside from the identification of genetic hot spots that are associated with the severity of duodenal adenomatosis, a genotype-phenotype correlation for the disease has not been well defined[12,47].

In a study conducted by Friedl *et al*[48], no correlation was detected between the locations of mutations and the severity of duodenal polyposis. Conversely, Soravia *et al*[49] described severe duodenal polyposis in patients with 5′ mutations. Additional reports have suggested that mutations in the central part of the APC gene and in exon 15 (particularly distal to codon 1400) may predispose an individual to a severe duodenal phenotype[50].

SURVEILLANCE AND MANAGEMENT

Why is surveillance necessary?

In patients with FAP, small bowel polyps are predominantly found in the duodenum and ampulla, although they may also develop in ileostomies and ileal pouches[51]. Within the duodenum, the cumulative incidence of polyp development increases with age (65% at 38 years and 90%-95% by 70 years)[14].

Recognition of the problem is essential toward establishing recommendations for surveillance of the upper gastrointestinal tract. The risk of malignancy increases with size, location (ampullary) and adenomatosis severity[35,52]. Thus, between the existence of an almost 100% lifetime risk of developing duodenal adenomatosis and the cumulative incidence rates of Spigelman stage Ⅳ disease and carcinoma (4% to 10%), there is a clear need for careful follow-up and surveillance of this population[14,52-54].

Improving prognosis through early detection of neoplastic changes is the basis for endoscopic surveillance, and decision analysis has shown that surveillance increases life expectancy by seven months[40]. Moreover, a surveillance program that was based on endoscopic/histological findings and associated with early diagnosis and resection of cancer was shown to improve the prognosis of selected patients[55].

How much and how often?

Adequate evaluation of the duodenum can be obtained with the use of frontal and side viewing (lateral) endoscopes, which facilitate evaluation of the Vater Papilla. Additionally, indigo carmine chromoendoscopy and electronic imaging techniques may improve the efficacy of detecting lesions. As periampullary carcinomas represent a leading cause of death in FAP patients, biopsies of this region should be performed regardless of whether mucosa appears normal, as approximately 7.6% of patients with normal endoscopic results exhibit adenomatous tissue on random biopsy[10,14,33].

When to begin surveillance of FAP patients is a controversial issue, with some clinicians supporting that surveillance begin when FAP is diagnosed and others proposing that it should not begin until patients reach 25-30 years in age, as a diagnosis of duodenal cancer before age 30 is rare[12,33,56,57]. Post-baseline evaluations should be planned according to Spigelman disease stage. This classification is widely accepted as the best option for stratifying the risk of duodenal cancer[54]. Surveillance is the most advantageous in stage Ⅳ patients, as their risk of duodenal carcinoma ranges from 7%-36% compared to non-stage Ⅳ patients, who have an overall risk of 5%.

Although published recommendations differ, in

Table 1 Spigelman classification for duodenal polyposis in patients with familial adenomatous polyposis

Criterion	Points		
	1	2	3
Polyp number	1-4	5-20	> 20
Polyp size (mm)	1-4	5-10	> 10
Histology	Tubular	Tubulo-villous	Villous
Dysplasia	Mild	Moderate	Severe

Stage 0: 0 points; stage I: 1-4 points; stage II: 5-6 points; stage III: 7-8 points; stage IV: 9-12 points

Table 2 Recommendations for surveillance and management of duodenal polyposis in familial adenomatous polyposis patients[11,12,28]

Spigelman stage	Suggested interval (yr) to next duodenoscopy	Conservative therapy	Surgical treatment
0 (0 points)	4 (maximum 5 yr)	No	No
I (1-4 points)	3 (maximum 5 yr)	No	No
II (5-6 points)	2-3	Chemoprevention with or without endoscopic therapy	No
III (7-8 points)	6-12 (maximum 1-2 yr)	Chemoprevention with or without endoscopic therapy[1]	Acceptable
IV (9-12 ponits)	6-12 (maximum 1-2 yr)	Endoscopic therapy and endoscopic ultrasonography	Duodenectomy with pancreas/ pylorus preservation

[1]Consider endoscopy general anesthesia.

general, early stage patients are advised to undergo endoscopy either every 4-5 years (stages 0-I) or every 3-5 years (stage II)[33,57-60]. In stage II patients, Groves *et al*[33] have suggested that endoscopic therapy include endoscopic mucosal resection (EMR). However, the above intervals may be reduced to 1-3 years for patients with mild polyposis (stage III) or to 6-12 mo for patients with severe polyposis, large adenomas or dysplasia[12,14,58]. It has been suggested that stage III patients undergo EMR to reduce duodenal adenomatosis[33,57]. As one third of stage IV patients may experience malignant transformation if they are not treated, these patients should also undergo endoscopic ultrasonography and computed tomography for staging during initial evaluation[14,61].

For patients with periampullary lesions, a different protocol has been proposed due to the greater associated risks[35,62]. This protocol recommends that patients with ampullary polyposis should be examined annually, irrespective of disease severity in other regions of the duodenum. Progression of the disease may be evaluated with magnetic resonance imaging and/or endoscopic ultrasound.

The majority of large studies have shown that the risk of advanced duodenal adenomatosis (stage IV) increases with age. Bulow *et al*[63] found a 52% cumulative risk at 70 years, which was similar to the 50% risk reported by *Saurin* et al[14] and the 20%-30% risk found by studies conducted in Sweden and Finland[14,34,63,64].

Therefore, endoscopic surveillance programs should be performed according to the following published recommendations (Table 2).

Endoscopic treatment

Ideally, treatment should include complete removal or destruction of adenomas and minimal morbid risk. Endoscopic management may be performed with standard polipectomy and local ablation techniques (thermal ablation, argon plasma coagulation or photodynamic therapy)[12,35]. Endoscopic therapy with argon plasma coagulation and Nd-YAG lasers has been attempted with varying results.

The plaque-like morphology of the majority of duodenal adenomas may pose some technical difficulties in performing endoscopic polipectomy, and new techniques of mucosal elevation/resection and hemostasis using different tools may reduce the risks of bleeding, pancreatitis and perforation. Another possible advantage of endoscopic treatment is the postponement of major operations such as duodenopancreatectomy. Although polipectomy or polyp destruction in stage II and stage III patients may be useful, long-term results have demonstrated adenoma recurrence rates of 50%-100%, and complications are not rare[26,49,65]. Thus, endoscopy generally does not affect disease course and follow-up remains necessary.

In this context, low-risk lesions (small, tubular, low-grade adenomas) should be biopsied and observed. Conversely, high-risk lesions (adenomas greater than 1 cm and those with villous patterns or high-grade dysplasia) may be treated *via* transduodenal resection[61]. Endoscopic or surgical ampullectomy should be used on lesions that have developed in the ampulla of Vater (mainly those with severe dysplasia, Tis or T1), despite the associated morbidity[66].

Patients with large stage III polyps (or stage IV, for which surgical treatment is not appropriate) may be candidates for endoscopic polipectomy. The use of general anesthesia may optimize therapeutic maneuvers by allowing the introduction of front and lateral endoscopes to evaluate the papilla, and third and fourth portions of duodenum. Such a strategy aims to avoid progression to stage IV disease, as this results in a greater risk (1 in 3 patients) of duodenal cancer[33]. The management of stage IV patients with desmoids disease, unfavorable clinical conditions or diffuse involvement of duodenal mucosa remains a significant problem.

Surgical treatment

Surgical management includes local procedures (duodenotomy with polypectomy and/or ampullectomy),

pancreas- and pylorus-sparing duodenectomies, and pancreatico-duodenectomy (Whipple's operation). The specific choice of which procedure to use appears to be related to technical expertise, local features (size and site of polyp) and disease severity. In the final analysis, the morbidity and mortality of these procedures must be weighed against the risk of developing duodenal adenocarcinoma.

Whereas radical resection is the obvious option for patients with carcinomas, a prophylactic operation (pancreas and pylorus sparing duodenectomy) to avoid cancer is also justified in cases of severe adenomatosis (Spigelman Ⅳ) or after a failed attempt at local resection (endoscopic or surgical)[33,67]. Even patients with stage Ⅲ polyposis have been considered for surgery[49,68,69]. However, no randomized studies to help guide surgical selection have been published thus far.

Duodenotomy with local resection may be indicated in selected patients who present with one or two dominant duodenal lesions and in whom endoscopic resection would be considered dangerous. In a recent review on this subject, Brosens *et al*[12] indicated that this approach might be useful for delaying major procedures in young patients. Otherwise, high recurrence rates have been reported after local surgical resection, similarly to what occurs after endoscopic resection. Moreover, patients who have previously undergone prophylactic colectomy and present with desmoids tumors have a significant risk of developing complications from duodenectomy[37,57].

Pancreatico-duodenectomy remains a last resort for advanced duodenal and ampullary adenomatosis, despite the risks of this complex procedure and the possibility of inducing desmoid tumor formation[58].

Pharmacological treatment

Chemoprevention is defined as the use of pharmaceutical drugs, natural agents or dietary supplements to reduce the incidence or delay the onset of diseases, including cancer[70]. In FAP patients, the colorectum, ileal pouch and duodenum represent the most clinically relevant sites of carcinogenesis[71]. Consequently, FAP patients constitute an ideal group for assessing the efficacy of various chemopreventive strategies at delaying polyp progression, postponing prophylactic colectomy and preventing the recurrence of adenoma following colectomy with IRA. These effects have also been evaluated in the upper gastrointestinal tract, particularly in the duodenum[72].

As prophylactic surgical resection of an ampulla and/or duodenum may be accompanied by significant morbidity, duodenal resection is currently reserved for only severe cases of duodenal polyposis or duodenal carcinoma. In this context, chemoprevention should be the strategy employed to control premalignant lesions[72]. Secondary chemoprevention has been attempted with the use of agents such as non-steroidal anti-inflammatory drugs (NSAIDs)[73-75]. The use of the cyclooxygenase (COX) non-selective inhibitor sulindac and of the selective COX-2 inhibitors celecoxib and rofecoxib may be beneficial when duodenal polyposis develops by inducing polyposis regression or stabilization.

Studies using sulindac have revealed the drug to have a statistically significant effect on small (2 mm) duodenal polyps, whereas larger (> 3 mm) polyps were unaffected[76,77]. In a different study, the administration of 300 mg/d of sulindac for 10 mo resulted in a 30% discontinuation rate due to side effects and no regression of polyps; furthermore, three patients developed large polyps and one developed an infiltrating carcinoma while on this drug[78].

In a large randomized trial, the use of celecoxib resulted in a 14%-31% reduction in the regions of the duodenum that were affected by adenomatosis and therefore this drug may be recommended as a therapeutic alternative to patients with moderate adenomatosis[33,79]. However, the promising use of coxibs in chemoprevention must be weighed against their potential cardiovascular and renal side effects[80,81]. In addition to the fact that celecoxib may delay worsening of polyposis, there have not been sufficient long-term results or evidence from controlled studies on cancer protection to routinely recommend these agents during follow-up[14,51,58].

In conclusion, although they may reduce the progression and even lead to regression of small adenomas, the role of NSAIDs and other compounds in duodenal polyposis regression remains unclear, and thus far the results have primarily been ambiguous[12]. The evidence must prove to be reproducible, and potential cardiovascular and renal side effects, in addition to the risk of gastrointestinal bleeding, must be taken into account[24]. Moreover, duodenal adenomas are less likely to degenerate compared to colonic polyps, and they also appear to be less responsive to chemoprevention with NSAIDs[12,82].

To date, no medical therapy has demonstrated long-term effectiveness and safety in the management of duodenal adenomatosis. There has been a single report indicating an apparent disappearance of duodenal polyposis in a patient who was treated with FOLFOX chemotherapy for an ileal pouch adenocarcinoma[83].

As dietary chemoprevention has shown no effective results, a new line of interventions focus on the role of the estrogen receptor (ER) in reducing polyp numbers and sizes, based on the supposed preventive effects of CRC. In an interesting study, Calabrese *et al*[84] evaluated whether dietary supplementation with phytoestrogens, which are selective agonists of the estrogen receptor, was able to prevent the progression of duodenal polyps. They demonstrated that short-term (90 d) supplementation with Eviendep® in FAP patients with recurrent adenomas in the duodenal mucosa resulted in a 32% reduction of polyp numbers and 51% reduction in polyp size.

This study clearly demonstrates that researches with FAP patients will always have a lead role in the testing

of new agents, favoring their own interests and those of non-familial adenomas, a problem with even greater social impact. For the next future, the role of NSAIDs in chemoprevention has gained renewed interest in sporadic adenoma prevention, although the long-term risks associated with its use have always been a source of concern[85,86].

As chemoprevention may eventually avoid surgical resection of at-risk duodenal adenomas, it would desirable to identify patients important to select advanced adenomas that would be candidates. In an interesting research, it was reported that mRNA levels of glutathione S-transferase A1 (28.16% *vs* 38.24%, P = 0.008) and caspase-3 (3.30% *vs* 5.31%, P = 0.001) were significantly lower in patients with FAP *vs* non-FAP patient controls, respectively[87]. This finding points at a lower capacity to detoxify toxins and carcinogens, with subsequent increased susceptibility for malignant degeneration[88]. Previous studies have already found lower GDT enzyme activity in colonic mucosa but no differences in duodenal mucosa when compared to patient controls[89,90]. Other eventual risk factors include the development of small intestinal adenomas and location of APC mutation[91-93].

All of these findings indicate that routine gastroduodenal endoscopy in FAP patients is necessary[94-96]. In this setting of surveillance, both endoscopy and EUS are extremely important to select advanced adenomas that are candidates for endoscopic intervention instead of surgical resection[97,98]. Moreover, although these lesions progress in severity (size and degree of dysplasia), their progression rate to carcinoma is slow[96,99].

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REVIEW

Uncommon complications of therapeutic endoscopic ultrasonography: What, why, and how to prevent

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Abstract

There is an increasing role for endoscopic ultrasound (EUS)-guided interventions in the treatment of many conditions. Although it has been shown that these types of interventions are effective and safe, they continue to be considered only as alternative treatments in some situations. This is in part due to the occurrence of complications with these techniques, which can occur even when performed by experienced endosonographers. Although common complications have been described for many procedures, it is also crucial to be aware of uncommon complications. This review describes rare complications that have been reported with several EUS-guided interventions. EUS-guided biliary drainage is accepted as an alternative treatment for malignant biliary obstruction. Most of the uncommon complications related to this procedure involve stent malfunction, such as the migration or malposition of stents. Rare complications of EUS-guided pancreatic pseudocyst drainage can result from air embolism and infection. Finally, a range of uncommon complications has been reported for EUS-guided celiac plexus neurolysis, involving neural and vascular injuries that can be fatal. The goal of this review is to identify possible complications and promote an understanding of how they occur in order to increase general awareness of these adverse events with the hope that they can be avoided in the future.

Key words: Complications; Endoscopic ultrasonography; Rare; Therapeutic; Uncommon

Core tip: This article reviews the rare complications that occur with endoscopic ultrasound-guided interventions, including those for biliary and pancreatic pseudocyst drainage and celiac plexus neurolysis. Knowledge

of the types of rare complications will promote an understanding of their causes, and help to reduce their occurrence.

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INTRODUCTION

Endoscopic ultrasound (EUS)-guided interventions have recently been accepted as an alternative to percutaneous or radiologic-guided treatments, as well as for more invasive treatments such as surgery, for many conditions. Accumulating evidence continues to demonstrate the feasibility, efficacy, and safety of these novel procedures. Although such methods are less invasive, there are reports of adverse events with EUS-guided transluminal therapies. It is important for endosonographers to have adequate knowledge of the indications, techniques, and potential risks before performing any given procedure. Indeed, many reviews have been published describing common complications related to EUS-guided procedures. However, only a limited number of studies report on rare complications. Thus, the purpose of this review was to identify the uncommon complications related to these interventions, evaluate how they occurred, and ascertain how to prevent them. To achieve this, a search was made of English-language human studies listed in the PubMed database that were published between1991 and December 2014. The following keywords were used alone or in combination with EUS: therapeutic complication, drainage, guidewire, celiac plexus neurolysis, tumor ablation, ethanol ablation, pancreatic fluid collection, pancreatic drainage, fiducial, cystogastrostomy, abscess drainage, antibiotics, endoscopy, vascular, glue injection, oncolytic virus, and cryotherapy. References of identified articles were also searched for potentially relevant studies.

EUS-GUIDED BILIARY DRAINAGE

EUS-guided procedures have recently gained popularity for performing biliary drainage in patients for whom endoscopic retrograde cholangiopancreatography (ERCP) has failed. The initial report of EUS-guided cholangiography in 1996 was followed by a description of EUS-guided choledochoduodenostomy in 2001[1]. Since then, additional techniques for EUS-guided transluminal biliary drainage have been described, including creating a bilo-enteric fistula, using an EUS-antegrade approach, and a rendezvous technique to assist transpapillary cannulation[2]. Fistula tracts can be created either between the intrahepatic bile duct and stomach, as in EUS-guided hepaticogastrostomy, or between the extrahepatic bile duct and duodenum, as in EUS-guided choledochoduodenostomy[3]. These procedures have become a rescue therapy[4]. Although small case series of no more than five patients describe successful procedures with no complications[5-7], larger series report complication rates ranging from 9.5% to 40%[3,8-14]. The most common complications were bile leakage, stent misplacement, bleeding, and pneumoperitoneum, which accounted for 5.2%, 3.1%, 2.1%, and 1.0% of cases, respectively[3,15].Other rare complications such as biloma, cholangitis and perforation were also reported, all of which were related to the use of needle knife cautery in the multivariate analysis[15].

Most complications can be treated conservatively[15,16]. For example, bilomaas a result of stent migration can be treated with a variety of methods[8,11], including percutaneous[3] or EUS-guided[17] drainage. Only one fatality was reported, which involved severe peritonitis[18]. A case of retrogastric fluid collection was successfully treated with antibiotics and percutaneous drainage[19]. Several series reported cholangitis as an early or late complication resulting from reflux of gastrointestinal (GI) contents or stent migration[11,14,15,20]. In other cases, shortening of the metallic stent after deployment caused misplacement into to the abdominal cavity or gastroduodenal perforation, which required surgical intervention[3,19,21]. Cases of bleeding from the puncture site[3,9,19] or from a hepatic artery aneurysm, which was treated by angiographic embolization[22], were also reported. One technical concern involving guidewire shearing by the EUS-needle bevel was reported, which was treated by radiologic intervention[23].

Preventative measures

When inserting stents into the bilo-enteric tract, the membrane from fully/partially covered or specially designed metal stents prevents leakage of bile from the newly created tract. As stent shortening was related to cases of biloma, perforation, and peritonitis, an appropriate-length stent should be carefully selected and placed in the optimal position. Stent dislocation can be prevented by placing clips at the endoluminal stent margins[9], or, as we have observed, by placing a double-pigtail plastic stent inside the fully covered self-expanding metal stent. In addition, the maneuver applied during stent deployment is critical, and it is recommended that the endoscopist perform the initial stent deployment under fluoroscopic monitoring, before switching to endoscopic monitoring.

Infectious complications were reported[3], including a case of cholecystitis due to previous ERCP contamination of the obstructed biliary system[20]. Although the role of antibiotic prophylaxis in such procedures has not been established[24], it has been used by several authors who found that 4-5 d (nil per mouth) of antibiotic treatment was essential for preventing minor leakage and perito-

neum contamination[4,10,20].

Although guidewire shearing during the procedure is not common during EUS-guided biliary drainage, the risk could be eliminated by avoiding acute angles during needle retraction and by retracting slowly with a lot of caution for any resistance. If any resistance is felt, the needle and the wire should be retracted concurrently[25]. Other authors recommend changing the EUS needle after puncture to a 4 Fr cannula for guidewire manipulation[26], or using a blunt-ended needle with a sharp needle-tip stylet (Access needle®; Wilson Cook Inc., Winston-Salem, NC, United States) for biliary access[23,27]. In one case, guidewire knotting occurred in an EUS-guided rendezvous procedure as a result of guidewire loop formation during endoscopic–catheter exchange[28]. In this report, the guidewire was untangled with rat-toothed forceps using a gastroscope, and the author suggested that, to prevent looping, constant tension on the wire should be maintained during exchanges. A summary of uncommon complications from EUS-guided biliary drainage is presented in Table 1.

EUS-GUIDED PANCREATIC DRAINAGE

EUS-guided pancreatic drainage can be performed to remove accumulated fluid due to acute pancreatitis or pancreatic duct obstruction. This procedure is typically performed *via* transpapillary, transluminal, or transanastomotic approaches with neotract formation or by the rendezvous technique in patients for whom ERCP has failed or who have surgically altered anatomy[25,29,30]. EUS-guided pancreatic drainage is effective with a lower morbidity compared to the other platforms[31]. The success rate depends on the type of fluid collection, and ranges from 50.0%-63.2% up to 100%[32,33]. The common complications of pancreatic duct drainage are pancreatitis, bleeding, perforation, and stent migration, with overall complication rates ranging from 0% to 52%[25,30,34]. In some case series, the complication rate was significantly higher in patients with necrosis compared to those with pseudocysts[34].

Less common complications that have been reported with EUS-guided pancreatic drainage include peri-pancreatic abscesses, fluid collection, and shearing of the guidewire during diagnostic pancreatography and therapeutic drainage[29,35-37]. In these reports, peri-pancreatic collection was the result of pancreatic fluid or pseudocyst leakage. To prevent bacterial peritonitis, some endoscopists recommend antibiotic prophylaxis[37]. Guidewire shearing occurred more frequently than was reported for EUS-guided biliary drainage, likely due to the greater angle between the EUS needle and the desired direction of the pancreatic duct[29,36], with similar remedies for prevention. A splenic artery aneurysm within the pancreatic pseudocyst was the cause of bleeding in one case, which was treated by selective angiographic embolization[38]. A summary of uncommon complications from EUS-guided pancreatic drainage is presented in Table 2.

The rare but fatal complication of air embolism was also reported, occurring in one patient who had previously undergone ERCP, and in one case of EUS with fine-needle aspiration of an accessory spleen[39]. A fatal case occurred in a patient who underwent EUS-guided pancreatic pseudocyst drainage[40]. Hikichi *et al*[41] reported a case of gallbladder puncture and drainage following misdiagnosis of a pancreatic pseudocyst, which was treated with nasocystic-tube drainage and antibiotic administration. The authors strongly recommended that every endosonographer should verify the location of the puncture site *via* EUS-scanning before initiating any drainage intervention.

EUS-GUIDED CELIAC PLEXUS NEUROLYSIS AND CELIAC PLEXUS BLOCK

Celiac plexus neurolysis (CPN) and celiac plexus block (CPB) have been performed for more than five decades in patients with upper abdominal pain of pancreatic origin and from stomach, intestinal, and intra-abdominal metastases. CPB has been performed under guidance of radiography, fluoroscopy, CT, and ultrasonography. Common complications with this procedure include local pain, diarrhea, and hypotension, whereas lower extremity weakness, paresthesia, lumbar puncture, pneumothorax, pleuritic pain, hiccups, and hematuria occur in only 1% of patients[42]. EUS-guided CPB has gained in popularity since the 1990sas it enables the endoscopist to easily and accurately determine the location for injection[43]. For EUS-guided CPN, the complications are similar, with hypotension, pain, and diarrhea occurring in 3.4%-20.0%, 6.8%-9.0%, and 10.3%-17.0% of cases, respectively[44-46].

Uncommon complications, which occurred less than 1%, from EUS-guided CPN have primarily been described within case reports. Despite the improved injection-site localization, there were reports of anterior spinal cord infarction due to alcohol-induced injury to the lumbar artery and prolonged hypotension[44-48]. Nevertheless, the occurrence is much more infrequent than is observed with other approaches[49-54]. It is possible that spinal arterial spasm or thrombosis due to the chemical agent or the direct injection into the cerebrospinal fluid in cases of percutaneous injection caused the infarctions[49,55]. Other reports describe celiac artery thrombosis resulting in gastric ulceration with hepatosplenic infarction[42,56,57] or fatal multiple organ ischemia[58]. In two of these cases[56,58], color Doppler was performed either before or after the procedure to ensure celiac artery patency. Aspiration tests were also conducted after needle puncture in two cases[56,57]. The cause of arterial thrombosis was attributed to a vasospasm of affected vessels from alcohol irritation, as the amount of alcohol was similar among the cases. There was one case of peri-pancreatic collection after absolute alcohol injection that was treated by EUS-

Table 1 Uncommon complications of endoscopic ultrasound-guided biliary drainage

Ref.	Procedure	Stent	Complications (*n*/total successful cases)	Postulated causes	Treatment	Prevention recommendation
Püspök *et al*[20]	EUS-CDS, EUS-HGS, rendezvous	Plastic stent, FCSEMS, UCSEMS	Cholangitis (1/6), cholecystitis from previous ERCP (1/6)	Cholangitis may result from previous ERCP attempt	Antibiotics, PTBD, surgery	Consider antibiotic prophylaxis
Bories *et al*[11]	EUS-HGS, rendezvous	FCSEMS	Biloma (1/11), cholangitis (1/11)	Stent shortening	Percutaneous drainage (biloma), second stent insertion (cholangitis)	Select a stent of appropriate length Observe stent position during deployment (both endoscopic and fluoroscopic views)
Attasaranya *et al*[19]	EUS-CDS, EUS-HGS, cholecystoduodenostomy, transduodenal FCSEMS insertion	Plastic stent, FCSEMS	Duodenal perforation (1/31), retrogastric collection (1/31), cholangitis (1/31)	Stent shortening	Surgery (duodenal perforation), percutaneous drainage (retrogastric collection)	Keep at least 2 cm length of stent at the mural site
Martin *et al*[18]	EUS-HGS	PCSEMS	Stent migration and biloma	Stent migration	(Dead)	
Siddiqui *et al*[21]	EUS-CDS	FCSEMS	Duodenal perforation (1/8)	Stent shortening	Surgery	
Khashab *et al*[23]	EUS-HGS	Not mentioned	Wire shearing (1/1)	Injury from EUS needle	Percutaneous intervention	Avoid acute angulation of guidewire and retract it gently Change needle to a small-size cannula during guidewire manipulation
Prachayakul *et al*[8]	EUS-CDS, EUS-HGS	FCSEMS	Biloma (1/21)	Malpositioned stent	Percutaneous drainage[17]	Observe stent position during deployment (both endoscopic and fluoroscopic views)
Prachayakul *et al*[22]	EUS-HGS	FCSEMS	Bleeding from hepatic artery aneurysm (1/1)	Iatrogenic trauma during EUS-HGS	Angiographic embolization	Puncture site should be away from major vascular structure
Kawakubo *et al*[3]	EUS-CDS, EUS-HGS	Plastic stents, FCSEMS	Cholangitis (1/61), biloma (1/61), perforation (1/61)	Stent misplacement	Percutaneous drainage (biloma), surgery (perforation)	Observe stent position during deployment (both endoscopic and fluoroscopic views)
Saxena *et al*[28]	Rendezvous	FCSEMS	Guidewire knot	Guidewire formed a knot during exchanges	Untangled using forceps	Maintain constant pressure on the guidewire during exchanges

ERCP: Endoscopic retrograde cholangiopancreatography; EUS-CDS: Endoscopic ultrasound-guided choledochoduodenostomy; EUS-HGS: Endoscopic ultrasound-guided hepaticogastrostomy; FCSEMS: Fully covered self-expandable metallic stent; PCSEMS: Partially covered self-expandable metallic stent; PTBD: Percutaneous transhepatic biliary drainage; UCSEMS: Uncovered self-expandable metallic stent.

guided drainage and intravenous antibiotics[59]. Another case involved a mixed fungal and bacterial brain abscess as a result of hematogenous spread[60]. As with the other EUS-guided procedures, the use of antibiotic prophylaxis has not been established for these rare infectious complications[24]. A summary of uncommon complications from EUS-guided CPN is presented in Table 3.

EUS-GUIDED INTRA-ABDOMINAL INTERVENTIONS

Intra-abdominalabscess drainage

Only a limited number of cases using EUS-guided intra-abdominal drainage for liver abscesses have been reported, which were performed without complications[61-65]. In addition, several reports involving 4-25 cases each of pelvic abscess drainage using a transrectal approach with or without an irrigation tube to prevent stent occlusion by fecal material have been described, also without complications[66-70]. One case series describes abscess drainage in nine patients through the esophagus, stomach, and colon[64]. Mediastinitis and pneumothorax developed in one patient who underwent transesophageal drainage of a pancreatic pseudocyst, and was treated conservatively. Stent migration occurred in another patient undergoing transcolonic drainage, which was treated endoscopically.

Vascular therapy

EUS-guided interventions have been used for creating portosystemic shunts to treat GI bleeding (both variceal and non-variceal bleeding)[71]. In addition, EUS-guided injection of cyanoacrylate or coil embolization has

Table 2 Uncommon complications of endoscopic ultrasound-guided pancreatic drainage

Ref.	Procedure	Stent	Complication (*n*/total successful cases)	Postulated causes	Treatment	Prevention recommendation
Hikishi *et al*[41]	EUS-cystogastrostomy drainage	Plastic stent, nasobiliary drainage	Gallbladder puncture and drainage	Marked distension of gallbladder with debris, overlapping location between pseudocyst and gallbladder in fluoroscopy	Conservative with antibiotics	EUS scanning prior to initiating drainage intervention
Barkay *et al*[29]	EUS-PD rendezvous, dye injection	Plastic stent	Peripancreatic abscess (1/10), wire shearing (1/10)	Failed to inject PD (peripancreatic abscess), repeated to-and-fro movements of wire	Percutaneous drainage (abscess), transluminal removal (wire)	Carefully manipulate the guidewire, avoid acute angles
Jows *et al*[40]	EUS-cystogastrostomy drainage	Not mentioned	Air emboli	Prolonged high pressure air sufflation, inflammation, mechanical injury	(Dead)	Use CO_2 inflation instead of air
Fujii *et al*[36]	EUS-PD stent (antegrade and retrograde)	Plastic stents	Peripancreatic abscess (1/32), wire shearing (1/32)	Balloon dilation? Multiple devices (peripancreatic abscess), injury from EUS needle (wire shearing)	EUS-guided transmural drainage (abscess)	Carefully manipulate the guidewire
Kurihara *et al*[38]	EUS-PD rendezvous, and PD stenting	Plastic stents, UCSEMS	Pancreatic pseudocyst with splenic artery aneurysm	Pancreatic juice leakage	Angiographic embolization	Avoid major vascular structures

EUS-PD: Endoscopic ultrasound-guided pancreatic duct drainage; PD: Pancreatic duct; UCSEMS: Uncovered self-expandable metallic stent.

Table 3 Uncommon complications of endoscopic ultrasound-guided celiac plexus neurolysis

Ref.	Composition of injection solution	Complication	Treatment and outcome	Prevention recommendation
Fujii *et al*[47]	0.25% bupivacaine in 99% alcohol (ganglia: 1 mL; plexus: 23 mL)	Paraplegia	Remained paraplegic until death	Use color Doppler to avoid intravascular injection
Mittal *et al*[48]	0.25% bupivacaine and epinephrine with alcohol (1:5) (ganglia: 5 mL; around the celiac artery: 19 mL)	Paraplegia	Lumbar drainage but no improvement	Minimize the volume of absolute alcohol
Jang *et al*[56]	0.25% bupivacaine (5 mL), 98% ethanol (10 mL), triamcinolone (1 mL)	Hepatosplenic, stomach, and small bowel infarctions, gastroduodenal ulcers	Supportive treatment, died 27 d later	
Ahmed *et al*[57]	0.25% bupivacaine (20 mL), 98% ethanol (20 mL)	Pancreaticosplenic infarction, gastric ischemia and stenosis	Subtotal gastrectomy with Roux-en-Y gastrojejunostomy	
Gimeno-García *et al*[58]	0.5% bupivacaine (5 mL), absolute alcohol (10 mL) on each side of the celiac takeoff	Thrombosis of celiac artery, pneumatosis of the stomach andsmall and large intestines, and liver, kidney, and spleen infarctions	Conservative treatment, died 8 d later	
Muscatiello *et al*[59]	Not mentioned	Peripancreatic abscess	EUS-guided aspiration of abscess and ceftazidime injection	Consider antibiotic prophylaxis
Lalueza *et al*[60]	Not mentioned	Brain abscess by *Cladosporium macrocarpum* and *Streptococcus constellatus*	Surgery, antibiotics, and antifungal	

EUS: Endoscopic ultrasound.

emerged for treatment of refractory variceal bleeding. Numerous studies have reported on the feasibility, efficacy, and safety of such methods with the aid of EUS Doppler for treatment of esophagogastric[72-75] and ectopic varices[76-78]. EUS-guidance allows for optimization of the obliteration rate as well as reduction of cyanoacrylate to lower the risk of embolization, which, though not completely eliminated, is not fatal[73]. Sclerotherapy and cyanoacrylate injections have also been used for non-variceal bleeding from duodenal

ulcers, aneurysms, and Dieulafoy's lesion[79,80]. EUS-guided injection of cyanoacrylate and polidocanol for treatment of upper GI bleeding had a success rate of 87.5%, with only one of these eight cases experiencing asymptomatic cyanoacrylate diffusion into the hepatic artery[79].

Tumor-ablative therapy

EUS-guided procedures have also shown promise for the treatment of intra-abdominal tumors and cystic lesions, such as pancreatic cystic neoplasms. Currently, there are only a few reports of ethanol ablation with or without paclitaxel lavage for pancreatic cystic lesions[81-86]. Common complications with these procedures included acute pancreatitis, abdominal pain, and hyperamylasemia. One case experienced asymptomatic splenic vein obliteration with collateral formations after 27 mo[86]. Ethanol ablation has also been described for solid tumors in the abdomen, including pancreatic neuroendocrine tumors[87-90], a GI stromal tumor[91], metastatic lymph nodes[92], and metastatic tumors in the liver[93,94] and adrenal glands[95]. The majority of these cases were treated successfully without complications, except for low-grade fever and hematomas following liver tumor ablation[94].

There are a few reports describing EUS-guided injection of biologic agents[96] and oncolytic virus therapy[97], and insertion of radioactive seed, cryotherapy, and fiducial placement for stereotactic body radiotherapy[98-103] to treat pancreatic adenocarcinoma, a deadly cancer for which only 15%-20% of patients are candidates for curative resection[96]. Adverse events were rare for these procedures, consisting of duodenal perforations due to the EUS tip, effects from the injected agents[97], mild pancreatitis, cholangitis, bleeding and fever[99-101]. Antibiotic prophylaxis was utilized in one study[100], in order to prevent cholangitis.

CONCLUSION

Therapeutic EUS is becoming more prominent in the treatment of many diseases due to the increased accuracy afforded by real-time high-resolution imaging. As a result, information regarding possible complications is greatly needed. The review presented here describes some of the less common complications that have been reported in various EUS-guided applications. By acknowledging the adverse events that occur, we can gain a better understanding of their causes and preventative actions to increase the safety of these techniques. EUS-guided interventions have been utilized for procedures of biliary and pancreatic drainage and CPN, as well as for various intra-abdominal conditions. Potential complications and preventive strategies will become clearer in the future as the number of patients treated and procedures reported increase. The authors recommended that endosonographers apply this knowledge in routine endoscopic practice for monitoring and early detection (including treatment) of these uncommon adverse events for the best clinical outcomes.

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New technologies and techniques to improve adenoma detection in colonoscopy

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Abstract

Adenoma detection rate (ADR) is a key component of colonoscopy quality assessment, with a direct link between itself and future mortality from colorectal cancer. There are a number of potential factors, both modifiable and non-modifiable that can impact upon ADR. As methods, understanding and technologies advance, so should our ability to improve ADRs, and thus, reduce colorectal cancer mortality. This article will review new technologies and techniques that improve ADR, both in terms of the endoscopes themselves and adjuncts to current systems. In particular it focuses on effective techniques and behaviours, developments in image enhancement, advancement in endoscope design and developments in accessories that may improve ADR. It also highlights the key role that continued medical education plays in improving the quality of colonoscopy and thus ADR. The review aims to present a balanced summary of the evidence currently available and does not propose to serve as a guideline.

Key words: Colorectal cancer; Adenoma detection; New technology; Techniques; Colonoscopy

Core tip: The most important quality indicator in colonoscopy is Adenoma detection rate. It is associated with outcomes from colorectal cancer, with low detection rates being associated with increased mortality and poor outcomes. Whilst a number of technologies are emerging to improve adenoma detection rate (ADR), at present, it seems that education, team work and optimising current practice will provide the biggest gains in ADR whilst maintaining financial acceptability.

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INTRODUCTION

Colorectal cancer is the third most common cancer in men and the second in women. Worldwide, an estimated 1.2 million cases of colorectal cancer occur annually[1]. The highest incidence rates have previously been in North America, Australia, New Zealand, Europe, and Japan. In recent years some of these incidences has stabilised and even began to reduce, *e.g.*, United States and this may, in some part, be related to the introduction of national screening programmes (Figure 1).

Worldwide, colonoscopy forms the basis of colorectal cancer screening programmes and has been shown to reduce the risk of death from colorectal cancer through detection of tumours at an earlier, more treatable stage and through removal of precancerous adenomas[2]. There are a number of quality assurance measures for colonoscopy in screening programmes include caecal intubation rate, bowel preparation quality, complications, cancer detection and adenoma detection rate (ADR, the proportion of colonoscopies performed by a physician that detect at least one histologically confirmed colorectal adenoma). However, ADR is now established as the most important quality indicator due to 2 landmark studies. The first demonstrated increased risk of interval cancer when the colonoscopy is performed by an endoscopist with a ADR below 20%[3]. As a result professional societies recommend a detection rate of > 25% in order to be deemed adequate[4]. The second demonstrated an inverse relationship between ADR and the risks of interval colorectal cancer, advanced-stage interval cancer, and fatal interval cancer. With each 1.0% increase in ADR was associated with a 3.0% decrease in the risk of cancer[2].

There are a number of techniques and technologies, both established and emerging that provide an exciting and promising potential to improve ADR. This article will discuss effective technique and behaviours, developments in image enhancement, advancement in endoscope design and developments in accessories that may improve ADR.

EFFECTIVE TECHNIQUE AND BEHAVIOURS

Bowel preparation

Good bowel preparation is vital for effective lesion recognition at colonoscopy. Consequently, guidance from the United States multi-society task force for colorectal cancer recently published strong recommendations for adequate bowel preparation with split-dose regimes in order to optimise ADR[5]. Poor bowel preparation has been associated with a adenoma miss rate of 43%[6]. Studies have demonstrated a clear improvement in ADR (35%) with split dose preparation ($P \leqslant 0.001$). They also showed a clear improvement in caecal intubation rate (95.5%) and preparation quality[7]. Attempts to implement further measures to improve bowel preparation have also been studied. One such scheme studied telephone education relating to the bowel preparation prior to colonoscopy. There was a improvement in compliance, preparation quality and ADR[8].

Insertion and withdrawal polypectomy

Colonic configuration during insertion phase and withdrawal phase is different and some polyps seen during insertion are difficult to find during withdrawal and vice versa[9]. It is typical practice to perform the formal mucosal examination and polypectomy on withdrawal, noting any pathology on insertion for subsequent intervention. One study suggested this may not be preferable, finding that polyp < 10 mm identified during insertion are frequently missed on withdrawal, suggesting polypectomy during insertion[10]. A more recent study compared 610 colonoscopies where patients were randomised to either polypectomy during insertion and withdrawal or just withdrawal. In both arms, mean number of adenomas detected per patient were similar. With the only significant difference being that of insertion time[9]. Overall, the evidence suggests neither technique is superior over the other.

Retroflexion in the caecum

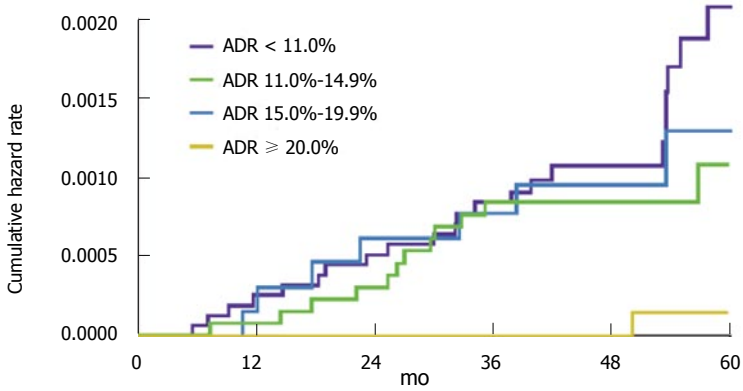
Rectal retroflexion forms part of the required standards for colonoscopy completion. Retroflexion in the right colon is not routinely performed but has been reported to improve ADR. A prospective cohort study conducted in the United States examined the potential impact of caecal retroflexion on ADR. One thousand consecutive adults undergoing colonoscopy were studied. A standard forward viewing colonoscopy of the right colon was performed and polyps were removed. There was then repeated examination in retroflexion from the caecum to the hepatic flexure. Retroflexion was successful in 94.4% of the patients. The subsequent examination in retroflexion demonstrated a 9.3% miss rate for the forward viewing method[11]. However, safety concerns have been raised due to the risk of perforation of using this technique.

Dynamic position change

Randomised controlled trials examining dynamic position changes have produced conflicting results regarding ADR, but predominate positive findings. It is clear that position change aids caecal intubation rate and patient comfort. Such position changes result in better distension with less insufflation of air, shifting of fluids and residues, and opening tight angles at flexures[12]. Specifically during withdrawal, such position changes have repeatedly been shown to improve ADR[13,14].

Antispasmodics

Hyoscine butylbromide is a relatively safe antispasmodic anticholinergic agent that blunts the response of colonic neurons to muscarinic and nicotinic stimulation which leads to inhibition of smooth muscle contraction in the



No. at risk

ADR < 11.0%	15883	15805	15744	15669	9355	4717
ADR 11.0%-14.9%	13281	13223	13182	13120	7571	4003
ADR 15.0%-19.9%	6607	6582	6562	6539	4022	2529
ADR ⩾ 20.0%	9255	9235	9202	9166	7155	5548

Figure 1 Cumulative hazard rates for interval colorectal cancer, according to the endoscopists adenoma detection rate. The graph shows cumulative hazard rates for interval colorectal cancer among subjects who underwent screening colonoscopy that was performed by an endoscopist with an ADR in one of the following categories: less than 11.0%, 11.0% to 14.9%, 15.0% to 19.9%, and 20.0% or more. ADR: Adenoma detection rate.

colon[15]. A recent meta-analysis assessed the results of 8 Randomised control trials (RCTs) conducted in Europe, Asia and Australia concluded hyoscine use in patients undergoing colonoscopy does not appear to significantly increase the detection of adenomas[16]. However, a recent study has shown that within the bowel cancer screening programme (BCSP) in England, it does improve ADR when used[17]. Recently, another antispasmodic topically applied: L-menthol (an organic compound found in peppermint oil, has been shown to improve ADR when sprayed on to the colonic mucosa during colonoscopy[18]. Whilst promising further studies are need to corroborate these findings.

Procedural factors-withdrawal time, use of sedation, colonoscopist and time of day

Variable factors inherent to colonoscopy have been shown to affect ADR. Time spent during the withdrawal phase is one such factor. A recent study within the BCSP in England demonstrated a plateau effect after approximately ten minutes. The lowest ADR was demonstrated if the withdrawal was less than 7 min, with the maximum ADR, seen with a withdrawal time of 9-11 min[17]. A multi centred RCT assessed multiple factors that may affect ADR, namely, bowel cleansing, sedation, withdrawal time in normal colonoscopies, and caecal intubation rates. They concluded a mean withdrawal time of > 8 min was the only modifiable factor related to the ADR in colorectal cancer screening colonoscopies[19].

Sedation use in one study found that larger amounts of sedation improved many aspects of colonoscopy quality. ADR increased (25.9% to 35%), early complications rate decreased (3.4% to 0.3%) and completion rates increased (88.3% to 96.4%)[20]. The mode of sedation that is used also appears to influence the quality of colonoscopy and particularly ADR. Again the literature reports conflicting results. A study which compared 843 colonoscopies found that deep sedation was associated with improved caecal intubation rates, and increased ADR. There were more immediate complications reported in the deep sedation group[21]. Another study suggested the type of sedation used during colonoscopy does not affect the number of patients in whom adenomatous polyps are detected. This followed a retrospective study that examined 3252 colonoscopies across two centres. ADR was the comparable for those receiving propofol and conscious sedation (midazolam and fentanyl)[22].

A variety of different studies have questioned whether the individual colonoscopist, *i.e.*, the person performing the examination, influences ADR. A study that assessed factors that influence the quality of 12000 screening colonoscopy found that annual case volume and life experience did not affect ADR but continued medical education (CME) was found to be most influential, with those who attended most CME meetings having the highest ADR[23]. These findings were supported by a study from the Mayo clinic that formally assessed the impact of a colonoscopy education program. An additional training program, known as Endoscopic Quality Improvement Program (EQUIP) was used. ADRs were measured at baseline, then half of the 15 colonoscopist were randomly assigned to EQUIP. Baseline and post training ADRs were then compared, a total of 1200 procedures were completed in each of the two study phases. In the post-training phase, the group of endoscopists randomized to EQUIP training had an increase in ADR to 47%, whereas the ADR for the group of endoscopists who were not trained remained unchanged at 35%[24].

The procedural start time may also affect ADRs

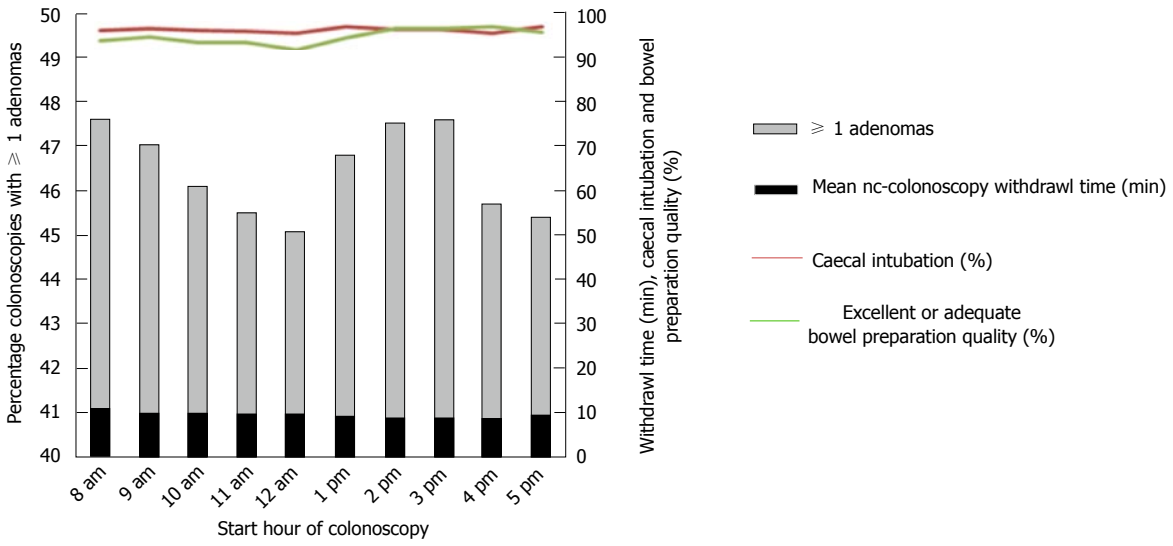


Figure 2 Relationship between start time of colonoscopy and adenoma detection, withdrawal time, caecal intubation, and bowel preparation quality.

as suggested by a study of > 31000 colonoscopies. Procedures starting in the second half of a session (11:00-14:00 or 16:00-18:00) were associated with a reduction in detection of adenomas and advanced adenomas compared with procedures starting between 08:00 and 11:00 or 14:00 and 16:00[17]. Having assistance from the entire technical team to spot abnormalities during the examination has also been shown to improve ADR. In one such study the process was termed "all eyes on screen", increasing ADR from 34% to 51% in 2 years[25]. A central visual gaze pattern on the colonoscopist has also been shown to improve ADR[26] (Figure 2).

Water infusion techniques

The original goal of this novel technique was to facilitate caecal intubation, reduce colonic spasms, lower patient discomfort and need for sedation, for which it performs well[27,28]. It works by combining or replacing air-insufflation with water infusion. Concerns have been raised about an impaired ability to detect lesions due to contaminated water impairing visibility[27]. A systematic review performed in 2012 reported no difference in ADR when comparing water infusion to conventional insufflations[29]. A similar technique is known as Water Exchange. The water-exchange method is a technique in which water containing residual faeces is removed and "exchanged" for clean water in lieu of air-insufflation. The exchange of large volumes of water during the insertion of the colonoscope results in additional cleansing of the mucosa[27]. A study in 2009 exploring this technique failed to reach statistical significance for an improved ADR[30]. Improved ADR was demonstrated in one study when they combined the water exchange technique with cap-assisted colonoscopy (P = 0.002)[31].

The prolonged insertion time, colonoscopist experience and general technicalities of these techniques including expense are likely to limit their introduction into routine practice.

IMAGE ENHANCEMENT TECHNIQUES AND TECHNOLOGY

Standard white light, high definition and zoom endoscopy

There is conflicting evidence when assessing the superiority of high definition colonoscopy *vs* standard white light. A meta-analysis involving 4422 patients provided data on ADR. There was no significant difference in detection of high risk ADR. The detection of small adenomas was slightly better in the high definition group, but overall the analysis concluded here were marginal differences between high definition colonoscopy and SVE for the detection of colonic polyps/adenomas[32]. A more recent study showed improved ADR with high definition colonoscopy, when used by endoscopists with a low ADR (< 20%). For those with an ADR already > 20% there was no improvement in detection of high risk polyps, flat polyps or proximal lesions[33]. In contrast, other studies that have directly compared high definition colonoscopy to standard video endoscopy have shown significant improvements in ADR. On such study did so without compromising procedure duration, caecal intubation or levels of sedation. The additional polyps detected were mainly flat and sessile[34]. A further study with similar design also showed a lower adenoma miss rate with high definition colonoscopy[35]. Interestingly, a study assessing the multiple factors that influence the quality of colonoscopy identified advancing generations of colonoscope technology as a positive effector over ADR[23].

In summary, it would appear there are gains to be made from the use of high definition colonoscopy, but these may be limited, but the use of new generation colonoscopes (compared to older ones) may be the important factor.

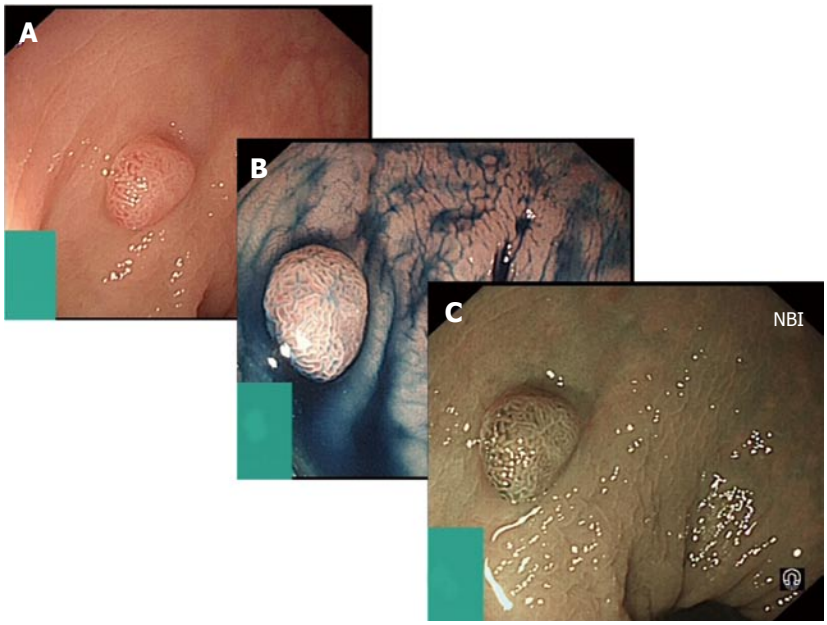


Figure 3 Digital chromoendoscopy. A: Represents sessile adenoma seen in standard white light; B: Shows the same adenoma after the use of indigo carmine applied for chromoendoscopy; C: Shows further assessment of the adenoma using narrow band imaging (NBI).

Chromoendoscopy

Chromoendoscopy refers to the topical application of stains or dyes at the time of endoscopy in an effort to enhance tissue characterization, differentiation, or diagnosis[36]. The stains that are used for chromoendoscopy are classified as absorptive, contrast, or reactive. Indigo carmine is an example of a contrast stain and is most commonly used to improve ADR. Indigo carmine staining combined with magnification endoscopy appears to be a useful technique for the detection of aberrant crypt foci in the rectum, a potential biomarker for proximal flat colonic neoplasia[36,37].

A number of studies have examined whether the use of chromoendoscopy can improve ADR when compared to conventional white light colonoscopy, many of which have demonstrated an increase in the yield of neoplasia detection[38-40]. Many of these studies examine its use in high risk groups[37], One study compared high-definition chromocolonoscopy with high-definition white light colonoscopy for the detection of colorectal adenomas in average-risk United States persons undergoing screening colonoscopy. They compared the colonoscopy results of 660 patients, finding no significant difference in the number of small adenomas, advanced adenoma or carcinoma. Concluding that their results do not support the routine use of high-definition chromocolonoscopy for colorectal screening in average-risk patients[41]. These conflicting results and the time consuming nature of dye spray may limit its adoption into routine screening of average risk patients.

New promising techniques are emerging, with stains incorporated into bowel preparation. One such formulation uses methylene blue (MB MMX, Cosmos Technolgies). This has been designed as a modified release device which ensures colonic release. The methylene blue is taken up by normal mucosa and poorly by neoplasia resulting in unstained areas where the lesions are present. A preliminary study has been promising on the efficacy of MB MMX 25 mg for the detection of polyps involved 96 patients undergoing routine colonoscopy. Polyps were detected in 61 patients, resulting in a 63.5% polyp detection rate[42].

Digital chromoendoscopy

Digital chromoendoscopy refers to advances in endoscope technology that manipulate wavelengths of the light source to create an effect similar to chromoendoscopy by accentuating lesion characteristics (Figure 3).

Narrow band imaging (NBI) is available on Olympus endoscopes. When used in colonoscopy, it allows potential improvement in ADR due to the enhanced appearance of certain mucosal and vascular features. A filter leads to the use of ambient light of wavelengths of 440 to 460 nm (blue) and 540 to 560 nm (green). Because the peak light absorption of haemoglobin occurs at these wavelengths, blood vessels will appear very dark, allowing for their improved visibility and the improved identification of other surface structures[43]. Compared with chromoendoscopy, classification of colorectal polyps by NBI appears to have a shorter learning curve. However, there is still substantial inter-observer variability, and classification of colorectal lesions based on vascular patterns is not objectively standardized yet[44]. A meta-analysis of 7 studies in 2936 patients showed no statistically significant difference in the overall adenoma detection rate with the use of NBI or white light (36% *vs* 34%, P = 0.4). They also showed no difference in the number of polyps detected between the two modalities (P = 0.2). A second met-analysis performed again failed

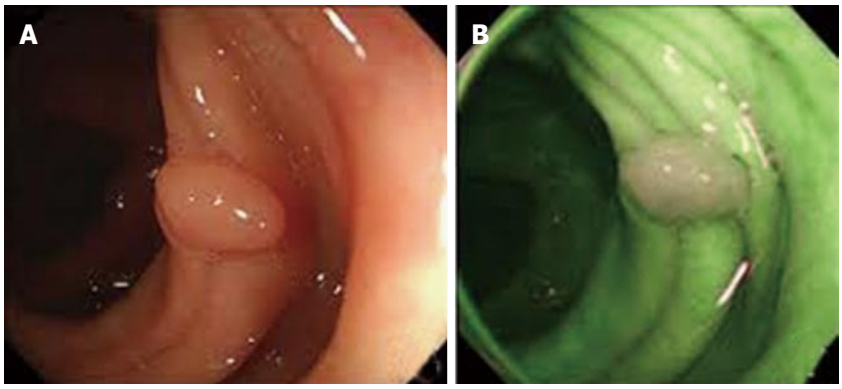


Figure 4 Digital-auto-fluorescence. A demonstrates polyp in white light, whilst B represents the same area in digital-auto-fluorescence. The normal mucosa appears green, with the adenoma appearing white.

show a significant difference in ADR between NBI and conventional white light. Concluding, NBI does not increase the yield of colon polyps, adenomas, or flat adenomas, nor does it decrease the miss rate of colon polyps or adenomas in patients undergoing screening/surveillance colonoscopy[45]. A further, larger, meta-analysis examined 11 RCTs evaluated NBI and ADR in a screening population of average- and higher-risk individuals and found limited benefit compared with white light colonoscopy[46]. These results were supported by a recent Cochrane review of 3673 patients in 8 randomized trials [relative risk (RR), 0.94; 95%CI: 0.87-1.02][47].

As with narrow-band imaging, the Fujinon intelligent colour enhancement (FICE) also narrows the bandwidth of conventional white-light colonoscopy to improve visualization, but it creates this effect electronically. Dedicated computer algorithms are used to generate the image. FICE enables the endoscopist to choose between different wavelengths for optimal examination of the colon mucosa[48]. It is reported to allow inspection of microvascular patterns as well as pit patterns and circumvents some limitations in conventional chromo-endoscopy[49]. Back to back studies have examined FICE and its impact upon ADR. Neither study demonstrated an improvement in ADR or adenoma miss rate when compared to NBI and white light[50,51].

The Pentax technology equivalent is i-Scan, for which there are limited RCT with most of the literature focusing on lesion characterisation. Some studies have compared high definition scopes coupled with i-Scan against standard resolution scopes. One such study demonstrated significantly more neoplastic lesions and more flat adenomas could be detected using high definition endoscopy with surface enhancement. Histology could be predicted with high accuracy (98.6%) within the HD+ group[52].

Digital-auto-fluorescence

Digital-auto-fluorescence (AFI) is technology available only in Olympus endoscopes where rotating filter wheel in front of the light source sequentially generates blue light (390-470 nm) and green light (540-560 nm)[53]. The exposure of tissue to this specific light leads to the excitation of some endogenous substances and subsequently the emission of fluorescent light. The reflected blue light is blocked by a second filter while the reflected red light and the emitted green autofluorescence from the tissue are used to obtain an image. AFI colonoscopy colours neoplastic lesions red-purple while non-neoplastic mucosa appears green[27] (Figure 4).

Three of the most widely reported studies comparing AFI and white light describe a lower adenoma miss rate with AFI, with up to a 20% difference[54-56]. One study reported that the detection rate of flat and depressed adenoma, but not elevated adenoma; by AFI is significantly higher than that by white light. In less experienced hands, AFI dramatically increased the detection rate (30.3%) and reduced miss rate (0%) of colorectal adenoma in comparison to white light (7.7%, 50.0%); this was not seen with more experienced endoscopists. They did describe a significantly longer duration time in the AFI group[54]. Another study explored the use of AFI in those undergoing colonoscopy for Lynch syndrome surveillance or those with a family history of colorectal cancer (one first-degree relative with colorectal cancer diagnosed at a young age (< 50 years) or two first-degree relatives regardless of age). This study reported a significantly higher sensitivity of AFI compared with white light (92% *vs* 68%; $P = 0.001$). The additionally detected adenomas with AFI were significantly smaller than the adenomas detected by white light (mean 3.0 mm *vs* 4.9 mm, $P < 0.01$)[55]. AFI also achieved better diagnostic accuracy (77%) than white light (57%) or NBI (63%) for polyp differentiation in the evaluation of still images by inexperienced endoscopists (accuracy compared with white light, $P = 0.001$; with NBI, $P = 0.016$)[57].

At present, whilst evidence exists that digital chromoendoscopic techniques (NBI, FICE and i-Scan) aide's lesion recognition, the evidence does not currently support that it improves ADR. There is some evidence to support of the positive effects of AFI, however, it is associated with added expense and poor image resolution, which are practical concerns for the

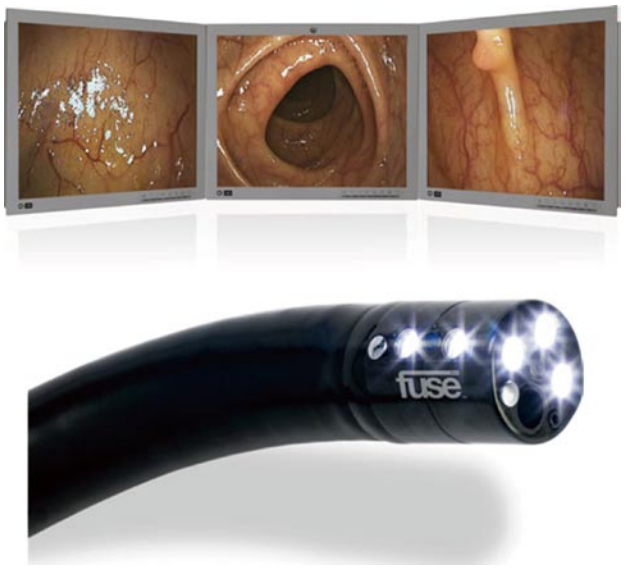


Figure 5 Example of the display module of the full spectrum endoscopy system and the 330° view (top). Bottom image is the full spectrum endoscopy scope demonstrating the side mounted camera and lights[27].

widespread introduction of this technology.

ADVANCEMENTS IN ENDOSCOPE DESIGN

Extra-wide angle view colonoscopes

This may represent one of the few recent developments in the design of the colonoscope that aide ADR. The full spectrum endoscopy (FUSE) system (EndoChoice) is currently on the market. It allows for full-spectrum views of the colon lumen, comprising 330 degrees. The colonoscope in the Fuse system has 2 additional cameras, on the left and right side of the scope's tip, to supplement the front camera. The video images transmitted from the cameras are displayed on 3 contiguous monitors corresponding to each camera. This array provides a comprehensive view of the total colonic lumen, including imaging of the traditionally encountered blind spots at the flexures or proximal edges of the mucosal folds (Figure 5).

During its initial development, trials revolved around anatomical models with simulated polyps, some of which were purposely placed in the tradition blind spot, *e.g.*, behind folds. In one such study 37 endoscopists performed colonoscopy by using the forward-viewing camera scope, followed by a colonoscopy with all 3 camera on; this increases the field of view to previously described 330 degrees. In total, 85.7% of the polyps were detected with the three cameras compared to 52.9% with only forward-viewing colonoscopy ($P \leqslant 0.001$). Particularly polyps that were "hidden" behind flexures and folds were more frequently detected with FUSE colonoscopy than with forward-viewing colonoscopy (81.9% *vs* 31.9%)[58]. An international, multicentre, randomised trial, the results of which were published in 2014 examined the use of FUSE further. Patients aged 18-70 years referred for colorectal cancer screening, polyp surveillance, or diagnostic assessment, were included. One hundred and eighty-five participants were assessed. The adenoma miss rate was significantly lower in patients in the FUSE group than in those in the standard forward-viewing procedure group: (7%) *vs* (41%) ($P = 0.0001$). In those who underwent standard colonoscopy first ($n = 88$), the FUSA system detected 39 additional polyps[59]. The authors reported a significantly longer withdrawal time ($P \leqslant 0.01$), however in real-time this was only a median time of 30 s. There certainly appears to be promise for ADR improvement with the FUSE system, more numerous and larger RCT's will be required to confirm this.

The findings from a study examining the effectiveness of a prototype wide angled colonoscopy were recently reported. The prototype colonoscope has a extra-wide angle of view has a 144°-232°-angle lateral-backward viewing lens in addition to a standard 140°-angle forward-viewing lens. Views from both lenses are simultaneously constructed and displayed on a video monitor as a single image. The ADR reported from this study was 57.1%, achieved whilst maintaining appropriate caecal intubation rate, completion times and no adverse event[60].

Balloon assisted colonoscopy

The NaviAid G-EYE colonoscope (SMART Medical Systems) is one such system. With this there is an integrated balloon on the flexible tip of the scope. The balloon can be reprocessed and reinflated by the endoscopist upon withdrawal of the scope. The mechanical flattening and straightening of haustral folds with the inflated balloon permit visualization of hidden anatomic areas, thus increasing the ADR[28]. Only simulated studies on anatomical models exist for this device. One such study showed a significantly greater ADR in the balloon assisted group ($P \leqslant 0.0001$)[61]. Clearly larger scale human studies are required to more about the utility of this device.

Real-time histology and confocal microscopy

Confocal laser endomicroscopy (CLE) is an emerging technology, which allows *in vivo* imaging of cellular and subcellular details of the gut mucosa and vessels during ongoing endoscopy. The most commonly used contrast agents are acriflavine hydrochloride and fluorescein sodium. For colon pathology assessment, the administration of fluorescein intravenously produces a strong staining of both surface epithelium and deeper layers of lamina propria[62,63]. Mounted into the end of a regular colonoscope is a miniature confocal microscope. When the tip of the scope is placed in direct contact with the mucosa and an argon ion laser excites the tissue a grayscale image can be produced, with a 7 μm thickness and a lateral resolution of 0.7 μm, the field of view being 475 μm × 475 μm[63] (Figure 6).

A number of studies have demonstrated the ability of confocal microendosocopy to perform real time

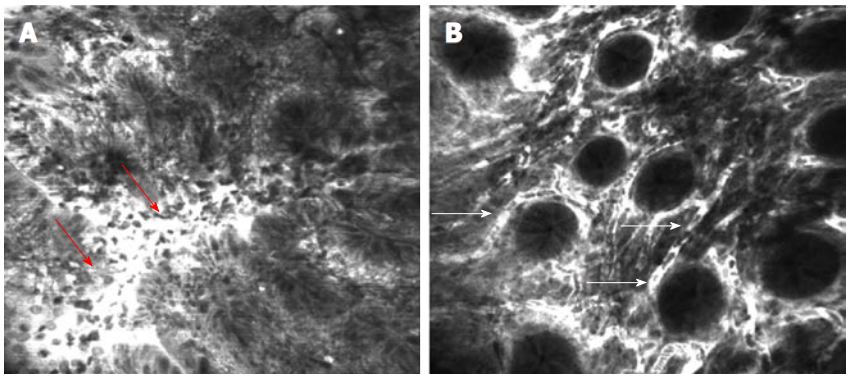


Figure 6 Confocal laser endomicroscopy of the colon using intravenous fluorescein. A: Colon carcinoma with total disorganization of cell architecture, invasion and destruction of the vessels with leakage of fluorescein (arrows); B: Severe inflammatory changes in ulcerative colitis with cellular infiltrate causing an increase in the distance between crypts and excessive vascularity (arrows)[63].

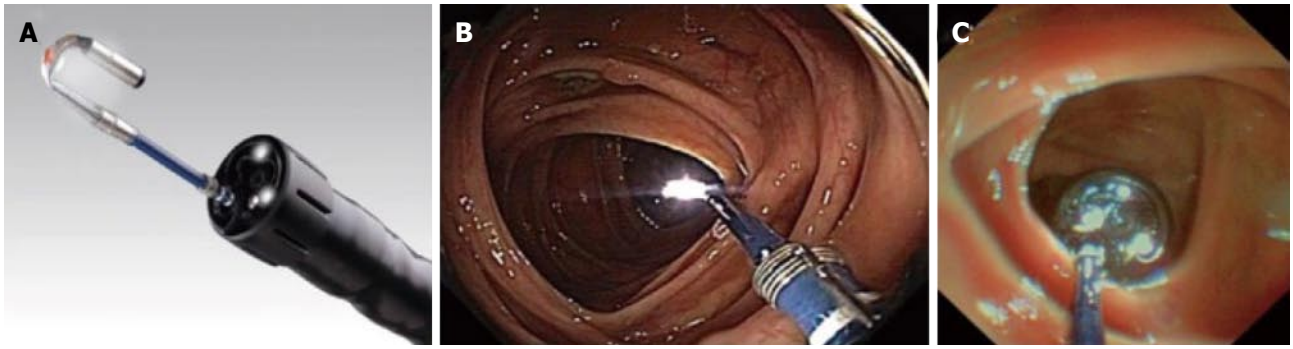


Figure 7 Third eye retroscope®. A: Image of the third eye retroscope® protruding from the working channel of the colonoscope; B: Forward view of third-eye retroscope®; C: View from lens of third-eye retroscope®[27].

histological analysis. Showing its ability to separate hyperplastic and adenomatous polyps, whilst identifying malignant features also[62-64]. The application of confocal is somewhat in its infancy, however as things develop real-time microendoscopy may become mainstream for endoscopist. There is little evidence to suggest that confocal can improve ADR, but it can improve decision making once the adenoma is detected.

DEVELOPMENTS IN ACCESSORIES

Third eye retroscope®

Third eye retroscope® (Avantis Medical Systems, Inc) consists of a video processor, a single-use polarizing filter cap for the colonoscope light source, and a 3.5 mm flexible single-use catheter with a camera and diode light source at the tip. The retroscope is retroflexed 180 degrees after being advanced through the working channel of the colonoscope and provides a 135 degrees retrograde view of the colon[27]. The system has been quoted to increase mucosal visualisation from 87% to 99%[65]. Like the FUSE system, initial studies of the third-eye system used anatomical models with simulated polyps. Standard colonoscopy detected 12% of the polyps located on the proximal aspects of folds, while 81% of these polyps were detected with the third eye retroscope[66]. A study demonstrated a 14.8% increase in polyp detection and a 16.0% increase in adenoma detection in their study that included 298 patients[67]. A further study reported similar result with a 13.2% increase in polyp detection and a 11.0% increase in adenoma detection[68]. The largest study for Third eye was the TERRACE study. TERRACE was a multi-centred study that included 349 patients. A net additional detection rate with the third eye retroscope of 29.8% for polyps and 23.2% for adenomas was reported. The study was criticised as the withdrawal time for the Third eye scopes were on average 2 min longer, however post-hoc analysis found withdrawal time to be independent of ADR[69] (Figure 7).

Despite the apparent improved ADR and reduced miss rate, third eye endoscopy has some significant flaws. It results in a 50% reduction in suction capacity; it needs to be removed from the working channel as another device is required and is very expensive[27].

Cap assistance

Transparent caps attached to the distal tip of the colonoscope were first designed to assist during endoscopic mucosal resection but they have also been suggested to be of help in depressing colonic folds to improve visualization of their proximal aspects[27]. Particularly in the hands of trainees and less-experienced colonoscopist they have been shown to improve

caecal intubation times and rates[70]. Most recently, a study, assessed ADR using cap-assisted colonoscopy *vs* normal colonoscopy. A total of 1380 patients were randomly allocated cap-assisted or normal, these consisted of asymptomatic participants (aged 50-75 years) in a primary colonoscopy screening programme. There was no significant difference in the type, location, size or number of polyps detected between the two groups. Caecal intubation time and Gloucester Comfort Scores were lower in the cap-assisted group[71]. A further study had similar finding, only demonstrated a superior ADR for polyps < 5 mm in the cap-assisted group[72]. Such finding have been persistent in other studies over the last decade with one of the original cap-assisted studies that examined 684 patients failing to demonstrate a significant difference in ADR[70]. This has been supported further by a meta-analysis performed in 2012 that concluded cap-assisted colonoscopy does not significantly improve ADR[73]. It would appear that cap-assisted colonoscopy may be of benefit in reducing caecal intubation time, but has limited or no benefit on polyp detection.

A similar device is Endocuff (Arc Medical, United States). Endocuff has been introduced as a means of enhancing visualization and scope stability during endoscopic mucosal resection of large or flat polyps of the sigmoid colon[74]. The Endocuff is a 2-cm long, flexible cuff with 2 rows of small flexible, hinged wings that help flatten large mucosal folds during withdrawal of the instrument. A prospective randomized trial in 498 patients undergoing screening colonoscopy showed Endocuff-assisted colonoscopy increased the absolute rate of polyp detection by 14% over unassisted colonoscopy from 42% to 56% (P = 0.001). The increase was particularly marked for polyps in the sigmoid colon 32% *vs* 15% (P = 0.0001) and caecum 4% *vs* 7% (P = 0.019)[75].

CONCLUSION

Novel and refinement of existing techniques, together with advancements in technologies can improve ADRs, and thus, potentially reduce cancer mortality. The use of chromoendoscopy in high risk groups such as colitis or HNPCC is becoming standard practice, but remains unsubstantiated for general use and is impractical. However, the development oral preparation given with the bowel preparation is a promising development. Increased ADR is yet to be proven with NBI, FICE and AFI beyond the use of high quality colonoscopes, and the marginal gains of using water exchange endoscopy are negated by time constraints, expense and further technical points for widespread application. Extra-wide angle colonoscopes such has FUSE has additional cost but its significant ADR may in the long-term make this economically viable, but more studies investigating the diagnostic before this device can be recommended for routine practice. The third-eye retroscope may be prohibited by cost, despite the apparent benefit, In contrast, cap-assistance is relatively inexpensive and further studies may show such devices as the Endo-cuff to be cost effective in improving ADR. However, at present, it seems that education, team work and optimising current practice will provide the biggest gains in ADR whilst maintaining financial acceptability.

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Current role of non-anesthesiologist administered propofol sedation in advanced interventional endoscopy

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Abstract

Complex and lengthy endoscopic examinations like endoscopic ultrasonography and/or endoscopic retrograde cholangiopancreatography benefit from deep sedation, due to an enhanced quality of examinations, reduced discomfort and anxiety of patients, as well as increased satisfaction for both the patients and medical personnel. Current guidelines support the use of propofol sedation, which has the same rate of adverse effects as traditional sedation with benzodiazepines and/or opioids, but decreases the procedural and recovery time. Non-anesthesiologist administered propofol sedation has become an option in most of the countries, due to limited anesthesiology resources and the increasing evidence from prospective studies and meta-analyses that the procedure is safe with a similar rate of adverse events with traditional sedation. The advantages include a high quality of endoscopic examination, improved satisfaction for patients and doctors, as well as decreased recovery and discharge time. Despite the advantages of non-anesthesiologist administered propofol, there is still a continuous debate related to the successful generalization of the procedures.

Key words: Non-anesthesiologist administered propofol sedation; Advanced interventional endoscopy; Endoscopic ultrasound; Endoscopic retrograde cholangiopancreatography

Core tip: A large amount of clinical research data demonstrated that propofol provides significant advantages over traditional sedation techniques during advanced endoscopic procedures like endoscopic retrograde cholangiopancreatography and/or endoscopic ultrasonography. Thus, propofol is more effective and safer than the combination of midazolam and meperidine to maintain an adequate level of sedation during advanced endoscopic procedures, with shorter recovery times and increased patient and endoscopist satisfaction. The trend of an increased usage of propofol and generalization of non-anesthesiologist administered propofol sedation in both hospital and private practice settings will certainly increase in the years to come.

Burtea DE, Dimitriu A, Maloş AE, Săftoiu A. Current role of non-anesthesiologist administered propofol sedation in advanced interventional endoscopy. *World J Gastrointest Endosc* 2015; 7(10): 981-986 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i10/981.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i10.981

INTRODUCTION

Most of the endoscopic procedures, either diagnostic or therapeutic, are nowadays performed under sedation, used as a standard practice in most of the centers[1]. Non-complex endoscopic examinations can be performed safely without any sedation, but with thorough psychological preparation and pre-procedural care, which might be good enough for patients to decrease procedure related anxiety[2]. However, the number and complexity of endoscopic procedures increased due to the generalized usage of sedation, which diminishes anxiety, discomfort and/or pain for the patients, thus improving patient acceptance and satisfaction[3-7]. Sedation is also important to medical practitioners as it improves the quality of endoscopic examinations and completion rate, but also treatment outcomes in therapeutic endoscopy, thus increasing endoscopist's satisfaction[3]. Sedation levels and medication types depend on a variety of factors, related to both patient characteristics (age, comorbidities, preference, *etc.*), as well as procedure types (simple diagnostic gastroscopy or colonoscopy, as opposed to prolonged complex therapeutic procedures)[4].

Sedation levels are variable and include a continuum of states ranging from minimal and moderate sedation to deep sedation and general anesthesia[4]. Conscious sedation assumes an *iv* administration of pharmacologic agents that lower the level of consciousness up to a state of drowsiness, relaxation, but the patient stays awake during the procedure retaining its ability to maintain an open airway and to breath spontaneously (patients do not require intubation and mechanical ventilation as with general anesthesia). Conscious sedation also helps to ensure adequate cardiac output, to communicate with the medical team and to respond to verbal commands[8,9]. Nevertheless, complex and lengthy procedures like endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) usually require a deeper sedation level[10]. Consequently, deep sedation makes the pain more tolerable, minimizes patient anxiety and/or discomfort, and has no memory effect (the patient will never recall any negative emotions) and thereby facilitates the procedure performance by the endoscopist[4]. Current guidelines also support the use of propofol-based sedation as compared with traditional (conventional) sedation with benzodiazepines and/or opioids, thus offering higher patient and endoscopist satisfaction, decreasing procedure-related time, as well as recovery time, without increasing the rate of adverse events[11].

On the other hand, the use of intravenous sedation has increased the demand of qualified medical providers to assess and intervene on behalf of the patient, before serious adverse events occur[6].

Due to limited anesthesiology resources in most countries, non-anesthesiologist administered propofol (NAAP) sedation has started to be used extensively[6]. Registered nurses have responded to this demand through implementation of educational programs, definition of clinical competencies and promulgation of recommended practice guidelines by professional practice organizations and nursing position statements[12].

The aim of this article was to critically review the available evidence on deep sedation procedures necessary for complex therapeutic EUS and/or ERCP procedures, highlighting the controversies that still concern sedation by non-anesthesiologists (either endoscopists or nurses) based on structured multisociety sedation curriculum programs.

METHODS OF SEDATION

Sedation methods differ widely from one country to another, from one health system to another and, of course, they depend on local circumstances and both patient's and endoscopist's preferences that all increased the threshold on quality[2]. On the other hand, the differences between various hospitals/departments, university/community hospitals, as well as public/private endoscopy units, and other systematic differences of practice, might influence a particular endoscopy unit concerning its own sedation practices. Various types and degrees of sedation techniques are thus used during gastrointestinal (GI) endoscopic procedures, although the optimal sedation is tailored according to the individual patient, based on the balance between clinical risks and type of procedure performed[13]. Even nowadays, there is no standard system of sedation, while in the private institutions the choice of sedation depends on endoscopist and/or anesthesiologist preference, as well as the complexity of procedures to be performed.

Recent pharmacological researches and progresses have also contributed to the increased use of conscious sedation for specific patient populations. The introduction of "non-barbituric" intravenous anesthetics (propofol, remifentanil, ketamine, etomidate) with shorter half-lives and having minimum cumulative active metabolites, have increased the safety and efficacy associated with the administration of sedation. Nevertheless, both propofol (alone or in combination with other agents), but also conventional/traditional sedation techniques (using benzodiazepines and/or opioids) can induce deep sedation, even though only moderate sedation is desired[5].

Benzodiazepines

Benzodiazepines, such as midazolam, alprazolam, bromazepam, diazepam, *etc.*, are among the most commonly prescribed drugs[2]. These drugs act as anxiolytics, sedatives, hypnotics, anesthetics, antiepileptic and muscle relaxants. Moderate sedation using midazolam and an opioid is still considered the standard method of sedation, although propofol is increasingly used in many countries, mainly because both the endoscopists', as well as patients' satisfaction are higher than for conventional sedation. Midazolam is currently considered the benzodiazepine of choice because of its shorter duration of action and better pharmacokinetic profile compared with diazepam. The duration of action of midazolam is dependent on the duration of its administration. Mental function returns to normal after approximately 4 h after administration, the drug being very useful for short procedures. One published meta-analysis reported that midazolam provided better patient satisfaction as compared to diazepam, and less frequent memory of procedures[9]. The recovery time can be shortened after midazolam usage by using the benzodiazepine antagonist flumazenil[14].

Opioids

Among the opioids, fentanyl and meperidine/pethidine and are the most popular[2]. Fentanyl is a synthetic narcotic analgesic characterized by a rapid onset and short duration of action. At the level of respiratory system, higher doses can cause respiratory depression, immediately, as well as late. It can induce chest muscle rigidity followed by a difficult or even impossible intubation. Also, the combination of fentanyl and midazolam that is used quite often in some endoscopy departments can produce apnea and cardiac arrest[9]. Pethidine/meperidine is a weak opioid (7-10 times weaker than morphine) which relaxes smooth muscles, produces sedation and mild euphoria. The combination between midazolam and meperidine is safe and effective for GI endoscopy[15]. Ketamine is also a suitable sedative for GI endoscopy[16], although it might stimulate salivary and tracheobronchial secretion, while it sometimes gives a dissociative anesthesia that can produce hallucinations and delirium awakening[17].

Propofol

Propofol is an ultra-short-acting, sedative-hypnotic agent that has multiple potential advantages compared with "traditional sedation" based upon administration of an opioid and benzodiazepine agents for endoscopic procedures[18]. Propofol is a highly soluble phenol derivative, consisting of an *iv* emulsion for injection or infusion (1% concentration, 10 mg/mL) containing also 10% soybean oil, 2.25% glycerol and 1.2% purified egg phosphatide[2]. Propofol has become undoubtedly the induction agent of choice in GI endoscopy, as it is really easy to administer and provides prompt awakening, with fewer side effects[19]. Postprocedure, propofol reduces nausea and vomiting as well as the time required for the ability to walk, as compared with thiopental and methohexital. The pain on injection of propofol may be reduced by injecting it into large veins or by mixing with 20-40 mL of lidocaine anesthetic agents. Co-induction with midazolam reduces the dose of propofol, produce sedation and amnesia without prolonging hospitalization time[20]. Nevertheless, recovery is slower, which for outpatient endoscopy cabinets can be an impediment.

ADVANCED ENDOSCOPY

Compared to standard diagnostic upper or lower GI endoscopy, advanced therapeutic procedures (EUS and/or ERCP) are often longer and complicated, thus requiring higher doses of sedatives for corresponding patient compliance, without recall of the procedure[10].

ERCP

ERCP is a technically demanding, but highly important modality to diagnose and treat pancreaticobiliary disorders. ERCP has progressed from an initial diagnostic technique to an exclusively therapeutic procedure used for the management of common bile duct stones, as well as biliary strictures. Pancreatic stones, strictures or even pseudocysts can be also managed by ERCP in highly specialized tertiary centers[21]. Traditional conscious (moderate) sedation with the combination between a benzodiazepine and an opiate is challenged nowadays by the use of propofol sedation. A Cochrane review on individual studies concluded that patients have a better recovery profile after propofol sedation, as compared to the combination midazolam - meperidine, with no difference in complication rate[22]. The same conclusion has been reached by several meta-analyses that indicated clear advantages for propofol sedation, without increased risk of cardiopulmonary adverse events[18,23]. In order to obtain the desired deep sedation effects, balanced propofol sedation (propofol in combination with midazolam and fentanyl) has been used showing a longer recovery time without any other difference in term of complications[24]. The conclusion was that non-anesthesiologists propofol sedation can also be administered safely by trained, registered sedation nurses, with the same being

valid also in emergency ERCP[25]. Although propofol is nowadays preferred, in high doses it induces a risk of cardiopulmonary complications (bradycardia, hypotension, apnea, hypoxemia, *etc.*), consequently various methods of administration have been designed. Target propofol infusion (TPI) consists of an initial bolus, followed by a rate of constant infusion controlled by a computer, and has been compared to self-administration of propofol through patient controlled sedation (PCS)[26]. The later technique showed a reduced consumption of propofol and a faster recovery, but no significant benefits over TPI.

EUS

EUS is a state-of-the-art method for the assessment of GI pathology, especially for pancreaticobiliary lesions, but also GI tract or lung cancers. Moreover, the procedure allows the performance of EUS-guided fine needle aspiration (FNA) used to obtain a final diagnosis through cytology or histology exams of the obtained samples[27]. While routine diagnostic or staging EUS carries a relatively low risk, it is usually more time consuming and more uncomfortable than a simple diagnostic upper GI tract endoscopy. Likewise, EUS-FNA procedures are more difficult and lengthier, therefore a deeper sedation is necessary. The same thing is valid for therapeutic procedures which start with the initial placement of a needle through EUS-guidance, for, *e.g.,* celiac plexus neurolysis or pancreatic pseudocyst drainage. Other therapeutic procedures performed under EUS-guidance or assistance, like hepaticogastrostomies, choledocoduodenostomies or cholecystogastrostomies, are also performed under deep sedation or general anesthesia, even in high risk patients [American Society of Anesthesiologists (ASA) Ⅲ-Ⅳ][28]. A large prospective study including 500 patients showed that administration of propofol by qualified persons, other than endoscopist, is safe and effective for patients with ASA less than 2, during upper GI EUS[29]. Balanced propofol sedation techniques have been used also during EUS-FNA procedures without any major complications[30]. Likewise, TCI during monitored anesthesia has been proven useful for safe sedation during EUS, without major complications[31].

NAAP

NAAP propofol sedation caused major debates due to limited anesthesiology resources that determined administration of NAAP by trained nurses or endoscopists in selected endoscopy procedures[6]. A comprehensive guideline endorsed by the European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastroenterology and Endoscopy Nurses and Associates established the role of NAAP in clinical endoscopy. Thus, trained registered nurses or endoscopists can safely administer propofol during ongoing endoscopy, with a very low rate of respiratory events requiring endotracheal intubation[32]. The recommendations from the ESGE guidelines are clear, indicating that propofol sedation has a similar rate of adverse events compared to conventional sedation (based on benzodiazepines ± opioids), with a high post-procedural satisfaction for both the patients, but also endoscopists. Moreover, the time for sedation decreases, with a higher quality of the endoscopic examination, while the recovery and discharge time will decrease[6]. Even psychomotor ability after the procedure seems to be improved leading to a possible continuation of daily routine (including driving after recovery in the medical suites)[33]. Because higher category of ASA physical status classification system leads to higher complication rate, an anesthesiologist is usually required on-site or for all patients with ASA category equal to or more than Ⅲ[34].

A dedicated person (usually a trained registered nurse) should be used for propofol administration, based on a clear protocol and adequate monitoring of the patient. An intravenous access should be maintained based on catheter with continuous supplemental oxygen, with careful continuous pulse oximetry and automated non-invasive blood pressure monitoring at 3-5 min intervals[6]. While simple endoscopic procedures can be performed with moderate sedation, complex procedures like EUS and/or ERCP are usually performed with deep sedation[10]. Currently, there is insufficient evidence that balanced propofol sedation with combination of drugs, beside propofol, has more beneficial effects[35,36]. The preferred mode of administration is with intermittent bolus administration or PCS in a minority of patients, if available[37]. Nevertheless, one large study from Germany showed that the combination of propofol and midazolam has a significantly lower sensation of pain, as well as reduced symptoms of dizziness, nausea and vomiting as compared to patients that received only propofol mono-sedation[38]. There is a lot of data to support the usage of patient-selected music during the procedures, which can decrease the dosage of propofol administered[39].

Both endoscopists and nurses should undergo a specific training program, which includes theoretical and practical parts on both basic life support and advanced cardiac life support[6]. A structured training program followed by an implementation phase documented a low incidence of adverse events, while the independent risk factors were: type of intervention and level of staff experience[40]. Thus, the patients had short duration hypoxia (4.7%), needed suction (2.4%) or bag-mask ventilation (0.9%), with only 0.3% of procedures that had to be discontinued[12]. Anesthetic assistance was necessary for only 0.4% of patients. A recent meta-analysis compared pooled results for NAAP and AAP studies, and showed the same rates of hypoxia (oxygen saturation less than 90%) and airway intervention in both arms[41]. Respiratory complications after endoscopist directed sedation were also shown to be important, with coughing or vomiting resulting in an increased risk of respiratory infections, thus requiring antibiotic treatment[42]. However, pooled patient satisfaction and

pooled endoscopist satisfaction rate, as well as the dose of propofol administered were lower in the NAAP group, as compared to the AAP group. In order to generalize this approach there are important legal issues that may arise if sedation complications occur during NAAP procedures, while these legal implications usually have country or even hospital specificities and particularities.

Nevertheless, cautious opinions on NAAP still exist, with more data required before transition of procedures from major hospitals to community practice[43,44]. Retraction of endorsement for the NAAP guideline by the European Society of Anesthesiology (ESA) came in line with the concerns of using NAAP by trained nurses or endoscopists, mainly in view with the possible complications and their proper management[45]. Our own approach for the patients with advanced interventional endoscopic procedures (EUS and/or ERCP) consists of exclusive use of propofol sedation in the presence of an anesthesiologist, as required by the current national and local legislation practices. Based on a total number of 192 patients examined during one year in the Research Center of Gastroenterology and Hepatology Craiova, Romania, we have encountered no severe adverse events, with drowsiness, nausea, vomiting, dizziness, headache, coughing or shivers being the most frequent, while less than 2% of patients had mild braycardia.

CONCLUSION

In conclusion, several large prospective studies and meta-analyses demonstrated that propofol provides significant advantages over benzodiazepine and opioid agents for deep patient sedation during advanced endoscopic procedures like ERCP and/or EUS: propofol was more effective and safer than the combination of midazolam and meperidine for achieving and maintaining an adequate level of sedation during endoscopic procedures, with better titration of the level of sedation and shorter recovery times. The trend of an increased usage of propofol and generalization of NAAP sedation in both hospital and private practice settings will certainly increase in the years to come.

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Endoscopic papillectomy: The limits of the indication, technique and results

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Abstract

In the majority of cases, duodenal papillary tumors are adenomas or adenocarcinomas, but the endoscopy biopsy shows low accuracy to make the correct differentiation. Endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography are important tools for the diagnosis, staging and management of ampullary lesions. Although the endoscopic papillectomy (EP) represent higher risk endoscopic interventions, it has successfully replaced surgical treatment for benign or malignant papillary tumors. The authors review the epidemiology and discuss the current evidence for the use of endoscopic procedures for resection, the selection of the patient and the preventive maneuvers that can minimize the probability of persistent or recurrent lesions and to avoid complications after the procedure. The accurate staging of ampullary tumors is important for selecting patients to EP or surgical treatment. Compared to surgery, EP is associated with lower morbidity and mortality, and seems to be a preferable modality of treatment for small benign ampullary tumors with no intraductal extension. The EP procedure, when performed by an experienced endoscopist, leads to successful eradication in up to 85% of patients with ampullary adenomas. EP is a safe and effective therapy and should be established as the first-line therapy for ampullary adenomas.

Key words: Epidemiology; Ampullary tumors; Endoscopic resection; Endoscopic ultrasound; Staging; Endoscopic papillectomy; Surgical ampullectomy

Core tip: Although the endoscopic papillectomy (EP) represent higher risk endoscopic interventions, it has successfully replaced surgical treatment for benign or malignant papillary tumors. The accurate staging of ampullary tumors is important for selecting patients to EP or surgical treatment. Compared to surgery, EP is associated with lower morbidity and mortality, and seems to be a preferable modality of treatment for small benign ampullary tumors with no intraductal extension.

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INTRODUCTION

Ampullomas represent an uncommon group of gastrointestinal malignancies. Advances in endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) have significantly impacted the clinical approach to patients with suspected premalignant or malignant lesions of the duodenal papilla[1]. The present review leads us to the discussion of numerous current issues related to the epidemiology of ampullary tumors, the role of the endoscopy biopsy, EUS, and ERCP, as well as indications, optimal technique, complications and outcomes in patients with benign or malignant tumor.

The term "endoscopic papillectomy" refers to the duodenal mucosa and submucosa resection, including all the anatomic attachments of the ampulla of Vater, and the tissues around the bile and pancreatic ducts. In turn, the term ampullectomy should be used to define this surgical procedure, which consists in the resection of the ampulla of Vater, through a duodenotomy including the cephalic pancreatic tissue resection, followed by reinsertion of common bile duct (CBD) and main pancreatic duct (MPD) in the duodenal wall[2].

The endoscopic papillectomy (EP) was first reported as a route of access to the biliary tract[3]. Years later, it was used as a treatment modality for two cases of duodenal papilla cancer[4], and today it is accepted as a viable alternative therapy to surgery in patients with sporadic adenoma of the major or minor duodenal papilla due to its high success rate and low recurrence[2].

EPIDEMIOLOGY

Tumors of the duodenal papilla may be classified as benign, premalignant, and malignant[5]. The annual incidence of ampullary lesions in the United States is 3000, with reported prevalence rates of 0.04%-0.12% in autopsy series[6,7]. Ampullary adenomas may occur sporadically or in the setting of hereditary polyposis syndromes, including familial adenomatous polyposis (FAP) with adenomatous polyposis coli gene mutations. In patients with FAP, ampullary adenomas occur in up to 80% of individuals during their lifetime and progress to malignancy in 4%[8]. Ampullary adenomas are likely to follow an adenoma-to-carcinoma sequence similar to colorectal adenocarcinoma[9]. These lesions are considered premalignant, with an incidence of transformation to carcinoma ranging from 25%-85% for sporadic adenomas. As with all neoplasms, tumor stage dictates the appropriate therapy[10].

DETERMINANT FACTORS IN THE RESECTION OF NON-INVASIVE NEOPLASMS OF THE VATER´S AMPULLA

It seems that the knowledge of the histological and immunohistochemical characteristics is useful for precisely indicate an EP. In this context, the study of such characteristics is useful for selecting the appropriate surgical or endoscopic procedure. To corroborate this fact, japanese authors reported the results of this analysis in 56 noninvasive ampullary tumors. They demonstrated that the intestinal type cancer of intra-ampullary location shows lower CK20 expression than tumors of the periampullary location, and besides that, the intestinal type tumors without CDX2 expression, that included extended and intra-ampullary location types, tend to show a compromised vertical margin after EP. This suggests that periampullary tumors, intestinal histology and high CK20-positive rate can be regarded as good indications for the EP procedure. On the other hand, this study shows that tumors that are either pancreatobiliary or intestinal type without CDX2 expression have a higher chance of involvement of the common channel inside duodenal papilla, CBD and MPD[11].

INDICATIONS

The indications for EP are based on features that can predict a complete tumor removal, while minimizing complications related to the procedure[1]. Currently the indications are not fully established and are far from a consensus.

The main criteria for EP include the lesion size (up to 5 cm), no evidence of intraductal tumor growth or malignancy in endoscopic findings, such as ulceration, spontaneous bleeding and friability[1,12-18]. However, the indications for EP are expanding[10,19-24]. For example, the endoscopic piecemeal resection technique, is used to removing tumors that can't be removed "*en bloc*", and provided increasing resections, when properly performed[25]. The clinical results of this technique are very good, but the chance of recurrence is higher.

The ductal invasion in an extension less than 1 cm does not seem to be an absolute contraindication for EP, because the tumor can be exposed by endoscopic maneuvers, such as the use of an extractor balloon into the lumen, and thus it can be completely resected with a polypectomy snare[26-28].

The cancer arising within an adenoma without

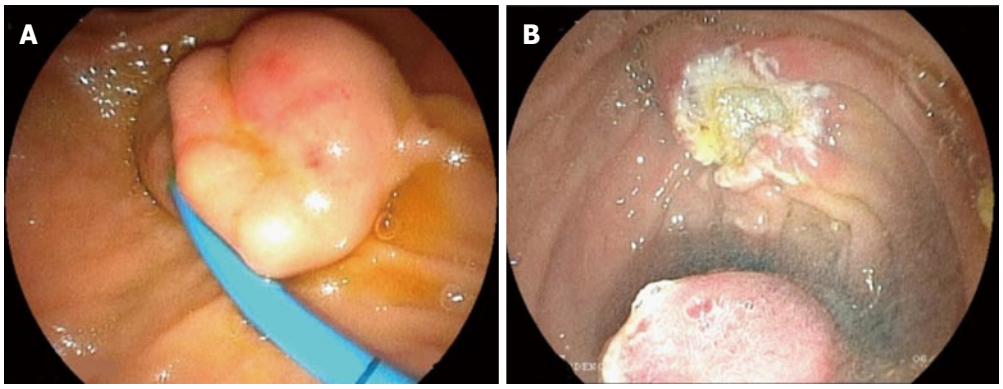

Figure 1 Endoscopic view of neuroendocrine tumor of the papilla with Fujinon intelligent chromo endoscopy. A: This picture show the depression in the center of the lesion; B: The picture shows the aspect of the papillary region after the "*en bloc*" resection.

invasion of duodenal muscularis propria and pancreas, or CBD and MPD, are liable to resection by EP[29-33]. However, in some situations, EP can be used as a macrobiopsy procedure for a simple local tumoral staging, if the resection margins are compromised[34].

PREOPERATIVE ENDOSCOPIC EVALUATION

The most common preoperative concern is to define if a papillary tumor is benign or malignant. The endoscopic aspect alone cannot always distinguish adenomas from carcinomas and even from adenomatous polyps, carcinoids, gangliocytic paraganglioma, and other tumors that may occur in this region[35,36]. Some endoscopic aspects like ulceration, friability, spontaneous bleeding are usually relate to malignant lesions. The use of endoscopic tools such as NBI, FICE and magnifying endoscopy are useful to select patients for EP (Figure 1)[37].

A definitive histological diagnosis is a basic prerequisite for adequate management of these patients, but we must remember that endoscopic biopsy of the duodenal papilla misses 30% of malignant tumors[38]. Moreover, the coexistence of carcinoma and adenoma cannot be excluded by endoscopic biopsy. Some authors advocate deep biopsy after sphincterotomy, to increase diagnostic accuracy of endoscopic biopsy[39]. We do not recommend this procedure, because endoscopic sphincterotomy eliminates the possibility of endoscopic *en bloc* resection of ampullary tumors, impeding a possible curative resection.

Favoring our impression, a prospective study showed that endoscopic biopsy is not reliable for preoperative diagnosis of tumors of the duodenal papilla (sensitivity of 21% before and 37% after sphincterotomy)[40]. Thus, in some cases, EP can be recommended as a technique for preoperative diagnosis because a high false negative rate of endoscopic biopsy[34].

PREOPERATIVE STAGING

EUS is the imaging modality of choice for local staging (T). EUS is superior to helical computed tomography (CT) for preoperative evaluation of tumor size, detection of regional lymph node metastasis, vascular invasion in patients with periampullary neoplasms and also to detect tumor infiltration of biliary and pancreatic ducts (Figure 2A)[40].

Many experts believe that EUS is not useful in lesions less than 1 cm in diameter, with no suspicious signs of malignancy (ulceration, induration, bleeding and/or biopsies with high-grade dysplasia or carcinoma)[12]. Our experience shows that, when EUS is performed for staging ampullary tumor prior to EP, it allows deciding for EP, because it shows the relationship between CBD and MPD, as well their diameter. EUS allows the verification of the relationship of the borders of the tumor in the duodenal wall, CBD and MPD, regardless of the size of the tumor. However, prospective studies are needed to evaluate the accuracy of these findings.

The use of intraductal ultrasound (IDUS), with a 20 MHz probe can be more accurate in visualizing mucosa layers compared to conventional EUS[41]. According to literature, EUS and IDUS accuracy before surgical resection or diagnostic EP was 97% and 94% for pTis, 73% and 73% for pT1, 50% and 50% for pT2 and 50% and 100% for pT3-4 respectively. The overall EUS and IDUS accuracy was 85% and 80% for T stage[42]. In our experience with this type of technology, the interpretation is more difficult, especially when the mini-probe is placed within the biliary or pancreatic ducts. If this is not done, the sensitivity is lower when compared with the conventional EUS[41].

From a technical standpoint, EUS and IDUS are able to detect, with high precision, tumoral infiltration of the common bile duct and main pancreatic duct (Figure 2B). Despite ERCP can detect CBD invasion, we believe that it should only be performed after EUS, if EP is indicated. EUS and IDUS can provide high precision diagnostic information for staging ampullary tumors, and are useful in identifying lesions selected for EP. However, these tools have limitations, because the occurrence of super and understating and the difficulty in assessing focal infiltration are relevant. The improvement of endoscopic procedures is necessary for an accurate assessment of

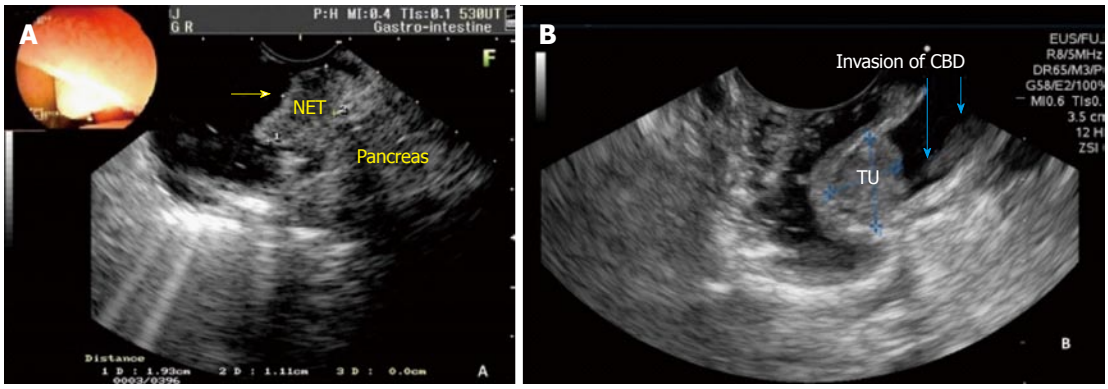

Figure 2 Endoscopic ultrasound staging of the duodenal papilla. A: Patient of the Figure 1. Endoscopic ultrasound staging shows the regular and hypoechoic nodule (1.93 cm) in the papilla without infiltration of the duodenal wall and pancreatic gland. The staging was uT1N0Mx; B: This picture shows the papillary tumor with 1.72 cm with invasion of the common bile duct wall (blue arrows). NET: Neuroendocrine tumor; TU: Tumor; CBD: Common bile duct.

ampullary tumors[43].

From a practical standpoint, ERCP should be performed before EP, if EUS is not available or inconclusive as to ductal involvement. Although intraductal invasion is usually an indication for surgery, it has been demonstrated that, when tumoral infiltration reaches ± 1 cm into CBD and MPD, tumor is amenable to endoscopic resection[26,27,44].

Positron computerized tomography (PET/CT) and magnetic resonance imaging (MRI) are highly sensitive for detection of distant metastases. MRI and CT was superior to EUS for assessment of nodal involvement[45].

ENDOSCOPIC PAPILLECTOMY TECHNIQUE

EP is performed after EUS staging confirming a less than 5.0 cm tumor confined to mucosa and/or submucosal (uT1), with intraductal tumoral infiltration less than 1 cm. It can be performed using the EUS device itself or a duodenoscope. With the duodenoscope rectified, a preferable monofilament polypectomy snare is used for grasping the tumor, always in the craniocaudal direction, *i.e.,* the snare tip is positioned on cranial tumor apex.

The snare is widely opened, duodenoscope is pushed in a craniocaudal direction, and tumor is grasped for en bloc resection (Figure 3). The papillary tumor is grasped at its base, always respecting a limit, up to 0.5 cm below the lesion border identified by FICE. Thereafter a constant tension is applied to the ring handle while using an electrocautery until tumor en bloc resection is completed. There are no specific equipment or a standard technique for EP.

There is also no guidance on the potency and mode of electronic current (cutting or coagulation). The authors prefer to use only cutting current (40 to 50 J) and the endocutter. Some authors recommend performing submucosal injection, ablative therapy after EP, and placement of a prophylactic pancreatic stent. The use of antibiotic prophylaxis before EP is not established[46]. The authors do not advocate its use.

Some experts use injection of contrast with methylene blue into MPD to identify the pancreatic orifice after tumor resection. This is not our practice. After complete removal of the lesion, which sometimes takes a few minutes, depending on its size and extension, a whitish rough area can be seen, which in some cases reveals the muscular layer of duodenal wall, as well two holes (biliary and pancreatic ducts).

Efforts should be exhaustive and mandatory to recover all resected tissue in all patients, for histopathological evaluation. Then CBD and MPD catheterization is performed, with contrast injection, to ensure easy recanalization after ampullary resection.

When *en bloc* resection is not feasible, a piecemeal resection is recommended. However, it should be noted that the en bloc resection is essential for the treatment of preneoplastic and/or malignant lesions, because this allows accurate histopathologic evaluation after tumoral resection[26].

The submucosal injection of diluted epinephrine is suggested as a means to lift the tumor from the wall, which at least theoretically may reduce the risk of bleeding. However, it is uncertain and questionable whether injection of adrenaline reduces the risk of bleeding and/or perforation[20,27,47]. The authors dismiss the submucosal injection of pharmacological agents, due to distortion of tumoral anatomy and its periphery, hindering an adequate grasping by the polypectomy snare. Moreover, a perforation following tumor resection may occur, due to a short distance between duodenal wall and pancreas, as seen by EUS.

If residual tumor tissue remains after resection, it should be destroyed! The use of coagulation with argon gas is the most widely used modality; it is safe because it is a non-contact technique, acting in tumor surface[12,46-48].

The use of stent in MPD, in order to reduce the risk of acute pancreatitis (AP) associated to EP, seems to be a consensus because it minimizes the risk of MPD stenosis, allowing the use of safer coagulation therapies. Anyway we must emphasize that this theory is unproven. Others advocate pancreatic stent placement only if MPD drainage is not sufficient after EP[49-52]. The only

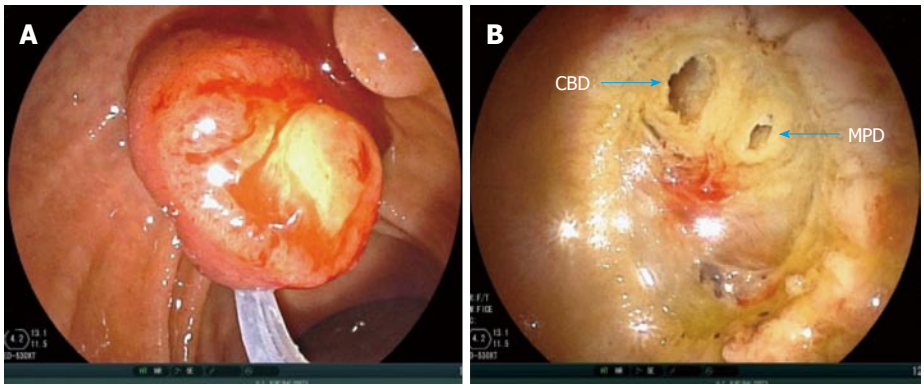

Figure 3 Endoscopic papillectomy immediately after endoscopic ultrasound for staging. A: *En bloc* resection of the tumor, after the snare is widely opened, duodenoscope is pushed in a craniocaudal direction; B: The endoscopic view of the common bile duct and main pancreatic duct (blue arrows) after a complete *en bloc* resection of the papillary tumor. CBD: Common bile duct; MPD: Main pancreatic duct.

Table 1 Result after endoscopic papilectomy

Ref.	Patients	Success/(%)	Complications/(%)	Mortality/(%)	Recidive/(%)	Surgery/(%)
Binmoeller *et al*[13]	25	23/92	5/20	0/0	6/24	3/12
Vogt *et al*[64]	18	12/67	4/22	0/0	6/33	NA
Zádorová *et al*[18]	16	13/81	4/25	0/0	3/19	1/6.2
Desilets *et al*[47]	13	12/92	1/7.7	0/0	0/0	1/7.7
Norton *et al*[48]	26	12/46	5/19	0/0	2/7.7	1/3.8
Bohnacker *et al*[20]	87	74/85	29/33	0/0	15/17	17/19
Catalano *et al*[14]	103	83/80	10/9.7	0/0	10/9.7	16/15.5
Cheng *et al*[15]	55	39/71	12/22	0/0	9/16.3	4/7.2
Han *et al*[21]	33	20/60.6	11/33.3	0/0	2/6	2/6
Ismail *et al*[65]	61	56/92	15/24.5	0/0	12/19.6	9/14.7
Napoleon *et al*[66]	93	84/90	39/42	1/1	5/5.3	NA
Ridtitid *et al*[67]	182	134/73.6	34/18.6	0/0	16/8.7	NA
Ardengh *et al*[58]	41	38/92	11/26.8	0/0	3/7.3	4/9.7

NA: Not available.

prospective, randomized, controlled study, to evaluate the role of prophylactic stent in MPD, to reduce AP after EP, showed a statistically significant decrease in the rate of AP after stent procedure[53].

Otherwise, the adequate MPD diameter and length for stenting are uncertain. In other work, for example, the authors suggests that routine use of prophylactic pancreatic stent in all patients is unnecessary and efforts should be directed to know which groups of patients actually benefit from its insertion[54]. Most pancreatic stents migrate spontaneously from MPD within 2 wk after insertion. Abdominal X-ray after 2 wk can confirm this finding. A stent, which remains "*in situ*" for more than 2 wk, should be removed endoscopically. The placement of a prophylactic plastic biliary stent, to reduce the risk of cholangitis, has not been widely performed and cannot be uniformly recommended at the present moment, unless there is concern about inadequate biliary drainage after EP.

COMPLICATIONS

The EP is a "high risk" procedure, due to complications inherent to the method. They can be classified as early: AP, bleeding, perforation and cholangitis or late: papillary stenosis. The overall complication rate reported by major centers of tertiary care varies between 8% and 35%, and the most common complications are AP (5%-15%) and bleeding (2%-16%)[10,25,48,55]. Most episodes of bleeding can be controlled immediately by conservative treatment and endoscopic hemostasis and most episodes of AP are mild and resolve with conservative treatment only. The rate of pancreatic and/or biliary ductal stenosis varies between 0%-8%, and can be treated by sphincterotomy, stent placement, and balloon dilation.

The use of pancreatic stent can prevent an episode of AP and papillary stenosis[49-54]. Another interesting fact reported by a recent randomized study showed that prophylactic rectal indomethacin significantly reduced the incidence and severity of AP post-ERCP, providing an additional benefit in pancreatic temporary stenting[56]. The mortality after-EP is rare, but it has been reported to be 0.4% (range 0% to 7%)[57].

RESULTS

The results of the endoscopic treatment of ampullary

tumors reported in the literature are shown in Table 1. The EP results are based on retrospective case series studies with heterogeneous groups. As there is no consensus on the definition of "success" after EP, it is difficult to compare the results of the reported studies. Conventionally, "success" can be defined as a complete tumor resection (as the proven absence of visible residual adenoma by endoscopy and histological analysis during a 3-6 mo follow up). In the literature the rate of the success varies between 46% to 92% in the different series. The complication rate after EP varies between 8% to 42% and the major problems are acute pancreatitis, perforation and bleeding. The most important complication after EP is the acute pancreatitis that could be diminished with the insertion of the plastic pancreatic stent. This is a controversial point, because in our experience if you have a dilated main pancreatic duct the use of the PPS is unnecessary[58].

Recurrence of benign lesions occur in up to 33% of patients depending on the tumor size, final histology, presence of intraductal tumor, coexistence of FAP and endoscopist experience[21,57,59-64]. If you use the endoscopic ultrasound before the EP you could find with precision the presence of intraductal tumor. In this case there are contraindication to submitted the patient to EP. Recurrent lesions are usually benign and most can be removed endoscopically.

CONCLUSION

EP is a safe and effective therapy and should be established as the first-line therapy for ampullary adenomas. The accurate staging of ampullary tumors is important for selecting patients to EP or surgical treatment. Compared to surgery, EP is associated with lower morbidity and mortality, and seems to be a preferable modality of treatment for small benign ampullary tumors with no intraductal extension. The EP procedure, when performed by an experienced endoscopist, leads to successful eradication in up to 85% of patients with ampullary adenomas.

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ORIGINAL ARTICLE

Retrospective Study

Gastric polyps: Association with *Helicobacter pylori* status and the pathology of the surrounding mucosa, a cross sectional study

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Abstract

AIM: To assess the endoscopic characteristics of gastric polyps and their association with *Helicobacter pylori* (*H. pylori*) status in a predominantly Hispanic population.

METHODS: We conducted a retrospective study of all esophagogastroduodenoscopies performed at our institution. Demographic, endoscopic and histopathological data were reviewed. Categorization of patients into Hispanic and Non-Hispanic was based on self-identification. Patients without resection/biopsy were not included in the analysis. Identification of polyps type was based on histological examination. One way analysis of variance was used to compare continuous

variables among different polyp types and Fisher's exact test was used compare categorical variables among polyp types. Unadjusted and adjusted comparisons of demographic and clinical characteristics were performed according to the *H. pylori* status and polyp type using logistic regressions.

RESULTS: Of 7090 patients who had upper endoscopy, 335 patients had gastric polyps (4.7%). Resection or biopsy of gastric polyps was performed in 296 patients (88.4%) with a total of 442 polyps removed or biopsied. Of 296 patients, 87 (29%) had hyperplastic polyps, 82 (28%) had fundic gland polyps and 5 (1.7%) had adenomatous polyps. Hyperplastic polyps were significantly associated with positive *H. pylori* status compared with fundic gland polyps (OR = 4.621; 95%CI: 1.92-11.13, *P* = 0.001). Hyperplastic polyps were also found to be significantly associated with portal hypertensive gastropathy compared with fundic gland polyps (OR = 6.903; 95%CI: 1.41-33.93, *P* = 0.0174). Out of 296 patients, 30 (10.1%) had a follow-up endoscopy with a mean duration of 26 ± 16.3 mo. Interval development of cancer was not noted in any of the patients during follow up period.

CONCLUSION: Gastric hyperplastic polyps were significantly associated with positive *H. pylori* status and portal hypertensive gastropathy as compared with fundic gland polyps.

Key words: Gastric polyps; Fundic gland polyp; Hyperplastic polyp; Adenomatous polyps; Chronic gastritis; *Helicobacter pylori*

Core tip: In a predominantly Hispanic population, the most common gastric polyps were hyperplastic and fundic gland polyps (more than half of gastric polyps). Gastric hyperplastic polyps were significantly associated with positive *Helicobacter pylori* status and portal hypertensive gastropathy as compared with fundic gland polyps. Hyperplastic polyps and fundic gland polyps were more prevalent in chronic gastritis, while adenomatous polyps were associated with intestinal metaplasia.

Elhanafi S, Saadi M, Lou W, Mallawaarachchi I, Dwivedi A, Zuckerman M, Othman MO. Gastric polyps: Association with *Helicobacter pylori* status and the pathology of the surrounding mucosa, a cross sectional study. *World J Gastrointest Endosc* 2015; 7(10): 995-1002 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i10/995.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i10.995

INTRODUCTION

Gastric polyps can be defined as abnormal luminal growths projecting above the plane of the mucosal surface. The incidence of gastric polyps has been estimated to be between 2% and 6%. The incidence of gastric polyps is gradually increasing due to expanded indications and widespread use of endoscopic examinations[1-4]. Gastric polyps are usually asymptomatic and discovered incidentally during endoscopic examination, but on rare occasions they can present with nonspecific symptoms such as abdominal pain, gastrointestinal bleeding, anemia, or symptoms of gastric outlet obstruction[5-8]. Determination of gastric polyp type is important as the risk for malignant transformation depends on the histopathological nature of the polyp[9-12]. The frequency of different types of gastric polyps varies widely depending on the population studied. It has been reported that hyperplastic polyps are relatively more frequent than fundic gland polyps in regions where *Helicobacter pylori* (*H. pylori*) infection is common[1,13]. A higher prevalence of *H. pylori* infection has been documented in Hispanics living in United States regions bordering Mexico compared with non-border areas[14,15]. There is a paucity of published data from the United States regarding the nature and various characteristics of gastric polyps, especially in Hispanics and other immigrant groups. The aim of this study is to assess the prevalence of gastric polyps and their endoscopic and histological characteristics in a predominantly Hispanic population on the United States-Mexico border.

MATERIALS AND METHODS

Study design

After receiving approval from Texas Tech University Institutional Review Board, we retrospectively reviewed all esophagogastroduodenoscopies (EGDs) performed at the University Medical Center, El Paso, TX for all indications. The review period of the study was from November 1, 2007 to July 30, 2013. The electronic database system (ProVation®, Minneapolis, MN) was used to identify the patient's demographic data, the indication for the procedure and gastric polyp characteristics. Categorization of patients into Hispanic and Non-Hispanic was based on self-identification. Patients without resection/biopsy were not included in the analysis. Identification of polyps type was based on histological examination.

Statistical analysis

Quantitative variables were described using the mean ± SD, whereas categorical variables were described using the frequency and proportion. One way analysis of variance was used to compare continuous variables among different polyp types and Fisher's exact test was used compare categorical variables among polyp types. Unadjusted and adjusted comparisons of demographic and clinical characteristics were performed according to the *H. pylori* status and polyp type using logistic regressions. The logistic regression analysis for *H. pylori* status was conducted after removing *H. pylori*

Table 1 Patient level summary of polyp histology

Polyp's type	Total patients (n = 296)	Percentage
Hyperplastic polyp	87	29.39
Fundic gland polyp	82	27.7
Chronic gastritis	41	13.85
Mixed	13	4.39
Intestinal metaplasia	12	4.05
Foveolar hyperplasia	10	3.38
Adenoma	5	1.69
Carcinoid tumor	4	1.35
Granulation tissue polyp	4	1.35
Adenocarcinoma	2	0.68
Gastric xanthelasma	2	0.68
Hamartomatous polyp	2	0.68
Lymphoid follicles	2	0.68
Submucosal Brunner glands	2	0.68
Lipoma	1	0.34
Normal	27	9.12

not tested patients. The logistic regression was used to find out factors associated with hyperplastic polyp type as compared with fundic polyp type after removing patients with adenoma, mixed polyps, and others. The results of logistic regression analysis were reported using odds ratio (OR), 95%CI and *P* values. Stepwise selection method using probability to enter = 0.10 and probability to stay = 0.05 was used to obtain the final model. All the statistical analyses were carried out using statistical analysis software (SAS) 9.3. Results were considered significant at the 5% level of significance. The statistical methods of this study were reviewed by Dr. Alok Dwivedi from the department of Biostatistics at Texas Tech University HSC at El Paso.

RESULTS

Demographic and clinical characteristics

A total of 7090 patients underwent 9450 EGD procedures. Of these, 335 patients had gastric polyps (4.7%). Resection or biopsy of 442 gastric polyps was done in 296 patients (88.4%). 39 patients did not undergo resection or biopsy of their gastric polyps because of the high risk of bleeding or obvious endoscopic diagnosis of fundic gland polyps (FGPs). The mean age of the patients was 58 years (SD: ± 12 years). The majority of the patients were females (74%) and most were Hispanics (85%). Portal hypertensive gastropathy was seen in 20 patients (7%).

Endoscopic and histopathological features

Polyps' histology: Of 296 patients, 87 (29%) patients had hyperplastic polyps and 82 (28%) patients had fundic gland polyps. There were 5 (1.7%) patients with adenomatous polyps while 13 (4.4%) patients had mixed types of polyps. Histology results of the remaining polyps revealed chronic gastritis in 41 patients (14%), intestinal metaplasia in 12 patients (4.1%), faveolar hyperplasia in 10 patients (3.4%), carcinoid tumor in 4 patients (1.4%) and granulation tissue polyps in 4 patients (1.4%). Adenocarcinoma, gastric xanthelasma, hamartomatous polyps, lymphoid follicles and submucosal brunner glands were each found in 2 patients (0.68%). There was one patient with lipoma. The histology of resected or biopsied polyp was normal in 27 patients (9.1%).

Pathology of the surrounding mucosa: Out of 296 patients, 266 (89.8%) patients had biopsies of the surrounding mucosa (Table 1).

Of these, 190 (64%) patients had chronic gastritis while 25 (8%) patients had intestinal metaplasia. Thirty (10%) patients were not biopsied. In regards to *H. pylori status, H. pylori* were positive in 71 (24%) patients, and negative in 211 (71%) patients, while 14 patients were not tested.

Clinical characteristics of gastric polyps: Table 2 shows the distribution of patient and clinical characteristics according to five categories (Adenoma, Hyperplastic, Fundic gland, Mixed and other) of polyps. The gender and ethnicity distributions were not found to be significantly different among different polyp types. The distribution of age, pathology of surrounding gastric mucosa, and *H. pylori* status were found to be associated with different polyp types. Adenomatous polyps were more common in advanced age ($P < 0.0013$). Fundic, hyperplastic and mixed polyps were more frequent in chronic gastritis while adenomatous polyps were more common (60%) in intestinal metaplasia ($P < 0.001$). Thirty-one percent of the patients with hyperplastic polyps tested positive for *H. pylori* status while 9.8% of the patients with fundic gland polyps tested positive for *H. pylori.* Portal hypertensive gastropathy was seen in 11.5% of patients with hyperplastic polyps compared to 2.4% of patients with fundic gland polyps.

Associations of *H. pylori* status and gastric pathology: The prevalence of hyperplastic polyps was 34% in the *H. pylori* positive group while the prevalence of fundic polyps was 10% in the *H. pylori* positive group. Table 3 shows the unadjusted and adjusted associations of cofactors with *H. pylori* status. Only the polyp type and the pathology of surrounding gastric mucosa were associated with *H. pylori* in unadjusted and adjusted models. Hyperplastic polyps have a 4.6 times higher odds of having a positive *H. pylori* status compared to fundic gland polyps (OR = 4.621; 95%CI: 1.92-11.13, $P = 0.001$).

Cofactors association of hyperlastic and fundic gland polyps: Table 4 shows the unadjusted and adjusted associations of cofactors with hyperplastic polyps as compared with fundic polyps. In the unadjusted analysis, age, *H. pylori* status and portal hypertension were found to be associated with hyperplastic polyps. Per unit increase in age increased the odds of hyperplastic polyp type by 3% as compared

Table 2 Distribution of patient and clinical characteristics according to different polyp types *n* (%)

Cofactor	Adenoma *n* = 5	Fundic *n* = 82	Hyperplastic *n* = 87	Mixed *n* = 13	Other *n* = 109	*P* value
Age (yr), mean ± SD	75.4 (3.3)	54.7 (13.0)	58.4 (10.8)	62.2 (14.0)	57.7 (11.9)	0.0013
Gender						0.2086
Female	5 (100.0)	67 (81.71)	64 (73.56)	9 (69.23)	75 (68.81)	
Male	0 (0.00)	15 (18.29)	23 (26.44)	4 (30.77)	34 (31.19)	
Ethnicity						0.7427
Hispanic	5 (100.0)	66 (80.49)	77 (88.51)	11 (84.62)	93 (85.32)	
Non-Hispanic White	0 (0.00)	5 (6.10)	4 (4.60)	0 (0.00)	8 (7.34)	
Other	0 (0.00)	11 (13.41)	6 (6.90)	2 (15.38)	8 (7.34)	
Pathology of surrounding gastric						< 0.0001[1]
Chronic gastritis	0 (0.00)	51 (62.20)	52 (59.77)	9 (69.23)	78 (41.05)	
Intestinal metaplasia	3 (60.00)	1 (1.22)	6 (6.90)	1 (7.69)	14 (56.00)	
Other	0 (0.00)	22 (26.83)	15 (17.24)	2 (15.38)	5 (16.67)	
Not biopsied	2 (40.00)	8 (9.76)	14 (16.09)	1 (7.69)	12 (23.53)	
Helicobacter pylori status						0.0006[1]
Negative	4 (80.00)	70 (85.37)	52 (59.77)	11 (84.62)	74 (35.07)	
Positive	0 (0.00)	8 (9.76)	27 (31.03)	2 (15.38)	34 (47.89)	
Not tested	1 (20.00)	4 (4.88)	8 (9.20)	0 (0.00)	1 (7.14)	
Portal hypertensive gastropathy						0.1821
No	5 (100.0)	80 (97.56)	77 (88.51)	12 (92.31)	102 (93.58)	
Yes	0 (0.00)	2 (2.44)	10 (11.49)	1 (7.69)	7 (6.42)	

[1]*P* value was obtained using χ^2 test.

Table 3 Unadjusted and adjusted associations of cofactors with *Helicobacter pylori* positive status (*n* = 262)

Cofactor	Unadjusted OR (95%CI), *P* value	Adjusted OR (95%CI), *P* value
Age (yr)	1.011 (0.988-1.034), 0.3686	
Polyp type		
Fundic (referent)	1	1
Hyperplastic	4.621 (1.918-11.133), 0.0006	4.621 (1.861-11.479), 0.0010
Other	3.469 (1.509-7.976), 0.0034	2.952 (1.250-6.972), 0.0136
Gender		
Female (referent)	1	
Male	0.891 (0.460-1.726), 0.7321	
Ethnicity		
Hispanic (referent)	1	
Non-hispanic White	0.205 (0.026-1.605), 0.1311	
Other	0.409 (0.117-1.435), 0.1629	
Pathology of surrounding gastric		
Chronic gastritis (referent)	1	1
Intestinal metaplasia	0.996 (0.407-2.437), 0.9931	0.827 (0.331-2.065), 0.6848
Other	0.088 (0.021-0.375), 0.0010	0.090 (0.021-0.390), 0.0013
Portal hypertension		
No (referent)	1	
Yes	0.569 (0.159-2.044), 0.3877	

Table 4 Unadjusted and adjusted associations of cofactors with hyperplastic polyps as compared with fundic polyps (*n* = 143)

Cofactor	Unadjusted OR (95%CI), *P* value	Adjusted OR (95%CI), *P* value
Age (yr)	1.031 (1.001-1.062), 0.0419	
H. pylori status		
Negative (referent)	1	1
Positive	4.622 (1.918-11.137), 0.0006	5.285 (2.166-12.892), 0.0003
Gender		
Female (referent)	1	
Male	1.804 (0.756-4.303), 0.1837	
Ethnicity		
Hispanic (referent)	1	
Non-Hispanic White	0.469 (0.083-2.655), 0.3922	
Other	0. 536 (0.150-1.923), 0.3390	
Pathology of surrounding gastric		
Chronic gastritis (referent)	1	
Intestinal metaplasia	5.997 (0.697-51.614), 0.1029	
Other	0.714 (0.331-1.542), 0.3917	
Portal hypertension		
No (referent)	1	1
Yes	5.080 (1.057-24.414), 0.0424	6.903, 0.0174

with fundic gland polyp. After adjusting for all other factors, *H. pylori* status and portal hypertensive gastropathy were the only remained significant factors in the final adjusted model. Positive *H. pylori* status has 5.3 times higher odds to have hyperplastic polyps compared with negative *H. pylori* status (OR = 5.285; 95%CI: 2.17-12.89, *P* = 0.0003) after adjusting for portal hypertensive gastropathy. Patients with portal hypertensive gastropathy are 6.4 times more likely to have hyperplastic polyps after adjusting for *H. pylori*

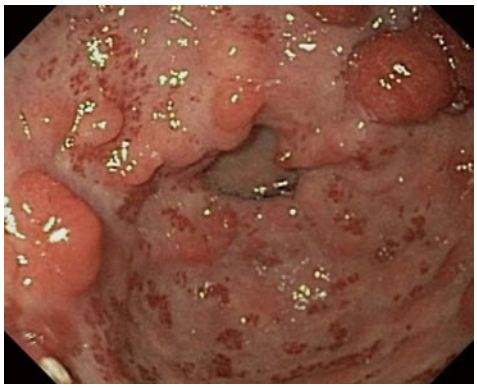

Figure 1 Multiple hyperplastic polyps in the setting of portal hypertensive gastropathy.

status (OR = 6.903; 95%CI: 1.40-33.93, *P* = 0.0174).

Long term follow-up

Out of 296 patients, 30 (10.1%) had a follow-up endoscopy with a mean duration of 26 ± 16.3 mo. Out of these 30 patients, 11 (36.6%) had hyperplastic polyps, 5 had chronic gastritis polyp, 4 had fundic gland polyp, two had intestinal metaplasia, two had carcinoid tumor, two had faveloar hyperplasia, one had adenomatous polyp and 3 patients were classified as other (gastric adenocarcinoma, brunner gland hyperplasia and normal pathology). Polyp's recurrence was noted in five out of eleven hyperplastic polyps and one out of four fundic gland polyps surveyed.

All Five adenomatous polyps were polypectomized during the initial endoscopy session. Four out of the five patients with adenomatous polyps were lost to follow-up in our system. Recurrence of the adenomatous polyp was noted in the one patient who had surveillance endoscopy.

Interval development of cancer was not noted in any of the patients during follow up period.

DISCUSSION

In this study, we found the prevalence of gastric polyps to be 4.7% in a predominantly Hispanic population, which is similar to the reported spectrum in previous series[1,13,16,17]. However, there is wide variation in the reported frequencies of different histological subtypes. Fundic gland polyps and hyperplastic polyps are the most prevalent types of gastric polyps in the current literature[1,2,16]. This was found in our study as well. We found 29% prevalence of hyperplastic polyps and 28% prevalence of fundic polyps. In addition, our data confirmed the positive association between *H. pylori* infection and hyperplastic polyps compared to fundic gland polyps.

There are several subtypes of gastric polyps which can be classified based on their endoscopic appearance or histopathological features. One of the most popular classifications is dividing the gastric polyps into two categories; epithelial and subepithelial. Epithelial polyps include fundic gland polyps, hyperplastic polyps, adenomatous polyps, polyps associated with familial adenomatous polyposis (FAP) and Peutz-Jeghers syndrome. Subepithelial polyps include gastrointestinal stromal tumors (GISTs]), inflammatory fibroid polyps, pancreatic heterotopia, leiomyomas, neuroendocrine tumors and granular cell tumors[17].

In our study, hyperplastic polyps were the most frequent subtype of polyps. We found a strong association between hyperplastic polyps, chronic gastritis and *H. pylori* infection which confirms what was reported in other studies[18,19]. A higher prevalence of *H. pylori* infection has been documented in Hispanics living in United States-Mexico border regions compared with non-border areas, which may explain the relatively high prevalence of hyperplastic polyps in our study population[14,15,20,21]. The risk of dysplasia and neoplastic progression of hyperplastic polyps is controversial with wide discrepancy between the reported rates (1.9% to 19%)[19,22-24]. However, this type of polyp has been reported to have an increased risk of neoplasia in the surrounding abnormal mucosa and is associated with higher incidence of synchronous gastric cancer[3,25]. In our series, 11 out of 87 patients who were found to have hyperplastic polyps, had follow-up endoscopy with a mean duration of 30 ± 18 mo. Five (45%) of these 11 patients were found to have residual polyps in follow up endoscopy and none (0%) of them developed dysplasia or cancer. Given this higher risk of developing adenocarcinoma in the surrounding mucosa of hyperplastic polyp, the guidelines recommend obtaining multiple biopsies of the intervening mucosa[26]. Polyp resection has been recommended for any hyperplastic polyp greater than 0.5 cm in size. Repeat surveillance endoscopy is recommended at 1 year after endoscopic resection[22,27,28]. Regression of hyperplastic polyps has been reported in many studies after effective treatment of *H. pylori* infection, it is thus essential to treat the patients with active *H. pylori* infection before entertaining any further management[18,19,29,30] (Figure 1).

FGPs were found to be the second most frequent type of polyp in our study population. The highest prevalence of fundic gland polyps was reported by Carmack *et al*[1] in a nationwide United States population from 2007-2008 in which FGP constituted 77% of the study cohort. FGP can be found sporadically or in patients with FAP syndrome[31,32]. Sporadic FGP has been reported in many studies to have a positive association with prolonged use of proton pump inhibitors (PPI)[33-36]. However, in other series this correlation was not confirmed[37,38]. Jalving *et al*[36] reported up to 4-times increased risk of fundic gland polyps with long-term proton pump inhibitor, and Ally *et al*[33] reported that the duration of PPI therapy greater than 4 years is an independent predictor for FGP development regardless of the used dosage. Due to the retrospective nature of our study, we were unable to obtain accurate data regarding PPI use among the study population. FGPs

have been reported to have a negative association with the presence of *H. pylori* infection[39]. This was found in our study as well. The risk of dysplasia in sporadic FGPs is rare, while it occurs in 25%-41% of FAP-associated polyps[31,40]. Biopsy of FGPs is recommended to exclude dysplasia or adenocarcinoma. Polyp resection is recommended for FGPs more than 1 cm in size to eliminate sampling error by missing any neoplastic foci within the polyp[26,41]. Further workup is recommended to exclude FAP in patients who are less than 40 years of age with numerous FGPs, or if the initial polyp biopsy showed dysplasia[26].

Raised Intraepithelial Neoplasia is the recent nomenclature for gastric adenomas as they are at increased risk for malignant transformation[3,42,43]. Three (60%) of the gastric adenomas in our study were associated with underlying atrophic gastritis and intestinal metaplasia which confirms what was reported in other studies[42,44]. The malignant potential of adenomatous polyps correlates with the polyp size and the age of the patient[3,24,45-47]. Polyps more than 2 cm in size had been reported to have higher risk of development of adenocarcinoma[3,45]. The guidelines recommend complete endoscopic removal of gastric adenomas or referral for surgical resection if lesions are not amenable to endoscopic resection or if they contain invasive carcinoma[26,27]. In addition, careful examination of the rest of the gastric mucosa and obtaining multiple biopsies is recommended to rule out any synchronous neoplastic process. In 2006, the American Society of Gastrointestinal Endoscopy guideline recommended endoscopic surveillance at 1 year for adenomatous polyps. The 2010 British Society of Gastroenterology guidelines recommended to repeat the endoscopic examination at 6 mo for incompletely resected adenomatous polyps or those with high grade dysplasia[26,27].

In our series, 20 (6.76%) patients were found to have portal hypertensive gastropathy. Half of these patients were found to have hyperplastic polyps. However, it has been reported that hyperplastic polyps in portal hypertensive patients are pathologically distinct from the typical hyperplastic polyps seen in nonportal hypertensive patients with uncertain malignant potential[48-52]. Management of portal hypertensive polyps is difficult as patients are at increased risk of post-polypectomy bleeding due to associated thrombocytopenia and coagulopathy. Conservative management and follow up endoscopy has been suggested as a safer strategy than multiple polypectomies[49,52].

There are some limitations to our study. One of the main drawbacks in our study is the lack of information on PPI use for the study cohort. As a result, we were unable to study the correlation between the various types of gastric polyps and PPI use. Second, this study was designed as a retrospective study with its obvious drawbacks. Although this study was performed in a unique practice setting on the United States-Mexico international border and the database used is significantly large, our results may not be applicable to all settings as our study is single-center study. However, one of the significant strengths of this study is the fact that the majority of the study population is Hispanic (85%) which may give more insight about the characteristics and the histopathologic features of gastric polyps in Hispanics.

In conclusion, the prevalence of gastric polyps in a predominantly Hispanic population is similar to what has been reported in the literature for other populations. Hyperplastic polyps were significantly associated with positive *H. pylori* status and portal hypersensitive gastropathy. Hyperplastic polyps and FGPs were more prevalent in chronic gastritis, while adenomatous polyps were associated with intestinal metaplasia.

COMMENTS

Background

Gastric polyps are usually asymptomatic and incidentally discovered during endoscopic examination. Determination of gastric polyp type is important as the risk for malignant transformation depends on the histopathological type.

Research frontiers

The relationship between *Helicobacter pylori* (*H. pylori*) and the different types of gastric polyps is not well studied.

Innovations and breakthroughs

This is one of a few studies focused on the prevalence and distribution of gastric polyps in Hispanic populations. Hyperplastic and fundic gland polyps accounted for more than half of the resected polyps in this study. Gastric hyperplastic polyps were significantly associated with positive *H. pylori* status and portal hypertensive gastropathy as compared with fundic gland polyps. Hyperplastic polyps and fundic gland polyps were more prevalent in chronic gastritis, while adenomatous polyps were associated with intestinal metaplasia.

Applications

When Hyperplastic polyp is suspected, biopsy of the surrounding mucosa should be done to rule out *H. pylori* infection. In case of an adenomatous polyp, biopsy of the surrounding mucosa should be done to rule out intestinal metaplasia.

Terminology

FGPs: Fundic Galnd Polyps; EGDs: Esophagogastroduodenoscopies.

Peer-review

The manuscript is concise, fluent and well-written. Strengths are the number of cases and the ethnicity orientation of the study group. The main drawback is that there is no new knowledge added, apart from ethnicity-targeted results. However, this is still of notice.

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Contents

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REVIEW

Endoscopic management of benign biliary strictures

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Abstract

Endoscopic management of biliary obstruction has evolved tremendously since the introduction of flexible fiberoptic endoscopes over 50 years ago. For the last several decades, endoscopic retrograde cholangiopancreatography (ERCP) has become established as the mainstay for definitively diagnosing and relieving biliary obstruction. In addition, and more recently, endoscopic ultrasonography (EUS) has gained increasing favor as an auxiliary diagnostic and therapeutic modality in facilitating decompression of the biliary tree. Here, we provide a review of the current and continually evolving role of gastrointestinal endoscopy, including both ERCP and EUS, in the management of biliary obstruction with a focus on benign biliary strictures.

Key words: Gastrointestinal endoscopy; Endoscopic cholangiopancreatography; Bile ducts; Biliary tract; Stricture; Stents

Core tip: Benign biliary strictures (BBSs) are commonly encountered by advanced endoscopists. As our understanding of longstanding techniques involving biliary dilation and plastic stent placement evolves, newer therapeutic options such as self-expandable metal stents and endoscopic ultrasound have become available. Here we review the literature pertaining to the most common etiologies of BBSs with current considerations for their respective endoscopic management.

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INTRODUCTION

Benign biliary strictures (BBSs) originate from a variety of etiologies (Table 1), most commonly post-operative

Table 1 Etiologies of benign biliary strictures

Postsurgical
Cholecystectomy (open or laparoscopic)
Liver transplantation (*i.e.*, anastomotic biliary stricture)
Bilio-enteric anastomosis
Sphincterotomy
Inflammatory
Chronic pancreatitis
Primary sclerosing cholangitis
Immunoglobulin G4-related cholangiopathy
Acquired immune deficiency syndrome cholangiopathy
Vasculitis
Other
Ischemia (*e.g.*, post-liver transplantation)
Trauma
Portal biliopathy
Infection (*e.g.*, Clonorchiasis)
Radiation injury
Idiopathic

injury (*e.g.*, post-cholecystectomy), chronic pancreatitis, and chronic cholangiopathies (*e.g.*, primary sclerosing cholangitis). The clinical presentation of BBSs depends greatly on the context, including the onset, degree, and sterility of obstruction, and ranges from subclinical (*i.e.*, incidentally detected biochemical abnormalities) to severe and life-threatening[1,2]. The diagnostic evaluation to determine the etiology of a BBS and exclude the possibility of underlying malignancy generally entails cholangiography *via* magnetic resonance (MRCP) and/or endoscopic retrograde cholangiopancreatography (ERCP) (with biliary brushings for cytology and/or intraductal biopsies for histology) in addition to serologic testing with serum liver tests and tumor marker carbohydrate antigen 19-9 (CA 19-9). Therapeutic interventions are aimed at providing durable biliary decompression, with options including ERCP, percutaneous, and surgical techniques.

Given its efficacy, safety, and less disruptive nature, ERCP has become the first-line therapeutic option for management of most cases of biliary obstruction, including but not limited to BBSs[3]. Since the introduction of ERCP in the 1970s, this technique has progressively evolved and enhanced the management of a variety of disorders of the biliary tract[4]. Currently, a wide array of catheters, guidewires, papillotomes, stents, and other accessories are available to facilitate diagnostic and therapeutic maneuvers in the management of BBSs.

In this review, we discuss the current role of, evidence for, and approach to endoscopic management in patients with BBSs.

PRINCIPLES OF BBS MANAGEMENT

Pre-procedure preparation

Owing to advancements in non-invasive imaging, ERCP has largely been supplanted by cross-sectional imaging for purposes of initial diagnosis. MRCP, facilitated by the high T2-signal intensity of bile as well as improvements

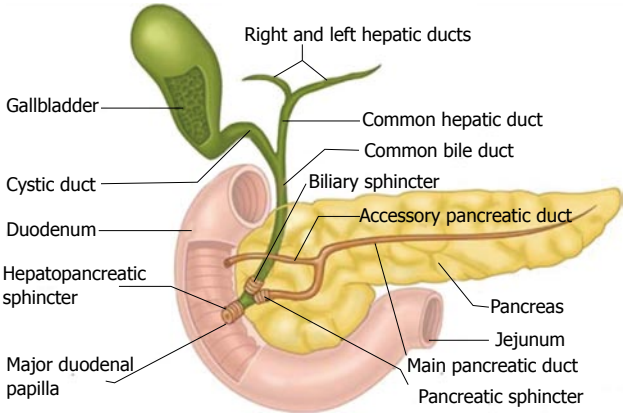

Figure 1 Normal biliopancreatic anatomy.

in MR imaging methods and post-processing tools, has essentially become the preferred modality for diagnostic cholangiography, with relatively few indications remaining for diagnostic ERCP[5]. Not all patients require cross-sectional imaging with MRCP or computed tomography prior to ERCP; however, having such data available can provide a useful roadmap and clarify the pre-procedural plan by shedding light on the patient's pancreatobiliary anatomy, which often does not follow the conventional teaching (Figure 1), and underlying disease. Patients who proceed to ERCP should, as with other endoscopic procedures, be fasting for a sufficient amount of time to allow gastric emptying (*e.g.*, 4-6 h), and careful review and management of antithrombotic medications (if applicable) should be undertaken[6]. Pre-procedural antibiotics should be administered in selected patients in whom adequate drainage is not anticipated such as those with complex hilar strictures and PSC.

Deep biliary access

Once bile duct cannulation has been achieved, attempts at guidewire passage beyond the BBS may prove challenging depending on the severity and anatomic location of obstruction. BBSs can be more difficult to traverse than neoplastic strictures due to greater asymmetry, angulation, and density of fibrous tissue[7]; nevertheless, forceful maneuvers should be avoided, as these may result in the creation of a false tract or perforation. If necessary, guidewire passage can be facilitated by: (1) positioning an inflated stone extraction balloon just below the stricture and withdrawing it, which allows for traction and better alignment between the guidewire and stricture axes; or by (2) selection of an alternative guidewire tailored to the particular stricture anatomy.

Multiple types of guidewires are commercially available and vary in their properties, including diameter, construction material (nitinol, stainless steel), type of coating (hydrophilic *vs* nonhydrophilic), and tip morphology (straight, angled) (Table 2). Comparative studies between guidewires are lacking, but standard 0.035-inch hydrophilic guidewires can be used for most BBSs, whereas tighter strictures may require

Table 2 Commonly used guidewires in endoscopic retrograde cholangiopancreatography

	Diameter (inch)	Length (cm)	Core material	Sheath material	Tip material/ properties	Tip shape	Comments	Cost ($)
Monofilament								
Amplatz (Boston Scientific)	0.038	260	Stainless steel	Uncoated	Platinum	Straight	Extremely stiff	149[1]
Coiled								
Standard (Cook Medical)	0.035	480	Stainless steel	Uncoated	Stainless steel coil	Straight	Must remove prior to sphincterotomy	90
Coated								
Tracer metro direct (Cook Medical)	0.021, 0.025, 0.035	260, 480	Nitinol	Teflon	Platinum; hydrophilic (5 cm)	Straight, angled	Kink resistant, graduated endoscopic markings	196
Delta (Cook Medical)	0.025, 0.035	260	Nitinol	Polyurethane	Hydrophilic (fully)	Straight	Kink resistant, fully hydrophilic, must remove prior to sphincterotomy	151
Roadrunner (Cook Medical)	0.018	260, 480	Nitinol	Teflon	Platinum	Straight, angled	Kink resistant, must remove prior to sphincterotomy	184
Jagwire (Boston Scientific)	0.025, 0.035 0.038 (260)	260, 480	Nitinol	Endo-Glide™	Tungsten, hydrophilic (5 cm)	Straight, angled; trim, round	Kink resistant, guidewire extension (0.035, 200) available	357/box of 2
Hydra Jagwire (Boston Scientific)	0.035	260, 450	Nitinol	Endo-Glide™	Tungsten, two hydrophilic tips (5 cm, 10 cm)	Straight, angled; round	Kink resistant; two tips of varying stiffness on a single guidewire	536/box of 2
NaviPro (Boston Scientific)	0.018, 0.025, 0.035	260	Nitinol	Endo-Glide™	Hydrophilic (fully)	Straight, angled	Fully hydrophilic; 0.035-in also available in stiff	1124/box of 5
Visiglide (Olympus)	0.025, 0.035	270, 450	Superelastic alloy	Fluorine	Hydrophilic (7 cm)	Straight; angled	0.025-in has same stiffness as 0.035-in guidewire	255
XWire (ConMed)	0.025, 0.035	260, 450	Regiliant™ Nitinol	PTFE	Nitinol and Tungsten and PTFE, hydrophilic (5 cm)	Straight; angled	5cm radiopaque tip; 0.035-in also available in stiff	460/box of 3 (260 cm) 583/box of 3 (450 cm)

Other less commonly used guidewires include Dreamwire (Boston Scientific), Savary-Gilliard (Cook Medical), Tracer Metro (Cook Medical), Fusion (Cook Medical), FXWire (ConMed), and Flex-Ez (Hobbs Medical). [1]Cost data obtained from ASGE "Guidewires for use in GI endoscopy," Table 1[97]. PTFE: Polytetrafluoroethylene.

guidewires with a smaller diameter and/or angled tip. Once a stricture has been traversed, the guidewire can be exchanged, if needed, for a stiffer or nonhydrophilic guidewire to facilitate dilation and stenting. Biliary sphincterotomy (*i.e.*, papillotomy) is also frequently necessary if large (cumulative) caliber stenting is anticipated.

Stricture dilation

Stricture dilation (*i.e.*, stricturoplasty) is primarily performed using a dilating balloon or bougie-like tapered catheter. Typical dilating balloon sizes range from 4 to 12 mm, and selection can generally be guided by upsizing 1-2 mm from the diameter of the distal bile duct. In the case of post-liver transplantation (LT) anastomotic biliary strictures (ABSs), dilating to the size of the adjacent donor or recipient duct, whichever is smaller, can be used as a guide[8]. Particular caution should be taken, however, when dilating ABSs during the early post-operative period (< 30 d after surgery) or while a patient is still on high dose immunosuppression, as both of these scenarios may be associated with a higher risk for anastomotic injury or disruption[8-12]. In such instances, less aggressive dilation using a smaller balloon or alternatively a tapered dilating catheter is advisable. With respect to duration of dilation intraprocedurally, most endoscopists adhere to 30 to 60 s of dilation, or until the stricture waist is fractured, before balloon deflation.

Stenting

Balloon dilation alone, although immediately effective, is associated with a high rate of stricture recurrence (up to 47%) depending on the underlying nature of the BBS[13]. Therefore, insertion of biliary stents is frequently required to maintain stricture patency while permitting ductal remodeling. Moreover, placement of several, large-bore plastic stents side-by-side (*i.e.*, multiple or "maximal" endoscopic stenting[8,14]) for up to 1 year has been shown to be superior than inserting only a single stent; this is therefore the currently recommended approach for the majority of BBSs[8,14-18].

The main limitation of endoscopic stenting in this setting is the need to undergo multiple ERCPs for stent exchange. This stems from the relatively short patency time of plastic biliary stents, although there is evidence to support that occlusion rates are similar between stents with dwell times shorter and longer than 6 mo[19]. In addition, and as alluded to above, placement of maximal stents may lessen the need

Table 3 Commonly used partially-covered and fully-covered self-expandable metal stents

Stent name (manufacturer)	Covering	Core material	Diameter (mm)	Length (cm)	Delivery system (Fr)	Features
Wallflex RX	Partial	Platinol	8, 10	4, 6, 8	8.5	Closed cell construction; retrieval loop; looped and flared ends; restrainable
(Boston Scientific)	Full	Platinol	8, 10	4, 6, 8	8.5	
Wallstent (Boston Scientific)	Partial	Elgiloy	8, 10, 12	2, 4, 4.2, 6, 6.8, 8, 9, 9.4	6, 7, 9	Closed cell construction; restrainable
Niti-S ComVi (Taewoong Medical)	Partial	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 9, 10, 12	8	Open cell; triple layered construction: mesh, membrane, and mesh to reduce migration
	Full	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 9, 10, 12	8	
Niti-S Kaffes (Taewoong Medical)	Full	Nitinol	6, 8, 10	4, 5, 6, 7, 8	9	Long retrieval string
Niti-S (Taewoong Medical)	Partial	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 9, 10, 12	8	Retrieval string at proximal end
	Full	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 9, 10, 12	8.5	
Niti-S Bumpy (Taewoong Medical)	Full	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 9, 10, 12	8.5	Irregular cell sizes; retrieval string at proximal end; flared ends
Nitinella Plus (ELLA-CS)	Partial	Nitinol	8, 10	4, 6, 8, 10	9	Reconstrainable; kink-resistant
	Full	Nitinol	8, 10	4, 6, 8, 10	9	
Hanarostent (M.I. Tech)	Full	Nitinol	8, 10	4, 6, 8, 10	8	Larger flared ends
Micro-Tech (Micro-Tech)	Partial	Nitinol	10	4, 6, 8, 10	9	
	Full	Nitinol	10	4, 6, 8	9	
Gore Viabil (CONMED)	Full (with sideholes)	Nitinol	8, 10	6, 8, 10	8.5	Sideholes allow branch drainage; anchoring fins
	Full (without sideholes)	Nitinol	8, 10	6, 8, 10	8.5	
Allium BIS (Allium Medical)	Full	Nitinol	8, 10	6, 8, 10, 12	10	Anchoring segment; non-shortening

for frequent stent exchange, as biliary drainage can continue to occur even after stent occlusion *via* the inter-stent spaces (*i.e.*, "wick effect")[8]. Avoiding multiple ERCPs can also be facilitated by placement of one or more (covered) self-expandable metal stents (SEMSs) instead of plastic stents. SEMSs offer an attractive alternative because of innate properties that allow them to self-expand to diameters 3 times that of 10-Fr plastic stents, thus resulting in longer duration of patency. SEMSs can also be delivered using smaller deployment systems (*i.e.*, 8-8.5-Fr) that do not require as aggressive dilation at the time of stent placement or biliary sphincterotomy. SEMSs of various configurations and properties are currently available[1]; to date, however, none are approved by the United States Food and Drug Administration for the treatment of BBSs. The three major categories of stents, uncovered, partially-covered, and fully-covered, are briefly reviewed below.

Uncovered SEMSs are plagued by the ingrowth of reactive tissue (*i.e.*, epithelial hyperplasia), which can lead to stent occlusion as well as irretrievable embedding of a stent in the ductal wall[20]. As a result, uncovered SEMSs should not be used in the treatment of BBSs[17]. Partially-covered stents, which leave proximal and distal ends bare, are consequently less prone to becoming embedded in issue and thus have improved ease of retrieval. In the largest study of partially-covered SEMSs used to treat BBSs of various etiologies (n = 79), Kahaleh *et al*[21] reported a stricture resolution rate of 90% following a 4-mo stenting period and 12-mo follow-up time. Although all attempted stent retrievals were successful in this study, the potential for tissue hyperplasia involving the bare ends, as reported in other studies, still exists[22,23]. In an effort to further reduce the risk of stent ingrowth and improve removability, fully-covered SEMSs (lined with silicone, polyether polyurethane, polyurethane, expanded polytetrafluoroethylene, or other materials) have been developed and investigated in the treatment of BBSs (Table 3). Most studies of fully-covered SEMSs, barring those with a predominance of patients with particularly refractory strictures (*e.g.*, chronic pancreatitis), have reported favorable clinical success rates, ranging 80% to 90%, as well as low recurrence rates ($\leqslant$ 10%)[24-33]. A tradeoff of this stent design, however, is their predilection for migration, with several studies reporting fully-covered SEMS migration rates between 20% to 40%[24,25,28,31-33]. Of particular concern is the potential for a migrated SEMS to complicate stent removal (proximal migration) or cause bowel obstruction (distal migration). Recent studies investigating anti-migratory modifications to fully-covered SEMSs (*e.g.*, anchoring fins) have reported reduced albeit not clinically insignificant rates of migration[27,29,30]. The role of fully-covered and partially-covered SEMSs is described further in forthcoming sections.

CONSIDERATIONS FOR SPECIFIC BBS ETIOLOGIES

Post-operative strictures

Post-cholecystectomy: Cholecystectomy remains a common etiology of BBSs, with an incidence of 0.2% to 0.7% among patients undergoing laparoscopic cholecystectomy[34]. Post-cholecystectomy BBSs develop as a consequence of bile duct injury that may occur intraoperatively (dissection, electrocautery, clip

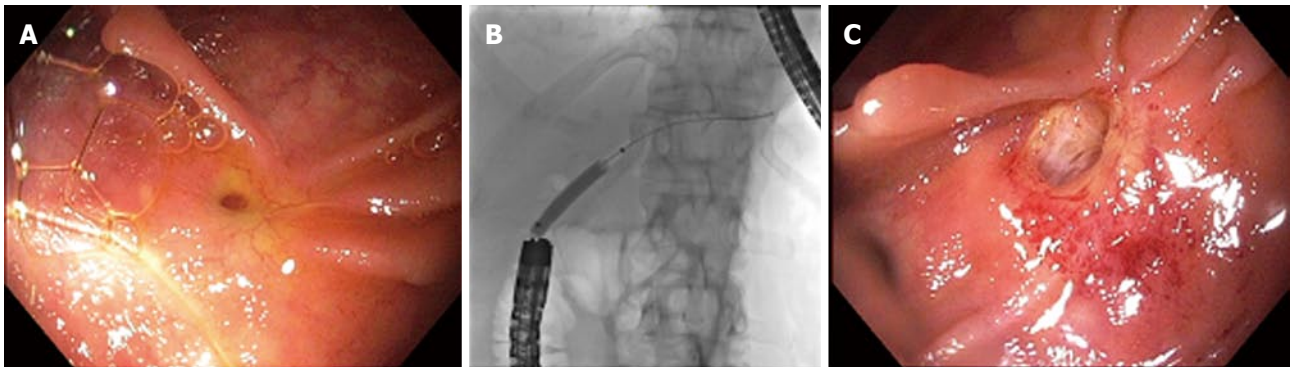

Figure 2 Anastomotic biliary stricture at the site of hepaticojejunostomy in a liver transplantation patient. A: Endoscopic view of hepaticojejunal anastomotic biliary stricture; B: Radiographic image taken during balloon dilation demonstrating the stricture waist; C: Endoscopic view immediately post-dilation of the anastomotic biliary stricture.

or suture placement, ligation) and/or post-operatively (adhesion formation)[35]. Long-term data of post-operative BBSs treated with multiple plastic stents and intermittent stent exchange (approximately every 3 mo) over the course of a year have demonstrated promising success rates ranging from 80% to 100%[15,18,36,37]. This approach has thus become the current standard of care when treating post-operative BBSs[38]. It should be noted, however, that post-operative strictures located at the hepatic ductal confluence may be less responsive to endoscopic stenting than strictures located more distally (25% *vs* 80% resolution rate)[15].

There are limited data regarding the use of fully-covered and partially-covered SEMSs in the treatment of post-cholecystectomy strictures. These data are derived from a small subset of patients with post-cholecystectomy strictures included in SEMSs studies. For example, in a large, multicenter study of fully-covered SEMS (n = 187), 18 patients with post-cholecystectomy strictures (14 of which were previously treated with plastic biliary stents) underwent SEMS placement. After 10-12 mo of stenting, 13 patients (72%) experienced stricture resolution without need for immediate re-stenting. Two-thirds, however, experienced stent migration by 12 mo, and 6 patients (33%) experienced cholangitis, fever or pancreatitis[39]. Based on these findings, SEMSs cannot be routinely recommended for treatment of post-cholecystectomy strictures.

Post-LT: Among patients who have undergone LT, BBSs are among the most common post-operative complications, with their incidence ranging from 5% to 15% and 28% to 32% following deceased donor and living donor LT, respectively, and even higher rates in cardiac death donor LT[12,40,41]. Post-LT BBSs can manifest early (< 30-90 d) or late (> 90 d) in the post-LT course and may occur at the anastomosis (*i.e.*, ABS) or elsewhere in the biliary tree (*i.e.*, non-anastomotic biliary stricture, NABS). Endoscopic therapy is the first line management approach for ABSs and for select NABSs, with percutaneous intervention and surgical revision or redo-LT being reserved for endoscopic treatment failures. ABSs and NABSs are further discussed below.

ABSs are a consequence of local trauma at the surgical juncture between the recipient's and donor's extrahepatic ducts (most commonly CBD-CBD choledocho-choledochostomy) and account for 80% of post-LT biliary strictures[42]. They appear as a short, single stricture localized to the anastomosis. Earlier presentations (< 30-90 d) generally respond well to endoscopic dilation (Figure 2) and a relatively brief period of plastic stenting (approximately 3 to 6 mo), whereas later presentations may require up to 1-2 years of stenting to avoid stricture recurrence based on the few available published series[42-44]. Unfortunately, most studies regarding management of ABSs are retrospective and heterogeneous (*e.g.*, in stricture etiology, severity, and other variables), yet several have shown consistent long-term success rates of approaching 90% to 100% with balloon dilation and multiple or maximal plastic stent therapy[8,45-49]. ABSs may also be treated with SEMSs, but this has been less studied and seldom practiced for a variety of reasons[23-26]. For example, a multicenter trial of partially-covered SEMSs was associated with a modest long-term success rate of 53%, and removal of the stent was technically demanding in 6 out of 21 (29%) patients due to embedding of the bare ends[23]. Conversely, studies using fully-covered SEMSs have reported more promising success rates (ostensibly due to longer dwell times), ranging 92% to 100%, but with higher stent migration rates (as high as 24%)[24-26].

NABSs account for 10%-25% of post-LT biliary strictures[50,51] and are typically a sequela of donor-recipient ABO incompatibility, prolonged graft ischemic time peri-LT, or post-LT hepatic artery thrombosis[52]. NABSs are often referred to as ischemic strictures, although it should be noted that not all NABSs have a clearly ischemic etiology. In contrast to ABSs, NABSs may be either unifocal or distributed diffusely throughout the extra- and/or intrahepatic biliary tree (Figure 3), are more technically challenging to access and treat, and have lower long-term endoscopic treatment success rates (50% to 75%)[45,53]. Nevertheless, maximal

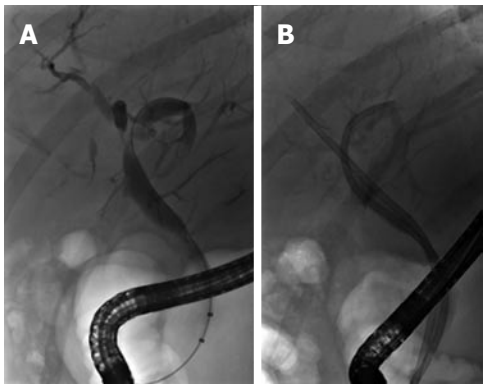

Figure 3 Anastomotic and nonanastomotic biliary strictures in a liver transplantation patient. A: Anastomotic biliary stricture and hilar nonanastomotic biliary strictures are present; B: Radiographic image taken immediately following placement of a 10-Fr 15 cm Cotton-Leung (Cook Medical) and a 10-Fr 22 cm (cut down to 16 cm) Johlin (Cook Medical) plastic biliary stent.

stenting, as with ABS, may result in graft preservation and overall favorable outcomes in a considerable proportion of patients with NABSs[14,45,53-55], although some will ultimately require re-transplantation[10,45,56].

Chronic pancreatitis

BBSs develop in approximately 25% of patients with chronic pancreatitis and represent a major clinical challenge[1]. These strictures occur in the distal CBD, and their refractory nature is largely attributable to robust periductal fibrosis secondary to the underlying chronic inflammatory process[57]. It is important to rule out underlying malignancy in this context, as it can have an initial presentation similar to BBSs and pancreatic cancer can occur in the setting of established chronic pancreatitis. With respect to treatment of chronic pancreatitis-associated BBS, biliary decompression is indicated in patients who are symptomatic (*e.g.*, cholangitic, deeply jaundiced), and as with post-operative BBSs, insertion of multiple plastic stents with 3-4 exchanges over a year appears to offer the highest likelihood of long-term benefit. Studies range in overall success of endoscopic therapy from 44% to 92%, with lower rates among those with dystrophic calcification of the pancreatic head[15,58-60]. Surgical intervention (*e.g.*, Puestow pancreaticojejunostomy, Traverso-Longmire pancreaticoduodenectomy[61]) is indicated in patients who fail endoscopic management and are fit for surgery[57,60].

A number of studies have investigated the role of fully as well as partially-covered SEMSs in chronic pancreatitis. Fully-covered SEMSs have demonstrated success rates ranging from 43% to 77% in patients with chronic pancreatitis-associated BBSs, but stent migration have historically been a common problem, as is the case with post-operative BBSs[21,27,62,63]. A recent, multicenter study of 118 patients with chronic pancreatitis-associated BBSs, however, found that fully-covered SEMS placement was associated with an 80% stricture resolution rate (median stent dwell time 11 mo) and a more acceptable stent migration rate (19% at 12 mo)[39]. Studies using fully-covered SEMSs with antimigratory modifications, or partially-covered SEMSs, have also reported encouraging stricture resolution rates (approximately 90%), and with even lower rates of stent migration[29,63,64].

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is an idiopathic disorder characterized by periductal inflammation and fibrosis involving the intrahepatic and/or extrahepatic biliary tree. Up to 50% of patients with PSC will develop "dominant" strictures, which are loosely defined as a CBD stenosis of $\leqslant$ 1.5 mm in diameter or hepatic duct stenosis $\leqslant$ 1 mm in diameter, during their disease course[65,66]. A major challenge in the setting of a PSC-associated dominant stricture is excluding underlying malignancy (*i.e.*, cholangiocarcinoma), which develops in up to 20% of patients with PSC[67-70]. At a minimum, brush cytology and/or intraductal biopsies, are required. If available, advanced cytologic and imaging methods should also be considered.

The overarching goal of endoscopic therapy in PSC-associated dominant BBSs is to improve signs, symptoms and sequelae of biliary obstruction; when performed appropriately (including both patient selection and procedural technique), endoscopic therapy can improve Mayo PSC risk score, which has been shown to translate into improved survival[68,71-74]. Biliary (balloon) dilation alone is the preferred therapeutic approach, as stenting has been shown to result in slightly higher rates of complications (*i.e.*, stent occlusion and cholangitis) in some series[75,76]. Repeated dilation (*i.e.*, multiple ERCP sessions) may be necessary in some patients to achieve maximal clinical benefit[77]. If dilation is unsuccessful (*i.e.*, persistent stricture waist), short-term stentings with plastic biliary stents has been shown to be safe and effective with durable benefit[78]. Prophylactic antibiotics should also be administered periprocedurally to reduce the risk of ERCP-related cholangitis unless full biliary drainage is highly anticipated[79,80].

Altered anatomy after hepatobiliary surgery

Biliary-enteric strictures can occur following pancreaticoduodenectomy (Whipple procedure), partial liver resection, and liver transplantation with Roux-en-Y hepaticojejunostomy in 12%-28% of patients[81,82]. Endoscopic therapy of these strictures was once felt to be impossible due to surgical alterations in intestinal anatomy that precluded access *via* conventional endoscopic methods. However, the use of colonoscopes and more recently, device-assisted enteroscopes (single, double, and short double balloon), combined with more widespread training of advanced endoscopists have brought these strictures within reach[83]. In patients post-standard Whipple, the hepaticojejunostomy is almost always reachable, whereas pylorus preserving Whipple, and choledocho- and hepaticojejunostomy

Roux-en-Y render more challenging, but often still conquerable anatomy in the hands of an experienced endoscopist with balloon-enteroscopes. A recent meta-analysis included 15 studies and 461 patients with surgically altered pancreaticobiliary anatomy (Roux-en-Y bypass, Roux-en-Y reconstruction, and standard and pylorus preserving Whipple) undergoing single-balloon enteroscopy-assisted ERCP. The pooled enteroscopy, diagnostic, and procedural success rates were 81%, 69%, and 62%, though a high degree of heterogeneity was reported[84]. Limiting analysis to patients with Roux-en-Y reconstruction or Whipple yielded higher diagnostic and procedural success rates at 79% and 63% with much lower heterogeneity[85]. In a retrospective study of patients with biliary-enteric strictures following surgical repair of iatrogenic cholecystostomy injuries (n = 32), Lee *et al*[86] reported balloon dilation alone to be successful in 66% of patients with only 1 (5%) recurrence over a mean 13.1 years of follow-up.

An endoscopic approach can be limited by time, availability, and endoscopist expertise. When unsuccessful, percutaneous transhepatic access (with or without rendezvous techniques)[86], percutaneous drains, and surgical revision remain alternative therapeutic options.

ENDOSCOPIC ULTRASOUND IN BBS MANAGEMENT

Even in expert hands, attempts at therapeutic ERCP for BBSs may fail in 2% to 10% of cases due to inability to cannulate the bile duct (*e.g.*, surgically altered anatomy, tumor infiltration) or traverse a tight bile duct stricture. In select cases, endoscopic ultrasound (EUS) may serve as ancillary therapeutic techniques prior to proceeding with options such as percutaneous or surgical intervention. EUS can be employed in a rendezvous technique that establishes transpapillary guidewire access, thereby allowing conventional ERCP with balloon dilation of a BBS followed by stent placement (if indicated).

EUS-guided biliary access and drainage can also be performed by needle puncture of the gastric wall and advancement into the left hepatic duct tributaries (*i.e.*, hepaticogastrostomy)[87-90] or through the duodenal wall into the CBD (*i.e.*, choledochoduodenostomy)[91,92]. Thereafter, drainage can be internalized through the papilla without requiring a rendezvous approach (although combination approaches can be useful as well)[93,94]. As alluded to before, this technique is particularly useful when biliary cannulation or access to the papilla cannot be achieved due to duodenal obstruction or other causes[95,96].

Adverse events

Adverse events related to endoscopic management of biliary strictures may occur secondary to stricture access or dilation, and stent placement or dwell time (early or late). Sphincterotomy can be associated with pancreatitis, luminal perforation, or bleeding, as seen in patients undergoing ERCP for other indications. Stricture dilation (particularly in the setting of a fresh surgical anastomosis) and stent deployment also run the risk of perforation. Stent-related adverse events include early or late migration, impaction or embedment (metal stents), or occlusion with the potential for cholangitis. Plastic stents therefore necessitate removal or exchange in 3 mo with concurrent removal of all stones and sludge.

CONCLUSION

Endoscopic therapy provides a minimally invasive, safe, and reliable first-line management option for most BBSs. An approach involving multiple plastic stent placement and intermittent stent exchanges works well in post-cholecystectomy strictures and ABSs, whereas other stricture types, such as NABSs and chronic pancreatitis-associated strictures, tend to be more challenging, with some patients ultimately requiring surgical intervention. The recent and rapid evolution of SEMSs may provide an alternative means to treat some BBSs while reducing the need for frequent ERCPs, but additional studies that better define their application, complications, and cost-effectiveness remain needed. Lastly, applications of therapeutic EUS for biliary disease are becoming increasingly recognized and implemented, and continued advancements in both ERCP and EUS are anticipated.

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REVIEW

Cell-block procedure in endoscopic ultrasound-guided-fine-needle-aspiration of gastrointestinal solid neoplastic lesions

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Abstract

In the present review we have analyzed the clinical applications of endoscopic ultrasound-guided-fine-needle-aspiration (EUS-FNA) and the methodological aspects obtained by cell-block procedure (CBP) in the diagnostic approach to the gastrointestinal neoplastic pathology. CBP showed numerous advantages in comparison to the cytologic routine smears; in particular, better preservation of cell architecture, achievement of routine haematoxylin-eosin staining equivalent to histological slides and possibility to perform immunohistochemistry or molecular analyses represented the most evident reasons to choose this method. Moreover, by this approach, the differential diagnosis of solid gastrointestinal neoplasias may be more easily achieved and the background of contaminant non-neoplastic gastrointestinal avoided. Finally, biological samples collected by EUS-FNA CBP-assisted should be investigated in order to identify and quantify further potential molecular markers.

Key words: Endoscopic ultrasound-guided-fine-needle-aspiration; Cell-block procedure; Gastrointestinal tract; Immunohistochemistry; Diagnosis

Core tip: Cell-block procedure (CBP) represents the most suitable complement in diagnostic cytopathology of many gastrointestinal lesions. Hence this method allows high quality morphological evaluation and immunocytochemical analyses. On this way, the differential diagnosis of solid gastrointestinal neoplasms may be more easily achieved and the background of contaminant non-neoplastic gastrointestinal avoided, with an evident gain compared to the traditional cytological techniques. In the present review, the application of CBP in gastrointestinal solid lesions approached by endoscopic ultrasound-guided-fine-needle-aspiration, the methodological aspects and the accuracy of this diagnostic process are analyzed and discussed.

Ieni A, Barresi V, Todaro P, Caruso RA, Tuccari G. Cell-block procedure in endoscopic ultrasound-guided-fine-needle-aspiration of gastrointestinal solid neoplastic lesions. *World J Gastrointest Endosc* 2015; 7(11): 1014-1022 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i11/1014.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i11.1014

INTRODUCTION

Endoscopic ultrasound-guided-fine-needle-aspiration (EUS-FNA) represents a useful diagnostic procedure in the field of gastrointestinal pathology[1-3]. It is performed by using a curved linear array video-echo-endoscope equipped with various needles which provide cytological samples; in this way, the ability to obtain cytologic material is greatly increased due to direct visualization, with a consequent better opportunity to perform an accurate diagnosis. Since its introduction, EUS-FNA emerged as a minimally-invasive, safe and accurate technique for the diagnosis of various luminal, submucosal and extra luminal gastrointestinal neoplasms[4].

The European Society of Gastrointestinal Endoscopy published the guidelines for EUS-guided sampling, with comments on the technical prerequisites for maximizing the diagnostic yield of this procedure[5]. However, the acquisition of diagnostic samples should be approached in different ways depending on the type of the lesion. Moreover, the actual efficacy of EUS-FNA partly depends on the site, size and characteristics of the target tissue as well as on the expertise, training and interaction between endosonographer and cytopathologist[6,7].

Cell-block procedure (CBP) is a diagnostic tool which has been carried out by using different procedural steps and protocols over the years[7-11]. This technique presents several advantages compared to the cytologic routine smear: preservation of cell architecture, achievement of routine haematoxylin-eosin staining equivalent to that of surgical samples and, finally, the possibility to perform ancillary methods, such as immunohistochemistry or molecular analyses[7,8,12,13]. In particular, CBP allows the availability of an adequate number of serial sections, with increased possibility to detect malignant cells and contaminating or reactive non-neoplastic elements[6,7,13].

Aims of the present review are to discuss the application of CBP in gastrointestinal solid lesions approached by EUS-FNA and to analyze the methodological aspects and accuracy of this diagnostic process.

Methodological aspects of EUS-FNA

One of the most debated issues on EUS-FNA relates to the number of needle passes required to provide adequate diagnostic material. The presence of a well trained cytopathologist, able to evaluate the quality of samples, is probably crucial in order to decrease the number of unsatisfactory results and to reduce the need for additional passes. Indeed, the prompt cytopathology response may be useful for the endosonographer to know whether the needle aspirate is diagnostic or not[2,4,14-19]. Although it has been repeatedly reported that on-site cytological evaluation improves the diagnostic yield and accuracy of EUS-FNA, other factors, such as the localization, nature, presentation, size and sonography characteristics of the lesion, may influence the number of needle passes[2-4,20]. In detail, the percentage of adequate specimens and sensitivity of EUS-FNA are lower in intra-parietal lesions of the gastrointestinal tract (GI) compared to those of lesions in other sites[1,21,22]. In addition, the diagnostic yield and accuracy for EUS-FNA also depend on the size of the lesion and they are significantly lower in lesions less than 10 mm in size[1,23,24]. On the whole, two to five needle passes are considered to be sufficient to obtain enough diagnostic material for a correct diagnosis by EUS-FNA[2,3,20,22,25,26]. The needle size is another relevant factor. 19-G needle seems to be the most adequate to provide higher amount of diagnostic material, especially when the cytopathologist is not present in the endoscopy room. Nonetheless the 22-G or 25-G are the most commonly used needles for the cytological sampling of gastrointestinal lesions because of their easier penetration without any further complications[2,16,27,28].

Finally, a special technical training in EUS-FNA should be mandatory, as recommended by the American Society of Gastrointestinal Endoscopy which codifies the minimum number of cases that should be analyzed depending on the site of lesion[29-31].

Needle-based confocal laser endomicroscopy (CLE) is a novel endoscopic method, in which imaging is based on tissue illumination and detection of tissue-reflected fluorescence; interestingly this technique gives high-quality images which are similar to those obtained by traditional histology[32-34]. The development of tissue specific contrast agents might further extend the application of CLE to pancreatic masses, either solid or cystic, intra-parietal or submucosal gastric and esophageal tumours, biliary tract and ampullary lesions[2,33,35].

Methodological aspects and advantages of CBP

CBP has been extensively used in cytology as a helpful tool to achieve a definitive diagnosis[8-10,36,37]. CBP may be carried out by using different protocols based on various fixatives and embedding techniques[8,10,38-40].

In the manual traditional method, following the rapid on-site evaluation of specimen adequacy and preliminary cytological diagnosis by quick stains, the needles and syringes used in the procedure are rinsed with 10 mL of 50% ethanol into a special container in order to recover further material. All content is centrifuged in a 10 mL disposable centrifuge tube at 4000 rpm for 6 min to create 1 or 2 pellets; the

supernatant fluid is decanted and the pelleted material obtained by sedimentation is immediately fixed in a freshly prepared solution of 4% neutral buffered formalin for 45 min. Then, the cell pellets are placed in a cassette and stored at 80% ethanol until they are ready for processing in an automatic tissue processor[36].

CBP may be based on thrombin or albumin methods. In the former, six drops of discarded human plasma and six drops of thromboplastin-DS are added to the cell sediment in order to form a clot, while in the latter 3-4 drops of 22% bovine albumin and 95% ethanol are added to the cell sediment to form a precipitate[9,41]. Whatever is the method, clots or/and precipitates are embedded in paraffin at 56 ℃ to realize cell blocks which are cut into 3 μm thick sections routinely stained with H and E or mounted on poly-lysine-coated glasses for immunocytochemical and molecular procedures.

A novel automated method for cell block production is the Cellient™ Automated Cell Block System. Compared to the traditional manual method, the automated one allows to achieve higher cellularity and better cellular presentation in terms of architecture and details; in addition it is faster and more reliable due to lack of operator dependency[9,39,42]. Gorman and coll. showed that Cellient cell blocks gives an adequate cellularity in all the analyzed cases, while formalin and thrombin cell blocks show a progressively decreasing adequacy[37]. The main drawback of Cellient system is methanol-based fixation, which may have negative impact on the following immunohistochemical analysis[8,9]. Indeed weaker staining intensity for ER, PR, MIB-1 and HER2 was shown by using this procedure[8,37,43,44]. However this issue may be overcome by formalin pre-fixation prior to Cellient[9]. Thirty minutes pre-fixation seems to be preferable to longer fixation to ensure good morphological quality[9].

On the whole, CBP allows the collection of higher quantity of diagnostic material. Hence it may be relevant in reducing the false negative diagnoses in EUS-FNA, which may depend, not only on erroneous interpretation of the cytological samples, but also on the availability of low cytological material. In addition it was shown that CBP greatly increases the diagnostic accuracy of EUS-FNA[7,22]. CBP also represents the most appropriate method to obtain cytological preparations for subsequent immunocytochemistry. Indeed immuno-stains on CBP sections show minimal background and appear similar to those observed in surgical pathology material. In addition, numerous serial sections may be obtained from a single cell block, allowing the evaluation of a large spectrum of antigens, also in archival samples. The number of antibodies that can be applied in routinely CBP has been expanding over the years[2,3,7-9,13,37]. The possibility to test serial sections with different antibodies may allow to identify and discriminate gastrointestinal hyperplastic or reactive contaminating cells from well differentiated tumour cells[7,13,45].

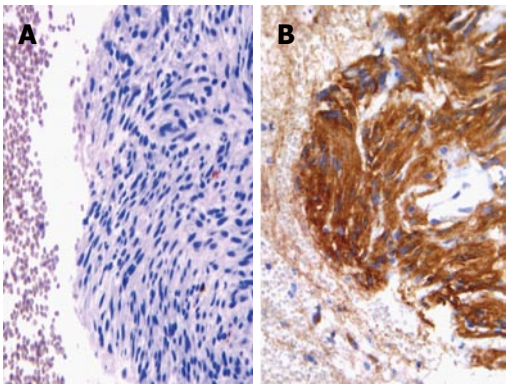

Figure 1 Cell block from gastrointestinal stromal tumour exhibiting aggregates of spindle cells with elongated nuclei (haematoxylin-eosin, × 200) (A), with an evident immunoreactivity for CD117 (immunoperoxidase, × 200, Mayer's Haemalum nuclear counterstain) (B).

CLINICAL APPLICATION OF EUS-FNA CBP-ASSISTED IN GI TRACT

Subepithelial/intramural neoplasms of the gastrointestinal wall

Although conventional endoscopy, CT scan and MRI may identify subepithelial/intramural lesions in the gastrointestinal wall, they can not reveal the nature and origin of those lesions. A wide range of subepithelial tumours, such as leiomyomas, neurinomas, granular cells tumours, gastrointestinal stromal tumours (GISTs), neuroendocrine tumours, leiomyosarcomas and lymphomas, may involve the GI tract[1,6,46] and many of those neoplastic entities exhibited over-lapping cytological features[6,46], being composed by monomorphic, uniform spindle shaped cells with eosinophilic cytoplasm, vesicular elongated nuclei characterized by finely granular chromatin, sometimes dispersed and inconspicuous nucleoli (Figure 1A). For this reason, the use of immunocytochemistry, which is easily applicable to CBP, may be helpful for the differential diagnosis. In detail, the coexistence of smooth muscle actin and desmin stains strongly supports the muscle origin of the lesion, while positivity for CD-34, CD-117 (Figure 1B) or S-100 suggests other diagnostic hypotheses, such as inflammatory fibroid polyp, GIST or schwannoma[6,46,47]. The assessment of the growth fraction by using Ki-67 labeling index (Figure 2A) may further discriminate the benign or malignant nature of intra-parietal neoplasias, and may allow distinction among leiomyoma, leiomyosarcoma, spindle cells amelanotic melanoma or undifferentiated sarcomatoid carcinoma[6,46,48].

The great efficacy of EUS-FNA associated with the higher accuracy obtained by CBP are helpful to achieve the correct preoperative diagnosis of a sub-epithelial mass which is relevant to establish the operative planning and type of surgery, and to avoid unnecessary procedures for extensive malignant lesions[6,46,49]. In addition, periodic follow-up with EUS is considered to be more acceptable to evaluate eventual changes in

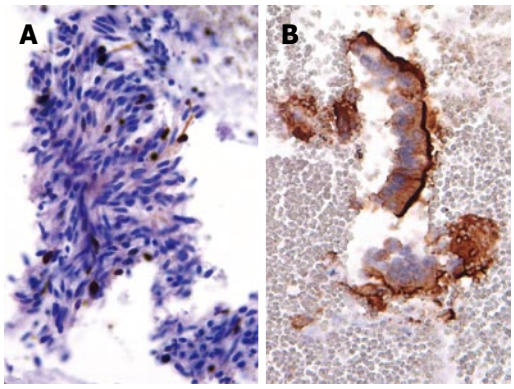

Figure 2 Spindle cells of gastric gastrointestinal stromal tumour documented only a sporadic nuclear Ki67 immunopositivity (immunoperoxidase, × 400, Mayer's Haemalum nuclear counterstain) (A) in benign contaminant gastrointestinal cells, the apical cytoplasm showed a peculiar CD10 immunoreactivity (immunoperoxidase, × 400, Mayer's Haemalum nuclear counterstain) (B).

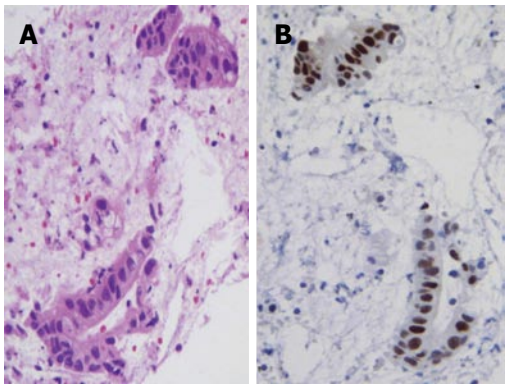

Figure 3 Well differentiated pancreatic carcinoma with a pseudoglandular pattern (haematoxylin-eosin, × 400) (A), a nuclear strong p53 immunostaining was encountered in neoplastic elements (immunoperoxidase, × 400, Mayer's Haemalum nuclear counterstain) (B).

tumour size in those patients who refused surgery[49-51].

Solid pancreatic masses

The pre-operative correct diagnosis of ductal pancreatic adenocarcinoma is crucial for patients management and prognosis, and to reduce costs due to unwarranted procedures[1,13,52,53]. The cytological detection of pancreatic ductal adenocarcinoma is usually not difficult for the experienced cytopathologist; indeed this neoplasia is characterized by distinctive cytological features, such as the presence of groups of atypical cells with irregular roundish hyperchromatic dense nuclei, evident nucleoli, mitotic figures and absence of the honeycomb benign pattern[13]. Frequently, pancreatic smears exhibited a hemorrhagic background with clusters or small aggregates of epithelial cells, occasionally arranged in glandular or pseudo-papillary structures. Nevertheless, in a subset of carcinomas the cytological diagnosis may be hard to achieve, due to the presence of extensive necrosis, associated inflammation, contaminating intestinal epithelial cells or limited sampling[7,13,54]. In those cases, again CBP appears as a significant tool for the pathologist, either the microscopic evaluation and application of immunostainings in serial sections. In fact, it has been shown that carcinoembryonic antigen was expressed in neoplastic pancreatic elements of great majority of ductal adenocarcinomas[13]. However, carbohydrate antigen (CA 19-9) represented the most widely used biomarker for pancreatic cancer, even if it showed limitations in differential diagnosis between pancreatic neoplasms, being positive also in solid pseudopapillary tumour and not only in cancer[55-61]. An intriguing challenge, even for the expert cytopathologist, is represented by the distinction between well differentiated pancreatic neoplastic cells and gastrointestinal epithelial contaminating elements, sampled by EUS-FNA through the stomach or the duodenum[7,13,55-58]. Several efforts were made to solve this crucial diagnostic point[7,13,20,55-58]. Firstly, it was reported that a mucin panel comprising four antibodies (MUC1, MUC2, MUC5AC, MUC6) may be helpful in differentiating normal/reactive gastroduodenal cells from neoplastic pancreatic elements[55]. Successively, the utility of immunocytochemistry against CD10 was highlighted (Figure 2B); indeed this antigen is expressed at the apical membrane of the benign contaminant gastrointestinal cells, but not in the neoplastic elements of well differentiated pancreatic adenocarcinoma[7,13,59,60]. The absence of CD10 stain in pancreatic adenocarcinomas has been also documented in surgical histological samples[59,60]. However, CD10 expression has been evidenced in 100% of solid pseudo-papillary pancreatic neoplasms[61-63] and in 30% of pancreatic endocrine tumours with focal staining[7,63,64]. As a consequence, CD10 immunostaining alone cannot be used for the differential diagnosis of pancreatic lesions[7]. An immunohistochemical panel against CK7, CDX2, chromogranin A and synaptophysin is useful for the differential diagnosis among invasive ductal carcinomas, endocrine tumours and acinar cell tumours of the pancreas[12,20,65]. Finally, a further analysis of p53 immunoreactivity may be of diagnostic help in pancreatic pathology (Figure 3); indeed immunocytochemical positivity for mutant p53 protein with long half-life has been recorded in 50%-70% of pancreatic carcinomas, but not in chronic pancreatitis[66-68].

Solid hepatic lesions

A variety of hepatocellular nodules (hyperplastic, benign, dysplastic and malignant) and secondary tumors can be detected in the liver and subjected to EUS-FNA, especially when they were confined to left hepatic lobe[3,69,70]. In particular, while a significant rate of lesions smaller than 1 cm in diameter is missed by CT and MRI, EUS shows excellent diagnostic accuracy in the identification of hepatic lesions less than 0.5 cm in size[69-72]. It is noteworthy that most of < 1 cm hepatic lesions are non-malignant, whereas the large majority of lesions exceeding 2 cm are represented

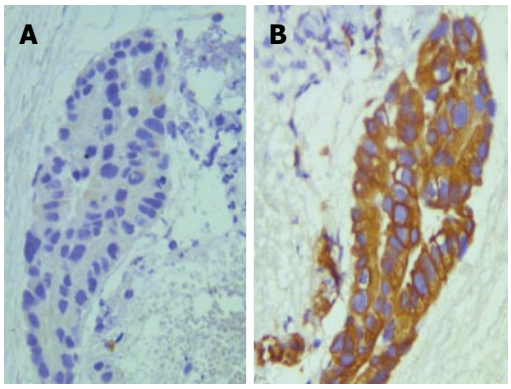

Figure 4 Peripheral cholangiocarcinoma with a papillary pattern (haematoxylin-eosin, × 400) (A), in a serial section obtained from CBP neoplastic elements exhibited an evident cytokeratin 7 immunoreaction (B) (immunoperoxidase, × 400, Mayer's Haemalum nuclear counterstain).

by hepatocellular carcinomas (HCCs); hence in the group of lesions greater than 2 cm a diagnosis of non-malignancy should induce the suspicion of a diagnostic error[73]. Although nodular precursors such as liver regenerative (LRN) or low-grade dysplastic (LGDN) and high grade dysplastic (HGDN) nodules are related to hepatocarcinogenesis, they should be discriminated from adenomas and differentiated HCCs. LGDN category also includes the so-called LRN and it shows mild increase in cell density with a monotonous pattern and bland cytological atypia[73]. On the other hand, HGDN always exhibit more marked cytological atypia and irregular trabecular pattern[73]. Discrimination of well differentiated and hypovascular HCCs from dysplastic nodules may be particularly challenging; in those cases, CBP associated with EUS-FNA or EUS-guided biopsy are warranted, as recently acknowledged[74]. Several immunomarkers were proposed for the distinction between well differentiated HCC and non-malignant lesions[75]. Specifically, Glypican 3 appeared as a good tissue marker with 77% sensitivity and 96% specificity for HCC[74]. In addition, Heat Shock Protein 70 was reported as the most abundantly up-regulated gene in early HCC, and the protein for which it encodes can be detected by immunocytochemistry in up to 78% of the cases with 95% specificity[74]. Finally, Glutamine Synthetase is overexpressed in malignant hepatocytes with diffuse and strong pattern in 50% of HCCs[74,76]. The combined use of the aforementioned was proposed in order to increase the diagnostic accuracy in cases with dubious morphology[76], and so the availability of serial consecutive sections obtained from CBP applied to EUS-FNA could represent the gold standard. With regards to cytokeratins (CK) profile, CK8 and 18 are expressed in both normal and neoplastic hepatocytes, while about 70% of HCC are negative for CK7, CK19, and CK20[73,77]. Furthermore, the combined use of CK7 and CK20 may help to identify the origin of adenocarcinomas occurring in GI tract; in particular, CK7 and CK20 expression in cholangiocarcinomas (CC) varies along the biliary tract, with higher sensitivity of $CK7^+/CK20^-$ profile in peripheral CC compared to non-peripheral ones (Figure 3)[73,77]. On the other hand, $CK7^+/CK20^+$ profile supports the diagnosis of pancreatic adenocarcinoma, while $CK7^-/CK20^+$ is the typical pattern of colonic cancer[73,77].

Gallbladder and biliary tract lesions

Approach by EUS-FNA of the lesions of biliary tract, and mainly of the hilar ones, may avoid the risk of unnecessary extensive surgery[78,79]. Indeed the sensitivity and specificity of obtaining diagnostic samples in biliary neoplasms is variable by endoscopic-retrograde cholangiography[3]. Moreover, the endoscopic retrograde cholangiopancreaticography (ERCP), used at times for hilar cholangiocarcinomas, has frequently inconclusive diagnosis[80]. Consequently, a morphological diagnosis on cytological samples provided by EUS-FNA and submitted to CBP may allow to recognize the nature of malignant biliary lesions (Figure 4) and to change the preplanned surgical approach. Generally, tumour cells appear in loosely structured groups or disorder flat sheets exhibiting as cytologic atypia that varies depending upon tumour grade; occasionally, tumour cells may exhibit cytoplasmic vacuolization and focal mucin secretion. What's more, regional lymph nodes may be evaluated for metastasis by EUS-FNA in patients with unresectable hilar carcinomas[81,82].

A sensitivity and accuracy of 95% have been recorded for EUS-FNA in distal biliary malignancies[7,83] and similar values have been reported in patients with obstructive jaundice due to nodular lesion such as epithelial and non-epithelial tumours, lymphomas and metastases[84-86].

In gallbladder masses, the CBP-assisted EUS-FNA procedure has been used either for diagnostic and staging purposes, with rates of sensitivity and specificity ranging between 80% and 100%, especially in lesions of the gallbladder wall[87-91].

In ampullary tumours, EUS-FNA has higher diagnostic accuracy in the distinction between benign and malignant tumours compared to other operative procedures such as biopsy or brushing cytology during ERCP[92,93]. In addition, it is of help in the identification of patients with low or high grade dysplasia or affected by adenocarcinomas[93].

In this anatomical district, some very severe complications such as bile peritonitis and cholangitis have been described[1]; they probably represent a consequence of inadvertent needle penetration inside intrahepatic or common bile ducts as well as gallbladder. By contrast, bleeding is mild and self-limited, even when patients were taken aspirin or anti-inflammatory drugs, in absence of portal hypertension[1].

CONCLUSION

The clinical applications of EUS-FNA and the methodological advantages obtained by CBP in the diagnosis of solid neoplasms of the GI tract were reviewed.

Although on-site cytological evaluation during the ultra-sonographic needle aspirative procedure may increase the diagnostic yield of EUS-FNA, in our opinion CBP represents its most appropriate diagnostic complement. Indeed this method allows high quality morphological microscopic evaluation and multiple immunocytochemical analyses. By this approach, the differential diagnosis of neoplasms may be more easily achieved, and the background of contaminant non-neoplastic gastrointestinal avoided, which represent evident advantages compared to the traditional cytological techniques. Finally, the identification and quantification of potential molecular markers may represent a promising field to be further investigated on the same biological samples collected by EUS-FNA CBP-assisted.

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REVIEW

Endoscopic retrograde pancreatography: When should we do it?

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Abstract

Endoscopic retrograde pancreatography (ERP) is an accurate imaging modality in the diagnosis of pancreatobiliary diseases. However, its use has been substantially reduced due to the invasiveness of procedure, the risk of complications and the widespread availability of non-invasive cross-section imaging techniques (computed tomography, magnetic resonance imaging, and endoscopic ultrasound). Since the introduction of endoscopic sphincterotomy, ERP has transformed from diagnostic method to an almost exclusively therapeutic procedure. Pancreatic duct injection substantially increased the risk of post-ERP pancreatitis (1.6%-15.7%); therefore, according to international guidelines ERP is recommended only in cases where biliary intervention is required. However, the role of ERP in the management of pancreatic diseases is currently not clearly defined, but in some cases the filling of pancreatic duct may provide essential information complementing the results of non-invasive imaging techniques. The aim of this publication is to systematically summarize the literature dealing with the diagnostic yield of ERP. We would like to define the precise indications of ERP and overview a diagnostic protocol of pancreatic diseases depending on international guidelines and the opinion of Hungarian experts, because it may improve the diagnostic accuracy, minimize of burden of patients and reduce the risk of procedure related complications.

Key words: Endoscopic retrograde cholangiopancreatography; Endoscopic pancreatography; Autoimmune pancreatitis; Pancreas divisum; Chronic pancreatitis

Core tip: Since the development and widespread availability of non-invasive imaging techniques the importance of diagnostic endoscopic pancreatography (ERP) has substantially reduced. However, in some complicated cases or during pancreatic interventional endoscopic procedures such as minor papilla sphincterotomy, pancreatic sphincterotomy, pancreatic stent implantation, ERP may provide essential information. This article seeks to summarize the results of previous studies and recommendations of international guidelines

to define the diagnostic yield and correct indications of ERP.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an invasive procedure that provides radiological visualization of the detailed structure and the pathological changes of the biliary tree and pancreatic ducts by injection of contrast agent into the common bile duct (CBD) and the main pancreatic duct (MPD). Since its development in 1968, it has become a widely used and accurate imaging modality in the diagnosis of pancreatobiliary diseases[1]. Since the introduction of endoscopic sphincterotomy in 1974[2], ERCP has become the most important minimal invasive treatment method for various biliary and pancreatic diseases including bile duct or pancreatic duct stones (choledocholithiasis or wirsungolithiasis), benign and malignant biliary and pancreatic duct obstructions. Recently ERCP has transformed from a diagnostic method to an almost exclusively therapeutic procedure due to the widespread availability of noninvasive cross-section imaging techniques such as abdominal ultrasound (AUS), computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS)[3]. Numerous studies emphasize the disadvantages of ERCP such as post-ERCP complications and the burden to patients. In a meta-analysis of 21 prospective trials the incidence of mild-to-moderate complications reached 5.17%, and that of severe events up to 1.67%[4] (Table 1). Post-ERCP pancreatitis (PEP) is the most frequent complication with approximately 3.5% but its incidence ranges widely (1.6%-15.7%) depending on the patient selection and the definition of pancreatitis[5-7]. Pancreatic duct injection substantially increased the risk of PEP, therefore the role of diagnostic endoscopic pancreatography (ERP) gradually decreased. International guidelines recommend ERCP only in cases where biliary intervention is required[3-8], but the indication of ERP is not clearly defined. According to the current guidelines routine rectal administration of 100 mg diclofenac or indomethacin immediately before or after ERCP is strongly recommended to prevent PEP. In patients with MPD filling and increased patient or procedure related risk factors for PEP temporary application of prophylactic small caliber pancreatic stents is also recommended to reduce the risk of severe PEP[9].

The aim of this article is to systematically review the literature dealing with the diagnostic yield of ERP in various pancreatic diseases, and to define the principles and indications of ERP depending on the recommendations of international guidelines and the opinion of Hungarian experts (Tables 2 and 3) .

Table 1 Frequency of procedure related complications of endoscopic retrograde pancreatography (6.85%) depending of the results of endoscopic retrograde pancreatography[4]

	Mild to moderate	Severe	Death
Pancreatitis	3.07%	0.40%	0.11%
Bleeding	0.95%	0.39%	0.05%
Perforation		0.60%	0.06%
Infection	1.15%	0.28%	0.11%
Total	5.17%	1.67%	0.33%

PANCREAS DIVISUM

Pancreas divisum (PD) is the most common congenital anomaly of the pancreas in which the dorsal and ventral pancreatic duct drain separately into the duodenum. Recently ERP has been the gold standard imaging modality for the diagnosis of PD due to its high diagnostic accuracy[10,11], but the rate of complete pancreatography and the success of minor papilla cannulation significantly influence the sensitivity of ERP[12] (Figure 1). The high rate of complications is the greatest disadvantage of ERP, therefore noninvasive procedures, such as MRCP and EUS are increasingly spreading worldwide in this indication as well. Sensitivity and specificity of MRCP in the detection of PD is 52%-73.3% and 96.8%-97%, and the diagnostic accuracy can further be improved with the use of secretin stimulation (73.3%-86% and 97%)[13,14] (Figure 2). A comparison study carried out by Lai *et al*[15]. has shown that adequate evaluation of the pancreatic duct by EUS is possible in 78% of cases, and the sensitivity, specificity, and positive and negative predictive values for EUS are 95%, 97%, 86%, and 99%.

ERP has an important therapeutic role in the endoscopic treatment (including minor papillotomy with or without pancreatic duct stenting) of patients with symptomatic PD. There is no prospective randomized controlled trial comparing endoscopic and surgical therapy, but previous retrospective studies could not detect any differences between the pooled overall response rates of the two treatment groups (endoscopic *vs* surgical treatment 54.3-79.2 *vs* 51.4-83.3 depending on the indication)[16].

ACUTE PANCREATITIS

The importance of ERCP in the identification of the etiology of acute pancreatitis (AP) has rapidly decreased in the recent decades due to the widespread availability of noninvasive imaging modalities[17]. The diagnosis of uncomplicated AP is mainly based on the clinical symptoms, elevated serum levels of pancreatic enzymes

Table 2 Indication of endoscopic retrograde pancreatography based on the opinion of Hungarian experts

	Indicated	Slightly indicated	Not indicated	Description
Pancreas divisum	83.6%	16.7%	0%	During therapeutic intervention
Acute pancreatitis	16.7%	50%	33.3%	Recurrent "idiopathic" acute pancreatitis
Chronic pancreatitis	83.3%	16.7%	0%	Complicated chronic pancreatitis (MPD stricture, pancreatic duct stones, chronic abdominal pain, obstructive jaundice)
Autoimmune pancreatitis	66.7%	33.3%	0%	Suspicion of autoimmune pancreatitis which has not identified by noninvasive imaging techniques
Pancreatic neoplasia	0%	50%	50%	Suspicion of pancreatic neoplasia with obstructive jaundice
Pancreatic cystic neoplasia	0%	16.7%	83.3%	In case of IPMN ERP associated with high risk of complications Pancreatic cysts and pseudocysts generally do not communicate with the pancreatic duct therefore the ERP cannot identify them
Pancreatic injury	100%	0%	0%	Suspicion of pancreatic ductal injury in stable patients
Postoperative pancreatic fistula	100%	0%	0%	Suspicion of pancreatic fistula Suspicion of fistula formation

ERP: Endoscopic pancreatography; MDP: Main pancreatic duct; IPMN: Intraductal papillary mucinous neoplasms.

Table 3 Indication of endoscopic retrograde pancreatography in the case of suprapapillary bile duct stenosis based on the opinion of Hungarian experts

Indicated	Not indicated	Description
50%	50%	ERP may help differentiate between cholangiocarcinoma and pancreatic illnesses

ERP: Endoscopic pancreatography.

(amylase, lipase) and the morphological changes in the pancreas on the AUS, CT or MRI images[18]. Therapeutic ERCP with biliary sphincterotomy and removal of CBD stones can effectively improve the outcome, and according to the recent international guidelines it is indicated in acute biliary pancreatitis within 72 h, if noninvasive examinations prove the presence of acute cholangitis or raise the suspicion of CBD obstruction in association with acute pancreatitis[19,20]. On the contrary, failed biliary cannulation and repeated MPD filling in patients with acute biliary pancreatitis may worsen the overall outcome and therefore some data suggest that small caliber prophylactic pancreatic stents may be applied as a bridging procedure to prevent complications in this group of patients[21].

In 10%-15% of patients with recurrent acute pancreatitis if the complete noninvasive diagnostic evaluation could not reveal the exact cause and etiology, and as a consequence the diagnosis of "idiopathic" acute pancreatitis may arise. Therefore in patients with idiopathic acute pancreatitis, after the cessation of an acute inflammatory attack an ERCP with biliary and/or pancreatic sphincter of Oddi manometry, an endoscopic ultrasound, and secretin enhanced MRCP may leads to a diagnosis of biliary microlithiasis, sphincter of Oddi dysfunction, PD, cystic fibrosis, a choledochocele, annular pancreas, an anomalous pancreatobiliary junction, small pancreatobiliary tumors, or early stage of chronic pancreatitis[22,23].

CHRONIC PANCREATITIS

Chronic pancreatitis (CP) is a progressive fibroinflammatory disorder with irreversible destruction of the pancreatic parenchyma and ducts. Frequently the complications, such as bile duct stenosis, obstructive jaundice, diabetes mellitus or malabsorption call the attention for the presence of the disease[24]. In advanced stages the recognition of parenchymal fibrosis and moreover calcification is relatively easy with AUS, CT, MRI and EUS, and typical ductal alterations with ERCP or MRCP[25]. The early recognition of CP and its differentiation from pancreatic cancer (PC) sometimes represents a real diagnostic challenge[26]. Currently ERCP has been replaced by EUS (especially with elastography), MRI, CT, and MRCP in the early diagnosis of CP. However, ERCP plays an essential role in the more precise identification of complications such as obstructive jaundice, pancreatic stones, MPD strictures, chronic abdominal pain, and also gives the opportunity for the minimally invasive treatment (pancreatic sphincterotomy or balloon dilatation, pancreatic duct stenting, *etc.*)[27] (Figure 3). The European Society of Gastroenterology recommends the endoscopic treatment as the first-line therapy for painful uncomplicated CP, and highlights its effectivity in the management of obstructive jaundice and pancreatic stones associated with CP[3] (Figures 4 and 5). In cases of complicated CP the long-term efficacy of surgical intervention is superior to endoscopy in most patients[28,29]. Despite the fact, that repeated pancreatography is usually necessary during the endoscopic intervention of the pancreatic duct, the risk of PEP is significantly reduced in CP as compared to the general population. However, the role of ERP as first examination in the diagnosis of suspected complicated CP is questionable[6]. Therefore, in our clinical practice, we perform ERCP in CP patients only in case of chronic pancreatic pain and suspected MPD obstruction (stricture with prestenotic dilatation) based on MRCP or EUS. In these patients, pancreatic sphincterotomy, pancreatic

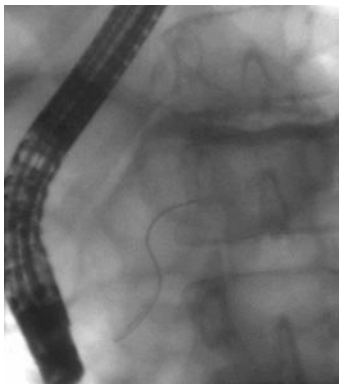

Figure 1 Endoscopic retrograde pancreatography image: Pancreas divisum with minor papilla cannulation.

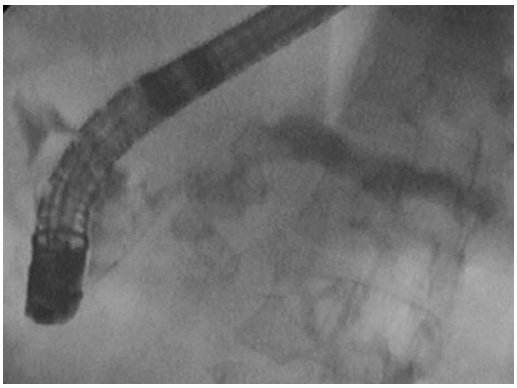

Figure 3 Endoscopic pancreatography image: Chronic pancreatitis with Wirsungolithiasis.

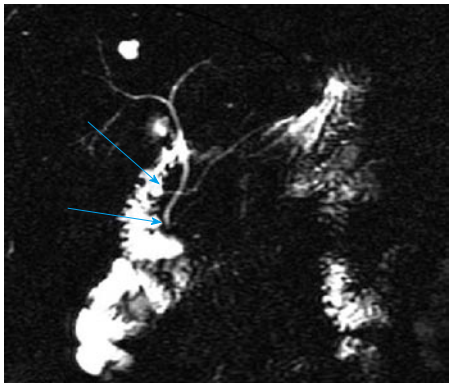

Figure 2 Secretin enhanced magnetic resonance cholangiopancreatography image: Pancreatic divisum and juxtapapillary diverticulum.

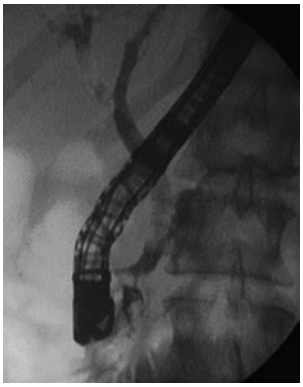

Figure 4 Endoscopic pancreatography image: Pancreatic duct stenosis with prestenotic dilatation after preventive pancreatic stent implantation.

stricture dilatation and multiple plastic or self-expanding metal stenting during ERP proved to be useful to achieve long term symptomatic improvement.

AUTOIMMUNE PANCREATITIS

Autoimmune pancreatitis (AIP) is an uncommon inflammatory disorder of the pancreas with a presumed autoimmune etiology[30]. It may present with a wide variety of clinical and morphological features including painless obstructive jaundice, asymptomatic focal mass or diffuse enlargement of the pancreas which mimic PC[31]. The diagnosis of AIP requires a multidisciplinary approach including imaging studies, histology, serology, assessment of other organ involvement and the therapeutic response to steroid treatment[32,33]. There were differences in the diagnostic approach and the techniques used between different countries. For instance, ERP is usually ignored in Western counties to avoid PEP in contrast to Japan where this examination is usually performed[34]. The correct diagnosis requires detailed information equally about the pancreatic parenchyma and ducts. In typical cases of AIP a diffusely enlarged or "sausage shaped" pancreas with featureless borders and/or loss of lobular architecture can be detected with AUS, CT and MRI[35]. In 30%-40% of the cases focal mass is found, which can lead to false diagnosis of pancreatic malignancy[36,37]. Ductal imaging, ERP and MRCP may show a long, narrow ductal stricture (greater than one-third the length of the MPD) or multiple, non-continuous strictures without marked upstream dilation, and side branches arising from the stricture[38-40]. However, given that ERCP is an invasive method which debit the patient and can cause adverse effects (pancreatitis, bleeding), the noninvasive MRCP is becoming the first choice examination for pancreatobiliary diseases. Previous comparison studies have shown that MRCP is less sensitive in the differentiation of focal form of AIP and PC, therefore cannot completely replace ERCP for the diagnostic evaluation of AIP[41,42]. The multicenter study carried out by Suguma *et al*[43]. has highlighted the ability of ERP to diagnose AIP based on ERP feature alone is limited, but taken together with clinical symptoms, serology and/or histology it can be useful.

PANCREATIC NEOPLASIA

Previously ERCP was the gold standard in the diagnosis of PC. Localized MPD stenosis with focal ductal branch dilation and with distal dilation of MPD ("double duct" sign) were the most frequently detectable morphological

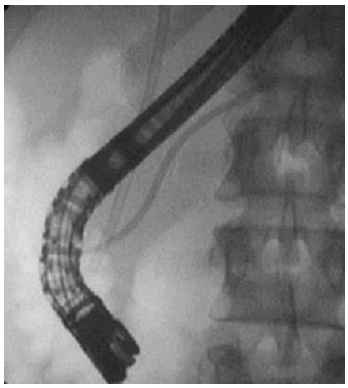

Figure 5 Endoscopic pancreatography image: Bile duct and pancreatic duct stent implantation in chronic pancreatitis.

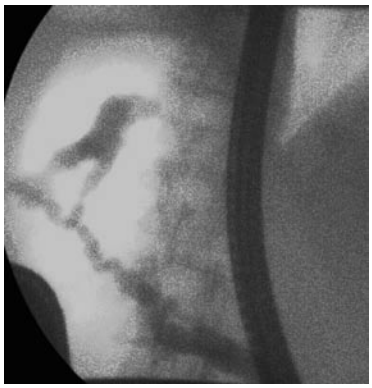

Figure 6 Endoscopic retrograde pancreatography image: Postoperative pancreaticopleural fistula.

changes[44,45]. The current role of ERCP is therapeutic rather than diagnostic. In cases of inoperable locally advanced and metastatic pancreatic malignancy the development of obstructive jaundice constitutes an absolute indication of ERCP[46]. Malignant biliary stenosis may be treated with plastic, but preferably with self-expandable metallic stent implantation[3]. Pancreatography, ERCP-guided brush cytological sampling and/or biopsy of the pancreatic duct may be useful to prove malignancy, but EUS-guided fine needle aspiration (EUS-FNA) is the first-choice sampling procedure in suspected unresectable pancreatic solid and cystic lesions due to minimal invasiveness, lower complication rate and higher sensitivity compared to ERCP sampling[47]. A meta-analysis performed by Li *et al*[48]. showed that ERCP combined with EUS was associated with a high diagnostic yield compared to ERCP or EUS alone, but the complete length of procedures substantially increased, however, it can be reduced if the two examination are performed under the same sedation, but the rate of complication not changed[49].

CYSTIC PANCREATIC LESIONS

Cystic pancreatic lesions represent a great diagnostic problem because of the morphological similarities between benign and malignant cysts and because of the possibility of malignant transformation[50] and the increasing number of the detected lesions due to the improvement of the abdominal imaging modalities and their availabilities. The differentiation between the four types of pancreatic cystic neoplasms (PCN) substantially may influence the therapeutic approach. Serous cystadenomas (SCA) and solid pseudopapillary neoplasms (SPN) are associated with lower malignant potential compared to intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN). Previously ERP was the gold standard diagnostic procedure in the identification and classification of IPMN. Diffuse or segmental dilation of the MPD or its side branches connected to the cyst can be recognized on the ERP images, with no other cause of the dilatation. The pathognomonic characteristic of IPMN is the gaping orifice of Vater papilla with thick mucus oozing (fish mouth papilla)[51]. The international consensus guidelines do not recommend the routine ERP for the morphological and cytological diagnosis of IPMN (fluid sampling or brushing of MPD) due to the invasiveness of the procedure and the high risk of complications. Currently MRCP, EUS and EUS-guided sampling are most preferred[52,53]. The other malignant cyst type and the pancreatic pseudocysts generally do not communicate with the pancreatic duct, therefore the ERP cannot identify them.

PANCREATIC INJURY

Blunt pancreatic trauma can frequently lead to acute pancreatitis with or without MPD disruption. Pancreatic injuries caused by blunt abdominal trauma are relatively rare with an overall incidence of 0.2%-12%[54]. Pancreatic injury occurs as a result of the traumatic compression of the pancreas between the vertebral column and the anterior abdominal wall. Pancreatic injury is more common in children and young adults because of decreased protective intra-abdominal fat. CT is the primary imaging modality of choice in patients with blunt abdominal trauma, with the sensitivity for pancreatic parenchymal injury between 67%-85%[55]. Although pancreatic ductal injury can frequently be detected with non-invasive MRCP, ERCP is the most accurate diagnostic tool for the assessment of ductal injury[56]. Besides, it can also provide endoscopic treatment. Delays in ERCP have led to significantly higher complication rates[57]. Although ERCP is the most useful procedure for the diagnosis of pancreatic ductal injury in stable patients, surgery should be considered without hesitation if the patient's condition is unstable. Recently, some case series proved that pancreatic duct plastic stent placement with and without pancreatic sphincterotomy can be an effective endoscopic therapy in resolving pancreatic duct disruption and preventing chronic fistula formation[58]. Although stent implantation can improve the clinical condition and resolve fistula and pseudocyst, stent induced ductal stricture is a major

long-term complication.

POSTOPERATIVE PANCREATIC FISTULA

Postoperative pancreatic fistula (POPF) formation is a frequent and severe complication of pancreatic surgery[59,60]. Its incidence ranges from 2% to 51% depending on the definition used. POPF was defined by International Study Group on Pancreatic Fistula as a measurable drain output on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase activity[61]. In the early postoperative phase the upper abdominal discomfort associated with fever, tachycardia, slower recovery and persistently high drain output raises the suspicion of postoperative complication, such as pancreatic fistula (Figure 6). The amylase level of drain fluid is extremely elevated in a typical case[62]. ERCP and MRCP are the two most widely used imaging modality in the confirmation of POPF with high diagnostic accuracy. In case of pancreaticopleural fistula their sensitivity may reach to 78% and 80%[63]. Recently ERCP was the most preferred investigation for confirming the diagnosis of POPF, but its use is reduced due to invasive nature and elevated risk of infective complications arising from fistula filling. However, it has the advantage of direct visualization of MPD and precise location of fistula, and the ability to simultaneously perform endoscopic therapeutic maneuvers[64].

PANCREATOBILIARY MALJUNCTION

Pancreatobiliary maljunction (PBM) is a rare congenital malformation in which the CBD and the pancreatic duct are united outside the duodenal wall with or without dilation of CBD[65]. The sphincter of oddi is located in the distal part of the common channel, therefore it cannot properly regulate the outflow of biliopancreatic juice, resulting regurgitation of bile into the MPD and pancreatic juice into the CBD. The elevated intraductal pressure often causes dilatation of CBD, and the chronic biliopancreatic reflux increases the risk of development of malignancy. The diagnosis of PBM is based on the identification of the anomalous union between the pancreatic and bile ducts by ERCP, MRCP, EUS or intraductal ultrasound. ERCP is the most accurate imaging method, and it provides an opportunity for the biliary intervention (biliary stone extraction, stent implantation) and bile sampling as well. High biliary levels of pancreatic enzymes are suggestive of regurgitation of pancreatic juice into the common bile duct[66]. In atypical PBM cases with relatively short common channel, the diagnostic accuracy of MRCP and EUS is lower, but they are very effective in the detection of PBM associated pancreatobiliary cancers at an early stage[67].

CONCLUSION

ERP is still one of the most accurate diagnostic procedures in patients with suspected pancreatic ductal disorders, including idiopathic acute recurrent pancreatitis, chronic pancreatitis, pancreatic ductal injuries and fistula formation, pancreatic cystic neoplasms and early pancreatic cancer. However, before performing ERP, endoscopists should carefully evaluate the extent of the clinically necessary pancreatogram, if there any, to establish the diagnosis. Increasingly widespread application of noninvasive methods for the diagnosis of pancreatobiliary diseases (such as MRCP and EUS), and less frequent use of diagnostic ERP could dramatically decrease post-ERCP complications. In contrast, pancreatic interventional endoscopic procedures, such as pancreatic sphincterotomy, dilatations and pancreatic stent implantation are necessitates for complete pancreatic ductal contrast filling and analysis of digitally enhanced pancreatogram with fluoroscopy to completely understand the anatomy and intraductal pathology before the initiation of endoscopic therapy.

In case of distal biliary obstruction, when the non-invasive imaging modalities are available we do not recommend the filling of pancreatic duct, selective biliary drainage is proposed. ERP should be considered in case of suspected pancreatic ductal abnormalities, such as pancreatic injury, fistula or congenital malformation, and when pancreatic ductal intervention is necessary.

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REVIEW

Current status of endoscopic biliary drainage for unresectable malignant hilar biliary strictures

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Abstract

The management of jaundice and cholangitis is important for improving the prognosis and quality of life of patients with unresectable malignant hilar biliary strictures (UMHBS). In addition, effective chemotherapy, such as a combination of gemcitabine and cisplatin, requires the successful control of jaundice and cholangitis. However, endoscopic drainage for UMHBS is technical demanding, and continuing controversies exist in the selection of the most appropriate devices and techniques for stent deployment. Although metallic stents (MS) are superior to the usual plastic stents in terms of patency, an extensive comparison between MS and "inside stents", which are deployed above the sphincter of Oddi, is necessary. Which techniques are preferred remains as yet unresolved: for instance, whether to use a unilateral or bilateral drainage, or a stent-in-stent or side-by-side method for the deployment of bilateral MS, although a new cell design and thin delivery system for MS allowed us to accomplish successful deployments of bilateral MS. The development of techniques and devices for re-intervention after stent occlusion is also imperative. Further critical investigations of more effective devices and techniques, and increased randomized controlled trials are warranted to resolve these important issues.

Key words: Malignant hilar biliary obstruction; Biliary drainage; Metallic stents; Stent-in-stent; Side-by-side

Core tip: The development of useful surgical devices, such as plastic or metallic stents, catheters and guidewires, has allowed us to achieve successful endoscopic drainage for unresectable malignant hilar biliary strictures (UMHBS), a technically demanding procedure. However, the most appropriate method of endoscopic drainage for UMHBS remains a contentious issue: for instance, whether to use a unilateral or bilateral drainage, or a stent-in-stent or side-by-side method for the deployment of bilateral metallic stents (MS) to accomplish successful deployments of bilateral MS.

Further critical investigations of more effective devices and techniques, and increased randomized controlled trials are warranted to resolve these important issues.

Kato H, Tsutsumi K, Kawamoto H, Okada H. Current status of endoscopic biliary drainage for unresectable malignant hilar biliary strictures. *World J Gastrointest Endosc* 2015; 7(11): 1032-1038 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i11/1032.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i11.1032

INTRODUCTION

The management of jaundice and cholangitis is important for improving the prognoses of patients with unresectable malignant hilar biliary strictures (UMHBS). In addition, effective chemotherapy, such as combination therapy with gemcitabine and cisplatin, for the treatment of cholangiocarcinoma requires the coincident effective management of both jaundice and cholangitis. Several methods exist for biliary drainage including: surgical drainage, percutaneous transhepatic drainage using ultrasound, and endoscopic transpapillary drainage. Of these, endoscopic transpapillary drainage has become the favoured method because of its minimal invasiveness while preserving the patient's quality of life. The development of useful surgical devices, such as plastic or metallic stents, catheters and guidewires, has allowed us to achieve successful endoscopic drainage for UMHBS, a technically demanding procedure. However, the most appropriate method of endoscopic drainage for UMHBS remains a contentious issue. In the present study, we review the current literature concerning endoscopic biliary drainage for patients with UMHBS.

PLASTIC *VS* METALLIC STENTS, AND NEWLY DESIGNED PLASTIC STENTS

Several studies have highlighted the advantages of metallic stents (MS) compared with plastic stents (PS) (Table 1)[1-4]. According to these studies, the median patencies of MS for UMHBS were of longer duration than those of PS (3.4-12.0 mo *vs* 1.2-6.7 mo); in spite of this, the technical success rate for the deployment of MS was similar to that of PS (83.3%-100% *vs* 85.2%-100%). In a randomized controlled trial comparing PS and MS as reported by Mukai *et al*[4], the 6-mo patency was significantly higher for the MS patient group than the PS group (81% *vs* 20%); the 50% patency period was 359 d for the MS group and 112 d for the PS group. In addition, the MS group had the advantage in terms of the number of re-interventions and the total cost of treatment compared with the PS group.

Reports concerning newly designed plastic stents are also increasing. PS occlusion occurs as a result of biofilm formation and bacterial adherence to the wall of the stent following the reflux of duodenal juice into the PS and bile duct. To avoid this phenomenon, Pedersen *et al*[5] reported a method of deploying PS above the sphincter of Oddi; such stents were named "inside stents". Recently, several reports have emerged on the deployment of "inside stents" with attached nylon thread that is easily removed from the distal end of the stent for UMHBS (Figure 1). Ishiwatari *et al*[6] reported on 26 patients with UMHBS and successfully deployed "inside stents" showing a median patency period of 136 d. Kaneko *et al*[7] reported that the patency of "inside stents" was 190 d. Inatomi *et al*[8] compared the patency period of conventional PS, MS and "inside stents" and found the patency period of "inside stents" to be significantly longer than that of conventional PS (142 d *vs* 32 d, $P = 0.04$), but was not significantly different to that of MS (142 d *vs* 150 d, $P = 0.83$). Further investigation is necessary to determine whether the patency period of "inside stents" is comparable to that of MS. However, the absolute advantage of PS, including "inside stents", are enable to be removed easily compared to MS. We intend to deploy PS more frequently as a temporal drainage procedure if UMHBS are completely cured *via* chemotherapy or other effective treatments.

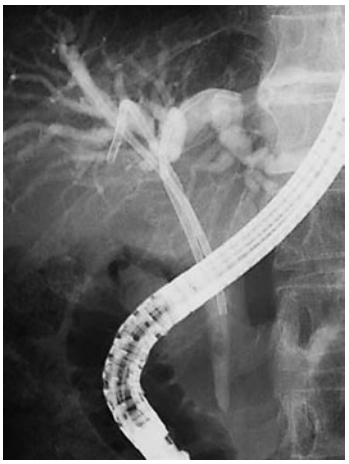

Figure 1 Multiple "inside stents" deployed above the sphincter of Oddi.

UNILATERAL *VS* BILATERAL DRAINAGE

One of controversies regarding unilateral and bilateral drainage is the perceived technical difficulty of these procedures, with bilateral stent deployment generally thought to be more difficult than unilateral stent deployment. There have only been two randomized controlled trials (RCTs) on this issue to date. In one undertaken by De Palma *et al*[9] comparing the unilateral and bilateral deployment of PS, the technical and clinical successes of the bilateral deployment group were significantly lower than those of the unilateral deployment group (Table 2). On the other hand, in a

Table 1 The results of comparison between metallic and plastic stents

Ref.	No. of patients		Successful deployment % (*n*)		*P* value	Patency (mo)		*P* value
	MS	PS	MS	PS		MS	PS	
Sangchan *et al*[1]	54	54	83 (45/54)	85 (46/54)	0.792	3.4	1.2	> 0.001
Perdue *et al*[2]	35	33	97 (34/35)	85 (28/33)		NA	NA	
Liberato *et al*[3]	249	231	99 (246/249)	88 (204/231)	> 0.001	6.3	4.7	> 0.0001
Mukai *et al*[4]	30	30	100 (30/30)	100 (30/30)		12	3.7	0.0002

PS: Plastic stents; MS: Metallic stents; NA: Not available.

Table 2 The results of comparison between unilateral and bilateral stent deployment

Ref.	No. of patients		Successful deployment [% (*n*)]		*P* value	Successful drainage [% (*n*)]		*P* value	Stent patency (mo)		*P* value	Survival period (mo)		*P* value
	Unilateral	Bilateral	Unilateral	Bilateral		Unilateral	Bilateral		Unilateral	Bilateral		Unilateral	Bilateral	
De Palma *et al*[9]	PS 79	PS 78	89 (70/79)	77 (60/78)	0.041	81 (64/79)	73 (57/78)	0.0482	NA	NA		4.7	4.7	0.482
Mukai *et al*[4]	PS 15	PS 15	100 (15/15)	100 (15/15)		100 (15/15)	100 (15/15)		3.4	3.7	0.746	NA	NA	
	MS 14	MS 16	100 (14/14)	100 (16/16)		100 (14/14)	100 (16/16)		12.1	9.8	0.3467	NA	NA	
Liberato *et al*[3]	PS 27	PS 40	NA	95 (38/40)		NA	95 (38/40)		4.0	4.2	0.0004	NA	NA	
	MS 33	MS 45	NA	93 (42/45)		NA	93 (42/45)		5.6	6.8	> 0.0001	NA	NA	
Chang *et al*[10]	PS or MS 69	PS or MS 29	NA	NA		NA	NA		NA	NA		2.7	7.5	> 0.01
Naitoh *et al*[11]	MS 17	MS 29	100 (17/17)	90 (26/29)		94 (16/17)	90 (25/26)		7.0	16.3	0.009	5.5	6.8	0.559
Iwano *et al*[12]	MS 63	MS 19	95 (60/63)	90 (17/19)		NA	NA		4.4	4.2	0.3220	5.7	6.1	0.4908

PS: Plastic stents; MS: Metallic stents; NA: Not available.

RCT by Mukai *et al*[4] comparing PS and MS, successful deployment was achieved in all patients undergoing the deployment of PS or MS, regardless of what type of deployment was employed. In other retrospective studies comparing the unilateral and bilateral deployment of MS, the technical success rate was similar for these two groups[3,10-12]. However, evidences of no obvious differences on the difficulty between unilateral and bilateral deployment are not still enough. Further RCTs at high-volume centers are warranted.

Another matter in question is whether bilateral drainage is superior to unilateral drainage in the management of jaundice and cholangitis, which relates to stent patency and survival periods. There are several studies showing no difference between unilateral and bilateral drainage on stent patency and survival periods, but several studies highlight an opposite stance[3,4,9-12]. Bilateral drainage, as the initial drainage, may not always be necessary for patients with UMHBS for the management of jaundice cholangitis. However, the function of the drained segment of the liver will diminish as the tumor gradually occupies the drain segment, which impacts on patient mortality. Vienne *et al*[13] analyzed the outcomes of drainage effectiveness during endoscopic stenting for malignant hilar biliary strictures. The main significant factor associated with drainage effectiveness was a liver volume drainage of > 50% (odds ratio 4.5, $P = 0.001$), which was associated with longer survival (119 d *vs* 59 d, $P = 0.005$). In addition, Mukai *et al*[4] reported that around 50% of patients required bilateral drainage to reduce jaundice and cholangitis, but instead recommended unilateral drainage. Miura *et al*[14] reported the results of preoperative biliary drainage for malignant hilar biliary stricture. Thirty-one of 122 patients (25.4%) initially underwent multiple biliary drainage; however 69 of 122 (56.6%) required multiple biliary drainage by the time of the operation. They concluded that patients with Bismuth-II, Bismuth-IIIa, and Bismuth-IV were at high risk for multiple biliary drainage. These results suggest that effective drainage of a malignant hilar biliary stricture frequently requires bilateral or multiple drainage.

Uchida *et al*[15] reported on the relationship between the number of deployed MS, the effectiveness of chemotherapy, the patency period of MS, and the survival period. Patients were divided into two groups, one in which four or three MS were deployed (4- or 3-branched group), or a group in which two or one MS was deployed (2- or 1-branched group). Although neither patency period nor survival time exhibited significant differences between the two groups, among the patients achieving complete response, partial response, or stable disease defined by World Health

Table 3 The results of comparison between stent-in stent and side-by-side method for deployment of bilateral metallic stents

Ref.	Method for deployment	No. of patients	Successful deployment % (*n*)	Successful drainage % (*n*)	Occlusion % (*n*)	Stent patency (mo)
Kawamoto *et al*[16]	SIS	9	100 (9/9)	100 (9/9)	33 (3/9)	NA
Lee *et al*[17]	SIS	10	80 (8/10)	100 (8/8)	25 (2/8)	7.2
Park *et al*[18]	SIS	35	94 (33/35)	100 (33/33)	6 (2/33)	5
Kim *et al*[19]	SIS	34	85 (29/34)	100 (29/29)	31 (9/29)	6.2
Chahal *et al*[20]	SIS	21	100 (21/21)	NA	38 (8/21)	6.3
Kogure *et al*[21]	SIS	12	100 (12/12)	92 (11/12)	50 (6/12)	6.7
Hwang *et al*[22]	SIS	30	87 (26/30)	100 (26/26)	39 (10/26)	4.7
Lee *et al*[23]	SIS	84	95 (80/84)	93 (78/84)	31 (24/78)	7.9
Dumas *et al*[24]	SBS	45	73 (33/45)	100 (33/33)	3 (1/33)	NA
Cheng *et al*[25]	SBS	36	97 (35/36)	NA	31 (11/35)	5.6
Chennat *et al*[26]	SBS	16	100 (16/16)	75 (11/16)	25 (4/16)	4.3
Lee *et al*[27]	SBS	44	91 (40/44)	98 (39/40)	45 (18/40)	5.2

SIS: Stent-in-stent; SBS: Side-by-side; NA: Not available.

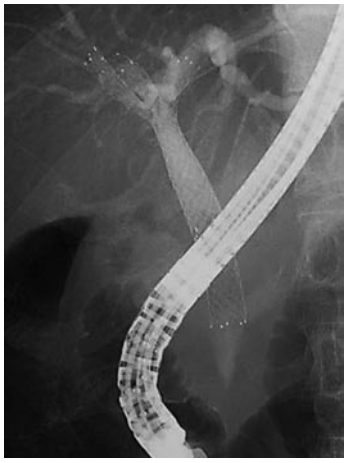

Figure 2 Multiple metallic stents deployed by the stent-in-stent method.

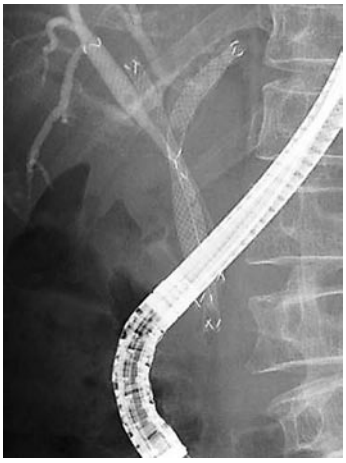

Figure 3 Multiple metallic stents deployed by the side-by-side method.

Organization during chemotherapy, the patency period and survival time of the 4- or 3-branched group were significantly longer than those of the 2- or 1-branched group. They concluded that the deployment of multiple MS prevented biliary infection and deterioration of liver function, which resulted in a long duration of stent patency and the continuation of stable chemotherapy in the disease control group. Consecutive and effective chemotherapy requires the preservation of the functional volume of the liver, and unilateral drainage is less effective than bilateral drainage for this perspective.

STENT-IN-STENT *VS* SIDE-BY-SIDE METHODS

Two methods exist for the endoscopic deployment of bilateral MS for UMHBS: stent-in-stent (SIS; Figure 2) and side-by-side (SBS; Figure 3) methods. Although several reports have been published on each method, no obvious difference was noted (Table 3). The technical success rate is 80%-100% for SIS[16-23] and 73.3%-100% for SBS[24-27], with the patency periods being 140-238 d and 130-169 d, respectively. There are only two retrospective reports on a comparison between SIS and SBS. The rate of successful deployment did not differ between SIS and SBS in both reports but several uncertainties existed surrounding complications and the patency period of these techniques. Naitoh *et al*[28] noted the incidence of complications was significantly higher (44% *vs* 13%, $P = 0.016$), and the cumulative stent patency was significantly longer, ($P = 0.047$) in the SBS, compared to the SIS, group. The median patency period was 469 in the SBS group and 181 d in the SIS group. On the other hand, no differences in complications rates and the patency period between SIS and SBS were reported by Kim *et al*[29]. A prospective randomized control trial, using the same type and diameter of MS, is needed for the evaluation of differences between SIS and SBS methods for the deployment of bilateral MS.

PROGRESS IN METALLIC STENTS FOR BILATERAL DEPLOYMENT

For the reliable and successful deployment of bilateral MS, several new MS designs have been described. The most difficult part for the successful deployment of a bilateral MS by SIS is the deployment of the second MS.

Table 4 The results of re-intervention after stent occlusion in the patients undergoing deployment of bilateral metallic stents

Ref.	Method for deployment	No. of patients	Occlusion % (*n*)	Endoscopic re-intervention % (*n*)	Bilateral or multiple drainage at endoscopic re-intervention % (*n*)
Naitoh *et al*[28]	SIS	24	42 (10/24)	90 (9/10)	NA
	SBS	25	20 (5/25)	100 (5/5)	NA
Lee *et al*[27]	SBS	40	45 (18/40)	92 (12/13)[1]	50 (6/12)
Fujii *et al*[33]	SIS	55	55 (30/55)	100 (30/30)	67 (20/30)
Lee *et al*[23]	SIS	78	31 (24/78)	96 (23/24)	83 (20/24)
Law *et al*[31]	SBS	17	53 (9/17)	75 (6/8)	75 (6/8)
	SIS	7	43 (3/7)	100 (3/3)	100 (3/3)

[1]Five patients with comorbidity underwent initial percutaneous intervention. SIS: Stent-in-stent; SBS: Side-by-side; NA: Not available.

This is because, in addition to the stricture, we have to negotiate the mesh of the first metallic stent when placing the second stent. Therefore, the clever cell design of a MS is crucial for the successful deployment of a bilateral MS by SIS. A newly designed MS with a large, open-celled wire mesh for the deployment of a bilateral MS has been reported in several studies[17,19,21], making the deployment of a bilateral MS for UMHBS a more feasible procedure. Lee *et al*[23] reported on the feasibility and efficacy of a newly designed, closed-cell and cross-wired MS: the technical success rate of endoscopic bilateral SIS deployment was 95.2%, and the median patency period was 238 d.

The difficulty of deployment of a bilateral MS by SBS is also related to the insertion of the second MS along the first MS. This is because we have to advance the second MS against the resistance of the first, already expanded MS. Therefore, although a delivery stuck in the mesh of the initially deployed MS sometimes results in an unsuccessful deployment, a thin delivery overcomes this issue. Kawakubo *et al*[30] reported that 6-Fr delivery systems could facilitate a single-step, simultaneous, SBS placement through the accessory channel of the duodenoscope. The rate of successful deployment was 84.6%, and the median procedure time was 25 min. Law *et al*[31] reported that a 6-Fr delivery MS were used for the deployment of a bilateral MS in 17 patients by SBS and seven patients by SIS. The rate of successful deployment was 100% for both groups, although SBS was attempted prior to SIS in four of seven patients in the SIS group. The 6-Fr delivery can pass through the mesh of the MS more easily, which may facilitate the deployment of a bilateral MS by not only the SBS, but also the SIS method.

RE-INTERVENTION AFTER STENT OCCLUSION IN PATIENTS UNDERGOING BILATERAL DEPLOYMENT OF METALLIC STENTS

Biliary tract cancer is the cause of most UMHBS, and effective chemotherapeutic agents, such as a gemcitabine plus cisplatin combination, have been described in several reports on the treatment of unresectable biliary tract cancer. Valle *et al*[32] reported that the median overall survival was 11.7 mo among 204 patients receiving a gemcitabine plus cisplatin combination, which is longer than the stent patency period already reported. Therefore, stent occlusion that causes jaundice and cholangitis will often happen in the course of chemotherapy, and re-intervention after stent occlusion plays an important role in continuing effective chemotherapy, especially in patients with the deployment of a bilateral MS whose re-intervention is thought to be difficult.

The results of re-intervention after stent occlusion in patients with a bilateral MS deployment are shown in Table 4. Few reports have analyzed the results of re-intervention in any great detail. Fujii *et al*[33] deployed multiple MS using a SIS method in 55 patients with UMHBS. Of these patients, 30 developed a MS occlusion. In twenty of the 30 patients, multiple PS deployments were attempted, with successful PS deployment and clinical success achieved in all 20 patients. Lee *et al*[23] reported on the success rate of bilateral stent deployment as a re-intervention procedure for patients undergoing the deployment of bilateral MS using a SIS method. Of 24 patients with a MS occlusion in which bilateral stent deployment was attempted, twenty patients achieved a successful deployment of bilateral stents. The clinical success of the deployment of bilateral MS was 79.2% (19/24). Law *et al*[31] reported on re-intervention after stent occlusion for 11 patients undergoing the deployment of bilateral MS using an SIS or SBS method. Successful re-intervention was defined as the ability to access and perform interventions in both the right and left hepatic ducts, and this was accomplished in 9 out of 11 patients (3/3 SIS, 6/8 SBS). Re-intervention after stent occlusion will be an important issue to resolve in coming years, with continued improvements seen in the prognosis of patients with UMHBS due to effective chemotherapy.

CONCLUSION

In the present review, we have described the current status of endoscopic biliary drainage in patients with UMHBS. Endoscopic biliary drainage for UMHBS is still technically demanding, with many unresolved issues,

including the choice of PS or MS, the choice of unilateral or bilateral drainage, and the use of either SIS or SBS deployment of bilateral MS. The development of new devices and techniques for stent deployment, and further randomized controlled trials are warranted to resolve these matters in question. The development of new methods of re-intervention after stent occlusion is also important to manage patient jaundice and cholangitis over a longer time period as continued advances in chemotherapy prolong the survival of patients with UMHBS.

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Update on novel endoscopic therapies to treat gastroesophageal reflux disease: A review

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Abstract

Endoscopic treatments for gastroesophageal reflux disease (GERD) have become increasingly popular in recent years. While surgical intervention with the Laparoscopic Nissen Fundoplication remains the gold standard, two endoscopic interventions, specifically, are gaining traction in clinical use (EsophyX and Stretta). The EsophyX (EndoGastric Solutions, Inc., Redmond, WA, United States) was developed as a method of restoring the valve at the GE junction through an endoluminal fundoplication (ELF) technique. Long-term data suggests that transoral incisional fundoplication (TIF) with EsophyX may be effective for symptom control and proton pump inhibitor reduction or cessation for up to 2-6 years. There is no evidence that EsophyX is more effective than surgical intervention. TIF may be most effective for patients with HH < 2 cm and Hill Grade I/II valves. Stretta (Mederi Therapeutics, Greenwich, CT, United States) was approved by the Food and Drug Administration in 2000. It delivers radiofrequency energy to the lower esophageal sphincter and gastric cardia. Published reviews of the literature are conflicted in their recommendations of Stretta in the management of GERD. The literature suggests that the Stretta procedure has an acceptable safety profile and may be effective in reducing symptom burden and quality of life scores up to 8 years post-intervention. However, there does not appear to be any sustained improvement in objective outcomes and there is no evidence that Stretta results in improved outcomes as compared to surgical intervention. Treatment modalities for GERD, as a field, suffer from a lack of standardization in primary and secondary outcomes. Although many studies have looked at health related quality of life, the tools used to do so are markedly heterogeneous. Future directions for the endoscopic treatment of GERD include novel techniques like endoscopic submucosal dissection.

Key words: Endoscopy; Reflux; Gastroesophageal reflux disease management; EsophyX; Stretta

Core tip: While surgical intervention with the Laparoscopic Nissen Fundoplication remains the gold standard for reflux, endoscopic treatments for gastroesophageal reflux disease have become increasingly popular in recent years. This review of endoscopic methods focuses on two procedures: the Esophyx, a procedure involving endoluminal fundoplication of the gastroesophageal junction, and Stretta, a procedure involving radiofrequency ablation of the gastro-esophageal junction. While these techniques have an acceptable safety profile and lead to subjective improvement in reflux, their objective efficacy remains unclear. The review highlights the lack of standardisation of outcome measures and heterogeneity of assessment tools.

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INTRODUCTION

The most widely accepted definition of gastroesophageal reflux disease (GERD), developed by the International consensus group, is "a condition that develops when stomach contents cause troublesome symptoms and/or complications"[1]. In North America, it has a prevalence of 18.1%-27.8%[2] and is estimated to be the most common reason for an outpatient gastrointestinal clinic visit[3]. This translates into significant economic burden through health-care associated costs, as well as reduced quality of life (QOL) for affected persons.

GERD is a multifactorial disease process. Factors affecting the development of GERD include mechanical impairment of the gastroesophageal (GE) junction, hiatal hernias (HH), and esophageal acid exposure (EAE). Pathological reflux can result in GERD type symptoms (heartburn, regurgitation, heartburn) and mucosal disease (esophagitis, strictures, metaplasia and cancer)[4].

The treatment of GERD changed dramatically after the advent of proton pump inhibitors (PPIs)[5]. In conjunction with lifestyle modifications, they are the current first line therapy for GERD[6]. While PPIs are often effective, there are patients who will be non-responders, require chronic PPI use or be subject to side effects of PPI therapy[7]. These side effects include enteric infections (*Clostridium difficile*), increased susceptibility to pneumonia, hypergastrinemia, osteoporosis and drug-drug interactions[8,9]. Furthermore, PPIs have a high drug expense and patient compliance with chronic daily use may be limited[10,11].

More invasive treatment options include surgical and endoscopic interventions. Laparoscopic Nissen Fundoplication (LNF) is considered the gold standard of treatment[12]. LNF differs from medical treatment in that it is directed at the underlying cause of GERD. The literature has demonstrated that LNF is able to provide improved relief of GERD symptoms and reduced PPI use with good long-term cost efficacy[13,14]. Furthermore, LNF may be more effective for those patients with abnormal symptoms[7,15].

Endoscopic treatments for GERD have become increasingly prevalent in recent years. There has been increased interest in these interventions by both patients and practitioners as an alternative to surgical intervention[12]. Endoscopic intervention is less invasive, typically involves a day procedure and avoids side effects of LNF such as bloating and dysphagia[9,16]. They are less permanent interventions; yet do not preclude the patient from being a future candidate for LNF[17-19]. Historically, endoscopic treatments have been divided into three separate categories: radiofrequency (RF) treatment of the GE junction, plication of the lower esophageal sphincter (LES) and injection of biopolymers[6,9]. Currently, there are two endoscopic interventions being used clinically - transoral incisional fundoplication (TIF) with the Esophyx device and RF treatment with the Stretta device.

The intent of this review is to provide an update on more recently published data regarding the two endoscopic interventions for GERD that are currently in clinical use (Stretta and EsophyX). Prior reviews have summarized short-term effects and suggest that long-term efficacy be studied and the appropriate patient populations be identified[16,20]. In the majority of published studies to date, the most common primary endpoint is subjective reduction in daily symptoms ($\geqslant$ 50%) or improvement in health related quality of life (HRQL) scores. Objective end point outcomes (pH studies, resolution of esophagitis and reduction of HH) have not been routinely studied in all patients up to this point in time.

DISCUSSION

Esophyx

The EsophyX (EndoGastric Solutions, Inc., Redmond, WA, United States) was developed as a method of restoring the valve at the GE junction through an endoluminal fundoplication (ELF) technique. The device is inserted transorally under direct vision with an endoscope. It allows for creation of 2-3 cm and 210°-300° fundoplication at the level of the GE junction. Twelve or more polypropylene, full thickness fasteners are used to create the omega-shaped valve. In a revision of the device (TIF 2), the fasteners are deployed 3-5 cm above the GE junction to create a flap valve similar to that of a LNF[12,16,21].

Randomized controlled trials

The first published randomized controlled trial (RCT) in 2011 by Svoboda *et al*[22] compared TIF against the gold standard Nissen fundoplication. The authors concluded no significance difference between the two therapies,

with a significant reduction in length of stay in favor of TIF (2.9 d *vs* 6.4 d).

The RESPECT trial was published in 2015[18]. It included 129 randomized patients. Results included a significant elimination of troublesome regurgitation in 67% (58 of 87) of TIF patients as compared to 45% (19 of 42) of PPI/sham patients. TIF patients also had significant decrease in EAE. At 18-mo follow, 71% (30 of 42) of the PPI/sham had crossed over to TIF and 28% (24 of 87) of the TIF group had resumed PPI.

The TEMPO trial was an open-label, randomized study of 60 patients who were followed up to 6 mo, with a primary end point of elimination of daily bothersome symptoms[23]. Troublesome regurgitation was eliminated in 97% (29/30) of patients undergoing TIF and off PPI, *vs* 50% (9 of 18) in the PPI group. At 6 mo, 90% (35 of 39) patients undergoing TIF had complete cessation of PPI use. EAE was normalized in 54% (21 of 39) of the TIF group *vs* 52% (11 of 21) in the PPI group. At 6 mo, 90% (18 of 20) of the TIF group had reduction of complete healing of esophagitis *vs* 38% (5 of 13) in the PPI group. Overall, the authors demonstrated that TIF had a more significant effect on controlling GERD symptoms compared to PPI.

A RCT was performed by Witteman *et al*[24], comparing TIF *vs* PPI treatment for GERD in 60 patients. They were followed up to 12 mo, with crossover of the PPI group to TIF at 6 mo. At 6 mo follow-up, HRQL scores were increased by ⩾ 50% in 55% of the TIF group *vs* 5% of the PPI group. Change in EAE, normalization of pH and healing of esophagitis was non-significant between the groups. While TIF2 had a significant increase in LES pressure, the total number of reflux episodes did not improve. In the TIF group, PPI was discontinued in 74%. Hill grade Ⅰ valves were created in 90% at the time of TIF, with only 35% remaining at 12 mo.

Long-term follow-up trials

Trials with long-term follow-up are limited in the literature. Bell *et al*[25] looked at prospectively collected data on TIF performed on 127 patients. Two year follow-up was completed on 100 patients with a primary endpoint of ⩾ 50% improvement in their regurgitation score. Of the 88 patients presenting with daily symptoms, 70% (60) reached the primary endpoint. Of the 98 patients starting with daily PPI use, 69 (70%) had complete cessation of PPI. HRQL scores remained stable to the 24 mo follow-up point. In regards to objective endpoints, 31 patients underwent endoscopic screening with healing of esophagitis seen in 75% (12 of 16). Furthermore, pH testing was performed in 50 patients preoperatively and 14 patients at 2 years. Eight of 14 (57%) patients had normalization of esophageal acid exposure.

Testoni *et al*[26], followed 50 patients who underwent TIF 2.0 with EsophyX. Mean follow-up was 52.7 mo, with 14 patients reaching 6-year follow-up. HRQL scores were significantly reduced compared to pre-intervention. In regards to PPI use, ⩾ 50% reduction or cessation was seen in 87.8% (36 of 41) at 24 mo, 84.4% (27 of 32) at 3 years, and 85.7% (12 of 14) at 6 years. There was no significant change in LES pressure at any time point. Overall, long-term response was best predicted by initial response in the first 6-12 mo, with best candidates for TIF being patients with Hill grade Ⅰ/Ⅱ valves and a hiatal hernia < 2 cm.

Literature reviews

In 2013, Wendling *et al*[19], published a systematic review of 15 observational studies of TIF. There was significant improvement in HRQL score compared to baseline score on PPI. Overall, the patient satisfaction rate with TIF was 72% at a mean of 8.5 mo. PPI cessation rates varied widely, with an overall rate of 67% at a mean follow-up time of 8.3 mo. There was weak correlation between discontinuation and follow-up length. None of the included studies were able to demonstrate reduced post-procedure EAE time. In total, there were 18 complications, with the most common being hemorrhage (1.1%) and an overall failure rate of 8.1%.

Overall, the limited long-term data reviewed here suggests that TIF with EsophyX may be effective for symptom control and PPI reduction or cessation for up to 2-6 years. There is no evidence that EsophyX is more effective than LNF. TIF may be most effective for patients with HH < 2 cm and Hill Grade Ⅰ/Ⅱ valves[23,26,27]. The ideal patient population has yet to be fully elucidated. The safety profile is acceptable, with low complication rates and no associated mortality.

STRETTA

Stretta (Mederi Therapeutics, Greenwich, CT, United States) was approved by the FDA in 2000. It delivers radiofrequency energy to the LES and gastric cardia. A gastroscope is first inserted to measure the distance to the Z-line. The gastroscope is then withdrawn and a catheter with a four channel RF generator is placed 1 cm proximal to the Z-line. Radiofrequency energy is then delivered to the muscularis propria for approximately 60 s to a target temperature of 65-85 degrees Fahrenheit. Tissue temperatures are constantly monitored using a thermocouple incorporated into the active electrodes[28]. Additional treatments are delivered by rotating the catheter circumferentially, as well as advancing it distally for a span of 2 cm towards the gastric cardia[12,16]. The mechanism of action of radiofrequency treatment for GERD has yet to be fully elucidated, but is thought to work *via* neurolysis or tissue necrosis causing local inflammation, collagen deposition and muscular thickening of the LES, resulting in fewer transient relaxations in LES pressure[28-30]. Clinical use was previously limited by safety concerns for esophageal perforation. In recent studies, the most commonly seen side effect was chest pain, which was self-limited and did not require intervention[31].

Gastroparesis has also been identified[32].

As it has been on the market for approximately 15 years, Stretta has been the topic of multiple studies and reviews, including four RCTs[29,32-34]. More recently published studies have focused on long-term efficacy of the procedure.

RCTs

In 2003, Corley *et al*[34], published the first randomized, sham-controlled trial for RFA in GERD patients, with follow-up at 0, 6, and 12 mo. At 6 and 12 mo, patients treated with RFA had significantly improved heartburn symptoms as well as improved QOL scores. No improvement was seen in the sham group. Prior to a medication withdrawal protocol there was no difference in daily PPI use between groups. Following this protocol the RF group reduced PPI usage by 46% compared to 29% in the sham group. There was no difference in EAE between RF and sham groups at 6 mo. A sub-group analysis of responders (> 50% reduction in QOL score) was shown to have significant decreases in 24-h acid exposure. Additionally, there was no difference in LES pressure or esophagitis between groups.

In 2008, Coron *et al*[29] published a prospective, randomized trial comparing PPI use *vs* RF energy in patients with PPI-dependent GERD. Results for their primary outcome demonstrated reduction or discontinuation of PPI in 18/23 (78%) of patients treated with RFA *vs* 8/20 (40%) in their control group at 6 mo follow-up. At 12 mo, this decreased to 12/23 (56%) and 7/20 (35%), respectively. Their secondary outcomes showed no difference in heartburn scores, no difference in QOL surveys, no difference in mean daily dose of PPI at 6 or 12 mo (P = 0.05) and no change in 24 h pH monitoring or endoscopic grade of esophagitis.

In another prospective, randomized, double-blinded, sham-controlled trial by Aziz *et al*[32] in 2010, patients were treated with either a single dose Stretta, a double dose of Stretta or with a sham procedure. At 12 mo there was a significant improvement in GERD-related symptoms in both active treatments, but not the sham group. In the double-dose group 50% were completely off their PPI, while only 16.6% in the single-dose group and none in the sham group were completely off of PPI therapy. LES pressure and esophageal acid exposure time was improved in both the single and double-dose treatment groups, with non-significant changes seen in the sham group.

In the latest RCT in 2012, Arts *et al*[33] reported outcomes of a double blind, sham-controlled study looking at the effect of the Stretta procedure on GERD symptoms, esophageal acid exposure and GE junction distensibility. They hypothesized that the procedure may decrease GE junction distensibility, thereby reducing the volume of refluxate and subsequently symptomatology. Symptom score was significantly reduced after the Stretta procedure, but not following a sham procedure. No change between the Stretta and sham groups was demonstrated in 3 or 6 mo follow-up endoscopy or 24-h pH monitoring. Medication use was not affected by initial Stretta procedure of sham. Finally, resting LES pressure did not change at 0, 3 or 6 mo following Stretta or sham procedure.

Long-term follow-up trials

Triadafilopoulos, in 2002, looked at Stretta durability at 6 and 12-mo follow-up[31]. They demonstrated significant improvement in heartburn scores, HRQL scores and patient satisfaction scores at both time periods. Eighty-eight percent of patients required daily PPI use at baseline, which decreased to 30% at 12 mo. Distal esophageal acid exposure time also decreased from 10.2% to 6.4%.

A prospective observational study of long term outcomes by Liang *et al*[35] in 2014, reported follow-up results on 138 of 152 initial patients. Overall symptom score was reduced at 6 mo and was sustained to the 5-year follow-up mark. At 6 mo, 38 (27.5%) of patients were completely off of PPI, which increased to 59 (42.8%) at 5 years.

Dughera *et al*[36] published long-term follow-up results of their single center study. Eight-year follow-up was achieved in 26 of 86 patients. In total, 7 patients restarted daily use of a PPI, of which 5 went on to have LNF. Overall, there was a significant decrease in heartburn score and increase in HRQL score that was still present at 8 year follow-up. Furthermore, 20/26 remained completely off a PPI. While none of the 26 patients developed endoscopic evidence of esophagitis, median LES pressure did not demonstrate any improvement at 8 years.

In the longest reported follow-up data, Noar *et al*[37] performed a 10-year, open label, prospective trial of patients with refractory GERD treated with Stretta. In total, 149 of 217 patients reached the 10-year follow-up, of which 72% had normalization of HRQL. Furthermore, 64% had $\geqslant$ 50% reduction in baseline PPI use with discontinuation in 41% at the 10 year mark. Fifty-one of 149 patients had no endoscopic evidence of erosive esophagitis at 10 years.

Literature reviews

Published reviews of the literature are conflicted in their recommendations of Stretta in the management of GERD. The most recent systematic review in 2014 by Lipka *et al*[38] concluded that was no evidence for the efficacy of radiofrequency ablation for the treatment of GERD. Their review included 4 randomized trials, all of which were determined to be of poor methodological quality. Overall outcomes showed no significant benefit of Stretta over sham therapy for mean time pH was less than 4, mean change in LES pressure, increase in discontinuation of PPI or improvement in HRQL scores[38]. This was in direct contrast to an earlier Review by Perry *et al*[3] and a subsequent recommendation review by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)[3,20,39]. Perry *et al*[3] found, in their 2012 review of 18 studies, that radiofrequency

produced significant improvement in reflux symptoms, with improved heartburn scores, esophageal acid exposure and QOL scores. The methodologically validity of both reviews continues to be debated[38,39].

Overall, the data suggests that the Stretta procedure has an acceptable safety profile and may be effective in reducing symptom burden and QOL scores up to 8 years post-intervention. There does not appear to be any sustained improvement in objective outcomes and there is no evidence that Stretta results in improved outcomes as compared to surgical intervention.

Limitations

Treatment modalities for GERD, as a field, suffer from a lack of standardization in primary and secondary outcomes. Although many studies have looked at HRQL, the tools used to do so are markedly heterogeneous. Furthermore, whether more subjective measures such as QOL and symptom control are equivalent to objective measurements has not yet been elucidated[17]. Subjective symptom improvement is clinically relevant, but there is no established correlation to severity of reflux[12]. PPI use is quantified in studies and is an objective outcome, but is not a specific marker for GERD and may be used for dyspepsia. Manometry and pH studies are more objective markers but may have less clinical relevance, particularly for the patient if symptom control is not improved.

Future direction

In a preliminary, prospective, single-arm trial, Ota *et al*[40], looked at a novel endoscopic fundoplication technique using endoscopic submucosal dissection (ESD) in 13 patients. Scarring post-ESD results in narrowing of the GE junction and reduced reflux. The demonstrated improved symptoms in 92% (12 of 13), cessation of PPI use in 23% (3 of 13) and reduced PPI use in 23% (3 of 13). There was no change demonstrated in pH studies.

Future directions may be aimed more towards novel surgical interventions, such as the LINX reflux management system, a ring of linked magnetic beads laparoscopically placed around the LES that improves pressure without any anatomical change[7,10]. The EndoStim is another device placed laparoscopically that delivers electrical energy to the LES in order to increase resting pressure[7,10].

CONCLUSION

In theory, endoscopic management of GERD is promising field with obvious advantages of a less invasive procedure, however the majority of procedures and devices released are no longer available for lack of reported efficacy. The published data for the two procedures with the most evidence, EsophyX and Stretta, generally show improvement over baseline (PPI therapy alone) or sham procedure but currently are second-line procedures to surgical intervention[20].

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Contents

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REVIEW

Laparoscopic surgery for rectal prolapse and pelvic floor disorders

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Author contributions: Rickert A and Kienle P designed the review, performed the literature search, interpreted the data, wrote the paper and finally approved the manuscript.

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Abstract

Pelvic floor disorders are different dysfunctions of gynaecological, urinary or anorectal organs, which can present as incontinence, outlet-obstruction and organ prolapse or as a combination of these symptoms. Pelvic floor disorders affect a substantial amount of people, predominantly women. Transabdominal procedures play a major role in the treatment of these disorders. With the development of new techniques established open procedures are now increasingly performed laparoscopically. Operation techniques consist of various rectopexies with suture, staples or meshes eventually combined with sigmoid resection. The different approaches need to be measured by their operative and functional outcome and their recurrence rates. Although these operations are performed frequently a comparison and evaluation of the different methods is difficult, as most of the used outcome measures in the available studies have not been standardised and data from randomised studies comparing these outcome measures directly are lacking. Therefore evidence based guidelines do not exist. Currently the laparoscopic approach with ventral mesh rectopexy or resection rectopexy is the two most commonly used techniques. Observational and retrospective studies show good functional results, a low rate of complications and a low recurrence rate. As high quality evidence is missing, an individualized approach is recommend for every patient considering age, individual health status and the underlying morphological and functional disorders.

Key words: Resection rectopexy; Pelvic floor disorders; Rectal prolapse; Laparoscopy; Mesh rectopexy; Suture rectopexy

Core tip: Pelvic floor disorders are dysfunctions of the pelvic organs which affect a substantial amount of people, predominantly women. Operative treatment is often necessary and laparoscopic procedures play a major role. Many different techniques are used but their functional and operative outcome is hardly evaluated in randomised studies. In this review we summarize the present status of laparoscopic surgery for pelvic floor disorders. The different techniques are described,

compared and rated concerning their operative outcome, functional results and recurrence rates. Clinically important topics like management of complications and surgery in elderly people are highlighted.

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INTRODUCTION

The term pelvic floor disorders summarises different dysfunctions of gynaecological, urinary or anorectal organs. These dysfunctions can present as incontinence, outlet-obstruction and organ prolapse or as a combination of these symptoms. The underlying reasons for these problems can be functional or morphological. Rectocele, enterocele and rectal intussusception are the most frequently encountered morphological manifestations and are commonly associated with a descensus of the perineum. The judgement on to what extent these anatomic disorders are clinically relevant and account for the associated bowel dysfunctions (incontinence, constipation) is difficult, as they often occur in combination and are also frequently found in healthy people[1,2]. The prevalence in women is about 25% for at least one of the above morphological pelvic floor abnormalities, somewhat questioning the clinical implications of such diagnosis *per se*.

Complete rectal prolapse is defined as protrusion of all layers of the rectum through the anal canal, full thickness rectal prolapse (FRP). A protrusion of mucosa only is called mucosa prolapse (MP). The clinical differentiation between these two can be difficult.

A common classification divides three grades: Rectal prolapse Ⅰ°: inner (recto-rectal) intussusception of the rectum proximal of the anal canal; Rectal prolapse Ⅱ°: inner (recto-anal) intussusception into the anal canal; Rectal prolapse Ⅲ°: prolapse of the rectum beyond the anus (external prolapse).

The aetiology is unclear. Rectal prolapse is often associated with obesity, pregnancy, chronic constipation and other conditions that lead to increased abdominal pressure.

The most common anatomic varieties in patients with rectal prolapse are redundant sigmoid, diastases of the elevator ani, loss of the vertical position of the rectum and its sacral attachments and a deep cul-de-sac[3,4].

The pathological relevance of an internal prolapse is unclear. A rectal prolapse Ⅰ° is present in 20% to 50% of healthy individuals[2,5]. On the other hand a recent study on 86 patients with internal rectal prolapse found faecal incontinence in 55% and showed incomplete evacuation in 45% of patients[6]. The intussusceptions that are found in people without symptoms are more often only a MP, whereas patients with evacuation problems significantly more often have a full thickness prolapse[7].

The differentiation to anal prolapse which is a protrusion of anoderm is important as the latter prolapse is generally operated *via* a perineal approach.

A rectocele is a protrusion of the rectum into the vagina. An enterocele/sigmoidocele is a prolapse of the peritoneal sack between rectum and vagina with herniation of small bowel respectively sigmoid. The clinical relevance of these anatomical varieties is also unclear. It is thought that larger rectoceles can lead to outlet obstruction with incomplete emptying. Defecographies showed an incidence of up to 93% in healthy women. Enteroceles can be found in up to 20% of healthy woman[2,5].

A prospective evaluation of 100 patients with obstructive defecation syndrome (ODS) found a combination of rectocele and MP in 54% of patients[8]. Dvorkin *et al*[7] tried to define certain predictive symptoms in 896 patients with evacuation disorders. They used an evacuation proctography and found 125 patients with rectal intussusception, 100 patients with rectocele and 152 patients with both pathologies. Anal pain and sensation of prolapse were predictive for the subsequent finding of an isolated intussusception rather than a rectocele.

In a systematic review on laparoscopic ventral rectopexy (LVR) for ODS all patients had a rectocele, 90% had an intussusception and 51% had an enterocele[9].

OPERATION PROCEDURES

Multiple operations have been described for the therapy of pelvic floor disorders. In the following section techniques and results of operations as far as they are performed laparoscopically are explained and rated (Tables 1 and 2).

The aim of the operation generally is to correct the morphologic alteration and thereby treat the symptoms of the patient, *e.g.*, improve incontinence or constipation and incomplete emptying, depending on what major symptoms the patient is suffering from. This can be achieved by three ways: (1) fixation of the rectum (rectopexy); (2) resection or plication of redundant bowel; and (3) mobilisation of the rectum. Most operations combine the two principles of rectal mobilisation and rectopexy, some operations add bowel resection.

The approach can be transanal/perineal or transabdominal. Abdominal operations seem to result in lower recurrence rates, but there are no randomised controlled trials substantiating this[10,11]. Perineal procedures avoid laparotomy/laparoscopy and therefore may have a lower operative risk and morbidity. They may therefore be more suitable for older or high-risk

Table 1 Abdominal procedures for pelvic floor disorders

Type of procedure	Operation technique
Suture rectopexy (Sudeck)	Complete rectal mobilisation to level of levators Suture of rectum to presacral fasica
Anterior sling rectopexy (Ripstein)	Complete rectal mobilisation to level of levators circular wrapping of mesh around rectum and attachment to the promontory
Lateral mesh rectopexy (Orr-Loygue)	Anterior + posterior complete rectal mobilisation fixation by two lateral mesh strips to promontory
Ventral mesh rectopexy (D'Hoore)	Strictly anterior rectal dissection to level of levators Fixation of mesh strip on distal rectum and to promontory
Posterior mesh rectopexy (Wells)	Complete rectal mobilisation to level of levators Semicircular mesh around rectum posterior, fixation to promontory
Resection rectopexy (Frykman-Goldberg)	Complete rectal mobilisation to level of levators sigmoid resection and suture fixation of rectum to promontory
Rectal mobilisation without rectopexy	Complete rectal mobilisation to level of levators no fixation

Table 2 Outcome of laparoscopic procedures for pelvic floor disorders

	Minor compl.	Major compl.	Mortality	Conversion	Incontinence	Constipation	Recurrence
LSR	0%-16%	2%-11%	0%	0%-5%	48%-82% (+)	11% (-)-70% (+)	2%-20%
LMR	0%-5%	0%-3%	0%	0%-5%	76%-92% (+)	38% (-)-36% (+)	1.3%-6%
LVR	0%-36%	0%-5%	0%-0.4%	0%-7.4%	70%-90% (+)	60%-80% (+)	0%-14%
LRR	11%-21%	0%-4%	0%-0.8%	0%-6%	62%-94% (+)	53%-80% (+)	0%-11%

Data from studies that report data of laparoscopic rectopexy. Incontinence/constipation: Improvement (+), worsening (-); Minor compl.: Dindo Ⅰ-Ⅱ; Major compl.: Dindo Ⅲ-Ⅳ. LSR: Lap. suture rectopexy; LMR: Lap. mesh rectopexy (Wells, Orr-Loygue); LVR: Lap. ventral rectopexy; LRR: Lap. resection rectopexy.

patients with a relevant co-morbidity, although again there are no adequately powered RCTs to back these recommendations up.

Virtually all abdominal procedures that were originally described *via* laparotomy can also be performed laparoscopically. The laparoscopic management of rectal prolapse was first introduced in 1992 and consisted of a suture-less rectopexy with staples without bowel resection. In the meantime, besides the conventional laparoscopic approach, there are new reports of a robotic-assisted approach with the da-Vinci system[12,13]. The transabdominal operations differ mainly in the extent of rectal mobilisation, the method of rectal fixation and the additional sigmoid resection.

RECTOPEXY

The fixation of the rectum to the sacrum is supposed to restore the physiological position of the rectum and thereby also correct the descensus of the pelvic floor. The fixation can be achieved by simple stitching, stapling or by meshes.

SUTURE RECTOPEXY (SUDECK)

This method was first described by Sudeck in 1922. The operation includes a complete mobilisation of the rectum down to the level of the levators. The rectum is then attached to the promontory by suture or staples. The dorsal mobilisation induces fibrosis which helps to fixate and hold the rectum in place[14].

In the literature this technique was used mostly to treat full rectal-prolapse in some cases combined with outlet obstruction or occasionally for outlet obstruction alone. Morbidity rates of 0% to 16% and no mortality were reported[15-18]. Conversion rates were between 0% and 5%. Most reports showed an improvement of incontinence, while constipation was mostly unchanged or even slightly worsened. Recurrence rates were between 2% and 9%[19]. A study which performed a longer follow-up found a recurrence rate of 20% ten years after laparoscopic suture rectopexy[17].

RECTOPEXY WITH MESH OR GRAFT

A mesh or graft is used to achieve a broader fixation and induce more fibrosis. Used materials include fascia lata, synthetic meshes and bio-meshes[20]. The mesh can be placed anteriorly, posteriorly, laterally or around the rectum.

ANTERIOR MESH RECTOPEXY (RIPSTEIN SLING RECTOPEXY)

Ripstein[21] described this operative technique in 1952. After complete mobilisation of the rectum a graft constructed out of the fascia lata was wrapped around the rectum and sutured to the promontory. Later instead of a fascia lata graft, synthetic meshes are used.

There is only one case report on this procedure using a laparoscopic approach which found a good clinical outcome (no morbidity, no recurrence)[22].

LATERAL MESH RECTOPEXY (ORR-LOYGUE)

In this procedure the rectum is completely mobilised anteriorly and posteriorly. Two mesh strips are sutured laterally to the rectum on both sides. The mesh strips are then sutured under tension to the promontory[23].

Several studies examined this technique with a laparoscopic approach. Lechaux *et al*[24] performed 35 laparoscopic Orr-Loygue rectopexies. They reported a surgical morbidity of 5% and no mortality. Incontinence improved in 27% of patients, constipation improved in 19%, but worsened in 27%. The recurrence rate was 6% after a follow-up of 36 mo. A study on 73 patients with an Orr-Loygue procedure with limited lateral dissection found an improvement of incontinence in 90% and of constipation in 60% of patients[25].

POSTERIOR MESH RECTOPEXY (WELLS)

After a complete mobilisation of the rectum a mesh is placed around the posterior circumference of the rectum (2/3) and then fixed to the promontory. The ventral third of the rectal circumference is spared to avoid fibrosis and stenosis by shrinking of the mesh.

A prospective study examined the Wells' procedure in 77 patients with FRP. It observed no major post-operative complications. Incontinence improved in 89% of patients, constipation improved in 36%[26]. Recurrent prolapse occurred in one patient (1.3%). Older studies evaluating laparoscopic posterior mesh rectopexy found similar results, but with a worsening of constipation in 20%-30% of patients, which might be caused by injury of autonomic nerves during posterior dissection[27].

VENTRAL MESH RECTOPEXY (D'HOORE)

In 2004 D'Hoore *et al*[28] published the results of a novel, autonomic nerve-sparing rectopexy technique. The dissection in this operation is strictly ventral in the rectovaginal space down to the pelvic floor. A lateral or dorsal mobilisation is not performed. The rectum is attached to the sacrum by a mesh which is sutured to the anterior side of the rectum. The ventral dissection and position of the mesh has several advantages: (1) a supra-anal rectocele can be corrected; (2) the rectovaginal septum is reinforced which prevents an anterior recto-rectal intussusception which may be one of the relevant mechanisms to a full rectal prolapse; and (3) a colpopexy is performed. The avoidance of any lateral or posterior mobilisation preserves the autonomic nerves[29].

Although LVR is a comparably new method it was rapidly adopted and up to now, more than 30 retro- and prospective series have reported outcome and postoperative function. Two systematic reviews have summarized the data.

Indications for the procedures were intussusception as well as overt rectal prolapse, rectocele, ODS and vaginal vault prolapse.

The rate for minor complications was 0% to 36%, major complications were observed in 0% to 5%. Reported typical but infrequent complications were erosions of the bowel or the vagina caused by the mesh or a dislocation of the mesh in about 4% of patients. Two studies reported the rare event of a lumbosacral discitis at the site of the proximal mesh fixation in 3 patients[30,31].

The conversion rate ranged from 0% to 7.4%. In most cases the conversions had to be made due to pelvic or abdominal adhesions after prior surgery.

Recurrence rates in the literature range from 0% to 15%, with most studies reporting recurrences in less than 5% of patients after a follow-up of a minimum of two years.

The median hospital stay ranged from 1 to 7.1 d. One study showed that a same day discharge was possible in selected patients and that more than 90% of patients could be discharged the day after surgery with the same long term outcome[32].

Fifty percent to 93% of patients operated with LVR suffered from constipation pre-operatively, between 44% and 93% of patients had faecal incontinence. Bowel function improved significantly in all studies with improvement rates from 70% to 90% for incontinence and 60% to 80% for constipation. Seven percent to 27% complained of persisting constipation and 0% to 18% of persisting incontinence. A new onset of constipation was found in 2% to 7% of patients[9,28,33]. Sexual function also showed significant improvement postoperatively[34,35].

Despite the good results, the rapid adoption and distribution of this new method without any high level evidence has to be seen critically[36].

RESECTION RECTOPEXY (FRYKMAN-GOLDBERG)

A sigmoid resection is combined with a rectopexy, mostly a sutured rectopexy. The resection results in the following morphologic changes: (1) an area of fibrosis develops around the anastomosis and the sacrum which leads to a rectal fixation to the sacrum; and (2) the colon lies in a straighter course which avoids torsion and sigmoidocele[37].

Especially in patients with an elongated sigmoid and slow-transit constipation it is postulated that constipation improves through the resection of redundant colon. A recent study, however, could not confirm an improvement in abnormal colonic transit time in patients after resection rectopexy[38].

Furthermore it must be considered that a removal of a part of the colon can alter bowel function independently from the underlying pelvic floor disorder. A recent study reported impaired bowel function and quality of life after sigmoid resection for diverticulitis[39,40]. Resection

of the sigmoid and creation of an anastomosis can contribute to perioperative morbidity (leakage, stenosis, ureter lesion).

Indications for resection rectopexy in the available studies were intussusception, external rectal prolapse, rectocele and ODS.

In studies for laparoscopic resection rectopexy (LRR) a minor complication rate between 11% and 21% and a major complication rate between 0% and 4% were observed. Anastomotic leakages occurred very rarely (< 1%). Only an older study from 1998 reported a leakage rate of 3.3%[41]. A low mortality rate between 0% and 0.3% was observed.

The conversion rate for LRR ranges from 0% to 6%. The reasons for conversion were mainly adhesions[42-45].

The recurrence rates ranged from 0% to 11% after a follow-up of a minimum of 4 years. The median hospital stay ranged from 4 to 9.7 d.

LRR improved incontinence in 62% to 94% of patients and constipation in 53% to 80% of patients with rectal prolapse[44,45].

LRR was performed for ODS in one study. Sixty percent of patients showed a rectocele, 60% had a rectal prolapse Ⅰ°-Ⅲ° and 50% had sigmoidocele. In 40% of patients the incontinence and the constipation ceased, in further 40% the symptoms improved irrespective of the underlying morphologic pathology[46].

ROLE OF ABDOMINAL PROCEDURES AND LAPAROSCOPY

Concerning the large number of different operative methods and the poor evidence it does not surprise that evidence based guidelines for treatment do not exist for pelvic floor disorders.

A recent survey asked 391 surgeons over 50 countries for their preferred method for the treatment of rectal prolapse. It revealed that 60% of surgeons would treat healthy patients with an external prolapse with a laparoscopic abdominal procedure, 20% would chose an abdominal method *via* laparotomy and only 20% favoured a perineal approach. For internal prolapse still 40% of the surgeons preferred laparoscopy. While in Europe LVR is the most popular treatment for external prolapse, surgeons in North America favour LRR[47].

An expert consensus paper published in 2013 explicitly recommends a laparoscopic or robotic approach for ventral rectopexy[48].

LEARNING CURVE OF LAPAROSCOPIC RECTOPEXY

The learning curve for laparoscopic colorectal surgery has been found to be around 150 to 200 cases for achieving a constant level of proficiency[49,50]. This also seems to apply to laparoscopic rectopexy. One large single-surgeon series found a proficiency level of 54 patients for operation time and about 100 patients for clinical and functional outcome parameters even for an experienced colorectal surgeon[51]. This adds to the difficulties in evaluating different procedures, as in most studies the experience of the surgeon was not defined.

COMPARISON OF LAPAROSCOPIC AND OPEN PROCEDURES

Evidence from randomised studies that compared laparoscopic with open rectopexy is rare. A Cochrane systematic review from 2008 found that the laparoscopic approach resulted in fewer postoperative complications and a shorter hospital stay compared to the open approach. But these findings are based on only two randomised studies comprising altogether 60 patients. Both studies used a ventral mesh fixation without resection[52-54] (Table 3).

Postoperative major complications were only cardiorespiratory and occurred only in the group with an open operation. A faster recovery (return to solid diet) and a reduced requirement for morphine were found for the laparoscopic group, which altogether resulted in a shorter hospital stay. But no difference was found for functional parameters (incontinence, constipation, rectal capacity, anal squeeze pressure) and recurrence rates.

Two case controlled studies compared open and laparoscopic surgery for rectal prolapse. Kairaluoma *et al*[55] used different procedures in 106 patients (LRR, suture rectopexy, Wells rectopexy). A longer operation time (170 min *vs* 100.5 min) but a shorter hospital stay (5 d *vs* 7 d) was found for laparoscopy. Functional outcome, recurrence rates and complications did not differ between case- and control-group. Kariv *et al*[56] found similar results. In this study also different techniques were applied. One third of patients in each group had resection rectopexy respectively suture rectopexy respectively mesh rectopexy (predominantly Ripstein anterior rectopexy for open surgery, Well's procedure in laparoscopic surgery). Incontinence and constipation improved in all patients, with a significant higher improvement in the laparoscopic group (74% *vs* 54%). A likely explanation for this finding was the much more frequent use of the Ripstein procedure in the open surgery group where the circular anterior mesh placement can result in a stenosis which obviously in turn contributes to the occurrence of constipation[57]. For this reason a circular mesh placement is now considered obsolete by most authors.

de Hoog *et al*[58] compared open rectal prolapse surgery to a conventional laparoscopic and a robot-assisted approach in a prospective non-randomised setting. Half of the patients were operated with the Wells procedure, the other half with a ventral rectopexy. While the functional outcome (incontinence, constipation) improved significantly in all three groups, the recurrence rates during a 2-year follow-up were significantly increased in the robot-assisted (20%) and the conventional laparoscopic group (27%) *vs* 2% in

Table 3 Comparative rectopexy studies (open *vs* laparoscopic, different procedures)

Study	Procedure	Patients	Results
Sajid (2009)	LR	330	No difference in Mort, Morb, Inc, Cons, recurrence shorter hospital stay for LR
Meta-analysis (12 studies)	OR	358	Shorter operation times for OR
different procedures			
Caddedu (2012)	LR	192	No difference in Mort, Morb, Inc, Cons, recurrence
Meta-analysis (8 studies)	OR	275	
different procedures			
Senapeti (2013)	SR	38	No difference in morbidity, recurrence and functional outcome
Randomised	RR	40	
Forminje (2014)	LVR	40	More minor complications in LRR
Retrospective	LRR	28	No difference in major complications, recurrence and functional outcome
Sahoo (2014)	LPR	38	No differences in morbidity, recurrence and functional outcome
Retrospective	LSR	32	
Lechaux (2004)	LRR	13	Significant more patients with worsening of constipation in the LMR-group (26% *vs* 8%)
Prospective	LMR	35	No differences in morbidity and improvement of continence
Madbouly (2002)	LRR	12	No difference in complications and functional outcome
Prospective	LPR	12	

Data from studies that compare open *vs* laparoscopic rectopexies or studies that compare different procedures. Mort: Mortality; Morb: Morbidity; Inc: Faecal incontinence; Cons: Constipation; LR: Laparoscopic rectopexy; OR: Open rectopexy; SR: Suture rectopexy; RR: Resection rectopexy; LPR: Laparoscopic posterior mesh rectopexy; HS: Hospital stay; OT: Operation time.

the open group. However, there was an imbalance in patient distribution, with more young patients in the laparoscopic group. In these patients a vaginopexy was generally not performed, which proved to be a protective factor in regard to recurrence on multi-variate analysis.

In a recent meta-analysis, 12 comparative studies comprising 688 patients (330 with laparoscopic rectopexy) were analysed[59]. A drawback of this meta-analysis was that only one study was randomised and that several different procedures (resection, non-resection) were used even within studies. Nevertheless a significant shorter hospital stay was found for the laparoscopic group, while no differences between the open and laparoscopic approach were found for complication rates, postoperative functional outcome, recurrence rates and mortality. A meta-analysis from 2012 showed the same results[60].

As a conclusion: the laparoscopic approach for rectal prolapse is equivalent to the open approach in terms of functional and clinical outcome. The recurrences rates do not seem to differ, although single studies suggest higher recurrence rates after laparoscopic surgery. Advantages are a shorter hospital stay. It has to be remarked that the evidence is based on only two randomised and a few prospective and comparative case-controlled studies with significant heterogeneity in patient characteristics and in applied surgical procedures, making a relevant selection bias very probably.

COMPARISON OF DIFFERENT LAPAROSCOPIC PROCEDURES

Studies comparing the different operation techniques are rare. One randomised trial compared suture rectopexy (38 patients) with resection rectopexy (40 patients). After a median follow-up of 36 mo fewer recurrences were seen in patients with resection (13%) compared to patients with suture rectopexy (26%), but the difference was not statistically significant. Functional results were not different expect that the use of laxatives was more common at all time points in the suture rectopexy group. This suggests that resection has a positive effect on constipation[11].

Formijne Jonkers *et al*[45] compared 40 patients with LVR to 28 patients with LRR for full rectal prolapse in a retrospective cohort study. Patients with LRR suffered from significantly more complications (32% *vs* 7.5%), but these were mainly minor complications (wound infections, pneumonia), the rate of major complications was not different. Both groups showed a significant improvement in faecal incontinence (LVR 40% *vs* LRR 57%) and constipation (LVR 36% *vs* LRR 32%). In this study no recurrences were observed in a median follow-up period of 4 years.

Laparoscopic posterior rectopexy was compared to suture rectopexy retrospectively by Sahoo *et al*[61] in 70 patients. Suture rectopexy had a shorter operation time (100 min *vs* 120 min). The improvement of constipation (suture rectopexy 61% *vs* mesh rectopexy 47%) and incontinence (SR 90% *vs* MR 80%) was not different.

A comparison between LRR and LR without resection in 67 patients with FRP revealed that more patients with resection improved in incontinence while constipation improved similarly in both groups.

In a multi-centre randomised trial, Karas *et al*[62] evaluated, if a sole rectal mobilisation without rectopexy was equal to a posterior mesh rectopexy. Two hundred and forty-five patients were randomised. In case of constipation sigmoid resection was added. The degree of rectal mobilisation (posterior or 360°) was up to the surgeon's decision.

After a 5-year follow-up the recurrence rate in the group without rectopexy was significantly higher than in

the group with rectopexy (8.6% *vs* 1.5%, P = 0.003). This was despite the fact that sigmoid resection was significantly more often performed in the group without rectopexy[62].

Madbouly *et al*[63] compared LRR with laparoscopic posterior rectopexy in 35 patients with rectal prolapse. The choice of operation depended on the symptoms: patients with constipation or normal bowel habits underwent LRR, patients with incontinence LPR. Constipation was improved in 90% of patients after LRR and incontinence was improved in 80% after LPR. This emphasizes the need to consider the underlying symptoms besides the morphologic alterations in the choice of procedure.

Raftopoulos *et al*[64] conducted a retrospective multicentre pooled data-analysis on 645 patients with rectal prolapse in order to determine the impact of the surgical approach and the method of rectopexy on recurrence rates (464 open, 179 laparoscopic operations). Used techniques were LPR, LRR, LSR or mobilisation only. They found recurrent rates from 20%-30% after a ten-year follow up irrespective of what operation method was used. A limitation of the study was the heterogeneity of the data with a variation of recurrence rates between the centres from 0% to 85%.

The limited data allows only modest conclusions: (1) rectopexy and resection rectopexy show equivalent functional outcome with a slight advantage of resection rectopexy in the improvement of constipation; (2) resection rectopexy leads to an increase of minor complications; (3) rectopexy should be performed in any case, as recurrence rates are higher if only rectal mobilisation is performed; and (4) recurrence rates do not differ between the procedures and reach 20% when a long term follow-up (about 10 years) is conducted.

LAPAROSCOPIC RECTOPEXY IN ELDERLY PATIENTS

It is thought that the group of elderly patients especially profits from laparoscopic surgery. A recent systematic review showed significant advantages in short term outcome in laparoscopic colorectal surgery for elderly people[65]. As the incidence of rectal prolapse and pelvic floor disorders increases with age it is important to know if laparoscopic procedures are safe for this group of patients and if they offer a good alternative to perineal procedures.

For ventral rectopexy a recent French study evaluated 4303 patients from a national database. Patients aged more than 70 years were compared to patients younger than 70 years. Elderly patients had more minor complications (urinary, wound complications) and a longer hospital stay, but major complication rate and mortality were not different[66]. Another study used a modified laparoscopic Orr-Loygue technique in 46 elderly patients (median age 83 years) with rectal prolapse. A significant cardiac morbidity was observed. Two patients died of cardiac arrest. Two patients were re-operated for recurrent prolapse after 2 mo. The reasons for the recurrences were mesh dislocations. Faecal incontinence improved significantly (Wexner-Score decreased from 19 to 5 points after one year). Constipation did not improve. Most patients were satisfied with the operation, but there was no association seen between satisfaction and functional result[67].

A German study from 2012 studied the outcome of LRR in elderly patients (> 75 years). The complication rate was slightly increased compared to the younger population. Incontinence and constipation improved in half of the patients irrespectively of age[68].

Dryberg used a laparoscopic dorsal mesh rectopexy in 81 older patients with FRP[69]. A remarkable major complication rate of 14.8% was reported. Port site hernias with consecutive ileus and postoperative haemorrhage each occurred in 5% of patients. Thirteen point five percent of recurrences were observed at a median follow-up of 2 years.

TYPICAL COMPLICATIONS AND THEIR MANAGEMENT

A study in a tertiary referral centre analysed the typical complications after mesh rectopexy: Mesh fistulation or erosion of the rectum, vagina or the bladder, recto-vaginal fistula, early symptomatic recurrence, rectal stricture and chronic pelvic pain were observed. In this study all complications could be managed laparoscopically[70].

The reasons for early recurrence were in all 27 cases an inadequate technique during the prior operation (only limited or no ventral dissection, no sutures in the recto-vaginal space, detachment or incorrect position of the staples, wrong placement of the mesh to the lateral instead the anterior rectal wall with development of an enterocele). These cases were treated by placement of a new mesh and fixation with staples and sutures. Recto-vaginal fistulas were treated with removal of the mesh and abdominal or transvaginal fistula repair. Rectal injuries and strictures were operated by anterior resection and a placement of a bio-mesh. In all patients with rectal strictures the mesh had been stapled to the mid-sacrum rather than to the promontory. Erosions of the vagina or the bladder were managed by mesh removal, defect repair and insertion of a bio-mesh. All women with this complication were postmenopausal and had previous hysterectomy. In patients that complained about chronic pain unresponsive to pain medication, the mesh showed an excessive inflammation. A replacement of the mesh by a teflon-coated mesh improved symptoms. After revisional surgery, quality of life and bowel function improved significantly.

Two case reports describe a mesh fistulation in the rectum[71,72]. Typical symptoms were recurrent fever, pelvic pain and rectal bleeding. Diagnosis was made

by flexible sigmoidoscopy. In one case therapy was anterior rectum resection, in the other case the mesh was extracted laparoscopically and a loop-ileostomy was performed.

Tranchart *et al*[73] observed 6 rectal mesh migrations after 312 laparoscopic ventral mesh rectopexies (1.9%). The median time interval between surgery and onset of symptoms was 53 mo (range 4 to 124 mo). The treatment was transanal partial mesh resection, in one case where a recto-cutaneous fistula was present, a deviating colostomy was added. A recurrent mesh migration was again treated with partial mesh resection. After a median follow-up of 40 mo all patients were free of complaints and showed no recurrent mesh, migration.

As a rare but serious complication lumbosacral discitis at the site of rectal fixation was observed after ventral rectopexy and resection rectopexy. Only four cases are reported in literature. Patients presented typically 1 to 3 mo after the initial operation with severe lower back pain, fever and malaise. An magnetic resonance imaging revealed the diagnosis. A contrast enema was helpful to rule out a rectal fistula. Broad spectrum iv-antibiotics covering colonic flora are the treatment of first choice. In some cases, antibiotic treatment was not sufficient, and removal of mesh or suture material was necessary, in one case with a deviating colostomy[31,74,75]. A gynaecological review found 26 cases of discitis after sacrocolpopexy or rectopexy in a 50-year period[76]. Although this complication is rare it should always be considered in patients complaining of persisting back pain after any type of rectopexy.

FINANCIAL CONSIDERATIONS

An Australian study from 2004 conducted a cost-effectiveness analysis for posterior mesh rectopexy in a randomised setting. When costs for theatre time, staff, laparoscopic equipment and hospital stay were included, the laparoscopic operation was less costly than the open operation. The shorter hospital stay in the laparoscopic group accounted for this saving[77].

ASSESSMENT OF DIFFERENT APPROACHES

The evaluation of the different operation techniques is difficult, as the quality of available studies is low and outcome parameters are not defined consistently.

Regarding complications and conversion rates all laparoscopic procedures provide similar good results with each having their typical complications (anastomotic leakage, mesh complications). Recurrence rates for all methods are below 10% within a follow-up of up to 5 years but studies that extended follow-up to 10 years found recurrence rates of up to 20%.

LRR and LVR improve both constipation and faecal incontinence in a similar degree, but randomised studies are missing. LSR and LPR have about the same effect on incontinence, but they tend to have a lesser effect on constipation, in some studies these operations even worsened constipation in a relevant number of patients.

As high quality evidence is missing, an individualized approach is recommend for every patient considering age, individual health status and the underlying morphological and functional disorders. Moreover, as most operations actually show acceptable results, the choice of procedure also depends on the experience and learning curve of the surgeon.

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REVIEW

Coagulation syndrome: Delayed perforation after colorectal endoscopic treatments

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Abstract

Various procedure-related adverse events related to colonoscopic treatment have been reported. Previous studies on the complications of colonoscopic treatment have focused primarily on perforation or bleeding. Coagulation syndrome (CS), which is synonymous with transmural burn syndrome following endoscopic treatment, is another typical adverse event. CS is the result of electrocoagulation injury to the bowel wall that induces a transmural burn and localized peritonitis resulting in serosal inflammation. CS occurs after polypectomy, endoscopic mucosal resection (EMR), and even endoscopic submucosal dissection (ESD). The occurrence of CS after polypectomy or EMR varies according previous reports; most report an occurrence rate around 1%. However, artificial ulcers after ESD are largely theoretical, and CS following ESD was reported in about 9% of cases, which is higher than that for CS after polypectomy or EMR. Most cases of post-polypectomy syndrome (PPS) have an excellent prognosis, and they are managed conservatively with medical therapy. PPS rarely develops into delayed perforation. Delayed perforation is a severe adverse event that often requires emergency surgery. Since few studies have reported on CS and delayed perforation associated with CS, we focused on CS after colonoscopic treatments in this review. Clinicians should consider delayed perforation in CS patients.

Key words: Endoscopy; Syndrome; Colorectal; Dissection; Coagulation

Core tip: Few studies have reported on coagulation syndrome (CS) and delayed perforation associated with CS. Thus, in this review, we focused on CS after

colonoscopic treatments. CS is found in around 1% of cases after polypectomy and endoscopic mucosal resection and in 7%-8% of cases after endoscopic submucosal dissection. The prognosis for CS is excellent. However, clinicians should be mindful of delayed perforation in CS patients.

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INTRODUCTION

Various endoscopic treatments such as polypectomy, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD) have been used to treat colorectal neoplasms[1-14]. Colonoscopic polypectomy reduces the incidence of colorectal cancer by 70%-80%, and it has been used worldwide[1,2]. EMR is indicated for the treatment of colorectal adenomas, intramucosal, and submucosal superficial cancers (SM1; invasion of < 1000 μm from the muscularis mucosae) because of the negligible risk of lymph-node metastasis and excellent clinical outcomes; however, there is a limit to the size of *en bloc* resection[3-11].

Recently, ESD is another procedure used to remove large colorectal lesions according to the EMR curative criteria. This procedure is frequently used for removing large lesions by *en bloc* fashion, which includes lesions that would require piecemeal EMR for removal[11-14].

With respect to these aforementioned procedures, various procedure-related adverse events have been reported. Serious complications included delayed bleeding and perforation. Previous studies on the complications of colonoscopic polypectomy or EMR have primarily focused on perforation or bleeding[15-17]. Coagulation syndrome (CS) following endoscopic treatment, which was first reported as post-polypectomy syndrome (PPS)[18], is another typical complication. This has syndrome has a variety of names, including post-polypectomy CS, post-polypectomy electrocoagulation syndrome, and transmural burn syndrome[17-33]. Recognizing CS is important to avoid unnecessary exploratory laparotomy, because the syndrome can resolve with conservative treatment in most patients[19,21,23,26,30,31]. However, little is known about the clinical characteristics, clinical outcomes, and risk factors associated with CS, and the frequency of CS varies in previous studies[17-33]. Additionally, CS occurs after polypectomy, EMR, and even ESD[26,34]. With the evolution of treatment, the occurrence of this syndrome is thought to increase. Furthermore, there is a possibility that CS causes delayed perforation, which is a very severe complication[25,26,33,35-42]. In this review, we clarify the present status of CS following endoscopic treatment for colorectal neoplasms.

Most previous studies have investigated CS after polypectomy and EMR. Thus, in this review, we defined PPS as CS associated with only polypectomy and EMR, while CS included ESD.

DEFINITION OF CS

CS is the result of an electrocoagulation injury to the bowel wall that induces a transmural burn and localized peritonitis resulting in serosal inflammation[17-33]. Patients with CS are diagnosed when they present with abdominal pain (sometimes tenderness with rebound); fever; leukocytosis; an elevated C-reactive protein level; or peritoneal irritation symptoms and signs that occur after colonoscopic treatment (polypectomy, EMR, and ESD) with electrocoagulation, in the absence of visualized perforation by abdominal radiography and/or computed tomography (CT)[26,34]. It is important to recognize that CS can be misleading, as it can resemble a true rupture of the colon and present with pain, a low fever, and mild leukocytosis. Typically, patients with CS present within a few hours to 7 d after colonoscopic treatment with fever, localized abdominal pain, and localized peritoneal signs[19,20,26,30]. It is important to recognize this condition, because it does not require surgical treatment in most cases[19,21,23,26,30,31]. There is a range in severity of PPS between admission to the intensive care unit and post-discharge, as it can lead to shock, additional surgery, or death from possible follow-up on an outpatient basis.

CLINICAL CHARACTERISTICS

The rate of occurrence

The occurrence rate of PPS varies widely from 0%-7.6% in previous reports; however, most studies report a rate around 1%. It is considered some reports had high percentages of occurrence due to small patient populations[18-21,23-26,28-33].

Risk factors

Some previous reports have investigated the risk factors of PPS Nivatvongs[18] showed that 83% of PPS patients had polyps in the right side of the colon, and all were sessile polyps. Choo *et al*[24] also showed that right-colon polypectomies had a statistically significantly higher tendency for developing PPS. Lee *et al*[20] reported that a polyp size > 2 cm (OR = 1.08) and hypertension (OR = 14.40) were associated with a significantly increased risk of PPS. The most recent report showed that hypertension, a large lesion size, and non-polypoid configuration of the lesion were independently associated with PPS according to multivariate analysis[19].

PPS develops when the electrical current applied during colonoscopic polypectomy extends past the mucosa into the muscularis propria and serosa, resulting in a transmural burn without perforation[17-33]. Therefore, larger lesions and non-polypoid configuration are logical

risk factors, as they usually require a large amount of thermal energy for a longer duration. However, the mechanism of hypertension to promote PPS is unclear. Patients with hypertension are more likely to have endothelial dysfunction[43] and atherosclerosis[44,45], which may be contributing factors.

However, with thinness of the wall, there is also concern regarding the frequency of PPS. The right colon wall is thin, and a large study that addressed major post-polypectomy complications reported barotraumatic perforations, and all of them were caused by cecal blow-out[34,46-48]. Regarding colonic perforation, it has been suggested that air insufflation during colonoscopy generates a higher pressure in the cecum than in the rest of the colon, increasing vulnerability to injury. In addition, Rutter *et al*[49] hypothesized that a more perpendicular approach to polypectomy in the cecum may increase the risk of complications. However, scientific evidence in support of these theories is lacking.

Loffeld *et al*[47] also reported that barotrauma caused by insufflated air occurs more often than therapeutic perforation due to polypectomy or coagulation.

Prevention of PPS

Theoretically, submucosal saline injections of large, non-polypoid lesions prior to EMR may reduce the risk of PPS. The rationale for this is that a submucosal saline injection may increase the thickness of the submucosal layer and consequently reduce the risk of PPS[32]. However, no studies have supported this assumption. Sethi *et al*[17] hypothesized that submucosal injection itself leads to serosal irritation and localized peritonitis, and then patients present with PPS symptoms. Therefore, the protective role of the saline "cushion" for PPS should be considered in future studies.

The improvement of devices would likely reduce PPS. Galloro *et al*[50] reported that steel snares induced significantly deeper tissue injury than tungsten snares in the pure cut mode; therefore, tungsten snares may reduce the risk of PPS[32]. Another way to reduce the risk of PPS is dependent on skill. Using lower risk procedures when clinically appropriate or referring patients to high-volume endoscopists can reduce the complication rates[51].

PPS is considered different from infection from a local mucosal defect. Min *et al*[52] reported that blood cultures at baseline and 5 min after the procedure were all negative, and a blood culture at 30 min after the procedure showed a positive result in only 1 of 40 patients (2.5%). However, this one positive sample was considered contamination. None of the 40 patients showed any signs or symptoms associated with infection. Therefore, the prior administration of antibiotics is considered controversial for preventing PPS.

Treatment and prognosis

Most cases of PPS have an excellent prognosis, and they are managed conservatively with medical therapy. In some reports, all patients were admitted to the hospital, while in other reports, some cases underwent outpatient observation[19,21,23,26,30,31]. Treatment of PPS requires bowel rest and the administration of intravenous fluids and broad-spectrum parenteral antibiotics to cover the colonic bacterial flora. Nothing is taken by mouth until the symptoms subside. Patients with mild symptoms and adequate outpatient follow-up can be managed with oral antibiotics and a clear liquid diet for 1-2 d.

In contrast, to diffuse peritoneal signs, there is an indication for immediate surgical intervention. Within the spectrum of post-polypectomy cautery injury, "mini-perforation" falls between a "serosal burn" and frank perforation (with diffuse peritonitis). It is a minimal defect that can be quickly covered by peri-intestinal fat and omentum[16]. Its clinical features include pneumoperitoneum without signs and symptoms of diffuse or spreading peritonitis, and with local tenderness that is characteristic of a full-thickness burn. The patient usually improves within 24 h, and the symptoms should resolve within 96 h with conservative treatment. The dilemma as to whether the conservative or surgical approach is more appropriate for managing this kind of perforation still exists[19-22,26,30,31].

Although conservative treatment can generally be performed in most patients, it is important to adopt careful measures such as prolonging the fasting period and considering the possibility of delayed perforation[26,35-39].

DELAYED PERFORATION

Immediate perforation is diagnosed by endoscopy during resection and by the presence of free air on plain abdominal film or abdominal CT scan[15-17,35,51,53]. This is very rare; however, delayed perforation, which is considered to be caused by an electrical or thermal injury after electrocoagulation, was reported in these cases. Delayed perforation after colonoscopic resection can begin as PPS, which can evolve into a perforation or as a free perforation with air and fluid leakage, resulting in pneumoperitoneum and peritonitis[35-39].

Japan Gastroenterological Endoscopy Society guidelines for colorectal ESD/EMR defined delayed perforation as an intestinal perforation that develops over a certain period postoperatively (*i.e.*, intestinal perforation that is detected after the scope has been withdrawn following completion of ESD/EMR during which perforation did not occur). This is diagnosed based on abdominal pain, abdominal findings, the presence of a fever, and an inflammatory response that is consistent with PPS. Most cases of delayed perforation occur within 14 h after endoscopic resection. However, approximately one-third of delayed perforation cases are confirmed within 24 h after treatment. Free air, which cannot be detected by simple radiographic imaging, is sometimes found on abdominal CT. Therefore, in cases where delayed perforation is suspected, abdominal CT should be performed. Surgeons must be called for emergency surgery, because it is essential in cases of delayed perforation[26].

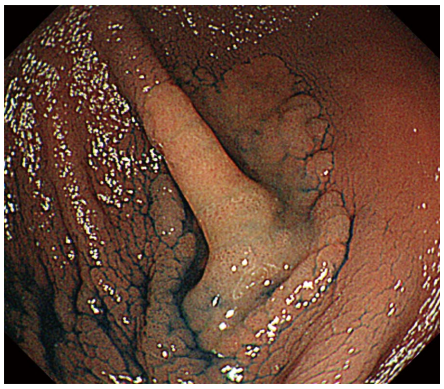

Figure 1 Chromoendoscopy showing a 30 mm laterally spreading tumor (non-granular type) located at the bottom of the cecum bottom.

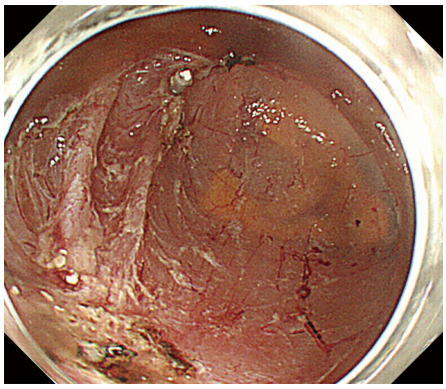

Figure 2 Endoscopic submucosal dissection is performed safely without intraoperative perforation. The procedure time is 47 min.

In 1994, Lo *et al*[54] reported that 43.8% of therapeutic perforations were managed conservatively with a mortality rate of 4.1%. This means that perforation is still a severe condition that reduces patients' quality of life[25,35-39]. Thus, prevention of PPS and its potential sequelae are most important, and clinicians must always consider the potential for delayed perforation due to PPS.

Only two studies have reported on the incidence of delayed perforation. Taku *et al*[39] reported delayed perforation in 7 of 15070 cases, while Waye *et al*[25] reported it in 1 of 777 cases. This is still not sufficient evidence. For ESD, the incidence of delayed perforation ranges from 0.1% to 0.4%[26,40-42].

THE RELATIONSHIP WITH ESD

CS after ESD

ESD has been a reliable method for en bloc resection of colorectal tumors regardless of the lesion size for years. Although colorectal ESD has been established as a procedure with reproducible safety and efficacy, complications such as intestinal perforation and delayed bleeding remain to be problematic. Similarly, few studies have reported CS after ESD[11-14,26].

Hong *et al*[48] reported that 8.6% showed CS after colorectal ESD. There were no differences in the demographic and endoscopic characteristics (age, sex, underlying disease, procedure time, tumor size, macroscopic type, location, and pathologic findings) between patients with CS and those without CS. The mean hospitalization stay was statically significantly longer in the CS group than that in the non-CS group. All patients with CS were treated with conservative (non-surgical) management (*e.g.*, fasting and intravenous antibiotics). CS showed a favorable progression even after ESD, and delayed perforation was not reported. See comment in pubmed commons below.

Delayed perforation after ESD

CS is reported even after ESD, and its frequency is clearly higher than polypectomy or EMR[26,34,48]. The procedure time and ulcer bed to energization that largely affects the characteristics of ESD procedures is evident theoretically. Delayed perforation in ESD is also a great concern. The indications for ESD are markedly different from those for conventional EMR, and the overall perforation rate is higher compared to conventional EMR[55]. Delayed perforation after ESD reportedly ranges from about 0.1%-0.4%; however, this may be because of the small number of reports[26,40-42,55].

Saito *et al*[41] reported that delayed perforations occurred in another 4 patients (0.4%) after ESD. Two of the 4 patients with delayed perforations were successfully treated conservatively, because the abdominal findings and inflammatory changes based on laboratory data were slight. However, other patients with delayed perforation required emergency surgery because of the risk of peritonitis. Saito *et al*[41] also reported that 0.11% (1/900) showed delayed perforation that required emergency surgery. Previous studies have cautioned that clinicians must carefully follow patients with delayed perforation, and continually close communication with consulting surgeons is essential since the number of such cases has been quite limited to date.

Few studies have reported on delayed perforation after ESD. While previous reports have shown the success of endoscopic clip closure with over-tube[42], the treatment and prognosis often require emergent surgery.

Case presentation

A 44-year-old woman underwent colonoscopy for surveillance of ulcerative colitis, and a 30 mm cecal sessile polyp was revealed (Figure 1). We diagnosed this tumor as a sessile serrated adenoma/polyp using the pit and narrow-band imaging patterns. Because of the size of the tumor and the tumor morphology, we chose ESD in order to perform en-bloc resection. ESD was performed safely without any perioperative complications (Figures 2 and 3), and she reported no symptoms. However, 24 h after ESD, she had a high fever (38.6 ℃) with slight abdominal pain and leukocytosis. Subsequently, she was diagnosed with CS after ESD. She fasted and received

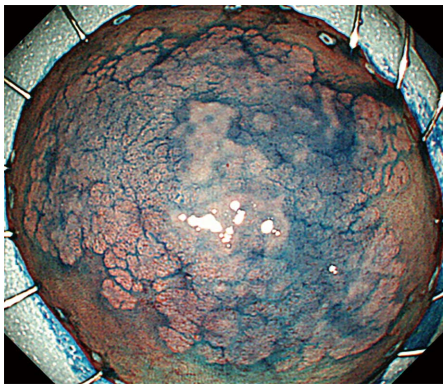

Figure 3 The tumor is resected in an *en bloc* fashion, and the specimen measures 51 mm × 40 mm.

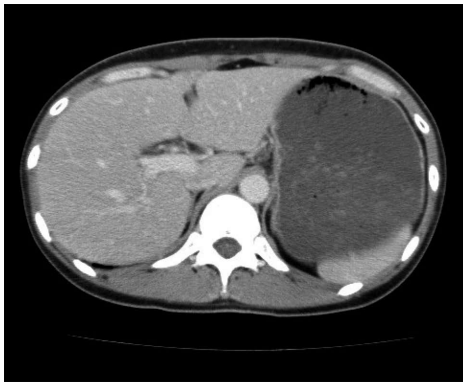

Figure 4 Abdominal contrast enhanced computed tomography 24 h after endoscopic submucosal dissection. Free air is not recognized.

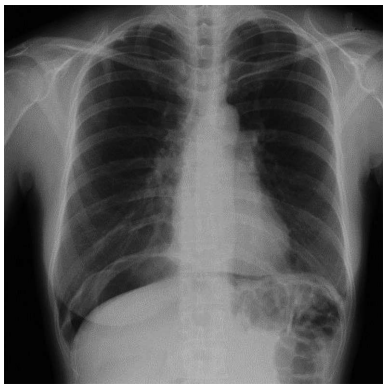

Figure 5 Abdominal radiography 36 h after endoscopic submucosal dissection because of a complaint of severe abdominal pain. A large amount of free air is observed under the diaphragm.

antibiotics (cefmetazole). CT was obtained immediately, but no findings were suggestive of perforation (*i.e.*, free air and ascites were not present) (Figure 4). Thirty hours after ESD, severe abdominal pain developed, and 36 h after ESD, free air appeared on radiography and CT (Figures 5 and 6). At this point, we diagnosed the patient with delayed perforation that developed after CS. Emergent laparoscopic surgery was performed, and a perforation site was found in the ESD ulcer at the bottom

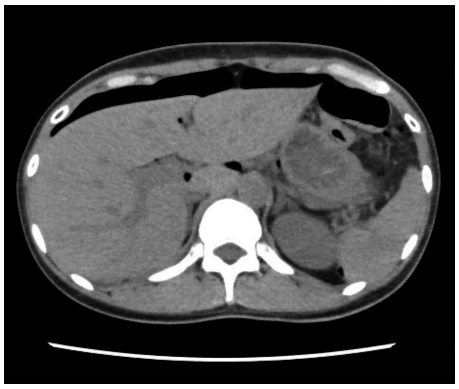

Figure 6 Abdominal computed tomography 36 h after endoscopic submucosal dissection. A large amount of free air is observed on the surface of the liver and the intraperitoneal cavity.

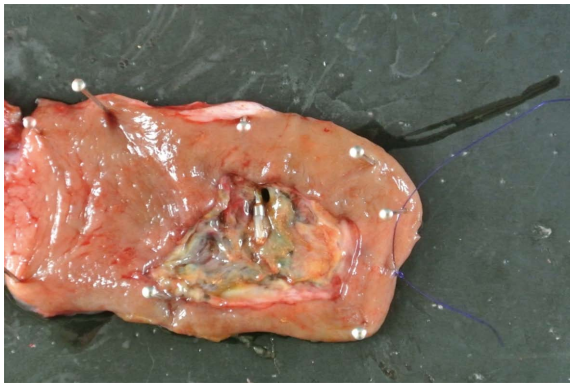

Figure 7 A small perforation site is present in the surgical specimen.

of the cecum (Figure 7). Partial cecum resection was performed, and the patient's condition improved rapidly.

CONCLUSION

CS is found in around 1% of cases after polypectomy and EMR and in 7%-8% of cases after ESD. Although the prognosis is excellent, clinicians should consider delayed perforation in CS patients.

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Treatment modalities for early gastric cancer

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Abstract

Different treatment modalities have been proposed in the treatment of early gastric cancer (EGC). Endoscopic resection (ER) is an established treatment that allows curative treatment, in selected cases. In addition, ER allows for an accurate histological staging, which is crucial when deciding on the best treatment option for EGC. Recently, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have become alternatives to surgery in early gastric cancer, mainly in Asian countries. Patients with "standard" criteria can be successfully treated by EMR techniques. Those who meet "expanded" criteria may benefit from treatment by ESD, reducing the need for surgery. Standardized ESD training system is imperative to promulgate effective and safe ESD technique to practices with limited expertise. Although endoscopic resection is an option in patients with EGC, surgical treatment continues to be a widespread therapeutic option worldwide. In this review we tried to point out the treatment modalities for early gastric cancer.

Key words: Early gastric cancer; Endoscopic submucosal dissection; Endoscopic mucosal resection; Pathological staging; Gastrectomy

Core tip: Gastric cancer is one of the main causes of cancer death. For early gastric cancer (EGC) endoscopic resection is an effective treatment modality for selected cases of EGC. Endoscopic submucosal dissection is designed to provide *en bloc* R0 resection regardless of size. Gastrectomy is the standard treatment for EGC with suspected lymph node metastases. This review describes the current different treatment modalities for early gastric cancer.

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INTRODUCTION

Gastric cancer is one of the leading causes of cancer worldwide, causing high mortality. In Asian countries, the frequency of early gastric cancer (EGC) is far superior to that of Western countries. Currently early gastric cancer (EGC) is defined as one that is limited to the mucosa or submucosa, regardless of the existence of nodal metastases[1]. The incidence of lymph node metastasis in EGC is very low. If the EGC is confined to the mucosa, the incidence is estimated at around 3%. When the EGC reaches the submucosa, rises to nearly 20%[2]. The existence of nodal metastases influence the type of treatment to be used. In these cases, surgical treatment is recommended along with adjuvant therapy. Overall the EGC has a good prognosis, with a 5-year survival rate of over 90%[3]. There are different therapeutic options for the treatment of early gastric cancer. At present, endoscopic resection provides a minimally invasive treatment with a similar efficacy to surgery.

TREATMENT MODALITIES

Therapeutic modalities for EGC range from endoscopic resection to gastrectomy and adjuvant treatments. Therefore, it is essential to perform an adequate staging of cancer as to determine which patients are candidates for either therapy.

ENDOSCOPIC TREATMENT

Endoscopic therapy is a minimally invasive treatment that allows the patient to preserve the entire stomach and maintain a good quality of life. Moreover, the cost is usually less and efficacy comparable to surgery. The degree of difficulty in performing endoscopic resection depends on the location of the lesion in the stomach, being the difficulty higher for resection of lesions localized on the posterior wall and lesser curvature. Depressed type of EGC is the most common. To facilitate the visualization of the lesion mucolytic and defoaming agents are used (*e.g.,* Acetylcysteine and Dimethicone, respectively). Endoscopic therapy is directed to selected patients in whom there is no evidence or risk of lymph node involvement. Endoscopic resection *vs* ablative technique allows assessing the specimen thus becoming the optimal method of staging for early gastric cancer[4]. Also, endoscopic therapy does not prevent a subsequent surgical therapy if needed. EUS has limited staging accuracy (80%-90%) and therefore would result in unnecessary surgery in up to 10%-20% of patients[5,6]. Endoscopic resection allows the pathologist to assess the depth of invasion, degree of differentiation and lymphatic and vascular involvement, thus allowing for a prediction of the risk of metastases in the lymph nodes. This is crucial for a correct diagnosis and risk stratification of metastasis. The main endoscopic techniques used are endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). According to the histological and morphological findings gastric carcinoma can be divided into differentiated (intestinal) and undifferentiated (diffuse)[7]. The risk for nodal metastasis for differentiated and undifferentiated EGC is around 0.4% and 4%, respectively. Endoscopic resection techniques can be applied, according to "standard" criteria, in patients with lesions resectable *en bloc* which meet histological criteria (intestinal type adenocarcinoma limited to the mucosa without venous or lymphatic invasion) and morphological criteria (< 20 mm without ulceration; < 10 mm for flat and depressed lesions)[8,9]. When these criteria are met, the risk of lymph node involvement is not more than 1.7%. In addition, "expanded" criteria for endoscopic resection have been defined which include: (1) EGC intestinal type mucosa confined to any size without ulceration; (2) EGC intestinal type confined to the mucosa < 3 cm with ulceration; and (3) EGC intestinal type < 3 cm confined to the upper 0.5 mm from the submucosa (sm1 < 500 μm) without lymphovascular involvement and 4. ECG poorly differentiated, < 2 cm, not ulcerated[10,11]. Expanded criteria for ER reduces the need for gastrectomy in EGC (Table 1). When ER has been performed for poorly differentiated type of EGC results for patients who declined surgical treatment showed: *en bloc* resection rate 83%, complete resection rate 81%, clinical remission 93%, and recurrence in only 7%[12].

Endoscopic mucosal resection

Currently endoscopic mucosal resection (EMR) is considered as an effective and safe treatment for superficial lesions. Requires specific endoscopic experience and the endoscopist needs to be prepared to try to resolve the possible complications that may arise during the implementation of the technique. Over the last years different EMR techniques have been described[13]: (1) Strip biopsy[14]. This resection technique designed to remove small lesions requires the use of a dual channel endoscope. It simultaneously uses a polypectomy snare and a biopsy forceps to achieve the resection; (2) Endoscopic double snare polypectomy; (3) EMR using a transparent plastic cap, initially developed in 1992 for resection of early oesophageal cancer and later for resection of early gastric cancer[15]; and (4) EMR using a ligation device (Multiband mucosectomy)[16,17] (Figure 1). These last two are the techniques for endoscopic mucosal resection most widely used in the treatment of EGC. However, in lesions greater than 20 mm, recurrence rate may be increased as they might require a piecemeal resection[18]. Therefore, EMR is the procedure of choice in patients with EGC who meet the standard criteria for endoscopic resection. Different studies have shown excellent results using EMR with figures for complete resection and survival at 5 years greater than 85%-90%[19,20]. The risk of local recurrence associated with EMR is variable. If the resection is piecemeal the risk of recurrence rate is set below 35%,

Table 1 Treatments options in a patient with early gastric cancer

Histology	Mucosal cancer					Submucosal cancer	
	⩽ 10 mm (flat/depressed)	⩽ 20 mm > 20 mm (No ulceration)		⩽ 30 mm > 30 mm (Ulceration)		Into the upper third (⩽ 30 mm)	Into the middle third (any size)
Intestinal type	EMR	EMR	ESD	ESD	Surgery	ESD	Surgery
Diffuse type	Surgery ESD[1]		Surgery	Surgery	Surgery	Surgery	Surgery

[1]Treatment option if the patient decline surgery. EGC: Early gastric cancer; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

Table 2 Process steps in endoscopic submucosal dissection treatment of the early gastric cancer

Process steps	Technique/devices
Estimation of lateral extension	Chomoendoscopy (indigo carmine) ± NBI
Marking	Mucosal markings are placed 5 mm lateral to the lesion margin
Submucosal injection	Injection of saline mixed with diluted epinephrine (1:100000) and indigo carmine into the submucosal layer
Mucosal incision (precutting)	A small initial mucosal incision is made to gain access to the submucosal space without to injure the muscularis propria (*e.g.*, by Dual knife)
Circumferential incisión	Carried out 5 mm lateral to the mucosal markings (*e.g.*, IT knife)
Submucosal dissection	The technique varies among endoscopist Adequate reinjection of fluid into the submucosa The parallel movement for muscle layer with the IT2 is typically lateral With the Dual knife forward

NBI: Narrow band imaging.

being practically nonexistent if *en bloc* resection was possible[21,22]. In cases of incomplete resection with EMR, gastrectomy might be indicated if the tumor has submucosal or lymphovascular involvement or positive resection margins. However, in cases where the patient is a poor surgical candidate further endoscopic resection could be considered with good results, especially if incomplete resection is due to the presence of positive lateral margins of resection[23,24]. In treatment with EMR a suitable distance of at least 2 mm between the EGC and the edge of the specimen is required to achieve complete resection. Indigo carmine chromoendoscopy is the most useful method to determine the lateral margin of EGC.

Endoscopic submucosal resection

Endoscopic submucosal resection (ESD) is a complex and demanding technique that allows *en bloc* resection of larger EGC, avoiding piecemeal resection of the EMR and therefore the risk of recurrence[25-27]. Similar to the EMR, its main indication is resection of superficial tumors with no risk of lymph node metastasis. Expanded criteria have been proposed for endoscopic resection with ESD, as with this technique large *en bloc* resections are possible. ESD for EGC with expanded criteria have long-term survival and outcomes similar to those of patients treated according to the traditional criteria (5-year survival rate 93% and 92%, respectively)[28]. In ESD, the lesion is marked circumferentially, usually by applying soft coagulation current. Then, a solution with saline (0.9% NS), adrenaline and dyes (indigo carmine, methylene blue) is injected into the submucosa allowing distinction between the submucosal and muscular layer. Some authors do not recommend the use of Methylene blue because it is absorbed into the cell nucleus, which results in intense staining that hampers visualization[29]. To avoid the short duration of the lifting effect of submucosal injection, others have suggested the use of substances with a viscosity grade higher than saline (0.9% NS). The use of hyaluronic acid has been proposed but its high price, has conditioned its use[30,31]. Glycerol 10% could be a good and cheap alternative[32]. Finally, the lesion is dissected and removed *en bloc* using different types of needles, specific for each step of the procedure (Needle Knife, IT Knife, Flex knife, Hook knife, Triangle-tip knife, Dual Knife, Hybrid Knife, Flush knife and others) typically done with coagulating current. Some needles have at the tip an insulating material with a protective function that allows for a safer dissection[33-35] (Figure 2). The main functions that must meet the ESD devices are: marking, injection, precutting, circumferential incision, submucosal disection and hemostasis (Table 2). However the choice of needle depends on the availability, familiarity and personal preference of the endoscopist as there are no studies that demonstrate the superiority of one over the other. Sometimes it can be useful to use a transparent plastic cap on the endoscope tip that allows more control during dissection. Moreover, these devices use cutting currents, coagulation or a mixture of both through electrosurgical generators. CO_2 insufflation is recommended because it causes less luminal distension. Furthermore, if there is a perforation the leaking CO_2 will rapidly be reabsorbed decreasing the intraperitoneal pressure and then the respiratory compromise[36]. From a technical point of view, ESD is more challenging than EMR and requires

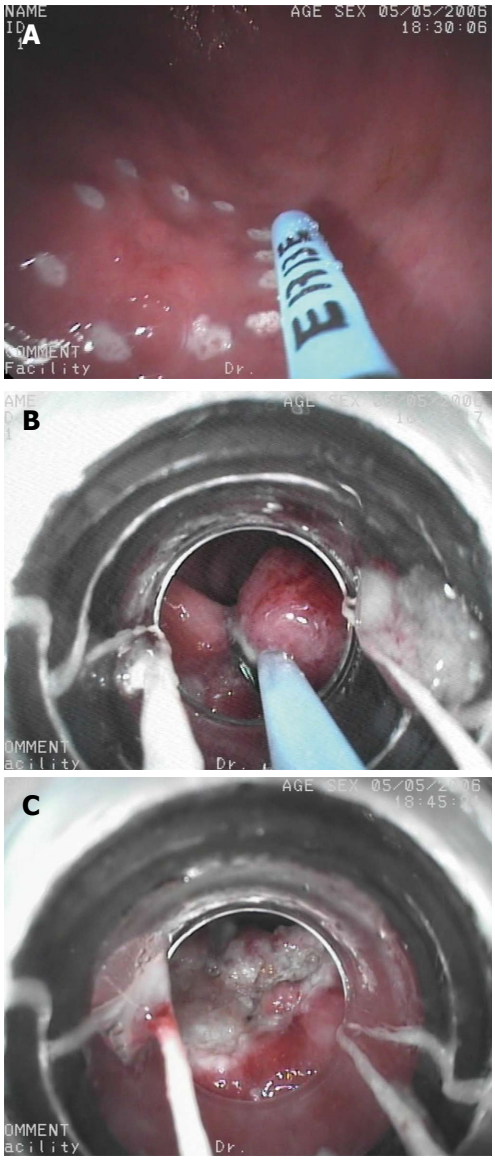

Figure 1 Endoscopic mucosal resection with Multiband Ligator for early gastric cancer. A: Argon plasma coagulation is used for marking early gastric cancer; B: A multiband ligator was used to create a pseudopolyp and it is removed by a minipolypectomy snare using pure coagulating current; C: Residual scar after Multiband Mucosectomy.

more "preparation". However, the main advantage of the ESD over other techniques is that it allows *en bloc* resection of larger lesions reducing the rate of local recurrence. As demonstrated in comparative studies between EMR and ESD, with ESD success rates between 95%-98% for in-bloc resection and survival at 5 years of 83%-97%[37,38]. The ESD requires skill and a long learning curve[39-42]. In cases when resection with ESD is incomplete (positive resection margins, invasion of the submucosa or muscularis, lymphovascular invasion or undifferentiated cancer), surgery should be considered (gastrectomy with perigastric nodal resection)[43]. The role of laparoscopic perigastric nodal resection is not clearly established but may be considered as an alternative[44]. ESD can be use in elderly patients as well as in those who require antiplatelet therapy for high risk of thrombosis[2]. Proposed strategy for endoscopic treatment by ESD set 4 levels: capability for EGC detection and knowledge of the indications of ESD, observation of several ESD procedures performed by expert endoscopists, perform dissections in *ex-vivo* animal models followed by procedures in animal models *in vivo* and finally performing selected (simple) ESD in humans under expert supervision. Then, continue with training in animal models to acquire more skill. About 20 annual cases of ESD are considered necessary to acquire competence in ESD[2]. In Japan and Korea the incidence of early gastric cancer is significantly higher compared to the West. Therefore in the West, the opportunities to conduct training in gastric EDS are scarce.

ENDOSCOPIC COMPLICATIONS

Various complications after endoscopic treatment for EGC have been described: bleeding, perforation, stenosis, aspiration pneumonia, phlegmonous gastritis, mediastinal emphysema. Of these, the most common is bleeding, the average incidence is set at 9% and usually occur during the process or within 24 h[45]. Depending on the time of onset, bleeding can be classified as: (1) immediate; (2) early (within the procedure); or (3) late (post-procedure). The immediate bleeding is less common in the distal portion of the stomach as the submucosal arteries are of lower caliber[46]. Acute bleeding may obscure the visual field, leading to a higher risk of complications. Therefore, endoscopic hemostasis should be immediately performed. The incidence of delayed bleeding after ESD is below 15%[37] and different factors have been related to its appearance: macroscopic appearance (large size > 40 mm, depressed or flat lesion), location in the middle or upper third, advanced age (> 80 years), limited endoscopic experience, timely procedure or treatment of recurrent lesions[47,48]. Late risk of bleeding after ESD may decrease significantly by prophylactic electrocoagulation of large visible submucosal vessels. This technique is preferable to other types of hemostasis such as clips that can hinder the completion of the procedure[49]. Currently, there is no evidence that the realization of a second-look contributes significantly to reduce the risk of late bleeding following ESD. While it is habitual to advice antisecretory therapy over the following weeks, this practice has not demonstrated benefit in lowering the rate of delayed bleeding[50]. The incidence of perforation ranges from 1%-20% depending on experience[51-53]. The use of dye injection (*e.g.,* Indigo carmine) allows to better identify the muscle layer making ESD a safer technique. Perforation can be diagnosed during or after the procedure (frank perforation or micro-perforation, respectively). However, no evidence of lymph node metastasis and/or peritoneal dissemination caused by gastric perforation has been reported[54]. If a perforation is immediately noticed during the procedure and its size is small, it can be treated endoscopically with clips

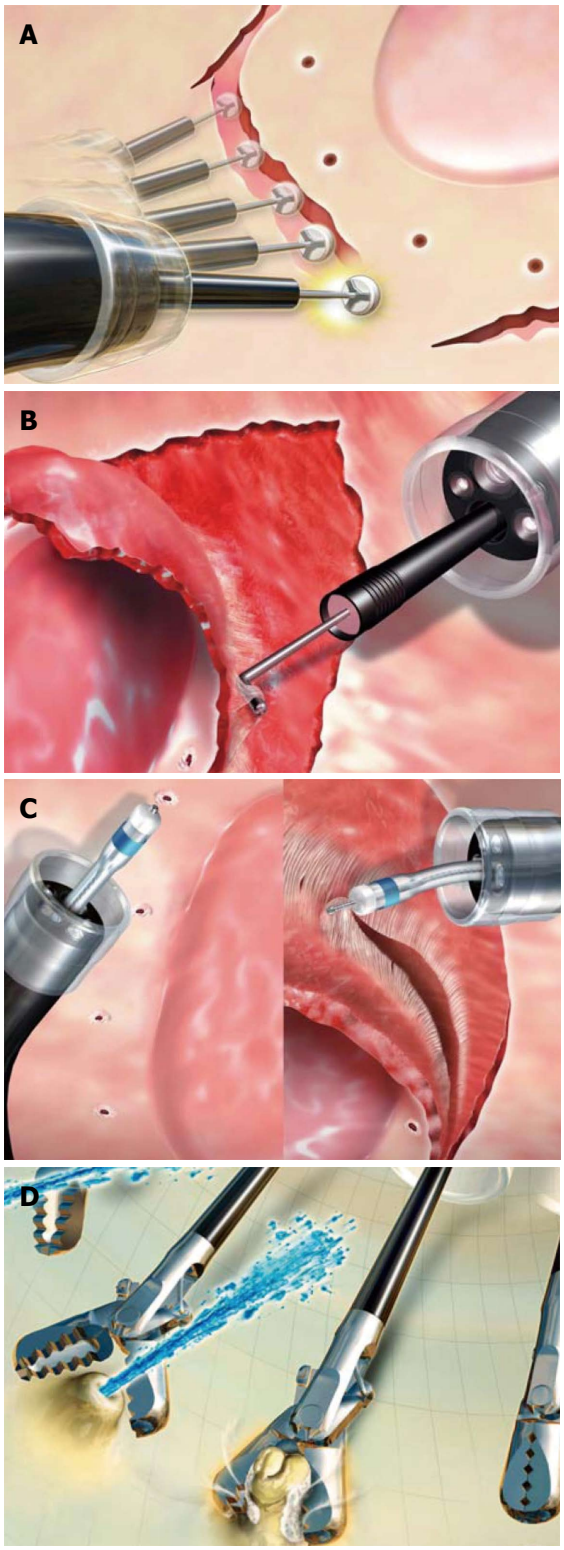

Figure 2 Different types of devices, specific for each step of the Endoscopic submucosal dissection procedure. A: ITknife-2; B: Hook knife; C: Dual knife; D: Grasper for haemostasis. (Courtesy of Olympus Medical Systems,Tokyo, Japan).

and broad spectrum antibiotics. In these cases absolute diet is recommended for at least 2 d[55]. Conversely, if the perforation is large, urgent surgery is required. It is possible that CO_2 insufflation may reduce the risk of perforation[56]. If free air is found on a plain chest X-ray after the ER (micro-perforation), the management (conservative or surgical) is not conclusively established. The appearance of scar stenosis is uncommon (0.6%-2%) and is associated with extensive resections in the gastric antrum[51]. Local administration triamcinolone can be used as an attempt to prevent this complication[57]. Balloon dilation is the endoscopic treatment most frequently used for this complication, but involves some risk of perforation[58]. Aspiration pneumonia is rare (0.7%-1.5%) and is associated with prolonged procedures.

FOLLOW-UP AFTER ENDOSCOPIC RESECTION

EGC patients treated by endoscopic resection with curative intent, require monitoring to detect local recurrence and metachronous gastric cancer. In patients with EGC who meet "standard" criteria for endoscopic resection, it is advisable to perform an upper gastrointestinal endoscopy yearly. Patients who meet "expanded" criteria, in addition to the annual endoscopy, monitoring can be performed alternating abdominal computed tomography and endoscopic ultrasound every 6 mo for 3 years. The objective of this additional monitoring is to detect lymph node and distant metastases[59].

SURGICAL TREATMENT

Although endoscopic resection is an option in patients with EGC who meet the above criteria, surgical treatment continues to be a widespread therapeutic option worldwide with survival rates at 5 years of 97%[60]. Currently, there are no comparative studies between gastrectomy and endoscopic treatment. However, several results show clinical prognosis to be similar although patients with endoscopic treatment benefit from a shorter hospital stay and lower costs[61,62]. Patients who do not meet the criteria for endoscopic resection have a higher risk of lymph node metastases which forces a gastrectomy with perigastric lymph node excision. Another indication for gastrectomy is the detection during staging of lymph nodes or a high suspicion of their existence. The type of gastrectomy (subtotal gastrectomy or total) is determined by the location of the lesion, reserving the subtotal gastrectomy for EGC located in the lower two thirds of the stomach. Another option is laparoscopic gastrectomy. Laparoscopic gastrectomy was initially reported in Japan in 1994[63]. Open gastrectomy is still performed more frequently in the Western countries than laparoscopic resection even for patients with early stage disease[64]. In Japan, EGC (T1N0 or T2N0) is considered as the only indication for laparoscopic gastrectomy. A recent review that included 22 studies show that laparoscopic gastrectomy *vs* open gastrectomy offers a similar prognosis with significantly lower postoperative morbidity, lower intraoperative

blood use, shorter hospital stay and no increased rates of recurrence. Furthermore conversion rates to open laparoscopic surgery were less than 3%[65].

The surgical outcome of gastric cancer in obese patients is controversial. The number of lymph nodes retrieved is, in these patients, higher[66]. Moreover, obesity is an independent risk factor for developing 30-d postdischarge complications[67].

ADJUVANT THERAPIES

It is known that chronic infection with *Helicobacter pylori* is a risk factor of developing gastric cancer. Currently, treatment of *Helicobacter pylori* infection in all patients with EGC is recommended, regardless of the chosen treatment option to reduce the risk of metachronous gastric cancer[68,69]. The need for adjuvant therapy (chemotherapy, radiotherapy) in patients with EGC treated with complete endoscopic resection is debated. Recent guidelines recommend observation, avoiding adjuvant therapy in patients with T1N0 disease without involvement of the resection margins. However, adjuvant treatment is clearly indicated in patients with positive lymph node involvement.

CONCLUSION

Endoscopic resection (EMR/ESD) is a safe and effective staging and therapeutic modality for selected patients with early gastric cancer. Patients with "standard" and "expanded" criteria can be successfully treated by EMR and ESD techniques, respectively. Surgical treatment continues to be a widespread therapeutic option in patients with incomplete endoscopic resection or advanced gastric cancer.

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ORIGINAL ARTICLE

Retrospective Study

Diagnosis of small intramucosal signet ring cell carcinoma of the stomach by non-magnifying narrow-band imaging: A pilot study

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Author contributions: Watari J and Miwa H designed and performed the research study; Tomita T, Ikehara H, Taki M, Ogawa T, Yamasaki T, Kondo T, Toyoshima F, Sakurai J, Kono T, Tozawa K, Ohda Y, Oshima T and Fukui H helped to collect the data; Ogawa T performed the quantification of endoscopic findings; Hirota S diagnosed the histology; Watari J performed statistical analysis and wrote the paper.

Institutional review board statement: This study was approved by Institutional Review Board at Hyogo College of Medicine, Nishinomiya, Japan.

Informed consent statement: All patients in the study gave informed consent prior to endoscopy.

Conflict-of-interest statement: None.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at (watarij@hyo-med.ac.jp). Consent for data sharing was not obtained from the participants but the presented data are anonymized and risk of identification is low.

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Abstract

AIM: To examine the efficacy of non-magnifying narrow-band imaging (NM-NBI) imaging for small signet ring cell carcinoma (SRC).

METHODS: We retrospectively analyzed 14 consecutive small intramucosal SRCs that had been treated with endoscopic submucosal dissection (ESD) and 14 randomly selected whitish gastric ulcer scars (control). The strength and shape of the SRCs and whitish scars by NM-NBI and white-light imaging (WLI) were assessed with Image J (NIH, Bethesda).

RESULTS: NM-NBI findings of SRC showed a clearly isolated whitish area amid the brown color of the

surrounding normal mucosa. The NBI index, which indicates the potency of NBI for visualizing SRC, was significantly higher than the WLI index (P = 0.001), indicating SRC was more clearly identified by NM-NBI. Although the NBI index was not significantly different between SRCs and controls, the circle (C)-index, as an index of circularity of tumor shape, was significantly higher in SRCs (P = 0.001). According to the receiver-operating characteristic analysis, the resulting cut-off value of the circularity index (C-index) for SRC was 0.60 (85.7% sensitivity, 85.7% specificity). Thus a lesion with a C-index $\geqslant$ 0.6 was significantly more likely to be an SRC than a gastric ulcer scar (OR = 36.0; 95%CI: 4.33-299.09; P = 0.0009).

CONCLUSION: Small isolated whitish round area by NM-NBI endoscopy is a useful finding of SRCs which is the indication for ESD.

Key words: Gastric cancer; Signet ring cell carcinoma; Narrow-band imaging; Intramucosal cancer; Endoscopic submucosal dissection

Core tip: Intramucosal signet ring cell carcinoma (SRC) $\leqslant$ 2 cm in diameter, for which endoscopic submucosal dissection is indicated, is very difficult to identify by white-light imaging (WLI) endoscopy. However, little is known regarding non-magnifying narrow-band imaging (NM-NBI) findings of early SRC. The strength and shape of the SRCs by NM-NBI and WLI were assessed with Image J. NM-NBI findings of SRC showed a clearly isolated whitish area amid the brown color of the surrounding normal mucosa. The NBI index, which indicates the potency of NBI for visualizing SRC, was significantly higher than the WLI index (P = 0.001).

Watari J, Tomita T, Ikehara H, Taki M, Ogawa T, Yamasaki T, Kondo T, Toyoshima F, Sakurai J, Kono T, Tozawa K, Ohda Y, Oshima T, Fukui H, Hirota S, Miwa H. Diagnosis of small intramucosal signet ring cell carcinoma of the stomach by non-magnifying narrow-band imaging: A pilot study. *World J Gastrointest Endosc* 2015; 7(12): 1070-1077 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i12/1070.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i12.1070

INTRODUCTION

Gastric cancer ranks as the fourth most common cancer and the second most frequent cause of death from cancer in the world[1]. *Helicobacter pylori* (*H. pylori*) infection is considered to be a main risk factor for the development of gastric cancer of either intestinal or diffuse type[2]. However, according to recent reports, the *H. pylori* infection rate has decreased over the last 40-50 years in both Asia and Western countries, with an overall decline in *H. pylori* seroprevalence[3,4]. In Japan, the prevalence of *H. pylori*-negative gastric cancer is extremely low; therefore, the prevalence of gastric cancer may continue to decrease substantially as the *H. pylori* infection rate continues to decrease[5,6]. The pathological characteristics of *H. pylori*-negative gastric cancer are different from those of *H. pylori*-positive gastric cancer; histologically, the diffuse type is dominant, especially signet ring cell carcinoma (SRC) (60%)[6]. Commonly, SRC of the stomach is thought to arise in the mucosa without metaplastic change and is typically confined to the glandular neck region in the original proliferation zone[7]. It is considered, therefore, that early-stage SRCs can be present beneath a flat, intact mucosal surface epithelium, and may be very difficult to identify by white-light imaging (WLI) endoscopy due to their slightly whitish discoloration.

Recently, magnifying narrow-band imaging (NBI) has been reported to be useful for the accurate diagnosis of gastric cancers, even for small, depressed gastric mucosal cancers[8-11]. Several studies have demonstrated an association between the histology, *i.e.*, differentiated *vs* undifferentiated type, and magnified NBI appearance[8,11-13]. In cases of SRC, the cancer-specific findings and identifiable demarcation line of the lesion may not be identified even by magnifying NBI endoscopy or chromoendoscopy[12,13]. We have found intramucosal SRCs by non-magnifying NBI (NM-NBI) endoscopy that we failed to detect by WLI endoscopy. Nonetheless, there has been little research into NM-NBI findings focused strictly on intramucosal SRCs.

It has been reported that patients with SRC caught at an early stage can expect a better prognosis than they might with other gastric cancers[14] and SRC is not a prognostic factor in early cancer[15]. The prognosis of those at the advanced stage is still controversial; a report by Otsuji *et al*[14] from Japan showed no significant difference in 5-year survival rates between patients with SRC and those with other histological types of gastric cancer, while other studies from the West[16-18] have found that SRC has a worse prognosis due to specific characteristics such as high rate of lymph node metastasis and peritoneal carcinomatosis. Clearly, it is best to discover gastric SRC early, but the early detection of lesions located beneath a preserved surface epithelium may be very difficult.

Although NBI is increasingly available in endoscopy units, only a limited number of cases are subjected to magnifying NBI endoscopy, even in hospitals specializing in gastroenterology. Many gastroenterologists or endoscopists use a conventional NM-NBI endoscope lacking a magnification function to screen for gastric cancer. In the present study, we (1) retrospectively investigated endoscopic findings of SRC by NM-NBI endoscopy and WLI endoscopy; and (2) compared the NBI findings of SRC and whitish gastric ulcer scars, in order to clarify the NM-NBI features of SRC.

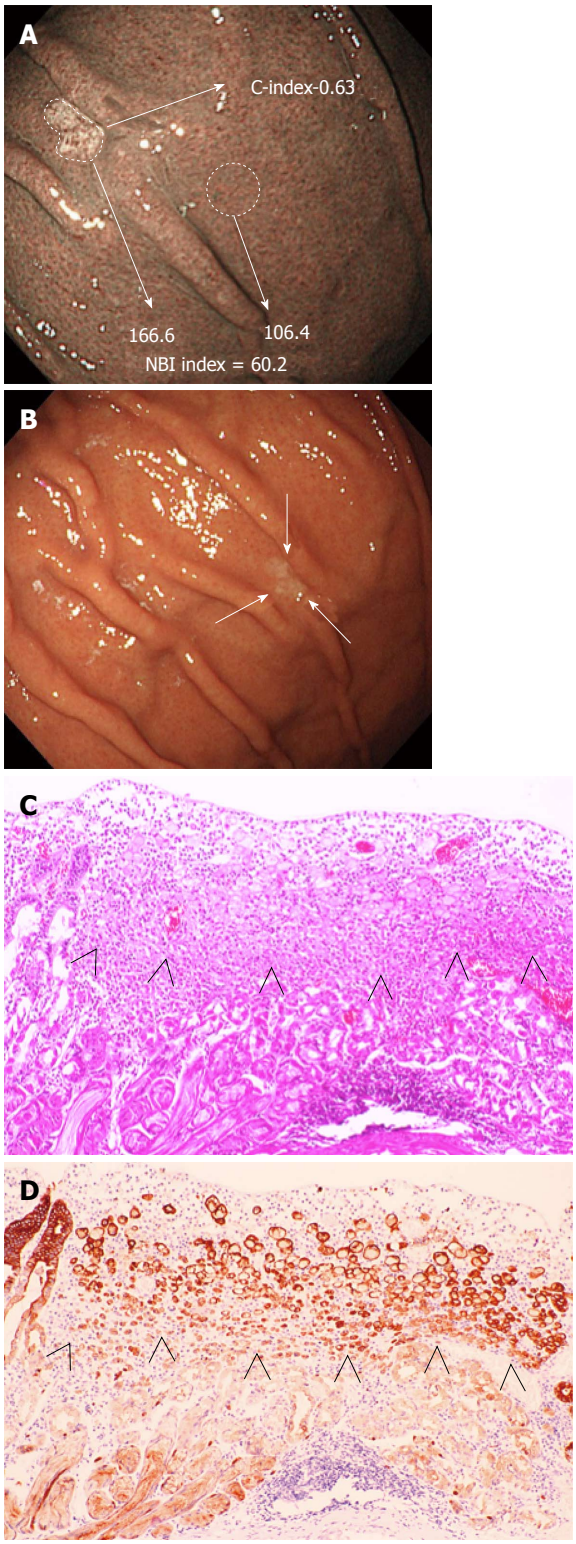

Figure 1 Endoscopic and histologic findings of signet ring cell carcinomas localized at the greater curvature of the corpus (Case 4). A: NBI of the cancer area showed an isolated oval-shaped whitish area. The NBI index was 60.2. The C-index was 0.63; B: Endoscopy with WLI showed a 0-IIc lesion with slight discoloration (arrows) at the greater curvature of the corpus. The WLI index was 4.5; C: The histology by endoscopic submucosal dissection showed an intramucosal SRC in the upper third of the gastric mucosa (arrowheads) with a partial defect of the foveolar epithelium; D: Immunohistochemical staining of SRC cells showed diffuse positive reactivity for cytokeratin AE1/AE3 (arrowheads). NBI: Narrow-band imaging; WLI: White-light imaging; SRC: Signet ring cell carcinoma.

MATERIALS AND METHODS

Patients

Between January 2011 and May 2014 in our department, 322 early gastric cancers or adenomas in 301 patients were treated with endoscopic submucosal dissection (ESD). The indications for ESD of intramucosal gastric cancer or adenoma, included the following[19]: (1) intramucosal differentiated-type adenocarcinoma of any size without ulceration; (2) intramucosal differentiated-type adenocarcinoma with an ulcer scar and measuring $\leqslant$ 3 cm in diameter; and (3) intramucosal undifferentiated-type adenocarcinoma, including poorly differentiated cancer or SRC, of less than 2 cm without an ulcer scar. In all cases, the histology, tumor location, macroscopic classification, and depth of invasion fulfilled the criteria of the Japanese Research Society for Gastric Cancer[20]. Among these cases treated with ESD, 14 (4.3%) were diagnosed histologically as intramucosal SRC ($\leqslant$ 2 cm) without any other findings of adenocarcinoma. During the same period, 14 patients with whitish gastric ulcer scars that were histologically confirmed by biopsy were randomly selected as controls.

Methods

Written informed consent was obtained from all patients who underwent a routine endoscopic examination and ESD, and this study was conducted in accordance with the guidelines of the Declaration of Helsinki. All patients underwent NM-NBI endoscopy by an endoscope (GIF-Q260) or high-vision endoscope (H260, H260Z, H290 and HQ290) with an electronic endoscopic system (Evis Lucera CV-260 SL or Elite CV-290; Olympus Medical Systems, Corp., Tokyo, Japan). The strengths of the NM-NBI and WLI images of 14 consecutive gastric SRCs undergoing ESD and the strength of the NM-NBI images of gastric ulcer scars (controls) were quantified with an image-analytical software program. Briefly, NBI images were converted into joint photographic experts group pictures; then the cancer or ulcer scar area on the pictures was manually traced with an image-analytical software program (ImageJ ver. 1.48; National Institutes of Health, Bethesda, MD). Using the default tool "Measure" under the "Analyze" menu, the mean gray value (MGV) of the cancer or ulcer area was calculated, and the MGV of a region of similar area of the perilesional normal mucosa was also measured. The MGV of the cancer or ulcer scar area minus that of the perilesional area was defined as the NBI index (Figure 1; note, a brighter image has a higher MGV). In addition, the values for several shape descriptors of the SRCs and gastric ulcer scars were also calculated to assess their shapes. Briefly, using the default tool "Measure" under the "Analyze" menu, "Circ." was adopted as the circularity index (C-index). The C-index value of a perfect circle is 1; as the shape deviates from perfectly circular, the C-index value decreases (Figure 2). The WLI strength was calculated as well as the NM-

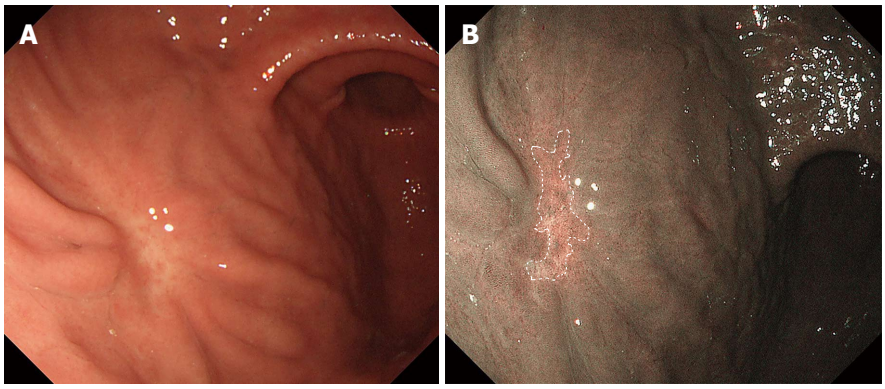

Figure 2 Endoscopic images of whitish gastric ulcer scars. White-light imaging (A) and non-magnifying narrow-band imaging (B). The NBI index and C-index were 44.9 and 0.29, respectively. NBI: Narrow-band imaging; C-index: Circularity index.

Table 1 Characteristics of signet ring cell carcinoma patients and controls

	SRC	Control	*P* value
Age, yr, mean ± SD	53.2 ± 14.2	69.1 ± 14.8	0.0008
Sex, male/female	7/6	10/4	0.44
Location: upper/middle/lower	2/7/5	4/8/2	0.36
NBI finding			
NBI index (mean ± SD)	27.9 ± 21.0[a]	24.8 ± 14.7	0.78
H. pylori: positive/negative	26.1 ± 20.5/29.0 ± 22.4	27.8 ± 15.4/19.3 ± 13.2	0.95 in SRC and 0.26 in control
WLI finding (mean ± SD)			
WLI index	5.3 ± 16.2[a]	-	0.001[a]
H. pylori: positive/negative	13.5 ± 16.4/0.7 ± 15.1	-	0.32
C-index (mean ± SD)	0.67 ± 0.13	0.50 ± 0.14	0.001

[a]*P* = 0.001 between NBI index and WLI index. SRC: Signet ring cell carcinoma; NBI: Narrow-band imaging; WLI: White light imaging; C-index: Circularity index.

NBI index, and was measured by "RGB Measure (R + G + B/3)" tool under the "Analyze" menu in "Plugins". The quantification was performed by an endoscopist who was not involved in the patients' original diagnoses or treatments.

To assess *H. pylori* infection, biopsy specimens, two from each site, were taken from the greater curvature of the antrum and body of the stomach. *H. pylori* status was analyzed in each patient by two methods: Giemsa staining and serum *H. pylori*-IgG antibody with an enzyme-linked immunosorbent assay kit using the E plate test (Eiken Kagaku, Tokyo, Japan). A patient was regarded as positive for *H. pylori* if at least one of these tests was positive.

Statistical analysis

The data were assessed by the Mann-Whitney *U*-test for comparisons between two independent groups and the Fisher's exact test for comparisons between two proportions. NM-NBI findings including the NBI-index and C-index were included as potential malignant features for SRC in univariate analysis. Multivariate logistic regression analyses were performed to identify significant predictive NBI findings. Odds ratios and 95%CIs were used to assess the statistical significance at the conventional level of 0.05. Statistical analysis was performed with StatView version 5.0 (SAS Institute Inc., Cary, NC). Receiver operating characteristic (ROC) curve was calculated for the highest diagnostic performance in terms of the shape of SRCs (C-index), and then the curve was plotted using JMP 10 software (SAS Institute Inc., Cary, NC). The area under the ROC curve and the optimal thresholds using the Youden index were calculated from ROC analysis[21].

RESULTS

Table 1 shows the characteristics of the 14 SRCs in the 13 patients who underwent ESD and the controls. In addition, clinical and endoscopic data of SRCs are shown in Table 2. Out of 14 SRCs, 10 lesions were detected at other hospitals and then referred to our department for ESD treatment. Two (cases 4 and 12) of the 14 SRCs were first identified by NM-NBI endoscopy, but not by WLI endoscopy, in our department (Figure 1). In SRC patients, the mean age was 53.2 ± 14.2 years (range: 23 to 74 years), and women accounted for 46.2% (6 of 13) of the group. In contrast, the mean age of the controls was 69.1 ± 14.8 years, significantly higher than that of the SRC patients. The *H. pylori*-negative rate was 69.2% (9 of 13) in the SRC patients, and none of these patients had received *H. pylori* eradication therapy. In the control group, 4 out of 5 *H. pylori*-negative patients (35.7%, 5 of 14) had undergone eradication

Table 2 Characteristics of signet ring cell carcinomas in the 13 patients

Case	Age	Sex	Type	Size (mm)	Location	Location	*Hp*	PDE	NBI index	WLI index	C-index	Endoscopic system
1	23	Female	Ⅱb	4	M	GC	+	-	22.5	3.5	0.75	CV-260 SL
			Ⅱc	6	L	GC		-	25.6	16.1	0.67	CV-290
2	63	Female	Ⅱb	14	M	LC	+	+	5.5	2.2	0.76	CV-260 SL
3	62	Male	Ⅱc	15	M	GC	+	-	16.8	41.1	0.61	CV-260 SL
4	74	Female	Ⅱc	4	U	GC	+	+	60.2	4.5	0.63	CV-260 SL
5	48	Male	Ⅱc	4	L	GC	-	-	59.6	0.22	0.66	CV-260 SL
6	62	Male	Ⅱb	5	M	LC	-	+	17.6	-2.7	0.81	CV-260 SL
7	48	Male	Ⅱc	2	U	GC	-	-	1.0	4.0	0.33	CV-260 SL
8	58	Male	Ⅱc	5	L	LC	-	-	19.5	-33.7	0.88	CV-260 SL
9	40	Female	Ⅱb	6	M	GC	-	-	25.6	12.8	0.77	CV-290
10	69	Female	Ⅱb	8	L	PW	-	-	68.5	-8.5	0.60	CV-290
11	46	Male	Ⅱb	5	M	GC	-	-	10.8	9.3	0.63	CV-290
12	60	Male	Ⅱb	6	M	GC	-	-	19.7	16.3	0.57	CV-290
13	38	Female	Ⅱb	6	L	PW	-	-	38.2	8.7	0.69	CV-290

Hp: *Helicobacter pylori*; PDE: Partially defect of epithelium; L: Lower third of the stomach; M: Middle third of the stomach; U: Upper third of the stomach; GC: Greater curvature; LC: Lesser curvature; PW: Posterior wall; C-index: Circularity index; NBI: Narrow-band imaging; WLI: White light imaging.

therapy previously.

Most SRCs were located in the middle or lower portion of the stomach (85.7%, 12 of 14) and at the greater curvature (64.3%, 9 of 14), with no significant difference in the distribution of lesions compared to the control. The average diameter of the major axis of the SRCs was 6.4 mm (range: 2 to 15 mm). Histologically, a partial defect of the foveolar epithelium was identified in only 3 cases (21.4%); thus, most SRC cells were found beneath a preserved surface epithelium. In all SRC cases, the histological growth pattern of cancer cells corresponded to the non-whole-layer type according to the definition by Okada *et al*[13].

NM-NBI and WLI findings

In SRCs, NBI findings showed a clearly isolated whitish area amid the brown color of the normal mucosa. The NBI index (27.9 ± 21.0) was significantly higher than the WLI index (5.3 ± 16.2) (P = 0.001), indicating that the contrast between the cancer and surrounding normal mucosa was more intense by NM-NBI than by WLI. This result indicates that the cancerous areas were more clearly captured by NM-NBI endoscopy than by WLI endoscopy (Figures 1 and 3). The overall mean NBI index was 27.9 ± 21.0; this value was not significantly different from that (24.8 ± 14.7) of the control. Moreover, the NBI indices were not significantly different between the *H. pylori*-positive and -negative cases in either the SRCs or controls. In addition, the WLI index of the SRCs was not significantly different between *H. pylori*-positive and -negative cases. In contrast, the C-index was significantly higher in SRCs (0.67 ± 0.13) than in controls (0.50 ± 0.14) (P = 0.001), indicating that SRCs are rounder in shape than ulcer scars (Table 1). The C-index was the only factor significantly associated with SRCs in the NBI findings.

Association between the shape of SRCs and C-index

The association between the shape of SRCs and C-index was evaluated using ROC curve analysis (Figure 4). According to this analysis, the resulting cut-off value of the C-index for SRC was 0.60 (sensitivity, 85.7%; specificity, 85.7%).

Based on the ROC curve analysis and optimal cut-off points of the C-index of SRC determined above, a C-index of ⩾ 0.60 was used in the analysis. We investigated the strength of the association between the C-index (⩾ 0.60) in the NM-NBI findings and that in the SRCs by means of a logistic regression analysis. The C-index (⩾ 0.60) was found to be a significant predictor of SRCs (OR = 36.0; 95%CI: 4.33-299.09; P = 0.0009).

DISCUSSION

As the *H. pylori* infection rate continues to decrease, cardiac or junctional gastric cancer and histologically undifferentiated-type adenocarcinoma including SRC will increase in proportion. Therefore, there is need of an easy method for detecting these cancers in an early stage by routine endoscopy. Magnifying NBI is definitely useful for the accurate diagnosis of gastric cancer or dysplasia using the criteria for gastric cancer: irregularity or disappearance of the mucosal structure or a microvascular pattern in a definite demarcation line[8-13]. However, small intramucosal SRCs (⩽ 2 cm), which are best treated by ESD, have fewer of these magnifying NBI findings, because most intramucosal SRC cells are covered by a normal foveolar epithelium. To the best of our knowledge, this is the first study to report on the NM-NBI findings and clinical features of small SRC, for which endoscopic treatment is indicated.

In a previous magnifying NBI study of undifferentiated-type early gastric cancer including SRCs[8,11-13], Okada *et al*[13] found that gastric cancers with a preserved but irregular surface pattern corresponded histologically to the non-whole-layer type of mucosal cancer, whereas cancers with an irregular microvascular pattern or mixed pattern upon magnifying NBI corresponded histopathologically to the whole-layer type of intramucosal cancer or submucosal invasion

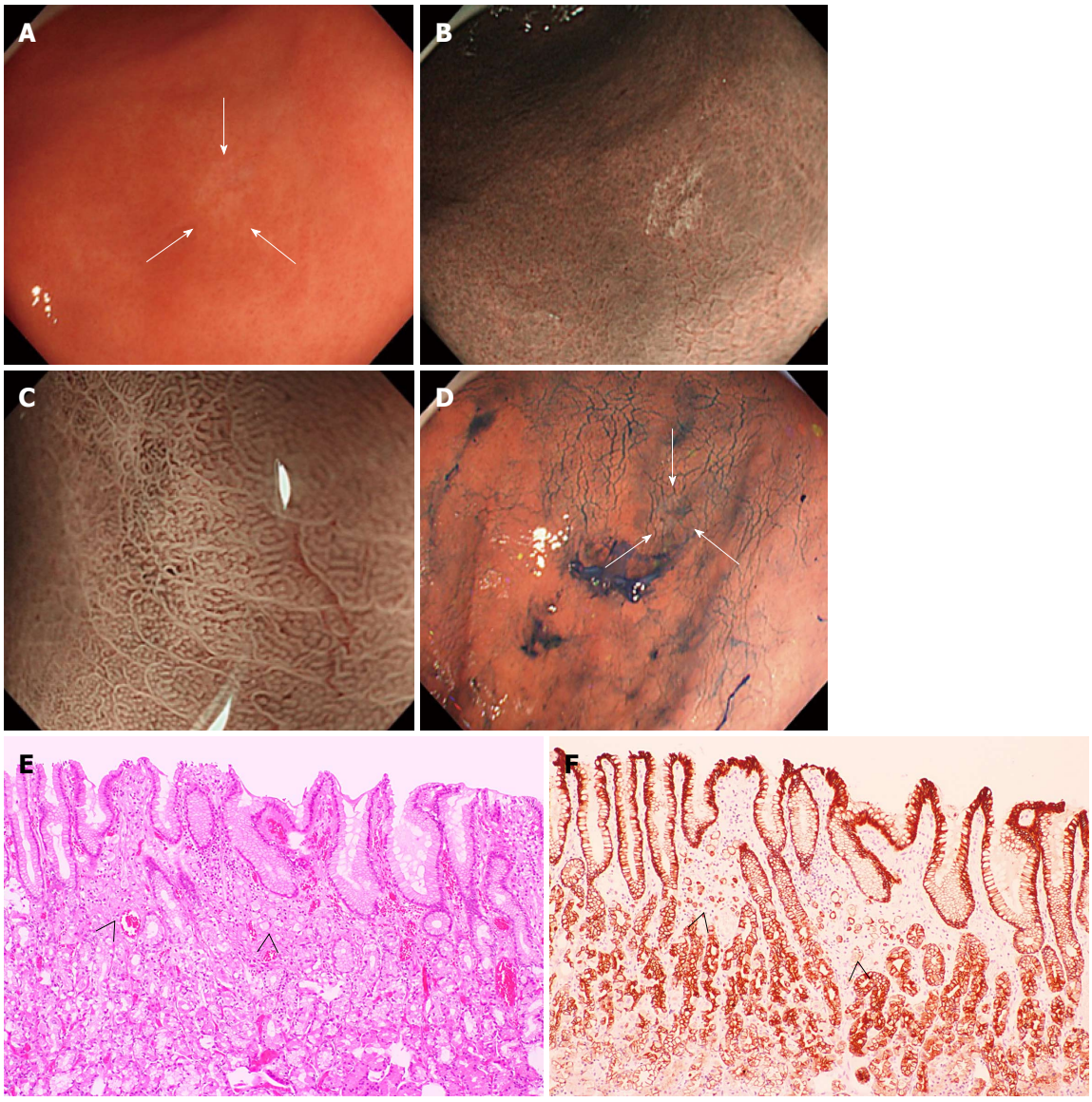

Figure 3 Endoscopic and microscopic images of signet ring cell carcinoma (Case 9). A: Endoscopy with WLI revealed a 0-IIb lesion with slight discoloration (arrows) at the greater curvature of the angulus; B: NM-NBI of the cancer area showed an isolated clear whitish area. The cancerous areas were more clearly captured by NM-NBI endoscopy than by WLI endoscopy. The NBI and WLI index were respectively 25.6 and 12.8, and the C-index was 0.77; C and D: The demarcation line of the SRC was not clearly identified even by magnifying NBI and chromoendoscopy (arrows); E: The histology of a specimen resected by endoscopic submucosal dissection revealed an intramucosal SRC (arrowheads) in the upper third of the mucosa beneath a preserved surface epithelium; F: SRC cells showed positive for cytokeratin AE1/AE3 staining (arrowheads). WLI: White-light imaging; NM-NBI: Non-magnifying narrow-band imaging; SRC: Signet ring cell carcinoma.

cancer[13]. In cases of small undifferentiated-type cancer in which cells infiltrate laterally in the lamina propria deep into the glandular neck, *i.e.*, the non-whole-layer type, magnifying NBI cannot detect any cancer-specific irregular microvascular or microsurface pattern[9]. Therefore, it is difficult to detect undifferentiated-type cancer developing laterally within the proliferative zone and to identify the demarcation line of the cancer even by magnifying NBI, as shown in Figure 3[13]. Moreover, the extent of the lateral margin in this type of cancer becomes less detectable by chromoendoscopy (Figure 3)[12].

In the current study, however, SRCs were captured more easily by NM-NBI without the use of a magnifying endoscope than by WLI endoscopy; on NM-NBI they appeared as isolated whitish round areas. It remains unclear why the cancerous area of the SRC is whitish when compared to the surrounding normal mucosa. One possibility is that the depth of the crypt is shallow and the surface of the mucosa is planarized because of closely aggregated SRC cells in the upper to middle third of the mucosa (Figures 1 and 3). Okada *et al*[13] similarly presumed that both the number and heights of the gastric pits were decreased due to the extension of cancer cells in the mucosa, which eventually obliterated the architecture of the microsurface. As *H. pylori* infection causes extensive infiltration of inflammatory cells into the gastric mucosa, one would think this inflammation might affect the NBI index. However, no significant difference in the NBI index was seen

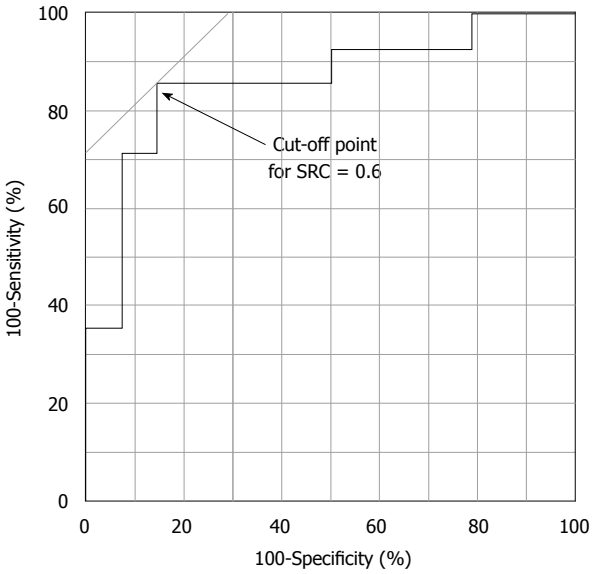

Figure 4 Receiver operating characteristic curve of the C-index of signet ring cell carcinoma. The curve is plotted as sensitivity (Y axis) and (100-specificity) (X axis). SRC: Signet ring cell carcinoma.

between patients with and without *H. pylori* infection in either SRCs or controls. There was also no significant difference in the NBI index between the SRC and control groups themselves, while the C-index results indicated that the SRCs were significantly rounder than the gastric ulcer scars of the controls. Since the 1980s, irregular shape lesion has been known to reflect malignant finding in the diagnosis of small gastric cancers, especially those of differentiated-type[22], and thus the NM-NBI shape of small SRC might be different from that of differentiated-type cancer. In the present work, a C-index exceeding 0.60 was considered to be the most reliable factor associated with SRCs. In logistic regression analysis, as well, the C-index ($\geqslant$ 0.60) was a highly significant predictor for SRC (OR = 36.0; 95%CI: 4.33-299.09; P = 0.0009). These results may suggest that NM-NBI could easily discriminate SRCs from gastric ulcer scars. However, gastric ulcer scars are histologically associated with complicated fibrosis in the submucosal layer, and thus it may not be surprising that their shape tended to be more irregular than that of SRCs.

More recently, novel electronic endoscopic systems (Evis Lucera Elite CV-290 and LASEREO, FUJIFILM Medical Co., Ltd., Tokyo) have been newly developed. These systems enable clearer and brighter NBI observation throughout the entire stomach than the existing systems (Evis Lucera CV-260 SL and Advancia, FUJIFILM Medical Co., Ltd., Tokyo). Therefore, it may be possible to identify small SRCs even from a relative distance by using a novel electronic endoscopic system. SRCs may be a form of incipient gastric cancer that may eventually develop into a linitis plastica-type cancer; hence, it is important to detect SRCs at an early stage. Our findings suggest the need to look carefully for isolated whitish round areas on NBI endoscopy, particularly in the greater curvature of the middle to lower portion of the stomach.

Nevertheless, the present study had some potential limitations. First, this was a retrospective study from a single institution with a small number of SRC cases. It will be important to perform a prospective study using the NBI criteria in order to confirm the reliability of these findings. However, the incidence of intramucosal SRC is low (4.3%) among the cases treated with ESD. Therefore, the incidence will be even lower in patients who undergo endoscopy for screening, indicating that a larger series of samples and an appreciable length of time will be required to assess the reliability. Second, ten of the SRC cases were referred to our department after biopsies at other clinics or hospitals; most lesions were biopsied prior to imaging. Thus, previous biopsy sites were covered by regenerated epithelium and might have influenced the NM-NBI findings[13]. However, the NBI index was not significantly different between biopsied and non-biopsied cases (data not shown).

In conclusion, it is best to look carefully for isolated whitish round areas by NM-NBI endoscopy for early detection of this malignancy. Here, we would like to emphasize that during an era when the incidence of *H. pylori* infection is decreasing, NM-NBI endoscopy should be used for the detection of small intramucosal SRCs.

COMMENTS

Background

As the authors described, the pathological characteristics of *Helicobacter pylori* (*H. pylori*)-negative gastric cancer are different from those of *H. pylori*-positive gastric cancer; histologically, the diffuse type is dominant, especially signet ring cell carcinoma (SRC). Since early-stage SRC develops beneath a flat, intact mucosal surface epithelium, it is very difficult to identify by white-light imaging (WLI) endoscopy.

Research frontiers

Magnifying narrow-band imaging (NBI) has been reported to be useful for the accurate diagnosis even in small gastric mucosal cancers. In cases of SRC, however, the cancer-specific findings and identifiable demarcation line of the lesion may not be identified even by magnifying NBI endoscopy or chromoendoscopy. To date, little is known regarding non-magnifying (NM)-NBI findings of small intramucosal SRC.

Innovations and breakthroughs

Intramucosal SRC could be clearly captured by NM-NBI as an isolated whitish area amid the brown color of the surrounding normal mucosa. SRCs were more clearly captured by NM-NBI endoscopy than by WLI endoscopy. Furthermore, although the NBI strengths of SRCs and whitish gastric ulcer scars were not significantly different, the two types of lesions' indexes of circularity determined by image-analytical software were significantly different, with the SRCs being distinctly rounder in shape than the ulcer scars.

Applications

This study emphasizes that during an era when the incidence of *H. pylori* infection is decreasing, NM-NBI endoscopy should be used for the detection of small intramucosal SRCs, which is indicated for endoscopic submucosal dissection. It is best to look carefully for isolated whitish round areas by NM-NBI endoscopy for early detection of this malignancy.

Terminology

NBI: Magnifying endoscopy with NBI is widely used in gastroscopy, especially in

the diagnosis of early gastric cancer. SRC: Signet ring cell carcinoma is thought to arise in the mucosa without metaplastic change and is typically confined to the glandular neck region in the original proliferation zone; therefore, it is difficult to detect those lesions.

Peer-review

The manuscript is excellent with perfect language.

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ORIGINAL ARTICLE

Clinical Trials Study

Laparoscopic right-sided colonic resection with transluminal colonoscopic specimen extraction

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Author contributions: Kayaalp C designed research; Kayaalp C, Kutluturk K, Yagci MA, Ates M performed research; Kayaalp C contributed to new reagents or analytic tools; Kayaalp C and Yagci MA analyzed data; Kayaalp C and Kutluturk K wrote the paper.

Institutional review board statement: The study was reviewed and approved by Inonu University Institutional Review Board.

Clinical trial registration statement: This study is registered at Inonu University Human Ethical Committee as a research. The registration identification number is 2014/33.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors declare no conflict-of-interest.

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Abstract

AIM: To study the transcolonic extraction of the proximally resected colonic specimens by colonoscopic assistance at laparoscopic colonic surgery.

METHODS: The diagnoses of our patients were Crohn's disease, carcinoid of appendix and adenocarcinoma of cecum. We preferred laparoscopic total mesocolic resections. Colon and terminal ileum were divided with endoscopic staplers. A colonoscope was placed per anal and moved proximally in the colon till to reach the colonic closed end under the laparoscopic guidance. The stump of the colon was opened with laparoscopic scissors. A snare of colonoscope was released and the intraperitoneal complete free colonic specimen was grasped. Specimen was moved in to the colon with the help of the laparoscopic graspers and pulled gently through the large bowel and extracted through the anus. The open end of the colon was closed again and the ileal limb and the colon were anastomosed intracorporeally with a 60-mm laparoscopic stapler. The common enterotomy orifice was closed in two layers with a running intracorporeal suture.

RESULTS: There were three patients with laparoscopic right-sided colonic resections and their specimens were intended to remove through the remnant colon by colonoscopy but the procedure failed in one patient (adenocarcinoma) due to a bulky mass and the specimen extraction was converted to transvaginal route. All the patients had prior abdominal surgeries and had related adhesions. The operating times were 210, 300 and 500 min. The lengths of the specimens

were 13, 17 and 27 cm. In our cases, there were no superficial or deep surgical site infections or any other complications. The patients were discharged uneventfully within 4-5 d and they were asymptomatic after a mean 7.6 mo follow-up (ranged 4-12). As far as we know, there were only 12 cases reported yet on transcolonic extraction of the proximal colonic specimens by colonoscopic assistance after laparoscopic resections. With our cases, success rate of the overall experience in the literature was 80% (12/15) in selected cases.

CONCLUSION: Transcolonic specimen extraction for right-sided colonic resection is feasible in selected patients. Both natural orifice surgery and intracorporeal anastomosis avoids mini-laparotomy for specimen extraction or anastomosis.

Key words: Colonoscopy; Colon cancer; Crohn's disease; Laparoscopic surgery; Natural orifice transendoscopic surger; Natural orifice specimen extraction

Core tip: Transcolonic extraction of the proximally resected colonic specimens by colonoscopic assistance can be an attractive method for some selected cases. This technique requires both advanced laparoscopic experience by intracorporeal anastomosis and interventional endoscopy. In this technique, there was a far distance between the resected specimen and the natural orifice. The specimen is moved about 100 cm in a hollow organ till the natural orifice. As far as we know, it has been the farthest distance that was reported yet for natural orifice specimen extractions. However, this technique is only suitable for small specimens which can pass through the sigmoid colon.

Kayaalp C, Kutluturk K, Yagci MA, Ates M. Laparoscopic right-sided colonic resection with transluminal colonoscopic specimen extraction. *World J Gastrointest Endosc* 2015; 7(12): 1078-1082 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i12/1078.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i12.1078

INTRODUCTION

Laparoscopic colectomy is going on to increase the number of its supporters. It lets smaller abdominal incisions and this reflects several advantages such as less pain, rapid recovery and wound problems. However, the required mini-laparotomy to extract the specimen during laparoscopic colectomy clearly compromise some advantages of the laparoscopic surgery. The use of natural orifices such as vagina or anus for colonic extraction is a new concept and it can avoid this mini-laparotomy and related morbidities. This new concept is called as Natural Orifice Specimen Extraction (NOSE) and the first laparoscopic colectomy with transanal specimen extraction has been described at the beginning of 1990's[1]. Up to the present time, transanal extraction was the main route for the rectal and left sided colonic specimens and transvaginal route was also available for both left and right sided colonic resections[1]. Transcolonic extraction by colonoscopic assistance can be an attractive method for some selected right-sided colonic resections but, as far as we know, there are only 12 cases reported yet[2-4]. Here, we reported three more patients with laparoscopic right-sided colonic resections and their specimens were intended to remove transanally by colonoscopy. The aim of this study was (1) to describe our initial clinical experience; (2) to outline our differences from the previous reports; and (3) to review all the available published cases.

MATERIALS AND METHODS

Mechanical bowel preparation was given the night before surgery. Broad-spectrum intravenous antibiotics were administered 30 min before skin incision and postoperatively for three days. Following induction of general anesthesia, a urinary catheter and a nasogastric tube were inserted. The patient were placed in the modified lithotomy position, with legs abducted and slightly flexed at the knees. The abdomen was insufflated by Veress and total of three or four abdominal trocars were used (two 5-12 mm and one or two 5 mm trocars) (Figure 1). The patient was placed in a 15 degree right-up lateral position. We preferred total mesocolic resections for all patients. Medial to lateral mesenteric dissection was carried out and when we identified the distal resection margin, we created a window in the mesocolon at this level and we divided the colon with a 60 mm endoscopic stapling device (EndoGIA, Covidien, Mansfield, MA). The lateral peritoneal attachments of the colon were mobilized from top-to-bottom until the cecum and terminal ileum was transected using the same endoscopic 60-mm linear stapler. A colonoscope was placed per anal and moved proximally in the colon till to reach the colonic closed end under the laparoscopic guidance. Laparoscopically, the stump of the colon was opened with endoscopic scissors and the colonoscope was visualized in the colon (Figure 2). A snare of colonoscope was released and the intraperitoneal complete free colonic specimen was grasped (Figure 3). Specimen was moved in to the colon with the help of the endoscopic graspers and pulled gently through the large bowel by colonoscope. If there was any invagination, it was reduced with graspers. The specimen was pulled through the remnant colon under laparoscopic guidance and extracted through the anus. The open end of colon was closed again with a laparoscopic stapler and the tiny remnant of colonic specimen removed through the 12 mm trocar. The ileal limb and the colon were anastomosed intracorporeally with a 60-mm laparoscopic stapler. The common enterotomy orifice was closed in two layers with a

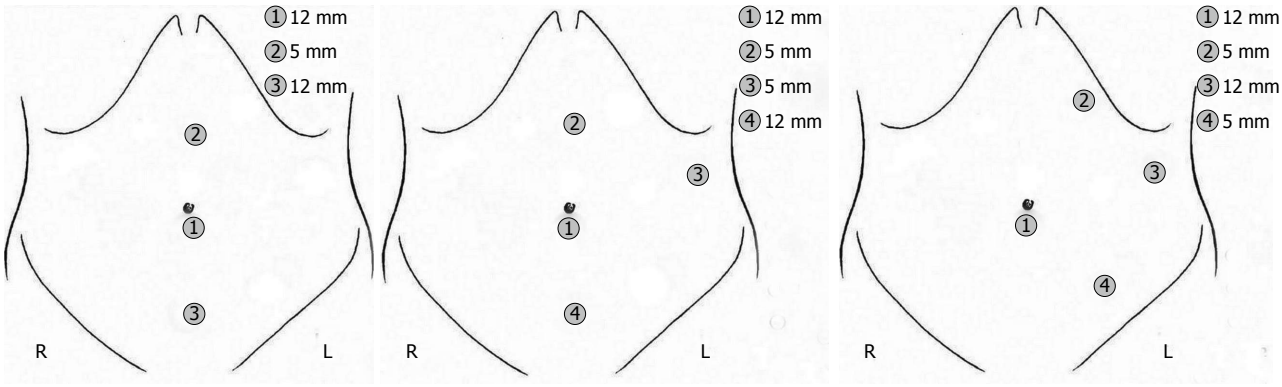

Figure 1 Trocar placements of the patients.

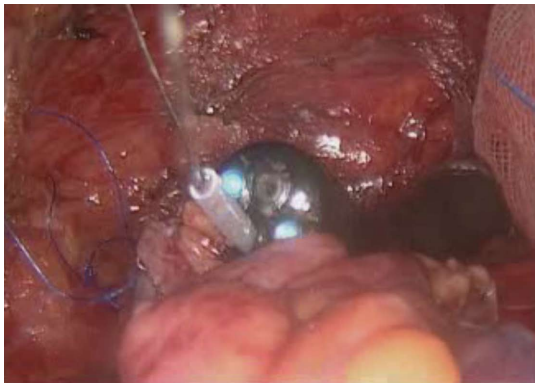

Figure 2 Intraperitoneal view of the colonoscope passed through the rectum, left colon and transverse colon. It is ready to grasp the laparoscopically resected right colon that was completely free in the abdomen.

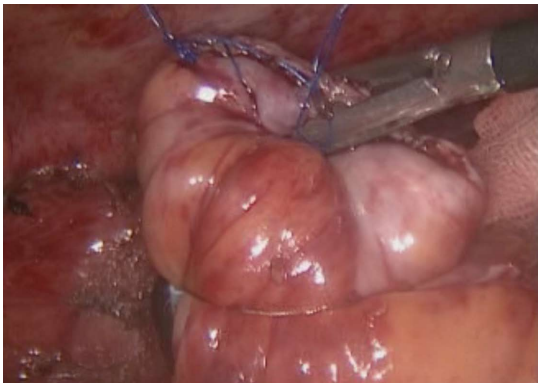

Figure 3 Colonoscopic transcolonic removal of the right colonic specimen.

running intracorporeal suture. An abdominal drain was placed. The nasogastric tube was removed at the end of the operation.

RESULTS

All the details of the patients, diseases and surgical procedures were summarized in Table 1. First patient had a Crohn's disease with intermittent bowel obstruction. He had a previous open appendectomy. Radiologically confirmed ileocolic stenosis was treated by laparoscopic ileocolic resection. There were bulky mesenteric lymph nodes which were very close to the stenotic part of the bowel. Bulky specimen caused some difficulties during transcolonic extraction and the specimen moved in the sigmoid colon in difficulty but the procedure was completed successfully without any complication. The second patient had a history of open appendectomy three months ago. The pathology reported carcinoid tumor with perineural invasion. A laparoscopic right hemi-colectomy with colonoscopy assisted transluminal specimen extraction was performed. There was no problem during transcolonic transit and extraction of the specimen. Pathological examination showed no malignancy. Last patient had a previous history of open pancreaticoduodenectomy due to chronic pancreatitis. While she was investigated for anemia, a 5-cm ulcerous cecal adenocarcinoma was detected. After laparoscopic right hemi-colectomy the specimen was tried to extract through the transcolonic route but it failed due to the bulky tumor and lymph nodes. In this case, we worried about jamming the specimen in the colon and it was removed from the vagina. The pathological analysis showed a pT3pN2 adenocarcinoma. None of the patients had early or late complication after a mean 7.6 mo (ranged 4-12) follow-up (Table 1).

DISCUSSION

Here, we intended to do a more minimal invasive colorectal surgery than the conventional laparoscopic technique and described three more cases of transcolonic extraction route for right-sided colonic pathologies. The potential advantages of natural orifice surgery are lower risks of incision related complications such as wound infections, postoperative pain, incisional hernias and better cosmesis. None of our cases had wound related early (surgical site infection) or late complication (hernia) in their follow-up. Because all our patients had previous open abdominal surgeries, there were no clear advantage of cosmesis. On the other hand, we learnt that previous abdominal surgery was not an obstacle for transcolonic specimen extraction.

Table 1 Published right hemicolectomies that the specimens were removed through the colon

	Patient No. 1	Patient No. 2	Patient No. 3	Eshuis[1] (*n* = 10)	Saad (*n* = 1)	Takayama (*n* = 1)
Age (yr)	55	20	68	31 (19-61)	70	71
Gender	M	F	F	3 M, 7 F	F	M
BMI	22	20	27	23.7 (18-31)	NA	NA
ASA	II	I	II	NA	NA	NA
Previous surgery	Yes	Yes	Yes	NA	NA	NA
Operating time (min)	210	300	500	208 (157-327)	NA	240
Blood loss (mL)	20	< 10	400	NA	NA	28
Specimen length (cm)	13	17	27	25.5 (16-64)	NA	8
Specimen width (cm)	8	6	12	> 7 cm (*n* = 2) < 7 cm (*n* = 8)	NA	NA
Failure	No	No	Yes	Yes (*n* = 2)	No	No
Complications	No	No	No	Yes (*n* = 3)	No	No
Resection location	Ileocolic	RHC	RHC	Ileocolic	Transverse	Ileocolic
Pathology	Crohn's	Carcinoid	Cancer	Crohn's	Adenoma	Adenoma
Oral diet (d)	3	3	2	NA	NA	1
Hospital stay (d)	5	5	4	5 (2-10)	5	4
Follow-up (mo)	12	7	4	NA	NA	NA

[1]Numbers of Eshuis are median and range in parenthesis. ASA: American Society of Anaesthesiologists physical status classification; NA: Not available; M: Male; F: Female; BMI: Body mass index.

There are two natural orifices for colorectal specimen extraction: the vagina and the anus. Transvaginal extraction can have some pitfalls. It is limited to female patients, requires an additional surgical trauma to an innocent organ and is not always suitable for patients of childbearing age, teenagers and virgins. Our second case was a virgin and she refused transvaginal access. She specified a preference for transabdominal extraction if the transcolonic extraction failed during surgery. The transanal route is more natural for colorectal specimen extractions and it can be considered as the first option for left sided colorectal resections[1] or total colectomies[5]. The transvaginal route can be kept particularly for bulky right sided colonic resections which are not suitable for transcolonic extraction. We preferred the transvaginal route for one case in which the transcolonic extraction failed due to a bulky specimen.

There is no clear description for the limitations of transcolonic specimen extraction. Splenic flexura of the colon (kinking) and the sigmoid colon (narrowing) are the two natural barriers during the transcolonic removal. It is a rational method to select the specimen sizes according to those natural narrow or kinking passes. After extractions, we measured the largest width of the specimens and they were 8, 6 and 12 cm (failed case), respectively. Although the largest width of the specimen is an important parameter, we believe that the largest diameter of the rolled specimen is more important. Eshuis *et al*[2] advocated performing transcolonic extraction of specimens with a maximum diameter of 5 cm in patients without inflammatory masses. They aborted two of ten cases due bulky volumes. It is not easy to estimate the largest diameter of every specimen by preoperative evaluation. Moreover, large masses at scans sometimes can be suitable for natural extraction and contrary, the procedure can fail for some small-looking lesions. Therefore we suggest intraoperative evaluation for decision. We decided to remove two specimens by transcolonic way and both resulted with successes but in one case we converted it to the transvaginal way. The overall success rate of the transcolonic removal of the proximal colon in all published cases was 12/15 (80%).

Transcolonic extraction of ileocolic resection has been first described for Crohn's disease[2]. Contrary to us, authors divided the mesentery close to the bowel for easier extraction. We believe that some modifications such as intracorporeal mesenteric division can reduce the largest diameter of the specimen and let the transcolonic extraction[6]. As a major morbidity, two postoperative intaabdominal abscesses were reported in the same study[2]. We believe that the main reason of high abdominal infection rate was related with the obstructed terminal ileum. In this study, the authors let the terminal ileum remained open freely to the abdomen for a long operating time. The authors created a side to side ileocolic anastomosis first and later they took out the specimen through this anastomosis. Till the end of the extraction, the distended small bowel went on to contaminate the abdomen. As a difference, we took the specimen into the colon before the anastomosis and the terminal ileum stayed as closed during the extraction time. The terminal ileum was opened just before the anastomosis and the common orifice of the linear stapler was closed immediately. We observed no deep or superficial surgical site infections.

For the first time, we reported that a right-hemicolectomy material was removed through the remnant colon. As mentioned before, Eshuis *et al*[2] preferred only ileocolic specimens, similarly Takayama *et al*[4] reported a case of ileocolic resection for a polyp. Lastly Saad *et al*[3] described a transverse colon resection for a polyp and extracted it through the transcolonic route. Those reported cases with owns all demonstrated that

transcolonic specimen extraction for ileocolic resection, transverse colon resection or even right hemi-colectomy is feasible in selected patients.

As a natural orifice surgery, transcolonic specimen extractions for some right-sided colonic resections and combination with intracorporeal anastomosis let to avoid mini-laparotomy during laparoscopic surgery.

COMMENTS

Background

At laparoscopic colorectal surgery, the use of natural orifices for colonic specimen extraction is a new concept. It can avoid mini-laparotomy and related morbidities.

Research frontiers

Transcolonic extraction of the proximally resected colonic specimens by colonoscopic assistance can be an attractive method for some selected cases. As far as we know, there are only 12 cases reported yet and here, the authors reported three more patients with laparoscopic right-sided colonic resections. All the specimens were intended to remove through the remnant colon by colonoscopy.

Innovations and breakthroughs

Transcolonic specimen extraction for ileocolic resection or even right hemicolectomy is feasible in selected patients.

Applications

Combination with natural orifice surgery and intracorporeal anastomosis avoids mini-laparotomy for specimen extraction or anastomosis.

Terminology

NOTES: Natural orifice transluminal endoscopic surgery. NOSE: Natural orifice specimen extraction.

Peer-review

The authors have performed a good study, the manuscript is interesting.

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EDITORIAL

High-resolution anoscopy: Unchartered territory for gastroenterologists?

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Abstract

High-resolution anoscopy (HRA) is a procedure where patients with an increased risk of anal cancer, like men who have sex with men, human immunodeficiency virus infected individuals, transplant patients and women with a history of lower genital tract neoplasia, with abnormal anal cytology results, are submitted to anal and perianal visualization under magnification. This will allow for a better detection of anal high-grade lesions that can be treated, in an effort to prevent anal cancer. Anal cancer screening follows the same principles that cervical cancer screening. During this procedure, an anoscope is inserted and a colposcope is used to examine systematically the squamocolumnar junction, the transformation zone and the perianal skin. Initially the observation is done with no staining and then with the application of acetic acid and Lugol's iodine solution, allowing for better lesion identification and characterization. Any suspicious lesion seen should be carefully evaluated and biopsied. Without HRA only a small percentage of suspicious lesions are identified. High-grade lesions that are detected can be ablated under HRA. This is a challenging exam to perform, with a long learning curve and the number of clinicians performing it is limited, although the growing number of patients that need to been screened. Specific equipment is required, with these patients ideally been followed by a multidisciplinary team, in a reference centre. HRA remains unfamiliar for many gastroenterologists.

Key words: High-resolution anoscopy; Anal cytology; High-grade squamous intraepithelial lesions; Low-grade squamous intraepithelial lesions; Anal cancer

Core tip: High-resolution anoscopy is a procedure where high-risk patients are submitted to anal and perianal visualization under magnification, allowing detection of anal high-grade lesions that can be treated. Anal cancer is histologically and biologically very similar to cervical cancer and the screening follows the same principles. The importance, difficulties and the description of the technique will be discussed. This is a difficult exam to perform, with a long learning curve that requires specific equipment and the need for a multidisciplinary team, ideally in a reference centre. It remains unfamiliar for many gastroenterologists.

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DEFINITION AND PRINCIPLES OF HIGH RESOLUTION ANOSCOPY

High-resolution anoscopy (HRA) is a procedure where high-risk patients are submitted to anal and perianal visualization under magnification, allowing detection of anal high-grade lesions that can be treated. HRA can simply be defined as a colposcopy applied to the anal canal and perianal region.

Men who have sex with men (MSM), human immunodeficiency virus (HIV) infected individuals, transplant patients and women with a history of lower genital tract neoplasia have an increased risk of anal cancer. HIV-negative MSM have an estimated incidence rate of 35 per 100000 person-year and anal cancer incidence rates in HIV-positive MSM are two times higher (about 70-100 per 100000 person-year)[1]. Anal cancer has become one of the most common non-AIDS-defining tumors in HIV-infected individuals[2]. Human papillomavirus (HPV) infection is almost always present in HIV-positive MSM, and infections with multiple HPV types are common[3]. Concerning transplantation, most data come from renal transplant recipients, and the relative risk of anal cancer in these patients is 10 fold[4,5].

Anal cancer screening follows the same principles that cervical cancer screening. Both tumors are caused by infection with oncogenic HPV strains, occur at the squamocolumnar transition zone and arise from same precancerous dysplastic lesions, anal intraepithelial neoplasia or cervical intraepithelial neoplasia[6]. Women are screened through cervical cytology and those with abnormal results are then referred for colposcopy. Abnormalities are biopsied, and if high-grade squamous intraepithelial lesions (HSIL) are present, the patient is treated, thereby preventing progression to cervical cancer. Cervical cancer rates have dramatically decreased through cytology screening[7,8], from 40-50 cases per 100000 individuals to about 8-10 cases per 100000 individuals. Anal cancer is likely preceded by HSIL, a colposcope may similarly be used to visualise it and permit biopsy and treatment in an effort to prevent anal cancer.

Progression of biopsy-proven anal HSIL to cancer in a group of 27 HIV-infected MSM has been recently reported[9] and confirmed that individual HSIL lesions can progress to cancer.

High-risk patients like HIV-positive men and women regardless of sexual orientation or HIV-negative MSM submitted to anal cytology as a screening test, that have an abnormal result should be refer to HRA. The prevalence of anal squamous intraepithelial lesions (SIL) has remained high among HIV-positive MSM after the introduction of highly active antiretroviral therapy (HAART); HAART is not associated with a reduced prevalence of anal SIL[10]. Other groups who should be considered for screening include women with cervical cancer, high-grade vulvar disease or cancer, individuals with perianal condyloma acuminata; and transplant recipients[11].

Anal cytology is classified on the basis of the 2001 revised Bethesda System of cervical cytology classification[12]. There is no specific terminology for anal cytology. The specificity and predictive value for anal high-grade lesions on biopsy are highest for HSIL, atypical squamous cells which cannot exclude high-grade squamous intraepithelial lesion(ASC-H), low-grade squamous intraepithelial lesions (LSIL) and atypical squamous cells of undetermined significance (ASC-US).

The severity of cytological findings and infection with high-risk HPV are the most significant predictors of significant preditors for HSIL, underscoring the importance of anal dysplasia screening[13]. A systematic review described that anal cytology has a sensitivity from 69% to 93% and a specificity from 32% to 59%, that is similar to those reported for cervical cancer screening[1]. Abnormal anal cytology seems highly predictive of anal dysplasia on biopsy, in a previous study by Cranston *et al*[14] 2007, the positive predictive value of anal cytological abnormality to predict any degree of anal dysplasia was 95.7%. Both sensitivity and specificity of anal cytology are higher for internal disease as compared to external disease (perianal region)[3].

HIGH RESOLUTION ANOSCOPY TECHNIQUE

Normally, during HRA the patient is in the left lateral position, in the foetal position, with the buttocks at the edge of the table. Bowel preparation is not needed. An anoscope is inserted and a colposcope is used to examine the squamocolumnar junction, the anal canal including the transformation zone and the perianal skin in a systematic manner. The inspection should be performed first with no staining and then with the topical application of acetic acid (3% or 5%), that will allow for better lesion identification and characterization. Most of the anal exam is done under 16 × magnification, once specific areas of interest are visualised, they should be examined under 25 × magnification and the anal verge is viewed with 10 × magnification[15]. After examination with acetic acid, application of Lugol's iodine solution may help to distinguish HSIL from LSIL, to assist the clinician in deciding where to biopsy, as well as to define the margin of the lesion[15].

Lesions seen during HRA should be carefully described concerning localization, contour, margins, acetic acid induced whitening, Lugol's staining, epithelial pattern, vascular pattern (mosaic pattern, punctation, warty vessels, atypical). This will help to distinguish between

low-grade and high-grade lesions. HSIL may be flat or thickened, and often have vascular changes including punctuation or a mosaic pattern, are acetowhite, with a poor uptake of Lugol's solution. In a study by Camus *et al*[16], the positive predictive value for HSIL increased to 68.6% with the following combination of criteria: Acetic acid-induced whitening, no Lugol staining, irregular epithelial pattern, and vascular changes. Many of these anal suspicious lesions have similar aspects to that initially describe in cervical colposcopy[7,8]. Cancers are often friable or ulcerated lesions with atypical vessels. Any suspicious lesion, namely of HSIL or anal cancer should be biopsied.

IMPORTANCE OF HIGH RESOLUTION ANOSCOPY

HRA is fundamental for high-grade lesion detection and subsequently guided treatment. Anal HSIL ablation treatment under HRA may reduce the rate of anal cancer[17].

Previous studies revealed that before HRA is performed, only a small percentage of suspicious lesions are identified. Camus *et al*[16], show that only 38.7% of the lesions were visible with the naked eye before HRA.

Few data are available on the progression of anal SIL to anal squamous-cell carcinoma (ASCC), the true rate of progression from high-grade dysplasia to invasive anal cancer remains unclear[1]. There are clearer data concerning perianal intraepithelial neoplasia or Bowen disease in which approximately 5% of lesions undergo malignant change[18].

Devaraj *et al*[19], published a series of 98 HIV-positive patients, with 40 patients with a follow-up of more than one year, with expectant management of anal squamous dysplasia. In this series, 28 of 40 patients had anal HSIL and three of these patients (11%) developed invasive carcinoma while under surveillance (expectant management). Scholefield *et al*[20] described a series of 35 non-infected HIV patients, all with anal HSIL. In this series, 7 patients where submitted to expectant management due to extensive or multifocal disease and three of these patients (9%) developed invasive ASCC during follow-up, median of 5 years after the initial diagnosis of anal HSIL. In a study by Sobhani *et al*[21], including 199 patients who were successfully treated for anal warts (HIV positive and HIV negative patients included), 38 (19%) later developed anal HSIL, and of these, seven (18%) developed ASCC, 13 to 108 mo after entry in the study.

Wide excision is a morbid procedure that also removes uninvolved healthy tissues to achieve widely clear margins. Nevertheless, there is still a risk of recurrence[22]. HRA guided ablation of anal HSIL has several advantages: It permits a full evaluation of the anorectal anatomy, detection of grossly invisible disease, allowing target therapy with protection of normal tissues, minimal morbidity and reducing the risk of anal stenosis[22]. Cervical HSIL is usually treated with the loop electrosurgical excision procedure, removing the squamocolumnar transformation zone where most dysplasia develops. This is not possible for anal HSIL and treatment most often relies on ablation of individual lesions with laser, electrocautery (ECA), and infrared coagulation (IRC). There is no significant difference in treatment success between IRC and ECA[17]. A recent study by Goldstone *et al*[17] showed that patients undergoing ablation of anal HSIL have high recurrence, but the probability of developing anal cancer is low. The recurrence 1 year after the first ablation for HIV-positive and -negative patients was 53% and 49%, respectively; at 2 and 3 years, the rate of recurrence was 68% and 77% for HIV-positive patients and 57% and 66% for HIV-negative patients. The probability of cancer 3 years post-ablation was 1.97%.

Perianal high-grade dysplasia (Bowen disease) it is traditionally treated with mapping (blind biopsies) and wide excision. A recent study by Johnstone *et al*[23], showed that perianal dysplasia can be successfully treated with HRA-guided targeted ablation (ECA, laser or IRC) with no morbidity, although recurrence remains high. Almost all of these patients have anal canal dysplasia and HIV-positive patients are at the greatest risk for disease and recurrence.

Recommendations on post-treatment follow-up intervals are lacking.

DIFFICULTIES IN PERFORMING HIGH RESOLUTION ANOSCOPY, CAN WE DO IT?

Probably due to the long learning curve, the number of clinicians performing HRA is limited. Although the similarities of HRA and colposcopy, HRA is a more challenging and demanding technique due to the anal anatomy, anal pathology and difficulties in the treatment (excision is not a real option). Previous training in colposcopy is important to understand how to work with the colposcope and detect the aspect of the lesions. To perform this technique, a colposcope is required, and this equipment is not normally available outside a gynaecology clinic. In some cases, patients have not been referred to this technique due to the lack of knowledge of the indications or trained clinicians that can observe these patients. These patients need to be followed by a multidisciplinary team, including the clinicians performing HRA, pathologists, infectiologists, and colon and rectal surgeons.

This is extremely important because there is a growing number of patients, namely, HIV and MSM who need to been screened. It will be a long journey until all of these high-risk patients are referred for screening and more clinicians feel motivated to learn this technique. Recently the results of an internet-based survey on attitudes and practice of Colon and Rectal surgeons (United States members of the American Society of

Colon and Rectal Surgeons) on anal dysplasia revealed that, although most of them treated patients at risk for anal cancer and had read research on HSIL, only one-third had performed HRA and of these less than half (46%) were formally trained. When evaluating patients for HSIL in surgery, only 31% used acetic acid with magnification[24]. Another internet-based survey to members of international surgical and dermatological societies concerning diagnosis, treatment and surveillance of patients with HPV-related anal diseases revealed that to detect dysplastic lesions, 42.0% of surgeons used acetic acid only, 23.2% used this in combination with HRA and 19.5% applied intra-anal cytological smears. Likewise, 64.6% of dermatologists applied acetic acid only, 16.5% combined acetic acid with HRA and 30.2% performed intra-anal cytological smears[25].

It is fundamental to have more and better trained clinicians performing it. This will never be a technique that can be performed by all.

Several clinicians can perform anal cytology, especially those involved with high-risk patients, namely infecciologists, dermatologists, gynaecologists, nephrologists. If an abnormal result is detected, patients should be referred, ideally to a reference centre, to a clinician properly trained in HRA and with a multidisciplinary team. Thus, regarding anal cancer screening, we should inform all clinicians, cytology should be performed by most and HRA by some.

HRA was developed in the 90's, but remains unfamiliar to many, including gastroenterologists, although in some countries gastroenterologists are also proctologists. Much of the gastroenterology daily routine involves diagnostic and interventional therapeutic procedures. These are central concepts of HRA. Basic knowledge regarding the technique and even proper training may well be in the present and future realm of gastroenterologists.

HRA is fundamental for high-grade anal and perianal lesion detection and subsequently guided treatment in an effort to prevent anal cancer in high-risk patients.

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Upper non-variceal gastrointestinal bleeding - review the effectiveness of endoscopic hemostasis methods

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Abstract

Upper non-variceal gastrointestinal bleeding is a condition that requires immediate medical intervention and has a high associated mortality rate (exceeding 10%). The vast majority of upper gastrointestinal bleeding cases are due to peptic ulcers. *Helicobacter pylori* infection, non-steroidal anti-inflammatory drugs and aspirin are the main risk factors for peptic ulcer disease. Endoscopic therapy has generally been recommended as the first-line treatment for upper gastrointestinal bleeding as it has been shown to reduce recurrent bleeding, the need for surgery and mortality. Early endoscopy (within 24 h of hospital admission) has a greater impact than delayed endoscopy on the length of hospital stay and requirement for blood transfusion. This paper aims to review and compare the efficacy of the types of endoscopic hemostasis most commonly used to control non-variceal gastrointestinal bleeding by pooling data from the literature.

Key words: Upper gastrointestinal bleeding; Non-variceal bleeding; Endoscopic hemostasis; Endoscopic therapy

Core tip: Review and comparison the efficacy of the most commonly used types of endoscopic hemostasis for the control of non-variceal gastrointestinal bleeding in clinical practice by pooling data from the literature.

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INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB) is a common medical entity for which endoscopy has become

the primary diagnostic and therapeutic technique. Endoscopy performed in patients with UGIB corresponds with a reduction in required blood transfusions and length of intensive care unit/total hospital stay[1]. Upper endoscopy is required for most patients with UGIB and should be performed within 24 h of hospital admission after adequate prior fluid resuscitation[2]. The key to improving outcomes is the proper initial management of individuals who present with UGIB. In most clinical conditions, the vast majority (80%-90%) of episodes of acute upper gastrointestinal bleeding are secondary to non-variceal origin. This review addresses different endoscopic techniques of hemostasis that are used to treat acute upper gastrointestinal bleeding of non-variceal origin (NVUGIB) in the world practice.

EPIDEMIOLOGY

UGIB is mostly non-variceal in origin and still remains one of the most common challenges encountered by surgeons, gastroenterologists and endoscopists in a daily clinical setting. The incidence rate of non-variceal UGIB ranges from 50 to 150 per 100000 adults/year[3]. In spite of major advances in the approaches used to manage non-variceal UGIB over the past 2 decades, including the peptic ulcer bleeding prevention, the optimal use of endoscopic therapy, as well as the use of adjuvant high-dose proton pump inhibitors (PPIs) to eradicate *Helicobacter pylori*, it is still associated with considerable morbidity, mortality, and health care costs. The most common non-variceal bleeding etiologies include gastroduodenal peptic ulcer (20%-50%), gastroduodenal erosions (8%-15%), Mallory-Weiss tears (8%-15%), erosive esophagitis (5%-15%), arteriovenous malformations/GAVE (5%); several other conditions [*e.g.*, Dieulafoy's lesion, upper gastrointestinal (GI) tract malignancy] make up the remaining causes[4-7]. Peptic ulcer disease still remains the most common cause of acute NVUGIB and accounts for at least 50% of cases. Ulcers with signs of active spurting (Forrest class ⅠA) or oozing blood (Forrest class ⅠB) and ulcers with a nonbleeding visible vessel (Forrest ⅡA) are at high risk of recurrent bleeding when only medical therapy is used. Thus, endoscopic hemostasis is required for patients with high-risk stigmata [ⅠA, ⅠB] or a visible vessel in an ulcer niche [ⅡA]. Clean-based ulcers (Forrest class Ⅲ) or flat pigmented spots in the ulcer bed (Forrest class ⅡC) are low-risk lesions that only rebleed in 4% to 13% of cases and can therefore be treated with pharmacotherapy alone and considered for outpatient management[8,9]. Ulcers with adherent clots (Forrest class ⅡB) have an intermediate risk of rebleeding (approximately 25%) that depends on the underlying lesion. For that reason, clot removal should be performed with vigorous irrigation and manipulation with an endoscope, forceps, or snare. In patients suffering from peptic ulcer disease, duodenal ulcer bleeding appears more frequently than from gastric ulcers[10]. A Blatchford score or pre-endoscopic Rockall score (based on age, comorbidity, and the presence or absence of hemodynamic instability) should be used to stratify risk and determine which patients require prompt endoscopy or, conversely, to determine suitability for early discharge (Table 1). The Blatchford score, a validated risk-stratification tool based solely on clinical and laboratory variables, is used to predict the need for endoscopic intervention in patients with acute upper GI hemorrhage. A higher score indicates a higher likelihood of needing endoscopic intervention (score ranges from 0 to 23). The clinical Rockall score (*i.e.*, the score obtained before endoscopy is performed) is calculated solely on the basis of clinical variables at the time of patient presentation. The complete Rockall score makes use of both clinical and endoscopic criteria to assess patient risk of re-bleeding and mortality. Rockall score ranges from 0 to 11 points, with higher scores indicating a higher risk for a poor outcome (Table 2)[11,12].

Table 1 Blatchford scoring: Admission risk markers and associated score component values[13]

Admission risk marker	Score component value
Blood urea, mmol/L	
6.5 to ≤ 8	2
8.0 to < 10.0	3
10.0 to < 25	4
≥ 25	6
Hemoglobin for men, g/dL	
12.0-13.0	1
10.0 to < 12.0	3
< 10.0	6
Hemoglobin for women, g/dL	
10.0 to < 12.0	1
10	6
Systolic blood pressure, mmHg	
100-109	1
90-99	2
< 90	3
Other markers	
Pulse ≥ 100/min	1
Presentation with melena	1
Presentation with syncope	2
Hepatic disease	2
Cardiac failure	2

ENDOSCOPIC MANAGEMENT

The aim of therapeutic endoscopy is to stop any ongoing bleeding and to prevent rebleeding. Cooper *et al*[13] studied the effectiveness of performing an early endoscopy within the first 24 h of an acute UGIB episode and found it to be associated with reductions in the length of hospital stay, the rate of recurrent bleeding, and the need for emergent surgical intervention. According to the 2010 international consensus on non-variceal upper gastrointestinal bleeding, early endoscopy (within 24 h of presentation) is appropriate for most patients with UGIB[2]. In cases of rebleeding, a second attempt at endoscopic therapy is recommended to reduce the need for surgery. In patients who have undergone failed endoscopic therapy, surgery should be considered.

Table 2 Complete rockall risk scoring system for assessment after an episode of acute upper gastrointestinal bleeding[12]

Variables	Score 0	Score 1	Score 2	Score 3
Age	Younger than 60 yr	60-79 yr	80 yr or older	-
Shock symptoms, systolic blood pressure, heart rate	Shock absent, blood pressure 100 mmHg or greater, heart rate 100 bpm or greater	Tachycardia, blood pressure 100 mmHg or greater, heart rate 100 bpm or greater	Hypotension, blood pressure less than 100 mmHg	-
Comorbidities	No major comorbidity	-	Heart failure, coronary artery disease, any major comorbidity	Renal failure, liver failure, disseminated malignancy
Endoscopic diagnosis	Mallory-Weiss tear or no lesion identified, and no stigmata of recent hemorrhage	All other diagnoses	Malignancy of upper GI tract	-
Stigmata of recent hemorrhage	Low-risk	-	High-risk	-

Low-risk stigmata of bleeding: Clean base ulcer, pigmented spots; High-risk stigmata of bleeding: Adherent clot, visible or spurting vessel, active bleeding; Bpm: Beats per minute; GI: Gastrointestinal.

Table 3 Recommendations of the american society for gastrointestinal endoscopy concerning upper gastrointestinal bleeding management[38]

We recommend that patients with UGIB be adequately resuscitated before endoscopy
We recommend antisecretory therapy with PPIs for patients with bleeding caused by peptic ulcers or in those with suspected peptic ulcer bleeding awaiting endoscopy
We suggest prokinetic agents in patients with a high probability of having fresh blood or a clot in the stomach when undergoing endoscopy
We recommend endoscopy to diagnose the etiology of acute UGIB. The timing of endoscopy should depend on clinical factors. Urgent endoscopy (within 24 h of presentation) is recommended for patients with a history of malignancy or cirrhosis, presentation with hematemesis, and signs of hypovolemia including hypotension, tachycardia and shock, and a hemoglobin < 8 g/dL
We recommend endoscopic therapy for peptic ulcers with high-risk stigmata (active spurting, visible vessel). The management of PUD with an adherent clot is controversial. Recommended endoscopic treatment modalities include injection (sclerosants, thrombin, fibrin, or cyanoacrylate glue), cautery, and mechanical therapies
We recommend against epinephrine injection alone for peptic ulcer bleeding. If epinephrine injection is performed, it should be combined with a second endoscopic treatment modality (*e.g.*, cautery or clips)
We recommend that patients with low-risk lesions be considered for outpatient management
We recommend against routine second-look endoscopy in patients who have received adequate endoscopic therapy
We recommend repeat endoscopy for patients with evidence of recurrent bleeding

UGIB: Upper gastrointestinal bleeding; PPIs: Proton pump inhibitors; PUD: Peptic ulcer disease.

Despite adequate initial endoscopic therapy, recurrent UGIB can occur in up to 24% of high-risk patients. The use of PPI therapy in addition to endoscopic therapy reduces the rate of recurrent bleeding to approximately 10%. Patients with recurrent bleeding generally respond favorably to repeated endoscopic therapy. Routine second-look endoscopy, defined as a planned endoscopy performed within 24 h of the initial endoscopy, is not recommended. In cases where the initial endoscopy failed to identify the source (*e.g.*, because of a large clot in the stomach) or if there are concerns that inadequate therapy was delivered, second-look endoscopy may be appropriate (Table 3).

Currently, the efficacy and safety of endoscopic hemostasis rely on the identification of lesions that are suitable for endoscopic therapy, the selection of the appropriate hemostatic devices, attention to technique, and prompt recognition and management of procedure-related adverse events. The suitable technique should be chosen based on the appearance of the bleeding focus and the related risk for persistent or recurrent bleeding.

The traditional endoscopic modalities are injection, mechanical therapy, and thermal approaches. Injection agents include saline, dilute epinephrine, sclerosing agents (ethanolamine, polidocanol, absolute alcohol, and sodium tetradecyl sulfate), and tissue adhesives (cyanoacrylate, thrombin, and fibrin glue). Mechanical therapy offers endoscopic clips and band ligation. Thermal devices deliver electrical current (through direct contact or *via* an inert gas plasma) or heat to the target tissue. Moreover, a few new technologies have emerged, such as hemostatic powders.

INJECTION TREATMENT

Injection needles consist of an outer sheath (plastic, Teflon, or stainless steel) and an inner hollow-core needle (19-25 gauge)[14]. Using a handle on the end of the needle sheath, the operator can retract the needle into the sheath for safe passage through the working channel of the endoscope. When the catheter is placed near the target tissue, the needle is extended a preset distance out of the end of the sheath, and a syringe attached to the handle is used to inject liquid agents into the target tissue. Dilute epinephrine in saline (1:10000) is applied with an injection needle in 0.5-1.0 mL boluses to the four quadrants around the high-risk

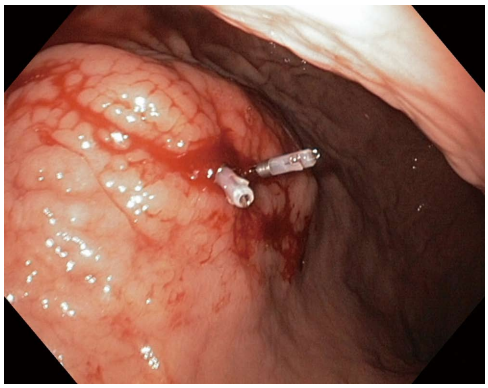

Figure 1 Endoscopic clips.

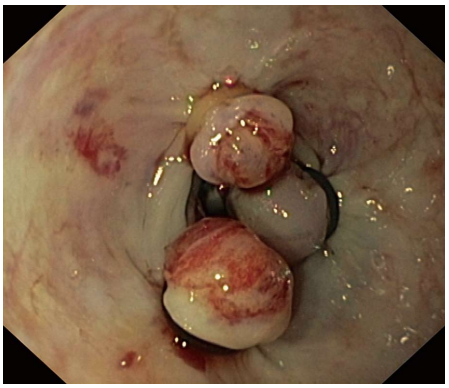

Figure 2 Endoscopic band ligation.

stigmata or to the base of the active bleeding site and then in the middle of it, up to a total of 10 mL[15,16]. Some practitioners prefer to use absolute alcohol in much smaller volumes (1-2 mL in 0.1 mL aliquots) or combinations of epinephrine and alcohol or sclerosants, which are used for the treatment of varices. Epinephrine injection therapy promotes initial hemostasis through a combination of vasoconstriction, compression (local tamponade), and platelet activation, but this effect declines after 20 min. If epinephrine injection is performed, it should usually be combined with a second endoscopic treatment modality (*e.g.*, electrocautery or clips)[17]. If epinephrine is used alone, there is a significant risk of rebleeding. This can be reduced by injecting large volumes, as high as 30 mL, which are associated with no clearly described cardiologic adverse events, and the rebleeding rate decreases linearly with the injected volume[18,19]. Dilute epinephrine injection is inferior at preventing rebleeding and surgery when compared with bipolar electrocoagulation, clips, or fibrin glue[20]. Other injected substances, such as sclerosing agents (*e.g.*, polidocanol, ethanolamine, and ethanol), have similar efficacy but more side effects, including transmural necrosis or perforation[21]. Another class of injectable agents are tissue adhesives, including cyanoacrylate glues, thrombin and fibrin, which are used to create a primary seal at the site of bleeding by inducing thrombosis through direct tissue injury. However, they may also evoke tissue necrosis and, hence, the limit for injected volumes is less than 1 mL. Cyanoacrylate (n-butyl-2-cyanoacrylate, Histoacryl; Braun, Germany) is a liquid tissue adhesive that consists of monomers that rapidly polymerize (creating long and strong chains) in an exothermic reaction after contact with hydroxide ions[22]. Cyanoacrylate is widely used for the management of bleeding esophageal and gastric varices, but it is not recommended for acute non-variceal upper gastrointestinal bleeding. However, in difficult-to-arrest non-variceal bleeding, it could be a useful and safe therapeutic tool.

MECHANICAL THERAPY

Mechanical therapy refers to the use of a device that causes physical tamponade at a bleeding site[15]. It includes endoscopic clips and band ligation (Figures 1 and 2). Metal clips are particularly useful for small bleeding ulcers (*i.e.*, Dieulafoy lesions), for Mallory-Weiss tears, and for large, visible vessels. Endoscopic clips are deployed over a bleeding site (*e.g.*, visible vessel) and typically slough off within days to weeks after placement. Endoscopic clips function by mechanical compression of the bleeding vessel and theoretically cause less tissue injury than cautery methods. Band ligation is widely used in variceal bleeding. However, it has also been found to be effective in treating bleeding Dieulafoy's lesions[23].

The Over-The-Scope Clip (OTSC; Ovesco, Tübingen, Germany) is a modern endoscopic clipping device designed for tissue approximation. It has been used for the closure of fistulas and perforations. OTSC consists of a nitinol clip mounted on an applicator cap that is affixed to the tip of the endoscope. The deployed clip captures and closes tissue suctioned into the applicator cap, thus compressing the lesions until healing. Studies on animal models and limited data from clinical use support the efficacy of OTSC for the treatment of GI bleeding, and a number of small case series have shown effective hemostasis resulting from the use of OTSC in patients for whom epinephrine injection or standard clip placement failed[24]. The OTSC is now available on the market and gives the physician a tool for the immediate management of complications, such as deep-wall lesions, difficult bleeding or perforations.

THERMAL THERAPY

Thermal therapies include electrocautery probes (monopolar, bipolar or multipolar) and heater probes, which are referred to as contact thermal modalities, and argon plasma coagulation (APC) and laser phototherapy, which are known as noncontact techniques. Bipolar and multipolar probes provide constant bipolar electrocoagulation, which is assumed to be safer than monopolar diathermy (which produces an unpredictable depth of damage and a higher risk of perforation). A foot pedal controls the delivery of energy. The power output is in watts (W). Maximum power settings are dependent

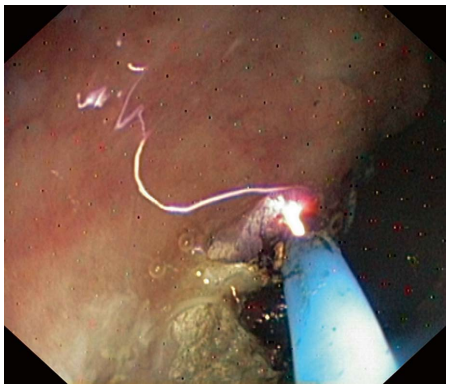

Figure 3 Argon plasma coagulation.

on the generator used but usually do not exceed 50 W. A standard setting is 20 W.

A heater probe provides constant heat at 250 ℃, which is released by a diode in the probe tip and directly transferred to tissue to affect coagulation. Contact treatment devices share some common principles. All can be applied tangentially but are better used face-on, if possible. When the vessel is actively bleeding, direct probe pressure on the vessel or feeding vessel will reduce the flow and increase the effectiveness of treatment. Mechanically pressuring the probe tip directly to the bleeding site, combined with heat or electrical current to coagulate blood vessels, is a process known as "captive coagulation". The bipolar and heater probes incorporate a flushing water jet, which helps to prevent sticking.

Argon plasma coagulation, which is performed without tissue contact, uses the electrical conductivity of argon gas (Figure 3). The argon, passed down an electrode catheter and energized *via* an intelligent-circuitry electrosurgical unit and patient plate, ionizes to produce a local plasma arc. The produced heating effect is inherently superficial (2-3 mm at most, unless the current is applied in the same place for many seconds). Therefore, APC is used to treat superficial mucosal lesions, such as vascular malformations and gastric antral vascular ectasias. The APC probe should be positioned 2-10 mm from the lesion and the argon gas flow should be 1.5-2 L/min at a power of 40-50 W[25,26].

Laser phototherapy uses an Nd:YAG laser to create hemostasis by generating heat to induce direct vessel coagulation. This is a noncontact thermal method. It is not as effective as captive coagulation because it lacks the use of compression to create a tamponade effect[27]. An additional deterrent to its use is expense.

To perform laser coagulation, the area near the vessel is first injected with epinephrine to reduce blood flow (reducing the heat-sink effect). Then, the laser is applied around the vessel, producing a wall of edema. Caution must be taken to avoid drilling into the vessel with the laser, which can cause increased bleeding.

TOPICAL HEMOSTATIC AGENTS

Topical hemostatic agents are new tools used in endoscopic hemostasis. Three different powders are available: Hemospray (Cook Medical, Winston-Salem, NC, United States), Ankaferd BloodStopper, and EndoClot (EndoClot Plus Inc., Santa Clara, CA, United States)[28].

Hemospray (TC-325), a novel proprietary inorganic powder, has recently been approved in Canada for the management of NVUGIB[29]. The powder is administered through a 10- or 7-French catheter *via* a CO_2-pressurised canister. It achieves hemostasis by adhering to the bleeding site, leading to mechanical tamponade and, by concentrating and activating platelets and coagulation factors, promoting thrombus formation. Its ability to cover large areas with multiple bleeding points makes it a suitable choice for hemorrhagic gastritis, gastric antral vascular ectasia, radiation-induced mucosal injury and malignancy-related bleeding[29]. Other advantages include ease of use, the lack of need for precise lesion targeting and access to lesions in difficult locations.

Hemostatic sprays derived from plants have also been invented. Clinical use of these agents for endoscopic hemostasis is currently limited to the off-label use of ankaferd blood stopper (ABS) (Ankaferd Health Products Ltd., Istanbul, Turkey), a mixture of extracts from several plants that is approved in Turkey for the topical treatment of dental and postsurgical external bleeding. ABS is delivered through the working channel of the scope using a spray catheter.

The EndoClot Polysaccharide Hemostatic System (EndoClot Plus Inc., Santa Clara, CA, United States) is the latest available hemostatic powder. It consists of starch, which explains its availability in European countries, Australia, Malaysia, and Turkey, despite a lack of rigorous scientific evidence for its efficacy. The effectiveness of the powder at controlling and preventing bleeding related to endoscopic mucosal resection has been recently described[28].

PRE-ENDOSCOPY PHARMACOLOGIC THERAPY

Prokinetic agents, such as intravenously administered erythromycin or metoclopramide, should be considered for use 30 min prior to endoscopy to improve visibility[30]. Intravenous prokinetic agents, when administered 20 to 120 min before endoscopy in patients with acute UGIB, decrease the need for a repeat endoscopy to determine the site and cause of bleeding. However, their use has not demonstrated any benefit to other clinical parameters, such as transfusion requirement, length of hospital stay, or need for surgery.

Proton pump inhibitor (PPI) therapy is another pharmacologic intervention that should be considered in patients suspected to have UGIB (*e.g.*, pantoprazole 80 mg bolus followed by 8 mg/h continuous drip or 40 mg intravenously every 12 h). The infusion is continued for 48-72 h. The relative efficacy of PPIs may be due to their superior ability to maintain gastric pH at a level above 6.0, thereby protecting ulcer clots

from fibrinolysis. Multiple analyses have shown that applying PPI therapy before a procedure significantly reduced the rate of high-risk stigmata that are identified by endoscopy and the need for endoscopic therapy. Therefore, intravenous PPI therapy is recommended for patients who are suspected of having acute NVUGIB.

EFFICACY AND COMPARATIVE ANALYSIS

Gastroduodenal peptic ulcers are by far the most common etiology of UGIB, accounting for 50% of admissions among patients with upper gastrointestinal hemorrhage[28]. Multiple meta-analyses evaluating endoscopic therapies for bleeding peptic ulcers have demonstrated that thermal devices, injectable agents other than epinephrine (*i.e.*, sclerosants and thrombin/fibrin glue), and clips were all effective methods for achieving hemostasis in PUD, with no single modality being superior to the others. In particular, hemoclip placement, thermocoagulation (*e.g.*, heater probe), and electrocoagulation (*e.g.*, Gold probe, BICAP probe) all seem to be equivalent alternatives[20,31-34]. Dual combination therapy (*i.e.*, epinephrine injection plus other injections or thermal or mechanical methods) was proven to be significantly superior to epinephrine injection alone, but displays no advantage over thermal or mechanical monotherapy. This means that epinephrine should no longer be applied as a monotherapy for treating lesions with high-risk stigmata and should only be used in combination with other methods as these combinations significantly reduce the risk of rebleeding and surgery. Prospective randomized trials have demonstrated that thermal therapy results in significant reductions in bleeding, blood transfusions, length of hospital stays, and the need for urgent surgery in patients with actively bleeding ulcers or nonbleeding ulcers with visible vessels[35]. A meta-analysis of randomized trials that evaluated rebleeding rates following injection, thermal therapy, clips, or combination therapy showed that clips were superior to thermal therapy[33]. The remaining causes of UGIB account for up to 50% of cases. For gastric antral vascular ectasia (GAVE), APC remains the most commonly reported modality that is usually performed over multiple endoscopic sessions. APC is associated with a decrease in transfusion requirements[36]. Mallory-Weiss tear bleeding usually spontaneously stops, with the rates of rebleeding from this etiology reaching up to 10%. Patients with active bleeding or oozing require endoscopic therapy. Bipolar electrocoagulation, epinephrine injection, clips, and band ligation have all been used successfully with no difference in immediate hemostasis or rebleeding. Endoscopic therapy is the first choice in bleeding Dieulafoy's lesions and is usually performed *via* clipping or banding of the lesion[23]. Endoscopic clipping is superior to endoscopic injection and is comparable to thermocoagulation in securing hemostasis in bleeding peptic ulcers and Dieulafoy's lesions[28]. Endoscopic hemostasis of bleeding upper GI tract tumors has proven to be less effective and to have higher rates of rebleeding. Various endoscopic treatment modalities have been described with no clear recommendations. Several studies have reported that cyanoacrylate was used for acute non-variceal gastrointestinal bleeding cessation[21]. Application of cyanoacrylate (by injection and/or spraying) is a safe and effective method for achieving immediate hemostasis when conventional endoscopic treatment has been unsuccessful. This technique is easy to perform and should be considered in cases of patients with difficult-to-arrest acute NVGIB. Recently, promising preliminary data have been reported following the use of the hemostatic powder TC-325 (Hemospray) for bleeding control from upper GI tract tumors[37].

CONCLUSION

Endoscopy is the mainstay for the modern management of NVUGIB. Ideally, endoscopy should be performed within 24 h of presentation, after adequate resuscitation has been performed. Many safe and effective devices are available for endoscopic hemostasis. Combination therapy using the injection of epinephrine plus another hemostatic technique is more effective than epinephrine alone. Hemospray is a new and promising endoscopic therapy. Patients with high-risk stigmata should receive continuous intravenous PPI administration for 72 h after endoscopy. After the acute phase, the underlying cause of the lesion should be verified and treated, when possible. The choice of therapy should remain at the discretion of the physician, based on the nature and position of the lesion, the availability and experience of the endoscopist and the previous endoscopic therapy that the patient has received.

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ORIGINAL ARTICLE

Retrospective Study

Hospitalization for esophageal achalasia in the United States

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Abstract

AIM: To assess the outcome of different treatments in patients admitted for esophageal achalasia in the United States.

METHODS: This is a retrospective analysis using the Nationwide Inpatient Sample over an 8-year period (2003-2010). Patients admitted with a primary diagnosis of achalasia were divided into 3 groups based on their treatment: (1) Group 1: patients who underwent Heller myotomy during their hospital stay; (2) Group 2: patients who underwent esophagectomy; and (3) Group 3: patients not undergoing surgical treatment. Primary outcome was in-hospital mortality. Secondary outcomes included length of stay (LOS), discharge destination and total hospital charges.

RESULTS: Among 27141 patients admitted with achalasia, nearly half (48.5%) underwent Heller myotomy, 2.5% underwent esophagectomy and 49.0% had endoscopic or other treatment. Patients in group 1 were younger, healthier, and had the lowest mortality when compared with the other two groups. Group 2 had the highest LOS and hospital charges among all groups. Group 3 had the highest mortality (1.2%, $P < 0.001$) and the lowest home discharge rate (78.8%) when compared to the other groups. The most frequently performed procedures among group 3 were esophageal dilatation (25.9%) and injection (13.3%). Among patients who died in this group the most common associated morbidities included acute respiratory failure, sepsis and aspiration pneumonia.

CONCLUSION: Surgery for achalasia carries exceedingly low mortality in the modern era; however, in complicated patients, even less invasive treatments are burdened by

significant mortality and morbidity.

Key words: Esophageal achalasia; Outcomes; Myotomy

Core tip: We aimed to assess the outcomes of different treatments in patients hospitalized for esophageal achalasia in the United States. We queried the Nationwide Inpatient Sample database from 2003 to 2010. Patients admitted with a primary diagnosis of achalasia were divided into 3 groups, based on treatment, and compared. About half of the patients did not actually undergo a surgical procedure; yet, they had the highest mortality and lowest home discharge rate. Our data suggest that when achalasia has gone too far and previous treatments have been untimely or ineffective, patients may face non-negligible mortality and morbidity even with endoscopic treatment or supportive care.

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INTRODUCTION

Achalasia is a chronic, progressive disease characterized by loss of peristalsis of the distal esophagus, failure of the lower esophageal sphincter to completely relax with deglutition, and elevated baseline intraluminal esophageal pressure[1]. The pathophysiology of the impaired peristalsis is represented by the progressive degeneration and destruction of a subpopulation of inhibitory neuronal ganglion cells of the Auerbach myenteric plexus of the esophagus[2]. The resulting long lasting contraction of the lower esophageal sphincter (LES) causes stasis of food within the esophageal lumen until the rising intraesophageal pressure overcomes the obstacle represented by the cardial spasm and the bolus slowly transits into the stomach. The outflow obstruction inevitably leads, over time, to progressive esophageal dilation and tortuosity, if the condition is left untreated.

The treatment of achalasia is substantially palliative and aims to relieve symptoms and to contrast the natural history of the disease through improvement of passive esophageal transit. The distal esophageal obstacle to food progression can be eliminated with endoscopic pneumatic dilation or surgical myotomy, both with similar short-term success of about 80%-90% and a long-term control of symptoms of approximately 50% with dilation, and 80%-90% with myotomy[3-6].

The therapeutic options for achalasia also include endoscopic botulin toxin injection, especially for the high-risk patients or those patients with contraindications to pneumatic dilation or surgery; this procedure, however, is burdened by high long-term costs, short lasting results and a high recurrence rate[7]. Pharmacological treatment of achalasia, targeted to induce LES relaxation with nitrates and calcium channel blockers, has been shown to yield unsatisfying results with poor control of symptoms[8,9].

We believe that the severity of the disease is often underestimated, especially in more advanced stages, due to its slow progression and to its common classification as a benign condition. We therefore queried the Nationwide Inpatient Sample (NIS), in order to assess the outcome of different treatments in patients admitted for esophageal achalasia in the United States.

MATERIALS AND METHODS

Data source and study population

A retrospective review was performed using the NIS database from 2003-2010. NIS consists of 20% stratified sample of all United States hospitals, and it provides discharge weights to produce a 95% of all discharges in the United States[10]. International Classification of Diseases, ninth revision (ICD-9) coding was used to establish the desired study population. All patients admitted with a primary diagnosis of achalasia (ICD-9 diagnosis code of 530.0) were included in the study. These patients were divided into 3 groups based on their in-hospital treatment: (1) Group 1: Achalasia patients who underwent Heller myotomy during their hospital stay (ICD-9 procedure code of 42.7); (2) Group 2: Achalasia patients who underwent esophagectomy (ICD-9 procedure codes of 150, 150.1, 150.2, 150.3, 150.4, 150.5, 150.8, 151); and (3) Group 3: Achalasia patients not undergoing surgical treatment. This study was limited to adult patients (> 17 years old) without a diagnosis of esophageal cancer (ICD-9 diagnosis codes of 150, 150.1, 150.2, 150.3, 150.4, 150.5, 150.8, 151). This study was granted exempt status by the Johns Hopkins Medicine Institutional Review Board.

Outcomes

The primary outcome was in-hospital mortality. Secondary outcomes included length of stay (LOS), discharge destination (home/transfer), total hospital charges (TOTCHG), and complications such as, pneumonia, urinary tract infection (UTI), shock/sepsis, and pulmonary compromise. These complications were obtained by using previously validated ICD-9 diagnosis codes (1-2) (Table 1). Total hospital charges were adjusted for inflation to reflect 2011 United States dollars.

Statistical analysis

All statistical analyses were performed using STATA/MP, version 11.2 (Stata Corp, College Station, Texas). Weighting strategy was applied prior to conducting statistical analysis. Adjusted Wald test and Pearson's χ^2 were used for continuous and categorical variables, respectively. Multivariable logistic regressions were performed to compare odds of each outcome while

Table 1 International Classification of Disease, ninth revision procedure and diagnosis codes used to determine surgical procedure categories and complications

	ICD-9 code
Achalasia	530
Heller[1]	427
Esophagectomy[1]	42.4, 42.41, 42.42, 42.5, 42.51-59, 42.6, 42.61-69
Esophageal cancer	150, 150.1, 150.2, 150.3, 150.4, 150.5, 150.8, 151
Complications	
Pneumonia	481, 482.0-482.4, 482.8-482.9, 483, 484, 485, 486, 507.0, 482.40, 482.41. 482.42, 482.49
Urinary tract infection	997.5, 599.0-599.9
Shock/sepsis	998.0, 995.9, 995.90, 995.91, 995.92, 038
Pulmonary compromise	514, 518.4, 518.5, 518.81, 518.82

[1]Indicates procedure codes. ICD-9: International Classification of Disease, ninth revision.

adjusting for age, gender, and Charlson Index score. Adjusted TOTCHG and LOS were obtained from a multiple regression, while adjusting for age, gender, and Charlson Index score. A level of significance was set at $\alpha = 0.05$.

RESULTS

Baseline demographic and clinical characteristics

A total of 31769 achalasia patients met the study criteria, including, 15567 Heller patients (49.0%), 785 esophagectomy patients (2.5%), and 15417 non-surgical patients (48.5%) (Table 2). The overall mean age was 59 (median 59), with 54.3% females, and 70.8% white patients. Heller group was the youngest (median age of 51) and the healthiest (mean Charlson score of 0.34). While the non-surgical group was the oldest (median age 72) with the highest comorbidity (mean Charlson score of 0.93). Among the most common procedures performed for patients who underwent non-surgical treatment of achalasia (group 3) were: esophagogastroduodenoscopy (65.2%), dilation of esophagus (26.9%), and injection of therapeutic/prophylactic substance-including botulism antitoxin (17.3%) (Table 3).

Unadjusted outcomes

The overall in-hospital mortality was 0.65%, with the highest unadjusted mortality seen in the esophagectomy group (1.96%) (Table 4). There was no significant difference between the in-hospital mortality for the esophagectomy group *vs* non-surgical group. The esophagectomy group stayed in the hospital the longest (median LOS of 13 d) and had highest total hospital charges (median TOTCHG of $134670.40). Achalasia patients undergoing Heller myotomy were the most likely to be discharged home (97.2%) and were less likely to acquire pneumonia, UTI, shock/sepsis, and pulmonary compromise (3.3%, 2.0%, 0.3%, and 1.6%, respectively). Pneumonia, shock/sepsis, and pulmonary compromise were the most common complications in the esophagectomy group. Mean LOS, TOTCHG, and pneumonia were significantly different across all three groups (even when the pairwise comparison was applied).

Adjusted outcomes

Multivariable logistic regression was performed for the two surgical groups *vs* the non-surgical group, while adjusting for age, gender, and Charlson Index score.

Heller vs non-surgical group

The likelihood of in-hospital mortality was more than four times higher in the non-surgical group (OR = 4.73, 95%CI: 1.16-19.31, $P = 0.03$), and the chance to develop pneumonia and UTI was doubled (OR = 1.91, 95%CI: 1.42-2.58, $P < 0.001$; OR = 2.31, 95%CI: 1.67-3.18, $P < 0.001$, respectively) when compared to the Heller group. Moreover, the non-surgical group was significantly more likely to be transferred (OR = 3.76, 95%CI: 2.85-4.97, $P < 0.001$). The non-surgical achalasia patients paid $14594.24 less ($P < 0.001$) in TOTCHG and stayed in the hospital about one day longer ($P < 0.001$) than the Heller patients (Table 5).

Esophagectomy vs non-surgical group

The esophagectomy group was seven times as likely to have an in-hospital mortality (OR = 7.28, 95%CI: 2.06-25.79, $P = 0.002$) and nearly twice as likely to be transferred compared to the non-surgical group (OR = 1.84, 95%CI: 1.16-2.94, $P = 0.01$). Achalasia patients who underwent esophagectomy had also higher complications such as pneumonia, shock/sepsis, and pulmonary compromise (OR = 3.68, 95%CI: 2.40-5.64, $P \leqslant 0.001$; OR = 16.53, 95%CI: 6.36-42.96, $P < 0.001$; OR = 37.97, 95%CI: 22.85-63.07, $P < 0.001$, respectively). Esophagectomy patients stayed in the hospital twelve days longer ($P < 0.001$) and paid $181167.90 more ($P < 0.001$) than the non-surgical patients (Table 6).

DISCUSSION

Our study shows that more than 30000 patients were hospitalized over an 8-year period for the treatment of esophageal achalasia in the United States. It would be intuitive to assume that most patients were admitted to undergo surgery, since endoscopic treatment is commonly performed in the outpatient setting. Only half of them underwent a surgical procedure instead, thus suggesting that the natural history of the disease can potentially lead to complications severe enough to require admission.

As broadly demonstrated in previous studies, we confirmed that patients treated with Heller myotomy benefit from low mortality, morbidity and LOS. The most frequent procedures performed among the non-surgical group were endoscopic pneumatic dilatation (25.9%) and endoscopic drugs injection (13.3%). It is common and widespread practice to elect non-surgical,

Table 2 Baseline demographic and clinical characteristics of patients among the three groups, Nationwide Inpatient Sample, 2003-2010 *n* (%)

	Total 31769	Group 1 Heller 5567 (49.00)	Group 2 Esophagectomy 785 (2.47)	Group 3 Non-surgical 15417 (48.53)	*P*
Age, mean (median)	59 (59)	51.2 (51)	53.8 (54)	67.1 (72)	< 0.001
Age category					< 0.001
18-44	8041 (25.31)	5576 (35.82)	251(31.97)	2214 (14.36)	
45-64	10554 (33.22)	6330 (40.66)	308 (39.24)	3916 (25.40)	
65-74	4746 (14.94)	2254 (14.48)	141 (17.96)	2351 (15.25)	
⩾ 75	8428 (26.53)	1407 (9.04)	85 (10.83)	6936 (44.99)	
Gender[1]					< 0.001
Male	14429 (45.73)	7883 (51.21)	371 (47.41)	6175 (40.17)	
Female	17120 (54.27)	7510 (48.79)	412 (52.59)	9198 (59.83)	
Race[2]					0.002
White	17663 (70.77)	8662 (71.64)	403 (65.96)	8598 (70.15)	
Black	3662 (14.67)	1533 (12.68)	75 (12.27)	2054 (16.76)	
Other	3633 (14.56)	1896 (15.68)	133 (21.77)	1604 (13.09)	
Charlson score	0.63	0.34	0.48	0.93	0.036
0	21147 (64.53)	11681 (75.04)	508 (64.71)	7958 (51.62)	< 0.001
1	7390 (22.55)	3015 (19.37)	206 (26.24)	4169 (27.04)	
⩾ 2	4232 (12.91)	871 (5.59)	71 (9.05)	3290 (21.34)	

[1]Missing data for 220 patients; [2]Missing data for 6811 patients.

Table 3 Most common procedure types for patients who underwent non-surgical treatment of achalasia

ICD-9 code	Procedure type	Group 3 Non-surgical 15417
45.13 and 45.16	Esophagogastroduodenoscopy	65.15%
42.92	Dilation of esophagus	26.94%
99.57 and 99.29	Injection of therapeutic/prophylactic substance-including botulism antitoxin	17.32%
98.02	Removal of intraluminal foreign body from esophagus without incision	6.44%
43.11	Percutaneous endoscopic gastrostomy percutaneous transabdominal gastrostomy	5.73%
29.31	Cricopharyngeal myotomy	2.77%

ICD-9: International Classification of Diseases, ninth revision.

Table 4 Observed unadjusted rates of outcomes across the three patient groups, Nationwide Inpatient Sample, 2003-2010 *n* (%)

	Total 31769	Group 1 Heller 15567 (49.00)	Group 2 Esophagectomy 785 (2.47)	Group 3 Non-surgical 15417 (48.53)	*P*
In-hospital mortality	206 (0.65)	16 (0.1)	15 (1.96)	180 (1.17)	< 0.001
Disposition					
Home[1]	27916 (87.87)	15130 (97.19)	637 (81.15)	12149 (78.80)	< 0.001
Transfer[2]	3504 (11.03)	416 (2.67)	133 (16.89)	2955 (19.17)	< 0.001
Pneumonia	1959 (6.17)	509 (3.27)	150 (19.11)	1300 (8.43)	< 0.001
UTI	1462 (4.60)	311 (2.00)	50 (6.37)	1101 (7.14)	< 0.001
Shock/sepsis	171 (0.54)	50 (0.32)	46 (5.86)	75 (0.49)	< 0.001
Pulmonary compromise	813 (2.56)	241 (1.55)	245 (31.21)	327 (2.12)	< 0.001
Median LOS (d)	3	2	13	4	< 0.001
Median TOTCHG	$26299.41	$30118.12	$134670.40	$21175.23	< 0.001

[1]Home is discharge to home with and without home health care; [2]Transfer is discharge to short term hospital, skilled nursing facility, intermediate care and other type of facilities. LOS: Length of hospital stay; TOTCHG: Total hospital charges; UTI: Urinary tract infection.

thus less invasive, treatment as the best option for high-risk patients. This phenomenon can be indeed observed in demographics of group 3, which included the oldest patients and those with highest comorbidity. Nevertheless, it is interesting to remark that, even after adjusting for age, gender, and Charlson Index score, the non-surgical group was more than four times as likely to have in-hospital mortality, and twice as likely to have pneumonia and UTI compared to the Heller group. This finding, which might appear counterintuitive at first glance, finds a logical explanation when recalling that non-surgical treatment of achalasia is usually administered in the outpatient setting. The youngest and most fit patients undergoing non-surgical treatment were therefore likely not captured by this analysis focusing on hospitalized patients. Conversely, many of

Table 5 Adjusted odds ratios of outcomes and complications for the non-surgical group (in comparison to the Heller group)

	OR	*P*	95%CI
In-hospital mortality	4.73	0.03	1.16-19.31
Disposition			
Home	0.24	< 0.001	0.19-0.31
Transfer	3.76	< 0.001	2.85-4.97
Pneumonia	1.91	< 0.001	1.42-2.58
Urinary tract infection	2.31	< 0.001	1.67-3.18
Shock/sepsis	1.18	0.726	0.47-2.97
Pulmonary compromise	0.83	0.413	0.54-1.29

All the analyses were adjusted for age, gender, and Charlson Index score.

Table 6 Adjusted odds ratios of outcomes and complications for the esophagectomy group (in comparison to the non-surgical group)

	OR	*P*	95%CI
In-hospital mortality	7.28	0.002	2.06-25.79
Disposition			
Home	0.54	0.009	0.35-0.86
Transfer	1.84	0.010	1.16-2.94
Pneumonia	3.68	< 0.001	2.40-5.64
Urinary tract infection	1.28	0.507	0.62-2.67
Shock/sepsis	16.53	0.001	6.36-42.96
Pulmonary compromise	37.97	< 0.001	22.85-63.07

All the analyses were adjusted for age, gender, and Charlson Index score.

the patients of our group 3 were probably complicated patients, such as subjects affected by advanced stage, recurrent or refractory achalasia, or individuals at high risk for surgery. In addition, our analysis is likely to have included in group 3 also those patients who faced serious complications of endoscopic treatments. Pneumatic dilation, although offering fast recovery and low overall complication rate, is burdened by a tangible risk of esophageal full-thickness perforation, especially when the procedure is repeated multiple times to maintain satisfactory results[11,12].

Heller myotomy is usually performed laparoscopically and an antireflux procedure is commonly added; randomized studies have in fact confirmed its efficacy in decreasing postoperative gastroesophageal reflux disease[13,14]. It is reasonable to hypothesize that the ongoing technical advancements in minimally invasive surgery, along with the widespread of advanced laparoscopic skills to an increasing number of surgeons, will strengthen the role of Heller myotomy as the safest and most durable choice for the treatment of achalasia.

The findings of our analysis outline the potential risks resulting from the insidious, slowly progressive nature of achalasia. When the disease has gone too far and previous treatments have been untimely or ineffective, patients may face non-negligible mortality and morbidity even with endoscopic treatment or supportive care. We therefore think that Heller myotomy should be strongly considered early in patients with esophageal achalasia and should be offered to all patients as the first therapeutic option, in absence of absolute contraindications to surgery.

This recommendation might change in the future, once the long term outcomes of patients treated with per-oral endoscopic myotomy (POEM) will become available. POEM, in fact, represents the cutting edge of minimally invasive treatment for achalasia and offers comparable early outcomes to Heller myotomy with the adjunctive benefit of being performed endoscopically[15,16]. Therefore, if randomized studies will demonstrate long-term outcomes similar to those of laparoscopic Heller procedure, POEM might become the new gold standard for the treatment of esophageal achalasia.

Pulmonary symptoms as well as functional abnormalities have been demonstrated to be present in a significant percentage of patients with achalasia and are readily apparent in the poor pulmonary outcomes of our non-surgical group[17]. Respiratory complications represent one of the most frequent causes of morbidity in patients with achalasia, if the natural history of the disease is not radically modified by treatment. In addition, radiological pulmonary abnormalities in the form of consolidation, ground glass opacities, nodular opacities, air trapping, fibrotic changes and bilateral alveolar findings that resemble aspiration pneumonia have been widely described in achalasia patients[18]. Data in the literature support the hypothesis that surgery could not only improve the symptoms, but also lead to regression of the functional and radiological pathologic findings[17,18].

The results of our analysis confirm that esophagectomy, as previously shown, is an operation burdened by significant mortality and morbidity. It has been reported that laparoscopic myotomy may still play a role and improve outcomes in patients with stage IV disease, even when a remarkable esophageal dilation is present; this is particularly true for patients with an enlarged but linear esophagus[19].

However, about 5% of all patients with achalasia will eventually require esophagectomy and it is our belief that this procedure remains a reasonable option and a precious last resort in patients with end stage disease[20-22]. Moreover, we have previously shown that operative outcomes, including mortality, overall morbidity, and LOS are comparable between patients undergoing esophagectomy for achalasia and for esophageal cancer[23].

Our study presents some limitations worth mentioning. First of all, NIS is an administrative database, which is prone to errors due to missing or inaccurately entered ICD-9 codes. This database does not include any outpatient information, therefore patients that may have been treated by pneumatic dilation and sent home the same day are not captured. In addition, ICD-9 coding system is not perfect and specific procedures might be difficult to identify using the current ICD-9 procedure codes. For example, there is no specific

code for pneumatic balloon dilation, but there exists an ICD-9 code (42.92) for dilation of esophagus. There is no way to know if these dilations were merely routine dilations *vs* true pneumatic dilations with a 30 mm balloon. This fact, together with a small number of patients in the endoscopic injection group, did not allow us to meaningfully compare treatment subgroups among the non-surgical patients. No information is given on symptomatic relief and functional outcomes with this database, nor there is trace of postoperative events occurred after patients' discharge. Finally, it is not possible to know the stage of patients' disease at admission or if previous treatments for achalasia had been attempted.

That said, this study provides a useful general overview of the trends and outcomes of achalasia management and, in particular, it sheds light over the less studied populations of non-surgical patients who nonetheless needed hospitalization.

In conclusion, it is important to remark that the common labeling of achalasia as "benign condition" can be misleading and delay referral for definitive treatment. If left untreated or if treated with less than optimal approach, the disease will progress and can lead to complications, which will significantly affect patients' quality of life or potentially become life threatening. Although this database does not allow us to compare outcomes between endoscopic and surgical treatment of achalasia, the analysis of our data suggests that a timely and effective relief of esophageal obstruction may avoid future complications brought by the natural history of the disease.

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COMMENTS

Background

Achalasia is a chronic, progressive disease characterized by loss of peristalsis of the distal esophagus, failure of the lower esophageal sphincter to completely relax with deglutition, and elevated baseline intraluminal esophageal pressure. The treatment of achalasia is substantially palliative and aims to relieve symptoms and improve passive esophageal transit. The authors believe that the severity of the disease is often underestimated, especially in more advanced stages, due to its slow progression and to its common classification as a benign condition. Comparing the outcomes after different treatments in patients hospitalized for achalasia can help provide additional clinical insights for providers who care for these patients.

Research frontiers

Early intervention and modification of the history of achalasia is paramount, since the disease is prone to an insidious and burdensome progression, as evidenced by several studies, including the authors'. Awareness should be raised and efforts focused on early diagnosis and treatments. Surgical treatment remains the gold standard for improving symptoms, however less invasive procedures, like per-oral endoscopic myotomy (POEM), are being frequently used. Studies of POEM's long-term outcomes is a current hotspot in the field.

Innovations and breakthroughs

This study takes an innovative approach, since it focuses on a different population than most other publications. It provides data and analysis of patients that were hospitalized for traditional treatments for achalasic in addition to patients that were admitted for complications of achalasia itself.

Applications

The data raises awareness for the common misconception in considering achalasia a benign condition. It is, in fact, an insidious disease that can lead to non-negligible mortality and morbidity when treated late or not incisively. This becomes apparent when analyzing the outcomes and characteristics in the authors' non-surgical group.

Peer-review

The authors have provided a valuable review on surgical treatment options in achalasia. The study design, discussion and conclusion are fine.

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ORIGINAL ARTICLE

Prospective Study

Triradiate caecal fold: Is it a useful landmark for caecal intubation in colonoscopy?

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Abstract

AIM: To determine the frequency of identification of the triradiate fold during colonoscopy and evaluate its reliability as a marker of caecal intubation.

METHODS: One hundred consecutive patients undergoing colonoscopy in a tertiary hospital colorectal unit from May to September 2013 were studied. Video documentation of the caecum was recorded and shown to consultant colorectal surgeons on the unit. Each reviewer was asked through a series of questions to independently identify the triradiate fold. The main outcome was the frequency of visualisation of the triradiate fold in the caecum.

RESULTS: The triradiate fold was seen on average in 18% of cases, but inter-observer agreement was poor. There were only four patients (4%) in which all reviewers agreed on the presence of a triradiate fold. In patients who had undergone previous appendicectomy, the appendiceal orifice was less frequently seen compared with patients who had not undergone appendicectomy.

CONCLUSION: The triradiate fold is infrequently seen during colonoscopy and is therefore an unreliable landmark of caecal intubation.

Key words: Colonoscopy; Triradiate fold; Appendiceal orifice; Caecal intubation; Prospective study

Core tip: The triradiate fold is often described as a major landmark of caecal intubation in colonoscopy, but its frequency of visualisation has not been previously documented. This study shows that identification of the triradiate fold is infrequent and its presence is subjective. Inclusion in guidelines or colonoscopy software programs as a sole marker of complete colonoscopy is questionable.

Finlayson A, Chandra R, Hastie IA, Jones IT, Shedda S, Hong MK-Y, Yen A, Hayes IP. Triradiate caecal fold: Is it a useful landmark for caecal intubation in colonoscopy? *World J Gastrointest Endosc* 2015; 7(13): 1103-1106 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i13/1103.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i13.1103

INTRODUCTION

Accurate assessment of the extent of colonoscopy relies on the identification and cognitive integration of several caecal landmarks to the trained endoscopist. These landmarks may include the ileocaecal valve, ileal mucosa, appendiceal orifice and caecal folds.

Of these many landmarks, the ileocaecal valve has been shown to be the single most reliable landmark, being viewed 98% of the time when caecal intubation had been confirmed with fluoroscopy[1]. The same study found the appendiceal orifice to be the second most reliable landmark. Others contend that the most accurate method to ensure caecal intubation is to enter the terminal ileum and confirm with a biopsy of ileal mucosa[2].

Various names and descriptions have been given to the folds in the caecum. The converging folds have been named the triradiate fold, Mercedes sign, crows-foot and caecal strap fold[2-5]. The term triradiate fold is used in many computerized colonoscopy databases and also by the Australian National Bowel cancer screening project as a landmark for caecal intubation with colonoscopy[6]. Last's Anatomy textbook describes the three taenia of the colon converging at the base of the appendix[7]. However in practice, a clearly defined triradiate fold is not always seen at colonoscopy. We undertook this study to document how frequently a triradiate fold is seen at the caecal pole during colonoscopy.

MATERIALS AND METHODS

This study was approved by the Melbourne Health Human Research Ethics Committee at the Royal Melbourne Hospital, Parkville, Australia. All consecutive patients undergoing colonoscopy from May to September 2013 either performed or supervised by two colorectal fellows were included in the study. Exclusion criteria were previous caecal resection, inadequate bowel preparation, technical issues with recording equipment and incomplete colonoscopies.

All colonoscopies were performed with an Olympus colonoscope. Once caecal intubation was reached, a short video was recorded on the Olympus Endobase® program. The caecal pole was thoroughly irrigated to adequately display the caecum. Caecal intubation was confirmed on collective visualisation of the ileocaecal valve, blind-ending caecal pole and appendiceal orifice when present. It was not routine in our institution to perform ileal intubation as a marker of complete colonoscopy unless clinically indicated. The videos were recorded in a standard fashion to give a panorama of the caecal pole including established landmarks of the appendiceal orifice and ileocaecal valve, and then zoomed in on the appendiceal orifice and surrounding folds.

All 100 videos were then edited using Corel Video Studio Pro® to delete unnecessary footage. The videos submitted for analysis included continuous footage so that each caecum was easily identifiable. The final length of edited videos ranged from 3 to 26 s. The shortest videos were those where all features of the caecum were very easily seen.

Each video was then shown to six consultant surgeons on the unit who then individually evaluated them. Prior to evaluation, a photograph of what we considered to be a triradiate fold was shown to all surgeons (Figure 1). A photograph showing an appendiceal orifice with no triradiate fold was also shown (Figure 2). For each video the following questions were asked:

Are you satisfied that this is a video of the caecum?

Can you identify the appendiceal orifice?

Is there a triradiate fold at the appendix orifice?

If the reviewer was not satisfied that the caecum was represented in the video, the remaining two questions were obsolete and not answered. Similarly if the appendiceal orifice could not be identified, no judgment could be made on the presence of a triradiate fold.

Statistical analysis

Statistical analysis was performed using Microsoft Excel®. Positive responses from the six reviewers were tallied for each of the 100 videos analysed and for each of the three questions asked. Individual and overall proportions of positive responses were calculated. Inter-rater reliability was measured using Conger's kappa coefficient for multiple raters. The relationship between previous appendicectomy and visualisation of the appendiceal orifice was analysed using Fisher's exact test on a 2 × 2 contingency table. Differences were considered significant when the probability was less than 0.05.

RESULTS

One hundred and thirty-four consecutive colonoscopies were either performed or supervised by two fellows. Of these 134 patients, 34 were excluded, leaving 100 colonoscopies for analysis. Of the patients excluded, 11 had a previous caecal resection, 14 had inadequate bowel preparation, 6 were incomplete colonoscopies and

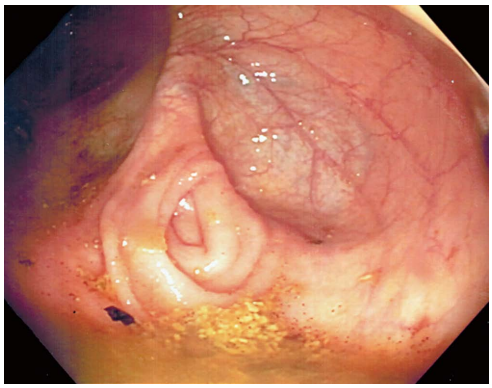

Figure 1 Photograph of a triradiate fold converging on the appendiceal orifice.

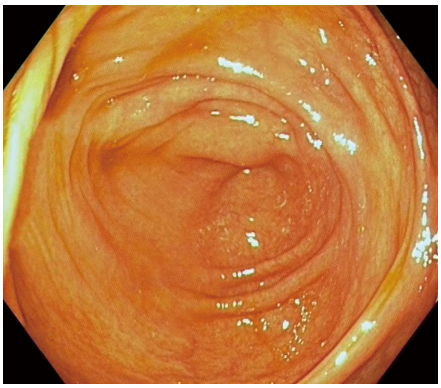

Figure 2 Photograph of an appendiceal orifice with no converging triradiate fold.

Table 1 Indications for colonoscopies

Indication	Number
Per rectal bleeding	26
Polyp follow up	17
Cancer follow up	14
Diverticulitis	9
Altered bowel habit	9
Abnormal imaging	8
Faecal occult blood test positive	6
Fistula investigation	3
Family history	2
Anaemia	2
Iron deficiency	2
Volvulus	1
Rectal prolapse	1

Table 2 Number and percentage of "Yes" answers for each question from each reviewer

Reviewer	Caecum	Appendiceal orifice		Triradiate fold	
1	99	76	77%	13	17%
2	95	79	83%	17	22%
3	96	76	79%	13	17%
4	93	89	96%	18	20%
5	100	89	89%	11	12%
6	97	73	75%	13	18%
Average	97	80	83%	14	18%

Percentages are calculated with denominator being number of "Yes" answers from previous question.

3 had technical problems with the recording equipment. Of the 100 included patients, there were 43 males and 57 females with a mean age of 61 ± 15.8 years. The indications for their colonoscopies are given in Table 1.

A Conger's Kappa coefficient for multiple raters was calculated to assess agreement between the answers to each of the three questions. This showed a strong agreement for each of the three questions, with coefficients of 0.93 for identification of the caecum, 0.79 for identification of the appendix and 0.81 for identification of the triradiate fold.

On average, the reviewers were satisfied the video depicted the caecum in 97% of cases. In those cases where the caecum was identified, the appendiceal orifice could be seen in 83%. In those cases where the appendix orifice was identified, a triradiate fold was seen in 18% (Table 2).

The Kappa coefficient for the triradiate fold was high due to strong agreement among observers about the non-visualization of the triradiate fold. In the smaller percentage of cases where the triradiate fold was identified, there was poor agreement among reviewers. There were only four patients in which all reviewers agreed on the presence of a triradiate fold. The appendiceal orifice was seen in 38 of 54 videos (70.4%) where the patient had undergone previous appendicectomy. When the patient had not undergone an appendicectomy the appendiceal orifice was seen in 444 of 527 videos (84.3%, $P = 0.014$).

DISCUSSION

Accurate identification of the caecum at colonoscopy relies heavily on visualising certain landmarks. The caecal folds have been previously suggested to be an unreliable landmark[8]. In this study we have demonstrated that a triradiate caecal fold is only seen 18% of the time when averaged across all observers. In cases where it was identified, there was poor inter-observer agreement.

Anatomically, the triradiate fold must be centred on the appendiceal orifice. Our study showed that the appendiceal orifice was less frequently seen in patients who had undergone previous appendicectomy. Elsewhere in the colon the intersection of haustral folds and a taenia coli may create a triradiate appearance that could be confused with the triradiate fold of the caecum.

This study is limited by its subjective design. The six consultants who analysed each video were aware of the study hypothesis, which may have influenced their response to the questions. However, they were not aware that all videos were of the caecum. Variables that may influence the identification of the caecal folds include the amount of insufflation. A large amount of inflation of the caecum may flatten the caecal folds,

and thus a triradiate fold that may have been seen in a less distended caecum may have "disappeared" with inflation. Although this theory was not directly tested, we did not observe that inflation had any bearing on the visualization of a triradiate caecal fold through the process of recording, reviewing and editing the videos.

Photo documentation of caecal intubation has been recommended as routine practice although some studies have shown that still photography has poor reliability[9]. Video documentation has previously been shown to be superior to still photography in identifying the caecum to independent observers[3]. Our initial proposal was to use photo rather than video documentation. On review of the first still photographs taken it was our belief that a photograph alone was not sufficient to identify the caecum with certainty. The video however, gave greater detail and provided an accurate depiction of the caecum as demonstrated by the 97% agreement among reviewers. If caecal intubation documentation is to become a marker of quality and successful completion, video documentation appears to be a more reliable method.

This is the first study to look specifically at the triradiate caecal fold as a landmark during colonoscopy. The triradiate fold is an infrequently seen feature of the caecum and as such should not be relied upon to confirm caecal intubation.

ACKNOWLEDGMENTS

We would like to thank the staff of the endoscopy suite at the Royal Melbourne Hospital for their assistance in the technical aspects of video recording.

COMMENTS

Background

Caecal landmarks are important for accurate assessment of the extent of colonoscopy. The triradiate fold in the caecum is referenced as a major landmark in some guidelines and endoscopy programs. This study was conducted to determine the frequency of identification of the triradiate fold.

Research frontiers

Colonoscopy is a common investigation modality. Quality assurance has become a global focus. One quality measure in colonoscopy is completion rate. This study explores the role of visualisation of the triradiate fold as a marker of colonoscopy completion.

Innovations and breakthroughs

This is the first study that quantifies the rate of visualisation of the triradiate fold, and shows that it is infrequently seen.

Applications

The inclusion of the triradiate fold as a marker of colonoscopy completion in guidelines and endoscopy programs is questionable.

Terminology

Triradiate fold is the appearance of three caecal folds converging upon the appendiceal orifice as seen at colonoscopy.

Peer-review

This is a very interesting, concise and "clever" paper. It is also written in excellent English, fluent and easy to read.

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CASE REPORT

Endoscopic ultrasound guided thrombin injection of angiographically occult pancreatitis associated visceral artery pseudoaneurysms: Case series

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Author contributions: Gamanagatti S contributed equally to conception, article design, and image preparation; Thinujam U helped with the literature search and article drafting; Garg P helped to procure the images, and final approval of version of article to be published; Nongthombam S and Dash NR, contributed in critical revision article concept, revision literature search and image preparation.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of the by the All India Institute of Medical Sciences (New Delhi, India).

Informed consent statement: Informed consent for performing the procedure was taken from all patients after explaining the risks and benefits. Regarding consent for the publication was not obtained and also these patients are no longer in communication with us (lost to follow up), hence we here by certify that, all the patient demographic information on images (figures) is hidden (cropped) to maintain confidentiality.

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Abstract

Pseudoaneurysm is a known complication of pancreatitis associated with significant mortality and morbidity. Imaging plays an important role in the diagnosis and management. Computed tomography (CT) helps localize the lesion and the severity of the background pancreatitis but digital subtraction angiography with coil embolization is recommended to avoid bleeding and inadvertent surgery. However, in cases where angiographic coil embolization is not feasible due to technical reasons, thrombin injection *via* CT or ultrasound guidance remains a viable option and often described in literature. In this series, effort has been made to highlight the role of endoscopic ultrasound guided thrombin instillation especially in patients with poorly visualized pseudoaneurysm on ultrasound thereby avoiding surgery and the associated mortality and morbidity.

Key words: Pseudoaneurysm; Angiography; Endoscopic ultrasound; Thrombin; Pancreatitis

Core tip: In cases where angiographic coil embolization is not feasible due to technical reasons, thrombin injection *via* computed tomography or ultrasound guidance remains a viable option. Endoscopic ultrasound guided thrombin injection is a new development in this realm especially in those patients where the visualization of the pseudoaneurysm is difficult on transabdominal ultrasound thereby avoiding the need of surgery and the associated morbidity.

Gamanagatti S, Thingujam U, Garg P, Nongthombam S, Dash NR. Endoscopic ultrasound guided thrombin injection of angiographically occult pancreatitis associated visceral artery pseudoaneurysms: Case series. *World J Gastrointest Endosc* 2015; 7(13): 1107-1113 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i13/1107.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i13.1107

INTRODUCTION

Pancreatitis is associated with high morbidity and mortality. Pseudoaneurysm is a commonly seen fatal complication of pancreatitis, noted in 10% of patients with chronic pancreatitis with the risk of rupture as high as 50% and the mortality after rupture as high as 15%-40%[1,2]. Hence, prompt diagnosis and treatment of pseudoaneurysm is recommended. Diagnostic modality like computed tomography (CT) angiography helps in picking up the lesion and delineating the vessel of origin however, digital subtraction angiography (DSA) and subsequent coil embolization is necessary to occlude the pseudoaneurysm to eliminate the risk of rupture and uncontrolled bleeding. Occasionally, coil embolization is not possible due to varied reasons like inaccessible vascular territory due to small caliber vessel or short neck of pseudoaneurysm. Some pseudoaneurysms may be angiographically occult and seen on ultrasound or CT only. In such cases ultrasound or CT guided percutaneous thrombin injection can be performed. Endoscopic ultrasound (EUS) guided thrombin injection is a new development in this realm especially in those patients where the visualization of the lesion is difficult on transabdominal ultrasound thereby avoiding the need of surgery and the associated morbidity. However, it requires a great deal of expertise. We review a few cases where pseudoaneurysms were occluded using endoscopic guided thrombin injection in our hospital.

CASE REPORT

We encountered three cases of pancreatitis related pseudoaneurysms, which were technically difficult to manage by endovascular route either because of previous surgical clipping of gastroduodenal artery by a laparoscopic surgeon (Figure 1) or that were angiographically occult.

In our center, in hemodynamically stable patients, the usual approach to manage the pancreatitis related pseudoaneurysm is to perform CT angiography for localization of pseudoaneurysm and also to provide road map for endovascular/surgical approach. Subsequently DSA is performed, depending upon the location of pseudoaneurysm on CT angiography; selective cannulation of the culprit vessel is done. If we are able to reach the pseudoaneurysm, coil embolisation is done by occluding the back door, neck and front door of the pseudoaneurysm, so that there is no collateral refilling of pseudoaneurysm. In our present series, we could not reach the pseudoaneurysm by endovascular route due to the reasons mentioned in Table 1. In all three cases, we attempted endoscopic ultrasound guided thrombin injection to treat these technically difficult pseudoaneurysms, after discussing with gastroenterologist experienced in EUS guided procedures. All these three pseudoaneurysms were easily visible on endoscopic ultrasound (Figure 2), which was performed prior to the thrombin injection for technical feasibility.

Technique of EUS guided thrombin injection

Gastroenterologist, who has got experience in EUS guided procedures, in collaboration with interventional radiologist performed this procedure. The procedure was performed without any anaesthesia. Initially EUS was performed using curved linear array transducer (Olympus-GF-UCT180) in conjunction with EVIS EXERA Ⅱ CLV-180 light source (Olympus Medical system Corp, Tokyo, Japan) was performed, pseudoaneurysm was localized and shortest path was chosen to target the pseudoaneurysm. We used the thrombin component of a Tisseel® kit (Baxter AG; Vienna, Austria), containing thrombin 500 IU/mL. Prior to targeting the pseudoaneurysm, thrombin component of Tisseel kit was reconstituted with 1 mL of calcium chloride and the reconstituted 1 mL thrombin was further diluted with normal saline to a total of 5 mL, so that each milliliter of reconstituted solution contains 100 IU of thrombin. Now, each milliliter of reconstituted thrombin was transferred to 1 mL insulin syringe and five such thrombin-loaded syringes were kept ready. Using 22G Echo Tip Ultra endoscopic ultrasound needle (Cook Medical Endoscopy, IN, United States), pseudoaneurysm was punctured under endoscopic ultrasound guidance, and then thrombin was injected in aliquots of 100 IU till the pseudoaneurysm become echogenic resulting in thrombosis. Under color Doppler, success of thrombosis was confirmed and the needle was removed when no color filling was seen inside the pseudoaneurysm sac. The entire procedure from start of localization of pseudoaneurysm to complete thrombosis of pseudoaneurysm lasted for about 15-20 min. After the procedure, patients were monitored closely for signs of internal bleeding. None of our patients developed any

Table 1 Demographic profile, clinical detail, angiographic and procedure details

Cases	Age/sex	Clinical presentation	Etiology of pancreatitis	Artery involved	Reason for angiographic failure	Amount of thrombin used	Follow up imaging	Figure No.
1	56/M	Pancreatitis with UGI bleed	Chronic alcoholic	Gastroduodenal artery	Previous surgical clipping	500 IU	Thrombosed	Figures 1-3
2	45/M	Pancreatitis with UGI bleed	Gall stone disease	Splenic artery	Not seen on DSA	300 IU	Thrombosed	Figures 4 and 5
3	30/M	Pancreatitis with UGI bleed	Gall stone disease	Splenic artery	Not seen on DSA	400 IU	Thrombosed	Figure 6

UGI: Upper gastrointestinal bleed; DSA: Digital substraction angiography; M: Male.

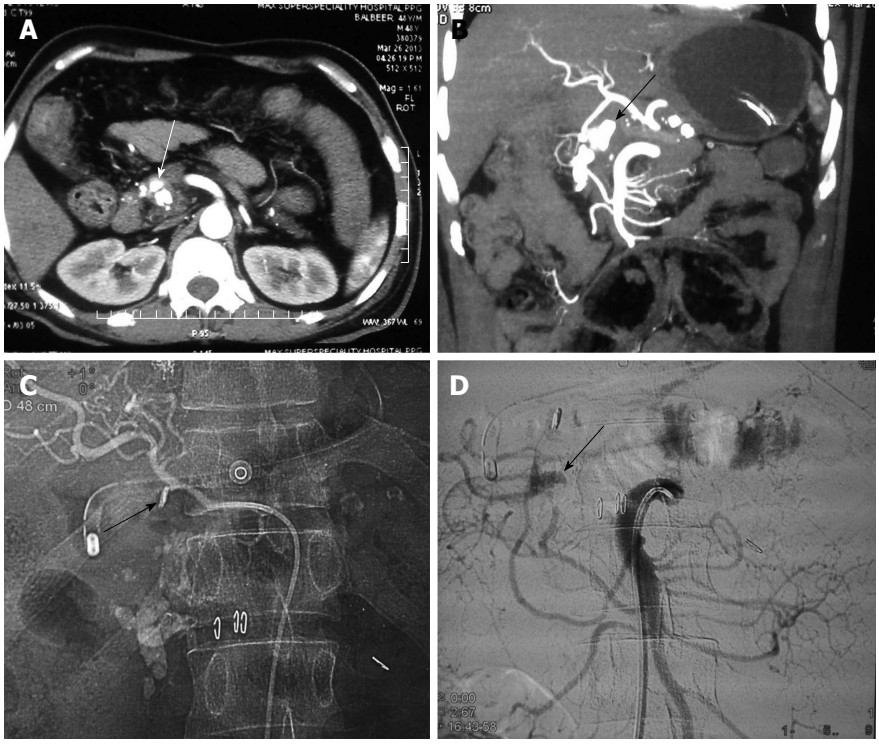

Figure 1 Chronic calcific pancreatitis with pseudoaneurysm of gastroduodenal artery (case 1). A: Axial Contrast enhanced; B: Coronal MIP (3-D reformatted) CT images; C: Angiographic spot image; D: Superior mesenteric DSA image. There is a pseudoaneurysm (arrow, A and B) arising from the gastroduodenal artery, which is filling from pancreatic arcade (Inferior pancreatic branches from SMA, D), because of metallic clip placed surgically at the origin of gastroduodenal artery origin (arrow, C). CT: Computed tomography; MIP: Maximum intensity projection; DSA: Digital substraction angiography; SMA: Superior mesenteric artery.

immediate or late complications. The next day, repeat EUS was done to reconfirm the success of the procedure. In one case we performed, CT angiography to confirmed the success of procedure (Figure 3). All three patients showed complete thrombosis of pseudoaneurysm on next day EUS. Clinical follow up was done after a month and none of these patients had recurrence of symptoms of bleeding.

DISCUSSION

Pseudoaneurysm formation is a known vascular complication of acute pancreatitis due to vessel injury as a result of proteolytic and lipolytic enzymes released due to severe inflammation and pancreatic necrosis[3].

The management of psuedoaneurysm in the setting of pancreatitis is challenging in view of the associated risk of rupture and haemodynamic compromise besides the background association of increased morbidity in pancreatitis itself. A diagnostic modality like CT angiography remains a preliminary imaging modality in acute pancreatitis. This provides a vascular road-map to the vessel of origin of the aneurysm besides adding vital information on the background pancreatitis.

DSA with coil embolization is the gold standard treatment. This offers the advantage of avoiding the associated surgical risks. Besides, it ensures adequate thrombosis of the pseudoaneurysm in most cases.

In situations where the access to the pseudoaneurysm is not possible due to previous clipping/tortuous anatomy (case 1) or not visible on DSA due to slow filling and narrow neck (Figure 4), angiographic coil embolization may not be feasible. Some pseudoaneurysms are occult and detected only with other imaging modality such as CT or endoscopic ultrasound, as seen in one of our case (Figure 5). If left alone, these pseudoaneurysms can rupture or rebleed. The risk of rupture in pancreatic pseudoaneurysms has been as high as 15%-40%[1].

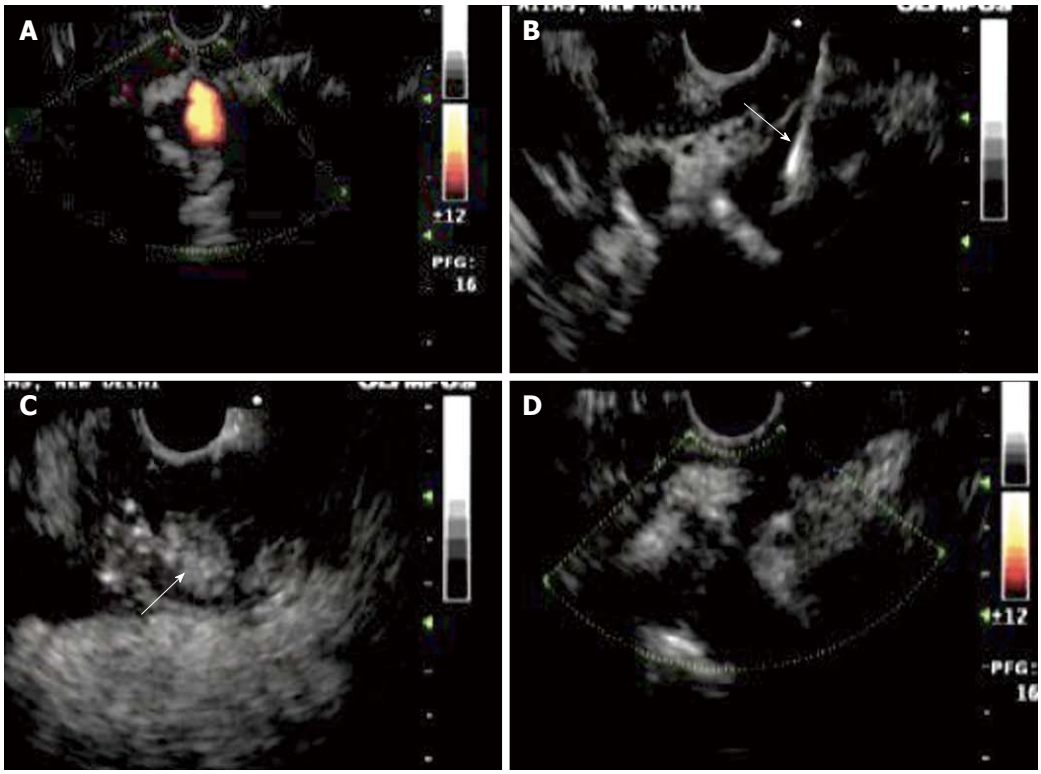

Figure 2 Endoscopic ultrasound guided thrombin instillation procedure (case 1). A-D: Endoscopic ultrasound images. There is a pseudoaneurysm sac (A) filling from pancreatic arcade (shown in Figure 1) with EUS needle (arrow, B) in the center of pseudoaneurysm sac with formation of echogenic thrombus (arrow, C) within the pseudoaneurysm sac following thrombin injection; D: No flow is seen within the pseudoaneurysm sac suggesting successful obliteration of pseudoaneurysm sac. EUS: Endoscopic ultrasound.

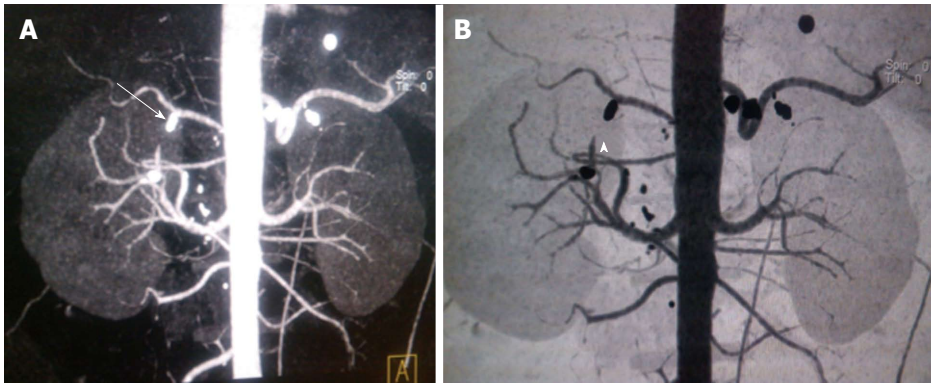

Figure 3 Follow up scan following thrombin injection procedure (case 1). A and B: Coronal MIP (3-D reformatted) CT images. There is non-visualization of the pseudoaneurysm sac (arrowhead, B) with metallic clip (arrow, A) seen at the gastroduodenal artery stump due to previous laparoscopic surgical clipping. CT: Computed tomography; MIP: Maximum intensity projection.

So, embolization is necessary to avoid rupture and rebleeding. Thrombin remains an alternative to coils. It can be instilled directly at the bleeding site and the flow cessation can be assessed. Thombin is a good alternative in those cases not feasible by endovascular route. The success of thrombin for embolization of peripheral pseudoaneurysms[4-6] as well as those of pancreas[7-10] have been described in literature.

Thrombin can be given through transcutaneous route through ultrasound or CT guidance. However, in our patients transabdominal ultrasound could not delineate the lesion clearly posing great challenge for thrombin instillation. EUS was the next step as most of these pseudoaneurysms were in the vascular territory in the vicinity of the peripancreatic region. The advantage of EUS lies in clearly delineating the extent and size of the pseudoaneurysm. Instillation of thrombin under EUS guidance requires a great deal of expertise. Thrombin could ensure immediate occlusion of pseudoaneurysms in all cases (Figure 6). Response assessment can also be done easily. The hallmark finding is the complete thrombosis of the pseudoaneurysm. No associated complications were noted. Follow up scans did not reveal rebleeding or rupture in our cases.

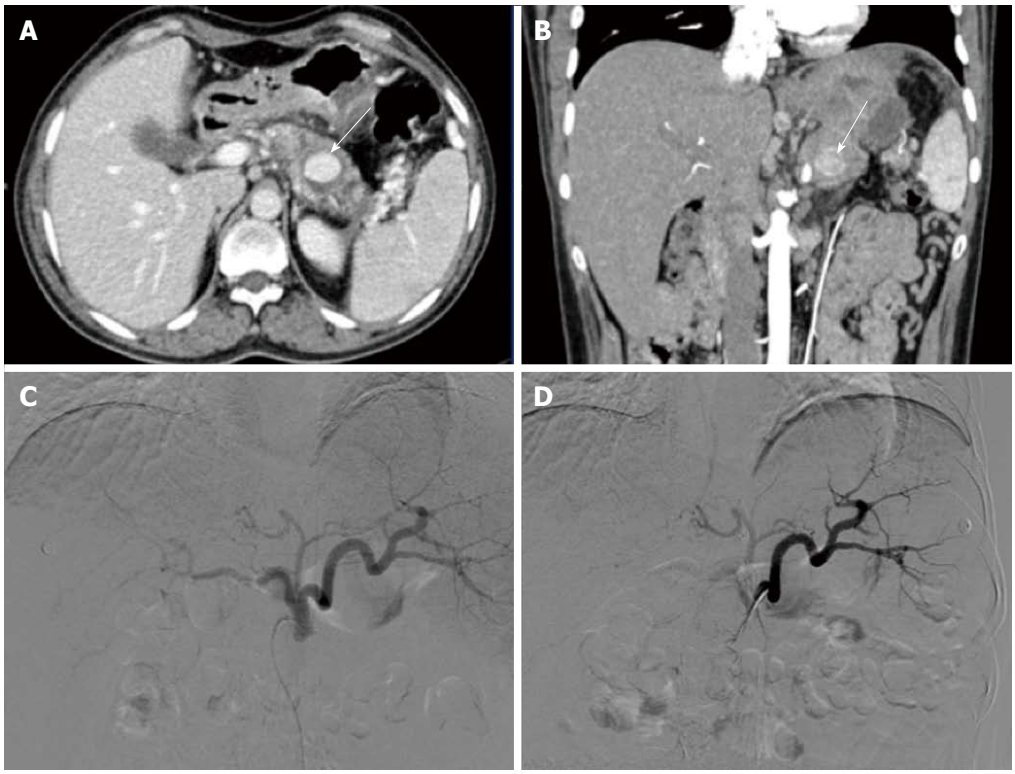

Figure 4 Pancreatitis related pseudoaneurysm (case 2). A: Axial contrast enhanced CT; B: Coronal maximum intensity projection CT images; C and D: Digital substraction Images. In the background of pancreatitis there is a pseudoaneurysm in the distal body of the pancreas (arrow, A and B) which was not revealed on either left gastric artery (C) or splenic artery (D) angiograms. CT: Computed tomography.

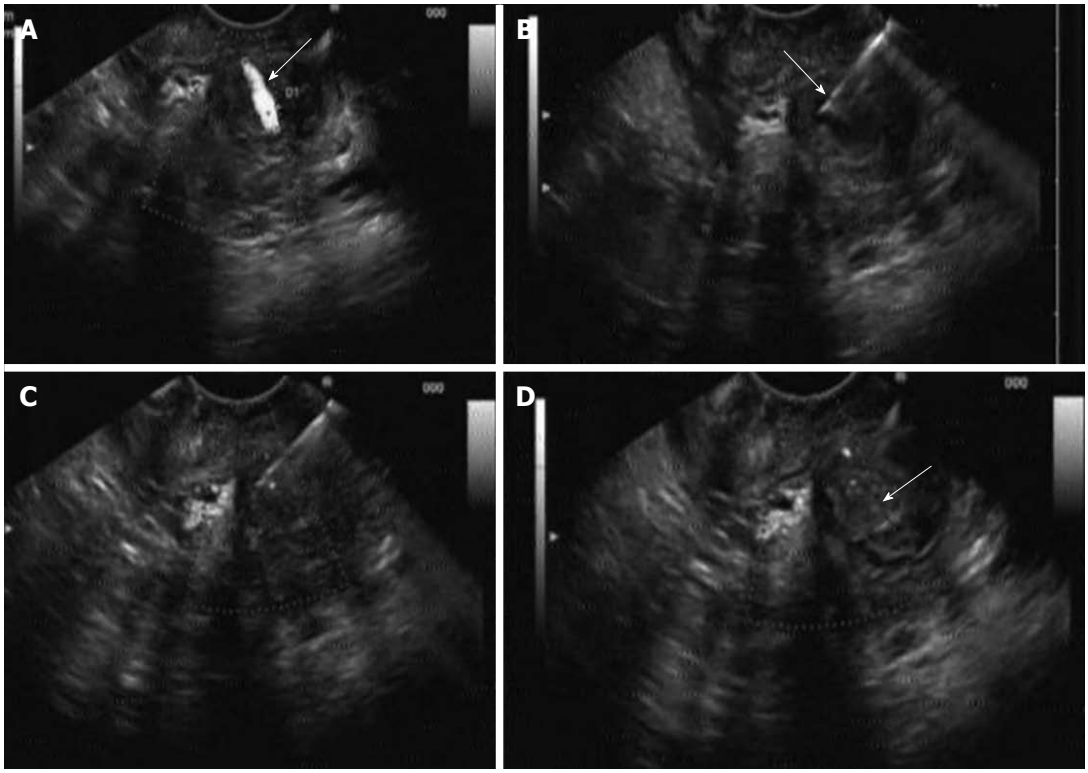

Figure 5 Endoscopic ultrasound guided thrombin instillation procedure (case 2). A-D: Endoscopic ultrasound images. There is a pseudoaneurysm sac (arrow, A) within pancreatic body region (A) with endoscopic ultrasound needle (arrow, B) inside the pseudoaneurysm sac, which was managed by instillation of thrombin (C) with subsequent thrombosis of the pseudoaneurysm sac as shown by echogenic pseudoaneurysm sac (arrow, D).

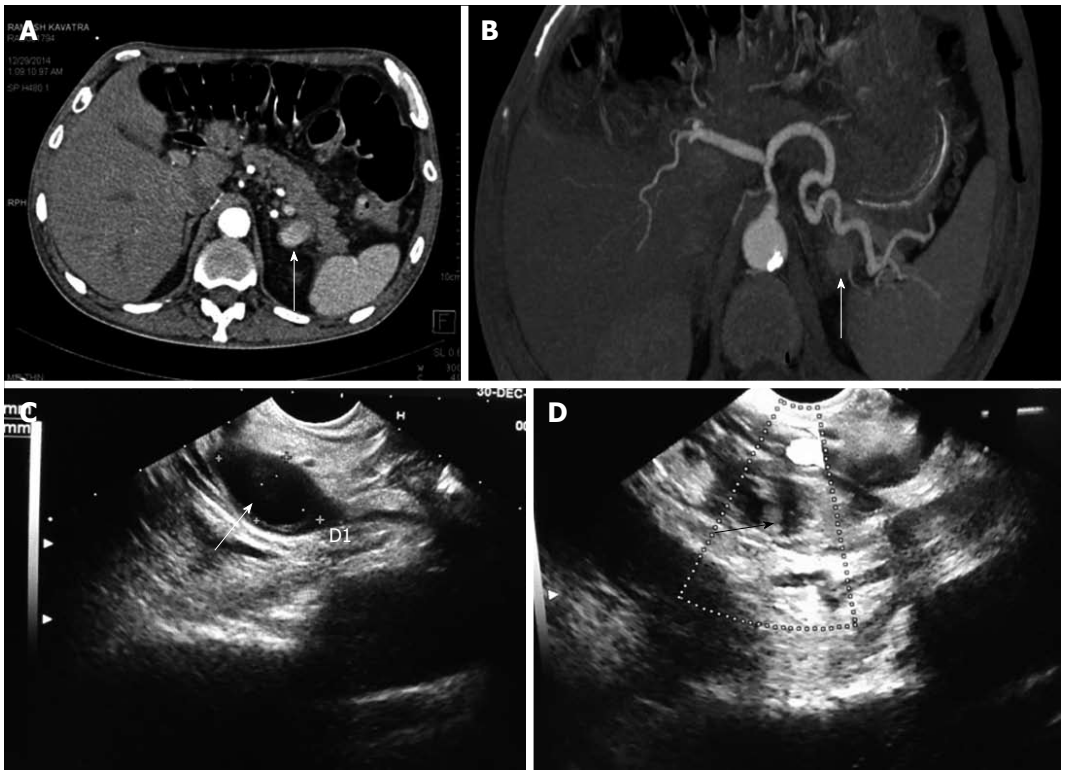

Figure 6 Chronic calcific pancreatitis with upper gastrointestinal bleed. A: Axial contrast enhanced; B: Axial MIP (3-D reformatted) CT images; C and D: Endoscopic ultrasound images. There is a pseudoaneurysm sac (arrow, A) in relation to distal body of the pancreas, in close relation to the splenic artery (arrow, B) and confirmed by endoscopic ultrasound (arrow, C) and subsequently managed by instillation of thrombin under EUS guidance with complete thrombosis of the pseudoaneurysm was achieved as revealed by the transformation of the previously anechoic lesion to an echogenic sac (arrow, D). CT: Computed tomography; MIP: Maximum intensity projection; EUS: Endoscopic ultrasound.

There are very few literature describing the use of EUS guided thrombin instillation of pancreatic pseudoaneurysm. In one of the earliest description Roach *et al*[11] described the EUS guided thrombin occlusion of a pseudoaneurysm arising from a branch of the superior mesenteric artery in a patient presenting with upper gastrointestinal bleed. This was done following failure to embolise angiographically as the feeding artery could not be catheterized.

Use of thrombin is recommended in cases of haemodynamically stable patients with small pseudoaneurysm[12]. Also it can be used in large lesions as an adjunct to coil embolization.

In haemodynamically unstable patients and those with large pseudoaneurysms or those with failure after repeated embolization, surgery remains the only option. But in the setting of pancreatitis, surgery is associated with a grim outcome. Non-invasive imaging modalities like ultrasound and CT have provided good alternatives as means of thrombin instillation. The advent of thrombin instillation through EUS guidance has opened an altogether new arena for managing the difficult pseudoaneurysms and thereby avoiding the surgical risks. Though one cannot undermine the expertise needed in EUS guidance, it offers a new hope to this special group of patients.

Some limitations of thrombin instillation, though rare, include risk of distal thrombosis though thrombin is rapidly diluted and inactivated by fast flowing blood stream[10]. Immunological reactions like sensitivities and cross-reactions are also known[10]. Recanalization after initial successful thrombosis of pseudoaneurysm is another complication. Lastly, the duration of follow-up required after treatment of pseudoaneurysms is not known.

The use of EUS guided thrombin instillation provides a new option for management of pseudoaneurysms caused by pancreatitis specially for those cohort of patients inaccessible angiographically or through transabdominal ultrasound. The avoidance of high risk surgeries, prompt occlusion of the pseudoaneurysm and ease of monitoring and follow-up are the hallmark features of this method though studies are needed to provide data as to efficacy of this method.

COMMENTS

Case characteristics

The three middle-aged male patients presented with similar symptom of upper gastrointestinal bleeding. One patient had surgical clipping of gastroduodenal artery.

Clinical diagnosis

Upon physical examination, all three patients were haemodynamically stable except for tachycardia. Pulse rates were in range of 110-120/min. No other

significant physical findings noted.

Differential diagnosis

Pancreatitis related bleeding pseudoaneurysm, variceal bleeding, peptic ulcer disease.

Laboratory diagnosis

All the patients had low hemoglobin level (range of 4-7 gm/dL). Upper gastrointestinal endoscopy showed blood clots within the stomach and duodenum. No active bleeding site could be seen on endoscopy.

Imaging diagnosis

All three patients had contrast enhanced computed tomography showed pseudoaneurysm arising from gastroduodenal artery (patient 1) and splenic artery (patients 2 and 3). There was evidence of surgical clip at the gastroduodenal (GDA) origin and chronic calcific pancreatitis in first patient.

Treatment

All the patients underwent digital substraction angiography. In first patient pseudoaneurysm could not be reached due to previous surgical clipping of GDA and tortuous collaterals feeding the pseudoaneurysm. In rest two patients, pseudoaneurysms were occult on angiography. All three patients were successfully managed by endoscopic ultrasound (EUS) guided thrombin injection in to the pseudoaneurysm.

Related reports

Thrombin injection into the iatrogenic related peripheral pseudoaneurysm is well known. Very few cases describing the use of EUS guided thrombin instillation of pancreatic pseudoaneurysm have been reported in literature. The advent of thrombin instillation through EUS guidance has opened an altogether new arena for managing the difficult pseudoaneurysms and thereby avoiding the surgical risks.

Term explanation

Thrombin (bovine/human), is available as powder form and is reconstituted with calcium chloride solution, injected into the pseudo aneurysm after direct puncture percutaneously under image guidance. Thrombin converts fibrinogen into fibrin resulting in formation of clots.

Experiences and lessons

This case series represents a new option of EUS guided thrombin instillation for management of pseudoaneurysms caused by pancreatitis especially for that cohort of patients where pseudoaneurysm is inaccessible angiographically.

Peer-review

This is an interesting paper highlighting a method of occluding pseudoaneurysms, which are otherwise difficult to reach.

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REVIEW

Colorectal endoscopic submucosal dissection: Recent technical advances for safe and successful procedures

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Abstract

Endoscopic submucosal dissection (ESD) is very useful in *en bloc* resection of large superficial colorectal tumors but is a technically difficult procedure because the colonic wall is thin and endoscopic maneuverability is poor because of colonic flexure and extensibility. A high risk of perforation has been reported in colorectal ESD. To prevent complications such as perforation and unexpected bleeding, it is crucial to ensure good visualization of the submucosal layer by creating a mucosal flap, which is an exfoliated mucosa for inserting the tip of the endoscope under it. The creation of a mucosal flap is often technically difficult; however, various types of equipment, appropriate strategy, and novel procedures including our clip-flap method, appear to facilitate mucosal flap creation, improving the safety and success rate of ESD. Favorable treatment outcomes with colorectal ESD have already been reported in many advanced institutions, and appropriate understanding of techniques and development of training systems are required for world-wide standardization of colorectal ESD. Here, we describe recent technical advances for safe and successful colorectal ESD.

Key words: Endoscopic submucosal dissection; Colorectal tumors; Mucosal flap; Clip-flap method

Core tip: Endoscopic submucosal dissection (ESD) is useful for *en bloc* resection of large colorectal tumors but is a technically difficult procedure. Good visualization of the submucosal layer is crucial for safely and successfully performing colorectal ESD because poor visualization of the operative field may result in perforation or unexpected bleeding. Creating a mucosal flap solves these problems; however, it is the

process that requires the most skill in this procedure. To facilitate the mucosal flap creation, we developed the clip-flap method, which is simple and very effective for colorectal ESD. We described recent advances in colorectal ESD techniques and devices.

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INTRODUCTION

Endoscopic submucosal dissection (ESD) was recently developed for *en bloc* resection of early stage gastrointestinal neoplasms with negligible risk of lymph node metastasis[1-5]. Higher rates of *en bloc* resection of large colorectal tumors have been reported with colorectal ESD than with endoscopic mucosal resection (EMR); however, colorectal ESD confers an increased risk of perforation[6-10]. A high degree of technical skill and the development of specific strategies for colorectal ESD are required because of the anatomical characteristics of the colon, namely being a long and winding tube with a thinner wall than other regions of the gastrointestinal tract[4,6]. To prevent complications such as perforation and uncontrollable bleeding, it is crucial to maintain good visualization of the submucosal layer to be dissected[4,11,12]. Therefore, the mucosal flap creation is the key procedure[12], although this process is technically challenging. To facilitate the mucosal flap creation, we recently developed the clip-flap method in which an endoclip is initially substituted for the mucosal flap[13-15]. Several types of endoknives were developed and properly utilizing them according to the requirements is also important. In this review, recent advances in techniques using various devices in colorectal ESD will be described.

INDICATION FOR COLORECTAL ESD

Before performing colorectal ESD, the determination of the indications for ESD by preoperative examination is highly important. EMR using a snare remains the main treatment for superficial colorectal tumors. However, EMR is not adequate for *en bloc* resection of flat lesions larger than 20 mm in diameter because incomplete removal and local recurrence are occasionally observed[16,17]. The indications for ESD are therefore considered for a tumor when using EMR for *en bloc* resection is difficult. The guidelines on the indications for colorectal ESD were published in Japanese and Spanish academic societies of gastrointestinal endoscopy[18,19]. Basically, the indications for ESD are colorectal tumors for which endoscopic *en bloc* resection is required but *en bloc* resection with EMR is difficult to apply. The primary objective lesions are large colorectal tumors, such as the laterally spreading tumor granular type (LST-G) with a large nodule or the laterally spreading tumor non-granular type (LST-NG)[20,21], which are suspected to be intramucosal or with slightly invaded submucosal cancers > 20 mm in diameter in the preoperative examinations. Large protruding lesions are also indications for colorectal ESD[18,19]. However, an abundance of caution is required to treat large protruding lesions because even experienced endoscopists sometimes cannot avoid discontinuation of submucosal dissection due to severe submucosal fibrosis and retracted muscle[22]. Even if the size of the tumor is less than 20 mm, mucosal lesions with submucosal fibrosis, which cannot be resected with EMR, can be the indications for ESD.

In contrast, the technical simplicity of EMR can permit its utilization for colorectal tumors > 20 mm in diameter when the preoperative diagnosis is adenoma or mucosal cancer in adenoma[18-20], although piecemeal mucosal resection includes the problem of a high local recurrence rate[20]. Magnifying chromoendoscopy for pit pattern observation[23] and magnifying image-enhanced endoscopy (narrow band imaging[24,25] or blue laser imaging[26], *etc.*) are useful for preoperative differential diagnosis of adenoma, intramucosal cancer, and submucosal invasive cancers. It is better to avoid preoperative biopsy if the endoscopic treatment is planned to be performed because biopsy often causes submucosal fibrosis, complicating further endoscopic treatment[18]. In addition, the endoscope maneuverability should be analyzed before performing ESD because poor endoscope maneuverability may cause incomplete resection or complications[27,28].

METHOD FOR SAFE AND SUCCESSFUL ESD

Preparation and oral intake

Bowel preparation is required for adequate visualization of the operative field and as prophylaxis against bacterial peritonitis in case of perforation. Patients are restricted to a low-fiber diet on the day before colorectal ESD and are instructed to orally consume 10 mL picosulfate after the last meal on the day before the procedure. Two-four liters of an electrolyte solution is orally administrated before the procedure[11,29].

In contrast, no food or drink is allowed on the day of the procedure or the following day. Provided that there are no signs or symptoms of complications, patients will begin drinking water on day 1 and have light meals (rice porridge) on day 2. Meals are upgraded to normal food with alcohol excluded from day 2 until day 3-5 or the date of hospital discharge[30-32].

Sedation and patient's position

Light or conscious sedation is appropriate for colorectal ESD because deep sedation makes alteration of the patient's position difficult and often leads to severe

respiratory fluctuations[11]. At our institution, midazolam (2 mg) and pethidine (17.5-35 mg) is initially intravenously administered. Light sedation is maintained with additional administration of midazolam or pethidine during the procedure. In cases where a long procedure duration is expected, the use of dexmedetomidine may be useful in maintaining good sedation levels[33,34]. Use of a carbon dioxide (CO_2) insufflation system (UCR; Olympus Co., Tokyo, Japan) is extremely helpful for reducing the patient's discomfort and risk of peritonitis in case of perforation[35-37]. Excessive air present during the procedure decreases the endoscope maneuverability, but carbon dioxide can be quickly absorbed[35-37]. Yoshida *et al*[38] reported that CO_2 insufflation during colorectal ESD was safe even for patients with obstructive ventilator disturbance.

Scopolamine butylbromide (10 mg) is administrated to all patients except those contraindicated because of reduced bowel movement immediately prior to the procedure. Additional doses may be administered during the procedure. Administration of intravenous glucagon[39] or intraluminal peppermint oil[40] may be useful for patients who are contraindicated for scopolamine.

The patient's position is critical in performing successful colorectal ESD. In principle, the lesion should be moved upward as far as possible against the force of gravity prior to ESD and followed by a postural change to take advantage of the counter-traction of gravity[4,11,41,42]. The direction of gravity can be understood by the pooling of water or indigo carmine dye[11]. However, the intestinal lumen may become narrower or broader on alteration of the patient's position due to the movement of air. ESD becomes particularly challenging in narrowed lumen. Therefore, it is recommended that ESD should be commenced after each position (supine, prone, left lateral decubitus position, and right lateral decubitus position) has been adequately assessed as far as possible. In case of large lesions, changing the patient's position during the procedure is often required to ensure optimal operative field[4].

Selection of endoscope

ESD is generally performed using a single-channel colonoscope. At our institution, PCF-H290I or CF-H290I (Olympus), which have a water-jet function, are currently predominantly used because the water-jet function is convenient for hemostasis during ESD. Moreover, a gastroendoscope (GIF-HQ290, GIF-Q260J; Olympus) may be used for lesions in the rectum or distal sigmoid colon because the shorter endoscope can be easily operated in such locations[11,43]. In addition, a gastroendoscope can be used to approach lesions from the oral side in retroflexion more easily than with a conventional colonoscope.

Endoscope maneuverability is crucial to precisely perform ESD. ESD is challenging in cases of poor endoscope maneuverability, although experts can overcome these difficulties in most cases. Straightening of the endoscope is important for maintaining good endoscope maneuverability. Single-balloon[44] (OBCU; Olympus) or double-balloon endoscopy systems[45,46] (PB-20; Fujifilm Co., Tokyo, Japan) may be useful in cases of extremely poor maneuverability.

Distal attachments (Hoods)

The use of distal attachments is essential in safely performing colorectal ESD. The cutting area can be broadened and visualized with the use of distal attachments during the procedure. The shapes of distal attachments for colorectal ESD are mainly divided into straight types (D-201; Olympus, Figure 1A) and tapered types. Straight distal attachments allow larger working spaces for the operation of endoknives or forceps; however, the submucosal layer must be cut more deeply to insert the attachment under the exfoliated mucosa compared with tapered distal attachments. At our institution, a distal attachment (F-050/020, M-02/03/01; Top Corp., Tokyo, Japan, Figure 1B and C), which is slightly tapered, is attached to the tip of the endoscope. Small-caliber tip transparent hoods (ST-hood; Fujifilm) (Figure 1D) are useful for accessing narrow cutting areas[4,47]. Furthermore, this distal attachment is used for the tunnel[41,48] or pocket-creation method[49].

Endoknives and high-frequency generators

Various types of endoknives are used for colorectal ESD. Short-needle knives are the most widely used type of endoknife for colorectal ESD. The DualKnife[50] (Olympus, Figure 2A) is a short-needle endoknife that has a small disk at the tip of a short needle. The FlushKnife BT[51] /FlushKnife (Fujifilm, Figure 2B), Jet B-knife (Zeon Medical, Tokyo, Japan, Figure 2C)[52], and Splash needle (Pentax Medical, Tokyo, Japan) are all short-needle knives with a water-jet function that enable submucosal injection without requiring the injection needle to be changed. The HookKnife[53] (Olympus, Figure 2D) has a hook on the tip that enables hooking and cutting of submucosal tissue. The HookKnife is particularly useful when the tangential approach is difficult or submucosal fibrosis is present because the submucosal tissue can be easily hooked and cut with this endoknife. The SBknife Jr[54-56] (Sumitomo Bakelite, Tokyo, Japan, Figure 2E) and Clutch Cutter[57] (Fujifilm) (Figure 2F) are scissor-type endoknives that have a rotation function. Scissor-type endoknives can be easily operated in the manner of forceps even by inexperienced operators. In addition, it can be efficiently operated even in cases when the tangential approach is difficult or endoscope maneuverability is extremely poor, because the submucosal tissue can be dissected simply by grasping, lifting, and applying an electrical current. The ITknife-nano (Olympus, Figure 2G) is an endoknife with an insulator on the tip of the blade that was developed for colorectal or esophageal ESD. Its use may allow increased dissection speeds[21] because it has a long blade between the insulated-tip and the sheath. The Mucosectom[58] (PENTAX, Figure 2H and I) and Swanblade (PENTAX, Figure 2J) have blades on

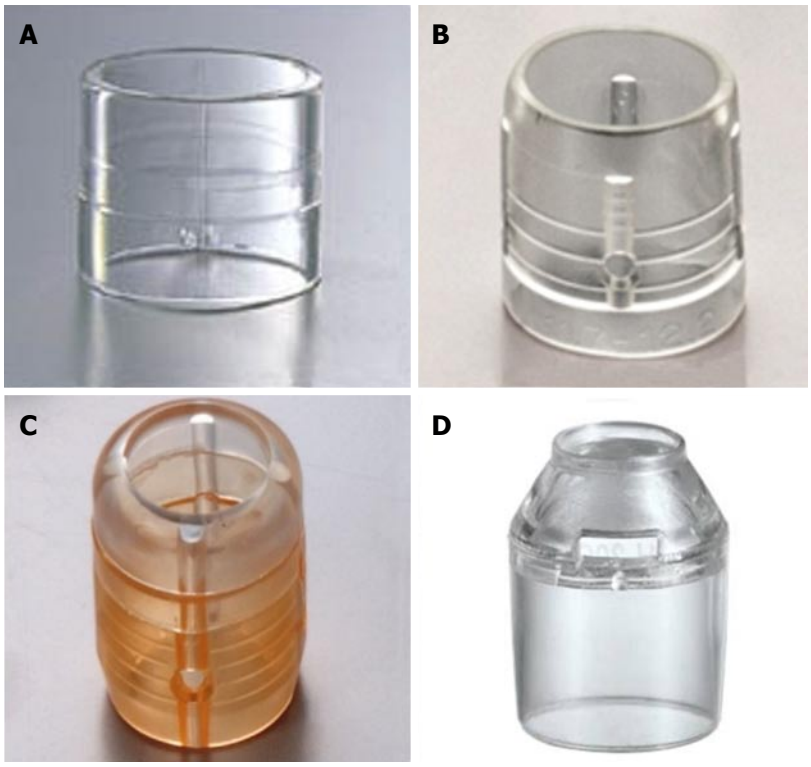

Figure 1 Distal attachments for colorectal endoscopic submucosal dissection. A: D-201; B: F-050; C: M-02; D: Short ST-hood.

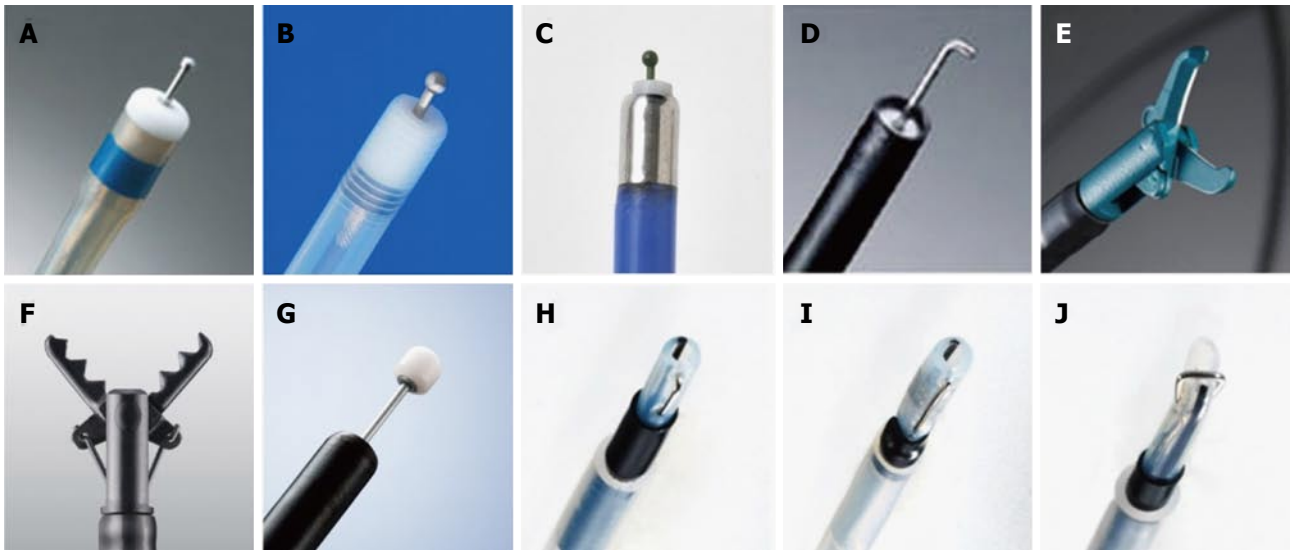

Figure 2 Various types of endoknives used for colorectal endoscopic submucosal dissection. A: DualKnife; B: FlushKnife BT; C: Jet B-knife; D: Hooknife; E: SBknifeJr; F: Clutch cutter; G: ITknife-nano; H: Mucosectom-short blade; I: Mucosectom-long blade; J: Swanblade.

an insulated rod that has a rotation function. These endoknives were developed for the safe and rapid dissection of the submucosal layer. At our institution, the FlushKnife BT (DK2618JB15/20) is predominantly used. According to the specific situation, other endoknives may be used in conjunction.

A high-frequency generator with an automated control system is required for ESD. At our institution, the VIO 300D (Erbe Elektromedizin GmbH, Tubingen, Germany) is predominantly used. ICC-200 (Erbe) or ESG-100 (Olympus) are also used for colorectal ESD. The settings on each instrument when using short-needle knives (FlushKnife BT, DualKnife) and hemostatic forceps (FD-410LR, FD-411QR; Olympus) are shown in Table 1[11,50,59].

Strategies for improving safety and efficacy of ESD

ESD is usually initiated either from the anal side of the lesion in a forward direction or from the oral side in retroflexion[11,43]. There are benefits and limitations to both methods. Dissection from the anal side can be performed in almost all cases; however, endoscope

Table 1 Setting of high-frequency generators for colorectal endoscopic submucosal dissection using Flush Knife BT, Dual Knife, and hemostatic forceps (FD-410LR, FD-411QR)

Device	Mucosal incision	Submucosal dissection	Hemostasis
FlushKnifeBT with VIO 300D (at our institution) with ICC 200 (at our institution)	Endocut I, effect 2, duration 3, interval 3 Endocut, effect 2-3, 80-120 W	Forced coag, effect 2, 40-50 W Swift coag, effect 2, 40-50 W Forced coag, 40-50 W Endocut, effect 2-3, 80-120 W	Forced coag, effect 2, 40-50 W Swift coag, effect 2, 40-50 W Forced coag, 40-50 W
DualKnife with VIO 300D[49] with ESG-100[59]	Dry cut, effect 2, 30 W Pulse-cut-slow, 50 W	Swift coag, effect 4, 30 W Forced coag, effect 2	Swift coag, effect 4, 30 W Forced coag, effect 2
Hemostatic forceps FD-410LR with VIO 300D[11] with ICC 200 (at our institution) with ESG-100[59]			Soft coag, effect 5, 50 W Soft coag, 80 W Soft coag, 80 W
FD-411QR with VIO 300D (at our institution)			Soft coag, effect 6, 80-100 W

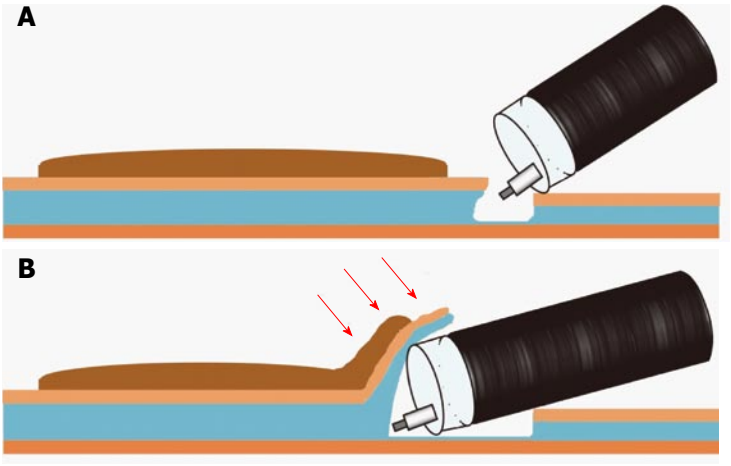

Figure 3 Schema of the mucosal flap. A: After injecting a solution in the submucosal layer, mucosal incision and deeper cut are made; B: Continuing to dissect the submucosal layer allows the creation of the "mucosal flap" (Red arrows point to the "mucosal flap"). Inserting the distal attachment under the mucosal flap provides good counter-traction to the submucosal layers and allows good visualization of the operative field. Therefore, completion of the mucosal flap facilitates subsequent submucosal dissection.

maneuverability is somewhat unstable, and the treatment of the mucosa just beyond a haustrum or a colonic flexure is occasionally challenging. Dissection from the oral side in retroflexion requires adequate space with a broad lumen; however, endoscope maneuverability is comparatively stable using this method[11,60]. The method selection by endoscopists largely depends on the institutions' established procedures and lesion location. At our institution, dissection from the anal side is predominantly performed and dissection from the oral side in retroflexion is occasionally performed in cases where approaching from anal side is difficult.

In either case, it is important to start dissecting the submucosa immediately proximal to the tip of the endoscope to avoid complications, such as perforation and unexpected bleeding, caused by blind procedures. Therefore, insertion of a distal attachment under the exfoliated mucosa of the lesion side is a crucial step in safely and effectively dissecting the submucosal layer. The lesional exfoliated mucosa is called the mucosal flap (Figure 3B)[12,61]. Formation of the mucosal flap facilitates safe and sequential dissection.

Submucosal injection, mucosal incision, and deeper cut

While approaching from the anal side, a solution is injected in the submucosal layer of the anal side of the lesion and then the lesion tends to be more tangentially approached and more easily dissected (Figure 4B). Saline, 0.4% sodium hyaluronate solution (MucoUp; Johnson and Johnson, Tokyo, Japan) (Sigmavisc; Hyaltech Ltd., Livingston, United Kingdom), or 10% glycerin with a small amount of indigo carmine dye and 0.001% epinephrine are usually used as the injected solution[11,41,47,62]. Sodium hyaluronate solution is the most long-acting agent that can be locally injected for colorectal ESD[63]. Suvenyl (2% hyaluronate, Chugai, Tokyo, Japan) or Artz (1% hyaluronate, Seikagaku Corp. Tokyo, Japan) may be used after coordinating their concentrations[4,47,63].

Following submucosal injection, the mucosa adjacent to the lesion is incised with an adequate margin before incision of the submucosal layer. A complete or partial circumferential mucosal incision is initially made according to the institutions' established procedures or characteristics of the lesion. A partial circumferential mucosal incision has recently been introduced at an increasing number of institutions because initial complete circumferential mucosal incision can make insertion of the distal attachment under the exfoliated mucosa difficult because of the loss of mucosal tension caused by extensive mucosal incision[4,11,30]. At our institution, a partial circumferential mucosal incision

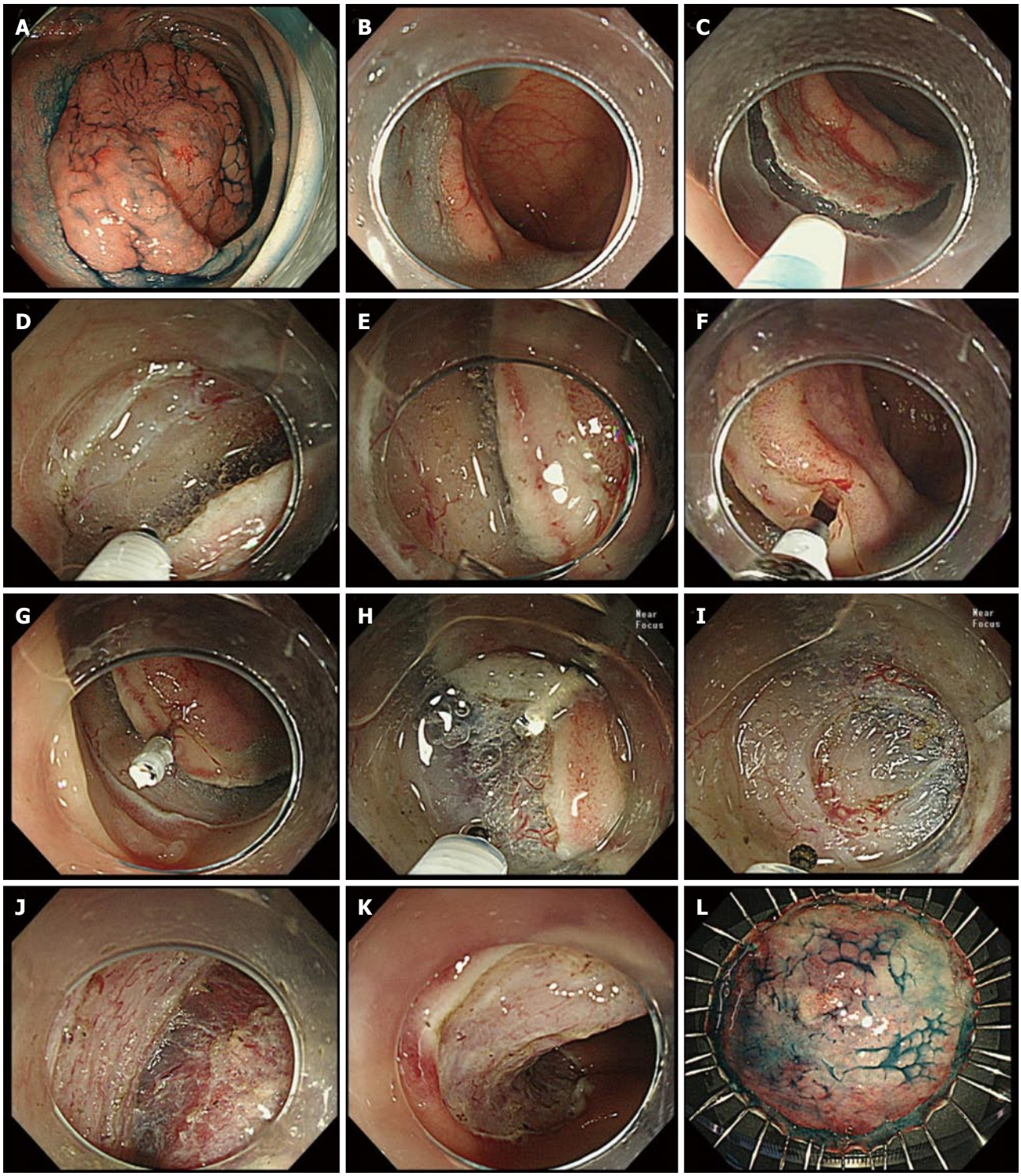

Figure 4 Endoscopic submucosal dissection of a laterally spreading tumor, non-granular type lesion using the clip-flap method. A: A 45 mm, LST-NG was located at the sigmoid colon. The patient was first positioned so that the bowel wall containing the lesion was uppermost, and this maximizes the assistance of gravity during ESD; B: Submucosal injection was performed from the anal side; C: Mucosal incision from the anal side was made using FlushKnife BT; D: Deeper cut of the anal side was made; E: The submucosal layer could not be adequately visualized because it was hidden by the exfoliated mucosa at this region. Insertion of the distal attachment under the exfoliated mucosa was difficult because of the tight space between the exfoliated mucosa and muscle, despite the condition after submucosal injection; F: After the width of endoclip's prongs was slightly narrowed, the edge of the exfoliated mucosa was clipped with an endoclip while lifting the exfoliated mucosa with the prongs of the endoclip, so that the deep layer of the submucosa was not grasped by the endoclip; G: The endoclip was attached to the exfoliated mucosa. The tail end of the endoclip attached to the mucosa slightly fell toward the intestinal lumen due to gravity, allowing the attachment to be easily inserted under the endoclip; H: The distal attachment was inserted under the endoclip, and then mucosa and the submucosal layer were elevated by the endoclip. The submucosal layer could be clearly visualized and dissected with the endoknife under the direct vision; I: The distal attachment could be inserted under the exfoliated mucosa by cutting the vasculature; J: Following mucosal flap formation, the submucosal layer could be dissected more easily; K: Dissection was completed following complete circumferential incision without any complications. Artificial ulcer after ESD; L: Resected specimen. Histopathological examination confirmed intramucosal cancer, and margin (-). LST-NG: Laterally spreading tumor, non-granular type; ESD: Endoscopic submucosal dissection.

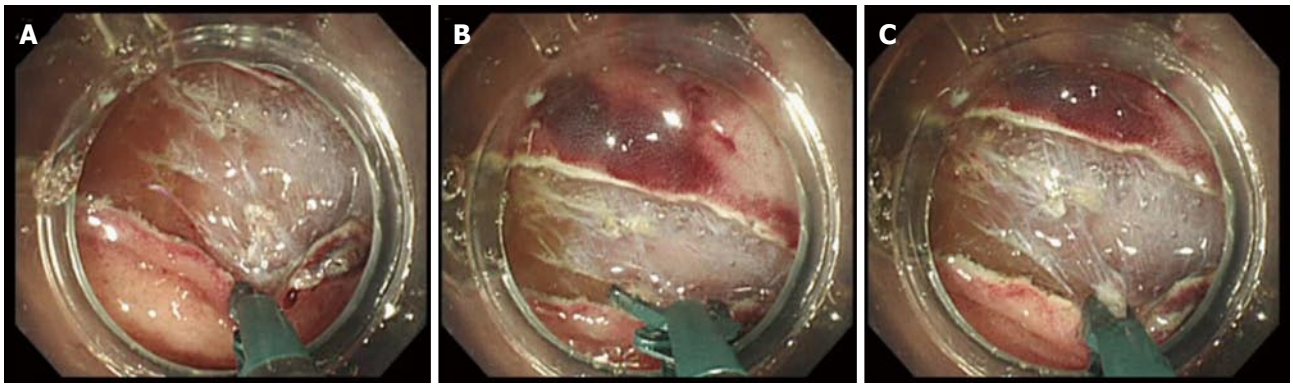

Figure 5 Three steps of safe submucosal dissection using a scissor-type endoknife (SBknifeJr) in case of a vertical approach. A: The endoscope was rotated and the exfoliated mucosa was turned down with a tip of an endoknife to clearly visualize the submucosal layer to be dissected along with the scissor tips; B: The edges of the scissor-type endoknife was opened; C: The submucosal layer under the exfoliated mucosa could be safely dissected by grasping and pulling up with the endoknife before application of an electrical current. Repeating these procedures led to the creation of the mucosal flap and successful endoscopic submucosal dissection.

from the anal side is usually made (Figure 4C) because it allows widening of the gap between lesional and non-lesional mucosa and greater ease of insertion of the distal attachment under the exfoliated mucosa. In partially circumferential mucosal incision, a complete circumferential mucosal incision is made after the creation of the mucosal flap.

At our institution, mucosal incision with the FlushKnife BT is performed with the endocut I mode. Deeper cut of the submucosal layer is performed with the forced coagulation or swift coagulation mode.

Creation of the mucosal flap

Insertion of the distal attachment under the exfoliated mucosa is critical in allowing dissection of the submucosal layer while maintaining a good operative field. However, adequate visualization of the submucosal area at the beginning of the dissection is difficult because it is commonly hidden under the exfoliated mucosa. Poor visualization of the submucosal layer to be dissected may cause perforation and unexpected bleeding. To enhance visualization and ensure safe dissection of the submucosal layer, a mucosal flap must be created. Insertion of the distal attachment under the mucosal flap elevates the mucosal flap and provides counter-traction to the submucosal layer that allows easier dissection (Figure 4J). Therefore, creation of the mucosal flap is the most important step of the ESD procedure[12]; however, this process requires the most technical skill. The presence of submucosal fibrosis or vasculature often hinders smooth dissection and vertical approaches make creation of the mucosal flap more challenging. Changing the type of endoknife (Figure 5A-C) or using a tapered-type distal attachment may have utility in cases where the creation of the mucosal flap proves difficult.

The Clip-flap method

To facilitate the mucosal flap creation, we developed the clip-flap method, in which an endoclip is substituted for the mucosal flap until the flap is completed[13-15]. The basic procedure is as follows.

After submucosal injection, the mucosa adjacent to the lesion on the anal side is incised with an adequate margin and then the submucosal layer is cut deeply (Figure 4A-E). The edge of the exfoliated mucosa is clipped with an endoclip (EZ Clip, HX-610-135; Olympus; Figure 4F and G) while lifting the exfoliated mucosa with the prongs of the endoclip, so that the deep layer of the submucosa is not grasped by the endoclip. The distal attachment is inserted under the endoclip, and then the endoclip is lifted with the distal attachment. Consequently, the exfoliated mucosa is pulled up by the endoclip, allowing clear visualization and effective dissection of the submucosal layer by counter-traction using the endoclip (Figure 4H and I). In addition, the distal attachment can be easily inserted under the endoclip when the tail end of the endoclip is directed toward the intestinal lumen (Figure 4G) by using gravity after a postural change or temporarily lifting the endoclip with the endoknife.

Other than a single endoclip (Figure 4G and H), a cross pattern of endoclips created by attaching one endoclip to another endoclip is used to provide good counter-traction according to the situations[14]. We use the EZ clip in the clip-flap method because it can be easily rotated, and it has a joint between the metal prongs and sheath, most of which is made of plastic. The joint may be utilized as a step difference with which to hook it to the distal attachment. A long endoclip may be inappropriate because it can be a hindrance in a narrow lumen.

In our experience, the clip-flap method was effective in most cases, even in the presence of submucosal fibrosis or with a vertical approach, but can be difficult to use in some situations. When lesions are located within a very narrow lumen, such as in the anal tube, just beyond the colonic flexure, or when endoscope maneuverability is extremely poor, attaching the endoclip to the exfoliated mucosa and inserting the

distal attachment under the endoclip may be difficult[14].

The clip-flap method is very simple and requires no special equipment other than common rotatable endoclips. Furthermore, various types of distal attachments, including a tapered type, can be used in the clip-flap method.

The endoscopists may apply the clip-flap method or change the endoknife or distal attachment according to the situation, when inserting the distal attachment under the exfoliated mucosa is difficult.

Submucosal dissection

Following mucosal flap formation, adequate visualization of the submucosal layer to be dissected is ensured by lifting the mucosal flap with the distal attachment. Many vessels are present in the submucosal layer. Bleeding worsens the translucency of submucosal layer and makes dissection of the submucosal layer much more challenging after bleeding. Thick vessels are pre-coagulated with hemostatic forceps using the soft coagulation mode and cut after precoagulation with an endoknife[12]. Fat tissue is occasionally observed in the submucosal layer, and the translucent layer to be dissected is found below submucosal fat tissue. The deep submucosal layer should be dissected to determine the presence or absence of massive malignant submucosal invasion[12].

At our institution, submucosal dissection is predominantly performed with the FlushKnife BT using forced or swift coagulation mode. Forced coagulation mode is superior to swift coagulation mode for hemostasis but inferior for incision. Therefore, we initially use forced coagulation mode and change to swift coagulation mode in cases where the submucosal tissue cannot be easily incised with forced coagulation mode because of submergence, fat rich tissue, fibrosis, or burnt tissue. Endocut I mode can also be used for incision of burnt tissue or tissue with severe fibrosis.

Submucosal fibrosis is an important factor that has a large impact on the technical difficulty of dissection[10,27,64-66]. Submucosal fibrosis complicates dissection by losing the translucency of the submucosal layer or narrowing the space between the mucosa and muscle. Furthermore, the presence of submucosal fibrosis is often preoperatively unexpected. Endoscopists must dissect the submucosal layer more carefully in cases of submucosal fibrosis because submucosal fibrosis increases perforation risk. Additional submucosal injection of solution widens the gap between the exfoliated mucosa and muscle layer and enhances the safety of submucosal dissection. A short needle knife with a water-jet function, such as FlushKnife BT, is very useful in these situations because it enables repeated submucosal injection without changing the injection needle[12,51,67,68]. A HookKnife or scissor-type endoknife, which enable the endoscopists to resect the submucosal tissue while pulling up on it, may also be useful in those situations[55].

SUCCESS RATES AND COMPLICATIONS

Single- and multi-center studies of colorectal ESD have reported *en bloc* resection rates of 61%-99.3%, perforation rates of 0%-20.4%, and bleeding rates ranging from 0% to 11.9% (Table 2)[8-10,12,14,29,52,54,56,62,64,65,69-88]. Numerous studies regarding colorectal ESD were reported in Japan where colorectal ESD was initially developed; furthermore, the reports from some other Asian countries and Western countries are continuously increasing. Direct comparison of treatment outcomes is difficult because the technical difficulty of ESD is greatly affected by tumor location, tumor size, the presence of submucosal fibrosis, and endoscope maneuverability. In addition, in some studies, treatment outcomes do not include data of earlier stage of colorectal ESD. However, recent single- and multi-center studies have reported improved treatment outcomes compared with previous studies[6,61,72,86,89]. Nakajima *et al*[86] recently reported a comparatively high *en bloc* resection rate (94.5%) and low perforation rate (2.0%) of colorectal ESD in a Japanese large multi-center prospective study. The development of various devices and improvement of the endoscopist's skill appear to have contributed to recent improvements in treatment outcomes[21,52,55,90,91]. Probst *et al*[62] reported low perforation rate (1.9%) and permissible *en bloc* resection rate (81.6%) of colorectal ESD in a European single-center study. Furthermore, higher *en bloc* resection rate (96.2%) in their late stage was reported compared with that in their early (60.0%) and middle stage (88.0%). These data reveal that colorectal ESD may be widely spread even in European countries where ESD experience is low.

In contrast, some studies have compared the local recurrence rates after EMR and ESD for large colorectal tumors (Table 3)[92-96]. Those studies demonstrated that local recurrence rates after ESD were significantly lower than after EMR because of the high *en bloc* resection rates with ESD despite the larger tumor sizes compared with EMR[92,93,95,96]. Oka *et al*[96] reported that piecemeal resection was the most important risk factor for local recurrence regardless of EMR or ESD in a large multicenter prospective study. Most local recurrences of mucosal lesions may be addressed with additional endoscopic treatment; however, close follow-up colonoscopy is required to detect local recurrence after piecemeal resection[92-96], even with ESD.

Perforation is a major complication of colorectal ESD; however, most cases of perforation can be conservatively treated by closure with endoclips (Figure 6A and B). However, endoscopists should give particular attention to the risks of perforation because open or laparoscopic surgery may be required for bacterial peritonitis, particularly with delayed perforations[77,85,97]. Larger lesional size, submucosal fibrosis, colonic location, and less experienced ESD operators have all been reported as risk factors for perforation during colorectal ESD[10,27,28,77,87].

Table 2 Previous reports of treatment outcomes following colorectal endoscopic submucosal dissection

Ref.	Year	Country	Study design	No. of cases	Tumor size (mm)	*En bloc* resection rate (%)	Complete *en bloc* resection rate (%)	Perforation (%)	Bleeding (%)
Fujishiro *et al*[69]	2007	Japan	S, R	200	29.9	91.5	70.5	6	1
Tamegai *et al*[70]	2007	Japan	S, R	71	32.7	98.6	95.6	1.4	
Hurlstome *et al*[29]	2007	United Kingdom	S, R	42		78.6	73.8	2.4	11.9
Taku *et al*[8]	2007	Japan	M, R	43				14	
Zhou *et al*[9]	2009	China	S, R	74	32.6	93.2	89.2	8.1	1.3
Iizuka *et al*[71]	2009	Japan	S, R	38	39	61	58	8	
Isomoto *et al*[64]	2009	Japan	S, R	292	26.8	90.1	79.8	8.2	0.7
Hotta *et al*[72]	2010	Japan	S, R	120	35	93.3	85	7.5	
Niimi *et al*[73]	2010	Japan	S, R	310	28.9	90.3	74.5	4.8	1.6
Matsumoto *et al*[65]	2010	Japan	S, R	203	32.4		85.7	6.9	
Yoshida *et al*[74]	2010	Japan	S, R	250	29.1	86.8	81.2	6	2.4
Tanaka *et al*[75]	2010	Japan	M, R	8303			83.8	4.8	1.6
Oka *et al*[76]	2010	Japan	M, R	688				3.3	1.7
Saito *et al*[77]	2010	Japan	M, P	1111	35	88		4.9	1.5
Kim *et al*[10]	2011	South Korea	S, R	108	27.6		78.7	20.4	
Shono *et al*[78]	2011	Japan	S, R	137	29.2	89.1	85.4	3.6	
Uraoka *et al*[79]	2011	Japan	S, R	202	39.9	91.6		2.5	0.5
Takeuchi *et al*[80]	2012	Japan	S, R	348	30	91.1		2.3	4.6
Probst *et al*[62]	2012	Germany	S, R	82	45.5	81.6	69.7	1.9	7.9
Toyonaga *et al*[12]	2012	Japan	S, R	1143		99.3		1.4	1.2
Homma *et al*[54]	2012	Japan	M, R	102	32.4	100		1	
Tseng *et al*[81]	2013	Taiwan	S, R	92	37.2	90.2	89.1	12	0
Thorlacius *et al*[82]	2013	Sweden	S, R	29	26	72	69	6.9	3.4
Hülagü *et al*[83]	2013	Turkey	S, R	44	30	77.3		4.5	9.1
Hsu *et al*[84]	2013	Taiwan	S, R	50	33	86	82	6	0
Saito *et al*[52]	2013	Japan	S, R	806	37	90		2.8	1.9
Lee *et al*[85]	2013	South Korea	S, R	1000	24.1	97.5		5.3	0.4
Nakajima *et al*[86]	2013	Japan	M, P	816		94.5		2	2.2
Hori *et al*[87]	2014	Japan	S, P	247	35	93.1	92.3	2	0.4
Bialek *et al*[88]	2014	Poland	S, R	37	37	86.5	81.1	0	5.7
Nawata *et al*[56]	2014	Japan	S, R	150		98.6	91.3	0	0
Yamamoto *et al*[14]	2015	Japan	S, R	119	32.5	97.5	90.8	0.8	1.7

S: Single center; M: Multicenter; R: Retrospective study; P: Prospective study.

Table 3 Comparison of local recurrence rates after endoscopic mucosal resection and endoscopic submucosal dissection for removal of large colorectal tumors from previous single-center or multicenter studies

Ref.	Study design	Recurrence rate after EMR (*En bloc* resection with EMR) (Tumor size with EMR)	Recurrence rate after ESD (*En bloc* resection with ESD) (Tumor size with ESD)	*P* value
Saito *et al*[92]	S, R	14.0%; 33/228	2%; 3/145	$P < 0.0001$
		(33%; 74/228)	(84%; 122/145)	$P < 0.0001$
		(28 ± 8 mm)	(37 ± 14 mm)	$P = 0.0006$
Tajika *et al*[93]	S, R	15.4%; 16/104	1.2%; 1/85	$P = 0.002$
		(48.1%; 50/104)	(83.5%; 71/85)	$P < 0.001$
		(25.5 ± 6.8 mm)	(31.6 ± 9.0 mm)	$P < 0.001$
Terasaki *et al*[94]	S, R	8.0%; 14/176	0%; 0/56	
		(39.3%; 70/178)		
Lee *et al*[95]	S, R	25.7%; 29/113	0.8%; 2/257	$P < 0.001$
		(42.9%; 60/140)	(92.7%; 291/314)	$P < 0.001$
		(21.7 ± 3.5 mm)	(28.9 ± 12.7 mm)	$P < 0.001$
Oka *et al*[96]	M, P	6.8%; 55/808	1.4%; 10/716	$P < 0.01$
		(53.2%; 430/808)	(95.0%; 680/716)	
		(32.8 ± 15.7 mm)	(39.6 ± 18.6 mm)	$P < 0.01$

S: Single center; M: Multicenter; R: Retrospective study; P: Prospective study; ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; Tumor size: Mean ± SD.

Post-operative bleeding is less common with colorectal ESD than with gastric ESD and can conservatively managed with hemostatic forceps or endoscopic clipping in the majority of cases[77,85].

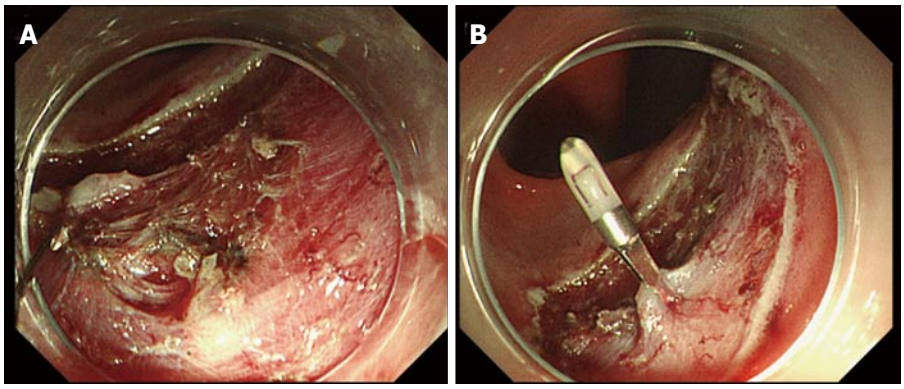

Figure 6 Management of perforation by clipping. A: Perforation occurring during colorectal endoscopic submucosal dissection; B: Perforation closure using an endoclip.

Abdominal pain or fever due to electrocoagulation syndrome after ESD is occasionally observed, particularly in the proximal colon, and when conservatively managed[98]. The occurrence of adverse events may cause an extension in hospital stay[31,32,98].

CURRENT STATUS AND FUTURE PERSPECTIVES

The safety and success rates of colorectal ESD have recently improved to favorable levels predominantly in advanced institutions in Japan, some Asian, and a few Western countries. However, colorectal ESD is still a technically difficult procedure for majority of endoscopists, and development of training systems is required for world-wide adoption of colorectal ESD[99,100]. ESD for rectal and smaller lesions, which is less technically difficult, is suitable for initial adoption of colorectal ESD. Substantial experience of gastric ESD, which is less technically challenging than colorectal ESD, is highly useful for performing colorectal ESD; however, it is difficult in Western countries because of the low morbidity rate of gastric cancer. EMR with circumferential mucosal incision may be option in cases where ESD cannot be successfully performed[101]. Before performing colorectal ESD, ESD training using animal models or observing the performance of procedure by ESD experts at other institutions have been shown to be extremely useful in improving operator skill[102-104].

In contrast, some cases are challenging even for experts in colorectal ESD, particularly because of the poor endoscope maneuverability or poor visualization of the operative field due to colonic flexure. Colonic flexure and extensibility commonly causes paradoxical movement of the endoscope. Therefore, double- or single-balloon endoscopy systems have recently been introduced for colorectal ESD at several institutions[44-46] because these endoscopy systems enable the endoscope to be straightened more easily than conventional endoscopy. Ohya *et al*[44] reported that a short-type single-balloon overtube through which a thin conventional endoscope can be introduced was useful for colorectal ESD, particularly for poor endoscope maneuverability in the proximal colon.

Sinker-assisted ESD[105], magnet anchor-guided ESD[106], clip with line-assisted ESD[107,108], clip with rubber- or spring-assisted ESD[109,110], clip-band ESD[111], a double-channel scope method[112,113], and a double endoscopic intraluminal procedure[114,115] have all been described as traction systems that facilitate ESD. Each system has a unique traction system that utilizes specialized equipment to provide counter-traction[107]. Because these traction systems are somewhat complicated or commercially unavailable, they are not widely used in colorectal ESD at present. The improvement of these traction systems or development of new tractions systems or devices[116] may facilitate improvements in the safety or efficacy of colorectal ESD in the future.

CONCLUSION

In this review, we have described the technical aspects and recent progresses in colorectal ESD. Maintaining good visualization of the operative field is the most important for safely and successfully performing colorectal ESD. Developments of various devices, novel procedures, and appropriate strategies have resulted in the recent improvement of the treatment outcome in colorectal ESD. Further development of training systems or devices will promote world-wide standardization of colorectal ESD.

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Peroral endoscopic myotomy: An emerging minimally invasive procedure for achalasia

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Abstract

Peroral endoscopic myotomy (POEM) is an emerging minimally invasive procedure for the treatment of achalasia. Due to the improvements in endoscopic technology and techniques, this procedure allows for submucosal tunneling to safely endoscopically create a myotomy across the hypertensive lower esophageal sphincter. In the hands of skilled operators and experienced centers, the most common complications of this procedure are related to insufflation and accumulation of gas in the chest and abdominal cavities with relatively low risks of devastating complications such as perforation or delayed bleeding. Several centers worldwide have demonstrated the feasibility of this procedure in not only early achalasia but also other indications such as redo myotomy, sigmoid esophagus and spastic esophagus. Short-term outcomes have showed great clinical efficacy comparable to laparoscopic Heller myotomy (LHM). Concerns related to postoperative gastroesophageal reflux remain, however several groups have demonstrated comparable clinical and objective measures of reflux to LHM. Although long-term outcomes are necessary to better understand durability of the procedure, POEM appears to be a promising new procedure.

Key words: Endoscopy; Achalasia; Peroral endoscopic myotomy; Myotomy

Core tip: With recent advancements in endoscopic techniques and technology, peroral endoscopic myotomy, also known as peroral endoscopic myotomy (POEM), has emerged as a promising minimally invasive procedure for treating achalasia. POEM uses the technique of endoscopic submucosal dissection to create a myotomy and palliate symptoms of achalasia. Although long-term outcomes are still needed, short-term outcomes show good safety and efficacy of the procedure that are comparable to laparoscopic Heller myotomy. In this review we will review the technical details of the procedure itself as well as the reported outcomes.

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INTRODUCTION

Achalasia is a rare motility disorder of the esophagus that is characterized by non-relaxation of the lower esophageal sphincter (LES) and aperistalsis of the esophagus. No cure exists for this idiopathic disease and thus treatment is aimed at palliation of the esophagus to allow for adequate emptying of the esophagus and improvement of symptoms. Palliation requires disruption of the LES, which has been traditionally accomplished by botulinum toxin injection, balloon dilation or surgical myotomy. Endoscopic botulinum toxin treatment is not often the therapy of choice in these patients, due to the short-term therapeutic effect in this chronic disease. Pneumatic balloon dilation forcefully disrupts the sphincter fibers and although several groups have demonstrated efficacy with this technique, dilation is still associated with a significant risk of perforation[1]. Surgical myotomy has been conventionally performed laparoscopically by dividing the LES above and below, known as a laparoscopic Heller myotomy (LHM) and typically performed with concurrent anti-reflux procedure. Reports of long-term outcomes have shown the superior efficacy of LHM and thus are often the therapy of choice in many of these patients. However with the advances in technology and endoscopic techniques, this concept of a surgical myotomy has lead to the development of an endoscopic approach, peroral endoscopic myotomy (POEM).

HISTORY AND DEVELOPMENT OF POEM

The use of endoscopic treatment for achalasia was first reported in a case series in 1980 by Ortega *et al*[2]. In this series of 17 patients, an endoscopic myotomy was performed using a modified needle knife to directly dissect through the mucosa into the muscular layer to perform a myotomy. Although showing good outcomes, at the time the technique was thought to be unsafe because a direct mucosal approach not only resulted in poor visualization of the muscular layer, but also could result in mediastinal contamination from luminal content. Additionally with limited available devices, the use of the needle knife did not allow for precise and controlled movement, which could potentially lead to high risks of perforation as well as injury to nearby structures. Although abandoned at that time, several decades later the evolution of natural orifice transluminal endoscopic surgery (NOTES) allowed for improvements in endoscopic techniques and technology that subsequently lead to the development of what we now know of as POEM.

As the growth of NOTES procedures continued, submucosal endoscopy developed as a method to not only work below the mucosa to remove mucosal disease, but also to safely enter sterile cavities by creating a mucosal flap to minimize contamination[3,4]. In 2007 using a pig mode, Parischa *et al*[5] reported submucosal tunneling with a balloon dilator to create a mucosal flap and a distal esophageal myotomy effectively reducing LES pressure. This addressed the first problem of direct dissection through the mucosa and risk of mediastinal contamination, but the use of the balloon dilator has limitations, due to the inability to accurately position within the wall as well as the associated risks of injury. However in 2010, Inoue *et al*[6] reported a modified technique and presented the first case series of successfully performed POEM in humans. The two important alterations included: (1) the use of electrosurgery for the endoscopic submucosal dissection rather than a balloon dilator, which is described below; and (2) the use of a triangle-tip knife for muscle dissection, which allowed for precise dissection under direct visualization. Variations of this technique are now performed by specialized centers worldwide for the treatment of achalasia.

OPERATIVE TECHNIQUE

Under general anesthesia patients are positioned supine. POEM places these patients at high risk for subcutaneous emphysema and accumulation of gas in the body cavities thus CO_2 should be used for insufflation and if possible positive pressure ventilation should be maintained at pressures higher than that of endoscopic insufflation to reduce the risk of these complications. Initial evaluation of the esophagus and stomach with a high-definition standard upper endoscope is performed to identify the gastroesophageal junction (GEJ). Once the GEJ is identified, an overtube is placed over the endoscope and dissecting cap placed on the endoscope. Approximately 10-15 cm proximal to the GEJ, the mucosa is injected with a mixture of methylene blue, saline, and epinephrine to create a mucosal bleb. Most groups perform this on the anterior aspect of the esophagus, however there may be variation to this positioning. If the patient is presenting for redo myotomy, the operator should typically perform the procedure on the right lateral aspect of the esophagus to avoid the previous myotomy site. The mucosotomy is then made to enter the submucosal space.

The submucosal tunnel is created from the mucosotomy along the lesser curvature to 2-3 cm distal to the GEJ where blanching is identified on the stomach side. The method to dissect this space is based on operator preference. The use of electrosurgery allows for a controlled dissection, with the use of either a triangular-tip knife (Olympus, Center Valey, PA, United States) or a T-type hybrid knife (ERBE, Tubingen, Germany). The alternative option is balloon dilation to develop

Table 1 Complications after peroral endoscopic myotomy

Complication	Treatment
Mucosal injury	After completion of myotomy, mucosal defects should be closed to minimize risk of leak with clips or suturing device
Full thickness injury	Although certain centers have demonstrated safety with full thickness myotomy, if occurs at site of mucosectomy the operator must consider closure of this myotomy site to prevent potential leakage
Gas escape related complications	
Subcutaneous emphysema	Observation
Pneumomediastinum	Observation, unless physiologic symptoms
Pneumothorax	Small volume closely observed with oxygen only. Volume > 30% may require decompression
Pneumoperitoneum	Large volume or physiologic symptoms requires decompression of the abdomen with Veress needle insertion
Pleural effusion	Small volume can be observed and will absorb. Larger volumes with symptoms require drainage
Bleeding	Most common at the GEJ or distal on stomach side due to increased vascularity. Supportive care and transfusions, endoscopic re-exploration if warranted for hemostasis
Leak/mediastinitis	Depending on time of presentation and extent of perforation will determine the interventions required, which may be as simple as endoscopic treatment or as severe as invasive surgical treatment

GEJ: Gastroesophageal junction.

the plane, however this is a less controlled method, as previously discussed.

The myotomy is started 2-3 cm distal to the mucosotomy and continued to the end of the tunnel at 2-3 cm distal to the GEJ. A partial myotomy is most commonly performed by careful dissection of the circular fibers only, avoiding the longitudinal fibers to avoid entry into the mediastinum. However several groups have explored the option of a complete myotomy through the longitudinal fibers as well[7,8]. The mucosotomy is then closed to avoid leak with the use of endoscopic clips or an endoscopic suturing device. After completion of the procedure, the scope should easily traverse the GEJ. The scope can be then removed and patient extubated and recovered.

COMPLICATIONS AND ADVERSE EVENTS

This invasive endoscopic procedure is not without risks and should only be performed at centers that are capable of treating these complications. Additionally POEM requires operators with specific surgical and endoscopic skills as well as a good understanding of esophageal motility disorders and the available interventions. All standard operative procedures should be followed, including appropriate preoperative evaluation and risk stratification of the patient. The most common complications encountered during or after POEM are listed in Table 1.

Inadvertent mucosotomy is a relatively common complication, especially early in the operators experience, due to the challenges in technique of submucosal tunneling. Although the clinical implications of mucosal injuries are unclear, most centers would recommend closing any defects prior to completion of the procedure to avoid any potential leaks. This is similar to full-thickness muscular injuries that in particular occur at the site of the initial mucosotomy.

Complications related to the insufflation are fairly common. These complications can be minimized by the use of CO_2 rather than room air, due to the quick diffusion of CO_2, and by also maintaining low insufflation pressures if possible. The subsequent complications due to insufflation are listed in Table 1 and in most cases have minimal clinical sequelae. However depending on the degree of gas accumulation in these cavities, the patient may require decompression as described in Table 1. All operators performing POEM should be aware of these risks and capable of treating them.

Similarly pleural effusions may commonly occur and depending on the degree of fluid accumulation and patient symptoms, may or may not require intervention. Delayed bleeding appears to be a rare complication of POEM (0.8%-2.7%)[9,10], but if diagnosed must be promptly intervened on. Lastly the most feared complication, esophageal leak with reported rates from 0% to 5.6%[7,11,12], can be a devastating complication if occurs. If the patient is slow to recover there should be high suspicion for gastrointestinal leak and appropriate work up with either endoscopy or imaging. The time to diagnosis of the leak in addition to the extent of the leak will largely determine the required interventions.

SHORT TERM OUTCOMES

Most centers perform this new procedure under institutional review board oversight as suggested by the NOSCAR POEM White Paper Committee[13] and thus several groups have published their initial outcomes. These preliminary results demonstrate highly skilled endoscopists can safely perform the procedure and short-term data suggests promising efficacy. Table 2 summarizes the reported outcomes seen by the experienced centers around the world.

Most centers evaluate efficacy based on symptomatic relief as measured by the Eckardt score and measure clinical success as Eckardt score $\leqslant$ 3. All of the centers described in Table 2 demonstrated significant improvement in Eckardt scores after POEM. At mean follow up from 1.5 to 12 mo, 89%-100% of patients

Table 2 Reported outcomes for Large Volume Single Centers after peroral endoscopic myotomy

Ref.	Study size	Myotomy thicknes/length	Morbidity	Follow up (mo)	Clinical outcome - before/after	Manometry before/after	Postop PPI
Inoue *et al*[14] 2013	300	Partial 14.1 cm	Pneumothorax 0.3% Mucosal Injury - 2.0%	12	Eckardt - 6.13/1.33 98.2% success	27.3/13.4	4.9%
Ren *et al*[10] 2012	119	Partial 9.2 cm	Pneumothorax - 25.2% Pneumoperitoneum - 39.5% Bleeding 0.8%	3	98.3% success	NA	NA
Friedel *et al*[15] 2013	45	Full 9 cm	Mucosal Injury - 20% Pneumoperitoneum - 13%	3	Eckardt - 7.8/0.4 95% success	NA	NA
Bhayani *et al*[9] 2014	37	Partial	Perforation - 10.8% Bleeding - 2.7%	6.8	Eckardt - 5.4/1.2 Dysphagia - 0%	41/16	NA
Vigneswaran *et al*[17] 2014	37	Partial 12.8 cm	Perforation - 5.4% Mucosal Injury - 2.7%	11.3	Eckardt - 6.8/0.6 100% success	29.1/NA	22%
Hungness *et al*[12] 2013	18	Partial 9 cm	Perforation - 5.6%	6	Eckardt - 7/1 89% success	19/9	NA
von Renteln *et al*[7] 2012	16	Partial and full 12 cm	Perforation - 0% Pneumoperitoneum - 50%	3	Eckardt - 8.8/1.4 94% success	27.2/11.8	6.3%

NA: Not available; PPI: Proton pump inhibitor.

received clinical success from POEM treatment[7,9-12,14,15]. Several centers also routinely use manometry postoperatively to evaluate the diagnostic outcomes after POEM, which revealed significant improvement in LES resting pressures[9,12,14]. When compared to patients undergoing a standard LHM, patients undergoing POEM had similar symptomatic relief and manometry findings[9,11,12,16]. Additionally quality of life improvements after POEM seem to be comparable to reported outcomes after LHM[17]. All of these results are promising, but only provide short-term results. Further observation is required to determine the durability of POEM outcomes at long-term follow up.

In addition to the durability, postoperative reflux after POEM has and continues to be a concern with the long-term outcomes. LHM, the gold standard for treatment of achalasia, has a reported occurrence of gastroesophageal reflux (GERD) anywhere from 20% to 100% after surgical myotomy without fundoplication[18,19]. This iatrogenic reflux due to the extensive disruption of the LES has lead to routine performance of an anti-reflux procedure in concurrence with the Heller myotomy. Thus without an anti-reflux procedure, GERD after POEM is an important endpoint for efficacy. Objective measures of GERD after POEM such as erosive esophagitis have been found at rates of 6%-40%[6,7,12,20] and abnormal pH studies at rates of 20%-40%[9,21]. Clinically, 4.9%-33%[6,7,12,20] of these patients have reflux symptoms and 4.9%-22% of patients appear to be restarted on proton pump inhibitor therapy after POEM[7,14,17]. However, all of these objective and clinical findings appear to be equivalent to LHM with fundoplication in several series[9,11,12,22]. The leading theory for possible comparable reflux outcomes is related to the maintained hiatal anatomy after POEM. With an endoscopic approach to the myotomy, the opportunity to preserve the longitudinal muscle fibers as well as not disrupting the GEJ innervation or the diaphragm and the phrenoesophageal ligament, may in fact be enough to avoid significantly worse GERD. However these reported outcomes of GERD are fairly short-term results and are difficult to compare to LHM outcomes because of the highly variable reported outcomes of reflux after LHM with fundoplication in the literature itself.

SPECIAL PATIENT COHORTS

Certain special patient cohorts have been studied as possible indications for POEM. These include patients with a previous failed Heller myotomy or POEM, sigmoid type achalasia, spastic esophagus and the pediatric patient. Due to the rarity of these cases, outcomes are not well understood but initial reports discussed below are encouraging.

Redo myotomy

Patents with failed LHM are difficult to treat. Traditionally patients who fail myotomy can be candidates for additional interventions including repeat Heller myotomy and as a last resort esophagectomy. However due to scarring and adhesive disease that develops around the GEJ from the initial operation, these redo cases can be quite challenging. Moreover, although repeat Heller myotomy is often successful, 20%-30% of patients will undergo this relatively risky procedure and still fail after second Heller myotomy[23,24]. Thus, POEM provides a unique opportunity to potentially treat these patients without enduring a challenging and involved operation. Several centers including our own have reported the use of POEM to treat patients with failed Heller myotomy. Initial outcomes show the procedure is safe and at short-term follow-up has 90%-100% success[25-27]. Even with previous fundoplication, the procedure is performed in these patients almost identical to patients without previous myotomy with exception of the location of the second myotomy. The recommendation is to avoid the previous myotomy that is conventionally performed anterior and to perform the repeat myotomy right lateral on the esophagus. Similar outcomes have been observed in those patients with previous POEM

presenting for redo POEM[28].

Sigmoid esophagus

Sigmoid-shaped esophagus is often seen in advanced achalasia cases and can be a complicated disease to treat. Although initial approaches to treatment are debatable, most would advocate for treating these patients with myotomy before discussing esophagectomy[29-32]. The use of POEM in these advanced staged patients has been reported with good feasibility and short-term success[6,33]. However, due to the anatomical changes in the esophagus these cases are particularly challenging, especially when developing the submucosal space, and should only be performed by highly experienced operators.

Spastic esophagus

Spastic disorders of the esophagus are characterized by abnormal contractility of the esophagus and can be divided into spastic achalasia, diffuse esophageal spasm, and hypercontractile or jackhammer esophagus. These motility disorders are difficult to treat and often long-term clinical success is only accomplished with surgical myotomy[34]. Treating these patients with POEM is safe and at initial short term follow up is efficatious[35,36]. In a recent multicenter study which included 73 patients with spastic esophagus, when an extended myotomy was performed with POEM, 93% clinical success was observed at an average of 8 mo[37]. However as with POEM in the typical achalasia patient, longer term studies are necessary to understand the durability of these treatments.

Pediatric patients

Though rare, achalasia presenting in pediatrics patients can lead to significant problems with malnutrition and subsequently mental and physical development. These patients are not good candidates for endoscopic therapies due to short term durability with the growing child and the gold standard of treatment is surgical myotomy. Chen *et al*[38] demonstrated POEM can be safely performed for pediatric patients and in 27 patients showed 100% clinical success at an average of 25 mo and thus can be considered in a pediatric patient.

CONCLUSION

POEM is an emerging new technique for treating achalasia that evolved from the era of NOTES. POEM may also expand the therapeutic options for patients with challenging esophageal disease due to the growing indications, including patients with previous myotomy, sigmoid esophagus and spastic esophagus. Short-term results from experienced centers allow for cautious optimism with this minimally invasive technique, however questions remain as to long-term durability and subsequent GERD. Patients offered POEM should be counseled about our limited knowledge of long-term outcomes as well as the potential risk of GERD. Continued observation of long-term outcomes will be necessary as we continue to understand this procedure.

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Endoscopic retrograde cholangiopancreatography-related perforations: Diagnosis and management

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) has become an important therapeutic modality for biliary and pancreatic disorders. Perforation is one of the most feared complications of ERCP and endoscopic sphincterotomy. A MEDLINE search was performed from 2000-2014 using the keywords "perforation", "ERCP" and "endoscopic sphincterotomy". All articles including more than nine cases were reviewed. The incidence of ERCP-related perforations was low (0.39%, 95%CI: 0.34-0.69) with an associated mortality of 7.8% (95%CI: 3.80-13.07). Endoscopic sphincterotomy was responsible for 41% of perforations, insertion and manipulations of the endoscope for 26%, guidewires for 15%, dilation of strictures for 3%, other instruments for 4%, stent insertion or migration for 2% and in 7% of cases the etiology was unknown. The diagnosis was made during ERCP in 73% of cases. The mechanism, site and extent of injury, suggested by clinical and radiographic findings, should guide towards operative or non-operative management. In type I perforations early surgical repair is indicated, unless endoscopic closure can be achieved. Patients with type II perforations should be treated initially non-operatively. Non-operative treatment includes biliary stenting, fasting, intravenous fluid resuscitation, nasogastric drainage, broad spectrum antibiotics, percutaneous drainage of fluid collections. Non-operative treatment was successful in 79% of patients with type II injuries, with an overall mortality of 9.4%. Non-operative treatment was sufficient in all patients with type III injuries. Surgical technique depends on timing, site and size of defect and clinical condition of the patient. In conclusion, diagnosis is based on clinical suspicion and clinical and radiographic findings. Whilst surgery is usually indicated in patients with type I injuries, patients with type II or III injuries should be treated initially non-operatively. A minority of them will finally require surgical intervention.

Key words: Endoscopic retrograde cholangiopancreatography; Endoscopic sphincterotomy; Perforation

Core tip: Perforation is one of the most feared complications of endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy. The

incidence of ERCP-related perforations is low (0.39%) with an associated mortality of 7.8%. Endoscopic sphincterotomy is responsible for 41% of perforations and endoscope manipulations for 26%. The mechanism, site and extent of injury, suggested by clinical and radiographic findings, should guide towards operative or non-operative management. Classification into types permits a tailored approach to management. Whilst surgery is usually indicated in patients with type Ⅰ injuries, patients with type Ⅱ or Ⅲ injuries should be treated initially non-operatively. A minority of them will finally require surgical intervention.

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INTRODUCTION

In the era of minimally invasive therapy, endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy has become an important therapeutic modality for the treatment of biliary and pancreatic disorders. Although considered as a safe procedure, it is associated with complications such as pancreatitis, bleeding and perforation. The incidence of ERCP-related complications is 5%-10% and the overall mortality 0.1%-1%[1-5].

Perforation is one of the most feared complications of ERCP and sphincterotomy. In a review of 21 prospective studies[6], addressing ERCP complications, between 1987-2003, perforations occurred in 101 patients (0.6%, 95%CI: 0.48-0.72) with a perforation related mortality of 9.90% (95%CI: 3.96-15.84).

Traditionally, the standard treatment for iatrogenic duodenal perforations has been early surgical repair. Recently, non operative management of ERCP-related perforations has increased. However, it is difficult to evaluate the efficacy of different treatments, because of the rarity of the complication and there is no consensus for optimal management.

This review aims to evaluate the incidence, diagnosis and treatment of ERCP-related perforations.

RESEARCH

A MEDLINE search was performed from 2000-2014 using the keywords "perforation", "ERCP" and "endoscopic sphincterotomy". All articles including more than nine cases were reviewed. No randomized controlled trial could be identified.

CLASSIFICATION

There are two proposed classifications of ERCP-related perforations. In 1999, Howard *et al*[7] classified perforations into three distinct types: type I, guidewire perforation; type Ⅱ, periampullary perforation; type Ⅲ, duodenal perforation remote from the papilla. In 2000 Stapfer *et al*[8] classified ERCP-related perforations into four types, based on the mechanism, anatomical location and severity of injury, which may predict the need for surgery. The Stapfer classification is the most commonly used and it divides perforations into: Type Ⅰ, lateral or medial wall duodenal perforation; type Ⅱ, perivaterian injuries; type Ⅲ, distal bile duct injuries related to guidewire-basket instrumentation and type Ⅳ, retroperitoneal air alone. Type Ⅳ is questionable and it is not a true perforation. Due to the excess compression of air in the duodenum, air bubbles can leak through the sphincterotomy area outside the duodenal lumen, into the retroperitoneal space. The presence of retroperitoneal air is a common finding after endoscopic sphincterotomy. CT scan, when used routinely after ERCP and sphincterotomy, may detect retroperitoneal air in 13% to 29% of patients[9,10]. In the absence of symptoms, it has no clinical significance and these patients do not require any further intervention.

INCIDENCE AND RISK FACTORS

Reviewing 18 studies[8,11-27], between 2000-2014 (mainly retrospective), addressing only ERCP-related perforations, including 142847 patients, the incidence was 0.39% (95%CI: 0.34-0.69). According to Stapfer classification, type Ⅰ counted 25%, type Ⅱ 46% and type Ⅲ 22%. The overall mortality was 7.8% (95%CI: 3.80-13.07) (Table 1).

A multivariate analysis to reveal risk factors was performed in two studies[4,14]. Precut, Billroth Ⅱ gastrectomy and intramural injection of contrast medium were significant risk factors for retroperitoneal duodenal perforation by Loperfido *et al*[4]. In Enns *et al*[14]'s study, factors existing prior to ERCP which predicted perforation included sphincter of Oddi dysfunction and a dilated common bile duct. Predictive factors related to ERCP itself included duration of procedure, biliary stricture dilation and performance of a sphincterotomy. Precut didn't reach statistical significance in that study.

ETIOLOGY

The mechanism of injury is mentioned in 573 patients from 18 studies[8,11-15,17-23,25-29] (Table 2). Endoscopic sphincterotomy was responsible for 41% of perforations, insertion and manipulations of the endoscope for 26%, guidewires for 15%, dilation of strictures for 3%, other instruments for 4%, stent insertion or migration for 2% and in 7% of cases the etiology was unknown.

DIAGNOSIS

Early diagnosis and prompt treatment during the endoscopic procedure are vital for a better outcome[7,30].

Table 1 Incidence of perforations and overall mortality

Ref.	Design	*n*	Perforations (%)		Types[1]				Mortality (%)	
					I	II	III	IV		
Assalia *et al*[11], 2007	Prosp	3104	22	(0.70)	2	17	2		1	(4.5)
Avgerinos *et al*[12], 2009	Retro	4358	15	(0.34)	9	3		1	3	(20)
Dubecz *et al*[13], 2012	Retro	12232	11	(0.08)	7	3	1		2	(18)
Enns *et al*[14], 2002	Case control	9314	33	(0.35)	5	13	15		1	(3)
Fatima *et al*[15], 2007	Retro	12427	75	(0.60)	8	26	35	6	5	(6.6)
Jin *et al*[16], 2013	Retro	22998	59	(0.26)	17	36	6		5	(8.4)
Kayhan *et al*[17], 2004	Retro	3124	17	(0.54)	2	15			-	-
Kim *et al*[18], 2011	Retro	7638	13	(0.17)	4	5	4		0	(0)
Kim *et al*[19], 2012	Retro	11048	68	(0.61)	13	31	22		4	(5.8)
Knudson *et al*[20], 2008	Retro	4919	32	(0.65)	6	11	7		0	(0)
Kwon *et al*[21], 2012	Retro	8381	53	(0.63)	21	24	8		3	(5.6)
Li *et al*[22], 2012	Retro	8504	16	(0.45)	7	5	4		0	(0)
Mao *et al*[23], 2008	Retro	2432	9	(0.37)	8	1			0	(0)
Miller *et al*[24], 2013	Retro	1638	27	(1.60)	5	12	5	5	9	(33)
Morgan *et al*[25], 2009	Retro	12817	24	(0.18)	12	12			1	(4.1)
Polydorou *et al*[26], 2011	Retro	9880	44	(0.44)	7	30	5	2	2	(4.5)
Stapfer *et al*[8], 2000	Retro	1413	14	(0.99)	5	6	3		2	(14)
Wu *et al*[27], 2006	Retro	6620	30	(0.45)	5	11	7		5	(16)
Total		142847	562	(0.39)	143 (25%)	261 (46%)	124 (22%)		43/545	(7.8)

[1]Classification of types is assumed, because not all studies clearly defined the type of perforation according to Stapfer classification[8].

Table 2 Assumed etiology of perforations

Ref.	Endo scope	ES	Guide wire	Dilation of strictures	Other instruments	Stent insertion or migration	Unknown
Alfieri *et al*[28], 2013	6	15	1				8
Assalia *et al*[11], 2007	2	17	2			1	
Avgerinos *et al*[12], 2009	9	3					3
Dubecz *et al*[13], 2012	7	3	1				
Enns *et al*[14], 2002	5	13	13	2			
Fatima *et al*[15], 2007	8	11	24	5	9	7	11
Krishna *et al*[29], 2011	11	1	2				
Kayhan *et al*[17], 2004	2	15					
Kim *et al*[18], 2011	4	3	4		2		
Kim *et al*[19], 2012	13	25	23		2		5
Knudson *et al*[20], 2008	6	11			4	3	8
Kwon *et al*[21], 2012	21	24	2	6			
Mao *et al*[23], 2008	-	8			1		
Li *et al*[22], 2012	7	5			4		
Morgan *et al*[25], 2009	12	12					
Polydorou *et al*[26], 2011	7	30	2	2	3		
Stapfer *et al*[8], 2000	5	6	3				
Wu *et al*[27], 2006	5	11	7				7
Total (%)	130 (25)	213 (41)	84 (16)	15 (3)	25 (5)	11 (2)	42 (8)

ES: Endoscopic sphincterotomy.

ERCP-related perforations can usually been diagnosed during ERCP, from the endoscopic view or using fluoroscopy. In a review of 437 cases from 15 studies[8,12-15,17-24,26,27] the diagnosis was made during ERCP in 73% of cases (Table 3). The definition of delayed diagnosis was inconsistent between studies, but it was considered to be associated with worst prognosis[11,16,22]. Type Ⅰ perforations can be diagnosed from direct visualization of the retroperitoneal space (Figure 1) or the abdominal cavity. In doubtful cases with bleeding and not clear endoscopic view, the use of fluoroscopy with or without contrast injection can confirm the diagnosis. Type Ⅱ perforations can be suspected after a large or wrong direction sphincterotomy and can be confirmed by fluoroscopy. Fluoroscopy will reveal the presence of retroperitoneal air, especially around the right kidney with delineation of kidney margin (Figure 2) and occasionally the outlining of psoas muscle. The injection of contrast can also show leaking from the sphincterotomy site. Type Ⅲ perforations can be diagnosed by the unusual passage of the guide wire or by the injection of contrast.

At the end of every endoscopic procedure, thorough control for any possible perforation should be performed.

Table 3 Time to diagnosis of endoscopic retrograde cholangiopancreatography related perforations

Ref.	During ERCP (%)	After ERCP
Avgerinos *et al*[12], 2009	4 (26)	11
Dubecz *et al*[13], 2012	5 (45)	6
Enns *et al*[14], 2002	28 (84)	5
Fatima *et al*[15], 2007	45 (60)	30
Kayhan *et al*[17], 2004	17 (100)	0
Kim *et al*[18], 2011	10 (77)	3
Kim *et al*[19], 2012	46 (95)	2
Knudson *et al*[20], 2008	11 (34)	21
Kwon *et al*[21], 2012	39 (73)	14
Li *et al*[22], 2012	16 (100)	0
Mao *et al*[23], 2008	8 (88)	1
Miller *et al*[24], 2013	18 (66)	9
Polydorou *et al*[26], 2011	42 (95)	2
Stapfer *et al*[8], 2000	13 (93)	1
Wu *et al*[27], 2006	19 (63)	11
Total	321(73)	116

ERCP: Endoscopic retrograde cholangiopancreatography.

Table 4 Comparison of different types of stents used for type II, III perforations

	Technical success	Biliary drainage	Covering the perforation	Repeat ERCP for removal	Cost
SEMS	+++	+++	+++	Y	+++
Plastic biliary stents	+++	++	+	Y	+
Nasobiliary drain	+++	+	_	N	+

SEMS: Covered self expanding metallic biliary stents; Y: Yes; N: No; ERCP: Endoscopic retrograde cholangiopancreatography.

The endoscopist should inspect the circumference of the duodenum carefully and check the X-ray for the presence of retroperitoneal air. This concern is especially true when the procedure is technically difficult; needle-knife precut has been performed; there are variations in the usual anatomy due to previous operative interventions; strictures are dilated. If there is high suspicion contrast medium can be infused through the endoscope to facilitate identification of the injury.

Patients with undetected leaks can present hours after the ERCP with pain, fever and leukocytosis. In cases of intraperitoneal type I perforations, the diagnosis is usually obvious with severe pain and signs of peritonitis. When a patient experiences severe pain after ERCP, a differential diagnosis between acute pancreatitis and perforation should be made. In cases of retroperitoneal perforations the diagnosis is not so obvious. The patient may complain of mild epigastric pain but signs of peritonitis may develop after several hours or may not develop at all, depending on the size of the leak. The presence of subcutaneous emphysema may be evident from the first hours, especially at right abdominal wall, back or even cervix. Tachycardia is a constant finding, but it can be caused by other factors including pain. Leukocytosis and fever are often seen

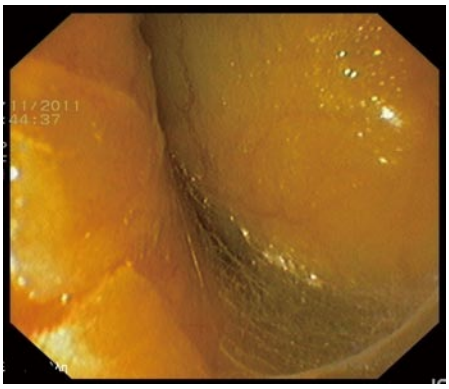

Figure 1 Endoscopic view of the retroperitoneal space after an endoscope-related perforation.

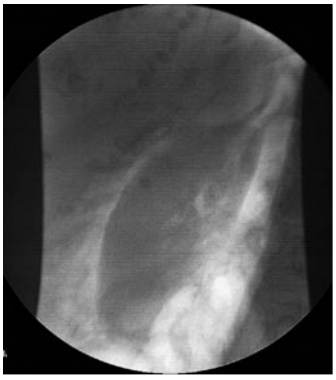

Figure 2 Retroperitoneal air delineating kidney margin after a sphincterotomy-related perforation.

12 h or more after completion of the procedure. A mild elevation of serum amylase levels is caused from the absorption of pancreatic fluid from the retroperitoneal space.

In cases with suspicion of perforation, a CT scan with oral contrast should be obtained. The presence of retroperitoneal air can also be detected by plain films, but CT scan is more sensitive[10,31], it may demonstrate the leak and the presence of fluid collections.

TREATMENT

After the recognition of an ERCP-related perforation, the first dilemma is conservative treatment or surgery. That depends on the mechanism of injury, site and degree of leak and patient condition[28,32]. Endoscope related perforations (type I) should be referred for immediate surgery, unless endoscopic closure can be achieved. Endoscopic closure using fibrin glue, endoloops and endoclips or an over the scope clipping device has been described[33-36].

In cases of endoscopic sphincterotomy related perforations (type II), when diagnosed during the procedure, biliary drainage is essential in order to prevent leakage of bile into the perforation site. In Enns study[14], 5/13 patients with type II injuries were managed successfully either with plastic biliary stents

Table 5 Outcome after initial non-surgical management of type II and III perforations

Ref.	Type II				Type III		
	n	Surgery (%)	Mortality (%)		*n*	Surgery (%)	Mortality (%)
			After surgery	Overall			
Assalia *et al*[11], 2007	17	2 (11)	1 (50)	1 (6)	2	0	0
Enns *et al*[14], 2002	13	2 (15)	0	0	15	0	0
Kim *et al*[18], 2011	3	1 (33)	0	0	4	0	0
Kwon *et al*[21], 2012	24	0	0	1 (4)	7	0	0
Li *et al*[22], 2012	5	0		0	4	0	0
Mao *et al*[23], 2008	8	3 (37)	0	0	1	0	0
Miller *et al*[24], 2013	9	7 (77)	5 (71)	6 (66)	5	0	0
Morgan *et al*[25], 2009	12	0		0			
Polydorou *et al*[26], 2011	30	6 (20)	0	0	5	0	0
Stapfer *et al*[8], 2000	5	3 (60)	1 (33)	1 (20)	3	0	0
Wu *et al*[27], 2006	11	5 (45)	4 (80)	4 (36)	7	0	0
Total	137	29 (21)	11 (38)	13 (9.4)	53	0	0

or percutaneous transhepatic biliary drainage. In Alfieri *et al*[28]'s study, 12/30 patients with early diagnosis were successfully treated conservatively with nasobiliary drainage.

Several case series have reported the use of fully covered self expandable metallic stents (SEMS) in sphincterotomy related perforations. SEMS have the advantage of covering the laceration and permit free flow of bile into the duodenum instead of into the retroperitoneal space. It seems better to use a covered SEMS because plastic stents or nasobiliary drains may not prevent bile flow into the perforation site completely. SEMS can also be used later with a repeat ERCP when the leak persists[37-40]. The advantages and disadvantages of different types of stents are shown in Table 4.

When a sphincterotomy related perforation is diagnosed after the procedure it should be assessed by a CT scan with contrast orally to demonstrate the degree of leak. Major contrast leak is an indication for immediate surgery, whilst minimal or no leak can be treated non-operatively[30,32]. Non-operative treatment includes nil by mouth, nasogastric tube, intravenous fluid resuscitation, broad spectrum antibiotics, repeat endoscopy for stenting in selected cases, and radiologic interventions for percutaneous drainage of fluid collections. Total parenteral nutrition is recommended in undernourished patients or when adequate enteral feeding will be impeded for at least seven days[41]. Generally, indications for surgery are: Major contrast leak; sepsis despite non-surgical treatment; presence of peritonitis or retroperitoneal fluid collections not amenable to percutaneous drainage; unsolved problems like stones or retained hardware (baskets)[28,30,32,41]. The clinical condition of the patient should be the key factor determining the mode of treatment[14,28,42]. Knudson *et al*[20] devised a clinical index score to predict the need for operative intervention. This 4-point scoring system assigned 1 point for each of the following: fever, tachycardia, guarding on examination and leukocytosis. The odds ratio for requiring operative management in patients with a score of greater than or equal to 3 was 40 (5.3-303.1, $P < 0.001$). In two studies[15,26] applying multivariate logistic regression analysis only ASA score and site of perforation remained significant for predicting operative treatment.

Reviewing 11 studies[8,11,14,18,21-27], after initial non-surgical treatment, surgery was required in 29/137 (21%) of patients with type II perforations, with an overall mortality of 9.4% (Table 5). The mortality of patients who required surgery was high (38%). Non-surgical management was successful in all patients with type III perforations (Table 4). In a recent review[32] conservative management was successful in 92.9% of patients with both types of injuries, treated initially non-operatively, with a final mortality of 0.6%.

In the available literature there are no prospective comparative studies between surgical techniques for ERCP-related perforations. Surgical technique depends on site and size of defect, timing of surgery and clinical condition of the patient.

The main goal of immediate surgery is to repair the perforation and diversion of bile and gastric fluid, if required. Endoscope related duodenal perforations (type I) can be closed primarily in one or two layers, following debridement of devitalized tissue. The closure should be oriented transversely in order to avoid compromising the duodenal lumen. In cases with large defects the options are jejunal serosal patch closure or tube duodenostomy. Leak from the duodenal closure line is a major concern and duodenal diversion should be suggested in large defects or delayed diagnosis. The rationale is to divert the gastrointestinal content and proteolytic enzymes from the duodenal repair site. In sphincterotomy related perforations (type II), a non-operative approach is successful in nearly 80% of cases. When the clinical condition of the patient or the size of the leak requires immediate surgery, a transduodenal approach and repair, by performing sphincteroplasty within 24 h, has been described with good results[43].

The main goals of delayed surgery are to control sepsis, to repair the perforation if possible, and diversion, if required[28,30,32,43,44]. Delayed surgery is performed in patients who remain septic despite non-

operative treatment, and debridement and drainage of the retroperitoneal space is required. That can be achieved by an extraperitoneal approach (right posterior laparostomy)[28] or transperitoneal approach when cholecystectomy, common bile duct exploration with T-tube placement or diversion techniques are required. The perforation site cannot be found in 16% to 80% in delayed surgery[24,27,44] or the tissues are too edematous for primary repair. The transduodenal approach is not indicated for delayed surgery.

Diversion of gastric and duodenal fluid is mandatory and can be achieved by: placement of a nasogastric or nasoduodenal tube; tube duodenostomy; pyloric exclusion and gastrojejunostomy; gastrojejunostomy alone; T-tube placement for bile diversion; duodenal diverticulization[7,8,11,12,15,20,23,25,27,29]. Duodenal diverticulization consists of Billroth Ⅱ gastrectomy, placement of a decompressive catheter into the duodenum, closure of duodenal wound and drainage[45]. The main drawback of duodenal diverticulization is that it is an extensive procedure which may be inappropriate in septic, unstable patients. Pyloric exclusion is a less invasive alternative. This procedure consists of duodenal wound repair, closure of the pylorus with a running suture or by stapling and gastrojejunostomy. Pyloric exclusion is a less extensive procedure, less time consuming, causes less physiological disturbances and it is advocated by most clinicians, when duodenal diversion is required.

In conclusion, ERCP-related perforation is uncommon (0.39%), but it is associated with an overall mortality of 7.8%. Early diagnosis and treatment are essential for a better outcome. The mechanism, site and extent of injury, suggested by clinical and radiographic findings, should guide towards conservative or surgical management. In type Ⅰ perforations early surgical repair is indicated, unless endoscopic closure can be achieved. Patients with type Ⅱ perforations should be treated initially non-operatively. Non-operative treatment is successful in 79% of patients with an overall mortality of 9.4%. Non-operative treatment is sufficient in all patients with type Ⅲ injuries. Surgical technique depends on size and site of defect, timing and clinical condition of the patient.

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ORIGINAL ARTICLE

Prospective Study

Histological diagnosis of gastric submucosal tumors: A pilot study of endoscopic ultrasonography-guided fine-needle aspiration biopsy *vs* mucosal cutting biopsy

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Author contributions: Ikehara H and Li Z contributed equally to this work; Watari J and Miwa H designed and performed the research study; Ikehara H, Li Z, Taki M, Kondo T, Tozawa K performed the procedures; All the authors helped to collect the data; Matsuda I and Hirota S diagnosed the histology; Watari J performed statistical analysis and wrote the paper.

Institutional review board statement: This study was approved by the Institutional Review Board at Hyogo College of Medicine, Nishinomiya, Japan.

Informed consent statement: All patients in the study gave informed consent for the procedures.

Conflict-of-interest statement: None.

Data sharing statement: The technical appendix, statistical code, and dataset are available from the corresponding author (watarij@hyo-med.ac.jp). Consent for data sharing was not obtained from the participants, but the presented data are anonymized and the risk of identification is low.

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Abstract

AIM: To compare the usefulness of endoscopic ultrasonography-guided fine-needle aspiration biopsy (EUS-FNAB) without cytology and mucosal cutting biopsy (MCB) in the histological diagnosis of gastric submucosal tumor (SMT).

METHODS: We prospectively compared the diagnostic yield, feasibility, and safety of EUS-FNAB and those of MCB based on endoscopic submucosal dissection. The cases of 20 consecutive patients with gastric SMT $\geqslant$ 1 cm in diameter. who underwent both EUS-FNAB and MCB were investigated.

RESULTS: The histological diagnoses were gastrointestinal stromal tumors (n = 7), leiomyoma (n =

6), schwannoma (n = 2), aberrant pancreas (n = 2), and one case each of glomus tumor, metastatic hepatocellular carcinoma, and no-diagnosis. The tumors' mean size was 23.6 mm. Histological diagnosis was made in 65.0% of the EUS-FNABs and 60.0% of the MCBs, a nonsignificant difference. There were no significant differences in the diagnostic yield concerning the tumor location or tumor size between the two methods. However, diagnostic specimens were significantly more frequently obtained in lesions with intraluminal growth than in those with extraluminal growth by the MCB method (P = 0.01). All four SMTs with extraluminal growth were diagnosed only by EUS-FNAB (P = 0.03). No complications were found in either method.

CONCLUSION: MCB may be chosen as an alternative diagnostic modality in tumors showing the intraluminal growth pattern regardless of tumor size, whereas EUS-FNAB should be performed for SMTs with extraluminal growth.

Key words: Submucosal tumor; Endoscopic ultrasonography-guided fine-needle aspiration biopsy; Gastrointestinal stromal tumor; Mucosal cutting biopsy; Endoscopic submucosal dissection

Core tip: We prospectively compared the diagnostic yield and the safety between endoscopic ultrasonography-guided fine-needle aspiration biopsy (EUS-FNAB) without cytology and mucosal cutting biopsy (MCB) based on endoscopic submucosal dissection. Although no significant difference in histological diagnosis was found between EUS-FNAB and MCB, diagnostic specimens were significantly more frequently obtained in the lesions with intraluminal growth compared to those with extraluminal growth by the MCB method. All submucosal tumors (SMTs) with extraluminal growth were diagnosed only by EUS-FNAB. No complications were found in either method. Therefore, MCB may be chosen as an alternative diagnostic modality in tumors showing intraluminal growth, whereas EUS-FNAB should be performed for SMTs with extraluminal growth.

Ikehara H, Li Z, Watari J, Taki M, Ogawa T, Yamasaki T, Kondo T, Toyoshima F, Kono T, Tozawa K, Ohda Y, Tomita T, Oshima T, Fukui H, Matsuda I, Hirota S, Miwa H. Histological diagnosis of gastric submucosal tumors: A pilot study of endoscopic ultrasonography-guided fine-needle aspiration biopsy *vs* mucosal cutting biopsy. *World J Gastrointest Endosc* 2015; 7(14): 1142-1149 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i14/1142.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i14.1142

INTRODUCTION

Gastric submucosal tumors (SMTs) including gastrointestinal stromal tumors (GISTs), leiomyomas, schwannomas, aberrant pancreas and more are frequently identified during routine upper endoscopies. Although endoscopic ultrasonography (EUS) is a useful modality for diagnosing gastric SMTs[1], it is not always possible to differentiate a GIST from a leiomyoma or schwannoma by EUS, especially when the tumor originated from the muscularis propria layer. GISTs are rare neoplasms that account for only 0.1%-3% of all gastrointestinal (GI) malignancies[2-4], whereas they represent approximately 80% of GI mesenchymal tumors[5]. As GISTs are potentially malignant, histological diagnosis by an EUS-fine-needle aspiration biopsy (FNAB) is recommended[6,7]. It is thus very important to discriminate these lesions from benign SMTs originating from the muscularis propria, such as leiomyomas and schwannomas. However, it may be difficult to arrive at the correct histological diagnosis with only a standard endoscopic biopsy, because the surface of an SMT is covered with normal epithelium.

EUS-FNAB is a reliable, useful and suitable method for the histological evaluation of SMTs[8-10]. Although EUS-FNAB is used widely, only a limited number of cases are subjected to this method, even in hospitals specializing in gastroenterology. In addition, EUS-FNAB systems including an echoendoscope and its observing system are very expensive and require not only experienced pathologists but also cytology technicians capable of handling and processing biopsy specimens[7]. The successful diagnostic rate for SMT by an EUS-FNAB combined with cytology has been reported to be relatively high (83%), but the success rate for histology is not satisfactory (50%)[9,11-13]. An alternative modality for the histological diagnosis of SMTs is thus needed.

Endoscopic submucosal dissection (ESD) was developed in Japan in the 2000s[14] and has since been widely adopted for the treatment of superficial gastric neoplasms. By applying this method, Lee *et al*[15] described cases in which an ESD-associated technique rather than EUS-FNAB was useful for the tissue sampling of SMTs. The applications of several similar methods for the histological diagnosis of gastrointestinal (GI) SMTs were also reported: mucosal cutting biopsy (MCB), a mucosal incision-assisted biopsy technique, and an "unroofing" biopsy based on endoscopic mucosal resection (EMR)[16-20].

A comparison of the histological diagnostic yield of SMTs between EUS-FNAB without its combination with cytology and MCB has not been published, to our knowledge. The aim of the present study was to prospectively compare the diagnostic yield of gastric SMTs and the feasibility, safety and complications between EUS-FNAB and MCB by performing both diagnostic modalities simultaneously for the same SMT patients.

MATERIALS AND METHODS

Patients

Between May 2012 and February 2015 in our depart-

ment, both EUS-FNAB and MCB were prospectively performed for 20 consecutive patients with gastric SMTs ⩾ 1 cm in diameter which were diagnosed by EUS (UM2000, UM-2R and 3R; Olympus Optical Corp., Tokyo) prior to the EUS-FNAB and MCB procedures. If the EUS finding of SMT showed mainly inward or outward growth from the gastric wall, the lesion was judged as intraluminal or extraluminal growth, respectively. Since hyperechoic lesions on EUS that originate from the submucosal layer are generally diagnosed as lipoma, these lesions were excluded from the study. All patients were admitted on the day of EUS-FNAB and MCB, and were usually discharged the day after the procedures. Thus the hospital stay for the patients without any clinical complications was generally 1 d, based on the clinical protocol at our hospital.

Written informed consent was obtained from all patients prior to the study, and the study design was approved by the Ethics Committee of Hyogo College of Medicine (No. 1710).

Operators of the EUS-FNAB and MCB procedures

Operator skill may affect the diagnostic yield and the complications of these procedures. In Japan, endoscopists receive board certification from the Japan Gastroenterological Endoscopy (JGES) after 5 years of training in a JGES-approved educational institution of endoscopy and after passing an examination administered by the JGES. Accordingly, the EUS-FNAB and MCB procedures in the present study were performed by expert endoscopists with board certification from the JGES. The same endoscopist performed the EUS-FNAB and MCB in a given patient.

EUS-FNAB procedure

The EUS-FNAB procedure was performed first with the patient under conscious sedation by midazolam with or without pethidine. The EUS-FNAB procedure was performed by expert endoscopists. Fundamentally, a convex linear-array echoendoscope (GF-UCT260; Olympus Optical) connected to an observing system (UM-ME1; Olympus Optical) was used in this procedure. A 22-gauge needle (EchoTip ProCore High Definition Ultrasound Biopsy Needle; Cook Japan, Tokyo) was used to obtain specimens for the histological analysis. After properly targeting the mass, the endoscopist punctured the lesion with the needle. Thereafter, the inner needle was pulled out, and the endoscopist moved the needle back and forth 20 times while applying suction using the connected 10-mL syringe. The EUS-FNAB was performed by making 1 to 4 passes, at the discretion of the endoscopist. That is, when the endoscopist judged that grossly visible material was obtained, the procedure was stopped.

The obtained material was immediately and directly exposed to 10% formalin, and then processed as a tissue block for histopathological evaluation using hematoxylin-eosin and immunohistochemistry (IHC) staining. Cytology was not performed as an on-site cytologist was not available in this procedure, and a cell block for confirmatory IHC was also not prepared.

Mucosal cutting biopsy

Immediately following the EUS-FNAB in each patient, an MCB was performed. The MCB technique was as follows: first, saline was injected into the submucosa and then mucosal cutting was performed using a needle-knife (KD-1L-1; Olympus Optical). Under direct vision of the SMT, several biopsy specimens were taken using conventional biopsy forceps (Radial Jaw™ 4: Boston Scientific, Natick, MA). One to six biopsy samples were taken at the discretion of the operators. As in the EUS-FNAB procedure, when the endoscopist judged that grossly visible material was obtained, the procedure was stopped. Thereafter, the mucosal incision was closed with hemoclips (EZ Clip™; Olympus Optical) to prevent post-procedure bleeding (Figure 1) and to reduce the risk of ulceration that may cause peritoneal dissemination.

The patient's oral intake was allowed starting the morning after the day of the procedure, and then the patient was discharged. A proton pump inhibitor was administered for 2 wk after the procedure.

IHC staining of the samples obtained by both methods was performed using the following antibodies: c-kit, CD34, S100 protein, and desmin. Patients diagnosed with a GIST were offered surgical resection.

Analysis parameters

We evaluated the diagnostic yield and post-procedure bleeding and other complications between the EUS-FNAB and MCB methods, and we tried to determine the causes of nondiagnostic cases.

Statistical analysis

The data were assessed by Welch's *t* test between two groups, and the chi-square test or Fisher's exact test was used to examine differences between two proportions. Statistical significance was defined as a P value < 0.05. Statistical analyses were performed with GraphPad Prism5 software (GraphPad Software, La Jolla, CA).

RESULTS

Patient characteristics and clinicopathological data of SMTs

Table 1 provides the characteristics of the 20 patients and a summary of the targeted SMTs. All patients underwent EUS prior to the EUS-FNAB and MCB procedures and were diagnosed as having a gastric SMT originating from the submucosal (third layer) or the muscularis propria layer (fourth layer). The mean age of the patients was 61.8 ± 12.5 years (range 39-77 years), and women accounted for 50.0% of the patients. The tumors had a mean size of 23.6 mm (range 10-57). Among the 20 cases, four showed extraluminal growth on EUS. The histological diagnoses were GIST

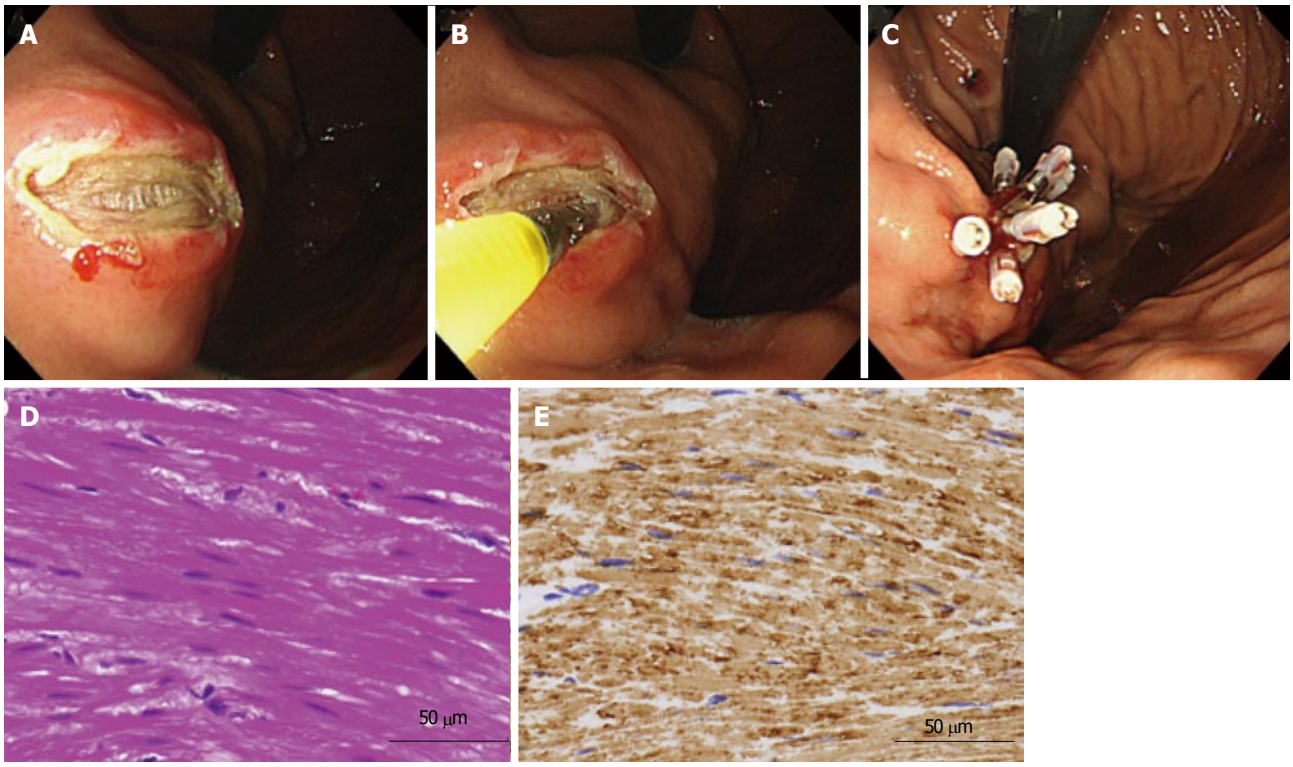

Figure 1 Mucosal cutting biopsy of a submucosal tumor with intraluminal growth in the lesser curvature of the corpus. A: The mucosal incision was made by a needle-knife after an injection of saline; B: Biopsy specimen obtained from the tumor using biopsy forceps under direct observation; C: The incision was closed with hemoclips; D: Histological examination of the biopsied specimen showing a spindle cell without mitotic figures (HE); E: Immunohistochemical staining was positive for desmin. This lesion was diagnosed histologically as a leiomyoma.

Table 1 Summary of the 20 patients with submucosal tumors who underwent endoscopic ultrasonography-guided fine-needle aspiration biopsy and mucosal cutting biopsy

Age, mean ± SD (yr)	61.8 ± 12.5
Male: Female	10:10
Tumor location (upper/middle/lower)	11/8/1
Tumor size ± SD (range) (mm)	23.6 ± 11.5 (10-57)
≤ 20 mm : > 20 mm	7:13
Growth pattern	
Intraluminal	16
Extraluminal	4
Histological diagnosis	
Gastrointestinal stromal tumor	7
Leiomyoma	6
Schwannoma	2
Aberrant pancreas	2
Glomus tumor	1
Metastatic hepatocellular carcinoma	1
Not diagnosed	1

(*n* = 7), leiomyoma (*n* = 6), schwannoma (*n* = 2), aberrant pancreas (*n* = 2), glomus tumor (*n* = 1), metastatic hepatocellular carcinoma (HCC, *n* = 1), and nondiagnostic (*n* = 1).

Of the three cases that could not be diagnosed by either method, two were treated surgically and diagnosed histologically as a schwannoma and a glomus tumor, respectively, and the third case is being followed closely without treatment. The tumors were located at the lesser curvature of the middle corpus in the schwannoma, at the greater curvature of the fornix for the glomus tumor, and at the greater curvature of the antrum in the nondiagnostic case. All seven GIST cases diagnosed by EUS-FNAB or MCB were surgically resected and confirmed histologically as GISTs.

Diagnostic yields of EUS-FNAB and MCB

The median values 3.0 [interquartile range (IQR): 2.0, 4.0] for the EUS-FNAB samples and 3.0 (IQR: 1.5, 4.5) for the MCB samples were obtained per patient. All 15 cases of GIST, leiomyoma and schwannoma were diagnosed by IHC. The rates of histological definitive diagnosis were 65.0% (13 of 20) by EUS-FNAB and 60.0% (12 of 20) by MCB, a nonsignificant difference. The concordance rate of the histological diagnosis between the two methods was 100%. There were also no significant differences in the diagnostic yield regarding tumor location or tumor size between the EUS-FNAB and MCB methods (Table 2). However, diagnostic specimens were significantly more frequently obtained in lesions with intraluminal growth than in those with extraluminal growth in the MCB method (*P* = 0.01). All four of the SMTs that showed extraluminal growth, including three GISTs and the single HCC, were correctly diagnosed only by EUS-FNAB (Figure 2), and not by MCB (*P* = 0.03). Seventeen of the SMTs (85.0%) were histologically diagnosed by both methods.

Complications in both procedures

Two cases showed mild bleeding during the MCB procedure, but both were successfully managed by

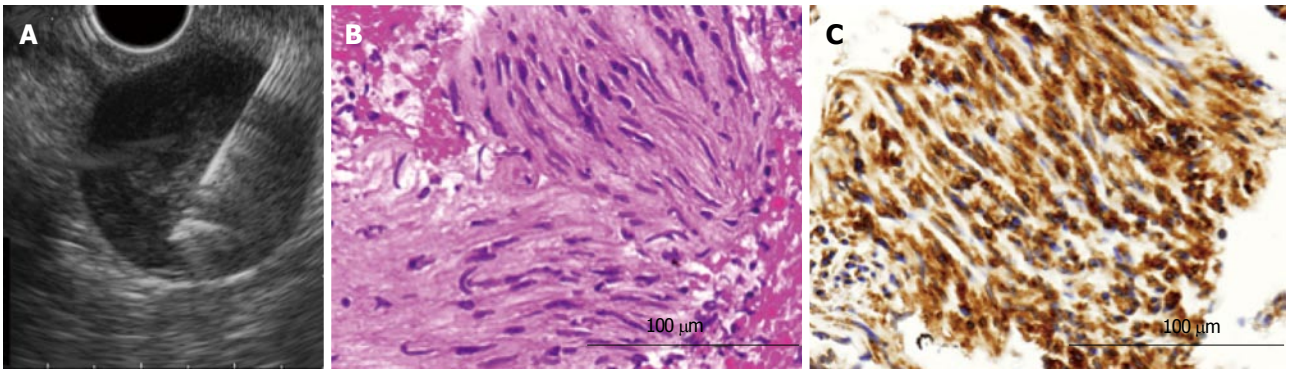

Figure 2 Endoscopic ultrasonography-guided fine-needle aspiration biopsy of a gastrointestinal stromal tumor with extraluminal growth. A: EUS-FNAB of a hypoechoic lesion in the muscularis propria layer showing extraluminal growth; B: Histological finding showing spindle cells in the EUS-FNAB specimen (HE); C: Immunohistochemical staining is positive for c-kit. EUS-FNAB: Endoscopic ultrasonography-guided fine-needle aspiration biopsy.

Table 2 Diagnostic yields obtained with endoscopic ultrasonography-guided fine-needle aspiration biopsy and mucosal cutting biopsy

	EUS-FNAB				*P* value	MCB				*P* value
	Diagnosed (%) (*n* = 13)		Not diagnosed (%) (*n* = 7)			Diagnosed (%) (*n* = 12)		Not diagnosed (%) (*n* = 8)		
Histological diagnosis	13 (65.0)					12 (60.0)				> 0.99
Location 1										
Upper	7	(63.6)	4	(36.4)	0.33	8	(72.7)	3	(27.3)	0.28
Middle	6	(75.0)	2	(25.0)		4	(50.0)	4	(50.0)	
Lower	0	(0)	1	(100)		0	(0)	1	(100)	
Location 2										
Lesser curvature	4	(66.7)	2	(33.3)	0.81	3	(50.0)	3	(50.0)	0.27
Greater curvature	2	(50.0)	2	(50.0)		1	(25.0)	3	(75.0)	
Anterior wall	4	(80.0)	1	(20.0)		4	(80.0)	1	(20.0)	
Posterior wall	3	(60.0)	2	(40.0)		4	(80.0)	1	(20.0)	
Tumor size										
≤ 20 mm	7	(58.3)[a]	5	(41.7)	0.64[1]	9	(75.0)[a]	3	(25.0)	0.17[1]
> 20 mm	6	(75.0)[c]	2	(25.0)		3	(37.5)[c]	5	(62.5)	
Growth pattern										
Intraluminal	9	(56.3)[e]	7	(43.8)	0.10[1]	12	(75.0)[e]	4	(25.0)	0.01[1]
Extraluminal	4	(100)[b]	0	(0)		0	(0)[b]	4	(100)	
Median number of samples to the diagnosis (IQR)	1	(1.0, 1.0)				1	(1.0, 1.75)			
Median number of samples (IQR)	3	(2.5, 3.5)	3	(3.0, 3.0)	0.93	5	(3.0, 6.0)	2.5	(1.0, 5.75)	0.17

[1]*P* values were calculated using Fisher's exact test; [a]*P* = 0.67 between EUS-FNA and MCB in tumor size ≤ 20 mm; Fisher's exact test; [c]*P* = 0.31 between EUS-FNA and MCB in tumor size > 20 mm; Fisher's exact test; [e]*P* = 0.46 between EUS-FNA and MCB in intraluminal growth pattern; Fisher's exact test; [b]*P* = 0.03 between EUS-FNA and MCB in extraluminal growth pattern. EUS-FNAB: Endoscopic ultrasonography-guided fine-needle aspiration biopsy; IQR: Interquartile range; MCB: Mucosal cutting biopsy.

hemoclips. The mean number of hemoclips for closing the incised mucosa was 3.4 (range: 1-6 clips). No post-procedural hemorrhage, fever, or peritonitis was seen following either procedure.

DISCUSSION

To date, there are many reports on the methods of tissue acquisition from SMTs: EMR, MCB and EUS-FNAB. Histological diagnosis by a standard biopsy or EMR may be confined to SMTs that arise from the muscularis mucosa or submucosa, which corresponds to second- or third-layer lesions on EUS. In contrast, it may be impossible to make a histologic diagnosis of the lesions located in the muscularis propria by these methods. Therefore, EUS-FNAB was suggested to play an important role in histological diagnoses such as gastric SMTs, although the results can be quite variable[10]. However, although the use of EUS-FNAB is quite prevalent, only a limited number of patients undergo this procedure - even in hospitals specializing in gastroenterology - because an expensive dedicated endoscopic system is needed to conduct an EUS-FNAB. For example, the price of the needle for EUS-FNAB is approximately $300 United States dollars (USD), and the total prices of devices such as the needle knife, injection needle and EZ Clip™ for MCB are also approximately $100 USD, and thus the cost may be

significantly cheaper in the MCB method than in the EUS-FNAB method. Additionally, the needle knife used in the MCB method is reusable. The EUS-FNAB system comprised of an echoendoscope and its observing system is very expensive, over $100000 USD. Therefore, MCB may be the less expensive procedure compared to EUS-FNAB.

Generally, the accuracy rates of EUS-FNAB in the histological diagnosis of gastric SMTs vary from approximately 60% to 80%[9,11]. It was noted that the sensitivity of EUS-FNAB for the diagnosis of GIST, especially in cases of small GISTs, is relatively low compared to that for other types of SMTs[21,22], indicating that the diagnostic yield may be influenced by the lesion's size[11,21-24], because technical expertise is required to diagnose smaller lesions by EUS-FNAB. Several studies showed that the diagnostic rate increased with the increase of tumor size[22-24], but another study did not observe this association[11]. A recent report by Sekine *et al*[25] showed that cytological or histological specimens obtained by EUS-FNAB met the diagnostic criteria of GIST in 81.3% of the cases, even among small GISTs (< 20 mm). In their procedure, the samples obtained by EUS-FNAB were examined immediately with a rapid staining method to verify the adequacy of the specimen and to provide a presumptive diagnosis. It was reported that when an on-site cytopathologist immediately reviewed the adequacy of the samples, the sensitivity of EUS-FNAB was > 90%[23,26]. It was also suggested that the sensitivity of EUS-FNAB drops by 10%-15% in the absence of an on-site pathologist to evaluate the cellular adequacy of the samples[27]. However, this diagnostic procedure for cytology during an EUS-FNAB may be troublesome for not only endoscopists but also cytology technicians in daily medical practice. For this reason, an easy and useful diagnostic tool for SMT regardless of the tumor size is needed.

In the present study, the histological diagnosis rate of MCB was significantly higher than that of EUS-FNAB in the lesions with intraluminal growth (P = 0.01). In addition, all four extraluminal-growth tumors could be histologically diagnosed only by EUS-FNAB. The diagnostic capability of MCB was thus increased from 60% to 75% when the four cases with extraluminal growth were excluded. Additionally, when we examined the histological diagnosis for both methods together, the accurate histological diagnosis increased to 85%. In previous studies, the accurate histological diagnosis of MCB ranged from 85% to 100%[16-18], which is relatively higher than that of our study. One of the reasons for the differences in diagnostic yield may be that the numbers of cases in those studies were relatively small, and they were retrospective studies. To date, there are two studies that compared the diagnostic yield between the jumbo biopsy "unroofing" technique and EUS-FNAB[28,29]. The results of both studies indicated a lower diagnostic yield than ours. In those studies, the diagnostic procedures (*i.e.*, jumbo biopsy *vs* EUS-FNAB) were not performed during the same session in the same patients, as was done in our study. In addition, both studies[28,29] included many cases of lipoma (16.6%-22.1%), which is considered to be easily diagnosed by the jumbo biopsy unroofing technique or only by EUS.

The diagnostic yield of the EUS-FNAB method in the present study was relatively lower compared to previous reports[26,30]. One of the reasons might be an effect of the difference in the FNA needle size used for the EUS-FNABs. The larger-bore 19-gauge needle may actually show a higher diagnostic yield compared to the 22-gauge needle used in the present study[24,31], but the exact difference in diagnostic yield between 19- and 22-gauge FNA needles remains unclear[24,30]. We did not adequately assess procedural factors such as the needle gauge and the number of needle passes in the present study. More passes or the use of a larger-bore needle would provide more tissue. However, Sepe *et al*[23] reported that the number of passes did not significantly affect the diagnostic capability of EUS-FNAB. In their study, as is standard practice, this decision regarding the number of passes was made at the discretion of the individual endosonographer and was based on a real-time assessment of presumed tissue adequacy, as in our study, and our finding is in agreement with their result[23].

No major complications were caused by either the EUS-FNAB or MCB method in the present study, although mild bleeding occurred in two cases during the MCB; both were successfully managed by hemoclips. Perforation did not occur in any of the 20 patients during MCB, but extra care should be taken to prevent perforation in cases with extraluminal growth[17]. A laparoscopic and endoscopic cooperative surgery (LECS) is now being performed for the treatment of gastrointestinal SMTs[32,33]. However, the MCB method is unlikely to preclude LECS for the treatment of SMTs.

The present study had some potential limitations. First, the sample size of this study was small and drawn from a single institution. When the diagnostic yield is assumed to be approximately 70% for the EUS-FNAB without cytology method and approximately 90% for the MCB method, 62 patients with SMT are needed in each group in order to have a power of 80% to detect a difference at the level significance of α = 0.05 (two-sided).

Second, there is the issue of EUS-FNAB- and MCB-related dissemination as a late complication, but this has not been reported to date. It is important to close the mucosal incisions appropriately with endoclips after tissue sampling to prevent post-procedure complications in MCB[17]. Third, if the diagnostic yield of the combination of EUS-FNAB and MCB is assessed, the histological diagnosis by the two methods should be compared to that of a surgically resected whole specimen as a "golden standard."

In conclusion, although EUS-FNAB is the widely used gold standard for the histological and cytological diagnoses of gastric SMTs, MCB may be chosen as an alternative diagnostic modality in tumors showing the

intraluminal growth pattern. A randomized controlled trial to compare the capability of MCB with that of EUS-FNAB is needed.

COMMENTS

Background

As gastric submucosal tumors (SMTs) comprise both benign and malignant lesions, histological diagnosis is needed. Endoscopic ultrasonography-guided fine-needle aspiration biopsy (EUS-FNAB) is a useful method for the histological evaluation of SMTs. However, EUS-FNAB systems are very expensive and require experienced pathologists and cytology technicians, and thus this procedure may be unavailable in hospitals not specializing in gastroenterology.

Research frontiers

Although the diagnostic yields of EUS-FNAB and mucosal cutting biopsy (MCB) have been reported, there are no studies comparing the diagnostic capabilities of EUS-FNAB and MCB based on endoscopic submucosal resection in the same patients. The authors prospectively compared the diagnostic yield, feasibility, and safety of these two methods.

Innovations and breakthroughs

In this prospective study, no significant difference in histological diagnosis was found between EUS-FNAB and MCB regardless of tumor location and tumor size. However, diagnostic specimens were significantly more frequently obtained in the lesions with intraluminal growth compared to those with extraluminal growth by the MCB method. All SMTs with extraluminal growth were diagnosed only by EUS-FNAB, not by MCB. No complications were produced by either method.

Applications

MCB may be chosen as an alternative diagnostic modality in tumors showing an intraluminal growth pattern regardless of tumor size, whereas EUS-FNAB should be performed for SMTs with extraluminal growth.

Terminology

EUS-FNAB: This method is a needle biopsy procedure considered to be a reliable and accurate method for the evaluation of SMTs in the gastrointestinal tract; gastrointestinal stromal tumor (GIST): GISTs are the most common mesenchymal neoplasms of the gastrointestinal tract.

Peer-review

The authors present an interesting result regarding the efficacy of MCB in the histological diagnosis of SMTs. This procedure will be accepted widely even in hospitals not specializing in gastroenterology.

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CASE REPORT

Laparoscopic endoscopic cooperative surgery as a minimally invasive treatment for gastric submucosal tumor

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Abstract

Laparoscopic wedge resection is a useful procedure for treating patients with submucosal tumor (SMT) including gastrointestinal stromal tumor (GIST) of the stomach. However, resection of intragastric-type SMTs can be problematic due to the difficulty in accurately judging the location of endoluminal tumor growth, and often excessive amounts of healthy mucosa are removed; thus, full-thickness local excision using laparoscopic and endoscopic cooperative surgery (LECS) is a promising procedure for these cases. Our experience with LECS has confirmed this procedure to be a safe, feasible, and minimally invasive treatment method for gastric GISTs less than 5 cm in diameter, with outcomes similar to conventional laparoscopic wedge resection. The important advantage of LECS is the reduction in the resected area of the gastric wall compared to that in conventional laparoscopic wedge resection using a linear stapler. Early gastric cancer fits the criteria for endoscopic resection; however, if performing endoscopic submucosal dissection is difficult, the LECS procedure might be a good alternative. In the future, LECS is also likely to be indicated for duodenal tumors, as well as gastric tumors. Furthermore, developments in endoscopic and laparoscopic technology have generated various modified LECS techniques, leading to even less invasive surgery.

Key words: Cooperative surgery; Endoscopy; Gastrointestinal tumor; Laparoscopy; Submucosal tumor

Core tip: Resection of intragastric-type submucosal tumor can be problematic due to the difficulty in accurately judging the location of endoluminal tumor growth, and often excessive amounts of healthy mucosa are removed; thus, full-thickness local excision using laparoscopic and endoscopic cooperative surgery (LECS) is a promising procedure for these cases. The important advantage of LECS is the reduction in the resected area of the gastric wall compared to that in conventional laparoscopic wedge resection using a linear

stapler. Developments in endoscopic and laparoscopic technology have generated various modified LECS techniques, leading to even less invasive surgery.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are common mesenchymal tumors among submucosal tumors (SMTs) of the gastrointestinal tract. Complete resection of GISTs is recommended because of their malignant potential, such as risk of tumor recurrence and progression to metastatic disease[1,2]. Lymphadenectomy is not recommended as lymph node involvement is rare. Laparoscopic surgery for GISTs is safe and effective and provides a minimally invasive approach for tumors less than 5 cm in diameter[3-5].

Extragastric-type SMTs can be treated relatively easily using a conventional laparoscopic wedge resection with adequate margins. However, resection of intragastric-type SMTs can be more problematic due to the difficulty of accurately judging the tumor's location under laparoscopic examination. This results in the necessity of removing relatively large sections of healthy stomach to remove the tumor, which sometimes leads to postoperative deformity of the stomach[6].

Laparoscopic endoscopic cooperative surgery (LECS) was first reported by Hiki *et al*[7,8] in 2008, and is a minimally invasive surgical technique designed to resect SMTs originating in the gastrointestinal tract. In recent years we have performed LECS in patients presenting with gastric SMT with mainly intraluminal growth. In the present study, we reviewed a number of clinical reports describing LECS, including our own series, to evaluate the procedure and its clinical outcomes.

CASE REPORT

LECS requires the participation of experienced laparoscopic surgeons and experienced endoscopists[7,8]. After inducing general anesthesia, a port for a camera is inserted through the umbilicus using an open technique, and a pneumoperitoneum is established by insufflation of carbon dioxide to 8-10 mmHg abdominal pressure. Four additional ports, two 5-mm ports and two 12-mm ports, are inserted into the upper left and right and lower left and right quadrants, respectively. The proximal jejunum near the ligament of Treitz is clamped using detachable forceps to avoid air inflating the distal intestine during endoscopic manipulation. When confirmation of the tumor location from the serosal side is difficult, it is confirmed by an intraluminal approach using endoscopy (Figure 1A). Blood vessels in the excision area around the tumor are then prepared using ultrasonically activated laparoscopic coagulating shears (Figure 1B).

The location of the tumor is first confirmed endoscopically, followed by submucosal dissection using intraluminal endoscopy to determine an appropriate resection line (Figure 1C). Endoscopic submucosal dissection (ESD) is widely accepted as the standard treatment for early gastric cancer without lymph node metastasis and enables a clinician to resect a target lesion *en bloc*[9]. This technique is applied to LECS using various endoscopic devices such as a needle knife to mark the mucosal resection line and an insulation-tipped diathermic electrosurgical (IT) knife to dissect the submucosal layer. After circumferential dissection of the mucosal to submucosal layers, a full-thickness incision into the serosal layer around the lesion is made using the needle knife to connect the endoscopic and laparoscopic approaches.

Subsequently, an ultrasonic coagulation incision device is inserted into the artificial perforation under laparoscopic view, and the seromuscular layer is dissected along the incision line made by ESD (Figure 1D). After circumferential full-thickness resection (Figure 1E), the resected specimen is put into a plastic bag, which is then removed through the umbilical incision. The edges of the incision line are then lifted up by an assistant using forceps, and the incision line is closed using laparoscopic stapling devices (Figure 1F). After completing the full-thickness closure, the endoscope can be inserted into the stomach to confirm that there is no air leakage, despite insufflation of the stomach. Gross examination of the resected specimen reveal that the resection margin of healthy gastric wall is limited to the minimum necessary (Figure 2).

Table 1 details the clinicopathological results of 19 patients who underwent laparoscopic resection for SMT in the stomach at the Kochi Medical School Hospital. Conventional laparoscopic resection of the tumor was undertaken in 11 patients, and LECS was performed in 8 patients. Basically, the indications of laparoscopic surgery including LECS for gastric SMT include the tumors less than 5 cm detected on esophagogastroduodenoscopy, computed tomography or upper gastrointestinal barium study. We performed LECS for gastric SMT when the main tumor location was intragastric type. Until the advent of LECS, we performed conventional laparoscopic resection for the gastric SMT less than 5 cm in diameter even if the main tumor location was intragastric type.

The median age of patients was 72 years (range, 35-86 years), and there was a female predominance, with a male-to-female ratio of 5:14. The tumor was located in the upper third of the stomach in 9 patients, in the middle third in 6 patients, and in the lower third in 4 patients. The tumor circumference included the lesser curvature in 7 patients, greater curvature in 7 patients, posterior wall in 4 patients, and anterior wall in 1

Table 1 Characteristics of patients who underwent laparoscopic surgery for a gastric submucosal tumor

Patient	Age	Gender	Tumor location	Main location of tumor	Operation method	Operating time (min)	Estimated blood loss (mL)	Tumor size (cm)	Histology
1	78	M	M, Less	Extragastric	Conventional laparoscopic approach	145	20	4.0 × 3.5	GIST (low risk)
2	60	F	U, Gre	Intragastric	Conventional laparoscopic approach	175	20	1.7 × 1.7	GIST (very low risk)
3	66	F	U, Post	Intragastric	Conventional laparoscopic approach	85	30	5.5 × 4.5	GIST (high risk)
4	42	M	L, Gre	Mixed	Conventional laparoscopic approach	155	5	3.0 × 2.7	Schwannoma
5	86	F	M, Less	Extragastric	Conventional laparoscopic approach	190	40	3.5 × 2.5	GIST (low risk)
6	35	F	U, Gre	Extragastric	Conventional laparoscopic approach	115	5	3.8 × 3.0	GIST (intermediate risk)
7	84	F	U, Gre	Intragastric	Conventional laparoscopic approach	235	130	4.0 × 3.3	GIST (intermediate risk)
8	78	F	M, Less	Extragastric	Conventional laparoscopic approach	145	5	4.5 × 4.0	GIST (low risk)
9	61	F	U, Post	Intragastric	LECS	130	5	4.4 × 2.2	GIST (low risk)
10	64	F	U, Post	Intragastric	LECS	250	5	3.1 × 3.0	GIST (low risk)
11	43	F	L, Less	Intragastric	LECS	155	5	2.0 × 1.7	GIST (very low risk)
12	72	M	M, Less	Extragastric	Conventional laparoscopic approach	165	70	5.0 × 3.5	GIST (low risk)
13	77	M	U, Gre	Mixed	LECS	230	5	3.0 × 1.5	GIST (low risk)
14	63	F	L, Gre	Intragastric	LECS	202	0	3.0 × 2.0	Schwannoma
15	73	M	U, Ant	Intragastric	Conventional laparoscopic approach	226	0	3.0 × 2.0	GIST (low risk)
16	36	F	M, Less	Mixed	LECS	214	0	4.0 × 2.5	GIST (low risk)
17	82	F	L, Gre	Mixed	LECS	212	10	2.8 × 2.0 × 1.8	GIST (low risk)
18	81	F	U, Post	Extragastric	Conventional laparoscopic approach	130	0	4.5 × 3.0	GIST (low risk)
19	81	F	M, Less	Intragastric	LECS	221	0	3.2 × 3.0	GIST (low risk)

U: Upper third; M: Middle third; L: Lower third; Less: Lesser curvature; Gre: Greater curvature; Ant: Anterior wall; Post: Posterior wall; LECS: Laparoscopic endoscopic cooperative surgery; GIST: Gastrointestinal stromal tumor.

Table 2 Clinicopathological characteristics of patients with gastric submucosal tumor who underwent either conventional laparoscopic surgery or laparoscopic endoscopic cooperative surgery

	LECS (n = 8)	Conventional laparoscopic approach (n = 11)	P value
Age, median (range), yr	64 (36-82)	73 (35-86)	0.51
Gender			0.52
Male	1	4	
Female	7	7	
Tumor location			0.7
Upper third	3	6	
Middle third	2	4	
Lower third	3	1	
Tumor size, median (range), cm	3.1 (2.0-4.4)	4.0 (1.7-5.5)	0.12
Estimated blood loss, median (range), mL	5 (0-10)	20 (0-130)	0.06
Operating time, median (range), min	213 (130-250)	155 (85-235)	0.05

LECS: Laparoscopic endoscopic cooperative surgery.

patient. The median tumor diameter was 3.5 cm (range, 1.7-5.5 cm), the median operating time was 175 min (range, 85-250 min), and the median estimated blood loss was 5 mL (range, 0-130 mL). The main location of the tumor was intragastric in 9 patients, extragastric in 6, and mixed (both intragastric and extragastric) in 4. The histological diagnosis was GIST in 17 patients, and schwannoma in 2 patients. Of the patients with GISTs, 2 were classified as very low risk, 12 as low risk, 2 as intermediate risk, and 1 patient as high risk, according to the modified Fletcher classification[10,11]. There were no remarkable postoperative complications including mortality, leakage or surgical site infection.

Table 2 compares the clinicopathological characteristics of the 19 patients in our current series who underwent either conventional laparoscopic surgery (n = 11) or LECS (n = 8) for gastric SMT. The clinicopathological characteristics included the tumor location, major axis of the tumor, estimated blood loss, and operating time. The median estimated blood loss in patients who underwent LECS tended to be smaller than in those who underwent conventional laparoscopic surgery (5 mL *vs* 20 mL, respectively; P = 0.06). The median operating time of patients who underwent LECS also tended to be longer than those who underwent conventional laparoscopic surgery (213 min *vs* 155 min, respectively; P = 0.05). There were no significant differences in the median age, gender, tumor location,

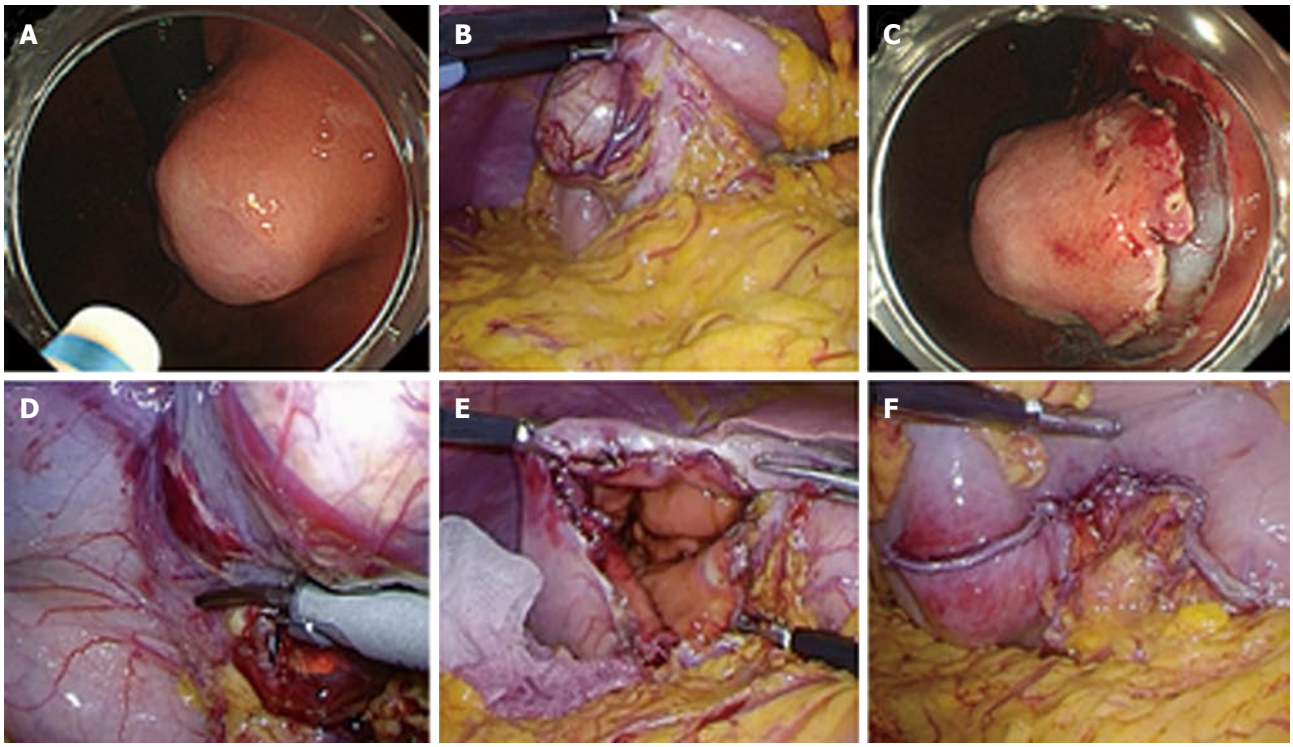

Figure 1 Laparoscopic endoscopic cooperative surgery for gastric submucosal tumor. A: The tumor is located in the lesser curvature of the middle third of the stomach; B: The stomach was mobilized by dividing the gastrocolic omentum and the lesser curvature vessels near the tumor by laparoscopic dissection; C: A circumferential incision was made around the tumor by an endoscopic submucosal dissection technique using an insulation-tipped diathermic electrosurgical knife; D: The seromuscular layer of the stomach was dissected along the incision line using the laparosonic coagulating shears; E, F: The post-excisional hole in the stomach was closed using a laparoscopic linear stapling device.

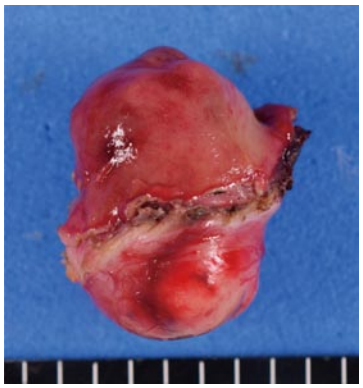

Figure 2 Gross appearance of the resected specimen. The tumor is a mixed-type, with a predominant intragastric component. The resection margin of healthy gastric wall is limited to the minimum necessary. The pathological diagnosis confirmed a gastrointestinal stromal tumor, classified as low risk.

or median tumor size in patients who underwent conventional laparoscopic surgery compared to LECS.

DISCUSSION

Conventional surgical operations may be excessively invasive for the treatment of gastrointestinal SMT. Successful laparoscopic wedge resection has been reported for 2-5 cm gastric GISTs, and confirmed by studies examining long-term surgical outcomes[3,12,13]. However, it is sometimes difficult to determine the appropriate resection line from the outside of the stomach when tumors are located intragastrically. There have been several reports on the use of LECS for SMT of the stomach including GISTs, leiomyomas, and schwannomas[6,7,14-19]. Table 3 summarizes the clinical variables of patients from a number of studies who underwent LECS, including our own series.

Kawahira *et al*[14] reported that the median ratio of the longest diameter of the tumor divided by the longest diameter of the surgical specimen was significantly greater in LECS compared to laparoscopic wedge resection (0.86 *vs* 0.69, respectively; P = 0.02). This means that LECS results in the resection of a smaller area of healthy gastric wall, which is an important advantage of LECS over conventional laparoscopic wedge resection using linear staplers. Therefore, LECS has good prospects for the treatment of GISTs, applying the modern concept of minimally invasive surgery, regardless of the location of the tumor even if it is adjacent to the esophagogastric junction or pyloric ring[16].

In our series, there was a tendency for the estimated blood loss to be lower in the LECS group than in the conventional laparoscopic resection group, with the difference just failing to reach significance. A major reason for this lower blood loss is that in the case of intragastric-type SMT, division of the extended gastric vessels or the omentum in the excision area around the tumor is needed to maintain a safe margin from the

Table 3 Previous clinical reports of laparoscopic endoscopic cooperative surgery for gastric submucosal tumor

Ref.	Year	Number of patients	Median tumor size (cm)	Median operating time (min)	Median estimated blood loss (mL)	Conversion to open surgery
Hiki *et al*[7]	2008	7	4.6	169	7	0
Kawahira *et al*[14]	2012	16	2.8	172	5	0
Tsujimoto *et al*[6]	2012	20	3.8	157	3.5	0
Dong *et al*[15]	2013	6	3.5	83.3	NA	0
Qiu *et al*[16]	2013	69	2.8	81.6	29.8	0
Hoteya *et al*[17]	2014	25	NA	156.3	NA	0
Waseda *et al*[18]	2014	27	3.6	167.5	5	0
Mori *et al*[19]	2014	12	3.9	146.3	NA	0
Our case	2015	8	3.1	213	5	0

NA: Not available.

tumor. There was also a tendency for longer operation times in the LECS group than in the conventional laparoscopic resection group, although this difference was not significant. This longer operation time for LECS is not surprising since time is required for both the ESD and laparoscopic procedures. Previous studies have not shown any difference in perioperative outcomes between LECS and the conventional approach, and a larger sample size would be useful to clarify this issue.

Developments in endoscopic and laparoscopic technology have yielded various modified LECS techniques aimed at further minimizing invasiveness. Examples of these improved techniques include the laparoscopy-assisted endoscopic full-thickness resection, a full-thickness resection method using the non-exposure technique (CLEAN-NET), and non-exposed endoscopic wall-inversion surgery (NEWS)[20-22]. Because LECS has an inherent risk of peritoneal infection due to the necessity for gastric perforation, CLEAN-NET and NEWS have been developed to prevent the risk of cancer cells seeding during open gastrectomy. These procedures might thus have potential minimally invasive resections of gastric tumors, even those in an ulcerated state[22].

Single-port LECS, which is a single-incision laparoscopic surgery combined with an endoscopic approach, might provide an alternative to gastric wedge resection with minimal transformation of the stomach[23]. It may contribute to reduced pain, faster recovery, and improved cosmesis for patients. However, careful selection of patients based on the tumor location and growth morphology is needed to clearly identify the risks and benefits of this new approach, also taking into account the need for needlescopic instruments.

Initially, the indication criteria for LECS was limited to SMT of the stomach measuring up to 5 cm in diameter without ulceration of the mucosa[7]. In the future, it is likely that LECS will also be indicated for tumors of the duodenum[24,25]. Although ESD is widely accepted as the standard treatment for gastric lesions including early gastric cancer, the duodenal wall is generally thinner than that of the stomach and ESD for duodenal tumors is associated with an increased risk of perforation[25]. Furthermore, maneuvering a flexible endoscope is technically difficult in the tiny duodenal lumen. In these cases, LECS might be a useful therapeutic modality not only for avoiding perforation of the duodenal wall by ESD, but also for achieving a more precise incision line[24].

Moreover, Nunobe *et al*[26] reported the successful use of LECS for a large spreading mucosal cancer in the stomach that would have been difficult to treat with ESD because of the high likelihood of complications and the long surgical time required for ESD. Thus, early gastric cancer that fits the criteria for endoscopic resection, but presents difficulties for ESD, is likely to be a candidate for the LECS procedure[26].

In conclusion, recent advances in endoscopic and laparoscopic techniques have facilitated several variations of endoscopic procedures derived from ESD, and created a fusion of endoscopy and laparoscopy technologies suitable for upper gastrointestinal SMTs. LECS is a useful and safe procedure for SMT that avoids excessive resection of healthy gastric wall. Further investigations, including a prospective randomized controlled trial and a study exploring long-term consequences, are needed to verify the usefulness of the LECS for gastrointestinal SMT.

COMMENTS

Case characteristics

The authors demonstrated the patients with gastric submucosal tumor treated by laparoscopic surgery.

Clinical diagnosis

The subjects were the gastric submucosal tumors including intragastric and extragastric type.

Differential diagnosis

Histopathological diagnosis of submucosal tumors includes gastrointestinal stromal tumor and schwannoma.

Laboratory diagnosis

Laboratory findings were within the normal range.

Imaging diagnosis

The gastric submucosal tumors were diagnosed by computed tomography and esophagogastroduodenoscopy.

Pathological diagnosis

Pathological findings of gastrointestinal stromal tumor were characterized by

interlacing bundles of elongated cells with c-KIT expression.

Treatment
The patients were treated by conventional laparoscopic wedge resection or laparoscopic endoscopic cooperative surgery.

Related reports
The authors summarized the clinical variables of patients from a number of studies who underwent laparoscopic endoscopic cooperative surgery, including their own series.

Term explanation
Laparoscopic surgery for submucosal tumors effective and provides a minimally invasive approach for tumors less than 5 cm in diameter.

Experiences and lessons
Laparoscopic endoscopic cooperative surgery is a useful and safe procedure for submucosal tumor that avoids excessive resection of healthy gastric wall.

Peer-review
Further investigations, including a prospective randomized controlled trial and a study exploring long-term consequences, are needed to verify the usefulness of the laparoscopic endoscopic cooperative surgery for gastrointestinal submucosal tumors.

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Contents

Biweekly Volume 7 Number 15 October 25, 2015

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Basic Study

Observational Study

Contents

World Journal of Gastrointestinal Endoscopy
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REVIEW

Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of pancreatic cysts by combined cytopathology and cystic content analysis

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Abstract

Recent advances in imaging technology have resulted in an increase in incidental discoveries of pancreatic cystic lesions. Pancreatic cysts comprise a wide variety of lesions and include non-neoplastic cysts and neoplastic cysts. Because some pancreatic cysts have more of a malignant potential than others, it is absolutely essential that an accurate diagnosis is rendered so that effective care can be given to each patient. In many centers, endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) has emerged as the modality of choice that enables one to distinguish between mucinous and non-mucinous lesion, diagnose malignancy and collect cyst fluid for further diagnostic studies, such as pancreatic enzyme levels, molecular analysis and other tumor biomarkers. The current review will focus on EUS-guided FNA and the cytological diagnosis for pancreatic cysts.

Key words: Pancreatic cyst; Endoscopic ultrasound; Fine needle aspiration; Diagnosis; Cystic fluid analysis; Cytology

Core tip: Pancreatic cysts comprise non-neoplastic cysts and neoplastic cysts. It is absolutely essential that an accurate diagnosis is rendered so that effective care can be given to each patient. In many centers, endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) has emerged as the modality of choice that enables one to distinguish between mucinous and non-mucinous lesion, diagnose malignancy and collect cyst fluid for further diagnostic studies, such as pancreatic enzyme levels, molecular analysis, and other tumor biomarkers. The current review will focus on EUS-guided FNA and the cytological diagnosis and new classification for pancreatic cysts.

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INTRODUCTION

The overall prevalence for cystic lesions of the pancreas has been estimated to be no more than 1% of all pancreatic neoplasms[1]. However, the advent of high-resolution imaging modalities has led to the increased frequency of incidentally discovered pancreatic cysts. In the United States, a prevalence of incidental pancreatic cysts estimates about 2.6% to 13.5% of adults[2-4]. The increasing incidence of pancreatic cystic lesions has been directly linked to increasing age[5]. Pancreatic cystic lesions are also being detected sooner rather than later as reflected in the decreasing median sizes of pancreatic cysts both in the United States and in other countries[6]. Although a recent study suggests that only 2% of pancreatic cysts are malignant at diagnosis[7], the trend of increasing discovery of pancreatic cysts is significant because some types of pancreatic cystic lesions carry an augmented risk for malignant transformation.

Pancreatic cysts comprise a wide variety of lesions and include non-neoplastic cysts and neoplastic cysts. The classification and nomenclature of pancreatic cysts are very important for pathologic and clinical diagnosis. The non-neoplastic cysts include pseudocysts, retention cysts, lymphoepithelial cysts, benign epithelial cysts, and congenital cysts. Non-neoplastic cysts are believed to have low to no malignant potential. Neoplastic cysts are typically categorized as mucinous and non-mucinous based on the type of epithelium they possess[8]. The mucinous cysts consist of mucinous cystic neoplasms (MCN) and intraductal papillary mucinous neoplasms (IPMN). The non-mucinous cysts include serous cystadenomas, solid pseudopapillary neoplasms (SPN), cystic pancreatic neuroendocrine tumors (PNET), cystic pancreatic ductal adenocarcinomas (PDA) and its variants, cholangiocarcinoma, acinar cell carcinoma, high-grade neuroendocrine carcinoma (small cell and large cell), pancreatoblastoma, lymphomas, sarcomas, and metastatic tumors. The neoplastic cysts are categorized as being malignant (*i.e.*, PDA, PNET) or having malignant potential (*i.e.*, MCN, IPMN, SPN). Among mucinous subtypes of cysts, it has also been suggested that branch duct IPMN (BD-IPMN), while having malignant potential, may exhibit more indolent behavior compared to main duct-IPMN[9,10].

The management options for pancreatic cystic lesions are as varied as the lesions they are designed to diagnose and treat. Endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) is a major technique used in many institutions to sample pancreatic cystic lesions. As will be described in this review, there are multiple ways available to further study these lesions, including cytologic diagnosis and cystic content analysis by chemical and molecular tests. A new histologic classification system for pancreatic lesions has also been introduced to help clinicians and patients understand the malignant potential of each type of pancreatic lesion. Based on new diagnosis and classification of the cystic lesions, most patients need no further treatment. However, many patients require surveillance or other more invasive therapies (*i.e.*, surgical resection) depending upon the risk of malignant transformation. Hence, obtaining an accurate differential diagnosis is of utmost importance in properly managing these patients in such a way that minimizes risk of complications[11].

EUS-GUIDED FNA SAMPLES FOR PANCREATIC CYSTS

Initial imaging studies

The initial clinical workup for incidentally discovered pancreatic cysts involves the use of radiologic imaging to further characterize the lesion[12]. MRI with magnetic resonance cholangiopancreatography (MRCP) is the preferred method over pancreatic protocol multidetector (MD) CT because MRCP is able to evaluate the presence of septa, nodules, main-duct involvement, and branch duct involvement. In many cases, it is also able to accurately distinguish between mucinous and non-mucinous cysts[13,14]. Studies have also found that, within the proper clinical context, MRI and CT are capable of determining which pancreatic cystic lesions are more likely to be malignant[15,16]. This is especially true if the features pathognomonic for a given lesion are present. However, in many instances, the combined clinical and radiologic picture is unable to elucidate the type of lesion or its likelihood of harboring malignancy, thus making definitive treatment difficult to achieve. Much of this has to do with the fact that morphologic features of many pancreatic cystic lesions frequently overlap and can appear similar on imaging studies[17]. In this regard, cytologic diagnosis with EUS-FNA is a good means to arriving at a more definitive diagnosis.

EUS-FNA procedure for pancreatic cysts

EUS-guided FNA is a safe procedure that employs the use of an image guidance system and an endoscope that is passed through the esophagus and into the stomach and/or duodenum. Because the importance of obtaining a good sample as well as adequate sample preparation cannot be overemphasized, many centers perform EUS-guided FNA in conjunction with rapid on-site evaluation (ROSE) by a cytopathologist or cytotechnologist. ROSE has been shown to improve the diagnostic yield of specimens and turnaround time obtained by EUS-guided FNA[18-21]. During ROSE, a cytopathologist or cytotechnologist screens air-dried smears that are first stained with rapid-Romanowsky method, such as Diff-Quik® and Hemacolor®, in order to

determine specimen adequacy and to give a preliminary diagnosis, if possible. The rest smears can be alcohol-fixed and stained with the Papanicolaou stain. Additional FNA samples are collected in saline or other alcohol-rich preservative solutions for liquid-based preparations (*i.e.*, ThinPrep®, SurePath®), cytocentrifuge preparations, or cell blocks. Cell blocks are especially helpful in the event that immunohistochemistry is needed to differentiate between the different types of pancreatic lesions. Specimens obtained by EUS-guided FNA can also be used for further diagnostic studies, such as enzymatic testing and molecular testing (to be discussed below in detail in this review).

The advantages of EUS-guided FNA are numerous and include direct real-time visualization of the needle, identification of smaller lesions that can be missed by imaging studies, as well as identification of local metastases and invasion of structures[22]. One study recently showed that the incremental increase in diagnostic yield of EUS and fluid analysis over CT and MRI for prediction of a neoplastic cyst is 36% and 54%, respectively. Complication rates were also low, with pancreatitis being the most common complication (1.1%)[23]. One large prospective multicenter study revealed a complication rate of 6%; bleeding was the most common complication[24]. An extremely rare complication associated with EUS-guided FNA is tumor seeding, especially with IPMN[25-27].

Despite the high specificity of EUS-guided FNA, the main disadvantage that comes with EUS-guided FNA is that samples obtained are often hypocellular. The study by de Jong *et al*[28] showed that a cytopathologic diagnosis was only possible in one-third to one-half of all cases examined. However, it has also been suggested that the sensitivity, which can range from 60% to 100%, often depends upon an institution's experience with the technique[29]. One way to potentially overcome the low sensitivity of this procedure is to do cystic wall puncture (CWP), a procedure in which a targeted FNA of the cyst wall is performed after removal of cyst fluid. One study utilizing this method reported adequate cytologic material in 81% of all cases. Complication rate was minimal with only one patient developing mild pancreatitis post-CWP[30]. The study by Rogart *et al*[31] also showed that CWP may also be helpful in increasing the diagnostic yield of mucinous cystic lesions of the pancreas. Furthermore, there are some important diagnostic pitfalls. For example, GI contamination can cause one to interpret an inadequate specimen as adequate, thus leading to a false-negative diagnosis. Conversely, markedly reactive epithelial cells can be mistaken for malignancy[32,33]. Fortunately, it is possible to avoid these diagnostic pitfalls by making sure cytopathologists have a working knowledge of normal, reactive, and neoplastic pancreatic conditions as well as being sure to correlate all cytologic findings with each patient's clinical history and imaging studies.

DIAGNOSIS OF PANCREATIC CYSTS BY CYTOLOGY

Standardized terminology and classification of pancreatic cysts

Aspirates obtained from EUS-guided FNA are graded in much the same way as aspirates obtained for other non-gynecological specimens. Specimens that lack sufficient cytologic material to render a diagnosis are designated as "unsatisfactory". Specimens that have adequate cytologic material and that are helpful in explaining the presence of a radiologically detected lesion are designated as "satisfactory". Satisfactory specimens are further characterized as "negative for malignancy", "atypical", "benign neoplasm", "suspicious for malignancy" or "positive for malignancy" depending upon the degree of cytologic atypia, cellularity (or lack thereof) and other background features present. Wherever possible, more descriptive terms are also used if a specific pathologic diagnosis can be made. However, there is variable, if not conflicting terminology, used in different institutes and even by individual pathologists. Therefore, tremendous effort has been made to develop a standardized system of classification for pancreatic cytopathology. Recently, Pitman *et al*[34] published a "standardized terminology and nomenclature for pancreatobiliary cytology: The Papanicolaou Society of Cytopathology Guidelines" (see modified guideline in Table 1). In their categorization, "Non-Diagnostic" lesions are in Category I, lesions classified as "Negative for Malignancy" are in Category Ⅱ, "Atypical" lesions are in Category Ⅲ, lesions classified as "Suspicious for Malignancy" are in Category Ⅴ, and lesions that are "Malignant" are in Category Ⅵ. Category Ⅳ consists of Category ⅣA for "Neoplastic: Benign" and Category ⅣB for "Neoplastic: Other". Serous cystadenoma is the main neoplasm in Category ⅣA. In Category ⅣB, they include both mucinous neoplasms, such as IPMN and MCN, and non-mucinous neoplasms, such as pancreatic endocrine tumor. However, as detailed below, the morphologic, molecular, and immunohistochemical features are very different for these lesions, with mucinous neoplasms having a greater potential to become malignant than non-mucinous neoplasms. Therefore, we suggest that Category ⅣB should be further separated into Category ⅣB1 as "Neoplastic: Mucinous neoplasm" and Category ⅣB2 as "Neoplastic: Non-mucinous neoplasm". IPMN, MCN, and intraductal papillary neoplasm of the bile ducts should be included in Category ⅣB1, and pancreatic endocrine neoplasm, SPN, and the rare gastrointestinal stromal tumor should be in Category ⅣB2. Nevertheless, this classification system serves a significant step towards a much needed uniform categorization of these lesions. Ultimately, the authors hope that each category of pancreatic tumor will be further discussed with gastroenterologists, GI surgeons, and GI oncologists. The following section will

Table 1 Pancreatic cytology terminology (modified from pitman *et al*[34], 2014)

Terminology category	Definition	Example interpretations
Category Ⅰ: Non-diagnostic	No diagnostic or useful information about the solid or cystic lesion sampled	Gastrointestinal contamination only; Non-specific cyst contents with insufficient cyst fluid volume for ancillary testing; Evaluation limited by scant cellularity
Category Ⅱ: Negative (for malignancy)	Adequate cellular and/or extracellular tissue to evaluate	Benign pancreatobiliary tissue in the setting of vague fullness and no discrete mass Acute pancreatitis Chronic pancreatitis Autoimmune pancreatitis Pseudocysts Lymph epithelial cyst Spleenful/accessory spleen
Category Ⅲ: Atypical	Cells present with cytoplasmic, nuclear, or architectural features that are not consistent with normal or reactive cellular changes of the pancreas or bile ducts and are insufficient to classify them as a neoplasm or suspicious for a high-grade malignancy	Atypical ductal cells obscured by crush artifact Scant population of small monomorphic polygonal cells of unclear origin: Normal cigar cells *vs* endocrine proliferation Atypical bile duct epithelium with nuclear features suggestive of repair in a background of acute inflammation Atypical bile duct epithelium with mucinous metaplasia and mild nuclear atypia
Category ⅣA: Neoplastic: Benign	The presence of a cytological specimen sufficiently cellular and representative, with or without the context of clinical, imaging and ancillary studies, to be diagnostic of a benign neoplasm	Scant non-mucinous cuboidal epithelium and scant hemosiderin-laden macrophages in a non-mucinous cyst fluid consistent with the clinical impression of a serous cystadenoma
Category ⅣB1: Neoplastic: Mucinous neoplasm	Premalignant such as intraductal papillary neoplasm of the bile ducts (IPN-B), IPMN or MCN with low, intermediate or high-grade dysplasia by cytological criteria	MCN: Typically a multiloculated, mucin-producing epithelial neoplasm with sub epithelial ovarian-type stroma that in almost all cases does not communicate with the pancreatic ductal system and in almost all cases occurs in women; located in the body or tail; easily removed comparing life-long surveillance IPMN: Primarily intraductal proliferations of ductal epithelium creating a macroscopic lesion resulting in ductal dilatation, cyst formation and/or a mass lesion 1 Main-duct IPMN: Associated with diffuse dilatation of any portion of the main pancreatic duct or the entire pancreas 2 BD-IPMN: Cysts adjacent to a non-dilated main pancreatic duct IPN-B: A papillary proliferation of mucin containing neoplastic cells that may occur anywhere in the ductal system; similar to IPMN
Category ⅣB2: Neoplastic: Non-mucinous neoplasm	A low-grade malignant neoplasm such as well-differentiated PanNET, SPN or rare GIST	PanNET (pancreatic endocrine tumor and pancreatic endocrine neoplasm): A well-differentiated proliferation of the pancreatic endocrine cells creating a mass lesion greater than 0.5 cm that may or may not be functional by producing inappropriate levels of various hormones and that may or may not demonstrate aggressive features on histological examination SPN: A solid, secondarily cystic low-grade epithelial neoplasm with established clonal mutations in cancer-associated genes and an ability to metastasize GIST: Spindle cell and/or epithelioid mesenchymal neoplasms with differentiation along the lines of the interstitial cell of Cajal that usually expression c-kit protein (CD117), DOG1 and CD34 by immunohistochemistry; located in a peripanreatic location
Category Ⅴ: Suspicious (for malignancy)	when some, but an insufficient number of the typical features of a specific malignant neoplasm are present, mainly pancreatic adenocarcinoma	Rare markedly atypical epithelial cells suspicious for adenocarcinoma Mucinous cyst with high-grade epithelial atypia and abundant coagulate necrosis suspicious for invasive carcinoma Solid cellular neoplasm with features suspicious for acinar cell carcinoma. Tissue for confirmatory ancillary studies is not available
Category ⅥA: PDAC and variants	A group of neoplasms that unequivocally display malignant cytological characteristics and include PDAC and its variants, cholangiocarcinoma, acinar cell carcinoma, high-grade neuroendocrine carcinoma (small cell and large cell), pancreatoblastoma, lymphomas, sarcomas and metastases to the pancreas	PDAC: A malignant invasive gland (duct) forming epithelial neoplasm typically composed of classic tubular glands; 85%-90% of all pancreatic malignancies Colloid carcinoma (mucinous, non-cystic): Abundant extracellular mucin production, with at least 80% of the tumor on histology demonstrating large pools of extracellular mucin and cuboidal epithelial cells "floating" in the mucin

		Medullary carcinoma: Poor histologic differentiation, syncytial growth pattern, pushing borders and an intense lymphoplasmacytic response Undifferentiated carcinoma with osteoclast-like giant cells: Distinctive type of sarcomatoid carcinoma with the striking and unique cytohistologic features characterized by a prominent component of reactive osteoclast-like giant cells in a background of spindle cells. Undifferentiated carcinoma: A high-grade carcinoma composed of large, undifferentiated, markedly pleomorphic cells; 2%-7% of PDAC
Category ⅥA: Malignancy: Others	A group of neoplasms that unequivocally display malignant cytologic characteristics excluding PDAC and its variants; including acinar cell carcinoma, high-grade neuroendocrine carcinoma (small cell and large cell), cholangiocarcinoma, pancreatoblastoma, lymphomas, sarcomas and metastases to the pancreas	Cholangiocarcinoma: The diagnostic criteria for invasive cholangiocarcinoma are the same as for ductal adenocarcinoma; usually diagnosis by bile duct brushings with high false negative rate due to overlying benign epithelium, insufficient sampling, reactive change with stent; degeneration due to bile Acinar cell carcinoma: A rare malignant epithelial neoplasm with exocrine acinar differentiation Poorly-differentiated neuroendocrine carcinoma (small cell carcinoma or large cell neuroendocrine carcinoma): Rare high-grade neuroendocrine tumor with < 1% of pancreatic tumor and 2%-3% of PanNETs Pancreatoblastoma: A rare neoplasm, primarily of childhood, characterized by acinar differentiation, endocrine differentiation and distinctive squamoid nests Non-Hodgkin lymphoma: Rare and usually involve the pancreas secondarily Metastatic tumors: Secondary neoplasms involving the pancreas are rare; most common: Renal cell carcinoma

MCN: Mucinous cystic neoplasms; IPN-B: Intraductal papillary neoplasm of the bile ducts; IPMN: Intraductal papillary mucinous neoplasm; cPanNET: Pancreatic neuroendocrine tumor; SPN: Solid pseudopapillary neoplasms; PDAC: Pancreatic ductal adenocarcinomas.

now describe the cytologic features of some of the more common pancreatic cystic lesions in accordance with the current classification described by Pitman *et al*[34].

Pseudo cyst (category Ⅱ: Negative): Pseudocysts are the most common type of pancreatic cysts, accounting for at least 75% of all pancreatic cystic lesions. They generally arise in the setting of acute pancreatitis and are due to autodigestion of the pancreatic parenchyma. By definition, pseudocysts lack an epithelial lining and are instead composed of an inflammatory, fibrous capsule surrounding a region of necrosis. Aspirates are typically paucicellular and consist of granular debris, hemosiderin-laden macrophages, and bile (Figure 1A).

Lymphangiomas and lymphoepithelial cysts (category Ⅱ: Negative): Lymphangiomas and lymphoepithelial cysts are both very rare benign lesions of the pancreas. The former is characterized cytologically by a uniform population of small, round lymphocytes accompanied by histiocytes, plasma cells, centrocytes, and centroblasts, whereas the latter is characterized by numerous anucleated squamous cells and amorphous debris with rare to no lymphocytes present. Aspirates from lymphangiomas tend to be very cellular[35] (Figure 1B); however, aspirates from lymphoepithelial cysts are largely acellular. Although EUS-guided FNA may have a limited role in identifying lymphoepithelial cysts, it has been proposed that paying attention to signal intensity on MRI may be helpful in identifying these lesions preoperatively[36].

Serous cystadenoma (category ⅣA: Neoplastic: benign): Serous cystadenomas comprise 1% to 2% of all pancreatic neoplasms. There are two types that are named based on the number and size of its cysts. Serous microcystic adenomas, which are the more common of the two types, have numerous small cysts, whereas serous oligocystic adenomas have fewer but larger cysts. Serous cystadenomas occur most frequently in older women, with the preferred sites being the body and tail of the pancreas. Aspirates of serous cystadenomas are sparsely cellular and may contain rare fragments of flat sheets and/or loose clusters of cuboidal cells with glycogenated cytoplasm and indistinct cytoplasmic borders (Figure 1C).

Mucinous neoplasm (category ⅣB: Neoplastic: others): There are two distinctive types of mucinous tumors, namely MCN and IPMN. Because both of these entities share many morphologic features, it is almost impossible to tell the difference between the two based on cytomorphologic features alone. In these cases, direct correlation with clinical and imaging studies is required. In general, MCNs occur almost exclusively in middle-aged women, with most being located in the body or tail of the pancreas. Of note, these lesions are closed cysts that do not communicate with the ductal system. A defining histologic feature of these lesions is the presence of ovarian-type stroma directly beneath mucinous epithelium that is positive for estrogen and progesterone receptors. On the other hand, IPMN is seen more commonly in men and are typically seen in the head of the pancreas. Unlike MCN, IPMN is radiologically shown to communicate with the ductal system (typically involving the main pancreatic duct)

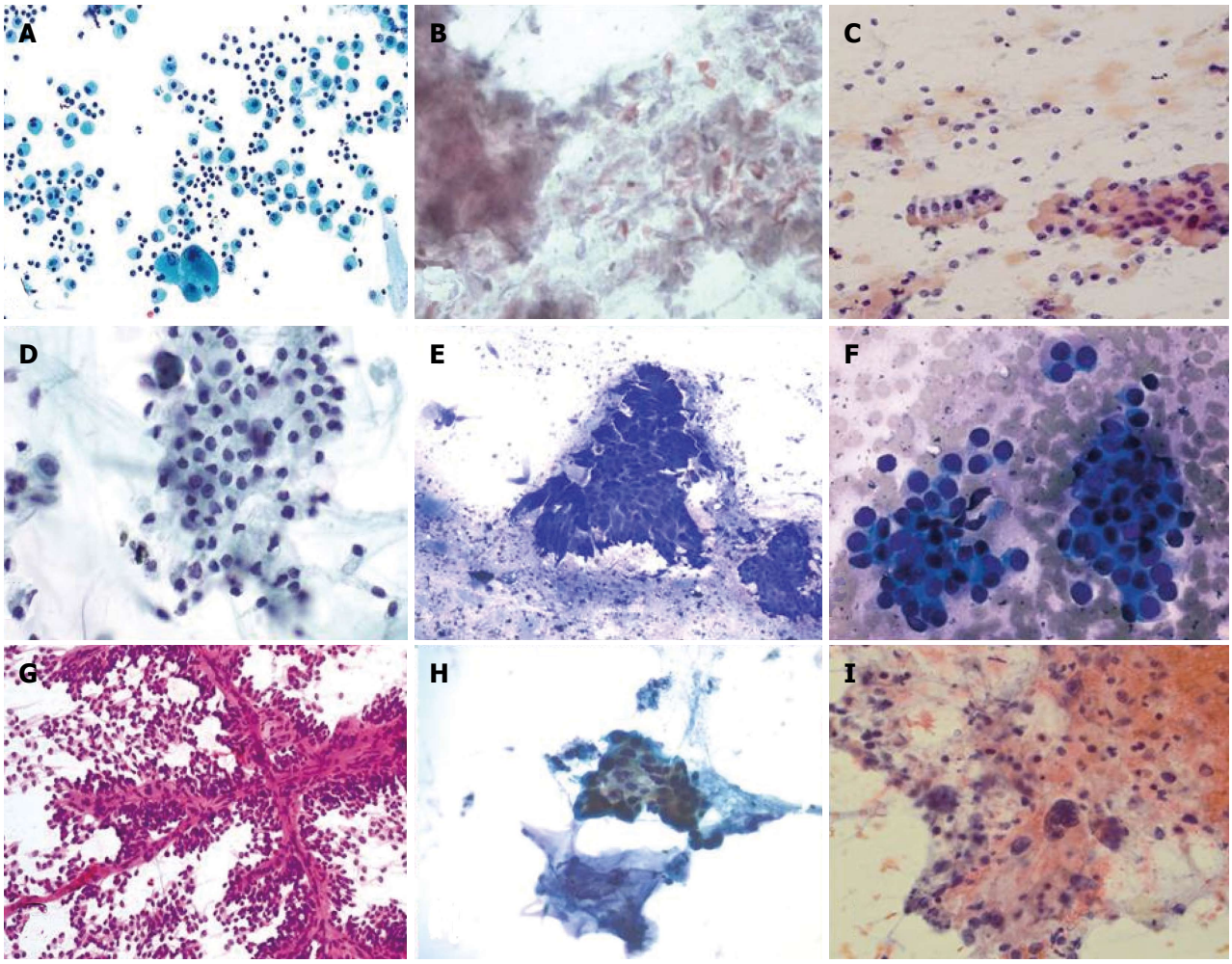

Figure 1 Cytopathologic features of pancreatic cysts. A: Pseudocyst: Notice the macrophages and inflammatory cells; epithelial cells are not seen; B: Lymphoepithelial cyst: Numerous anucleated squamous cells and keratinized debris are seen; C: Serous cystadenoma: One group of bland, monomorphic epithelial cells is present along with background histiocytes; D: Mucinous cystic neoplasm: A sheet of columnar cells with low-grad dysplasia in the background of mucin; E: Intraductal papillary neoplasm: Large papillary clusters are lined by tall, columnar cells containing intracytoplasmic mucin in the background extracellular mucin; F: Pancreatic neuroendocrine neoplasm: Bland, monomorphic epithelial cells with eccentrically placed nuclei arranged singly and in clusters characterizes this lesion; G: Solid pseudopapillary neoplasm: Notice the delicate, branching vessels and the poorly cohesive, bland epithelial cells; H: Pancreatic ductal adenocarcinoma with mucinous cyst: The ductal cells are arranged haphazardly and are characterized by hyperchromasia, nuclear pleomorphism and irregular nuclear contour; I: Undifferentiated carcinoma with osteoclast-like giant cells and mucinous cystic neoplasm: Multiple osteoclast-like giant cells and large haphazardly nucleus in the background of mucin.

and has the ability to grow along the entire length of the pancreatic duct and its branches. Aspirates of MCN and IPMN are hypocellular specimens that contain thick mucin and, if present, columnar mucinous sheets (Figure 1D and E). Cytologic interpretation is somewhat less problematic if nuclear and architectural atypia indicative of dysplasia or malignancy is identified. The WHO uses a three-tier classification based on degree of dysplasia present: benign, borderline, or malignant. Recent years, molecular tests such as KRAS and GNAS mutation are developed for differentiating MCN and IPMN. Nevertheless, given the malignant potential of these lesions, surgical resection is the most often utilized treatment of choice. Since cystic mucinous neoplasms have unique cytopathologic, molecular features and high risk for malignancy compared to non-mucinous neoplasms, we suggest that the Category Ⅳ B should be separated into two subcategories: Category ⅣB1: Neoplastic: Mucinous and ⅣB2: Neoplastic: Non-mucinous.

Cystic PNET (category ⅣB: Neoplastic: others): PNET represent approximately 1% to 2% of pancreatic neoplasms. Most PNET are small, functional solid tumors, but cystic pancreatic neuroendocrine tumors (cPanNETs) account for 13% to 17% of PanNETs[37]. PNET can secrete a variety of hormones, including insulin, glucagon, and somatostatin, and adrenocorticotrophic hormone. Although they can occur in any age group, they most commonly occur in adults. Aspirates of well-differentiated PNETs can range from sparsely cellular to highly cellular specimens consisting predominantly of abundant isolated cells and numerous bare nuclei. However, loosely cohesive clusters of cells and pseu-

dorosette formation are not uncommon. The cells are characterized by uniformly round, eccentrically placed nuclei with "salt-and-pepper" chromatin and moderate amounts of cytoplasm (Figure 1F). More poorly differentiated PNETs display more nuclear pleomorphic and higher mitotic activity. In doubtful cases, immunohistochemical stains for chromogranin and synaptophysin can be extremely helpful in confirming the diagnosis if the cell block is available. The surgical resection is the first line treatment. Enucleation or cytoreductive surgery is also recommended for patients with locoregional recurrences or hepatic metastases. Regional adjuvants such as radiofrequency ablation, transarterial chemoembolization, and others are often employed in an attempt to palliate symptoms and prolong survival[38]. Again, because cystic PNETs can be both functional and non-functional tumors with special morphological and immunohistochemical features, it should be separated from MCN into category IVB2: Neoplastic: Non-mucinous.

SPN (category ⅣB: Neoplastic: others): SPN are uncommon tumors of unknown malignant potential that predominantly occur in young women. Aspirates of these lesions are highly cellular, with the most characteristic features being myxoid or hyalinized vascular stalks lined by single or multiple layers of cells exhibiting round to oval nuclei, nuclear grooves, and indistinct cell borders (Figure 1G). Immunostain for β-catenin with nuclear positivity has emerged as a helpful attribute in diagnosing SPN. Other immunohistochemical stains that are helpful in confirming the diagnosis include CD10, CD56, vimentin and SMAD4. Surgical resection of these tumors leads to a good prognosis. With the special morphological features and immunohistochemical features of these lesions, SPN should be classified as Category ⅣB2: Neoplastic: non-mucinous.

Pancreatic ductal adenocarcinoma with cystic neoplasm (Category Ⅵ: Malignant): Pancreatic ductal adenocarcinomas (PDAC) with cystic neoplasm is the most common malignant cystic neoplasm of the pancreas and usually arises from MCN and IPMN. PDAC typically occur in older individuals, with smoking and alcohol abuse being major risk factors. Despite being able to detect these lesions at earlier stages, long term survival remains abysmal, with 90% of all patients dying within one year of diagnosis. Cytologically, aspirates are usually very cellular and consist of atypical ductal cells with irregular nuclear contours and prominent, centrally placed nucleoli arranged singly or in clusters and sheets (Figure 1H). Mitotic figures can also be seen.

Sensitivity and specificity of cytology based EUS-guided FNA

Although it has been established that EUS-guided FNA has a valuable role in the multidisciplinary approach to the management of pancreatic cystic lesions, much controversy remains in regards to its ability to accurately triage patients with incidentally discovered lesions that appear benign on imaging. In one of the early studies performed by Frossard *et al*[39] in 2003, it was determined that EUS-guided FNA successfully identified the lesion of interest in 65 cases (97%). The overall sensitivity, specificity, positive predictive value, and negative predictive value for EUS-guided FNA in this study were 97%, 100%, 100%, and 95%, respectively[39]. The cytologic diagnosis of cystic lesions with EUS-FNA has been studied extensively with widely variable sensitivity[40-44]. The sensitivity has been reported to range from 23% to 100% and specificity has been reported to range from 71% to 100%[40,45,46]. One meta-analysis showed that the pooled sensitivity and specificity in diagnosing mucinous cystic lesions were 63% and 88%, respectively, in 11 studies and 54% and 92%, respectively, in 4 prospective studies[45]. In one recently published meta-analysis study, the sensitivity and specificity of cytology was 0.42 and 0.99; the sensitivity and specificity of K-RAS was 0.39 and 0.95; and the sensitivity and specificity of the combined test of cytology and K-RAS was 0.71 and 0.88, respectively[47]. The sensitivity in our study (47%) was between two meta-analysis results[46]. We further studied the false negative rate of EUS-FNA, and we found that the false-negative rate (3%) caused by an interpretative error was significantly lower than that caused by a sampling error (23%) (P = 0.003). This finding suggests that sampling error, rather than interpretative error by cytology, is a major cause of high false-negative rates. We further examined the false-negative rate for solid lesions and cystic lesions. The false-negative rate for cystic lesions was significantly higher than that for solid lesions (53% *vs* 15%; P = 0.005). Recently, Rogart *et al*[31] reported that cyst wall puncture performed during FNA improved the diagnostic yield for mucinous cysts[31]. In addition, cytologic classification with high-grade epithelial atypia in cystic lesion FNA specimens demonstrated a higher prediction for malignancy and added value for the clinical evaluation of cystic lesions[42,48]. One study also found that certain factors, such as the identification of a solid component and performing more than one pass, resulted in significant increases in sensitivity (as high as 78%)[49]. In light of these issues with sensitivity, a newer series has suggested that EUS-guided FNA, when used in conjunction with other "screening" tests, contributes to a triple-negative screening test (*i.e.*, no high-risk stigmata, no worrisome features, and no high grade atypia on cytology) that has a negative predictive value for malignancy of 99%[50]. In general, EUS-guided FNA has a low sensitivity, but good specificity[45]. More sensitive and specific techniques are needed and should be developed as new technologies emerge, such as cystic fluid analysis by chemical or molecular tests and confocal laser endomicroscopy.

Recently, cystic PNET diagnosis and management received a lot of attention. In one study, cytology made a specific diagnosis of a cystic PNET in 71% of the biopsies

compared with a specific diagnosis by EUS in 38% of cases[37]. All cysts but one revealed low carcinoembryonic antigen (CEA) levels (range, 0.2 to > 500 ng/mL; mean, 29.5 ng/mL), and amylase levels were < 500 U/L in all but 2 cases (range, 16-1493 U/L; mean, 205 U/L). In another study, cystic PNETs were found to be larger than solid PNETs (mean 26.8 mm *vs* 20.1 mm, $P = 0.05$) and more frequently nonfunctional (96% *vs* 80%, $P = 0.03$). With histology as the reference standard, EUS-FNA accuracies for malignancy of cystic and solid PNETs were 89.3% and 90%, respectively; cystic PNETs were less associated with metastatic adenopathy (22% *vs* 42%, $P = 0.03$) and liver metastasis (0% *vs* 26%, $P < 0.001$). Cystic fluid analysis ($n = 13$), showed benign cystic PNETs had low CEA, Ki-67 ⩽ 2%, and no loss of heterozygosity (LOH). Patients with cystic and solid PNETs had similar recurrence risk up to 5 years after complete resection[51]. In one review which compared EUS and EUS-FNA for cystic PNET, they found that EUS-FNA cytology and cyst fluid analysis is a useful adjunct to abdominal imaging in the diagnosis of pancreatic cystic lesions. They hypothesize that cyst fluid characteristics, including cytomorphological features, is the most accurate test to achieve a preoperative diagnosis and to provide a basis for prognostic prediction[52].

Another technique that shows promise in improving the sensitivity and specificity of detecting and diagnosing pancreatic cystic lesions is confocal laser endomicroscopy. Confocal laser endomicroscopy is a novel imaging technology in which a low-power laser illuminates and scans a single focal plane of the tissue[53-56]. This technique allows for the detection of the microscopic detail of the surface epithelium in pancreatic cysts. Needle-based confocal laser endomicroscopy (nCLE) utilizes a sub-millimeter probe that is compatible with an EUS needle and enables real-time imaging with microscopic detail of pancreatic cystic lesions[56]. The presence of epithelial villous structures based on nCLE was associated with pancreatic cystic neoplasm ($P = 0.004$) and provided a sensitivity of 59%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 50%. This technique is rather new for evaluating the pancreatic cystic lesions. However, we believe that the development of this new technique may facilitate sampling the most suspicious area of a cyst in the future.

CYST FLUID ANALYSIS

As mentioned previously, pancreatic cystic neoplasms represent a diagnostic challenge for EUS-guided FNA because lining cells may or may not be adequately sampled, thus precluding further classification. The current way of solving this dilemma relies upon a combination of methods and includes visual cyst fluid evaluation at the time of immediate assessment, chemical analysis of cyst fluid, and molecular testing. All of these tests can be utilized to help to differentiate between mucinous and non-mucinous cysts.

Non-molecular methods

The possibility of a mucinous cyst can be strongly suggested by looking for the "string sign". This can be assessed by stretching out a drop of cyst fluid between the thumb and index finger and subsequently measuring the length of the string of cyst fluid. A length of at least 3.5 mm is believed to be consistent with that of a mucinous cyst. Studies have also shown that mucinous cysts consistently have a higher relative viscosity compared to serum, whereas the opposite is true for non-mucinous cysts, which a lower relative viscosity compared to serum[57].

Amylase: The chemical analysis of cyst fluid relies upon examining pancreatic enzyme levels as well as the presence of tumor markers. Pancreatic enzyme levels are typically used to differentiate between pseudocysts and neoplastic cysts. One of the most important enzymes studied in making this distinction is amylase. Pseudocysts and other non-neoplastic cysts consistently show elevated levels of amylase. In fact, one study showed that an amylase level below 250 U/L virtually excludes pseudocysts from the differential diagnosis[58]. Conversely, amylase is low in neoplastic cysts.

CEA: A variety of tumor markers have been studied for their ability to discriminate between mucinous and non-mucinous cysts[57-60]. According to many studies, CEA levels are the most accurate[60,61]. Although CEA cutoff values of > 192 ng/mL have been shown to have an accuracy of 79%[60], levels > 800 ng/mL have been shown to be highly predictive of mucinous neoplasms with a specificity of 98%. Unfortunately, the sensitivity, even at these markedly elevated levels, is still less than 50%[58]. It is also important to note that CEA cannot be used to distinguish between benign and malignant lesions[62,63]. Amylase, however, may be helpful in this regard[64]. In contrast, a very low CEA level ⩽ 5 is 95% specific for pseudocysts, neuroendocrine tumors, and serous cystadenoma[58].

Other markers: Multiple biomarkers have also been studied to identify pancreatic ductal carcinoma (PDAC). Plectin-1, a marker related to PDAC, was found to be a potentially promising biomarker for the detection of malignancy in IPMNs[65]. Plectin-1 expression was assayed using immunohistochemistry in cyst fluid and tissue sample from benign and malignant IPMN, as well as lymph node metastasis from carcinoma arising from IPMN. The sensitivity and specificity were 84% and 83%, respectively. In animal models, Cathepsin E is specifically and highly expressed in PDAC and pancreatic intraepithelial neoplasias (PanINs), A prospective double-blind control study was performed to evaluate the accuracy of this method in diagnosing PDAC and PanINs of all grades (> 82.7%)[66].

Molecular methods

K-RAS mutation: Molecular analysis of cyst fluid shows

Table 2 Criteria for integrated molecular pathology diagnostic categories

Diagnostic category	Molecular criteria[1]	Co-existing concerning clinical features[2]
Benign	DNA lacks molecular criteria	Not considered for this diagnosis
Statistically indolent	DNA meets 1 molecular criterion	None
SHR	DNA meets 1 molecular criterion	1 or more
Aggressive	DNA meets at least 2 molecular criteria	Not considered for this diagnosis

[1]Four molecular criteria that have been independently correlated with pancreatic malignancy or high-grade dysplasia are used to make an integrated molecular pathology diagnosis: (1) a single high-clonality mutation; (2) elevated level of high-quality DNA; (3) multiple low-clonality mutations; and (4) a single low-clonality oncogene mutation; [2]Include any of the following: cyst size > 3 cm, growth rate > 3 mm/year, duct dilation > 1 cm, carcinoembryonic antigen level > 1000 ng/mL, cytologic evidence of high-grade dysplasia. (Table 2 from Al-Haddad *et al*[75] 2015 was permitted by publisher). SHR: Statistically higher risk.

promise in distinguishing not only between mucinous and non-mucinous cysts, but also in the diagnosis of malignant cysts. One study that examined surgically resected specimens showed that the identification of the K-RAS mutation had a sensitivity of 54% and a specificity of 100% for mucinous cysts. The combined used of CEA and K-RAS improved the sensitivity to 83% while decreasing the specificity to 85%[67]. However, a smaller study found that there was no increase in sensitivity when combining CEA and K-RAS[68]. LOH and increased DNA quantity have also been tried as a means of accurately predicting the presence of a mucinous lesion, but the sensitivity for each method is less than 11%. However, the detection of any molecular changes (*i.e.*, K-RAS mutation, LOH, or increased DNA quantity) has been found to be 90% specific for mucinous cysts[12]. Recently, one meta-analysis study found that the sensitivity and specificity of K-RAS was 0.39 and 0.95; and the sensitivity and specificity of the combined test of cytology and K-RAS was 0.71 and 0.88, respectively[47]. The K-RAS mutation combined with cytology test greatly increases the sensitivity of EUS-FNA. K-RAS mutation analysis may also prove to be a powerful ancillary for testing cystic samples with scant cellularity.

GNAS mutation: Another diagnostic marker that has received considerable interest is the presence of GNAS mutations. Recent studies have shown that GNAS mutations can be detected in IPMNs[69,70]. It has also been shown that the combination of GNAS and KRAS mutations in cyst fluid is very specific for IPMNs. One study found GNAS mutations to be significantly more prevalent in IPMNs (42%) than in SCAs (10%), adenocarcinomas (0%), and MCNs (0%). This same study also showed that double GNAS and KRAS mutations only occur in IPMNs (P = 0.006) and that mutations in either gene equated to a sensitivity of 98% and a specificity of 84%[71]. GNAS mutations are rare to absent in MCN, SCA, PNET, or PDAC.

MicroRNA change: MicroRNA (miRNA) expression profiles have also received considerable interest and are currently being studied as another way to characterize pancreatic lesions. miRNA is nineteen to twenty-four nucleotide long single-stranded, non-coding regions of RNA that are highly stable and which may be useful in diagnosing various malignancies as well as pancreatic cystic neoplasms. In a recent study, together with IPMN surgical specimens, 65 cyst fluid samples were examined for differential selective miRNA candidate expression. A subset of 18 miRNAs separated high-grade from low-grade lesions. A logistic regression model using nine miRNAs allowed prediction of high-grade IPMNs, PNET and SPN *vs* low-grade IPMNs and SCA with a sensitivity of 89%, a specificity of 100% and area under ROC curve of 1[72]. Another study evaluated miRNA in 69 pathology specimens and identified several miRNA panels that enabled them to differentiate SCA from MCN and IPMN, and MCN from BD-IPMN with a sensitivity ranging from 85%-100% and a specificity of 100%[73].

Integrated molecular pathology: Perhaps the greatest dilemma in managing pancreatic cysts is the fact that none of the currently recommended guidelines can accurately predict the malignant potential of pancreatic cysts. For example, the current IAP 2012 criteria risk stratifies patients into two categories: "surveillance" criteria (low malignant potential) and "surgery" criteria (high malignant potential). Symptomatic patients with mucinous cysts and at least one other "high-risk stigmata" (*i.e.*, obstructive jaundice with a cyst located in the pancreatic head, a post-contrast enhancing solid component, a main pancreatic duct diameter $\geqslant$ 1 cm, abrupt change in duct caliber, cyst size $\geqslant$ 3 cm, presumptive diagnosis of MCN, and "suspicious" cytology) as detailed by the 2012 International Association of Pancreatology (IAP) guidelines should be referred for surgery[74]. Patients with cysts less than 1 cm and no concerning radiologic features can be monitored with periodic imaging studies. If more worrisome features are detected, the patients are subsequently referred for EUS-guided FNA to help determine the nature of the cyst (*i.e.*, mucinous versus non-mucinous) and whether malignancy is present. Nevertheless, given the high mortality rate for pancreatic cancer, the IAP ultimately recommends that any patient with "worrisome" features associated with malignancy undergo surgery. However, it has

been shown that approximately 60%-80% of patients undergoing surgery often have non-malignant disease. Therefore, other methods that prevent overtreatment of benign disease while providing early detection of cancer are needed.

Integrated molecular pathology (IMP) testing addresses this need it that incorporates all of the testing methods mentioned above (*i.e.*, cytology, imaging studies, fluid chemistry, and molecular analysis). Unlike other guidelines, it utilizes four different diagnostic categories of "benign", "statistically indolent", "statistically higher risk", or SHR, and "aggressive" based on both the number of molecular criterion met and other clinical features, if applicable (Table 2)[75]. In one study, 492 patients were categorized using IMP. Follow up for at least three years was available for 46% of patients. The overall accuracy was found to be 90%, and the specificity and negative predictive value were 91% and 97%, respectively. The sensitivity for malignant outcome with this cohort of patients was 83%, and the positive predictive value was 58%. When compared to the 2012 IAP criteria, it was found that the IAP criteria and IMP showed similar sensitivity and negative likelihood ratios. However, there was a statistically significant difference between the IAP guidelines and the IMP in that the specificity and positive likelihood ratios were higher using IMP criteria. These findings suggest that IMP is very useful in not only risk stratifying patients, but also in preventing patients with indolent disease from undergoing unnecessary surgeries[75].

CONCLUSION

EUS-guided FNA serves a pivotal role in the accurate diagnosis of incidentally discovered pancreatic cysts. Its advantages over imaging alone include the ability to confirm the presence or absence of suspicious features identified on radiologic imaging, determine whether a lesion is malignant, and monitor for changes in cystic lesions. The new classification schema, while not perfect, goes hand-in-hand with the role of EUS-guided FNA in that it helps clinicians and patients to have a better understanding of which lesions need to be treated as opposed to those which do not, thus sparing patients from undergoing procedures that may result in increased morbidity and/or mortality. Despite these advantages, arriving at a proper diagnosis still requires the integrated use of clinical, radiologic, and cytological findings. Newer chemical and molecular studies show promise in improving the ability of clinicians to effectively diagnose and treat these lesions.

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REVIEW

Imaging of common bile duct by linear endoscopic ultrasound

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Abstract

Imaging of common bile duct (CBD) can be done by many techniques. Endoscopic retrograde cholangiopancreaticography is considered the gold standard for imaging of CBD. A standard technique of imaging of CBD by endoscopic ultrasound (EUS) has not been specifically described. The available descriptions mention different stations of imaging from the stomach and duodenum. The CBD lies closest to duodenum and choice of imaging may be restricted to duodenum for many operators. Generally most operators prefer multi station imaging during EUS and the choice of selecting the initial station varies from operator to operator. Detailed evaluation of CBD is frequently the main focus of imaging during EUS and in such situations multi station imaging with a high-resolution ultrasound scanner may provide useful information. Examination of the CBD is one of the primary indications for doing an EUS and it can be done from five stations: (1) the fundus of stomach; (2) body of stomach; (3) duodenal bulb; (4) descending duodenum; and (5) antrum. Following down the upper 1/3rd of CBD can do imaging of entire CBD from the liver window and following up the lower 1/3rd of CBD can do imaging of entire CBD from the pancreatic window. This article aims at simplifying the techniques of imaging of CBD by linear EUS.

Key words: Endoscopic ultrasound; Common bile duct; Pancreas; Pancreatic duct; Portal vein

Core tip: Endoscopic ultrasound (EUS) is a new technology which has a steep learning curve. It is difficult to learn EUS as the standard techniques of EUS imaging have not been established. The common description of every organ or structure has been done by a station-wise imaging by most of the authors. The imaging of common bile duct (CBD) is an important part of EUS examination. The techniques of imaging of CBD by EUS have not been defined so far. This article aims at simplifying the techniques of imaging of CBD by linear EUS.

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INTRODUCTION

The common bile duct (CBD) can be imaged by many imaging modalities. Endoscopic ultrasound (EUS) is closest to endoscopic retrograde cholangio pancreaticography, which is the gold standard for imaging of CBD. A standard technique of imaging of CBD by EUS has not been specifically described and the available descriptions mention different stations of imaging from the stomach and duodenum[1-12]. Most operators prefer multi station imaging during EUS and the choice of selecting the initial station varies from operator to operator. The CBD lies closest to duodenum and choice of imaging may be restricted to duodenum for many operators where the imaging scanners do not allow deep image penetration. Detailed evaluation of CBD is frequently the main focus of imaging during EUS and in such situations multi station imaging with a high-resolution ultrasound scanner may provide useful information. In this article we review the techniques of linear imaging of CBD by EUS.

Applied anatomy of extra hepatic biliary tract

The right and left hepatic ducts unite in the hilar plate close to the right end of porta hepatis in front of right branch of portal vein to form the common hepatic duct (CHD). The cystic duct (length, 3-4 cm) runs postero inferiorly and to the left from the neck of gall bladder to join the right border of CHD at an acute angle. The CBD is 6.0 to 8.0 cm long and is generally divided into supraduodenal (upper 1/3rd), retroduodenal (middle 1/3rd), retropancreatic (lower 1/3rd) and intraduodenal segments. The supraduodenal CBD lies in the right border of lesser omentum (hepato-duodenal ligament) anterior to portal vein and to the left of hepatic artery proper[1]. The retroduodenal part passes behind the superior part of duodenum, to the right of gastroduodenal artery and in front of portal vein. The retropancreatic part runs behind the head of the pancreas to reach the medial border of second part of duodenum. In the retropancreatic course, CBD is intrapancreatic in 83% and retropancreatic in 17% cases[2]. The CBD and the main pancreatic duct (of Wirsung) unite to form the common channel (hepatopancreatic ampulla of Vater) which opens at the major duodenal papilla 8 cm distal to pylorus. The formation of a common channel occurs in 85% cases and in the rest 15% cases, the two ducts either open separately or form a V junction before opening.

Materials and methods

All images in the present study have been generated from a detailed review of real-time recordings using the curved linear scanning echoendoscope EG-3830 UT (Pentax corporation, Tokyo, Japan), coupled with a Hitachi Avius and Hitachi 7500 processor (Hitachi Aloka Medical, Tokyo, Japan). Our image orientation is with the cranial aspect of the patient directed towards the right side of the screen. Four positions are commonly used during imaging from EUS: (1) the neutral position is where the front of the handle is facing the patient; (2) the open position to left is where the front of the handle is facing the patient's feet. It is reached by turning anti clockwise through 90° from the neutral position; (3) the open position to right is the opposite of the open position to left. It is reached by turning clockwise through 90° from the neutral position; and (4) a further 90° rotation from open position to right can bring the handle in a position opposite to the neutral position.

Stations of imaging

EUS of the CBD can be done from five stations: (1) the fundus of stomach; (2) body of stomach; (3) duodenal bulb; (4) descending duodenum; and (5) antrum (Figure 1 and Table 1).

MOVEMENTS DURING IMAGING

Rotation of the scope is the most important key to linear imaging of CBD. Rotation moves the imaging axis from one part of bile duct to other. Imaging with the scope in a straight position is helpful in transferring the effect of rotation of scope to the tip of ultrasound transducer. Most of the movements are done in a straight position of scope, except during imaging from station of duodenal bulb where the scope is placed in a J shaped position. Appropriate adjustments in right and left knobs along with in and out movement are also required to gain proper contact with the wall from all stations.

Imaging from fundus of stomach/OG junction

Manipulation around/ just beyond OG junction (40 cm) should be done under vision to avoid perforation. The imaging around/just beyond OG junction is best started from an open left position but can be also tried from an open right position.

Table 1 Common bile duct imaging from various stations during endoscopic ultrasound

Station	Home base structure	Main part of bile duct seen	Part of CBD seen on clockwise rotation[1]	Part of CBD seen anti clockwise rotation[2]
OG junction	l tributaries of LPV segment 2 and 3	Segment 2 and 3 duct	Upper 1/3	None
Body of stomach	Portal vein, splenic vein	Mid 1/3	Lower 1/3	Upper 1/3, left hepatic duct
Duodenal bulb	Portal vein	Mid 1/3	Lower 1/3	Upper 1/3
Descending duodenum	SMV	Lower 1/3	Mid 1/3, upper 1/3	Intrapancreatic
Antrum	SMV	Lower 1/3	Mid 1/3, upper 1/3	None

[1]Clockwise rotation needs to be combined with additional push in and out, and up and down movements; [2]Anti-clockwise rotation needs to be combined with additional push in and out, and up and down movements. Each of these positions brings the transducer closer to one of the four parts of CBD (upper 1/3, mid 1/3, lower 1/3 or intraduodenal) and the rest of CBD can be imaged by appropriate movement (clockwise or anti clockwise rotation, right or left movement or up and down movement). If mid 1/3 of CBD is identified in bulb an anti-clockwise rotation shows upper 1/3 CBD and clockwise rotation shows lower 1/3 of CBD. Similarly in stomach once mid 1/3 of CBD is identified clockwise rotation traces CBD towards lower 1/3 and anti-clockwise rotation traces CBD towards upper1/3. CBD: Common bile duct; SMV: Superior mesenteric vein; LPV: Left portal vein; OG: Oesophagogastric junction.

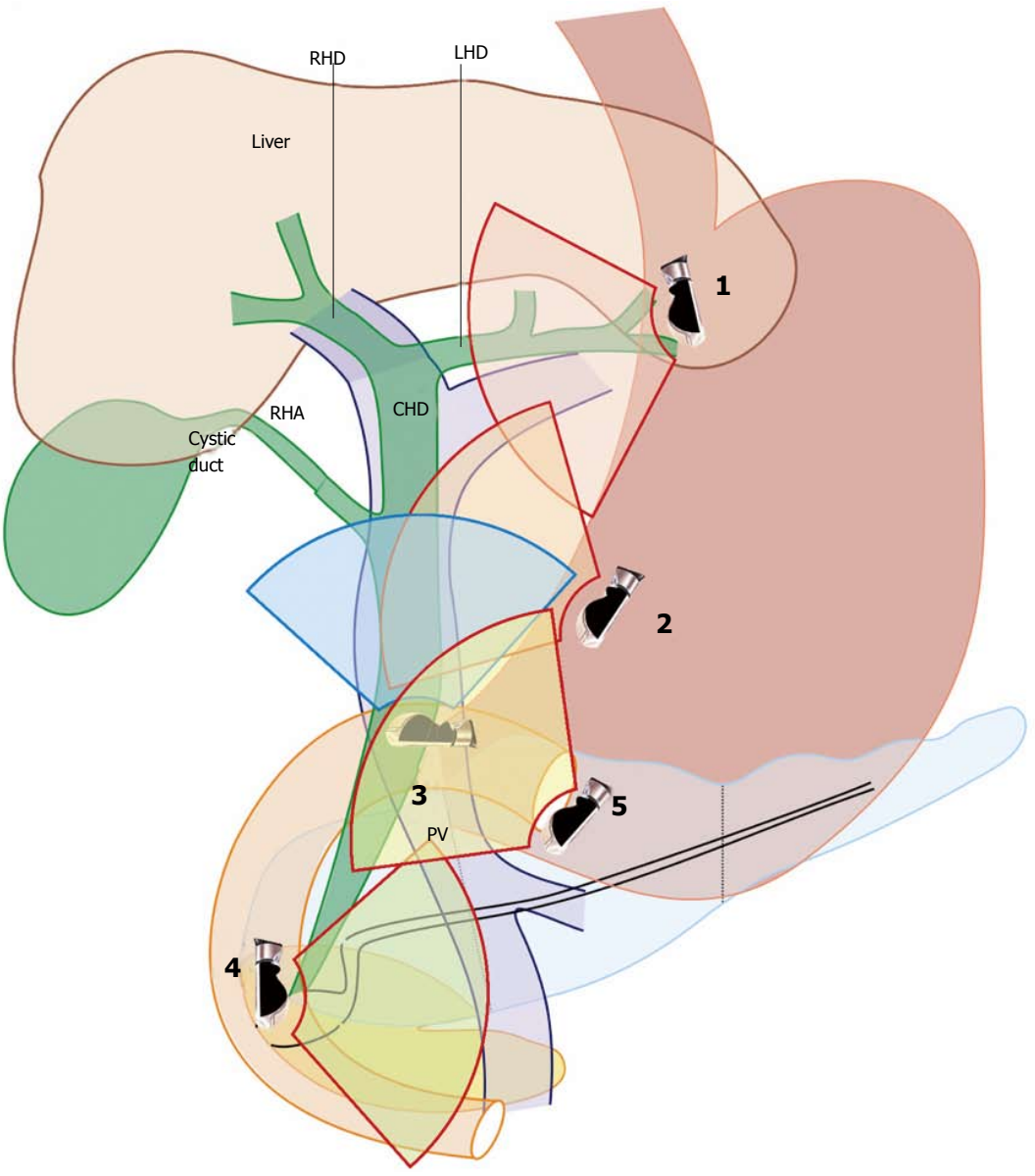

Figure 1 Five positions of Common bile duct imaging by endoscopic ultrasound are shown. CHD: Common hepatic duct; RHA: Right hepatic artery; RHD: Right hepatic duct; LHD: Left Hepatic duct.

Imaging from open left position: Clockwise rotation from an open left position follows the left lobe segment

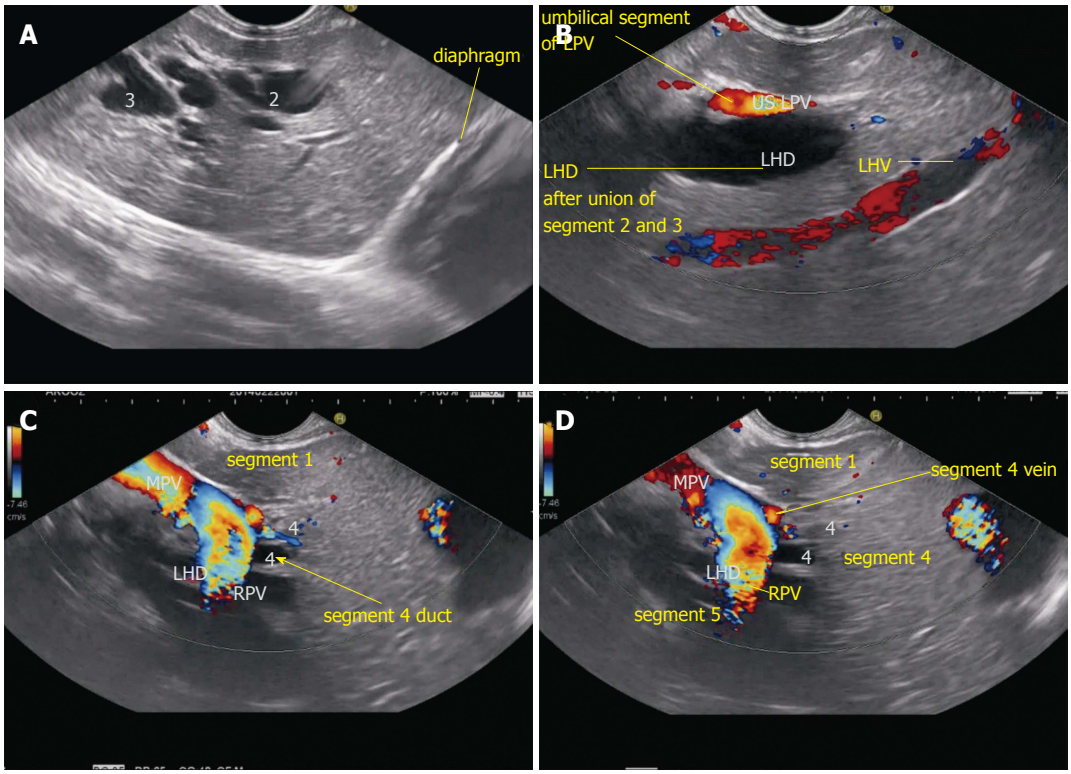

Figure 2 Segmental ducts as seen on endoscopic ultrasound. A: The dilated ducts of segment 2 and 3 ducts are seen in an open position to left; B: On clockwise rotation the segment 2 and 3 ducts fuse together in front of umbilical part of left portal vein. The left hepatic vein is also identified going from 2 o'clock position to 7 o'clock position; C: On further clockwise rotation the fused part of segment 2 and 3 ducts is joined by segment 4 duct from the cranial aspect (arrow) in front of the transverse segment of left portal vein; D: On further clockwise rotation the right portal vein is seen joining the left portal vein and the liver segment lying below the plane of right portal vein belongs to segment 5. RPV: Right portal vein; LPV: Left portal vein; LHD: Left hepatic duct; LHV: Left hepatic vein.

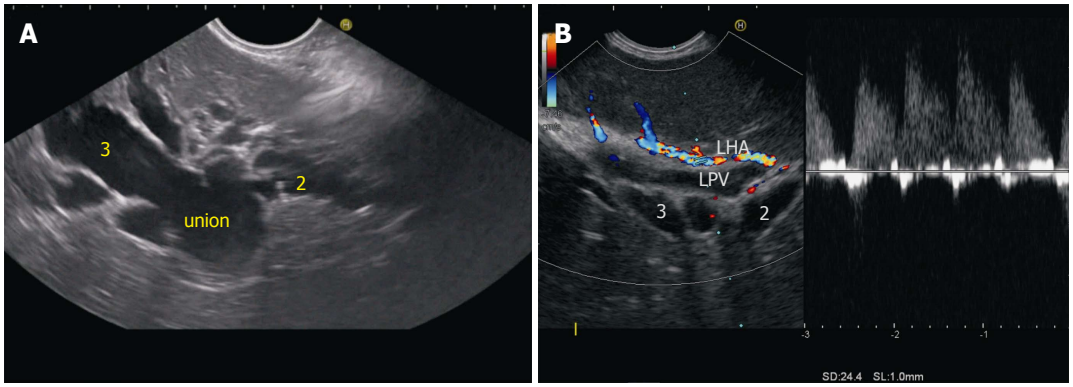

Figure 3 Union of segmental ducts. A: Segment 2 is identified as duct coming from cranial part of liver segment and segment 3 duct is identified as duct coming from caudal part of liver segment; B: Sometimes the ducts are not dilated and in such situation the tributaries of left portal vein can be identified after application of color doppler and followed to the union and formation of umbilical part of portal vein. LPV: Left portal vein; LHA: Left hepatic artery.

2 and 3 ducts to left hepatic duct and further rotation traces the left hepatic duct towards the liver hilum. If the intrahepatic biliary radicles (IHBR's) are dilated it is easy to follow the course of ducts by clockwise rotation. If the IHBR's are not dilated the segmental portal vein radicles should be followed. The gastrohepatic ligament (GHL), which come between the EUS probe and left lobe of liver, interferes with the imaging during rotation (Figures 2-4).

Imaging from open right position: Generally imaging of right lobe of liver is not possible from OG junction, as the right lobe ducts generally lies farther away from the probe. However the GHL does not interfere in imaging of right hepatic duct and with suitable adjustments of focus and frequency the right lobe and ducts of segment 4/5 (if dilated) can be identified and followed towards the upper CBD near the hilum by anti-clockwise rotation.

Imaging from body of stomach

Following down the upper 1/3rd of CBD can do imaging

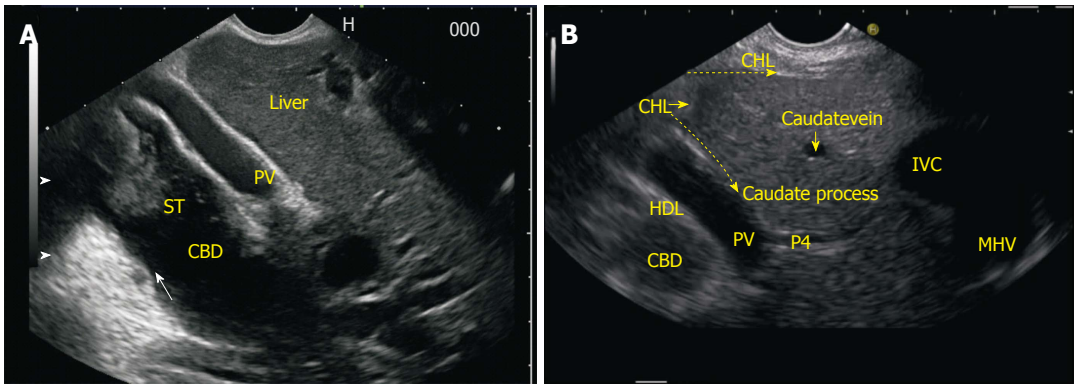

Figure 4 Common bile duct as seen from the gastroesophageal junction. A: A clockwise rotation moves the axis of imaging from an anterior position in stomach to a lateral position where the liver hilum is placed and follows the segmental duct towards the confluence of both the right and left hepatic ducts; B: In this figure the two limbs of GHL are seen. One of the limb runs on the under surface of liver and the other limb goes in the area between abdominal part of esophagus and liver. As the rotation is executed the presence of hyperchaotic GHL between esophagus and liver and the hepatoduodenal ligament near the liver hilum may interfere with imaging of part of the left or right hepatic ducts near the confluence. CHD: Common hepatic duct; IVC: Inferior venacava; HDL: Hepatoduodenal ligament; IVC: Inferior venacava; GHL: Gastrohepatic ligament.

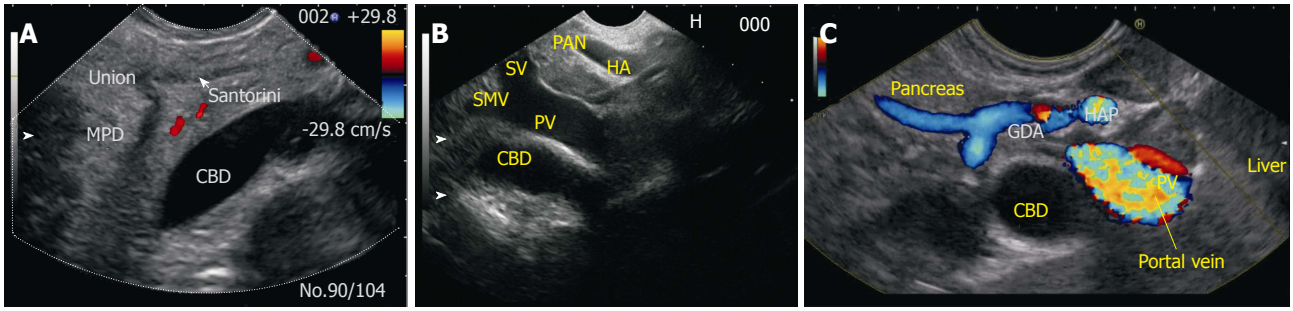

Figure 5 Following down from upper 1/3. A: A dilated bile duct can be easily followed down and push of the scope in a forward direction along with slight rotation changes the window of imaging from the liver window to pancreatic window. The parenchyma of head of pancreas provides an excellent window for visualization of dilated CBD. With experience even a non-dilated duct can be easily visualized from this position; B: When the probe comes to lie in fundus of stomach the stack of hepatic artery, portal vein and common bile duct can be seen through the liver window. In this picture the hepatic artery lies closest to the transducer, the portal vein lies on the undersurface of liver and the CBD is seen beyond the portal vein. The portal vein and the bile duct can be followed down towards the pancreas from the liver. The portal vein is followed down as SMV; C: When the probe comes to lie anterior to head of pancreas the stack of gastroduodenal artery, portal vein and bile duct can be seen with the help of the pancreatic window. CBD: Common bile duct; SV: Splenic vein; PV: Portal vein; HA: Hepatic artery; MPD: Main pancreatic duct; SMV: Superior mesenteric vein.

of entire CBD from the liver window and following up the lower 1/3rd of CBD can do imaging of entire CBD from the pancreatic window.

Following down from liver window: Imaging of CBD while following it down from the fundus towards body of stomach requires a movement of the EUS probe along lesser curvature. This movement can be easily executed under vision after distension of stomach with air but the presence of air usually creates interference with ultrasound imaging. To avoid this interference due to air, a smooth combination of three movements: (1) push in of about 25 to 30 cm. from fundus; (2) clockwise rotation of 90 degree; and (3) up movement of up and down knob for about 90 degree is generally preferred. This movement allows a relative blind slide of the transducer along lesser curvature with nil or minimum distension of air and follows down the CBD from upper 1/3rd towards the lower 1/3rd. Once the movement is completed the scope comes to lie in a position near the antrum and the left hand comes to lie close to the chest of the operator (Figure 5).

Following up from pancreatic window: A reversal of the movement described above can be done under vision by initially proceeding towards antrum after air inflation and subsequently coming back after air suction from antrum towards the fundus. This reversal movement follows up the CBD from the lower 1/3rd towards the upper 1/3rd. If it is difficult to trace the course of CBD by this movement, the home base of portal venous confluence of splenic vein with superior mesenteric vein is initially located in the neck of pancreas. The lower 1/3rd of CBD is easily identified behind the portal venous confluence (Figure 6).

Imaging from bulb

The pylorus is located by "setting sun sign" and slight down angulation of tip may be required to get an end view of pylorus. Once the pylorus is seen the scope is

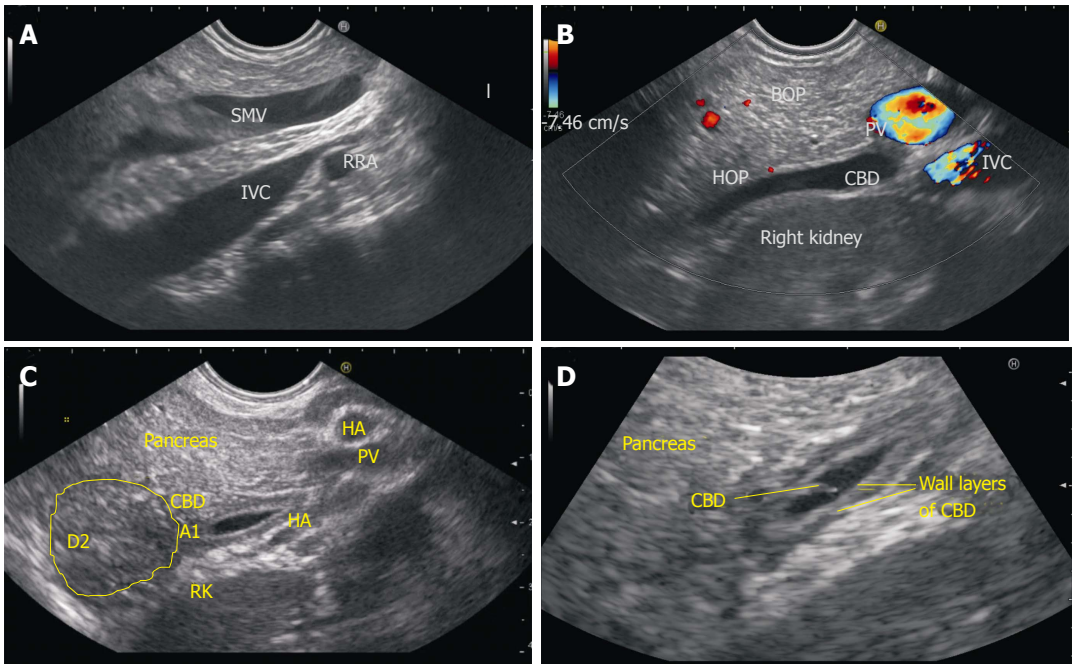

Figure 6 Lower Common bile duct imaging from D2-D3. A: In the hilum of liver the CBD lies anterior to the portal vein and both CBD and portal vein are positioned anterior to inferior vena cava. As the CBD is followed down towards ampulla the IVC remains goes posterior to head of pancreas whereas the SMV (followed down as a continuation of portal vein) comes to lie anterior to posterior part of head of pancreas. The CBD occupies the area of posterior part of head of pancreas between the SMV and IVC. This figure shows the typical appearance of SMV lying in front of IVC from stomach. If it is difficult to trace the course of CBD, the IVC, portal vein or superior mesenteric vein can be followed as a vascular home bases for tracing of CBD; B: In this figure the CBD is identified in posterior part of head of pancreas with slight anticlockwise rotation after visualizing the typical appearance of SMV lying in front of IVC; C: Once the Lower 1/3 of CBD is located it can be followed down towards the intrapancreatic part of CBD and zooming can help in imaging of papilla as well as 2nd part of duodenum; D: With selective zooming of bile duct the individual layers of bile duct can be identified. SMV: Superior mesenteric vein; CBD: Common bile duct; IVC: Inferior venacava; HOP: Head of pancreas; BOP: Body of pancreas; PV: Portal vein.

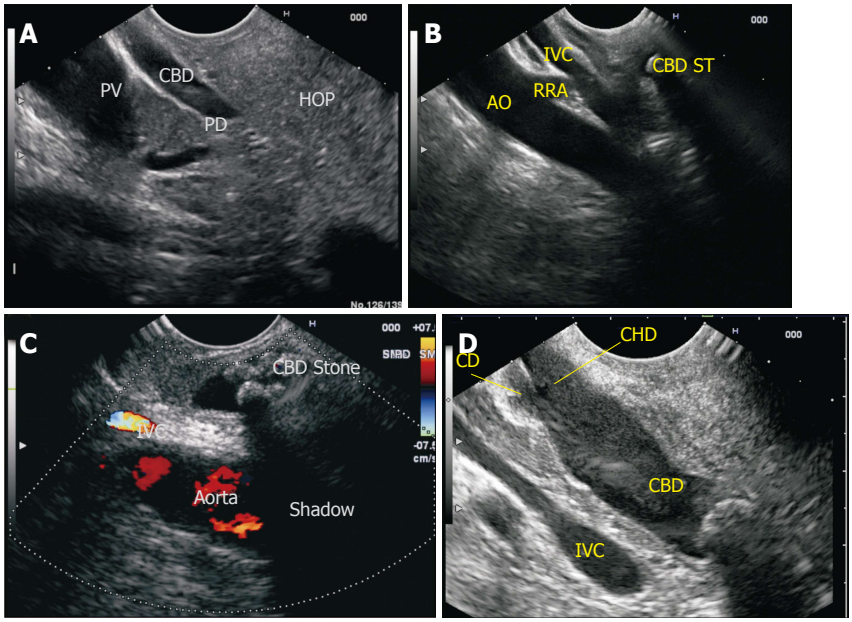

Figure 7 Common bile duct Imaging from duodenal bulb. A: The portal vein is identified as the home based position from duodenal bulb. From the home base position a limited range of movement of 90 degree to either side traces the entire CBD. A clockwise rotation traces the CBD towards the ampulla and identifies the middle and lower 1/3 of CBD and anticlockwise rotation traces the CBD towards the upper 1/3 and the GB/CD/CHD are also identified near the liver hilum. In this image the CBD is seen in a long axis for a long distance and the PD and portal vein are seen in a long axis for a short distance. This has been called as reverse stack sign; B: In this figure the stack of bile duct (with a stone) aorta and IVC is seen from duodenal bulb. The right renal artery is seen going behind the IVC. The CBD in this case lies in the retropancreatic part anterior to IVC; C: Two stones are seen in the path of acoustic shadow. Although both stones have same acoustic impedance yet it is the second stone, which is causing acoustic shadow. The second stone is surrounded by fluid and the sound waves go through acoustic medium of different acoustic impedance; D: The pyramidal shaped neck of pancreas and pancreatic duct are commonly identified between the probe and portal vein. CBD: Common bile duct; CHD: Common hepatic duct; IVC: Inferior venacava; PV: Portal vein; PD: Pancreatic duct; HOP: Head of pancreas; RRA: Right renal artery; AO: Aorta.

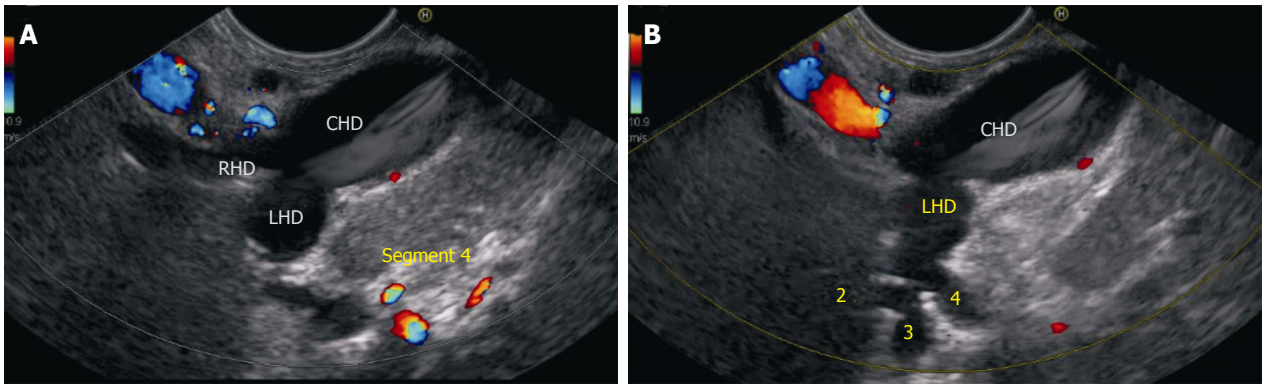

Figure 8 Hilum imaging from duodenal bulb. A: Imaging from duodenal bulb shows the proximity of CBD to the probe. The middle and upper 1/3rd of CBD and CHD dividing into RHD and LHD are seen. The RHD (average length 0.9 cm) and left hepatic duct (Average length 1.7 cm) unite in the hilar plate, close to the right end of porta in front of right branch of portal vein, to form the CHD; B: In this case it is possible to see the segmental ducts to segment 2, 3 and 4 through upper 1/3rd of CBD. CBD: Common bile duct; CHD: Common hepatic duct; RHD: Right hepatic duct; LHD: Left hepatic duct.

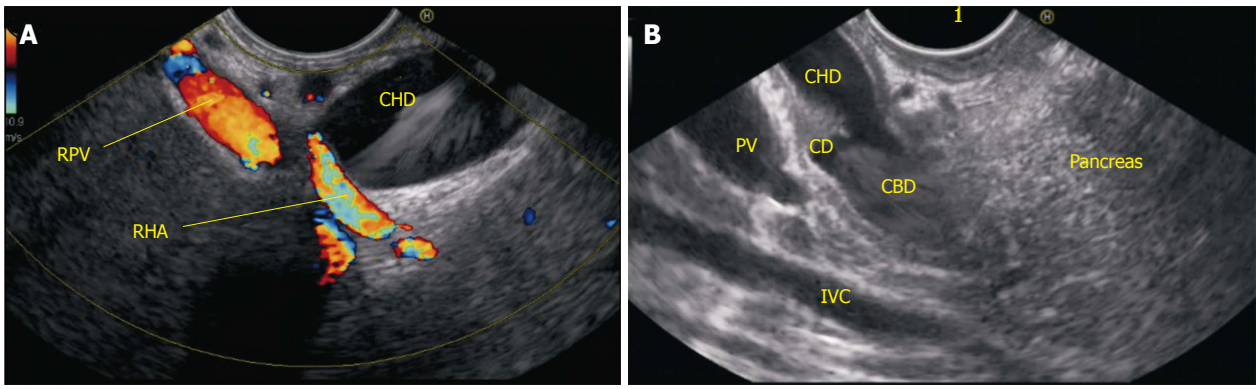

Figure 9 Hepatocystic triangle seen from the duodenal bulb. A: Imaging from duodenal bulb shows the relationship of right hepatic artery which goes behind the CHD to come and lie in the hepatocystic triangle; B: The bulb provides an opportunity to visualize the mid 1/3rd of CBD and usually provides an excellent window to see the division of CBD into CHD and CD. Most of the time the structure lying farther away from the screen is CD and can be traced towards the gall bladder. CBD: Common bile duct; CHD: Common hepatic duct; CD: Cystic duct; RPV: Right portal vein; RHA: Right hepatic artery; IVC: Inferior venacava.

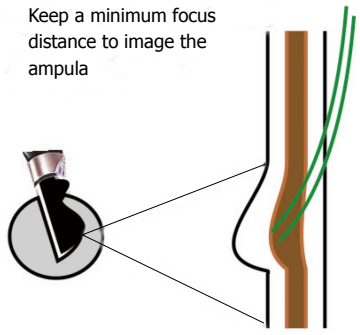

Figure 10 Imaging of Common hepatic duct at papilla can be done after apposition of transducer with the papilla, which is the main endoscopic landmark. It is appreciated as a thickening of the duodenal wall and a rounded 5-layered structure. Good views of papilla require three things: (1) transducer perpendicular to papilla; (2) good water coupling; (3) and motionless duodenum). If a balloon is used only a small amount of water should be filled in balloon to avoid smashing the delicate papilla. The imaging of papilla after instillation of about 50 to 100 mL water keeps the transducer away from papilla, increases the focal distance of imaging of transducer from papilla and places the papilla as well as lower 1/3 of CBD in the optimum focal distance of imaging (usually about 1 cm). CHD: Common hepatic duct.

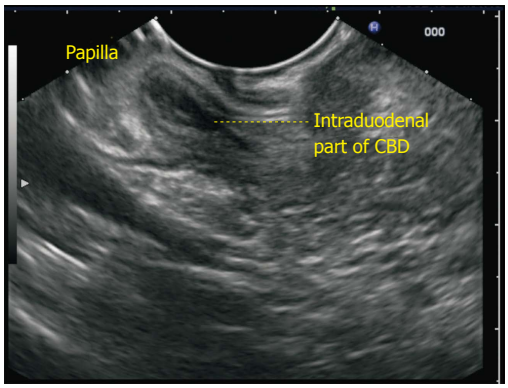

Figure 11 The papilla is the protruding structure in the lumen of the duodenum and is covered on both sides by the muscular layer of the wall. At the point of the entry of papilla into the duodenal bulb the continuity of muscular layer as a smooth duodenal fall is absent. At the point of union of bile duct and pancreatic duct the dilation of both ducts is named as ampulla. An attempt should be made to trace the intra papillary part of pancreatic duct all the way to the tip of the papilla or into a common ampulla. This can help in identifying the three patterns of opening of the bile duct and pancreatic duct, *i.e.*, common channel, V shaped or separate opening. CBD: Common bile duct.

pushed into 1st part of duodenum with slight upwards angulation and imaging from bulb is started after

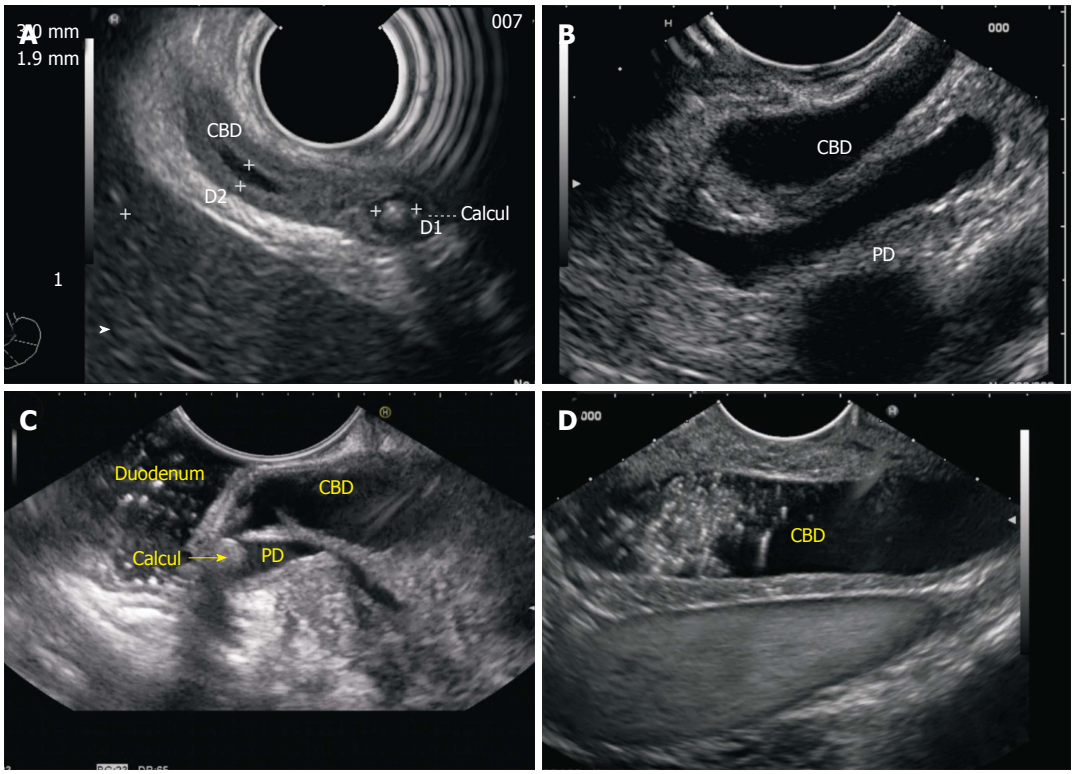

Figure 12 Imaging from 2nd part of duodenum. A: The intrapapillary part of CBD and the lower 1/3 of CBD is sometimes best visualized with the radial EUS scope as they provide a long axis of imaging of the entire bile duct in a long axis; B: However good view of CBD in a long axis can be also obtained by linear EUS scope. This image shows the dilated CBD and PD in a long axis in a case of periampullary carcinoma; C: The distended CBD may not provide room for good visualization as it comes very close to probe in a pathology involving papilla. This figure shows good view of CBD after instillation of 100 mL water which provides good coupling and also provides adequate focal distance. The stone is impacted in the common channel where it is also obstructing and dilating the pancreatic duct; D: The dilated CBD with sludge is seen from 2nd part of duodenum. On the far side of screen the IVC is also seen beyond the IVC. CHD: Common hepatic duct; EUS: Endoscopic ultrasound; IVC: Inferior venacava; CBD: Common bile duct; PD: Pancreatic duct.

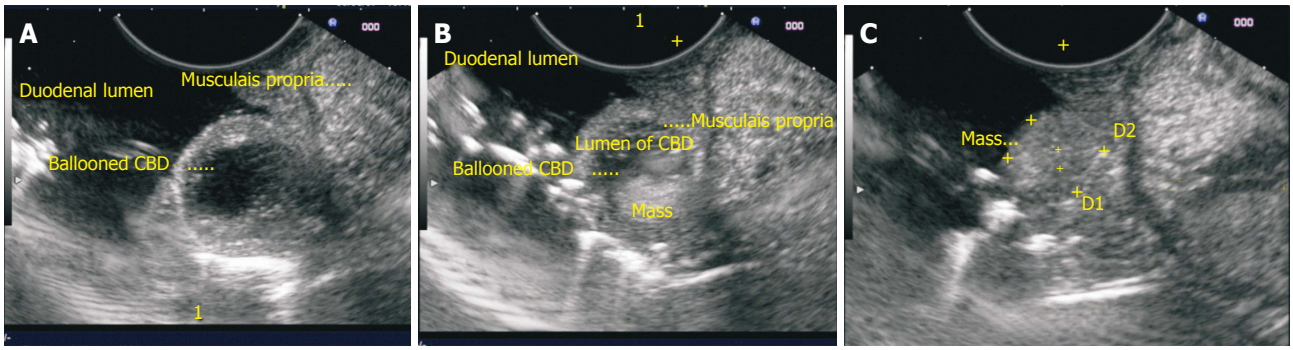

Figure 13 Imaging of common hepatic duct from second part of duodenum. A: A distended CBD is seen after good water coupling from 2nd part of duodenum but this image does not provide a clue to the diagnosis; B: An Ampulloma is seen within the distended intraduodenal part of bile duct; C: The tumor is seen within the intraduodenal part of CBD but it appears separate from the muscularis propria layer. CBD: Common bile duct.

establishing contact with posterior duodenal wall. The contact with wall is generally established by turning in an anticlockwise (ACW) direction with down angulation of up and down knobs. Sometimes in this imaging the ACW rotation of the scope may take the scope down and below the level of table in a straight scope position. With suitable rotation and minor adjustments of knobs a home base position is identified where the portal vein is seen on the far side of the screen going from 5 o' clock position to 11 o'clock position. In this home base position the middle 1/3rd of CBD is commonly identified with slight adjustments of right and left knobs between the transducer and portal vein. Clockwise rotation from this position traces the lower 1/3rd of CBD and ACW rotation traces the upper 1/3rd of CBD as well as the cystic duct and gall bladder (Figures 7-9).

Imaging from duodenum

Imaging from duodenum requires two key movements. The first is entry into 2nd part of duodenum and the

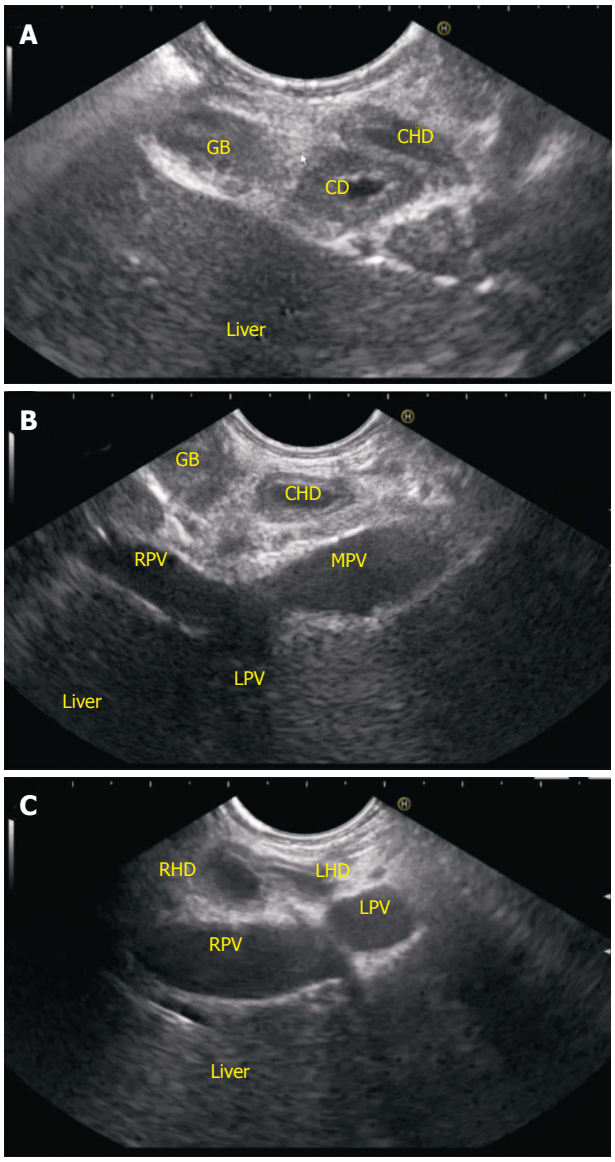

Figure 14 Hilum imaging from D2. A: Anticlockwise rotation from the 2nd part of duodenum traces the CBD towards the hilum. The cystic duct is seen taking origin from the aspect away from transducer and the gall bladder is visualized; B: When imaging is done from below upwards the imaging shows the CHD going towards the right portal vein; C: Further anticlockwise rotation towards hilum can show the left and right hepatic duct. The division of CHD into RHD and LHD occurs in front of right branch of portal vein. CBD: Common bile duct; CHD: Common hepatic duct; RHD: Right hepatic duct; LHD: Left hepatic duct; LPV: Left portal vein; RPV: Right portal vein.

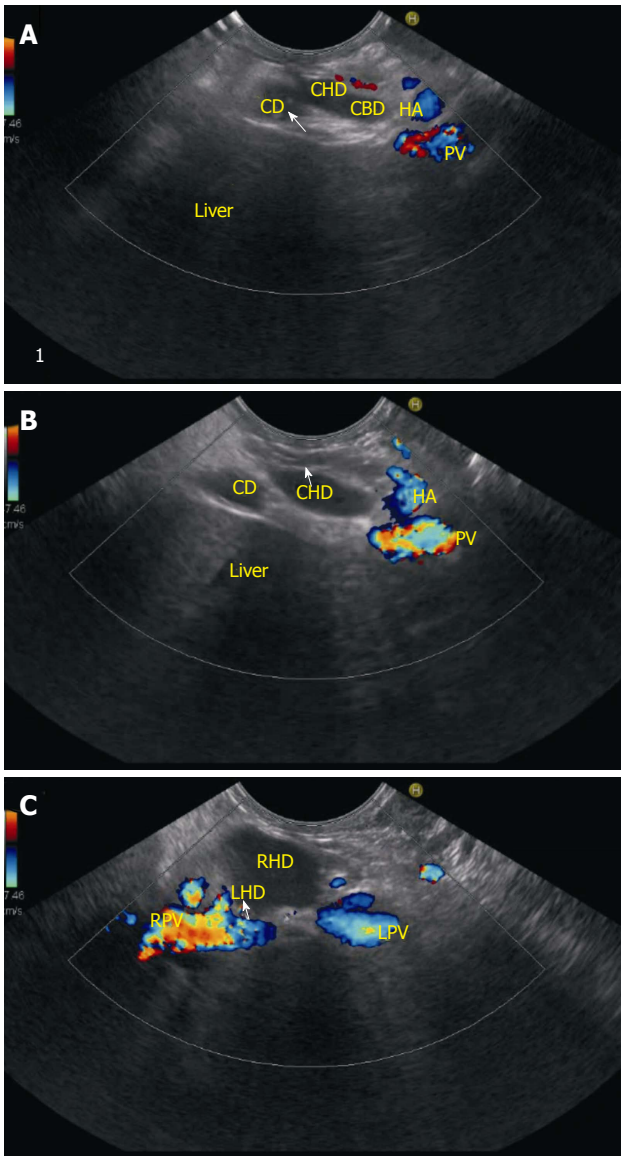

Figure 15 Cystic duct and common hepatic duct imaging. A and B: The cystic duct terminates at the right wall of the common hepatic duct in 85 to 90% of cases. In this case the CD is seen joining the right aspect of CHD; C: When the CHD is followed up it divides into right and left hepatic duct and this bifurcation generally lies in front of the right branch of the portal vein. As the echoendoscope is rotated counter clockwise the portal vein is followed up to its bifurcation and the RPV is seen on the right side of the screen. CHD: Common hepatic duct; CD: Cystic duct; CBD: Common bile duct; PV: Portal vein; HA: Hepatic artery; RHD: Right hepatic duct; LHD: Left Hepatic duct; LPV: Left portal vein; RPV: Right portal vein.

second is deep intubation into 3rd part of duodenum.

Passage into D2: Entry into D2 is facilitated by engagement of the tip of the probe at D1/D2 junction (superior duodenal angle). Four movements of knob at the superior duodenal angle, *i.e.*, "right turn of knob, up turn of knob, clockwise rotation of the scope and pulling back of the scope" help in passage of probe into second part of duodenum. These movements bring the scope in a short position and place the tip of scope near the papilla once the scope is shortened to about 55 cm. Slow pulling back for shortening can be done by pulling the shaft of scope with the use of right hand or by the use of outward pressure on the shaft of scope by ulnar aspect of the left hand in an open right position. Endoscopic view should be always maintained during a combination of these movements while shortening to avoid a sudden jerk and entry of the transducer into 2nd part of duodenum.

Passage into D3: Once the second part of duodenum is entered two to three times pushing in and out is required to position the scope deeper into the third part

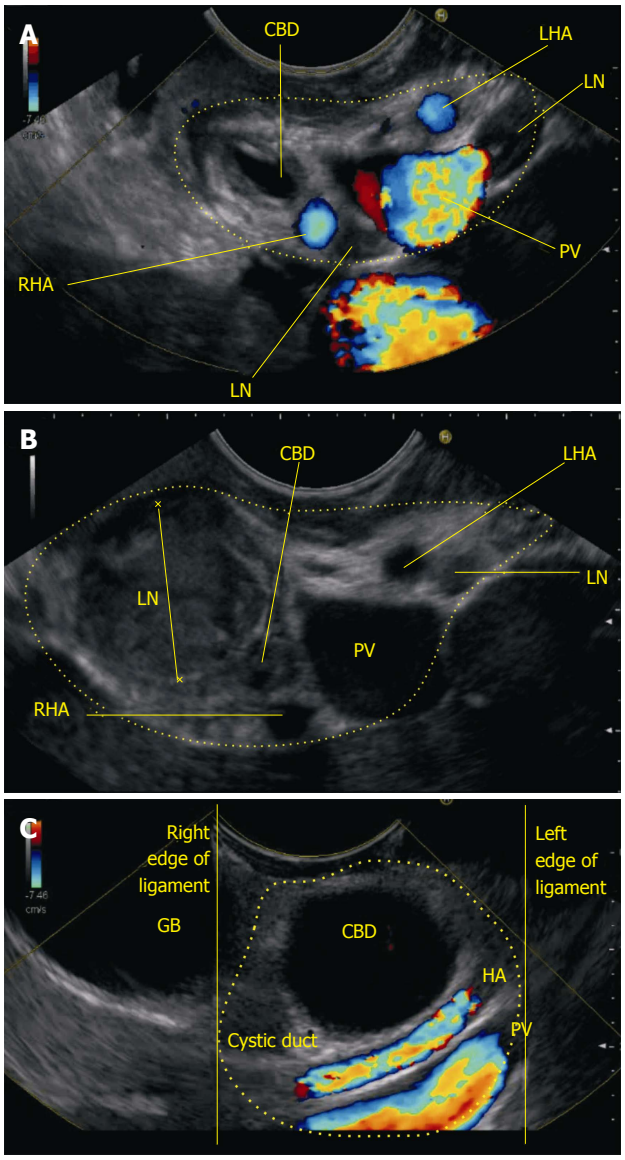

Figure 16 Hepatoduodenal ligament. A: The anticlockwise rotation takes the probe towards the hilum of liver the bile duct is demonstrated in a transverse axis. The HDL contains the structures of portal triad; B: Further anticlockwise rotation shows an abnormal lymph node within the hepatoduodenal ligament which is causing obstruction of CBD; C: On further anticlockwise rotation the probe moves towards the hilum of liver and the dilated bile duct is demonstrated in a transverse axis along with cystic duct and gall bladder. The portal vein and hepatic artery are demonstrated in long axis. All these structures shown lie in the hepatoduodenal ligament near the hilum except the gallbladder. CBD: Common bile duct; CHD: Common hepatic duct; RHA: Right hepatic artery; LHA: Left hepatic artery; LN: Lymph node; PV: Portal vein; HDL: Hepatoduodenal ligament.

of duodenum.

Imaging from duodenum: From the third part of duodenum a combination of three movements, *i.e.*, slow withdrawal up to the first part of duodenum, clockwise and ACW torque and upward movement of the up and down knobs is required for getting good views of lower 1/3rd of bile duct. This combined movement traces the CBD from the lower 1/3rd towards the upper 1/3rd but as the scope comes towards the first part of

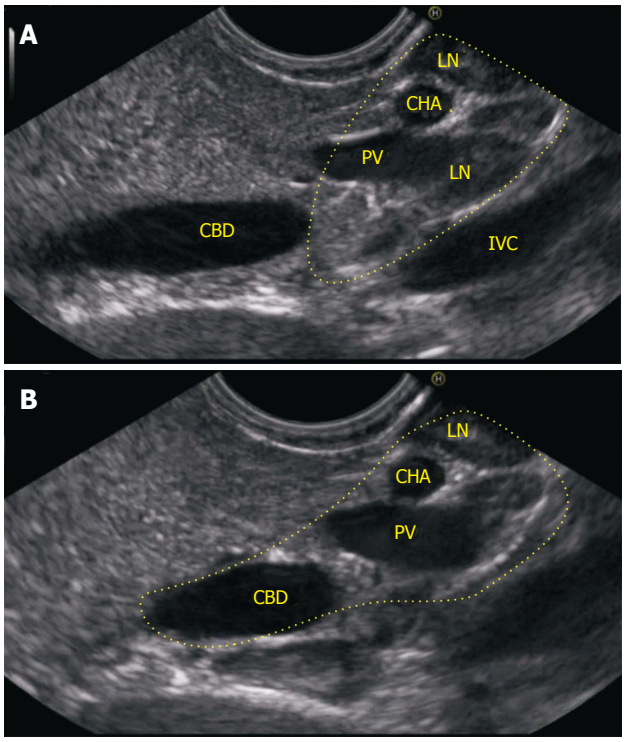

Figure 17 When the scope comes to lie in antrum the splenic vein can be followed towards the portal venous confluence easily. Once the portal venous confluence is identified a slight anticlockwise torque with push generally identifies the lower 1/3 of CBD in head of pancreas. Once the duct is identified the adjustment of focus, on the far side of screen with adjustment to lower frequency may be required for proper visualization of CBD behind the confluence. CBD: Common bile duct; LN: Lymph node; CHA: Common hepatic artery; PV: Portal vein; LN: Lymph node; IVC: Inferior venacava.

duodenum it tends to slip back into stomach. Movement of the up knob in a fully up position and maintaining a clockwise stance during slow torque from the 2nd part of duodenum helps in preventing the scope from slipping back. Wedging the scope at D1/D2 junction with an inflated balloon is an alternative, which is preferred by some operators to prevent slipping back, but carries a small disadvantage of reverse intussusception of the 2nd part of duodenum into stomach.

In a small number of cases it may be difficult to trace a normal CBD during this combined movement as most of the lumen of CBD gets compressed due to the pressure of transducer. In such cases the combined movement should be done with a main thrust on ACW rotation till it visualizes the anechoic bile duct within the bean shaped hepatoduodenal ligament. A clockwise rotation with slight push and relaxation of the pressure on up and down knob (reverse of the combined movement) now traces the CBD from the liver hilum towards the papilla.

Imaging of CBD should be done from below the papilla from the third part of duodenum after instillation of water whenever pathology of papilla (stone or a periampullary tumor) causes distension of intraduodenal part of CBD. This technique provides adequate focal distance for imaging of papilla and good water coupling

(Figures 10-16).

Imaging from antrum

This imaging is similar to imaging through the pancreatic window from stomach as already described above. It can be done if evaluation of CBD is considered necessary once the scope slips back from the 2nd part of duodenum or once the examination from duodenum is completed. As the scope comes to lie opposite the head of pancreas the pancreatic window provides optimum imaging of lower 1/3rd of CBD (Figure 17).

CONCLUSION

The techniques described in the above section can be expected to reproduce the images as discussed in majority of cases and from most of the stations. The only station of CBD imaging which may not reproduce the images as described is from duodenal bulb. This difference in reproducing the images and a great variability of images comes mainly due to the variability of the position of scope (short loop, or J shaped position) and due to the use of balloon (nestled, wedged, withdrawn wedged, intussuscepted). The basic concept of imaging however remains simple: stomach shows mainly the upper 1/3rd of CBD, bulb shows mainly the middle 1/3rd of CBD and duodenum shows mainly the lower 1/3rd of CBD. The follow up imaging to trace entire CBD requires a clockwise rotation and push from upper 1/3rd of CBD. The follow up imaging to trace entire CBD requires an ACW rotation and pull from lower 1/3rd of CBD. The follow up imaging to trace entire CBD requires a clockwise rotation to trace the lower 1/3rd and an ACW rotation to trace the upper 1/3rd when imaging is started from middle 1/3rd of CBD.

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Reality named endoscopic ultrasound biliary drainage

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Abstract

Endoscopic ultrasound (EUS) is used for diagnosis and evaluation of many diseases of the gastrointestinal (GI) tract. In the past, it was used to guide a cholangiography, but nowadays it emerges as a powerful therapeutic tool in biliary drainage. The aims of this review are: outline the rationale for endoscopic ultrasound-guided biliary drainage (EGBD); detail the procedural technique; evaluate the clinical outcomes and limitations of the method; and provide recommendations for the practicing clinician. In cases of failed endoscopic retrograde cholangiopancreatography (ERCP), patients are usually referred for either percutaneous transhepatic biliary drainage (PTBD) or surgical bypass. Both these procedures have high rates of undesirable complications. EGBD is an attractive alternative to PTBD or surgery when ERCP fails. EGBD can be performed at two locations: transhepatic or extrahepatic, and the stent can be inserted in an antegrade or retrograde fashion. The drainage route can be transluminal, duodenal or transpapillary, which, again, can be antegrade or retrograde [rendezvous (EUS-RV)]. Complications of all techniques combined include pneumoperitoneum, bleeding, bile leak/peritonitis and cholangitis. We recommend EGBD when bile duct access is not possible because of failed cannulation, altered upper GI tract anatomy, gastric outlet obstruction, a distorted ampulla or a periampullary diverticulum, as a minimally invasive alternative to surgery or radiology.

Key words: Endoscopic ultrasound; Rendezvous; Biliary drainage; Obstrutive cancer; Papillary obstrution

Core tip: In this minireview, we will discuss about endoscopic ultrasound-guided biliary drainage (EGBD) and new interesting endoscopic ultrasound therapeutic biliary methods. We recommend EGBD when bile duct access is not possible because of failed cannulation, altered upper gastrointestinal tract anatomy, gastric outlet obstruction, a distorted ampulla or periampullary diverticulum, as a minimally invasive alternative to surgery or radiology.

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INTRODUCTION

Endoscopic ultrasound (EUS) is used for diagnosis and evaluation of many diseases of the gastrointestinal tract. In the past, it was used to guide a cholangiography[1], but nowadays it emerges as a powerful therapeutic tool in biliary drainage.

Endoscopic retrograde cholangiopancreatography (ERCP) is the procedure of choice for drainage of an obstructed common bile duct (CBD) in patients with distal obstruction. Lower success rates are seen in patients with surgically altered anatomy and neoplastic diseases due to failure to access the duodenum or more difficult duct access[2]. However, EUS-guided biliary drainage (EGBD) may be a viable alternative to ERCP in patients with malignant distal CBD obstruction[3].

In 2001, Giovannini *et al*[4] performed the first palliative hepaticogastrostomy (HGS) under EUS guidance in a patient with inoperable hepatic hilar obstruction. Recently, experience from EUS-guided biliary duct drainage attempts at 6 international centers was reviewed and showed successful bile duct drainage for all techniques combined in 87% cases[5]. Although performed for almost two decades, during the last five years there was a substantial increase in this type of procedure. These publications suggest that EGBD can provide high levels of technical success with acceptable complication rates[6].

The indications for EGBD include: failed conventional ERCP; altered anatomy; tumor preventing access into the biliary tree; and contra-indication to percutaneous access[7].

If the papilla is accessible, a rendezvous technique (EUS-RV) can be adopted wherein EUS is used to puncture the bile duct and a wire is negotiated through the papilla and further therapy is carried out through ERCP. If the papilla is not accessible then EUS is used to access the bile duct and create a fistula for placement of a stent called the transmural technique[8].

The objectives of this review are: Outline the rationale for EGBD; detail the procedural technique; evaluate the clinical outcomes and limitations of the method; and provide recommendations for the practicing clinician.

RATIONALE FOR USE EGBD

In cases of failed ERCP, patients are usually referred for either percutaneous transhepatic biliary drainage (PTBD) or surgical bypass. Both these procedures have high rates of undesirable complications. EGBD is an attractive alternative to PTBD or surgery when ERCP fails[9]. In a prospective single-center randomized study, EGBD and PTBD were compared in patients with unresectable malignant biliary obstruction. Technical success and clinical success were 100% in both groups. The complication rate for PTBD was 15.3% and the complication rate for EGBD was 25% (P = 0.2), and the cost of the procedures was similar (7570 USD and 5573 USD respectively, P = 0.39)[10]. The surgical bypass is an option only for patients who are good surgical candidates. Despite the more invasive approach, surgery produced better drainage.

ERCP may be challenging or may fail in certain situations, including post-surgical anatomy, periampullary diverticula, ampullary tumor invasion, and high-grade strictures. EUS-guided interventions may allow access or direct therapy in ERCP failures. In a retrospective single-center cohort study, if the primary intended EUS-guided anterograde cholangiopancreatography (EACP) intervention failed, crossover to other type of EACP therapy was performed, when clinically appropriate-in 95 of 2566 ERCP procedures (3.7%). EUS-guided cholangiography and pancreatography were successful in 97% and 100%, respectively (Figure 1). EUS-RV and ERCP was successful in 75% of biliary procedures and in 56% of pancreatic procedures. Direct EUS-guided therapy was successful in 86% and 75% of biliary and pancreatic procedures, respectively[11]. Another systematic review evaluated the efficacy of EGBD in patients with surgically altered anatomy with 74 cases included for analysis. The pooled technical success, clinical success, and complication rates of all reports with available data were 89.18%, 91.07% and 17.5%, respectively[12].

We recommend surgical bypass for patients with both duodenal and biliary obstructions who are good surgical candidates, but EGBD might be better than PTBD in patients with large volume ascites or patients who refuse external drainage[13].

A gallbladder biliary drainage is necessary in acute cholecystitis with poor performance status and septic shock patients. Jang *et al*[14] showed that EUS-guided naso-gallbladder drainage *via* transluminal technique is safe, effective and similar compared to percutaneous transhepatic gallbladder drainage, with a significant lower rate of postoperative pain (1 *vs* 5; P < 0.001).

Others therapeutics modalities guided by EUS are transmural drainage of pancreatic pseudocysts[8], treatment of distal inflammatory biliary stricture[15], renal biopsy by fine neddle aspiration (EUS-FNA)[16], preoperative fine-needle tattooing insulinoma[17].

PROCEDURAL TECHNIQUE

EGBD can be performed at two locations: transhepatic (TH), through segment Ⅲ, when the probe is placed at the stomach cardia and lesser curvature or jejunum (in altered anatomy) or extrahepatic (EH) when the needle access the CBD directly, either using the

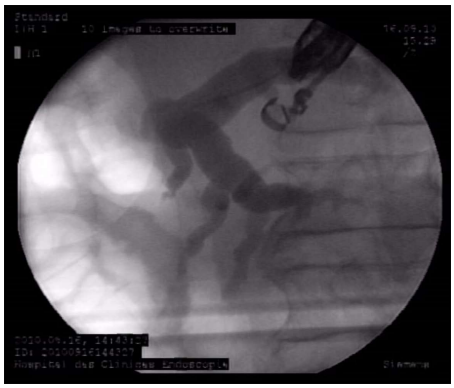

Figure 1 Intra-hepatic cholangiography.

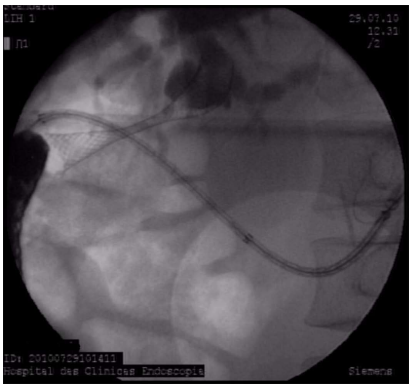

Figure 3 Cholangiographic aspect after biliary stent release.

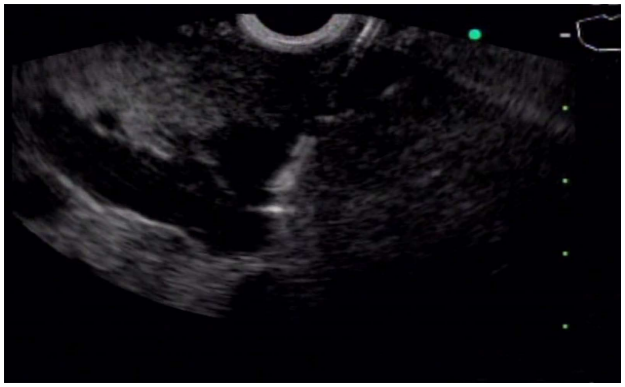

Figure 2 Biliary puncture.

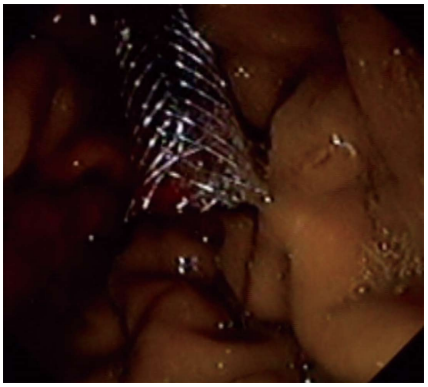

Figure 4 Endoscopic final aspect.

transmural access from the antral part of the stomach or duodenum[7] (Figure 2). Some endoscopists consider the latter as a route of access to the biliary system due to the anatomical position of the CBD (located in the retroperitoneal space), which might be safer in patients with ascites[18].

The stent can be inserted in the direction of the papilla (antegrade insertion, AG) or in the direction of the liver (retrograde insertion) (Figure 3). Finally, the drainage route can be transluminal {between the bile duct and either the stomach HGS or the duodenum [choledochoduodenostomy (CDS)]} or transpapillary, which, again, can be antegrade or retrograde (rendezvous, EUS-RV)[19].

The best EGBD route is not defined. Dhir *et al*[20] compare the success, complications, and duration of hospitalization for patients undergoing EUS-RV by the TH or the EH route. A total of 35 patients were analysed (17 TH, 18 EH). The mean procedure time was significantly longer for the TH group (34.4 *vs* 25.7 min; $P = 0.0004$). There was no difference in the technical success (94.1% *vs* 100%). However, the TH group had a higher incidence of post-procedure pain (44.1% *vs* 5.5%; $P = 0.017$), bile leak (11.7 *vs* 0; $P = 0.228$), and air under diaphragm (11.7 *vs* 0; $P = 0.228$). All bile leaks were small and managed conservatively. Duration of hospitalization was significantly higher for the TH group (2.52 *vs* 0.17 d; $P = 0.015$)[20]. Nevertheless, Artifon *et al*[21] compared the outcomes of 2 non-anatomic EGBD routes: Hepaticogastrostomy (HPG) - 25 patients and CD - 24 patients. HPG and CD techniques were similar in efficacy and safety (Figure 4).

Khashab *et al*[22] compared outcomes of rendezvous and transluminal techniques. During the study period, 35 patients underwent EGBD (rendezvous $n = 13$, transluminal $n = 20$). Technical success was achieved in 33 patients (94%), and clinical success was attained in 32 of 33 patients (97.0%). The mean post-procedure bilirubin level was 1.38 mg/dL in the rendezvous group and 1.33 mg/dL in the transluminal group ($P = 0.88$). Similarly, length of hospital stay was not different between groups ($P = 0.23$). There was no significant difference in adverse event rate between rendezvous and transluminal groups (15.4% *vs* 10%; $P = 0.64$). Long-term outcomes were comparable between groups, with 1 stent migration in the rendezvous group at 62 d and 1 stent occlusion in the transluminal group at 42 d after EGBD. Both rendezvous and direct transluminal techniques seem to be equally effective and safe[22].

According to previous reports, a 19G or 22G FNA needle or needle knife is used to puncture the CBD, followed by the passage of a 0.025-inch or 0.035-inch guidewire was inserted through the needle and looped in the biliary tree[7]. However, there are no randomized controlled trials comparing the outcomes of various FNA needles in the aforementioned procedure[23]. Various

devices have been previously described for dilatation of the fistula after puncturing the CBD[23]. The most common devices for transmural tract dilation are the rigid dilator 6 Fr up to 10 Fr, 4-8 mm balloon catheter, diathermic dilator or needle knife. The feasibility of graded dilation in EUS-HGS was superior to that of EUS-CDS[24].

In a series of 101 cases, Poincloux *et al*[25] placed the EUS in the cardia or the lesser curvature of the stomach and oriented it to view the dilated intrahepatic lateral sector bile ducts. Color Doppler ultrasound was used to confirm absence of vascular structures before EUS-guided puncture through the gastric body. The left bile duct puncture was performed using a 19-gauge access needle and a 0.035- inch super stiff guidewire was introduced through the EUS needle and advanced in an antegrade fashion to the main left bile duct. A hepatogastric fistula was created using a 5.5-Fr wire-guided needle-knife. 6-Fr and 7-Fr tapered biliary dilator catheters to dilate the fistula tract. Under EUS and fluoroscopic view, a stent was placed through the hepatogastrostomy between the main left bile duct and the gastric lumen.

Dhir *et al*[20] used a 19-gauge needle to puncture in the EUS-RV procedure. Attempt was made to puncture with the echoendoscope in a straight position and the needle pointing in the direction of the CBD. Once biliary access was confirmed by aspiration of 5-10 cc bile, contrast was injected to evaluate the ductal system and, a 0.032-inch hydrophilic angled-tip guide wire was inserted through the needle and directed in an anterograde fashion downstream across the stricture and/or the papilla into the duodenum. Once the guide wire crossed the papilla and looped in the duodenum, the echoendoscope was withdrawn and an ERCP scope was positioned at the papilla. Due to the short length of wire, continuous water injection was used to keep the wire in position. The guide wire was pulled into the biopsy channel of duodenoscope with a snare and ERCP was completed[20].

The stent selection is very important. Plastic stent has a low cost, but, self-expandable metal stents offer superior patency to plastic stents for palliation of malignant distal bile duct obstruction. Even though, the superiority of covered self-expandable metal stents to multiple plastic stents for treatment of benign biliary strictures has not been proven[26]. Covered metal stents may be useful to reduce bile leakage in EGBD.

PROCEDURAL LIMITATIONS

Most studies about EGBD are single center and based on case reports or small series. Many studies described this procedure with high success rates (more than 90%) and low rate of procedure-related complications (around 19%)[27], however, data from a large multicenter retrospective trial failed to report advantages of any of these techniques[5].

The main risk of EGBD is bile leakage. Complications of all techniques combined included pneumoperitoneum in 5%, bleeding in 11%, bile leak/peritonitis in 10%, and cholangitis in 5%. Complication rates were similar in benign and malignant disease. No significant difference in complication rates was noted when comparing plastic to metal stents, although a trend toward a better outcome was observed for metal stents (P = 0.09). There was a significantly higher incidence of cholangitis in patients with plastic stents (11% *vs* 3%; P = 0.02)[5].

The use of a needle-knife for fistula dilation was the single risk factor for post procedural adverse events after EGBD. Thus, use of a needle-knife for fistula dilation should be avoided if possible[24], with a risk of creating an unhealthy fistula. This problem does not arise with a cystotome or ring knife fistula creation.

In Dhir *et al*[19] retrospective multicenter study, death was a major complication reported in 4% of cases. All cases used EUS-RV TH route. Nevertheless, the success rate was equal for the various techniques.

CONCLUSION

Data involving mostly small series from expertise centers suggest that EGBD can be performed with high therapeutic success (87%) but it might be associated with 10% to 20% morbidity (mostly mild to moderate) and rare serious adverse events[28].

We recommend EGBD when bile duct access is not possible because of failed cannulation, altered upper GI tract anatomy, gastric outlet obstruction, a distorted ampulla, a *in situ* enteral stent or periampullary diverticulum, as a minimally invasive alternative to surgery or radiology.

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ORIGINAL ARTICLE

Basic Study

Transgastric endoscopic gastrojejunostomy using holing followed by interrupted suture technique in a porcine model

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Abstract

AIM: To demonstrate the feasibility and reproducibility of a pure natural orifice transluminal endoscopic surgery (NOTES) gastrojejunostomy using holing followed by interrupted suture technique using a single endoloop matched with a pair of clips in a non-survival porcine model.

METHODS: NOTES gastrojejunostomy was performed on three female domestic pigs as follows: Gastrostomy, selection and retrieval of a free-floating loop of the small bowel into the stomach pouch, hold and exposure of the loop in the gastric cavity using a submucosal inflation technique, execution of a gastro-jejunal mucosal-seromuscular layer approximation using holing followed by interrupted suture technique with endoloop/clips, and full-thickness incision of the loop with a Dual knife.

RESULTS: Pure NOTES side-to-side gastrojejunostomy was successfully performed in all three animals. No leakage was identified *via* methylene blue evaluation following surgery.

CONCLUSION: This novel technique for preforming a gastrointestinal anastomosis exclusively by NOTES is technically feasible and reproducible in an animal model but warrants further improvement.

Key words: Endoscopic gastrojejunostomy; Endoloop; Endoscopic clips; Natural orifice transluminal endoscopic surgery; Pigs

Core tip: A pure natural orifice transluminal endoscopic surgery gastrojejunostomy procedure may be successfully performed in a non-survival porcine model using holing followed by interrupted suture technique using one endoloop matched with a pair of clips, without the need of any additional devices.

Chen SY, Shi H, Jiang SJ, Wang YG, Lin K, Xie ZF, Liu XJ. Transgastric endoscopic gastrojejunostomy using holing followed by interrupted suture technique in a porcine model. *World J Gastrointest Endosc* 2015; 7(15): 1186-1190 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i15/1186.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i15.1186

INTRODUCTION

Gastro-jejunal side-to-side anastomosis is clinically designed for palliation of malignant gastric outlet obstruction (GOO)[1], performed primarily *via* open[2] and laparoscopic surgery[3]. Natural orifice transluminal endoscopic surgery (NOTES) may represent an alternative for the execution of gastro-jejunostomy procedures[4-10] due to less invasiveness and postoperative pain compared with the above-mentioned two procedures. To date, dozens of successful gastric bypass procedures by pure or hybrid NOTES have been reported, however, these methods are associated with some limitations, including being time-consuming, technically demanding and requiring specialized suturing devices.

Our experimental study aimed to demonstrate the feasibility and reproducibility of a pure NOTES gastrojejunostomy procedure using holing[11] followed by interrupted suture technique using a single endoloop matched with a pair of clips[12] in a non-survival porcine model.

MATERIALS AND METHODS

Animal model

Our study involved three healthy female domestic pigs weighing between 15 and 20 kg. All animals were fasted for 24 h prior to surgery. Induction of anesthesia was achieved *via* an intramuscular injection of 100 mg ketamine, 10 mg droperidol and 1 mg atropine, and anesthesia was maintained by intravenous drip of propofol at a rate of 10 mL/h with endotracheal intubation. Heart rate and oxygen saturation were monitored during the operation. Animals were kept in a supine position to allow for the best access and optimal peritoneal exploration. This study was approved by the Institutional Animal Use and Care Committee of Fujian Provincial Tumor Hospital, Teaching Hospital of Fujian Medical University, Fuzhou, China.

NOTES gastrojejunostomy

Gastrostomy: A small incision was created in the horizontal portion of the anterior pre-antral zone, which was determined *via* finger indentations of the abdominal wall, away from the small and large curvature, using a Dual knife (KD650L Olympus), followed by dilation using an 18-mm CRE balloon. The dual-channel therapeutic endoscope (GIF2TQ260M, Olympus Tokyo Japan) was subsequently advanced into the peritoneal cavity through the gastrostomy site.

Selection and retrieval of a free-floating loop of the small bowel into the stomach pouch: Loop selection was guided by loop proximity to the gastrostomy site to minimize the risk of tension and possible ischemia. An appropriate segment of the upper small intestine on its anti-mesenteric side was grasped by an endoscopic alligator forceps (FQ-46L-1, Olympus) through one channel of the endoscope and dragged through the incision into the stomach for the intra-gastric anastomosis, taking care not to include the mesenteric vascular supply to avoid unexpected incarceration.

Hold and exposure of the loop in the gastric cavity *via* submucosal inflation: An endoscopic injector (NM-400L-0423 Olympus) was passed through the other channel of the endoscope. Five to ten mL mL of saline solution mixed with 0.1 mL of 2% methylene blue was immediately injected into the submucosal layer circumferentially along the periphery of the gastrostomy site. Submucosal inflation temporarily decreased the size of the orifice of the gastrostomy to prevent the loop from falling back to the peritoneal cavity.

Execution of a gastro-jejunal mucosal-seromuscular layer approximation using holing followed by interrupted suture technique with endoloop/clips: First, a total of five to seven holes were made circumferentially along the periphery of the gastrostomy by using the Dual knife. An endoloop followed by an endoclip delivery system was inserted into the gastric cavity through the double-channel endoscope and placed at the side of one hole. One prong of the clip

Table 1 Summary of the procedures and outcomes following creation of pure natural orifice transluminal endoscopic surgery side-to-side gastrojejunostomy in three female pigs

Observation parameters	Pig 1	Pig 2	Pig 3
Time required to enter the peritoneal cavity and pull the loop intro the stomach (min)	35	19	18
Time required to suture the anastomosis (min)	58	44	47
Number of the stitched pairs	5	6	7
Complications			
Minor bleeding	+	+	-
Anastomotic leak	-	-	-

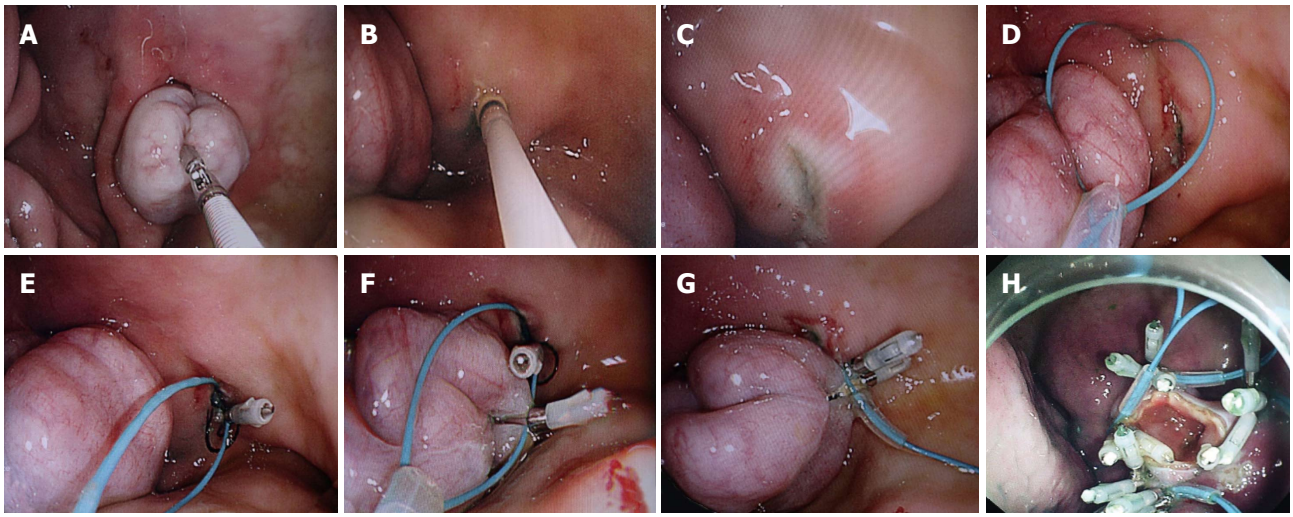

Figure 1 Step-by-step procedure of pure natural orifice transluminal endoscopic surgery side-to-side gastrojejunostomy. A: Endoscopic view of a loop of the small bowel in the stomach grasped by an endoscopic alligator forceps on its anti-mesenteric side; B: Image taken during submucosal injection around the loop; C: Endoscopic view of one hole made on gastric mucosal surface; D: Endoscopic view of an endoloop placed around the hole; E: Endoscopic view of one clip clipped to anchor the endoloop on the side of the stomach after the prong of the clip was inserted in the hole of the stomach wall; F: Endoscopic view of the second clip clipped to anchor the endoloop on the side of the small intestine; G: Endoscopic view of the endoloop tightened to approximate the gastric mucosal layer and the intestinal serosal layer; H: Endoscopic view of gasto-jejunal mucosal-seromuscular layer anastomosis followed by the loop full-thickness incision.

was then inserted in the hole of the stomach wall and clipped to anchor the endoloop. The second clip was used to anchor the same endoloop to the serosal surface of the small intestine. The gastric mucosal layer and the intestinal serosal layer were approximated by tightening of the endoloop. Briefly, gastro-jejunal mucosal-seromuscular layer anastomosis was created in pairs through the mucosa of the stomach and the serosa of small intestine to join the tissues based on the cooperation between one loop and a pair of clips. Five to seven pairs of interrupted sutures were placed to secure the anastomosis.

Full-thickness incision of the loop with the Dual knife: Jejunal loop incision was made longitudinally on its anti-mesenteric aspect to turn the inside mucosa out.

Euthanasia and necropsy

Euthanasia was performed immediately after the procedure. Necropsy results including injuries to adjacent organs, vascular bleeding, anastomotic patency and leakage evaluation were recorded.

RESULTS

Detailed data of pure NOTES side-to-side gastrojejunostomy performed on the three animals are shown in Table 1 and Figure 1. The procedure was technically successful in all cases. The duration of the procedure ranged from 1.0 to 1.5 h. Minor bleeding occurred from the right gastroepiploic artery during gastrostomy in 2 pigs and treated efficiently with the endoscopic hemostatic forceps (FD-410LR, Olympus) (80 W/soft-coagulation). On the postmortem examination, the immediate patency of the anastomosis was satisfactory, and no evidence of anastomotic leakage was identified *via* methylene blue evaluation[13] (Figure 2).

DISCUSSION

The advent of NOTES has made a minimally invasive endoscopic technique possible for creation of gastrojejunal anastomosis, being faced with opportunities and challenges at the same time.

Previous studies[4,7,8-10] have reported three full-thickness suturing methods summarized as the small intestine being pulled into the stomach lumen and

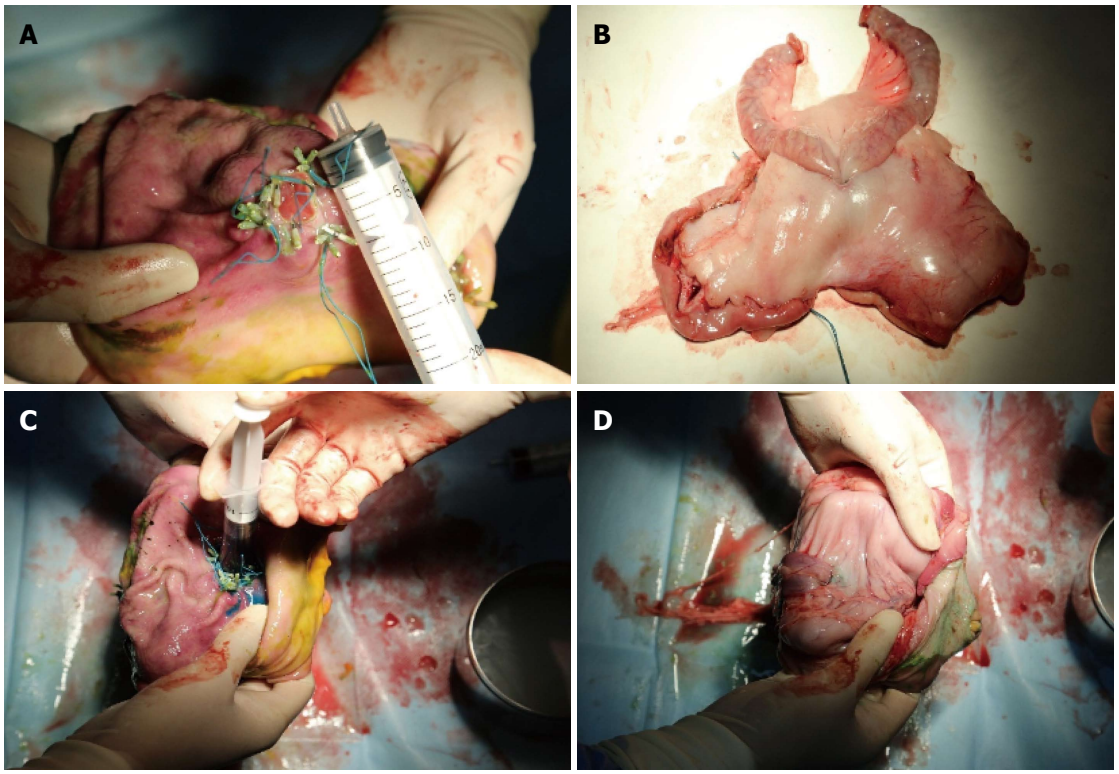

Figure 2 Postmortem appearances of anastomosis. A: Macroscopic appearance showing that the intestinal wall had been joined to the stomach wall; B: Macroscopic appearance of gastrointestinal side-to-side anastomosis; C: Methylene blue instilled into the anastomotic lumen; D: No methylene blue observed on the surface of gastric serosa around the anastomosis.

then sutured to the stomach wall using newly designed endoscopic suturing devices as follows: (1) a prototype endoscopic suturing device (Eagle Claw; Olympus)[7]; (2) a prototype "T-tag" suture system (BraceBar; Olympus)[4,9,10]; and (3) an EndoGIA stapler (Covidien)[8]. Here we reported for the first time, the use of interrupted suture technique using one endoloop matched with a pair of clips in a non-survival porcine model. This new technique resembles T-tag suture system, one of the aforementioned three methods, with its own unique characteristics. First, submucosal saline solution injection around the gastrostomy site made a slight cushion that prevented unexpected perforation by electric knives and allowed space to create holes deep enough to insert the prongs of the clip and to facilitate the subsequent secure clipping. Furthermore, submucosal inflation temporarily decreased the size of the orifice, and the smaller orifice allowed us to manipulate the loop of the small intestine in place more easily. Second, creating several holes at the edge of gastrostomy provided strong anchoring points for one prong of a clip in order to avoid clip slippage during grasping gastric thick mucosal surface. Third, interrupted suture method using one endoloop matched with a pair of clips was derived from the principle of "sewing" using a pair of T-tags with a single puncture needle, which may be done successfully by using only endoscopes and common endoscopic accessories, without the need of any extra devices.

In particular, if the small intestine was inadvertently dropped during the procedure, no leakage of small bowel contents occurred because the bowel wall was not incised until the anastomosis was complete.

Our pilot study had several limitations, however. First, endoscopic selection of an appropriate loop of the small bowel and secure fixation of the small bowel to the gastric wall without intra-peritoneal manipulation remains challenging[14]. In our current study, the appropriate portion of the small bowel was identified based on its proximity to the gastrostomy site and the left upper abdominal anatomical landmarks such as the spleen. For clinical studies, EUS guidance could be used to direct the targeted jejunal segment near the ligament of Treitz in non-altered anatomy patients[1,15]. Second, both of the endoscopic endoloop/clips utilized in our study, as well as the sewing devices (such as T-bar sutures) predominantly approximate the mucosa, and the reliability and durability of the anastomosis under gastric pressure should be estimated in the porcine model of GOO. Ryou *et al*[16] demonstrated that gastric mucosal closure with endoscopic clips may result in significant air and fluid leakage *via* the line of clips, however, this was not observed in our study.

In conclusion, this novel technique of performing gastrointestinal anastomosis exclusively by NOTES is technically feasible and reproducible in an animal model, although further improvement is warranted.

COMMENTS

Background

Gastro-jejunal side-to-side anastomosis is clinically designed for palliation of malignant gastric outlet obstruction (GOO), mostly performed *via* open and

laparoscopic surgery. Natural orifice transluminal endoscopic surgery may represent an alternative method of performing gastro-jejunostomy procedures due to its less invasiveness and lower incidence of postoperative pain compared with the above-mentioned two methods.

Research frontiers

To date, dozens of successful gastric bypass procedures *via* either pure or hybrid natural orifice transluminal endoscopic surgery (NOTES) have been described, however, these methods are associated with some limitations, as they are time-consuming, technically demanding and require specialized suturing devices.

Innovations and breakthroughs

A pure NOTES gastrojejunostomy procedure may be successfully performed in a non-survival porcine model using holing followed by interrupted suture technique using one endoloop matched with a pair of clips, without the need of any additional devices.

Applications

This study demonstrates the potential application of pure NOTES gastrojejunostomy using holing followed by interrupted suture technique using one endoloop matched with a pair of clips for palliation of malignant GOO.

Terminology

A NOTES gastrojejunostomy using interrupted suture technique with a single endoloop matched with a pair of clips resembles the technical principle of T-tag suture system, without the need of any additional devices.

Peer-review

The advent of NOTES has made a minimally invasive endoscopic technique possible for creation of gastrojejunal anastomosis, being faced with opportunities and challenges at the same time. A pure NOTES gastrojejunostomy procedure may be successfully performed in a non-survival porcine model using holing followed by interrupted suture technique using one endoloop matched with a pair of clips.

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ORIGINAL ARTICLE

Observational Study

Unsedation colonoscopy can be not that painful: Evaluation of the effect of "Lamaze method of colonoscopy"

Shao-Ping Yu, Xiao-Dong Lin, Guang-Yao Wu, Song-Hu Li, Zong-Quan Wen, Xiao-Hong Cen, Xian-Guang Huang, Mei-Ting Huang

Shao-Ping Yu, Xiao-Dong Lin, Guang-Yao Wu, Song-Hu Li, Zong-Quan Wen, Xiao-Hong Cen, Xian-Guang Huang, Mei-Ting Huang, Department of Gastroenterology, Dongguan Kanghua Hospital, Dongguan 523000, Guangdong Province, China

Author contributions: The study was designed by Yu SP; data were obtained by Lin XD, Wu GY, Li SH, Wen ZQ, Cen XH, Huang XG, Huang MT; endoscopy is performed by Yu SP, Lin XD, Li SH, Wen ZQ and Cen XH; data were analyzed by Wu GY; the report was mainly written by Yu SP, Lin XD and Wu GY; all authors approved the final version.

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Institutional review board statement: The Ethics Committee of Dongguan Kanghua Hospital had approved the experiment and all the data and photos used in this manuscript were approved.

Informed consent statement: All study participants, or their legal guardians, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: No conflicts of interest exist.

Data sharing statement: No additional data are available.

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Abstract

AIM: To evaluate the pain relieving effect of intervention with "Lamaze method of colonoscopy" in the process of colonoscopy.

METHODS: Five hundred and eighty-five patients underwent colonoscopy were randomly divided into three groups, Lamaze group, anesthetic group and control group. Two hundred and twenty-four patients of Lamaze group, the "Lamaze method of colonoscopy" were practiced in the process of colonoscopy. The Lamaze method of colonoscopy is modified from the Lamaze method of childbirth, which helped patients to relieve pain through effective breathing control. One hundred and seventy-eight patients in anesthetic group accepted sedation colonoscopy. For 183 patients in control group, colonoscopy was performed without any intervention. The satisfactory of colon cleaning, intestinal lesions, intubation time, success ratio, pain grading and complications were recorded. All data were statistically analyzed.

RESULTS: There were no significant differences at base line of the three groups ($P > 0.05$). Anesthetic group shows advantage in intubation time than the other two groups ($P < 0.05$). Lamaze group shows no advantage

in intubation time than that in control group ($P > 0.05$). The anesthetic group showed an apparent advantage in relieving pain ($P < 0.01$). Therefore, the "Lamaze method of colonoscopy" performed in colonoscopy could relieve pain effectively comparing with control group ($P < 0.05$). The patients in anesthetic group had the highest incidence of complications ($P < 0.05$).

CONCLUSION: The performance of the "Lamaze method of colonoscopy" in the process of colonoscopy could relieve patients' pain, minimize the incidence of complications, and is worthy promotion in clinical practice.

Key words: Colonoscopy; No sedation; Pain; Lamaze technique

Core tip: Colonoscopy is used as primary investigation of colorectal neoplasm worldwide and is of great value in detection of colorectal cancer in early stage. Though, it is not widely accepted by patients due to the uncomfortable feeling, especially pain, during the process. Recent years, sedation colonoscopy has developed rapidly, it has led to a great promotion of the increase of the patients' acceptance of follow up examination. Therefore, complication of sedation colonoscopy such as bleeding, perforation, cardiopulmonary events happens once in a while. Some kinds of unsedation colonoscopy had been reported by several scholars. Music, warm water infusion is the two most often reported methods. Here we evaluated the effect of a new method of unsedation colonoscopy we called "the Lamaze method of colonoscopy"(Lamaze colonoscopy) modified from the Lamaze method of childbirth. Our study suggested that Lamaze colonoscopy is an effective way to relief pain during colonoscopy.

Yu SP, Lin XD, Wu GY, Li SH, Wen ZQ, Cen XH, Huang XG, Huang MT. Unsedation colonoscopy can be not that painful: Evaluation of the effect of "Lamaze method of colonoscopy". *World J Gastrointest Endosc* 2015; 7(15): 1191-1196 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i15/1191.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i15.1191

INTRODUCTION

Colonoscopy plays a big part in primary investigation of colorectal diseases and screening for colorectal neoplasm[1]. Some patients find it difficult to endure the procedure and refuse the follow up examination due to the pain during the procedure. In recent years, the administration of anesthetics during endoscopy introduced by some scholars has achieved extraordinary results[2,3]. Meanwhile, some patients are susceptible to intestinal bleeding, bowel perforation and sedation-related cardiopulmonary adverse reaction due to the loss of pain and throat reflex in anesthesia[4,5].

"The Lamaze method of childbirth", developed by the French obstetrician Ferdinand Lamaze, has been used to decrease the level of maternal pain during natural birth since late 1950s, and plays a good role in the area[6]. Pain during delivery is mainly caused by contraction of uterus. Colonoscopy requires gas infusion during the process, which can stretch the colon like a balloon if gas accumulated; the retroaction against stretching of colon may cause the pain and uncomfortable feeling[7]. The mechanism of pain in childbirth and colonoscopy is similar. We created "The Lamaze method of colonoscopy" (Lamaze colonoscopy), which was modified from "The Lamaze method of childbirth", and practiced it in the process of colonoscopy. In our study, we verified the effect of Lamaze colonoscopy in reducing pain during colonoscopy.

MATERIALS AND METHODS

Patients

The study included consecutive patients underwent colonoscopy at endoscope center in our hospital from November 2012 to October 2014. The first 3 patients whom underwent sedation colonoscopy were enrolled in anesthetic group every Monday (Monday is our sedation colonoscopy day) except for holidays and those whom needed endoscopic treatment such as polypectomy. The first 3 patients whom underwent unsedation colonoscopy were enrolled in Lamaze group every Tuesday. Those whom needed endoscopic treatment were also ruled out. The first 3 patients whom underwent unsedation colonoscopy were enrolled in control group every Thursday. Those whom needed endoscopic treatment were excluded too. Patients with severe cardiopulmonary dysfunction, stroke, moderate to severe ascites, renal insufficiency, severe malnutrition and patients who were bed ridden were excluded from the study. All patients enrolled in the experiment had signed a consent form of colonoscopy examination. Patients in anesthetic group all signed a consent form of sedation. A total of 585 patients aged from 25-82 years old were enrolled. There were 224 patients in Lamaze group, 178 patients in anesthetic group and 185 patients in control group finally.

Examination

Bowel preparation was routinely accomplished with a 2 L electrolyte solution of polyethylene glycol (all patients were chinese which belongs to yellow race). All patients were given supplemental oxygen intranasal (2 L/min). Heart rate, blood pressure and oxygen saturation were monitored throughout the procedure. Intravenous sedation-analgesics provided by the anesthetist in anesthetic group using a combination of fentanyl (0.5-1 μg/kg) and propofol (1.5-2 mg/kg) at the discretion of the endoscopists. Five doctors with at least 5-years-experience of performing colonoscopy performed the procedure. We began to insert

Table 1 Lamaze method of childbirth and the Lamaze method of colonoscopy

Lamaze method of childbirth[8,9]	Thoracic breathing: Used in initial stage of uterus contraction, method: (1) completely relaxed; (2) eyes fixed on a certain point; (3) abdominal stay relaxed while breath in from nose, breath out from mouth; (4) a total of 6-9 times of inspiration and expiration per minute; and (5) practice 5 times a day, 60 s each time Shallow and slow accelerating breathing: Use when the uterus contracts each 2-4 min, cervix opened to 2-8 cm. Method: Step (1-3) is the same with thoracic breathing; and (4) accelerate the breathing when uterus contraction enhanced, slow it down while contraction relieves Shallow breathing: Use when the uterus contracts lasts for 60-90 s each 30-90 s , cervix opens to 8-10 cm Method: Step (1-2) is the same with thoracic breathing; (3) open mouth slightly to help breath (making a sound "hee-hee"); (4) breathing with nose, making noise from the larynx; (5) adjust the respiratory rate according to intensity of the contraction; (6) inspiration and expiration the same volume of air to avoid hyperventilation; and (7) 4-6 quickly continue inspiration and expiration then vigorously exhale, repeat until uterus contraction stops Close air-way and force movement: Used when cervix is full opened to 10 cm. Method: (1) legs apart, hands holding handrail of obstetric delivery bed; (2) vigorously aspirated and close air-way, force down; (3) head up slightly staring at navel with jaw neck down forward; and (4) hold breath for 20-30 s as far as possible, exhale and hold breath at once and force movement until uterus contraction stops Halitus movement: Used when cannot exert herself but cannot help to do it. Method: (1) mouth open, breathing quickly like gasping; and (2) the whole body is relaxed totally
The Lamaze method of colonoscopy	Thoracic breathing: Used when the procedure begins, method: (1) completely relaxed; (2) eyes fixed on a certain point; (3) abdominal stay relaxed while breath in from nose, breath out from mouth; and (4) a total of 6-9 times of inspiration and expiration per minute Shallow and slow accelerating breathing: Used when the scope is crossing the junction of sigmoid colon and descending colon from the sigmoid colon. Method: Step (1-3) is the same with thoracic breathing; and (4) accelerate the breathing when pain enhanced, slow it down while pain relieved Shallow breathing: Used when the scope is crossing the splenic flexure. Method: (1) completely relaxed; (2) eyes fixed on a certain point; (3) open mouth slightly to help breath (making a sound "hee-hee"); (4) breathing with nose, making noise from the larynx; (5) adjust the respiratory rate according to pain intensity; (6) inspirate and expirate the same volume of air to avoid hyperventilation; and (7) 4-6 quick continue inspirate and expirate then vigorously exhale, repeat until the pain disappear Close air-way and force movement: Used when the pain is moderate or severe. Method: (1) vigorously aspirated and close air-way, force down; and (2) hold breath for 20-30 s as far as possible, exhale and hold breath at once and force movement until pains relieves or disappeared

colonoscope when patients fell asleep when their eyelash reflex disappeared, breathed calmly and muscle relaxed. Patients in Lamaze group were trained "the Lamaze method of colonoscopy" (detailed in Table 1), by the assigned nurse in endoscope center, 5-8 min before examination. It would be continuously practiced during the whole process of colonoscopy. The control group was given no intervention. The colonoscopy was categorized as completed when reached the cecum or the ileocolic anastomosis (in case of colonic surgery).

The endoscopists graded the quality of bowel preparation immediately after the procedure. Grade 1 as excellent with no stool visualized, Grade 2 as satisfactory with a small amount of stool visualized not blocking the view, Grade 3 as unsatisfactory with stool blocking the view and/or the passage of the colonoscope. He/she also evaluated the difficulty of insertion of the colonoscopy on a 100 mm visual analog scale, with 0 "very easy" and 100 "very difficult." All patients were asked to finish a questionnaire after the procedure in which they graded abdominal pain using a visual analogue scale (VAS) from 0 to 10 (0 as extremely acceptable/least severe, 10 as least acceptable/extremely severe). Patients marked the point on the line that they feel representing their pain grade. The VAS score is determined by measuring in millimeters from the left hand end of the line to the point that the patient marks.

Equipment and record

Age, gender, history of previous colonoscopy or previous abdominal surgery was recorded before examination. The satisfaction of colon cleaning, intestinal lesions, intubation time, success ratio and complications were also recorded after examination.

Equipment and personnel

Bowel preparation was done in all patients before the examination using 2 L electrolyte solution of polyethylene glycol. Colonoscopy examinations were performed by an experienced endoscopist, using a video colonoscope (FUJINON). Technique assistance is performed by the same assistant when needed during examination. Patients were sedated in presence of an aesthetist. The endoscopists, assistant and nurse received the "Lamaze method of childbirth" course before trial. They were also trained to perform Lamaze colonoscopy using the method above.

Statistical analysis

SPSS 19.0 was used to process data. Quantitative data were reported as means ± SD. One-way ANOVA was used to compare the age and intubation time of the three groups, least-significant difference is used to compare the differences within groups if difference is significant between groups and the test of homogeneity of variances shows $P < 0.05$. χ^2 test was used to compare gender, history of previous colonoscopy, previous abdominal surgery history, intestinal lesions, success ratio and complications. The satisfactory of colon cleaning and the pain grades of the three groups were

Table 2 Comparison on patients' age, gender, previous colonoscopy history and previous abdominal surgery history

	Age (yr)	Gender (male/female)	Previous colonoscopy(Y/N)	Previous abdominal surgery(Y/N)
Lamaze group	54.9 ± 9.9	118/106	88/136	43/181
Anesthetic group	55.6 ± 9.7	76/102	62/116	25/153
Control group	56.3 ± 8.6	98/85	66/117	31/152
P	0.197	0.07	0.633	0.403

Table 3 Comparison on the quality of bowel cleanliness

	Grade 1	Grade 2	Grade 3
Lamaze group	168	36	20
Anesthetic group	123	38	17
Control group	137	29	17

$\chi^2 = 2.657$; $P = 0.617$.

Table 4 Comparison on intestinal lesions

	Normal	Colon polyps	Colonic diverticulum	IBD	Colon cancer
Lamaze group	127	69	11	8	9
Anesthetic group	107	46	9	9	7
Control group	115	39	8	12	9

$\chi^2 = 6.293$; $P = 0.614$. IBD: Inflammatory bowel disease.

compared with crosstable Pearson χ^2 test. Criterion for statistical significance was $P < 0.05$.

RESULTS

There were no significant differences between the three groups in age, gender, history of previous colonoscopy and history of abdominal surgery (Table 2).

According the endoscopists' finding, there was no difference in the quality of colon cleanliness and the intestinal lesions between the three groups (Tables 3 and 4).

The anesthetic group was much more successful in alleviating pain comparing to the other two groups, 57.3% (102/183) of patients feel completely no pain at all. The Lamaze group of colonoscopy is also more efficient in relieving pain than the control group (Tables 5 and 6).

The time required for intubation in anesthetic group is shorter than the other two groups. But the Lamaze group did not demonstrate its improvement compared with control group in this aspect (Tables 7 and 8).

Only 1 case failed to complete colonoscopy in anesthetic group, the patient was a thin women who had a previous history of cesarean section. That number in Lamaze group and control group are 7 and 12. But there is no significant difference between the three groups ($P = 0.06$) (Table 9).

The complication rates of both the Lamaze group and control group were lower and complication is milder than the anesthetic group. In anesthetic group, 5 patients incurred a decrease of pulse oxygen saturation (< 90%), and 2 of the patients' heart rate drops to < 60 bpm, but all of them recovered immediately after effective intervention. There were no deaths in all three groups. The difference on complications of the three groups was significant ($P = 0.001$) (Table 10).

Table 5 Comparison on patients' pain grading

	0-2	2-4	4-6	6-8	8-10
Lamaze group	47	96	77	3	1
Anesthetic group	142	35	1	0	0
Control group	6	7	71	88	11

$\chi^2 = 506.579$; $P < 0.001$.

Table 6 Further pair-wised comparison of patients' pain grading

	χ^2	*P*
Lamaze group *vs* control group	194.43	< 0.001
Lamaze group *vs* anesthetic group	150.92	< 0.001
Anesthetic group *vs* control group	310.68	< 0.001

Table 7 Comparison on intubation time

	Intubation time (min)
Lamaze group	9.21 ± 2.76
Anesthetic group	7.46 ± 2.93
Control group	9.45 ± 2.38

F = 29.696, $P < 0.001$

DISCUSSION

Colonoscopy is used as primary investigation of colorectal neoplasm worldwide and is of great value in detection of colorectal cancer in early stage[1]. Though, it is not widely accepted by patients due to the uncomfortable feeling, especially pain, during the process. Recent years, sedation colonoscopy has developed rapidly, it has led to a great promotion of the increase of the patients' acceptance of follow up examination[10-12]. Therefore, complication of sedation colonoscopy such as bleeding, perforation, cardiopulmonary events happens once in a while[13]. Some kinds of unsedation colonoscopy had been reported by several scholars. Music, warm water infusion is the two most often reported methods[14-16]. Here we evaluated the effect of a new method of unsedation colonoscopy we called "the Lamaze method

Table 8 Further pair-wised comparisons on intubation time

	Mean difference	Standard error	*P*	95%CI	
				Lower bound	Upper bound
Lamaze group *vs* control group	-0.243	0.269	0.368	-0.77	0.29
Lamaze group *vs* anesthetic group	1.75	0.271	< 0.01	1.22	2.28
Anesthetic group *vs* control group	-1.993	0.285	< 0.01	-2.55	-1.43

Table 9 Comparison on the quality of bowel cleanliness

	Success(Y/N)
Lamaze group	217/7
Anesthetic group	177/1
Control group	171/12

$\chi^2 = 9.918$, $P = 0.06$.

Table 10 Comparison on complications

	Total	Bleeding	Perforation	Cardiopulmonary complications	Normal
Lamaze group	224	2	0	1	221
Anesthetic group	178	9	0	7	162
Control group	183	3	0	1	179

$\chi^2 = 18.043$; $P = 0.001$.

of colonoscopy" (Lamaze colonoscopy) modified from the Lamaze method of childbirth. The Lamaze method of childbirth could reduce pain by effective breathing and relaxation training. Acknowledge of pre-delivery and delivery rule could be applied to different stages and different grades of pain to intentionally control pain caused by contractions and other discomfort feeling. The pain was transferred since mothers focus on breathing control[17]. In our study, we found Lamaze colonoscopy which modifying from "the Lamaze method of childbirth" according to the characteristics of colonoscopy. It was applied to the examination. The results indicated that the pain could be alleviated when use Lamaze colonoscopy. The mechanism of pain during colonoscopy is similar to that of childbirth. Both are caused by the spasm of smooth muscle. But the pain during colonoscopy is artificially caused by the insertion of endoscope. Also, severe pain is caused by the knotting of endoscope during operation. Lamaze colonoscopy may could maintain a relatively constant position of intestinal tract by deepening abdominal respiration, made colonoscope passed easily.

This study compared with the difference of anesthetic group, Lamaze group and control group from several aspects at the same time. Judging from the outcome, the applications of Lamaze colonoscopy did not shorten the time of intubation. The main reason of time increasing is due to the needs of helping patients get into the right step during operation. Considering from the success ratio, the anesthetic group got the highest success ratio, but it did not demonstrate a statistical difference. Too many factors working on the success ratio, research shows that age, gender, preparation of intestine, history of previous abdominal surgery, chronic colitis all contribute to it[18,19]. There is no statistical difference among the three groups in age, gender, preparation of intestine, history of previous abdominal surgery and intestinal lesions.

The usage of sedatives in colonoscopy obviously improves the acceptance and tolerance of the examination in patients. However, some issues still cannot be avoided in anesthetic colonoscopy. Venous channel must be built before the exam, medical fee increased, recovery time was prolonged, complications such as cardiopulmonary events happens. The usage of sedatives can suppress respiratory directly, causing blood pressure drops. Severe allergic reaction can be life threatening, anesthetic colonoscopy causing aspiration pneumonia leads to Acute Respiratory Distress Syndrome (ARDS) finally caused death is reported in China[20]. In this study, 2 subjects' heart rate decrease to < 60 beat per minute, 5 subjects' SPO_2 declined to less than 90% in anesthetic group, all those recovered after proper intervention. The incidence rate of complication especially severe complication is lower in Lamaze group and control group than that in anesthetic group. There is some deficiency in our study, the follow-up period is only one week, some delayed complication might be neglected. Some studies expended the follow-up period up to 30 d in accordance with complication[5,21]. This is a single center study, multiple center study using the same standard may provide more evidences of the value of Lamaze colonoscopy.

To sum up, the application of "the Lamaze method of colonoscopy" in colonoscopy can ease the pain of patient effectively, enhance the tolerance of colonoscopy and avoid the adverse effect of anesthetics. This method is worthy of wide promotion, summary and improvement.

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COMMENTS

Background

Colonoscopy plays a big part in primary investigation of colorectal diseases and screening for colorectal neoplasm. Some patients find it difficult to endure the procedure and refuse the follow up examination due to the pain during the procedure. Sedation colonoscopy developed quickly in recent years, but the adverse reaction happens once in a while. Some unsedation colonoscopy had been used to relieve patients' pain.

Research frontiers

Some kinds of unsedation colonoscopy had been reported by several scholars. Music, warm water infusion is the two most often reported methods. They can all relief pain during unsedation colonoscopy, but not as effect as sedative colonoscopy. New method could be explored.

Innovations and breakthroughs

The use of Lamaze colonoscopy modified from Lamaze childbirth had never been reported. They explored the possibility of it, which is another way of pain-relief in patient undergoes colonoscopy.

Applications

The application of "the Lamaze method of colonoscopy" in colonoscopy can ease the pain of patient effectively, enhance the tolerance of colonoscopy.

Peer-review

The study is interesting and can be very useful in the pain-relief area of study.

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TOPIC HIGHLIGHT

2015 Advances in Laparoscopic Surgery

Pancreatic insulinomas: Laparoscopic management

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Abstract

Insulinomas are rare pancreatic neuroendocrine tumors that are most commonly benign, solitary, and intra-pancreatic. Uncontrolled insulin overproduction from the tumor produces neurological and adrenergic symptoms of hypoglycemia. Biochemical diagnosis is confirmed by the presence of Whipple's triad, along with corroborating measurements of blood glucose, insulin, proinsulin, C-peptide, β-hydroxybutyrate, and negative tests for hypoglycemic agents during a supervised fasting period. This is accompanied by accurate preoperative localization using both invasive and non-invasive imaging modalities. Following this, careful preoperative planning is required, with the ensuing procedure being preferably carried out laparoscopically. An integral part of the laparoscopic approach is the application of laparoscopic intraoperative ultrasound, which is indispensable for accurate intraoperative localization of the lesion in the pancreatic region. The extent of laparoscopic resection is dependent on preoperative and intraoperative findings, but most commonly involves tumor enucleation or distal pancreatectomy. When performed in an experienced surgical unit, laparoscopic resection is associated with minimal mortality and excellent long-term cure rates. Furthermore, this approach confers equivalent safety and efficacy rates to open resection, while improving cosmesis and reducing hospital stay. As such, laparoscopic resection should be considered in all cases of benign insulinoma where adequate surgical expertise is available.

Key words: Pancreatic insulinoma; Laparoscopic surgery; Technique; Outcomes; Minimally invasive surgery

Core tip: Insulinomas have always fascinated physicians and surgeons alike, due to the difficulties in: (1) diagnosing them; (2) obtaining accurate preoperative and intraoperative localization; and (3) actually performing

the operation safely and effectively. Laparoscopy stands out in the current literature as the approach of choice, and is employed for virtually all benign insulinomas. Enucleations for insulinomas in the head and body, as well as distal pancreatectomies for lesions in the body and tail of the pancreas, have been shown to be safe and effective in the current series. Laparoscopic intraoperative ultrasound localization has emerged as a standard adjunct to these procedures.

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INTRODUCTION

Insulinomas are insulin-secreting neuroendocrine tumors deriving from neoplastic pancreatic islet cells, and occurring almost exclusively in the pancreas[1,2]. They are gastroenteropancreatic neuroendocrine tumors (GEP-NETs) belonging to the subgroup of neuroendocrine tumors (NETs) known as pancreatic endocrine tumors (PETs)[3]. In contrast to other PETs, approximately 90% of insulinomas are sporadic, solitary, and benign, measuring less than 2 cm in diameter[1,2,4-6]. These characteristics, along with their highly symptomatic presentation, make complete surgical removal the treatment of choice for affected patients[2,7,8]. Surgical treatment options include tumor enucleation and regional pancreatic resection[8]. However, until recently, the only available approach was open surgery.

Laparoscopic enucleation and distal pancreatectomy were first reported in the 1990s by Gagner *et al*[9]. In fact, the small, benign, and solitary nature of insulinomas makes them ideal candidates for a laparoscopic approach, particularly in overweight or obese patients. In the last 20 years, several case reports[10,11] and case series[9,12-31], including our own[32-34], have explored the technical aspects of laparoscopic insulinoma resection. The results presented in these studies demonstrate the feasibility, safety, and reproducibility of laparoscopic insulinoma resection in experienced hands. Consequently, recently published guidelines now consider laparoscopic enucleation an appropriate treatment modality for the majority of insulinomas[8,35-37]. This article reviews the current status of laparoscopic insulinoma management and discusses both the strategic and technical aspects of surgical care in these patients.

BACKGROUND

Insulinomas are rare and exhibit a number of unique characteristics when compared to other PETs. These differences in the epidemiology, clinical features, and biological behavior of insulinomas impact significantly on their management and define the role and limitations of laparoscopic surgical intervention.

EPIDEMIOLOGY: SURGICAL MANAGEMENT OF RARE PATHOLOGY

The estimated annual incidence of insulinomas is 0.7-4 diagnosed cases per million persons[38]. Their rarity, combined with the unique challenges presented throughout the course from diagnosis to therapy, requires expert referral and management. Centralization of care is therefore of utmost importance for these patients, and tertiary referral to centers of excellence that follow a multidisciplinary approach is strongly advocated in current treatment guidelines[8,35-37]. The low incidence of insulinomas makes it difficult for any surgeon outside of pancreatic centers of excellence to gain sufficient experience in insulinoma resection[8,35-37]. Furthermore, although a laparoscopic approach is encouraged, the choice between open and laparoscopic surgery should be left to the discretion of the surgical team. It is therefore paramount that surgeons making such decisions are experienced in both open and minimally invasive procedures, in order to offer their patients the optimal treatment.

INSULINOMAS IN THE CONTEXT OF MULTIPLE ENDOCRINE SYNDROME TYPE 1

The vast majority of insulinomas are sporadic, but in 5%-10% of cases they present in the context of multiple endocrine syndrome type 1 (MEN1)[6,7]. MEN1-related insulinomas are frequently multifocal and coincide with several other pancreatic lesions (most commonly non-functioning pancreatic endocrine tumors)[6,39]. It therefore becomes very difficult preoperatively to determine with certainty the lesions for resection that are responsible for the clinical syndrome. This is further confounded by the fact that not all pancreatic lesions with immunohistochemically proven insulin production capacity produce clinical symptoms[39,40].

As such, it is both difficult to determine preoperatively the lesions responsible for the clinical syndrome and to definitively state whether surgical resection has been curative, even when insulin-producing lesions are documented in the pathology report. Consequently, significantly higher failure and recurrence rates are documented after surgery for MEN1-related insulinomas when compared to sporadic lesions[39,41].

In view of the difficulty in achieving complete clearance, a more radical surgical approach is preferred in MEN1-associated insulinomas[39,41,42]. Current surgical practice depends on the site of the tumor. For distal lesions, distal pancreatectomy with or without splenic preservation is required. Proximal tumors located in the pancreatic head may be enucleated, but total pancreatectomy may be required in selected

cases[35,36,39,41-44]. Local resections are not routinely indicated, despite some recently promising results in selected solitary or dominant lesions[45]. Moreover, the procedure of choice should be decided after careful preoperative localization, and take into account the need for symptom alleviation (*i.e.*, complete resection of all insulinomas), the malignant potential of all existing pancreatic lesions (including, but not limited to, insulinomas), and the expected complications, together with the existence of any previous surgical attempts. It is notable that laparoscopic resection in the context of MEN1 requires advanced minimally-invasive surgical skills due to the inherent difficulties of laparoscopic distal pancreatectomy, particularly where combined enucleations in the head of the pancreas are required. Finally, it should be mentioned that, in our recent experience, enucleation of single lesions in the head of the pancreas in the context of MEN has been successful in rendering the patient asymptomatic 12 mo after surgery.

BIOLOGICAL BEHAVIOR

Although the majority of insulinomas are benign and curable by surgical resection, approximately 5%-10% show malignant behavior[38]. However, with an annual incidence of approximately 0.1 per million persons per year[46], malignant insulinomas are extremely rare. Similar to all other neuroendocrine pancreatic tumors, the malignant potential of insulinomas is assessed by tumor differentiation (extent of resemblance to normal cells), grade (degree of biologic aggressiveness), and stage (extent of tumor spread)[47]. Of note, although a number of different pathological grading and clinicopathologic staging classifications have been suggested, no single system has been universally adopted[47].

Local invasion and/or evidence of liver metastases clearly demonstrate malignancy[7]. However, in the absence of these findings, malignant behavior must be determined from the pathologic characteristics of preoperative tissue biopsies when they were taken, because in most cases, EUS-guided Fine Needle Aspiration is performed at most. Although the course of malignant insulinomas is more indolent than other malignant neuroendocrine pancreatic tumors, the median survival is only 2 years, while the 10-year survival rate is only 29%[5,6,48]. Although, in some cases, malignant insulinomas have been reported with higher survival rates[49], this prognosis remains significantly poorer than for benign insulinomas, which present a 95%-100% surgical cure rate[5-7,48].

These key facts define the role and the limitations of both laparoscopic and open surgery in patients with malignant insulinoma. However, it is possible that extensive surgical resection of the primary tumor, affected lymph nodes, and distant metastases may provide alleviation for hypoglycemia and long-term survival when combined with adjunctive therapy such as medical treatment, radiofrequency ablation, transarterial chemoembolization, somatostatin analogues, chemotherapy, or biological agents. In resectable malignant disease, surgical options may provide a cure, and include distal pancreatectomy, pancreaticoduodenectomy with or without metastasectomy, segmentectomy, formal hepatectomy, or even liver transplantation[6,30,36,37,49,50]. Where the disease is unresectable in its entirety, debulking surgery may provide symptomatic relief when combined with medical and ablative therapy. Whenever malignancy is determined preoperatively, these operations are performed exclusively *via* laparotomy. Laparoscopic resection is not routinely practiced and no guidelines currently exist as to the role of laparoscopic intervention in these cases. Conversely however, in some cases the malignant potential of an insulinoma may only be acknowledged after laparoscopic resection as a result of specimen histology, symptom recurrence, and/or metastasis development during follow-up. In these cases, a multidisciplinary assessment is mandatory, and is most commonly followed by secondary radical open resection in combination with adjunctive therapy.

CLINICAL SYMPTOMS AND BIOCHEMICAL DIAGNOSIS

Insulinomas most commonly present with hypoglycemia caused by inappropriate excessive endogenous insulin production. Physical exercise and fasting usually provoke the symptoms, which fall in two major categories: Neurologic and adrenergic[4,6,7,43,51]. Neurologic symptoms are attributed to the effects of low blood glucose on the nervous system (neuroglycopenia) and include visual disturbances (diplopia and blurred vision), altered mental status, abnormal behavior, seizures, amnesia, and even coma[4,6,7,43,51]. Adrenergic symptoms are attributed to reactive catecholamine overproduction and include nausea, excessive sweating, anxiety, palpitations, weakness, tremors, increased appetite, and heat intolerance[4,6,7,43,51]. Each patient usually reports a specific collection of symptoms[52,53], which are relieved almost immediately after carbohydrate consumption, a feature that is included in Whipple's diagnostic triad[54]. Furthermore, the combination of weakness and increased appetite, alongside the ability of carbohydrate consumption to act as a relieving factor, frequently leads to excessive calorie consumption, weight gain, and eventual obesity[4,43,51].

When there is clinical suspicion of insulinoma, the autonomous overproduction of endogenous insulin must be confirmed biochemically. The basis of this diagnosis is the Whipple's triad[54] of biochemically-proven hypoglycemia, hypoglycemic symptom development, and swift reversal after carbohydrate consumption that occurs during a supervised fasting period. When symptoms occur concurrently with hypoglycemia (glucose levels around or below 2.2 mmol/L), increased insulin ($\geqslant$ 6 μIU/mL with standard non-specific insulin radioimmunoassay or $\geqslant$ 3 μIU/mL

with immunoradiometric or immunochemiluminescent insulin specific assays which are devoid of cross-reactivity for proinsulin and proinsulin-like components), proinsulin (≥ 5 pmol/L), and C-peptide (≥ 200 mmol/L) levels, this suggests the presence of an autonomous source of insulin production which is insensitive to hypoglycemia[1,8,43]. In order to rule out the presence of exogenous insulin (factitious hypoglycemia), a negative sulfonylurea/meglitinide screen test is also required that corroborates with the increased levels of C-peptide[1]. Surrogate markers of insulin presence, including low β-hydroxybutyrate levels (no more than 2.7 mmol/L) and a generous rise of glucose levels (more than 1.4 mmol/L) after the administration of 1 mg glucagon at the end of the fasting period[55], have been used by some authors for decades[56], especially for patients in which their blood glucose does not fall below 2.5 mmol/L during fasting. Indeed, β-hydroxybutyrate levels have now been included in recent guidelines[8,57], despite recent contradicting reports[58].

The actual cut-off points for insulin during fasting vary throughout the literature[52,59-61]. The reasons for this variation are complex and reflect both the altered biochemistry of insulin produced by insulinomas (increased proinsulin and proinsulin-like components, as well as insensitivity *vs* partial sensitivity of insulinomas to hypoglycemia) and the inherent limitations of detection assays (minimum detection levels and non-specificity to insulin in older radioimmunoassays). As such, despite a general agreement in the published cut-off values for insulinoma diagnosis, it is likely that this will remain a matter of contention. In fact, results from a recent comparative study have demonstrated proinsulin levels exceeding 5 pmol/L to be a more reliable diagnostic test for endogenous hyperinsulinism than absolute insulin levels at the time of hypoglycemia (< 2.5 mmol/L)[62]. Subsequent to this study, proinsulin measurement has since been recognized in recent consensus guidelines[8].

Practically, it is important to also consider the duration of these fasting tests when providing a biochemical diagnosis of endogenous hyperinsulinism. Traditionally, the gold standard has been a 72-h supervised inpatient assessment[52,53]. More recently however, modern insulin and pro-insulin specific assays have shown that a fasting period of 48 h is sufficient[60]. The lower cost and reduced invasiveness of this 48-h test have led to its rapid uptake across many institutions, thereby providing a new standard of care[1,43] that is reflected in updated diagnostic guidelines[8,57].

Surgeons currently have a limited role in the diagnosis of insulinoma, as this is usually confirmed prior to surgical referral. However, this by no means obviates the need for careful clinical assessment and thorough review of the patient's records and biochemistry prior to intervention. In a recent study, out of 17 patients referred to the United States National Institute of Health after a failed blind distal pancreatectomy, 5 were eventually diagnosed as having factitious hypoglycemia[63]. These patients underwent completely unnecessary major surgery. It is therefore the surgeon's professional and ethical responsibility to comprehend and fully agree with the diagnosis of insulinoma prior to undertaking any surgical intervention.

PREOPERATIVE AND INTRAOPERATIVE LOCALIZATION

Once biochemical diagnosis of insulinoma has been confirmed, the next important and demanding task is to accurately determine the location of the lesion within the pancreas[1,2,4-6,48]. In the past, surgeons were reliant on blind distal pancreatectomies for occult impalpable insulinomas due to limited imaging and diagnostic tools[64-66]. However, blind distal pancreatectomy was associated with a high failure rate (> 20%) that was exaggerated by the fact that non-palpable insulinomas often reside in the thicker pancreatic head[63]. Over the past 25 years, novel diagnostic modalities have rendered this blind approach obsolete[67] in favor of targeted resection.

Although in the past open surgeons had often bypassed preoperative localization in favor of intra-operative palpation and ultrasound (IOUS)[64-66], this approach was never widely adopted[1,53,67,68] and is certainly unacceptable for laparoscopy. Reliance on laparoscopic intraoperative ultrasound (LIOUS) alone led to open conversion in one of every three cases[16]. As a result, more recent series[17-19,31], including our own, reflect the current guidelines advocating accurate localization prior to laparoscopic surgical intervention[8]. We strongly advise against laparoscopic intervention without accurate preoperative localization[32] for a number of reasons: Firstly, the lack of intraoperative tactile feedback removes the ability to assess the tumor by palpation; secondly, patient positioning and trocar placement is determined by the location of the tumor; and finally, whilst LIOUS is a mandatory intraoperative adjunct for accurate localization and delineating regional anatomy, it is certainly not a diagnostic tool. Furthermore, the prolonged time required and inability to apply the probe to the whole pancreas without additional port placement limits its diagnostic role. Appropriate use of LIOUS requires knowledge of the regional location of the tumor (head, uncinate process, body, or tail) from preoperative investigations. In this way, the surgeon may utilize this tool to exactly locate and delineate the anatomic relationships of non-palpable lesions. It is the failure of accurate preoperative imaging that makes some authors use LIOUS to detect undiagnosed lesions or those found not to be located in the area indicated by preoperative assessment[9,16,69]. However, it is our opinion that this use limits the diagnostic yield of LIOUS, making it much lower than when used in conjunction with accurate preoperative localization. As such, we believe that accurate preoperative localization is a requirement of the laparoscopic approach. Failure to adequately assess tumor location should initially lead to repeat imaging and reassessment in an attempt

to improve localization accuracy. However, where this fails, surgeons should reconsider the appropriateness of laparoscopic intervention.

STRATEGY FOR PREOPERATIVE LOCALIZATION

There is no consensus on either the optimal type of preoperative localization modalities or on the exact order in which they should be performed. Recent guidelines suggest that non-invasive imaging should be performed first[8,35-37,57], and should include one or two from the following: transabdominal ultrasound (US), computerized tomography (CT), and magnetic resonance imaging (MRI). These modalities are usually readily available and, with the recent addition of contrast enhancement (CE), have been reported to have a high sensitivity in insulinoma detection (about 90% for CE US[70] and about 100% for CE CT and MRI[71]). However, due to variation in technology and radiological expertise, not all institutions may be able to achieve such excellent detection rates. In our experience, transabdominal unenhanced ultrasound has been associated with a sub-optimal diagnostic yield and, as such, we do not routinely employ this modality in our preoperative assessments. Although this approach is in line with recent guidelines[35-37,57], it is contrary to the reports of some authors who have had excellent results from the use of US[7].

Failure to obtain diagnosis through CT or MRI should lead to further assessment using endoscopic ultrasound (EUS)[8,35-37,57]. Although this modality is invasive, operator dependent, and of limited availability, it may yield an accuracy exceeding 90%[72,73], and is thus now advocated in all established guidelines[8,35-37,57]. As EUS performs better in the head, but less well in the body and worse in the tail of the pancreas[74,75], it may be considered a complementary modality to CT[73], which may miss lesions in the pancreatic head[76]. Notably, in our experience, lesions of greater tumor density are best detected on the arterial phase of the CT.

Following these investigations, the next test we routinely employ is selective pancreatic angiography with venous sampling after intra-arterial calcium stimulation (ASVS)[67,77]. Although highly invasive, ASVS is associated with a sensitivity of approximately 95% and is indispensable when previous tests are equivocal. ASVS allows hypervascular insulinomas to be detected by arteriography, with added regional localization in difficult cases through stimulated venous sampling. Using this technique, localization can be determined according to the arterial branch injected. The presence of insulinoma in a particular territory is indicated by a greater than two-fold elevation in insulin levels (sampled at 30 and/or 60 s from the hepatic vein) on calcium gluconate stimulation[78]. The use of ASVS is now widespread[7,79] and is included in most[8,36,37,57], but not all[35], recent guidelines.

Whilst other authors advocate the use of PET/CT[80] and SPECT/CT[81], this is not routine practice in our experience, as both techniques remain investigational[8]. However, promising results have recently been reported with glucagon-like peptide-1 (GLP-1) analogue SPECT/CT[82] imaging. Insulinomas are known to overexpress GLP-1 receptors in high density[83], thus overcoming the limitations of somatostatin-like tracers. The high selectivity of GLP-1 receptor agonists and their high affinity for insulinoma cells provides a promising future for preoperative insulinoma localization, and is likely to have increasing clinical importance with the development of novel tracers and improved imaging diagnostics[84].

SURGICAL DECISION-MAKING

Multidisciplinary assessment should form the cornerstone of insulinoma management. However, prior to intervention, the surgeon must be certain of both the biochemical diagnosis and localization of the insulinomas. Where results remain equivocal, we strongly advocate further testing or repeat imaging until adequate information is provided.

A summary of our surgical decision-making is shown in Figure 1. Of note, although we do not recommend enucleation of lesions less than 2 mm (preferably 3 mm) from the main pancreatic duct (MPD) or portal vein (due the risk of pancreatic fistula), solitary lesions in the head close to the MPD should be considered an exception, as the only alternative is a duodenopancreatectomy.

Malignant insulinomas are generally not amendable to laparoscopic surgery[7,8,35,49,50]. In these cases, resection of liver metastases ideally precedes excision of the pancreatic lesion[35], and the resultant extensive adhesions preclude a laparoscopic approach. When suspicion of malignancy is raised during planned laparoscopic surgery (Table 1), we prefer to convert to open resection[85-87], however we do acknowledge the work of other surgeons who advocate laparoscopic resection of malignant lesions[26].

In the context of MEN1, we follow a conservative but widely-accepted approach[8,37], due to the increased failure and reoperation rate inherent in the resection of MEN1-related insulinomas[43]. However, laparoscopic management of insulinomas in the context of MEN1[20,88,89] is possible in appropriate cases, particularly where only a single lesion is identified preoperatively. Where multiple lesions are present, distal pancreatectomy combined with multiple enucleations of pancreatic head lesions may also be considered. However, the laparoscopic approach to MEN1-related insulinomas is not currently widely accepted, and it should also be noted that MEN1 is considered a contraindication to laparoscopy in several large comparative series[30,31]. As mentioned previously, in our recent experience, enucleation of a single lesion in the pancreatic head has been successful in a single case.

Table 1 Features suggestive of malignant insulinoma[43]

Features suggestive of malignant insulinoma
Hard lesions
Infiltration of the surrounding pancreatic parenchyma
Evidence of tissue scarring
Major pancreatic duct dilatation

Contrary to several other published studies[16-18,21,29], we routinely perform laparoscopic enucleation of solitary pancreatic head insulinomas, not only for protruding lesions, but also for those embedded in the parenchyma, provided there is sufficient distance from the main pancreatic duct and the portal vein (Figure 1). We appreciate that some authors have expressed concern over the high complication rates in these cases[90], however we do believe that enucleation has a valuable role to play in the treatment of solitary lesions of the pancreatic head and uncinate process. Exposure is of paramount importance when dealing with pancreatic head and uncinate process insulinomas, however there are a number of techniques that can be employed to provide direct access to the posterior aspect of both[33,91]. Such approaches minimize unnecessary damage to the pancreatic parenchyma and the subsequent risk of complications.

Non-visible lesions embedded in the pancreatic head present a particular challenge, and classically have been treated with multiple extensive pancreatotomies. However, we have recently described a technique similar to wire-guided breast biopsy, which may enable the surgeon to accurately localize and laparoscopically resect these difficult insulinomas[34], thus minimizing the number and size of pancreatotomies. Assisted by LIOUS, an 18 G fine-needle may be inserted directly into the lesion to act as a probe, accurately defining the position of the insulinoma. The parenchyma of the pancreas can subsequently be divided following the needle, until the dome of the insulinoma is identified and a localized resection is performed[34].

The decision to plan a distal pancreatectomy over enucleation based on preoperative data is a rather difficult one. For lesions > 3 mm away from the pancreatic duct, enucleation is always the procedure of choice; however, we have a low threshold for distal pancreatectomy, and the more distal the position of the insulinoma, the greater the likelihood that this will be required. This is evident in several series[19,29-31] and is a natural consequence of the fact that the metabolic effects of added resection become less as the pancreatic parenchyma becomes thinner towards the tail.

TECHNICAL CONSIDERATIONS

Patient positioning can either greatly assist or hinder laparoscopic resection, and is thus crucially important to surgical set-up. For lesions in the anterior aspect of the head, isthmus, and body/proximal tail of the pancreas, the patient may be placed in a supine position with an anti-Trendelenburg tilt. A right tilt (left side up) is applied for lesions in the body/proximal tail of the pancreas. For lesions of the posterior aspect of the pancreatic head, both supine[12] and left semi-lateral positions have been reported in the literature[88]. In our experience, a full left lateral position is preferable, especially when combined with a retroduodenal and retropancreatic approach to the lesion following full kocherization[33]. We prefer this to the gastrocolic ligament approach proposed by other authors[88]. For lesions in the distal pancreatic tail, positioning may be either supine with a right tilt, right semi-lateral, or right full lateral. The choice of position for these lesions is therefore a matter of personal preference, similar to that with laparoscopic splenectomy[91]. Our practice is the right full lateral position because: (1) the chances of a distal pancreatectomy for lesions located in this area are higher and a right table tilt always facilitates this procedure; and (2) this position can easily be changed to semi-lateral with a generous left table tilt, giving the surgeon the liberty to choose between an anterior approach of the tail without spleen mobilization and a posterior one with full medial mobilization of the spleen.

Similarly, the number and position of trocar placements is at the discretion of the operating surgeon and varies throughout published reports[12,17,24,26,91]. Generally, we use a standard array of five ports: the first for the laparoscope at the center of the operating field, then two working ports for the surgeon on each side of the first, one laterally to the surgeon's right hand for the assistant, and one 5 mm in the epigastric area for a Nathanson liver retractor. For lesions in the posterior aspect of the pancreatic head where retraction of the kidney is sometimes required, a sixth trocar may be introduced to accommodate a second liver retractor for this purpose[33].

Gaining wide access to the pancreatic region of interest is of utmost importance in order to provide adequate space for surgical maneuvers and instruments such as the LIOUS probe and endoscopic stapler. For insulinomas of the posterior aspect of the pancreatic head, full mobilization of the hepatic flexure and the placement of two Nathanson liver retractors (one for the liver and possibly one for the right kidney) greatly facilitates surgical access[33]. On the other hand, for insulinomas of the anterior aspect of the pancreatic head, body, and tail, mobilization of the splenic flexure and retraction of the stomach to access the lesser cavity serves the same purpose.

After adequate mobilization of the pancreatic region of interest, the next step is LIOUS performed by a dedicated radiologist. This forms an integral part of laparoscopic insulinoma resection, as it not only allows for accurate localization of the lesion, but also outlines the surrounding anatomy in terms of tumor size, local invasion, and distance from the pancreatic duct and/or portal vein. If the combination of careful inspection and thorough LIOUS evaluation fails to adequately localize or characterize the insulinoma, we advocate that further

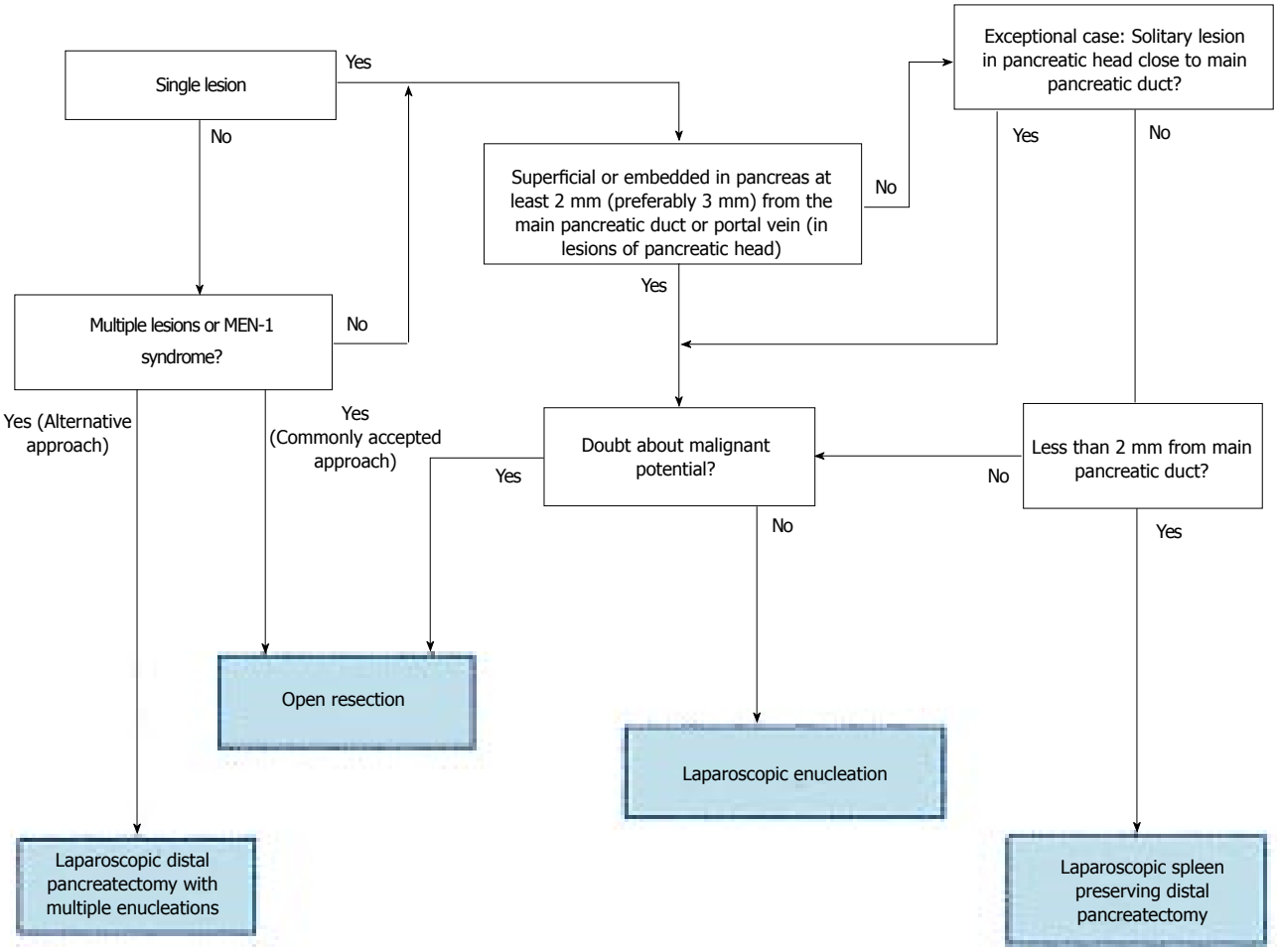

Figure 1 Flow chart demonstrating our surgical decision-making in pancreatic insulinomas. MEN-1: Multiple endocrine syndrome type 1.

surgical intervention be postponed in favor of repeat imaging and biochemical testing[92].

Once accurate intraoperative localization has been determined, surgical dissection is straightforward and performed with hook electrocautery and/or ultrasonic dissection. Generally, this is greatly helped by the placement of a traction suture through the insulinoma, which then can be exteriorized using an Endo Close. For lesions embedded in the pancreatic parenchyma but amenable to enucleation (Figure 1), the shortest route is chosen for dissection in order to minimize surgical trauma to the normal pancreatic parenchyma. As previously described, the LIOUS-guided placement of a fine needle in the center of the insulinoma greatly facilitates this dissection, which may be further aided by the placement of additional traction sutures to progressively open the pancreatotomy. Again, when the dome of the insulinoma becomes apparent, a further traction suture may be placed to improve the ease of enucleation.

For lesions in the body/tail of the pancreas that are not amendable to enucleation, the procedure of choice is spleen-preserving distal pancreatectomy. Careful dissection is necessary to avoid bleeding, particularly in the groove of the pancreas in which the pancreatic vein lies. In the event of inadvertent injury to the splenic vessels, if the left gastroepiploic and short gastric vessels remain intact, splenectomy can be avoided in favor of spleen-preserving distal pancreatectomy without splenic vessel preservation. However, where the left gastroepiploic and the short gastric vessels are not preserved, splenectomy is mandated. Division of the pancreas is usually carried out with an endoscopic linear stapler, combined with either oversewing the entire staple line or selectively oversewing the main pancreatic duct.

LAPAROSCOPIC SURGICAL OUTCOMES IN INSULINOMA MANAGEMENT

Due to the rarity of insulinomas and the retrospective nature of published series, it is difficult to extract robust data on the outcomes of laparoscopic insulinoma resection. Furthermore, these results have often been grouped with other pancreatic NETs and/or pancreatic tumors (*e.g.*, cystadenoma) making it impossible to separate insulinoma specific outcome data[9,17,85,89,93]. This is likely to be as a result of the small number of cases reported in early series and from the collective approach to tumor categorization later employed by major governing bodies and reflected in

published guidelines[8,35-37]. Whilst this classification is taxonomically accurate, it produces difficulties when studying insulinoma-specific outcomes, as insulinomas exhibit very distinct characteristics to other PETs and non-endocrine pancreatic tumors. Fortunately, however, the intriguing nature of these tumors has resulted in a number of laparoscopic case series specific to insulinomas[7,12-16,19-23,28,32], as well as those in the context of other PETs[26] and those comparing open and laparoscopic cases[18,24,25,27,29-31]. Furthermore, a recent meta-analysis comparing safety outcomes between laparoscopic and open approaches has been published[94].

The majority of published series[14,15,18-22,24-32] report established preoperative localization in > 90% of patients, with very few exceptions[12,16]. This highlights that preoperative localization has now become common practice, rather than the sole reliance on intraoperative LIOUS. Furthermore, this practice has increased the intraoperative accuracy of LIOUS to almost 100%, as well as almost eliminating inadequate localization as a cause for open conversion in the majority of cases[14,15,20-22,26,28,32]. Conversely, it is also notable that series reporting low preoperative localization rates[12,16] or limited use of LIOUS[19] also often describe inadequate localization as a common reason for conversion.

Median operative time is between 2 and 3.5 h, and varies significantly in published series[12,14-16,19-22,26,28,32]. However, these figures may be somewhat misleading due to small patient numbers and significant outliers. For example, in our own experience, operating time demonstrates a broad range from 25 to 420 min, with a median of 120 min[32]. Furthermore, although comparative studies demonstrate, as expected, that laparoscopic procedures take longer than their open counterparts[18,24,31] and that enucleation may be performed in a shorter time than distal pancreatectomy[16,19,20,28], this was not evident when pooled operative time was examined in the aforementioned meta-analysis[95].

Estimated median blood loss during laparoscopic insulinoma resection is limited and varies between 50 and 300 mL. Notably, however, there was no reported requirement for blood transfusion[12,15,28,32], and laparoscopic procedures resulted in significantly reduced blood loss when compared to open procedures[18,25,29,30,95]. Again, however, it is important to consider these results in the context of small sample numbers.

Laparoscopic treatment of insulinomas is safe and accompanied by minimal mortality in almost all published series[12,14-16,19-22,26,28,32]. Morbidity, on the other hand, may be high, and is reported to vary between 15% and 77%[12,14-16,18-22,24-32]. The most common complication is pancreatic fistula[95], however these are usually simple to manage and commonly resolve spontaneously within 2-3 wk. Nonetheless, in rare cases, specific treatment, drainage, or reoperation may be required. Importantly, the aforementioned recent meta-analysis has highlighted that laparoscopic insulinoma resection is not associated with a higher rate of fistula formation compared to open surgery[94]. Surgical precautions to avoid fistula formation first and foremost require respect for the minimum distance between the insulinoma and main pancreatic duct. Secondly, it is paramount to limit tissue damage by avoiding unnecessary dissection and keeping electrocautery heat production to a minimum. Oversewing the transection line after distal pancreatectomy and suture closure, or fibrin glue application to the site of enucleation, may also reduce fistulation, however in no cases do these measures counterbalance lacerations in the pancreatic duct, extensive destruction of the parenchyma, or inappropriately applied staples.

The length of in-hospital stay after laparoscopic insulinoma resection is difficult to determine, due to the inherent differences in institutional protocols and because patients from far away can be referred to a tertiary center. Indeed, uncomplicated laparoscopic resection required a hospital stay of one to two days in some studies[16,22,32], while patients remained hospitalized for 5-7 d in others[18,21]. However, it is notable that laparoscopic procedures are associated with a significantly shorter overall hospital stay than open procedures (without significant heterogeneity) when pooled data from directly comparative studies are meta-analyzed[94].

Importantly, laparoscopic insulinoma resection is associated with good long-term outcomes. In fact, whilst some series report long-term normoglycemia to be maintained in at least 95% of cases[24,25,30,31], others demonstrate a long-term cure rate of 100%[12,14,19-22,26,28,32].

CONCLUSION

Insulinomas are rare pancreatic neuroendocrine tumors that may be definitively cured with surgical resection. A dedicated multidisciplinary assessment is paramount prior to surgical intervention and should include thorough clinical and biochemical diagnosis. Localization of the tumor should be achieved through an array of non-invasive (US, CT, and MRI) and inevitably some invasive (EUS and AVSV) investigations, and the subsequent decision to undertake laparoscopic resection should only be made by an experienced laparoscopic pancreatic surgeon. For solitary benign insulinomas, laparoscopic enucleation suffices irrespective of location, provided the lesion lies a safe distance from the pancreatic duct and associated large vessels. Where these conditions are not met, laparoscopic distal pancreatectomy is advisable for lesions of the body/tail of the pancreas. This decision should be aided by LIOUS, which forms an indispensable part of any laparoscopic resection. In this way, localization of the lesion can be confirmed intraoperatively, and the tumor can be clearly delineated from adjacent structures. From a technical perspective, it is paramount to ensure ample access to the operating field in order to minimize damage to the

normal parenchyma, pancreatic duct, and associated vessels. Although no prospective randomized trials exist comparing laparoscopic and open approaches to insulinoma resection, case series, comparative series, and a recent meta-analysis supports the notion that laparoscopic resection is equally as safe and effective as an open approach. Moreover, laparoscopic intervention may not only improve cosmesis, but also reduce post-operative stay. Further large series and comparative studies are required in order to establish the true potential for laparoscopic resection and to continue to advance both diagnostic and technical aspects of surgical insulinoma management.

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Cutting edge of endoscopic full-thickness resection for gastric tumor

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Abstract

Recently, several studies have reported local full-thickness resection techniques using flexible endoscopy for gastric tumors, such as gastrointestinal stromal tumors, gastric carcinoid tumors, and early gastric cancer (EGC). These techniques have the advantage of allowing precise resection lines to be determined using intraluminal endoscopy. Thus, it is possible to minimize the resection area and subsequent deformity. Some of these methods include: (1) classical laparoscopic and endoscopic cooperative surgery (LECS); (2) inverted LECS; (3) combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique; and (4) non-exposed endoscopic wall-inversion surgery. Furthermore, a recent prospective multicenter trial of the sentinel node navigation surgery (SNNS) for EGC has shown acceptable results in terms of sentinel node detection rate and the accuracy of nodal metastasis. Endoscopic full-thickness resection with SNNS is expected to become a treatment option that bridges the gap between endoscopic submucosal dissection and standard surgery for EGC. In the future, the indications for these procedures for gastric tumors could be expanded.

Key words: Gastrointestinal stromal tumor; Early gastric cancer; Full-thickness resection; Laparoscopic and endoscopic cooperative surgery; Sentinel node navigation surgery

Core tip: Several studies have investigated local full-thickness resection techniques using flexible endoscopy for gastric tumors. These techniques are advantageous because a resection line can be determined more precisely using intraluminal endoscopy. Thus, it is possible to minimize the resection area and subsequent deformity, and better secure the surgical margins. In the near future, endoscopic full-thickness resection is expected to become a treatment option that bridges the gap between endoscopic submucosal dissection and standard surgery for gastric tumors.

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INTRODUCTION

Laparoscopic wedge resection (LWR) has been accepted as a minimally invasive surgical technique for gastric tumors such as gastrointestinal stromal tumor (GIST)[1], early gastric cancer (EGC) without the risk of lymph node metastasis[2,3]. However, patients frequently experience severe deformity and gastric stasis as a result of excessive gastric resection. This occurs because identification of the proper incision line is complicated. From this point of view, several studies have reported that endoscopic submucosal dissection (ESD) and endoscopic submucosal enucleation are feasible for the resection of gastric tumors in the muscularis propria[4,5]. Furthermore, ESD has performed for the diagnosis of suspected submucosal EGC. However, some tumors are resected incompletely because they have positive surgical margins; thus, the risk of recurrence exists[6]. Therefore, a full-thickness resection would be more appropriate to secure the surgical margins. This suggests the need for function-preserving or reductive surgeries that bridge the gap between ESD and standard surgery. Recently, some publications have described local resection techniques using peroral flexible endoscopy. Endoscopic full-thickness resection (EFTR) of the gastric wall using a snaring technique has been applied for gastric subepithelial tumors[7-9]. In addition, Hiki *et al*[10] reported that classical laparoscopic and endoscopic cooperative surgery (classical LECS) provides an alternative gastric wedge resection. However, these procedures (EFTR and classical LECS) have inherent risks of peritoneal infection and cancer cell seeding because intentional perforation of the gastric lumen is required during the procedures. As a result, some procedures [*e.g.,* inverted LECS[11], a combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique (CLEAN-NET)[12] and non-exposed endoscopic wall-inversion surgery (NEWS)[13]] have been developed to mitigate these risks. These techniques are advantageous because a more precise resection area can be determined using intraluminal endoscopy, thus minimizing the resection area. This will result in less deformity and better surgical margins.

In the current review, recent developments related to full-thickness resection using flexible endoscopy for gastric tumors are presented and discussed.

EFTR WITHOUT LAPAROSCOPIC ASSISTANCE

Endoscopic full-thickness resection of the gastric wall using a snaring technique has been applied for gastric subepithelial tumors[7]. Nevertheless, this technique has limitations from the perspective of the localization and size of the lesion. Ikeda *et al*[14]. reported EFTR using an ESD technique with a sewing method and have shown that it is possible to resect larger specimens. In addition, Zhou *et al*[8] and Feng *et al*[15] reported successful resection of gastric subepithelial tumors originating from the muscularis propria layer[8,15] (Table 1).

Table 1 Representative publications reporting endoscopic full-thickness resection for upper gastrointestinal tumors

Ref.	*n*	Mean operation time (min)	Mean tumor diameter (mm)	Complete resection rate (%)	Complication rate (%)
Zhou *et al*[8]	26	105	28	100	0
Feng *et al*[15]	48	60	16	100	0
Huang *et al*[16]	35	90	28	100	0
Schmidt *et al*[17]	31	60	20.5	90.3	9.7 (perforation)
Guo *et al*[9]	23	40.5	12.1	100	0

After the periphery of the lesion is marked endoscopically, a solution is injected into the submucosal layer circumferentially. A circumferential incision is then made to the depth of the muscularis propria around the lesion using ESD devices and techniques. Next, the serosal layer around the lesion is incised using ESD devices to create an intentional perforation. The tumor, including the surrounding muscularis propria and serosa, is subsequently removed using the snare. Finally, the gastric wall defect is closed with several metallic clips (Figure 1).

There are difficulties associated with these techniques. For example, it is unknown whether a large iatrogenic perforation can be successfully closed using the endoscopic technique. Guo *et al*[9] have reported the safety and feasibility of the over-the-scope clip system for the closure of gastric defects following EFTR. After all, EFTR is expected to prevent the severe complications can occur due to iatrogenic perforation. Although EFTR seems to be an effective and minimally invasive treatment for patients with gastric subepithelial tumors, it is necessary to demonstrate the efficacy and safety of EFTR in a large number of cases.

CLASSICAL LECS

Hiki *et al*[10] reported that the LECS technique provides an alternative gastric wedge resection for the removal of GISTs, and combines gastrointestinal endoscopy and laparoscopy. The advantage of this technique is that it avoids excessive resection of the gastric wall because a resection line can be determined more precisely using intraluminal endoscopy.

The periphery of the lesion is first marked endoscopically, and after a submucosal injection around the lesion, a circumferential incision is made using ESD devices and techniques. Then, an artificial perforation

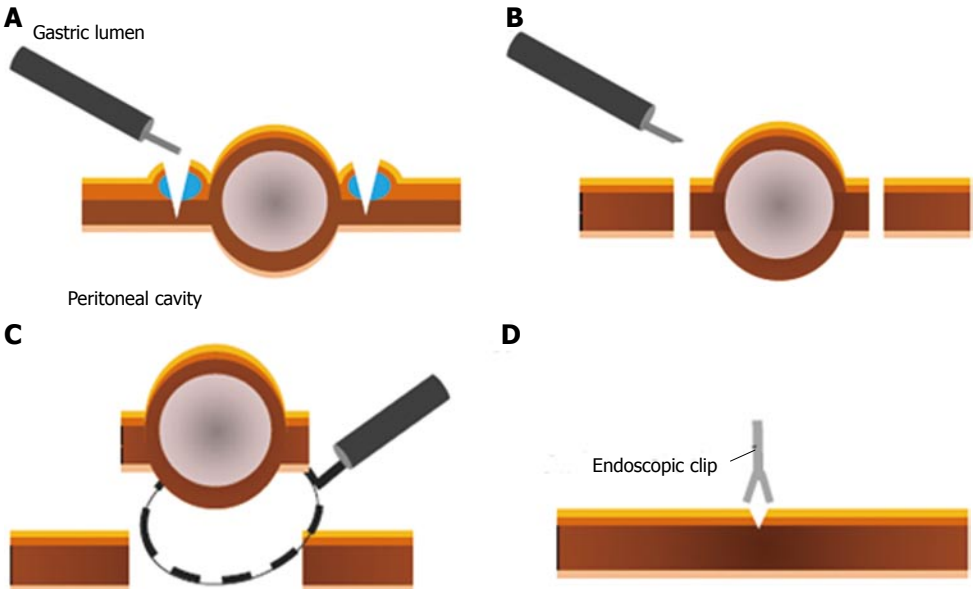

Figure 1 Illustration of the procedure for endoscopic full-thickness resection without laparoscopic assistance. A: A circumferential incision is made to the depth of the muscularis propria around the lesion using endoscopic submucosal dissection (ESD) devices and techniques; B: After intentional perforation, the serosal layer around the lesion is incised using ESD devices; C: The tumor, including the surrounding muscularis propria and serosa, is removed using the snare; D: The gastric wall defect is closed with several metallic clips.

is performed from the inside of the stomach and a seromuscular incision is performed, as much as possible, with laparoscopic assistance. Next, a laparoscopic incision of the remaining seromuscular layer is performed. Finally, the defect closure of the gastric wall is performed by laparoscopic linear staplers or a laparoscopic hand sewn suture technique[16,17] (Figure 2).

Some pilot studies have reported the feasibility of LECS for GISTs, and have presented favorable results[18-20]. This procedure is also feasible for lesions that cannot be treated with LWR[1,21] (*e.g.,* the esophagogastric junction)[22]. However, there is a major limitation associated with classical LECS. This technique requires opening the gastric wall, and the gastric lumen is opened to the abdominal cavity. As a result, gastric contents (*e.g.,* bacteria and tumor cells) flow into and contaminate the clean peritoneal cavity, increasing the risk of bacterial contamination and dissemination of peritoneal tumor cells.

INVERTED LECS

As described above, there are several drawbacks associated with classical LECS especially for gastric cancer. Therefore, a modified LECS procedure, referred to as inverted LECS, was developed to prevent the implanting of tumor cells[11].

The procedure, from placing the markings to performing the artificial perforation, is similar to the classical LECS. To prevent contact between the tumor and the visceral tissue, the gastric wall is pulled up circumferentially to the incision line as a crown using some stitches. Then, the seromuscular layer is dissected using ESD or laparoscopic devices around the incision line of the submucosal layer. The tumor is then resected into the abdominal cavity and the specimen is retrieved perorally. Finally, the gastric wall defect is closed by laparoscopic linear staplers.

This procedure was developed to prevent stomach contents from spilling into the clean abdominal cavity. However, since the gastric lumen is opened to the peritoneal cavity, there is still a risk of gastric content contamination. Furthermore, there is a risk of cancer recurrence caused by instrument contact.

CLEAN-NET

CLEAN-NET is another promising non-exposure method[12]. After mucosal markings are made endoscopically around the tumor, the mucosal layer is fixed to the seromuscular layer with four full-layer stay sutures, and a sub-mucosal cushion is created circumferentially using an endoscopic injection. The seromuscular layer is then dissected laparoscopically around the four stay sutures. Consequently, the full-layer specimen and the mucosal layer that surrounds it are lifted by the stay sutures. Finally, the specimen is resected using a linear stapler (Figure 3). The CLEAN-NET is useful as a non-exposure technique for full-thickness resection.

NEWS

NEWS was developed as a novel, full-thickness resection technique, without intentional perforation[13,23,24]. With this procedure, markings are made around the tumor on the mucosa while serosal markings are made laparoscopically. The serosal markings are made by pressing on the gastric wall, on the side opposite the mucosal markings. A sodium hyaluronate solution, that includes a small amount of indigo carmine dye, is

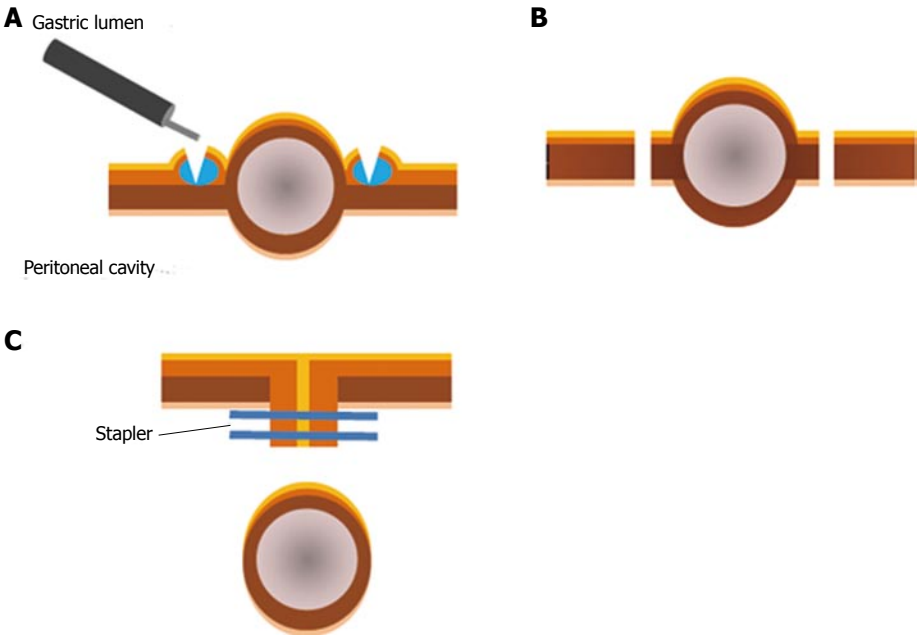

Figure 2 Illustration of the procedure for classical laparoscopic and endoscopic cooperative surgery. A: A circumferential incision is made using endoscopic submucosal dissection (ESD) devices and techniques; B: An artificial perforation is performed from the inside of the stomach and a seromuscular incision is performed along the incision line with laparoscopic assistance. A laparoscopic incision of the remaining seromuscular layer is performed; C: The defect closure of the gastric wall is performed by laparoscopic linear staplers.

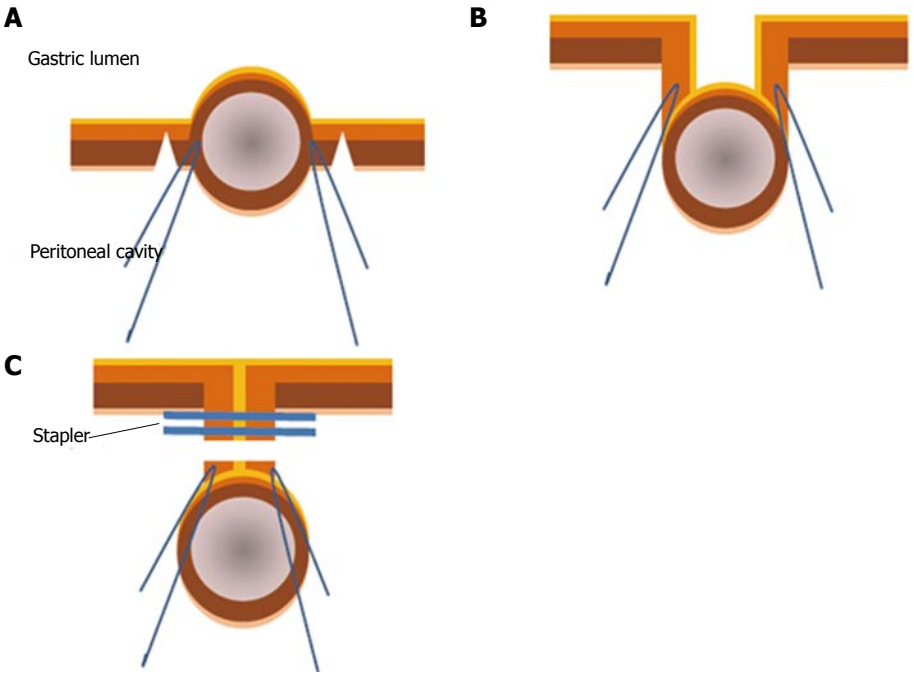

Figure 3 Illustration of the procedure for a combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique. A: Seromuscular layer is dissected using a laparoscopic electrocautery knife; B: Full-layer specimen is lifted by the stay sutures; C: Full-layer specimen is resected using a linear stapler.

endoscopically injected into the submucosal layer circumferentially. A circumferential seromuscular incision is performed laparoscopically around the serosal markings. After a flap is created by cutting the submucosa deeper toward the outside, the seromuscular layers are linearly sutured with the lesion inverted toward the inside of the stomach. Prior to the suturing, a laparoscopic surgical sponge is inserted as a spacer between the serosal layer of the inverted lesion and the suture layer. This is done to provide counter-traction to the mucosa and prevent cutting of the suture. Finally, the circumferential mucosal incision and the subsequent incision of the remnant submucosal tissue are made a few millimeters outside of the mucosal markings around the inverted

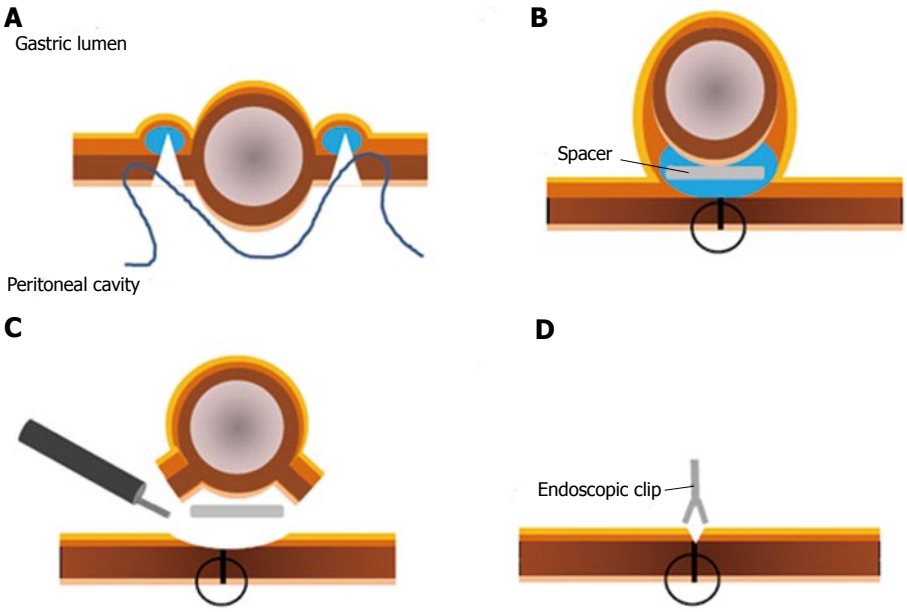

Figure 4 Illustration of the procedure for non-exposed endoscopic wall-inversion surgery. A: circumferential seromuscular incision is performed laparoscopically outside the serosal markings after endoscopic submucosal injection; B: seromuscular layers are linearly sutured with the lesion inverted toward the inside of the stomach. A surgical sponge as a spacer is inserted between the serosal layer of the inverted lesion and the suture layer; C: Circumferential mucosal incision and the remnant submucosal incisions are made using ESD devices and techniques; D: Defect is closed with several metallic clips. ESD: Endoscopic submucosal dissection.

Table 2 Comparison of each procedure

	Instruments	Indication for EGC	Retrieval route	Intentional gastric perforation	Advantage	Limitation
EFTR	Endoscopy only	No	Transroral	Required	Simple methods using intraluminal endoscopy only	Risk of contamination, endoscopic skills required
Classical LECS	Endoscopy = laparoscopy	No	Transabdominal	Required	Accurate to determine the resection line, laparoscopic assistance	Risk of contamination Risk of contact to tumor surface
Inverted LECS	Endoscopy = laparoscopy	Indefinite	Transoral	Required	Accurate to determine the resection line, laparoscopic assistance	Risk of contact to cancer surface, tumor size
CLEAN-NET	Endoscopy < laparoscopy	Yes	Transabdominal	Not required	No transluminal communication	Excessive resection of the mucosa, difficult to determine the resection line
NEWS	Endoscopy = laparoscopy	Yes	Transoral	Not required	Accurate to determine the resection line, laparoscopic assistance, no transluminal communication	Tumor size, experience required, time-consuming

EFTR: Endoscopic full-thickness resection; LECS: Laparoscopic and endoscopic cooperative surgery; CLEAN-NET: Combination of laparoscopic and endoscopic approaches to neoplasia with a nonexposure technique; NEWS: Nonexposed endoscopic wall-inversion surgery; EGC: Early gastric cancer.

lesion using ESD techniques. The resected specimen and the spacer are retrieved perorally and the mucosal edges are closed with several endoscopic clips (Figures 4 and 5).

The NEWS technique has been developed as a full-thickness resection method without transluminal communication and is similar to the CLEAN-NET. It is a non-exposure technique. However, there are several differences between the two procedures. First, the seromuscular hand suturing and circumferential mucosal incision can be skipped in CLEAN-NET, which results in a shorter procedural time than that for NEWS. Secondly, the incision line is determined from the serosal side; as a result, proper mucosal incision could be complicated to determine resulting in a relatively large resection area. However, due to the lower risk of peritoneal cavity infection and the seeding of tumor cells, NEWS has already been clinically introduced for gastric subepithelial tumors as well as gastric cancers at selected hospitals[24]. This procedure is technically feasible and, theoretically, safe.

APPLICATION TO GASTRIC CANCER

ESD is widely accepted as a minimally invasive curative treatment for early stage gastrointestinal cancer[25-27]

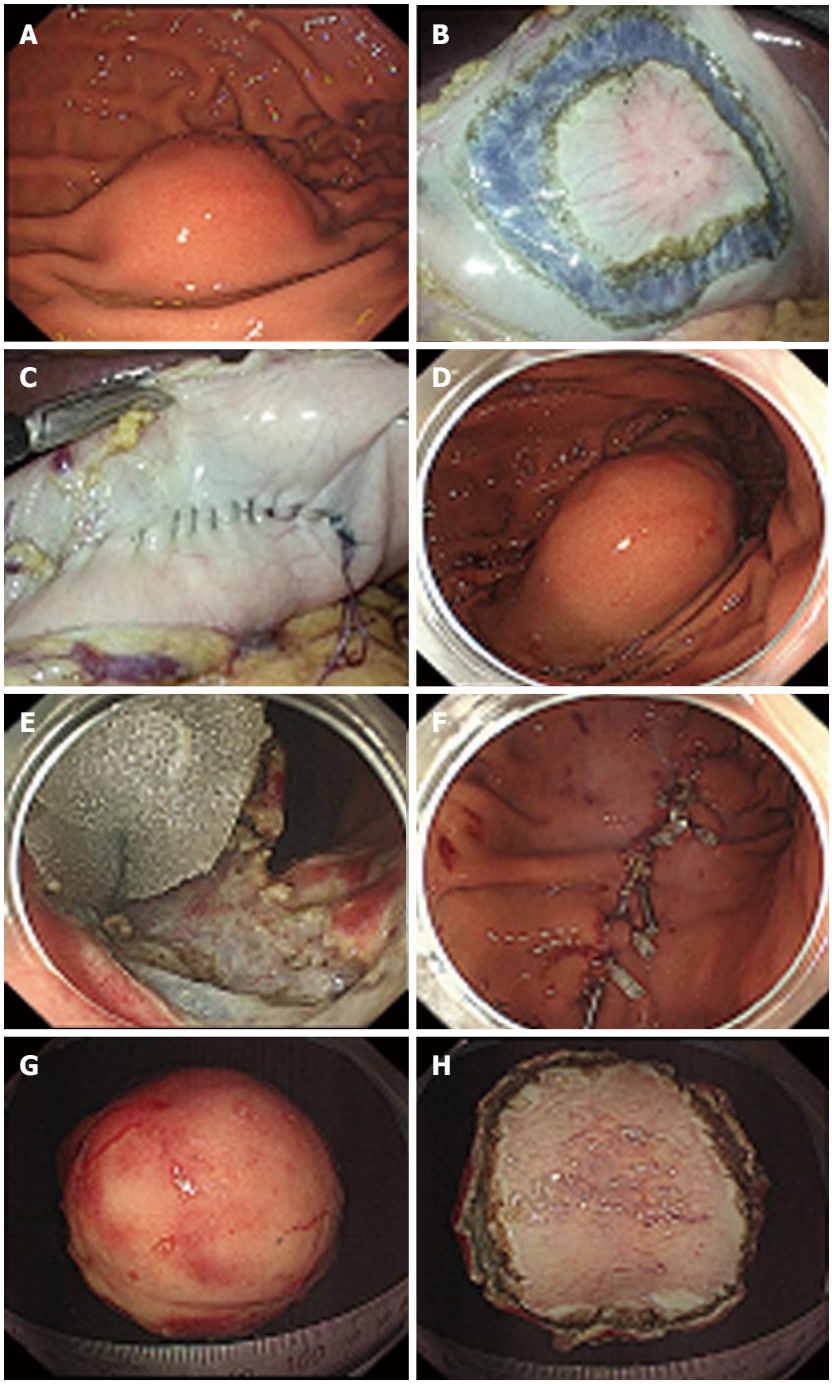

Figure 5 Procedures of non-exposed endoscopic wall-inversion surgery. A: Protruding submucosal lesion is seen at the greater curvature of the middle gastric body; B: Circumferential seromuscular incision is made outside the serosal markings after endoscopic submucosal injection; C: Lesion is inverted with a surgical sponge used as a spacer; D: Massive protrusion of the inverted tissue; E: Surgical sponge as a spacer and a suturing line during endoscopic mucosal incision; F: Mucosal clipping after the resection; G: Resected specimen: Mucosal side; H: Resected specimen: Serosal side.

that enables the preservation of function and maintains the patients' quality of life. However, ESD still requires a skilled and experienced surgeon for large lesions located at the greater curvature of the upper gastric body and fornix, and for lesions with severe ulcerative changes. In these situations, ESD has a higher incidence rate of complications such as perforation and bleeding. Furthermore, ESD may be associated with longer operation times[28]; therefore, LECS may be an alternative treatment option especially for lesions difficult to resect by ESD[11].

In contrast, EGC with possible lymph node metastasis should be treated with gastrectomy with wide resection of the regional lymph nodes because the presence and site of lymph node metastasis are unclear. Approximately 10%-20% of patients with EGC, especially those with deep submucosal invasion, have lymph node metastasis[29]. In other words, the incidence of node-negative gastric cancer accounts for at least 80% of all EGCs and therefore, most of the patients

with EGC have undergone an unnecessarily wide gastrectomy with lymphadenectomy. If node-negative gastric cancer is confirmed, local resection (*e.g.,* full-thickness resection) might be the best option.

Sentinel node navigation surgery (SNNS) is expected to be able to diagnose lymph node metastasis intraoperatively, and this could result in minimally invasive and function-preserving gastrectomy with selective lymphadenectomy[30]. Theoretically, the sentinel node (SN) is the first lymph node or group of nodes capable of draining cancer cells and is considered the first site of metastasis along the route of lymphatic drainage. However, it remains controversial whether the SN concept is feasible in EGC. In response, the Japan Society of Sentinel Node Navigation Surgery conducted a prospective multicenter trial to confirm the SN concept. It reported that patients with clinical T1N0 ($\leqslant$ 4 cm) gastric cancer can undergo sentinel node mapping and biopsy without limitation of tumor location[31]. Currently, surgical treatment of cT1N0 gastric cancer, of $\leqslant$ 4 cm, can be individualized on the basis of the SN concept. Furthermore, some studies have reported that in the absence of metastasis to the SNs, a surgery that combines ESD and SNNS[32] may be adequate. However, ESD cannot guarantee secure vertical margins or accurate preoperative diagnosis of tumor invasion. Hence, for submucosal EGC, a full-thickness resection would be more appropriate to secure the vertical margins and identify intramural cancer cells. Abe *et al*[33] first reported EFTR for EGC under laparoscopic guidance, combined with lymphadenectomy. Similarly, Hur *et al*[34] reported laparoscopy-assisted endoscopic full-thickness resection with sentinel node navigation surgery. However, as previously mentioned, these procedures require opening of the gastric wall, thus opening the gastric lumen to the peritoneal cavity. As a result, cancer cells may spill into the peritoneal cavity. Consequently, peritoneal dissemination of cancer cells as well as bacterial contamination during the procedure might occur. Therefore, it is desirable to use a non-exposure technique to prevent bacterial contamination and peritoneal dissemination of tumor cells. Hence, full-thickness resection such as NEWS and CLEAN-NET, in combination with sentinel node basin dissection, may be an ideal treatment that bridges the gap between ESD and standard surgery with respect to the invasiveness of the treatment[35,36] (Table 2).

CONCLUSION

The endoscopic full-thickness resection for upper gastrointestinal subepithelial tumors and EGC has been developed as a novel and minimally invasive surgery. In particular, NEWS with sentinel node basin dissection may be an ideal, minimally invasive, and function-preserving gastrectomy with selective lymphadenectomy for EGC. However, reports of these procedures are limited to case reports. Pilot studies need to be performed, and the long-term efficacy of these procedures need to be clarified. Therefore, further studies such as prospective clinical trials with a large number of patients are required to show the feasibility of these treatment methods, especially with regard to safe and complete resection. In the near future, the concept of endoscopic full-thickness resection is expected to become a treatment option that bridges the gap between ESD and standard surgery for subepithelial tumors and EGC.

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MINIREVIEWS

Emerging role of narrow band imaging in duodenum

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Abstract

Endoscopy using magnification narrow band imaging (mNBI) allows detailed assessment of mucosal surface and vascular pattern. This may help in better identification and prediction of the nature of the lesion. The role of this technology in duodenum is still evolving. Studies have shown that mNBI has high accuracy in predicting villous atrophy in the duodenum. Limited data suggests that this technique can provide additional information on duodenal polyps, nodules and ampullary tumour which can help guide their management. In this paper we describe the technique for duodenal assessment using NBI and review the existing literature evaluating its role in diagnosis of various duodenal pathologies.

Key words: Narrow band imaging; Duodenum; Villous atrophy; Correlation; Polyp

Core tip: Narrow band imaging endoscopy with magnification (mNBI) enables detailed assessment of duodenal villous morphology. This advantage over white light endoscopy has potential clinical benefits. There is good evidence to show that villous morphology on mNBI correlates well with histopathology. Hence villous atrophy can be diagnosed with good accuracy during mNBI and targeted biopsy can be obtained from abnormal appearing areas. Preliminary data suggest that this technology may also aid in assessment of neoplastic lesions in duodenum.

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INTRODUCTION

Endoscopic examination of mucosal surface of the gut

is an integral part of evaluation of patients presenting with gastrointestinal symptoms. The quest for obtaining additional information from direct visualisation of mucosa has led to several advances in imaging techniques. These include narrow band imaging (NBI, Olympus), optical coherence tomography, Fujinon intelligent chromo endoscopy (FICE, Fujinon) system, I-Scan (Pentax) and confocal laser endomicroscopy[1,2]. NBI, as the name suggests, uses a narrow wavelength of light in the blue and green region instead of the entire visible spectrum which gives a dark appearance to blood vessels[3]. This in combination with magnification endoscopy enables characterisation of microsurface and microvascularity of mucosa and identifies abnormalities in different part of digestive tract[4]. Magnification NBI (mNBI) has been shown to play a useful role in evaluation of duodenal villus abnormalities seen in diseases associated with malabsorption as well as in assessment of polyps and tumours of the duodenum[5-9]. A search of published literature reveals that among the more than one thousand publications relating to NBI, less than thirty have focussed on duodenum. However, the number of publications on the role of NBI in duodenum has risen in recent years as its value in assessment of duodenal disorders is recognised. In this paper we have reviewed the available literature on use of NBI in evaluating the duodenum.

ASSESSMENT OF DUODENUM USING MAGNIFICATION NBI

In our experience we have found the following scheme of examination adequate for comprehensive assessment of duodenum[5]. The examination should begin with an initial assessment of duodenal mucosa with conventional white light endoscopy. Any debris on the mucosal surface should be cleared. In most situations examination is performed upto second part of duodenum. The characteristics of duodenal mucosal folds including atrophy, scalloping and nodularity should be assessed and presence of any surface lesion like polyp, nodule or tumour determined. Duodenal ampulla should also be examined although a forward viewing endoscope makes this slightly difficult.

Next the endoscope should be switched to magnification NBI mode. mNBI examination is undertaken in two steps. In the first step, the morphology of duodenal villi in second part of duodenum is evaluated. The magnification and contrast offered by mNBI enables clear visualisation of duodenal villi. Bile appears pink and blood appears black on NBI. Due to use of narrow band of light, the images on NBI are not very bright but as the duodenal lumen is narrower than stomach, this is less of a problem. This limitation is also being overcome by newer endoscope processors. Some centers have reported the use of water instillation in lumen to improve the visualisation of villi and we have also found it useful in our experience[10]. This technique can be used in selected situations where the assessment is otherwise difficult. Several studies have reported excellent performance of mNBI in assessing villous morphology[5,7,11,12]. In normal subjects the villi have greater length than breadth which gives them a leaf or finger like appearance (Figure 1)[5,7]. Atrophy of villi alters this ratio and makes them appear shortened or convoluted or stubbed or even absent in patients with total villous atrophy (Figure 1)[5,7]. The next step involves assessment of any protruding mucosal lesion like polyp, nodule and tumour. The microsurface and microvascular pattern with special attention to irregularity should be determined. There are only few reports on mNBI characteristics of various duodenal mucosal lesions which makes confident correlation of surface/vessel pattern with histology of lesion difficult but presence of irregularity of pattern generally signifies a high grade lesion[6,13].

NBI IN ASSESSMENT OF DUODENAL VILLOUS MORPHOLOGY

Emerging data from several studies have shown that mNBI has a very good correlation with histology in assessment of duodenal villous atrophy[5,7,10,11]. This has few potential benefits: (1) in situations where duodenal biopsy is taken only to evaluate for villous atrophy, normal villi on mNBI may preclude biopsy and save procedure cost and time. The same is not the case with white light endoscopy where mucosal fold abnormalities like atrophy, scalloping and nodularity have a poor sensitivity when compared to histology[14]. Therefore all patients undergoing white light endoscopy for suspected celiac disease will require duodenal mucosal biopsy irrespective of endoscopic appearance; (2) in subjects with patchy villous atrophy, mNBI may help target the biopsy to regions with atrophy and improve the diagnostic yield[15]; (3) ease of the procedure which does not require spray of dye to improve contrast; and (4) ease of identification of villous morphology as evidenced by most studies reporting very good interobserver agreement[5,10,11].

While celiac disease is the dominant cause of villous atrophy in developed nations, other diseases like tropical sprue associated with villous atrophy and malabsorption are seen in tropical countries. It is therefore not surprising that about half of the studies on the role of NBI in duodenal villous assessment are from India[5,11,16]. We have recently published a prospective study from our center in India on a hundred patients with suspected malabsorption and evaluated the ability of mNBI to assess duodenal villi[5]. Celiac disease was present in seven patients with villous atrophy while conditions like tropical sprue, infections and Crohn's disease were present in eight patients and the cause of atrophy was unknown in one. Overall, villous atrophy was present in 16 patients and mNBI had a sensitivity of 87.5% and specificity of 95.2% in detecting this

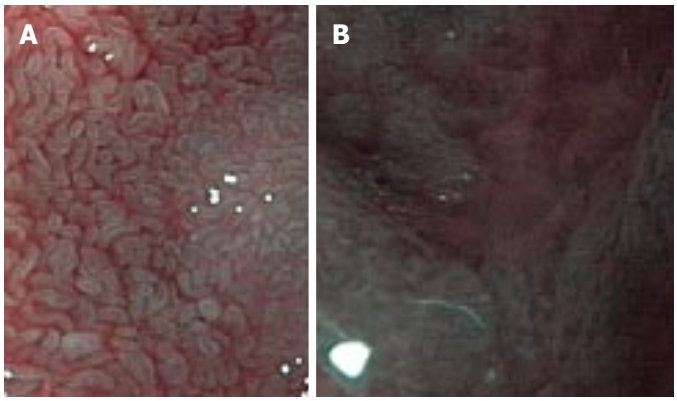

Figure 1 Appearance of normal duodenal villi on magnification narrow band imaging (A) and severe villous atrophy on magnification narrow band imaging (B).

by one of the two examiners. The sensitivity and specificity were 81.3% and 92.9% respectively for the second assessor with high interobserver agreement (kappa 0.87). We therefore found mNBI examination of duodenum to be a promising modality in predicting villous atrophy. Subsequently another study from India on 105 subjects with suspected malabsorption (villous atrophy in 58 on histology) showed that mNBI had a sensitivity of 95% and specificity of 90.2% (interobserver kappa 0.89)[11] in predicting villous atrophy. A third study from north India, published only in abstract form also assessed correlation of mNBI with histology for detection of duodenal villous atrophy in 80 patients and reported a sensitivity of 87.03% and specificity of 84.61%[16].

A couple of studies have been published from Italy comparing standard white light endoscopy and mNBI in patients with celiac disease. De Luca *et al*[12] prospectively studied 44 patients and found that mNBI was able to identify villous atrophy in all 17 patients with confirmed celiac disease (100% sensitivity) while standard white light endoscopy showed abnormalities in only 7 of them (41% sensitivity). All cases of partial villous atrophy were identified on mNBI while standard endoscopy was normal in all of them. The mean additional time required for NBI examination was four and half minutes. Another study from Italy on pediatric patients with suspected celiac disease investigated the use of NBI with water immersion technique and obtained single NBI guided biopsy instead of conventional multiple biopsies[10]. NBI guided single biopsy had a sensitivity of 87.5% in diagnosing celiac disease, suggesting that this technique has the potential to reduce the need for multiple biopsies. An earlier study from Australia assessing villous atrophy using mNBI showed mNBI to have a sensitivity of 93.3% and specificity of 97.8% in patients with suspected celiac disease[7].

We performed a meta-analysis on diagnostic accuracy of mNBI to detect duodenal villous atrophy with histology as a reference standard. The above six studies were screened for inclusion[5,7,10-12,16]. The study by Sinha *et al*[16] was excluded as only abstract was published and more data was required for meta-analysis[16]. The study by Singh *et al*[7], included 10 videos from 3 patients with celiac disease which implied multiple assessments for same patient. This significantly differed from other study designs and hence was not appropriate for pooling of data with other studies. Valitutti and colleagues studied pediatric patients only and for this reason their data was also not included. Finally we included three studies in the meta analysis[5,11,12]. The analysis was performed using the software Meta-DiSc[17]. The pooled sensitivity (Figure 2) was 0.96 (95%CI: 0.89-0.99) and the pooled specificity (Figure 3) was 0.94 (95%CI: 0.89-0.97). These impressive data further strengthen the evidence in favour of mNBI in assessing duodenal villous atrophy.

Atrophy of villi may be patchy in some patients with celiac disease and this may be missed on random mucosal biopsy. By identifying atrophic villi based on morphology, mNBI can overcome this limitation and help obtain targeted biopsies. Few case series and reports have demonstrated the capability of mNBI to detect patchy villous atrophy[15,18,19]. This perhaps is one area where mNBI can play an important role in avoiding false negative biopsies but more data is required. It is clear from the above studies that mNBI can play a useful role in aiding the diagnostic evaluation of celiac disease and other malabsorption syndromes.

NBI IN ASSESSING PROTRUDING DUODENAL MUCOSAL LESIONS

Unlike gastric, colonic and esophageal lesions, mNBI characteristics of duodenal mucosal lesions like polyps and tumours have been less well studied. Most of the available studies are from Japan and except for a few, these are in the form of case reports[6,13,20,21]. In contrast to assessment of villous morphology where surface characteristic is the focus of attention, both surface and vascular characteristics are important in assessing neoplastic lesions. Abnormal angiogenesis is a feature of neoplasia and alteration in vascular pattern is a reflection of this.

Kikuchi *et al*[6] retrospectively analysed the surface/vascular pattern of duodenal non-ampullary tumours on mNBI and identified characteristics suggestive of high grade dysplasia and invasive tumour. The surface patterns were classified as monotype or mixed type

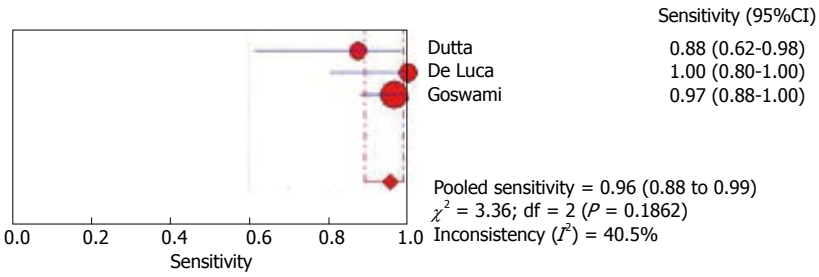

Figure 2 Pooled sensitivity of narrow band imaging in detecting duodenal villous atrophy.

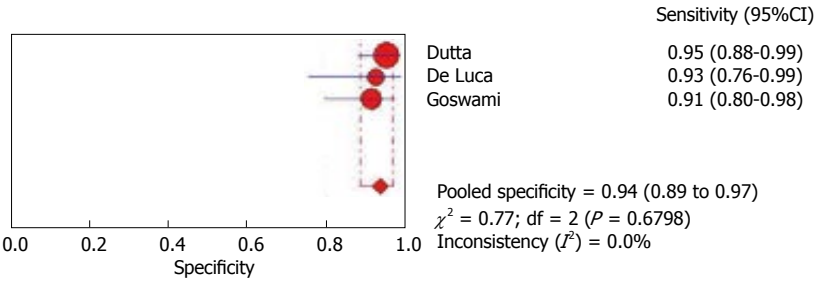

Figure 3 Pooled specificity of narrow narrow band imaging in detecting duodenal villous atrophy.

when they had single or multiple surface patterns respectively. Vascular patterns were classified as network, intrastructural vessel, unclassified or absent. They found that presence of mixed type surface pattern was suggestive of high grade dysplasia or invasive lesion in all 23 cases. In the remaining 23 lesions which had monotype surface, presence of unclassified vascular pattern and intrastructural vessels were associated with advanced lesions. Other vascular patterns were also seen with advanced lesions. The study therefore suggested that a mixed surface pattern was strongly suggestive of advanced lesion but confident diagnosis of low grade dysplastic or non-neoplastic lesion based on surface/vessel characteristics was not accurate. Another study assessed 65 duodenal sites in 36 subjects which were normal or had polyps[22]. Duodenal polyp with dysplasia was seen at 24 sites and mNBI had sensitivity of 83% and specificity of 78% in detecting dysplasia. They also examined the mucosa using probe based confocal endomicroscopy which was found to be better than mNBI. These data suggest that mNBI may help the endoscopist avoid biopsy (which makes subsequent resection difficult) and proceed directly to EMR in suspected dysplastic lesions.

A couple of case reports have described the appearance of follicular lymphoma in duodenum on mNBI. Chowdhury *et al*[20] from Morioka, Japan reported coiled, elongated microvascular pattern in two patients with follicular lymphoma and similar findings was observed by Iwamuro *et al*[23] in a 57-year-old patient from Niihama, Japan[20,23]. Inoue *et al*[24] reported whitish areas in enlarged villi in a patient with primary follicular lymphoma of duodenum. Elongated microvessels with white spots on surface was observed in a case of duodenal lymphangioma[21]. Another case report described saucer shaped lesions and multiple swollen villi like "moth eggs" on mNBI in a case of interdigitating dendritic cell sarcoma in duodenum[25]. While mNBI showed interesting abnormalities in the above reported lesions, its impact on management of patient is uncertain as biopsy may still be required.

NBI TO SCREEN FOR DUODENAL POLYPS IN POLYPOSIS SYNDROMES

Duodenum is an important site of polyps in familial adenomatous polyposis[26]. Surveillance endoscopy is recommended as duodenal tumours are the second most common cause of mortality in FAP after colonic tumours[27]. A study from Netherlands on 37 patients with FAP who underwent surveillance endoscopy using mNBI found NBI detected more adenomas than high resolution endoscopy and increased the Spigelman stage in 2 patients[28]. Another group used NBI for surveillance of polyps in patients with carriers of PTEN mutation seen in Cowden's syndrome[29]. Nine out of ten patients were found to have duodenal polyps but the role mNBI in this high diagnostic yield was not very clear.

NBI FOR DUODENAL AMPULLARY LESIONS

Ampullary adenomas may harbour malignant foci which may be missed on random biopsy due to sampling error. A study on 14 patients with bulky ampulla investigated the correlation between findings on mNBI and histology[13]. The surface pattern was divided into three types (type Ⅰ - oval villi; type Ⅱ - pinecone/leaf

Table 1 Overview of current status of magnification narrow band imaging technology in duodenum

Merits	Real time assessment of duodenal villous morphology with excellent accuracy
	Enables targeted biopsy of abnormal appearing area
Demerits	Added procedure time and cost
Potential applications	Assessment of duodenal villous atrophy in malabsorption syndromes
	Data on role in assessing duodenal neoplastic lesion is still preliminary

shaped villi; type Ⅲ - irregular or nonstructured villi). Presence of tortuous, dilated and network vessels were considered abnormal. Inflammatory and hyperplastic lesions had type Ⅰ surface pattern while adenomas and adenocarcinomas had type Ⅱ and/or Ⅲ surface pattern. Adenomas did not have abnormal vessels. A case report also showed the absence of vascular abnormality to be associated with no foci of malignancy on histology[30]. This is another potential area where NBI may play a role in obtaining targeted biopsies and help decide management strategy. Apart from assessing lesion characteristics, mNBI may also help in determining the lesion margin in patients undergoing duodenal papillectomy. Itoi *et al*[31] found mNBI to be better than indigo carmine chromoendoscopy for this indication. These preliminary observations suggest that mNBI may be useful in assessment and management of ampullary lesions. Larger studies are however required before recommending this technique for routine use.

CONCLUSION

Magnification endoscopy with NBI (mNBI) seems to have a potential role in evaluating duodenal mucosal morphology. Table 1 summarises the merits, demerits and potential application of this technology in clinical practice. While there is robust evidence for its role in assessing villous morphology, more data is required before recommending it for routine use in assessment of duodenal neoplastic lesions. There is also a need for uniform terminology and classification in describing villous morphology and protruding lesions which can enable comparison of published literature and facilitate training. The recent increase in interest on NBI in duodenum is encouraging because it can lead to new diagnostic possibilities which may impact therapy.

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ORIGINAL ARTICLE

Basic Study

Optimization of the generator settings for endobiliary radiofrequency ablation

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Author contributions: Barret M analysed the data and drafted the manuscript; Leblanc S, Vienne A and Prat F conceived and performed the animal experiments; Rouquette A and Beuvon F preformed the histologic study; Chaussade S provided critical revision related to the intellectual content of the manuscript; all authors approved the final version of the article to be published.

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Data sharing statement: Technical appendix, statistical code, and dataset are available from the corresponding author at frederic.prat@aphp.fr.

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Abstract

AIM: To determine the optimal generator settings for endobiliary radiofrequency ablation.

METHODS: Endobiliary radiofrequency ablation was performed in live swine on the ampulla of Vater, the common bile duct and in the hepatic parenchyma. Radiofrequency ablation time, "effect", and power were allowed to vary. The animals were sacrificed two hours after the procedure. Histopathological assessment of the depth of the thermal lesions was performed.

RESULTS: Twenty-five radiofrequency bursts were applied in three swine. In the ampulla of Vater (n = 3), necrosis of the duodenal wall was observed starting with an effect set at 8, power output set at 10 W, and a 30 s shot duration, whereas superficial mucosal damage of up to 350 μm in depth was recorded for an effect set at 8, power output set at 6 W and a 30 s shot duration. In the common bile duct (n = 4), a 1070 μm, safe and efficient ablation was obtained for an effect set at 8, a power output of 8 W, and an ablation time of 30 s. Within the hepatic parenchyma (n = 18), the depth of tissue damage varied from 1620 μm (effect = 8, power = 10 W, ablation time = 15 s) to 4480 μm (effect = 8,

power = 8 W, ablation time = 90 s).

CONCLUSION: The duration of the catheter application appeared to be the most important parameter influencing the depth of the thermal injury during endobiliary radiofrequency ablation. In healthy swine, the currently recommended settings of the generator may induce severe, supratherapeutic tissue damage in the biliary tree, especially in the high-risk area of the ampulla of Vater.

Key words: Endobiliary radiofrequency ablation; Biliary stricture; Ampullary tumor; Endoscopic retrograde cholangio-pancreatography

Core tip: The use of endoscopic retrograde cholangio-pancreatography-guided endobiliary radiofrequency ablation is expanding quickly, from the clearing of obstructed biliary stents in malignant biliary stenoses, to the treatment of benign biliary strictures. However, the morbidity associated with this procedure remains high, of course because of the severity of the disease treated, but also possibly due to suboptimal generator settings. Therefore, we conducted an animal study in live pigs. We report novel data, highlighting the importance of the effect setting on the generator, and suggesting specific settings for radiofrequency ablation in the ampulla of Vater.

Barret M, Leblanc S, Vienne A, Rouquette A, Beuvon F, Chaussade S, Prat F. Optimization of the generator settings for endobiliary radiofrequency ablation. *World J Gastrointest Endosc* 2015; 7(16): 1222-1229 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i16/1222.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i16.1222

INTRODUCTION

Radiofrequency (RF) ablation is currently used for the destruction of a wide range of liver neoplasms, including hepatocarcinoma, intrahepatic cholangiocarcinoma, and colorectal metastases[1]. RF waves can be applied either intraoperatively or percutaneously. The recent development of endobiliary RF ablation devices has been justified by two situations in which pre-existing methods were non or partially satisfactory: (1) unresectable extrahepatic cholangiocarcinoma[2], in which chemotherapy is poorly efficient and tumor response is difficult to assess[1]; and (2) obstruction of biliary stents by tumor ingrowth in unresectable pancreatic head cancers, which requires endoscopic desobstruction. Endobiliary RF ablation is currently performed using a device which can be used percutaneously[3,4] or through retrograde endoscopic cannulation of the main bile duct[5]. After preclinical studies in *ex vivo*[6] and *in vivo* pig livers[7], early endobiliary RF experience has been reported in patients. Because of the lack of control group in these retrospective or pilot prospective studies, the clinical efficacy of the method cannot be assessed with a high degree of confidence. However, endobiliary RF ablation in the setting of malignant biliary strictures of the common bile duct was technically feasible in a small series of patients presenting one of the above-mentioned indications. The method seems capable of clearing occluded metal stents[4] and may have the potential to improve medium to long-term biliary stent patency[5,8]. Other indications of choice could be foreseen, such as the destruction of benign biliary lesions or the ablation of shallow intraductal or intra-ampullary neoplasia. However, in view of the limited preclinical data and the need for an accurate assessment of tolerable electrosurgical settings before using endobiliary RF in such indications, additional animal data is needed. We therefore conducted a preclinical study on live pig liver to assess the tissular effect of endobiliary RF ablation in the intrahepatic, common, and periampullary bile ducts with various generator settings.

MATERIALS AND METHODS

Landrace pigs weighing 30-35 kg and stemming from the same farm were used for the study. The pigs were accommodated at our facility for 48 h prior to the procedure. Procedures were performed under general anesthesia. The animal protocol was designed to minimize pain or discomfort to the animals. All animals were prepared for anesthesia with a 12-h diet, and administered an intramuscular injection of 10 mg/kg ketamine and 2 mg/kg azaperone 30 min before induction. After induction with 8 mg/kg intravenous 1% propofol and endotracheal intubation, anesthesia was maintained through inhalation of 1% to 2% isoflurane. All animals received an intravenous infusion of 10 mg/kg per hour crystalloid solution. Median laparotomy was performed, and anterior duodenotomy at the level of the first portion of the duodenum was made in order to expose the duodenal papilla, which is located 15 mm distal to the pylorus. The common bile duct was cannulated using a 0.035 Inch guidewire (Jagwire, Boston Scientific, Natick, MA, United States) and its actual position was ascertained by direct visualization of the hepatic pedicle. A Habib EndoHPB™ (EMcision UK, London, United Kingdom) probe was used for RF ablation. It is a bipolar device, 8 F (2.6 mm) in diameter, 1.8 m long, that passes over 0.035-inch guidewires, has 2 ring electrodes disposed on the catheter 8 mm from one another, with the distal electrode 5 mm from the leading edge; bipolar current activation allows for tissue ablation by creating coagulation necrosis over a 2.5 cm length[9]. The endoHPB™ probe was connected to a VIO300D electrosurgical generator (Erbe, Tübingen, Germany) in bipolar mode, delivering a high-frequency (450 kHz) electrical effect. The catheter was

Table 1 Outcomes of endobiliary radiofrequency ablation in the liver parenchyma

Effect	Power (W)	Time (s)	Maximal extent of tissue necrosis mean ± SD (depth in μm)
4	20	90	3950 ± 71[a]
4	40	90	3385 ± 21[a]
6	10	90	2850 ± 212[a]
6	20	90	3850 ± 71[a]
8	4	90	2850
8	6	90	3200
8	8	90	4480
8	10	15	1620
8	10	30	1720
8	10	60	2500
8	10	90	3578 ± 698[b]

[a]Mean ± SD (n = 2); [b]Mean ± SD (n = 4).

introduced manually inside the common bile duct and RF ablation was performed: (1) in the ampulla of Vater by positioning the space between both electrodes, which is the zone of highest energy deposition, exactly within the ampullary area, meaning that the most distal electrode was inside the bile duct and the most proximal one mostly within the duodenum; and (2) in the common bile duct. One or two separate thermal lesions could be performed along the bile duct, and only one in the ampullary region. The RF procedures on the ampulla of Vater are shown on Figure 1. Because of the limited space in the biliary tract and the ampullary region, separate tests were performed on the hepatic parenchyma prior to those biliary lesions, in order to predetermine a range of parameters most likely to provide the best safety-to-effectiveness balance for biliary lesions. Liver thermal injuries were performed by inserting the RF probe into the liver after a small incision in the Glisson's capsule. Different ablation parameters, such as effect and power, but also duration of RF shots, were allowed to vary. Two hours after the procedure, with the animals still under general anesthesia, the pigs were euthanized with 100 mg/kg intravenous injection pentobarbital. The liver, the common bile duct, and the duodenum were collected en-bloc with the pancreatic head and fixed for 24 h in 10% buffered formalin. After macroscopic examination, ablated segments were embedded in paraffin, processed into 3 μm-thick sections, and stained with hematoxylin, eosin and saffron. Histological assessment was performed by a pathologist experienced in digestive pathology (AR), using an ocular micrometer to measure the maximal extent of tissue necrosis in depth from the epithelial surface. Tissue presenting disorganization of the layers, absence of normally shaped native cells, edema and/or inflammatory cell infiltrate was considered necrotic. Statistical analysis was performed using Graphpad Software (GraphPad Software Inc., San Diego, CA). Results are expressed as mean values ± SD.

The experimental protocol was approved by the scientific committee of the Surgery School of Paris (Ecole de Chirurgie de l'Assistance Publique-Hopitaux de Paris, France) and the experiments were performed according to the standard animal research guidelines established by the French Ministry of Agriculture.

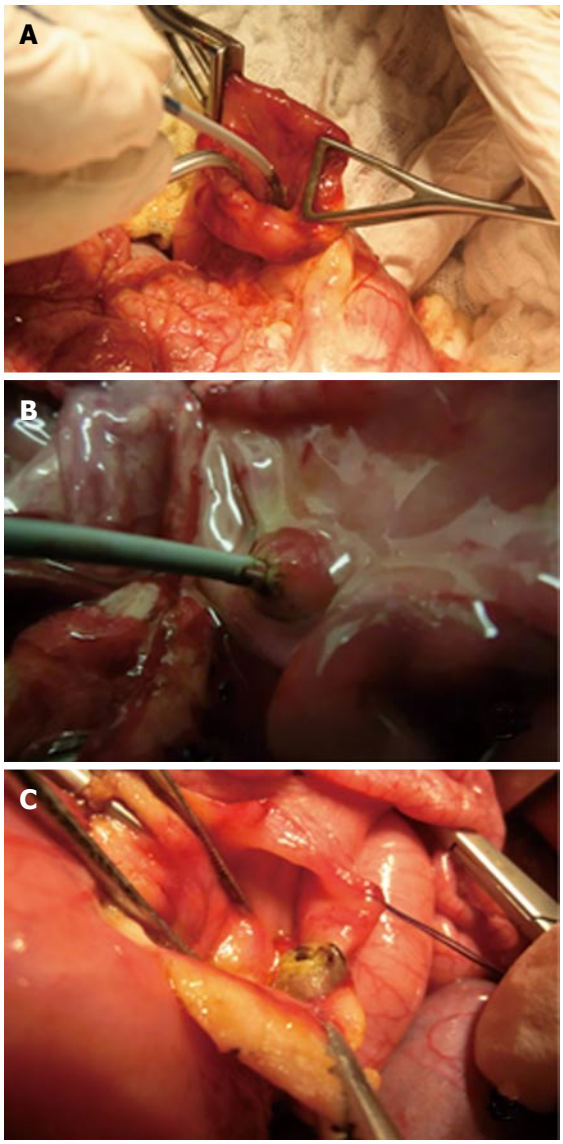

Figure 1 Radiofrequency ablation on the ampulla of Vater. A: The introduction of the probe (pig #3); B: The early mucosal changes visible during radiofrequency procedure (pig #2); C: Features of early and excessive tissue damage after probe withdrawal (pig #1).

RESULTS

Three pigs, on which 25 RF ablations were conducted, were included in the study. Eighteen RF ablations were conducted in the hepatic parenchyma allowing the testing 11 ablation conditions. The depth of tissue necrosis ranged from 1620 μm for an effect of 8, a power of 10 W, and a 15 s ablation time, up to 4480 μm for an effect of 8, a power of 8 W, and a 90 s ablation. The full set of corresponding figures is displayed in Table 1. Based on those results, RF shots conducted in the common bile duct allowed the testing of three ablation settings. With an effect varying from 4 to 8, a

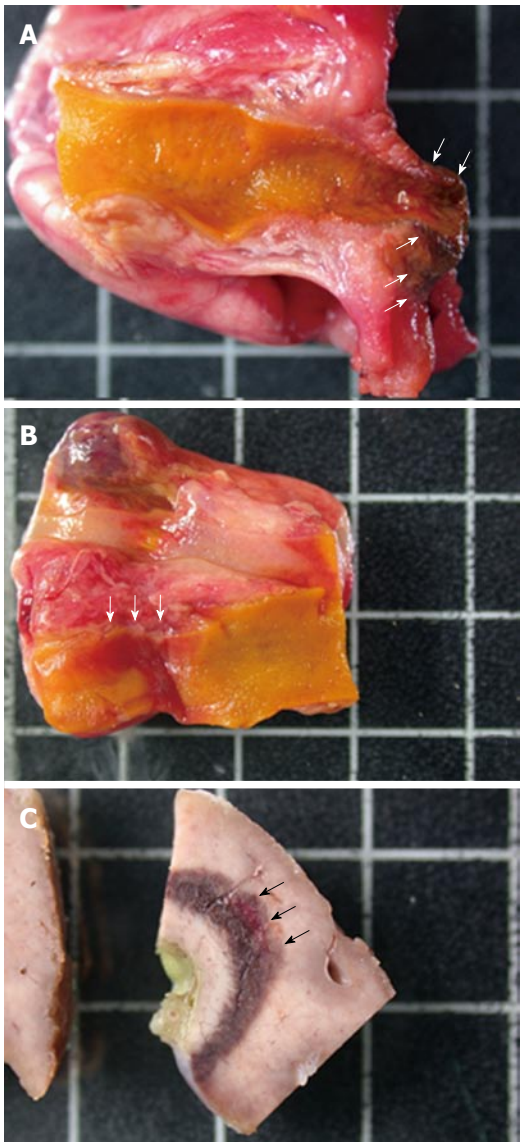

Figure 2 Macroscopic findings on the bile tract after radiofrequency ablation in pig #2. A: The papillary region and distal common bile duct, with tissue damage reaching the duodenal wall (arrows); B: An ablated zone limited to the wall of the common bile duct (arrows); C: An example of intrahepatic parenchymal damage up to 4 mm away from the bile ducts (arrows).

power output from 6 to 20 W, and shot duration from 30 to 90 s, a depth of tissue injury allowing for deep, yet non transmural tissue necrosis up to 1075 μm was obtained with an effect set at 8, a power of 8 W, and a short ablation time of 30 s; longer or more powerful or intensive shots led to transmural tissue necrosis up to 2700 μm away from the epithelium, with destruction of the peribiliary adipose tissue. Finally, three RF ablations were conducted in the ampullary region under three different ablating conditions. Effect was set at 8, power varied from 6 to 10 W, and the duration of ablation shots from 30 to 90 s. The depth of the tissue injury ranged from 350 μm, with ablation limited to the mucosa, for a power output of 6 W and an ablation time of 30 s, up to 2810 μm, with extensive tissue necrosis involving the adipose tissue and the pancreas, for a power of 10 W and a 90 s long shot. The results of RF in the bile duct and the ampulla of Vater are presented in Table 2. Macroscopic assessment of the ablated tissues is presented in Figure 2, and histological views of ablated ampullae are shown in Figure 3. Figure 4 presents the respective impact of power and ablation time variation on tissue damage after RF. Whereas power and ablation time appeared to be linearly correlated to the depth of tissue damage, variations in effect settings only had a modest influence on tissue damage, although our results showed an inverse relationship between effect and power output (Figure 5).

Table 2 Outcomes of endobiliary radiofrequency ablation in the main bile duct and ampulla of Vater

Effect setting	Power output (W)	Shot duration (s)	Shot location	Depth of tissue injury (μm)	Observations
4	20	90	Bile duct	2700	Transmural necrosis
6	10	90	Bile duct	2600	Transmural necrosis
8	10	90	Ampulla	2810	Extensive necrosis of the papilla, involving pancreas and adipose tissue
8	10	30	Ampulla	1530	Deep coagulation, necrosis of the duodenal wall. No significant pancreatic injury
8	6	60	Bile duct	1420	Deep transmural coagulation, involving peribiliary adipose tissue
8	8	30	Bile duct	1075 ± 417[1]	Coagulation involving almost the entire duct wall
8	6	30	Ampulla	350	Superficial coagulation, moderate duodenal lesion

[1]Mean ± SD, 2 measurements have been performed.

DISCUSSION

Clinical studies of RF endobiliary ablation with the EndoHPB™ probe have not been undertaken without previous animal studies designed to assess the depth of tissue damage[6,7,10]. It is noteworthy that EndoHPB probes are designed to be used only with VIO200-300, which is one of the most popular HF units in endoscopy wards. This should make comparisons between studies relatively easy and reliable, since the parameters used are strictly comparable. Itoi *et al*[6] assessed thermal injury in the hepatic parenchyma in three *ex vivo* pig livers, and tested 12 ablation settings, with power varying from 5 to 20 W and ablation times ranging from 60 to 120 s. Their observations were mainly macroscopical, and the authors reported tissue necrosis extending from 4.3 ± 0.6 mm to 11.3 ± 1.2

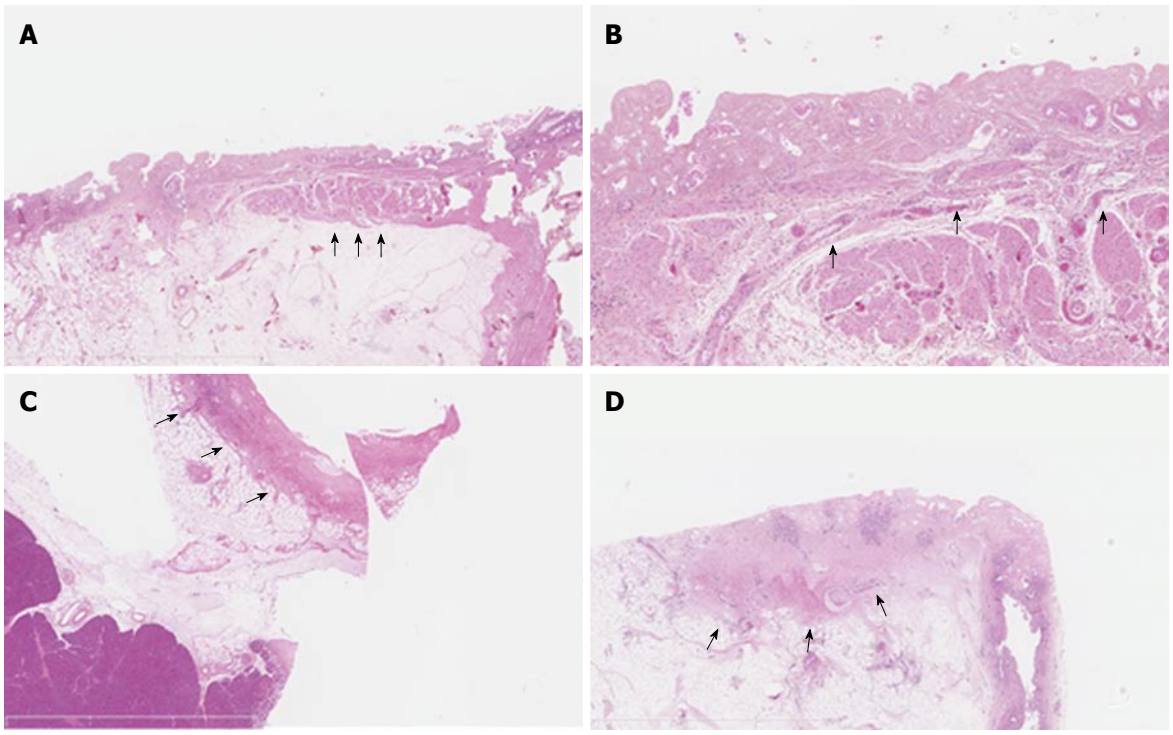

Figure 3 Histological findings in the three ampullae Vaterii treated by radiofrequency ablation. A: Taken from pig #3, shows satisfying ablation of the ampulla of Vater sparing the submucosa; arrows indicate the intact submucosa; hematoxylin eosin and saffron, original magnification × 25; B: The vertical extension of tissue damage in pig #1, reaching the muscularis mucosae; arrows indicate the muscularis mucosae; hematoxylin eosin saffron, original magnification × 100; C and D: The ampullae of pigs #1 and 2 (respectively), with deep tissue necrosis extending far beyond the muscularis propria up to the adipose tissue; arrows indicate the extent of coagulation necrosis; hematoxylin eosin and saffron, original magnification × 25.

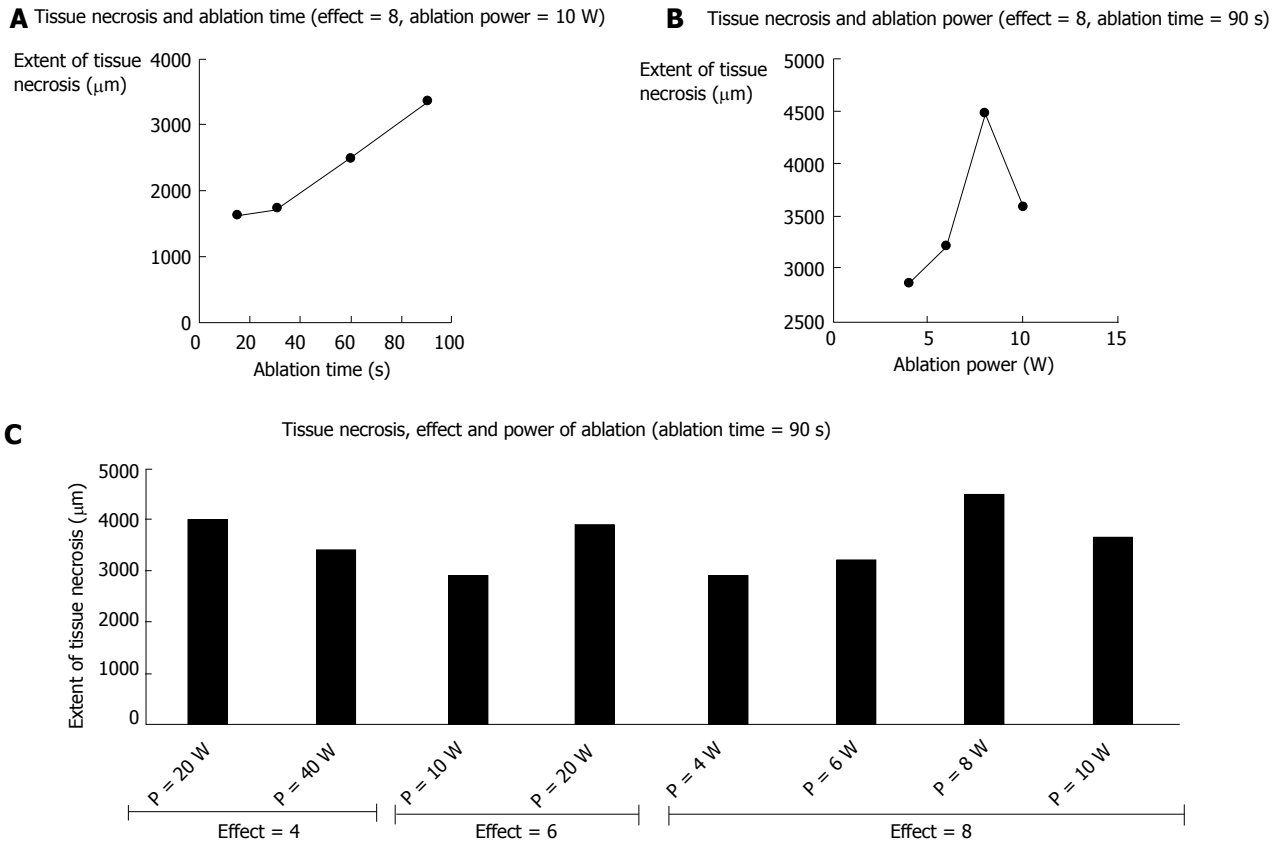

Figure 4 Variation of the extent in depth of thermal tissue damage after radiofrequency ablation in the liver according to electrical settings (VIO 300D). A: Variation of depth with shot duration; B: Variation of depth with power output setting; C: Variation of depth with effect.

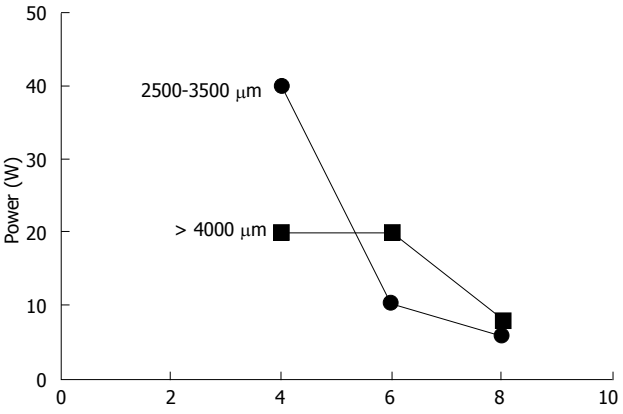

Figure 5 Relative variation of power output and effect setting for a given depth of tissue ablation and a 90 s ablation time in the liver.

mm in depth. However, these numbers are hardly comparable with ours, as the authors measured the entire thickness of the damaged tissue, including the proper width of the catheter. They concluded that: (1) for the 5 W power value, 60 and 90 s ablation times were insufficient to achieve tissue necrosis; (2) the 5-10 W power output range was a zone of continuously increasing tissue damage, as opposed to power values of 15 W and over, for which tissue necrosis seemed to be stable. However, this study was performed *ex vivo*, lacked thorough histological analysis, was limited to the liver parenchyma, and did not take into account the effect parameter, which was set a priori at 8. In a study closer to clinical conditions, Zacharoulis *et al*[7] assessed the effects of endobiliary RF ablation on the bile ducts of 20 live pigs. The authors tested 10 different conditions of power output ranging from 1 to 10 W, left a plastic stent in the common bile duct, and performed histological assessment of the common bile duct 24 h after the procedure. They concluded that power as well as ablation time had an impact on the depth of tissue damage, and found the optimal settings to be a power of 6-7 W and an ablation time of 60 s[7]. In this study however, the variation of the effect was also not taken into account, histological assessment was semi-quantitative, and only the common bile duct was studied.

Based on the results of those preclinical studies, it has been suggested that the Habib EndoHPB™ probe be set at a power of 10 W, an effect of 8, and a shot duration of 90-120 s[9]. In published clinical reports, endobiliary RF has been associated with a 10%-20% morbidity rate[5,8,11,12], including cases of cholangiosepsis, liver infarction, hepatic coma, cholecystitis, and pancreatitis, all of which can be explained at least in part by excessive tissue damage to the distal bile duct or to the hepatic parenchyma. Moreover, generator settings reported in clinical studies have been heterogeneous, ranging from 5 W and 120 s[13] to 10 W and 120 s[4], and frequent use of intermediate power values or ablation times[5,8,11,12]. Only one publication reported the use of endobiliary RF ablation on a periampullary tumor, but RF was actually used to treat a malignant stricture at the proximal end of a biliary stent, thus at a distance from the ampulla[14]. For these reasons, we chose to re-assess the effects of RF on living pig liver before undertaking evaluations on the healthy bile duct and the ampullary region.

In its step-by-step guide to endobiliary RF procedures, the manufacturer suggests that for periampullary procedures, the power should be lowered to 7 W, and the procedure should be stopped as soon as the duodenal mucosa started blanching[9]. We first confirmed that the standard settings of the RF generator (effect 8, power 10 W) resulted in excessive damage to the ampulla of Vater, even with very short RF ablation times such as 30 s. An effect of 8, a low power of 6 W, and a short ablation time of 30 s seemed to provide optimal tissue ablation of the epithelium and the lamina propria in the ampulla. In the common bile duct, we observed a deep tissue necrosis reaching the entire bile duct wall and the peribiliary adipose tissue with settings as low as effect 8, power 6 W, and a 60 s ablation. This is consistent with the observations of Zacharoulis *et al*[7] who observed damage to adjacent organs or full thickness tissue necrosis (leading to bile duct perforation in three cases out of four at 24 h) in all animals treated with a power > 6 W. We can also conclude from these data that the effect setting has a major importance in the RF energy delivered: indeed, for a 90 s RF shot, a four point variation (from 4 to 8) of the effect causes the same tissue damage as a 30 W variation of the power (from 10 to 40 W). In the hepatic parenchyma, a 3 mm tissue damage around the probe could be achieved equally with either high power values or a 2 point increase of the effect setting. Power values, as reported by others, seemed to clearly influence the depth of tissue damage up to 10 W[6,7]: The impact of raising the power beyond 10 W did not appear to be significant. By contrast, the time of RF ablation was linearly correlated to the extent of tissue necrosis.

To our knowledge, this is the first study that considers the impact of effect variation in endobiliary RF. Furthermore, based on consistent data obtained in the hepatic parenchyma, we tested RF ablation in the whole biliary tree, including the ampulla of Vater.

However, our study presents some limitations; first, given the small number of animals, we only tested a limited number of generator settings, and did not duplicate the measurements for most values obtained in the common bile duct, although the figures found are in keeping with those reported by other authors[6,7]. Second, the short time span between RF and the sacrifice of animals could have led us to overlook the actual extent of the lesions. However, we waited for two hours before the animals were euthanized in order for the tissue damage to appear, which was sufficient to make coagulation necrosis clearly visible with standard staining. Third, although the *in vivo* pig liver is currently the cheapest and most easily available, it may not be a perfect model for thermal ablation, since it lacks

tumoral or inflammatory thickening of the biliary wall. This could account for the supratherapeutic effects of the recommended RF generator settings in swine. Other explanations have been suggested, such as different blood supplies between the swine and human common bile duct, or major heat sink phenomenon in humans compared with swine due to higher blood flow in the hepatic pedicle[7]. Furthermore, the dramatic RF impact in other swine epithelia, such as esophageal has also been reported to be more severe than in humans[15].

In conclusion, our work demonstrates that the currently recommended settings for endobiliary radiofrequency ablation may result in supratherapeutic effects in the pig liver, bile duct and periampullary region. Our data also underlined the critical importance of the effect setting on the VIO™ RF generator for this application. These points should be kept in mind when designing RF ablation clinical trials, especially since clinical indications of endobiliary RF ablation tend to spread outside the field of malignant stricture management, such as benign biliary stricture[16] or possibly residual neoplastic tissue after endoscopic papillectomy.

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COMMENTS

Background

Endoscopic endobiliary radiofrequency (RF) ablation has been developped for the treatment of malignant biliary obstructions. It currently allows to clear occluded metal stents and may have the potential to improve medium to long-term biliary stent patency.

Research frontiers

Endobiliary RF ablation has mainly been studied for lesions of the common bile duct. The optimal generator settings for the treatment of ampullary or intrahepatic lesions is uncertain. Moreover, the consequences of the variations of « effect » parameter of the generator have not been studied.

Innovations and breakthroughs

This is the first study that considers the impact of effect variation in endobiliary RF. Furthermore, based on consistent data obtained in the hepatic parenchyma, the authors tested RF ablation in the whole biliary tree, including the ampulla of Vater.

Applications

Results of this study should be kept in mind when performing endobiliary radiofrequency ablation for intrahepatic or ampullary lesions, or for non-neoplastic, shallow lesions of the common bile duct.

Terminology

Endobiliary radiofrequency ablation consists in the application of radiofrequency energy using a bipolar probe inserted into the biliary tree, either percutaneously, or by retrograde cannulation *via* endoscopic retrograde cholangiopancreatography.

Peer-review

This study gave a good result for using endobliary radiofrequency ablation or not in clinic, and did have clinical value to guide the treatment procedure.

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PillCam COLON 2© as a pan-enteroscopic test in Crohn's disease

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Abstract

A recent paper by Boal Carvalho *et al* demonstrates the potential of PillCam COLON 2© (PCC2) as a pan-enteric investigation in Crohn's disease (CD). Our own prospective data in patients with known CD also shows good correlation between PCC2 and small/large bowel investigations (R = 0.896, $P < 0.0004$/R = 0.6667, $P < 0.035$). Larger studies are warranted to prospectively validate the use of PCC2 in the investigation and monitoring of both small and large bowel CD.

Key words: Capsule endoscopy; Panenteroscopy; Small bowel Crohn's disease; Mucosal healing; Colon capsule

Core tip: Mucosal healing has been shown to reduce the need for surgery and hospitalisation in patients with Crohn's disease. Currently, assessing small bowel and colonic mucosal healing requires separate imaging/endoscopic modalities. Recent data suggests that the PillCam Colon 2© (PCC2) is capable of assessing mucosal healing of the small intestine and colon in a single, non-invasive test. Our own prospective data corroborates these findings demonstrating good correlation between investigations. Larger studies assessing the viability of PCC2 as a pan-enteric investigation are warranted.

Hall B, Holleran G, McNamara D. PillCam COLON 2© as a pan-enteroscopic test in Crohn's disease. *World J Gastrointest Endosc* 2015; 7(16): 1230-1232 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i16/1230.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i16.1230

TO THE EDITOR

We read with interest the recent article by Boal Carvalho *et al*[1] entitled "PillCam COLON 2© in Crohn's disease: A new concept of pan-enteric mucosal healing assessment". Mucosal healing in Crohn's disease (CD) remains a current hot topic. Numerous colonic studies suggest that mucosal healing leads to increased steroid-free remission and decreases surgical and hospitalisation rates[2-5]. More recent studies have established that small bowel capsule endoscopy (SBCE) is capable

Table 1 Bowel preparation regime for study participants undergoing same day colon capsule and colonoscopy

Schedule	Intake
Day 1	
All day	10 glasses of water throughout the day
Evening	Four senna tablets
Day 2	
All day	Clear liquid diet
Evening	2l Klean prep
Day 3 (exam day)	
Morning	2l Klean prep
10-11 am	Colonoscopy + capsule ingestion
1st boost	1 sachet sodium picosulfate
(upon small bowel entry)	
2nd boost (4 h later)	1 sachet sodium picosulfate

Table 2 Baseline characteristics of study patients (n = 10)

Median age in years (range)	31 (19-47)
Female	7 (70%)
Smoker	5 (50%)
Disease extent	
Ileo-colonic	10 (100%)
Disease subtype	
Inflammatory	4 (40%)
Stricturing	6 (60%)
Previous resection	
Ileo-caecal surgery	4 (40%)
Ilealsurgery	1 (10%)
Medications	
Thiopurine	3 (30%)
Biologic	9 (90%)

of safely monitoring small bowel mucosal healing[6,7] although long-term follow up studies are required to demonstrate the efficacy of small bowel mucosal healing. The use of PillCam COLON 2 (PCC2) as a pan-enteric device has been previously investigated by Negreanu *et al*[8].

This current study by Boal Carvalho *et al*[1] again demonstrates the potential of PCC2 as a "one-stop", non-invasive mucosal healing assessment of both the large and small bowel. In total, 12 patients were enrolled in the study. Each patient underwent an ileocolonoscopy and SBCE at diagnosis. All patients had a PCC2 performed following one year from diagnosis. The aim was to evaluate the ability of PCC2 to assess mucosal response to therapy in both the large and small bowel. At one year, mucosal healing of the small bowel and large bowel was 33% and 50%, respectively. The combined mucosal healing rate was only 25%. However, perhaps most importantly, PCC2 was shown to be capable of adequately assessing both small and large bowel CD.

Our own data would appear to support these findings in terms of the viability of PCC2 as a pan-enteric device. We performed a prospective comparative study of PCC2 *vs* both ileo-colonoscopy and SBCE in patients with known CD. Following ethical approval, patients were recruited from our clinic at Tallaght hospital over a 6-mo period. Major exclusion criteria included known small bowel stricture, recent gastrointestinal surgery (within 3 mo of study recruitment) and chronic NSAID use or NSAIDS within 6 wk of study recruitment (apart from 5-ASA therapy). SBCE and PCC2 investigations were performed using PillCam technology (Given Imaging, Yoqneam, Israel). SBCE followed our standard protocol without bowel preparation. PCC2 and colonoscopy were performed no longer than 14 d following SBCE. Bowel preparation regimen was performed over a 3 d period (Table 1). One experienced endoscopist performed all study colonoscopies. PCC2 was performed on the same day as ileo-colonoscopy. All SBCE and PCC2 images were reviewed by two clinicians experienced in reading and interpreting capsule examinations. The capsule endoscopy CD activity index (CECDAI) was utilised to assess the severity of disease activity. The CECDAI divides the small bowel into proximal and distal segments and uses three major criteria to grade severity: Inflammation, extent of disease and the presence of stenosis with the addition of proximal and distal scores leading to an overall CECDAI score. The authors utilised the CECDAI score for this study due to the fact that it is the only capsule scoring system which has been prospectively validated to date[9]. Activity was graded as follows; inactive disease (CECDAI = 0), mild disease activity (3.5 < CECDAI < 5.8), moderate to severe disease activity (CECDAI $\geqslant$ 5.8). Colonic disease activity was based on the Simple Endoscopic Score for Crohn's Disease (SES-CD); inactive disease (SES-CD = 0-3), mild disease activity (SES-CD = 4-10), moderate disease activity (SES-CD = 11-19) and severe disease activity (SES-CD $\geqslant$ 20).

In total, 10 participants were enrolled; median age of 31 years (range 19-47), 7 (70%) female. Every participant had previously documented ileo-colonic disease. Baseline demographics are summarised in Table 2. All capsules reached the caecum ensuring complete small bowel views for both SBCE and PCC2. Overall image quality was adequate for both modalities. Upon review of SBCE images, 2 (20%) had no small bowel disease activity, 5 (50%) had mild/moderate severity with the remaining 3 (30%) having severe small bowel CD. In terms of disease distribution, the majority 7 (88%) had distal ileal disease only with only one (12%) participant having evidence of more proximal small bowel disease. In comparison, PCC2 detected the following disease activity; 2 (20%) normal, 6 (60%) mild/moderate with the remaining 2 (20%) having severe disease. There appeared to be good correlation between SBCE and PCC2 images in terms of the recognition and grading of disease activity (R = 0.896, P < 0.0004). The caecal intubation rate for colonoscopic procedures was 100%. Overall, the terminal ileum was intubated in 9 (90%) participants. All CCE procedures successfully reached the rectum. Of note, there were no complications with any of the capsule or colonoscopic procedures. On colonoscopy, 8 (80%) had no disease activity with 2 (20%) having mild disease. The majority of participants (9, 90%) had

no disease activity on PCC2 with only one participant meeting the criteria for mild disease activity. There was good correlation between the two modalities (R = 0.6667, $P < 0.035$).

Despite limited numbers between all of the studies performed to date, PCC2 does appear capable of successfully examining the small and large bowel and also accurately detecting small bowel and colonic CD. With regard to our own data, PCC2 did appear to miss disease in the proximal small bowel that was detected by SBCE. This may be due to the PCC2 technology itself which "shuts down" in the proximal small bowel to conserve battery life. Alternatively, reader error may be at fault. The development of a "pan-enteric" capsule designed specifically for both small and large bowel imaging may ultimately be required. In terms of colonic disease, the correlation between modalities was not quite as strong as that witnessed for small bowel images. However, this may be due to the scoring system utilised. There was discrepancy between PCC2 and colonoscopic disease activity scores in only two participants. The actual numerical difference in the SES-CD scores for both participants was a solitary point. In both cases, this increased the disease severity into a higher bracket of disease activity which likely skews the correlation between the two modalities. The development of a combined scoring system encapsulating both small and large bowel disease activity may be a viable option in the progression of this technology. Certainly based on the evidence to date, larger studies are warranted to prospectively validate the use of PCC2 in the investigation and monitoring of both small and large bowel CD.

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EDITORIAL

Use of blood based biomarkers in the evaluation of Crohn's disease and ulcerative colitis

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Abstract

Despite significant improvements in our understanding of Crohn's disease (CD) and ulcerative colitis (UC) in recent years, questions remain regarding the best approaches to assessment and management of these chronic diseases during periods of both relapse and remission. Various serologic biomarkers have been used in the evaluation of patients with both suspected and documented inflammatory bowel disease (IBD), and while each has potential utility in the assessment of patients with IBD, potential limitation remain with each method of assessment. Given these potential shortcomings, there has been increased interest in other means of evaluation of patients with IBD, including an expanding interest in the role of gene expression profiling. Among patients with IBD, gene expression profiles obtained from whole blood have been used to differentiate active from inactive CD, as well as to differentiate between CD, UC, and non-inflammatory diarrheal conditions. There are many opportunities for a non-invasive, blood based test to aid in the assessment of patients with IBD, particularly when considering more invasive means of evaluation including endoscopy with biopsy. Furthermore, as the emphasis on personalized medicine continues to increase, the potential ability of gene expression analysis to predict patient response to individual therapies offers great promise. While whole blood gene expression analysis may not completely replace more traditional means of evaluating patients with suspected or known IBD, it does offer significant potential to expand our knowledge of the underlying genes involved in the development of these diseases.

Key words: Inflammatory bowel disease; Ulcerative colitis; Gene expression analysis; Whole blood gene expression analysis; Biomarkers; Crohn's disease; Gene

profiling

Core tip: Questions remain regarding the best approaches to the assessment and management of patients with inflammatory bowel disease (IBD) during periods of both relapse and remission. Given the existing limitations of other serologic biomarkers, the development of whole blood gene expression profiling as a non-invasive method of assessment of patients with IBD is appealing. In an era of increased focus on personalized medicine, the potential expansion of our understanding of the genes underlying these diseases and their potential utility in predicting an individual's disease course or response to therapy offers great promise.

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INTRODUCTION

Though great strides have been made in our understanding of Crohn's disease (CD) and ulcerative colitis (UC) in recent years, questions remain regarding the best approaches to assessment and management of these chronic diseases during periods of both relapse and remission. These two subtypes of inflammatory bowel disease (IBD) have a presumed genetic predisposition, which when combined with multiple environmental exposures including changes to the gut microbiome, lead to clinically evident CD or UC. While the traditional evaluation of patients with IBD has been largely centered on endoscopic and radiographic examination, along with histological assessment of biopsy specimens, newer techniques focusing on gene expression profiling have been increasingly utilized to examine the differential expression of genes between disease states and normal. The use of gene expression profiling has significant potential within the field of IBD, both in differentiating CD and UC from non-IBD conditions, as well as determining activity of disease and response to treatment.

CURRENT APPROACHES TO EVALUATION

Various serologic biomarkers have been used in the evaluation of patients with both suspected and documented IBD. Erythrocyte sedimentation rate and C-reactive protein (CRP) are non-specific markers of inflammation that can be elevated in patients with active CD and UC. Although CRP can be useful in differentiating IBD from other non-inflammatory gastrointestinal conditions[1], given their non-specific nature, reliance on these biomarkers alone can be problematic. While CRP is an acute phase protein thought to increase in patients with active IBD, up to 50% of patients with an active flare of UC can demonstrate normal CRP levels[2]. In patients with clinically active CD, normal CRP levels can be noted[3,4], as biomarker levels are not necessarily correlated with mucosal lesions noted on endoscopy[3]. Additionally, certain populations of patients with CD can demonstrate persistently low CRP levels in the setting of active disease, including patients with an ileal disease distribution or low body mass index[5].

Other strategies have been developed in attempts to use serologic testing to differentiate CD from UC, such as the tests for anti-Saccharomyces cerevisiae antibodies (ASCAs) and perinuclear antineutrophil cytoplasmic antibodies (pANCAs). Increased titers of ASCA have been associated with CD, whereas increased levels of pANCA are more commonly seen in patients with UC[6]. However, when evaluated in a meta-analysis of 60 studies, the sensitivity and specificity of a $ASCA^+/pANCA^-$ pattern for identification of CD was only 55% and 93% respectively[7]. In addition to ASCA, multiple other antibodies to bacterial proteins (Omp-C and I2), flagellin (CBir1), and bacterial carbohydrates have been studied and associated with CD, including laminaribioside (ALCA), chitobioside (ACCA[2]) and mannobioside (AMCA). These existing serological markers tend to have low sensitivity and specificity due to the potential for elevation in levels caused by autoimmune diseases, infectious processes, and inflammation outside the GI tract[8].

In contrast to the serologic biomarkers, fecal markers such as fecal calprotectin (FC) and fecal lactoferrin are more specific for intestinal inflammation. FC serves as an indirect estimate of the neutrophil infiltrate in the bowel mucosa. When evaluating a patient with suspected IBD, one meta-analysis concluded that measuring FC can be used as a screening tool for identifying patients who are likely to need endoscopy for further evaluation of suspected IBD[9]. Among patients with previously diagnosed IBD, FC serves as a reliable indicator of disease activity, though it's greatest utility may be in the evaluation of UC[10]. While FC has demonstrated significant utility in differentiating IBD from other chronic abdominal syndromes such as Irritable Bowel Syndrome[1,11], FC does not reliably differentiate between UC and CD[12].

DEVELOPMENT OF NEW BIOMARKERS

Given the shortcomings of these established serologic and fecal biomarkers in the evaluation of a patient with suspected or documented IBD, there has been an increased interest in other means of evaluation, including gene expression profiling. One of the more recent advances in this field has been the development of techniques allowing for the evaluation of mRNA extracted from whole blood[13,14]. The use of whole blood

mRNA gene expression methodology has been validated and utilized to stratify an individual into high and low risk groups for the development of colorectal cancer[15], as well as to predict an individual's current risk for having colorectal cancer[16], Additionally, RNA expression profiles obtained from whole blood have been used to identify patients with other conditions such as lung cancer[17], bladder cancer[18], kidney diseases[19,20], cardiovascular diseases[21-23], osteoarthritis[24], and psychiatric disorders such as schizophrenia and bipolar disorder[25,26]. Among patients with IBD, gene expression profiles obtained from whole blood have demonstrated the ability to differentiate active from inactive CD[27], as well as the ability to differentiate between CD, UC, and non-inflammatory diarrheal conditions[28].

The ability of a blood based biomarker to differentiate active from inactive disease states, as well as the ability to differentiate between CD, UC, and non-inflammatory conditions, holds great promise as a clinical tool in the evaluation of patients with suspected or known IBD. While mucosal biopsy and histologic evaluation remains a gold standard in the traditional evaluation of patients with IBD, the ability of a non-invasive, blood based test to differentiate disease states could indicate significant promise as a tool for monitoring IBD disease activity and predicting response to therapy.

Few studies have evaluated whole blood gene expression analysis as a biomarker and clinical tool in the evaluation of patients with UC and CD. One recent study utilized Affymetrix GeneChip technology to generate genome-wide expression profiles used in the prediction of disease activity in patients with UC and CD[8]. In this study, whole blood gene panels reliably distinguished UC and CD, in addition to determining the activity of disease with high sensitivity and specificity[8]. As previously noted, whole blood gene panels have previously demonstrated the ability to differentiate active CD from CD in remission[27], as well as UC from CD and non-inflammatory diarrhea[28]. One early study utilized transcriptional profiling of peripheral blood mononuclear cell RNA to distinguish UC from CD with high accuracy[29]. Another study used peripheral blood-derived mononuclear cells to evaluate mRNA expression levels among patients with IBD, rheumatoid arthritis, and psoriasis[30]. Using this technique, the authors were able to identify disease specific gene panels that could differentiate each disease type and could separate the disease state from healthy controls[30]. Other authors have used peripheral blood MicroRNAs (miRNAs) to distinguish active CD and UC from healthy controls[31]. Finally, in an evaluation of pediatric patients with IBD, patients in clinical remission had distinct gene expression profiles obtained from peripheral blood leukocytes when compared to healthy controls[32].

Gene expression profiling from mucosal biopsies has also been an area of increasing interest. One prior study utilized gene expression profiling from mucosal biopsies to differentiate between normal mucosa, adenoma, colorectal cancer and IBD[33]. Other studies have utilized gene expression profiles obtained from mucosal biopsies to differentiate patients with UC from controls[34], patients with IBD from infectious colitis[35], and patients with IBD from normal controls[36]. Arijs *et al*[37,38] have published data demonstrating the ability of mucosal gene expression profiles to predict response to infliximab in patients with UC and CD. While each of these studies is indicative of the significant promise for gene expression analysis as a clinical tool in predicting disease activity, response to therapy, and disease course in patients with IBD, the fact that they require mucosal biopsy for analysis makes the non-invasive option for gene expression analysis *via* whole blood potentially more attractive.

When evaluating specific patterns identified by gene expression profiling, trends along biological processes have been identified. In an evaluation of response to infliximab among patients with UC[37] using mucosal biopsies, patterns along several biological functions were identified including immune response, cell to cell signaling, cellular movement, cell death and tissue morphology and development. In addition, there was considerable overlap when the gene sets used in this study were compared to the gene sets identified in patients with the colitis subtype of CD[38]. When evaluating patterns identified by whole blood gene expression analysis, a similar trend around immune functions has been demonstrated. A four gene panel used to differentiate UC from CD included *CD300A* which potentially plays a role in modulating proinflammatory stimuli among neutrophils, as well as *IL1R2* which is involved in cytokine-cytokine receptor interactions[28]. In an evaluation of the ability of biomarkers to predict disease activity among patients with UC and CD, some of the genes that were identified within groups of patients with active disease had previously been associated with UC and CD[39]. These target genes included *NLRP12* (a member of the Nod-like receptor family) and *TAGAP*, which is one of 22 genes previously identified as downregulated at week 8 and week 30 among responders to infliximab in the Active Ulcerative Colitis Trial 1 (ACT 1)[39].

CONCLUSION

Given these recent successes, there remain many opportunities for further utilization of whole blood gene expression analysis to evaluate and treat patients with IBD. Current work is ongoing to evaluate the ability of whole blood gene expression analysis to predict response to biologic therapy for UC and CD. Additionally, given the initial success in differentiating UC from CD and other non-inflammatory diarrheal illnesses, further attention will be paid to the potential clinical utility of whole blood gene expression as a clinical biomarker used in the assessment of patients with IBD. Recent work has demonstrated the utility of whole blood gene expression analysis as a measure of effectiveness of

novel therapies such as leukocytopharesis for UC[40], and further studies will be necessary to evaluate the utility of gene expression biomarkers in monitoring clinical improvement in that population.

Despite the recent successes, some limitations of this expanding area of research must be identified. To date, the majority of the studies evaluating the use of whole blood gene expression analysis in the evaluation of patients with IBD have examined small populations. These small study populations may lead to evaluations of heterogenous patient groups, including patients with varying degrees of disease activity. This introduces heterogeneity into the ultimate population of cells used for the sample analysis, and thus larger studies are still necessary for further exploration. In addition, when target genes have been identified in IBD and other inflammatory conditions, difficulty in the evaluation of which genes represent underlying etiologies and which represent consequences of the disease remains[30].

Each of the significant developments outlined indicates the potential for this non-invasive serologic test to become an important blood based biomarker in the evaluation of patients with IBD. While we do not expect whole blood gene expression analysis to completely replace the traditional means of evaluating patients with suspected or known IBD, it does offer significant potential to expand our knowledge of the underlying genes involved in the development of these diseases. Perhaps most promising, whole blood gene expression analysis offers a non-invasive method of evaluation that may ultimately lead to personalized predictions of disease activity, disease course, and response to therapy.

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TOPIC HIGHLIGHT

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Endoscopic resection of tumors in the lower digestive tract

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Abstract

As endoscopic technology has developed and matured, the endoscopic resection of gastrointestinal tract polyps has become a widely used treatment. Colorectal polyps are the most common type of polyp, which are best managed by early resection before the polyp undergoes malignant transformation. Methods for treating colorectal tumors are numerous, including argon plasma coagulation, endoscopic mucosal resection, endoscopic submucosal dissection, and laparoscopic-endoscopic cooperative surgery. In this review, we will highlight several currently used clinical endoscopic resection methods and how they are selected based on the characteristics of the targeted tumor. Specifically, we will focus on laparoscopic-endoscopic cooperative surgery.

Key words: Colorectal tumor; Endoscopic resection

Core tip: The best case scenario for patients with lower digestive tract tumors is to detect and resect the tumor before it undergoes malignant transformation. However, modern technologies for tumor resection are numerous and there may be specific indications for the implementation of one technology over another. Therefore, we will discuss the current clinical endoscopic resection methods and the process for selecting specific interventions. We wish to highlight laparoscopic-endoscopic cooperative surgery, because it may be of assistance in endoscopic treatment and could remarkably decrease the rate of later surgical repair.

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INTRODUCTION

Colorectal tumors are common in modern society and

although numerous new technologies have become available to locate, identify, and treat these tumors, early detection and removal (*e.g.,* during the polyp stage before malignant transformation) are still the key to long term survival and a favorable overall prognosis[1,2]. As a result, endoscopic methods have steadily developed to better meet these requirements. A study by Winawer *et al*[3] showed that endoscopic removal of colorectal adenomas can reduce the incidence rate of colorectal cancer by about 76%-90%. The current clinical endoscopic polypectomy methods are numerous and varied. Through careful observation of the distribution, size, morphology, and pathological features of colorectal polyps, clinicians/endoscopists can select the appropriate endoscopic resection treatment to avoid repeated unsuccessful procedures and improve the quality of life of the patient[2].

ENDOSCOPIC DIAGNOSIS BEFORE RESECTION

Before endoscopic resection, a comprehensive evaluation of the lesion is required. Ordinary endoscopy, magnifying endoscopy, or narrow-banding imaging (NBI) can be used to make a preliminary observation[4]. If the pathology confirms that the lesion is an adenoma, endoscopic resection can be performed. Pedunculated adenomas can be removed easily by endoscopic resection, regardless of the size of tumor; if the adenoma is sessile, the resection will be based on relevant patient parameters (age, body condition, and the patient's wishes)[5]. If pathological examination shows that the lesion is malignant, a "lifting sign" should be judged by injecting normal saline and indigo dye at the basal submucosal layer of the lesion. If the "lifting sign" is negative, the tumor has invaded and extended into the submucosa or even below[6]. Research has confirmed that for lesions confined to the mucosal layer, lymph node metastasis generally does not occur. Tumors that extend deeper into the submucosal layer can be divided into categories SM1-SM3. SM1 tumors (submucosal invasion < 1000 μm) have a low risk of lymph node metastasis, while the SM2 and SM3 tumors (submucosal invasion more than 1000 μm) have a higher lymphatic metastasis risk-up to 12.5%[7-9]. Tumors with a negative "lifting sign" should be surgically removed, rather than removed endoscopically.

ENDOSCOPIC RESECTION METHODS

Argon plasma coagulation

The principle of argon plasma coagulation (APC) is to use a specialized device to deliver ionization energy from argon; this high frequency energy can be implemented to solidify the tissue surface. Presently, APC plays an important role in maintaining hemostasis and cauterizing lesions during surgical and endoscopic procedures taking place in the human gastrointestinal tract[10]. The advantages of APC for treating colorectal lesions are that it is a rapid and efficient procedure that produces only a small vulnus and is generally well-tolerated by patients[11]. Some studies show that the most outstanding advantage of APC is its self-limited solidification depth. The damage of solidification generally does not extend more than 3 mm, minimizing the risk of perforation[12]. Based on the characteristics of the laser and the high frequency electric knife, APC can effectively be used to stop bleeding during a gastrointestinal procedure. Furthermore, during the operation, the probe does not need to contact the tissue, reducing the risk for adhesions or hemorrhages[13]. However, APC does have some limitations. Mainly, it is difficult to obtain pathological specimens with this technique, making it nearly impossible to determine the invasion depth, such that the cutting edge of the polyps is unclear.

Endoscopic mucosal resection

Endoscopic mucosal resection (EMR) has become a routine method for the treatment of early gastrointestinal mucosal lesions[14]. The general method of EMR is adapted to the submucosal injection of liquid saline to separate the lesions from the underlying muscle layer, after which lesions can be completely removed with a snare. The method is simple, safe, produces a small vulnus, is easily adaptable, and fairly easier to master, even for less experienced endoscopists[15,16]. However, there is the risk for rare and serious complications, such as intestinal perforation and bleeding, although these can be remedied by endoscopy or surgery. The incidence of perforation is very low (0.7%-1.3%), and the risk for bleeding is also fairly low (5.0%-8.1%)[17,18]. Some studies show that effective/optimized submucosal injection can help to prevent complications and ensure the safety of EMR[19]. Compared to APC, EMR has some advantages. Namely, EMR allows for pathological examination of the lesion after EMR to determine invasion depth and the cutting edge. However, due to the likelihood for electrocoagulation through snaring, EMR is only suitable for the complete resection of tumors with diameters that are less than 20 mm. Here, the complete resection rate is 64.3%-77.4%, and the recurrence rate is very low (0%-3.6%)[20,21]. If the tumor is larger than 20 mm, the complete resection rate drops significantly to 48.1%-32.9%, while the recurrence increases to 16%-25.7%[22,23]. Therefore, EMR is not an appropriate choice for the treatment of particularly large (greater than 20 mm) gastrointestinal tumors.

Endoscopic submucosal dissection

Endoscopic submucosal dissection (ESD) was developed based on EMR techniques and was named after it was approved as a new resection method in 2003. In this procedure, an insulation tipped knife (knife IT) is

instrumental for performing ESD. Compared to EMR, ESD can not only provide complete specimens for more reliable pathological examination, but it can also be used to fully resect the tumor with a low rate of recurrence[24]. For tumors less than 20 mm, the complete resection rate is 82.6%-97.7% and the recurrence rate is nearly 0%[21,25,26]. However, if the tumor is larger than 20 mm, the complete resection rate drops a little to 74%-91.8%, but the recurrence rate remains 0%-1%[17,22,23,25]. During the ESD procedure, the operator should pay attention to the "lifting sign" after submucosal injection, which can be used to determine the lesion depth. If the lesion is located in the mucous layer with a proper boundary to the muscularis propria and has a positive "lifting sign," it can be removed by ESD[27,28]. However, the rate of perforation in ESD is higher than that for EMR, because the submucosal layer is nearer to the muscularis. For this procedure, which is more complicated than EMR, the incidence of complications also correlates with the operator's technical proficiency[29]. Nonetheless, in some studies, the bleeding rate of ESD remains low (0.4%-2.5%), although the risk of perforation is slightly higher (2.9%-5.3%)[30,31].

Laparoscopic-endoscopic cooperative surgery

At present, endoscopic therapy is not only applied to resecting colorectal polyps, but also to the treatment of early colorectal cancers that are located in the mucosal layer. Through endoscopic resection, patients can avoid laparotomy, sustain lesser injury, and recover quickly[32]. However, the colonoscopy field of vision is limited in the intestinal lumen, such that the condition of the bowel wall or abdominal cavity is unclear. Some lesions located in the splenic or hepatic flexure can make endoscopic resection difficult. Laparoscopic-endoscopic cooperative surgery (LECS) takes advantage of characteristics of both laparoscopic and colonoscopic procedures. LECS is often implemented when the lesion is difficult to be removed or cannot be completely resected by endoscopic methods alone[33]. Under the guide of a colonscope, the laparoscope can look for and identify the intestinal site where the lesion is located and dissociate it from this site if necessary. By pulling and pushing the laparoscope upward, the lesion may be exposed so that endoscopists can use EMR or ESD to remove the lesion. During this process, the operator can focus on the complete excision of the lesion and does not need to be concerned with possibility of perforation. If perforation or bleeding occurs, laparoscopy can be used to repair the perforation and return to hemostasis immediately. However, no randomized controlled trials have been performed to evaluate LECS in the treatment of lower digestive tract tumors. Nonetheless, select published LECS cases suggest that it is a feasible procedure for the *en bloc* resection of some colonic lateral spreading tumors that would be otherwise difficult to resect using exclusively endoscopic methods[34-36].

CHOOSING THE ENDOSCOPIC TREATMENT

Tumors with a diameter less than 3 mm

For small tumors less than 3 mm in diameter, APC can be used for solidification of the lesion. However, as this technique cannot be used to collect pathological specimens, long-term endoscopic follow-up is required[37].

Tumors with a diameter less than 20 mm

For lesions in this size category, according to a study by Lee *et al*[26], there are no significant differences in the complete resection rate between EMR (82.6%) and ESD (64.3%) techniques. Although EMR has a recurrence rate of 3.6%, the risk of cancer progression for small tumors is minimal and the main pathological type for this size tumor is adenoma; therefore, EMR is suitable for the removal of small lesions and is a fairly easy technique to master, even for less experienced endoscopists. The risk of perforation with EMR is lower than that with ESD, and it is regarded as a quicker and safer choice for lesions with a relatively smooth surface without signs of bleeding and erosion[18,38]. However, there are some exceptions. If the endoscopic diagnosis (NBI or magnifying endoscope) strongly indicates that the lesion is malignant and the pathological examination shows the same results, the tumor must be excised by ESD and the patients should undergo close follow-up in the future.

Tumors with a diameter more than 20 mm

Some studies report that the proportion of adenocarcinomas significantly increases in tumors larger than 20 mm in diameter, since the degree of tumor malignancy is often associated with the relative tumor size[39]. Other studies report that the size of the tumor can be at least partly used as an index to predict the degree of malignancy. The possibility of recurrence for tumors greater than 10 mm diameter is relatively high[26]. Early adenocarcinomas have characteristics of invasion, recurrence, and metastasis, and due to a lower complete resection rate and high recurrence rate, EMR is not suitable for these kinds of tumors. Fortunately, ESD can be used to remove larger tumors with much higher complete resection rates and lower recurrence rates. However, ESD still has some limitations, especially for larger laterally spreading tumors. Here the excised area is often too large, translating to an extremely high risk of perforation[40]. Once a perforation occurs, a surgical repair or intestinal resection is needed to repair the large defect left by ESD. Therefore, LECS may be a better choice to ensure a complete resection, while minimizing the risk of serious complications. Based on the assistance of a laparoscope, the visibility of lesion is greatly enhanced and the operator can focus on the complete excision of the lesion while not worrying about the possibility of perforation, which can easily

and rapidly be repaired using the laparoscope to stitch the perforated area. Rapid detection and repair of any perforations greatly reduce the risk of abdominal infection. Therefore, in certain situations, LECS can not only be minimally invasive, but also offers better and safer therapeutic effects[41,42].

CONCLUSION

Endoscopic resection presents a great technological leap in the diagnosis and treatment of colorectal tumors, as well as an important preventive measure to remove polyps in their premalignant stages. In recent years, some new technologies, such as magnifying endoscopy and NBI have improved the detection rate of early colorectal cancers, which improves long term survival and the resulting quality of life. At the same time, with the continuous development of endoscopic treatment equipment and the introduction of new technologies, most colorectal polyps and early cancers can now be resected by minimally invasive EMR, ESD, or LECS techniques, which can now achieve the same effects as surgery. However, when endoscopic treatment is to be used, the indications should be carefully considered following evaluation of the relevant patient and pathological parameters, along with the likelihood of complete resection and risk for complications. Therefore, initial colonscopy examination is crucial. Although minimally invasive and often successful in full resection, endoscopic resections do have some limitations. If the cancer invades deep into the submucosal layer, belongs to the lower differentiation, or contains a lymphatic or venous tumor thrombus, additional radical surgical operation will still be required.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Endoscopic submucosal dissection *vs* laparoscopic colorectal resection for early colorectal epithelial neoplasia

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Abstract

AIM: To compare the short term outcome of endoscopic submucosal dissection (ESD) with that of laparoscopic colorectal resection (LC) for the treatment of early colorectal epithelial neoplasms that are not amenable to conventional endoscopic removal.

METHODS: This was a retrospective cohort study. The clinical data of all consecutive patients who underwent ESD for endoscopically assessed benign lesions that were larger than 2 cm in diameter from 2009 to 2013 were collected. These patients were compared with a cohort of controls who underwent LC from 2005 to 2013. Lesions that were proven to be malignant by initial endoscopic biopsies were excluded. Mid and lower rectal lesions were not included because total mesorectal excision, which bears a more complicated postoperative course, is not indicated for lesions without histological proof of malignancy. Both ESD and LC were performed by the same surgical unit with a standardized technique. The patients were managed according to a standard protocol, and they were closely monitored for complications after the procedures. All hospital records were reviewed, and the following data were compared between the ESD and LC groups: patient demographics, size and location of the lesions, procedure time, short-term clinical outcomes and pathology results.

RESULTS: From 2005 to 2013, 65 patients who underwent ESD and 55 patients who underwent LC were included in this study. The two groups were similar in terms of sex (P = 0.41) and American Society of Anesthesiologist class (P = 0.58), although patients in the ESD group were slightly older (68.6 ± 9.4 *vs* 64.6 ± 9.9, P = 0.03). ESD could be accomplished with a shorter procedure time (113 ± 66 min *vs* 153 ± 43 min, P < 0.01) for lesions of comparable size (3.0 ± 1.2 cm *vs* 3.4 ± 1.4 cm, P = 0.22) and location (colon/rectum:

59/6 *vs* colon/rectum: 52/3, $P = 0.43$). ESD appeared to be associated with a lower short-term complication rate, but the difference did not reach statistical significance (10.8% *vs* 23.6%, $P = 0.06$). In the LC arm, a total of 22 complications occurred in 13 patients. A total of 7 complications occurred in the ESD arm, including 5 perforations and 2 episodes of bleeding. All perforations were observed during the procedure and were successfully managed by endoscopic clipping without emergency surgical intervention. Patients in the ESD arm had a faster recovery than patients in the LC arm, which included shorter time to resume normal diet (2 d *vs* 4 d, $P = 0.01$) and a shorter hospital stay (3 d *vs* 6 d, $P < 0.01$).

CONCLUSION: ESD showed better short-term clinical outcomes in this study. Further prospective randomized studies will be required to evaluate the efficacy and superiority of colorectal ESD over LC.

Key words: Early colorectal neoplasia; Laparoscopic colectomy; Endoscopic submucosal dissection

Core tip: This is the first study that compares endoscopic submucosal dissection (ESD) *vs* laparoscopic colorectal resection (LC) for endoscopically benign lesions that could not be adequately removed by conventional polypectomy. Case inclusion was based purely on the pre-operative/pre-procedure endoscopic findings. Although the difference in morbidities did not reach statistical significance, the absolute number of complications and the number of patients involved were much higher in the LC arm. The current study provided evidence that surgeons are capable of performing high-quality colorectal ESD procedures. We expect that the participation of the surgeons as well as the close collaboration with gastroenterologists will play a pivotal role in the formulation of a management plan for patients with early colorectal neoplasms.

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INTRODUCTION

Laparoscopic colorectal resection (LC) is currently a widely accepted treatment for colorectal neoplasms that are deemed not amenable to endoscopic removal[1-4]. However, LC carries an inherent complication rate of over 15%[1,2]. Therefore, one could argue that surgery may be too invasive or aggressive as a treatment for early colorectal neoplasms. The potential risks of laparoscopic resection may outweigh the estimated risk of lymph node metastasis if the neoplasms are not resected[5-7]. On the contrary, endoscopic piecemeal removal of large sessile or flat polyps by conventional polypectomy or by endoscopic mucosal resection (EMR), although it is less invasive, is known to be associated with a high local recurrence rate of 14%-19.5%[8,9]. Endoscopic submucosal dissection (ESD) is a novel technique that was originally developed in Japan more than 10 years ago. ESD was developed to achieve an *en bloc* mucosal resection with wider margins[10-13]. Currently, an increased number of endoscopists throughout the world have acquired this skill and have published promising outcomes of ESD[14-19]. The recent retrospective analysis reported by Kiriyama *et al*[20] that compared ESD for colorectal intramucosal or slightly submucosal invasive cancers *vs* LC for T1 cancer demonstrated a lower complication rate in the ESD group. Another similar prospective study also compared ESD for adenoma or T1 cancer with less than SM-s (superficial submucosal invasion) *vs* LC for SM-d (deep submucosal invasion)[21]. Until now, no worldwide consensus has been adopted as to whether the treatment of benign colorectal neoplasms with advanced endoscopic techniques (*i.e.*, ESD) is superior to surgical approaches[22]. From the very beginning of the development of colorectal ESD, the procedure was performed primarily by gastroenterologists. No published data exists on the comparison of the clinical outcomes of ESD *vs* those of LC when both procedures were performed by the same group of surgeons. Surgeons who can perform both procedures may be in an advantageous position in that they can balance the risks and benefits of the endoscopic approach *vs* the surgical approach. Therefore, we performed a retrospective cohort study that aimed to compare ESD *vs* LC for endoscopically benign lesions that could not be adequately removed by conventional polypectomy. This is the first comparative study of a similar topic, and this is also the first series where both procedures were performed by the same group of surgeons.

MATERIALS AND METHODS

This was a retrospective cohort study conducted at Prince of Wales Hospital at, The Chinese University of Hong Kong. Since 2005, LC has been the gold standard surgical treatment for all colorectal lesions that are not amenable to endoscopic removal. Colorectal ESD was first established at our centre in 2008, and since that time, it has enriched the armamentarium of endoscopic interventions. Consecutive patients who underwent ESD or LC for early colorectal neoplasms (endoscopically benign lesions larger than 2 cm in diameter) from 2005 to 2013 were included.

Lesions were excluded when endoscopic signs of massive submucosal invasion were present as evidenced by the existence of excavated/depressed morphology or

Kudo's pit pattern type Ⅴ. Lesions proven to be malignant by initial endoscopic biopsies were also excluded. Mid and lower rectal lesions were not included because total mesorectal excision, which intrinsically bears a more complicated post-operative course and has a negative impact on gastrointestinal function, would not be offered to patients who were diagnosed with benign lesions by endoscopy. Nevertheless, the input of the patients would also influence the selection between ESD and LC because ESD was a relatively new procedure at that time.

Patients were instructed to eat a low residue diet two days before ESD or laparoscopic colectomy. They received four litres of polyethylene glycol solution as a mechanical bowel preparation on the day of ESD or one day before LC. Both ESD and LC were performed by surgeons who were capable of executing these procedures independently.

All hospital records were reviewed, and the following data were compared between the ESD and LC groups: patient demographics, size and location of the lesions, procedure time, short-term clinical outcomes and pathology result.

The ESD procedure and postoperative care

Our techniques for colorectal ESD have been previously reported[23]. In short, all ESDs were performed when the patients were under conscious sedation after intravenous administration of midazolam and pethidine. Intravenous Buscopan was used if significant colonic spasms were encountered during the ESD procedure. All procedures were performed with a water-jet gastroscope or with a paediatric colonoscope with a transparent cap attached to the tip. Carbon dioxide insufflation was routinely used to reduce patient discomfort. The margins of the lesions were determined by either dye (0.4% indigo carmine spray) or digital (narrow band imaging) chromoendoscopy. Submucosal cushions were created by a mixture of normal saline, adrenaline, indigo-carmine and sodium hyaluronate. Circumferential mucosal incision and submucosal dissection were performed by dual knife or insulated tip knife (Olympus Medical System, Tokyo, Japan), depending on the location of the lesion and the preference of the endoscopists. Haemostasis after ESD was achieved by Coagrasper (Olympus Co. Ltd., Tokyo, Japan).

When perforations were encountered during the ESD procedure, they were immediately closed by endoscopic clips; otherwise, salvage surgery was arranged. For optimal procedures without significant bleeding, a diet would be resumed on the following day. Stable patients who managed to tolerate a full diet were discharged. For those patients with perforations that were managed by endoscopic clipping, they were kept nil per oral and monitored closely for signs of sepsis including fever, tachycardia, leukocytosis and peritonism. Depending on the clinical parameters, parenteral antibiotics were given and diet was gradually introduced. Salvage surgery was offered in cases of persistent or deteriorating sepsis.

All patients were encouraged to maintain mobility, and a diet was introduced gradually as tolerated. Patients were discharged when they could tolerate a full diet without signs of sepsis and the absence of rectal bleeding.

The LC procedure and postoperative care

All LCs were performed under general anaesthesia by the same group of colorectal surgeons, as described in our previous study[24]. In short, the colon or rectum was mobilized laparoscopically from the lateral to the medial area. The isolated lymphovascular pedicles were then transected with either laparoscopic linear staplers or with self-locking plastic clips. One of the working ports was later extended for specimen retrieval. Extracorporeal anastomosis was fashioned for a right-sided resection, while intracorporeal stapled anastomosis was performed for a left-sided resection.

After surgery, the patients were allowed to ingest oral fluid on day one. Diet was resumed gradually during the days following the surgery and depended on the progression of the patients. All patients received regular physiotherapy and were mobilized as soon as possible after surgery. Pain control was achieved by either regular analgesics or by patient-controlled analgesia. Ambulatory patients were discharged if they could tolerate a full diet with no signs of sepsis.

Histological assessment

All ESD specimens were mounted on a foam board for pathological examination by a designated pathologist. Deep and peripheral margins, cellular differentiation as well as the depth of submucosal invasion were recorded. R0 resection was defined as a complete *en bloc* resection with deep and circumferential margins that were free of adenomatous proliferation or dysplasia. Colectomy specimens were evaluated after fixation in 10% formalin and after staining with haematoxylin and eosin. Macroscopic and microscopic examinations for histological type, depth of invasion, lymph node status and resection margins were performed. Malignant lesions were classified according to the AJCC Cancer Staging Manual, 7th Edition (2010)[25].

Outcomes measurement

In regards to the short-term clinical outcomes, we studied the procedure time, the time to resume diet, the time to full ambulation, the duration of the total hospital stay and the complication rate.

Lesions that were located in the colon and at the rectosigmoid junction were defined as "colon", while lesions in the upper rectum were defined as "rectum".

Complications were defined as any event that required re-intervention, re-operation, re-admission or a prolonged hospital stay (namely, Clavien-Dindo Grade Ⅱ or above). Bleeding from the ESD procedure was defined as any bleeding episodes after ESD that warranted

Table 1 Demographic background

	Lap colectomy	ESD	*P* value
Number of patients	55	65	
Age (yr), mean ± SD	64.6 ± 9.9	68.6 ± 9.4	0.03
Sex	Female: 27 Male: 28	Female: 27 Male: 38	0.41
ASA	< 3 *vs* ≥ 3 : 43 *vs* 12	< 3 *vs* ≥ 3 : 48 *vs* 17	0.58
Size of lesion (cm), mean ± SD	3.4 ± 1.4	3.0 ± 1.2	0.07
Location of lesion	Colon: 52 Rectum: 3	Colon: 59 Rectum: 6	0.43

ASA: American Society of Anaesthesiology; ESD: Endoscopic submucosal dissection.

Table 2 Comparisons of the short-term outcome

	Lap colectomy	ESD	*P* value
OT/procedure time (min), mean ± SD	153 ± 43	113 ± 66	0.000
Post-op stay (d), median (range)	6 (3-41)	3 (1-13)	0.000
Days to diet, median (range)	4 (1-13)	2 (0-5)	0.000
Short-term complications	13/55 (23.6%)	7/65 (10.8%)	0.06
Pathology	Benign: 39 T1: 16	Benign: 56 T1: 9	0.04

ESD: Endoscopic submucosal dissection; OT: Operation time.

re-intervention, readmission, or a blood transfusion. ESD-related perforations were either detected during the procedure or were diagnosed radiologically by the presence of intra-peritoneal free gas.

Statistical analysis

Categorical data were analysed using χ^2 or Fisher's exact test, while continuous variables were analysed by *t* test, as appropriate. *P* values < 0.05 were considered statistically significant. All calculations were conducted with SPSS statistical software package (SPSS version 15.0, Chicago, IL, USA). Data analysis was based on the intention to treat principle.

RESULTS

From 2005 to 2013, 55 patients who underwent LC and 65 patients who underwent ESD were included in this study. The mean age of the patients in the ESD group was slightly higher than that of the patients in the LC group. The two groups shared comparable sex and ASA class distributions (Table 1).

No statistically significant differences were observed in terms of lesion size or location, yet ESD could be accomplished with a significantly shorter procedure time (113 ± 66 min *vs* 153 ± 43 min, *P* < 0.01) and a faster recovery course, as illustrated by earlier resumption of a full diet (2 d *vs* 4 d, *P* = 0.01) and a shorter hospital stay (3 d *vs* 6 d, *P* < 0.01) (Table 2).

The overall short-term complication rate for ESD and LC was 10.8% and 23.6%, respectively. Although we could not demonstrate a significant difference between the two groups (*P* = 0.06), the ESD group exhibited a trend towards a lower short-term complication rate. In the LC arm, a total of 22 complications occurred in 13 patients (Table 3). These included 1 anastomotic leak, which necessitated a laparotomy and stoma formation, 1 mechanical small bowel obstruction, which required re-operation, 6 wound infections, 1 chest infection, 4 urinary tract infections, 1 acute urine retention, 6 cases of prolonged ileus, 1 deep vein thrombosis and 1 mental confusion. A total of 7 complications occurred in the ESD arm, including 5 perforations and 2 bleeding episodes. The remainder of the patients in the ESD arm experienced a smooth intra- and post-procedure course without complications. All of the perforations were observed during the procedure and were successfully managed by endoscopic clipping. Therefore, no emergency surgical intervention was needed. One of the bleeding episodes was successfully stopped during the procedure, and blood transfusion was required. Unfortunately, the other incident was encountered during the removal of a caecal lateral spreading tumour (LST). As a result of malfunction in the water-jet, a clear endoscopic view could not be achieved for safe haemostasis and dissection. Hence, the procedure was abandoned and was followed by emergency LC. The patient was discharged home 4 d after surgery. No delayed perforation, bleeding or other post-procedure complications were recorded in the ESD arm (Table 4).

En bloc resection was achieved in 81.5% (53/65) of the ESD procedures. For the remaining 12 lesions, 6 were completely removed by piecemeal EMR. Endoscopic removal had to be abandoned for the other six lesions due to instrumental failure in one case and the presence of dense adhesions in five cases. Amongst the 5 lesions that harboured these dense adhesions, 3 were confirmed T1 adenocarcinomas.

In this study, histological analysis revealed the presence of T1 adenocarcinomas in 25 lesions (LC: 16 and ESD: 9). The proportion of invasive neoplasms was significantly higher in the LC arm (29.1% *vs* 15.3%, *P* = 0.04. *En bloc* ESD resection was successfully achieved in 4 of 9 malignant lesions, and all four of these patients were subsequently managed according to the level of submucosal (sm) invasion and other associated histological features. Although salvage surgery was offered to the two patients with sm2 lesions, they both rejected this procedure. On the contrary, one patient with an sm3 lesion agreed to undergo LC, and the pathology of the resected specimen showed no residual primary tumour; however, one metastatic lymph node was identified. The remaining patient with an sm1 lesion was put under close surveillance in light of an adequate resection margin and the absence of lymphovascular permeation. ESD was abandoned in 3 of 9 malignant lesions due to dense submucosal adhesion, of which 2 were salvaged by LC and 1 by TEO (transanal endoscopic operation).

Table 3 Complications of laparoscopic colectomy (22 events in 13 patients)

	Number of complications	Surgical intervention required
Anastomotic leak	1	1
Mechanical small bowel obstruction	1	1
Wound infection	6	0
Chest infection	1	0
Urinary tract infection	4	0
Urinary retention	1	0
Ileus	6	0
Deep vein thrombosis	1	0
Confusion	1	0

Table 4 Performance indicators of endoscopic submucosal dissection

	n	(%)
En bloc resection	53	81.5
R0 resection	47	72.3
Perforation	5	7.7
bleeding	2	3.1

No other complication apart from perforation and bleeding were observed.

Piecemeal resection was performed in the other 2 of 9 lesions, of which one refused salvage surgery and the other one accepted salvage LC.

DISCUSSION

Since the development of colorectal ESD, its feasibility, safety and oncological outcome have been reported in numerous contemporary studies[14-20]. Currently, nearly 3000 colorectal ESDs are performed each year in Japan[26]. The Japanese healthcare insurance system has also approved a reimbursement scheme for colorectal ESD[26]. On the contrary, the adoption rate of ESD is variable in the rest of the world, especially among surgical societies. To explain this, two potential hurdles have been identified. First, the technique of LC had already been widely practised and supported by a high level of evidence at the time when colorectal ESD was introduced outside of Japan. Second, the volume of cases did not justify a large number of endoscopists having to learn and master the technique of ESD. Moreover, current literature that directly compares LC *vs* ESD for early colonic neoplasms is not available. Two recent studies compared ESD for mucosal or slight submucosal invasive lesions *vs* LC for T1/deep submucosal invasive lesions[20,21], but the pathological nature of the two comparative groups was different.

This is a retrospective cohort study that compared ESD *vs* LC for endoscopically confirmed benign lesions that could not be adequately removed by conventional polypectomy. Case inclusion was based purely on the pre-operative/pre-procedure endoscopic findings, and no crossover of abandoned ESD to LC occurred. The results of this study suggested that ESD was superior to LC with respect to short-term outcomes and that ESD leads to a faster recovery. Despite the fact that perforation and bleeding did occur in the ESD arm, all but one of these events could be managed endoscopically. The post-operative course of the only patient who underwent salvage surgery for complications was also uneventful. Although the difference in morbidities did not reach statistical significance, the absolute number of complications and the number of patients involved are much higher in the LC arm.

Moreover, all ESD procedures were performed when the patients were under conscious sedation without general anaesthesia. This definitely avoided the risks of general anaesthesia and post-operative wound pain. Almost immediate mobilization was feasible once the sedative effect subsided. Therefore, we believe that ESD might be more reasonable and acceptable for patients with early colorectal neoplasia or LSTs.

The ESD perforation rate in this study was 7.7%, which was comparable with quoted figures in the literature. In a recent meta-analysis, the highest reported perforation rate was 12%[18], and most of the reported rates in published series were well below 10%[27]. Although these perforation rates might be considered higher than those at some of the high-volume Japanese centres[14,28,29], they were comparable with large series that have been conducted outside of Japan[30,31]. This cohort study only reflected the early phase of our learning curve, and we expect a further reduction in morbidity in the future. Due to the increasing popularity of screening colonoscopy and image-enhanced endoscopy, a greater number of early colorectal lesions might be detected. Therefore, we expect a higher ESD throughput and an improved performance at our centre.

In reality, whether an endoscopically assessed benign lesion is subjected to ESD or colectomy depends to a large extent on who detects the lesion. For instance, if a gastroenterologist who is capable of performing ESD detects an LST, then an ESD procedure might be attempted. Likewise, if the same lesion is detected by a surgeon who does not possess the skills to perform ESD, then colectomy would be offered instead. In our locality, it is rather unique that surgeons actively participate in advanced diagnostic and therapeutic endoscopies. At our centre, we have a group of surgeons who have acquired the skills to perform both LC and colorectal ESD, and who can confidently counsel patients and offer them both options (ESD *vs* LC). One can also comprehensively balance the risks and benefits between conservative management *vs* salvage surgery for histologically confirmed malignant lesions that are removed by ESD. The current study provided evidence that surgeons are capable of performing high-quality colorectal ESD. We expect that the participation of the surgeons as well as the close collaboration with gastroenterologists will pay a pivotal role in the formulation of a management plan for

patients with early colorectal neoplasms.

The major limitation of the current study was its retrospective nature that extended through a period of eight years, during which time major advances in both laparoscopic and endoscopic technology occurred. Most of the LC cases were recruited prior to the availability of image-enhanced endoscopy (2005-2008), when endoscopic diagnoses were less accurate. This explained why patients in the LC arm had more malignant lesions, which was also a major bias of the current study. During the past few years, we have introduced enhanced recovery protocols in our unit, and thus the same LC group may experience a faster recovery and potentially fewer morbidities. To address these biases, a randomized controlled trial is necessary to provide a higher level of evidence to compare these two intervention modalities. We are currently awaiting the results of our randomized controlled trial.

In conclusion, by a comparison of LC and ESD performed by the same group of surgeons for the treatment of early colorectal neoplasms, ESD produced better short-term clinical outcomes with respect to a shorter procedure time and an earlier recovery. Therefore, ESD may be superior to LC for the treatment of this specific type of colorectal lesion.

COMMENTS

Background

Before the development of colonic endoscopic submucosal dissection (ESD), colorectal lesions that were not deemed to be suitable for conventional endoscopic removal were classically treated by colorectal resection. Currently, although minimally invasive surgery can often be performed, the risks associated with surgery should be considered especially for the treatment of benign lesions. While colorectal ESD has become popular in Japan, its adoption rate and its performance quality are still variable in all other areas of the world. It is unknown whether ESD leads to a better short-term outcome for the treatment of early colorectal epithelial neoplasms.

Research frontiers

Results from this study may help surgeons to appreciate the potential benefits of ESD, which has not yet been widely adopted by surgical societies outside of Japan for the treatment of early colorectal epithelial neoplasms.

Innovations and breakthroughs

To date, no worldwide consensus has been adopted as to whether the treatment of benign colorectal neoplasms with ESD is superior to the use of colorectal resection. Moreover, there is no published data on the clinical outcomes of ESD *vs* laparoscopic colorectal resection (LC), where both procedures were performed by the same group of clinicians. In this retrospective study, the authors compared the short-term outcomes between ESD and LC and focused on the immediate recovery course and the complications.

Applications

This retrospective cohort study suggested that ESD produced better short-term clinical outcomes. The results from future randomized controlled trials would be expected to provide a higher level of evidence in regards to the potential superiority of ESD.

Terminology

In this study, early colorectal epithelial neoplasms referred to lesions without endoscopic signs of massive submucosal invasion, as evidenced by the absence of an excavated/depressed morphology or Kudo's pit pattern type Ⅴ.

Peer-review

The authors evaluated one hundred and twenty patients (ESD: 65, LC: 55) who underwent treatment for early colorectal epithelial neoplasms. ESD could be accomplished in a shorter time, and patients experienced a faster recovery. Although the difference in the occurrence of morbidities did not reach statistical significance, the absolute number of complications and the number of patients involved were much higher in the LC arm. Therefore, the option of ESD should be seriously considered in the contemporary management of early colorectal epithelial neoplasms.

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ORIGINAL ARTICLE

Retrospective Study

Feasibility of cold snare polypectomy in Japan: A pilot study

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Institutional review board statement: The Local Ethics Committee of Osaka Medical Center for Cancer and Cardiovascular Diseases approved the protocols of this study.

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Abstract

AIM: To investigate the feasibility of cold snare polypectomy (CSP) in Japan.

METHODS: The outcomes of 234 non-pedunculated polyps smaller than 10 mm in 61 patients who underwent CSP in a Japanese referral center were retrospectively analyzed. The cold snare polypectomies were performed by nine endoscopists with no prior experience in CSP using an electrosurgical snare without electrocautery.

RESULTS: CSPs were completed for 232 of the 234 polyps. Two (0.9%) polyps could not be removed without electrocautery. Immediate postpolypectomy bleeding requiring endoscopic hemostasis occurred in eight lesions (3.4%; 95%CI: 1.1%-5.8%), but all were easily managed. The incidence of immediate bleeding after CSP for small polyps (6-9 mm) was significantly higher than that of diminutive polyps (≤ 5 mm; 15% *vs* 1%, respectively). Three (5%) patients complained of minor bleeding after the procedure but required no intervention. The incidence of delayed bleeding requiring

endoscopic intervention was 0.0% (95%CI: 0.0%-1.7%). In total, 12% of the resected lesions could not be retrieved for pathological examination. Tumor involvement in the lateral margin could not be histologically assessed in 70 (40%) lesions.

CONCLUSION: CSP is feasible in Japan. However, immediate bleeding, retrieval failure and uncertain assessment of the lateral tumor margin should not be underestimated. Careful endoscopic diagnosis before and evaluation of the tumor residue after CSP are recommended when implementing CSP in Japan.

Key words: Colonoscopy; Endoscopic gastrointestinal surgery; Colorectal neoplasm; Polypectomy; Cold snare polypectomy

Core tip: Cold snare polypectomy (CSP) was completed for 232 of the 234 polyps. Immediate postpolypectomy bleeding requiring endoscopic hemostasis occurred in eight lesions (3.4%), but all were easily managed. The incidence of immediate bleeding after CSP for small polyps (6-9 mm) was significantly higher than that for diminutive polyps (≤ 5 mm; 15% *vs* 1%, respectively). Three (5%) patients complained of minor bleeding after the procedure but required no intervention. In total, 12% of the resected lesions could not be retrieved for pathological examination. Tumor involvement in the lateral margin could not be histologically assessed in 70 (40%) lesions.

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INTRODUCTION

Colorectal cancer is one of the most common causes of cancer-related death worldwide[1]. The adenoma-carcinoma sequence is thought to be the main route of colorectal cancer development[2], and the removal of colorectal adenomas is known to reduce the risk of subsequent colorectal cancer development and colorectal cancer death[3,4]. Endoscopic removal of all detected adenomas during colonoscopy screening is the standard strategy for the prevention of colorectal cancer, although more than 90% of the polyps are less than 10 mm in size, and most will never develop into cancer during the lifetime of the patient[5]. However, in this context, it is important to note that endoscopic resection is associated with potential complications that include bleeding and perforation[6-8]. Thus, endoscopists should always consider the most likely natural history of the lesion and balance those considerations against the risks associated with endoscopic resection[5]. Indeed, Japanese guidelines do not recommend the removal of diminutive (≤ 5 mm) colorectal polyps[9], and most Japanese endoscopists follow up diminutive colorectal polyps that are not endoscopically removed based on their experience[10].

Several techniques are available for the removal of diminutive or small (6-9 mm) (subcentimetric) polyps, although the optimal method remains unclear, and the method selection is often based on expert opinion. One approach that is used in Western countries for the removal of subcentimetric polyps is cold polypectomy, *i.e.*, removal without electrocautery. This approach seems to minimize the risks of complications when removing subcentimetric lesions[11]. Two different cold polypectomy techniques are available. Cold forceps polypectomy (CFP) is a simple and easy procedure using endoscopic forceps without electrocautery[12]. The second technique is cold snare polypectomy (CSP), which uses snare resection without electrocautery and has been reported to be a safe method for the removal of subcentimetric polyps[13]. Although CSP appears to be a promising procedure for endoscopic removal of subcentimetric colorectal polyps, CSP is not yet widely used in Japan because of the lack of sufficient data about this procedure. Therefore, the purpose of the present study was to examine the feasibility of the use of CSP in a Japanese center.

MATERIALS AND METHODS

Study design

This retrospective study was performed at the endoscopy unit of the Osaka Medical Center for Cancer and Cardiovascular Diseases. The study protocol was approved by the center's local ethics committee. Patients with colorectal polyps larger than 5 mm who were recommended to undergo polypectomy and all polyps detected during screening colonoscopies were included in the study. All consecutive patients who underwent colorectal CSP for a subcentimetric polyp between November 2012 and March 2013 were included in a prospectively maintained database. CSP was not performed in patients who were undergoing anticoagulant and antiplatelet therapy. Additionally, CSP was not performed for lesions with suspected intramucosal or invasive carcinomas based on endoscopic assessments. Written informed consent was obtained from all patients upon inclusion.

Procedures

All procedures were performed by nine experienced colonoscopists who had each conducted more than 100 colorectal polypectomies. None of the colonoscopists had performed CSP prior to this trial. A standard type colonoscope (EVIS CF-240I or CF-260DI; Olympus

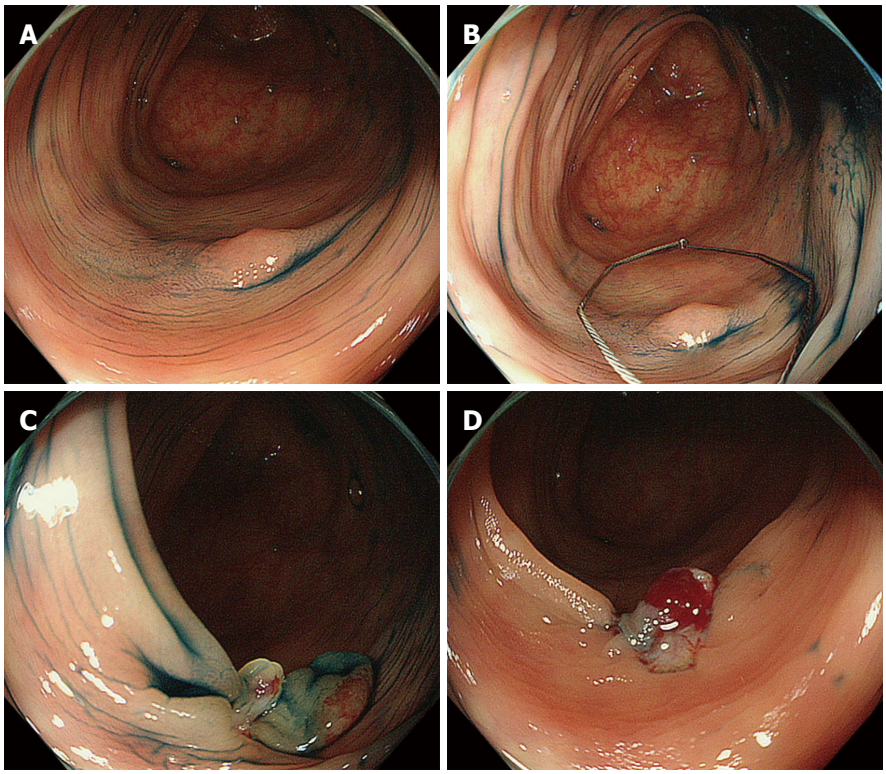

Figure 1 Actual cold snare polypectomy procedure. A: A 5-mm flat adenoma located in the sigmoid colon; B: The electrosurgical snare is opened and pressed against the colonic wall; C: The lesion and surrounding normal non-neoplastic mucosa are grasped and cut without electrocautery; D: Mucosal defect after cold snare polypectomy. Oozing immediately occurred after the procedure but stopped within a few minutes.

Medical Systems, Co., Ltd., Tokyo, Japan) or a high-definition magnifying colonoscope (CF-FH260AZI or CF-H260AZI; Olympus) with a light source (EVIS CLV-260SL; Olympus) and video processor (EVIS LUCERA CV-260SL; Olympus) were used for all patients. A transparent hood (D-201 series; Olympus) was attached to the tip of the colonoscope[14]. All patients were prepared the day before colonoscopy with a low fiber diet and preparatory medicines. Bowel preparation and sedation were administered as previously described in detail[15]. The colonoscope was first inserted into the cecum using the conventional white light mode. In cases of incomplete total colonoscopy (*e.g.*, stenosis with advanced colorectal cancer, pain or discomfort or difficult insertion caused by looping), any detected lesions were recorded and removed within the range of observation. The location, size, and macroscopic type of all of the lesions were documented according to the Paris classification[16,17]. The size was determined using biopsy forceps with a 2.2-mm outer diameter (Radial Jaw 3; Boston Scientific, Natick, MA, United States) or a 13-mm small hexagonal electrosurgical snare (Captivator; Boston Scientific). Magnifying endoscopy was performed to predict the tumor histology when available. CSP was performed using an electrosurgical snare (Captivator; Boston Scientific) without electrocautery (Figure 1, videos). The polyp was snared including normal surrounding mucosa to maintain a non-neoplastic mucosal margin around the lesion. Blood oozing was usually observed immediately after CSP. In the first 10 cases, we observed the resection sites until the oozing stopped. After these 10 cases, oozing wounds were left behind, and endoscopic hemostasis was only performed when spurting or massive bleeding occurred. If the polyps were unresectable with CSP, electrocautery was used for their removal. The removed lesions were suctioned and retrieved after CSP. The retrieved specimens were immersed in 20% formalin without pinning on a plate and examined using standard hematoxylin and eosin staining. Two experienced histopathologists who were blinded to the endoscopic findings evaluated all of the specimens according to the Japanese classification of colorectal carcinomas[18].

Statistical analysis

The procedural details were prospectively recorded in a database, and the medical records were thoroughly investigated. The collected data included patient age, gender, polyp location (*i.e.*, cecum, ascending colon, transverse colon, descending colon, sigmoid colon, or rectum), polyp size, endoscopist (expert or senior resident), morphological type (*i.e.*, protruded/sessile or superficial/elevated), histological diagnosis, incidence of immediate postpolypectomy bleeding requiring endoscopic hemostasis, incidence of delayed bleeding (clinically evident after examination) and any abdominal symptoms. Endoscopic hemostasis was usually performed for delayed postpolpectomy bleeding

Table 1 Baseline data of the participants (n = 61)

Male/female (%)	44 (72%)/17 (28%)
Median age	65
(range, yr)	(40-86)
Total detected lesion	234
Median detected lesion per patient (range)	3 (1-16)
Location	
Cecum	19 (8%)
Ascending colon	61 (26%)
Transverse colon	56 (24%)
Descending colon	33 (14%)
Sigmoid colon	52 (22%)
Rectum	13 (6%)
Morphology	
Protruded, sessile	205 (88%)
Superficial, elevated	29 (12%)
Median detected polyp size	4
(range, mm)	(1-9)
Endoscopist	
Expert	79 (34%)
Senior resident	155 (66%)
Histological type	
Not retrieved	28 (12%)
Non-neoplastic polyp	28 (12%)
Neoplastic polyp	176 (76%)
Horizontal margin (neoplastic lesion only)	
HM 0	104 (59%)
HM 1	2 (1%)
HM X	70 (40%)

HM X: Tumor involvement of the lateral margin could not be assessed; HM 0: No tumor identified at the lateral margin; HM 1: Tumor identified at the lateral margin.

when patients experienced repetitive bloody bowel discharges or became hemodynamically unstable. The study investigators assessed the symptoms in the outpatient department during follow-up appointments. Because this was a pilot feasibility study, the sample size was not estimated. The results related to non-parametric data are reported as the medians (ranges) and were compared by Wilcoxon test. The incidence (%) was used for the categorical variables, which were compared using the Yates' χ^2 test. The data analyses were conducted using the statistical package JMP 10 (SAS Institute, Cary, NC, United States).

RESULTS

Baseline data

Two-hundred patients underwent colorectal endoscopic resection (including conventional polypectomy, endoscopic mucosal resection, and endoscopic submucosal dissection) between November 2012 and March 2013. CSP was attempted in 61 patients in this study. The baseline data of the participants are shown in Table 1. The median age (range) of the patients was 65 (40-86) years. The patients comprised 44 (72%) men and 17 (28%) women. In total, 234 subcentimetric lesions were detected during colonoscopy screening. The median and maximum numbers of polyps detected per patient were 3 and 16, respectively. Thirteen (21%) patients presented with only one subcentimetric polyp, and 48 (79%) patients presented with at least two subcentimetric lesions. Two hundred five (88%) of the lesions were protruded/sessile (0-Ⅰs), and 29 (12%) were superficial/elevated (0-Ⅱa). The median (range) size of the polyps was 4 (1-9) mm. Among these lesions, 186 (80%) were diminutive (≤ 5 mm), and 48 (20%) were small (6-9 mm). One hundred and thirty-six (58%) polyps were located proximal to the splenic flexure, and 98 (42%) were situated distal to the splenic flexure. In total, 79 (34%) CSP procedures were performed by four experts, and 155 (66%) were performed by five senior residents.

Procedures for and outcomes of CSP

CSP was attempted for 234 subcentimetric polyps in 61 patients. Two (0.9%) polyps could not be resected without electrocautery and were thus removed by conventional polypectomy with electrocautery. One of these was a 2-mm protruded type inflammatory polyp that was located near a scar from a previous polypectomy in the transverse colon. The other polyp was an 8-mm protruded type adenoma located in the rectum. Thus, CSP was completed for 232 polyps in 61 patients. Immediate postpolypectomy bleeding requiring endoscopic hemostasis occurred in eight lesions (3.4%; 95%CI: 1.1%-5.8%). Although no differences were observed in sex, age, location, morphology, endoscopist or histological type between the lesions with and without immediate bleeding, the median lesion size with immediate bleeding was larger than that of the lesions without immediate bleeding (7.5 mm *vs* 4.0 mm, respectively, P = 0.002), and the incidence of immediate bleeding after CSP was greater for the small than the diminutive polyps (15% *vs* 1%, respectively, P = 0.001) (Table 2). All eight cases of immediate postpolypectomy bleeding were easily managed by endoscopic clipping alone. All patients who underwent CSP visited our outpatient department 7-35 d (median, 14 d) after the procedures. Three (5%) patients complained of minor bleeding after the procedure that stopped without any intervention. Therefore, the incidence of delayed bleeding requiring endoscopic intervention after CSP without prophylactic clipping was 0.0% (95%CI: 0.0%-1.7%). No other complications, such as perforation or postpolypectomy syndrome, were observed. Twenty-eight (12%) of the 232 lesions could not be retrieved after resection for pathological analysis. The remaining 204 (88%) polyps underwent histopathological assessments that revealed 176 (76%) neoplastic polyps (163 low-grade adenomas, 1 tubulovillous adenoma, 4 high-grade adenomas, 5 sessile serrated adenomas/polyps and three serrated adenomas) and 28 (12%) non-neoplastic lesions. The horizontal margins (HMs) of the neoplastic lesions that were removed by CSP underwent pathological assessments. One hundred four (59%) lesions were classified as HM 0 (*i.e.*, no tumor identified at the lateral margin),

Table 2 Procedure-related outcomes

	Immediate bleeding (n = 8)	Non-immediate bleeding (n = 224)	P-value
Male/female	8/0	146/78	0.10[a]
Median age	64.5	68	0.27[b]
(range, years)	(50-76)	(40-86)	
Location			0.40[a]
Proximal to splenic flexure	3 (38%)	132 (59%)	
Distal from splenic flexure	5 (62%)	92 (41%)	
Morphology			0.59[a]
Protruded, sessile (0-Is or Isp)	7 (88%)	196 (88%)	
Flat, elevated (0-IIa)	1 (12%)	28 (12%)	
Median size	7.5 (3-9)	4 (1-9)	0.002[b]
(range, mm)			
≤ 5 mm (%)	2 (22%)	183 (82%)	0.001[a]
> 6 mm (%)	6 (78%)	41 (18%)	
Endoscopist			0.54[a]
Expert	4 (50%)	74 (33%)	
Senior resident	4 (50%)	150 (67%)	
Histological type			
Not retrieved	0 (0%)	28 (12.5%)	
Non-neoplastic polyp	0 (0%)	28 (12.5%)	0.53[a]
Neoplastic polyp	8 (100%)	168 (75%)	

[a]Yates' χ^2 test; [b]Wilcoxon test.

2 (1%) were classified as HM 1 (*i.e.*, tumor identified at the lateral margin), and 70 (40%) were classified as HM X (*i.e.*, tumor involvement at the lateral margin could not be assessed).

DISCUSSION

Although CSP has been reported to minimize the risk of complications when removing subcentimetric polyps in Western countries[19,20], this technique has not yet been widely implemented in Japan. The present study represents one of the largest patient samples regarding CSP from any Japanese institution to date[21-23]. Our results indicate that CSP is a safe and effective method for resecting small colorectal lesions and suggest that CSP is also a feasible method for the removal of subcentimetric polyps in Japan.

Herein, we observed that the incidence of immediate bleeding requiring endoscopic treatment after CSP was 3.4%, which is somewhat higher than that reported in the prospective multicenter study conducted by Repici *et al*[11] (1.8%). However, only 37% of the procedures were CSPs, and the others were CFPs in the study by Repici *et al*[11]. Thus, the incidence of immediate bleeding after CSP might be different from that after CFP. In this context, it should also be mentioned that none of participating endoscopists herein had performed CSP prior to this study, and some of them might have been cautious about oozing that occurred after CSP and unnecessarily used endoscopic clips. Regardless, all cases of immediate CSP-associated bleeding were easily managed endoscopically. Caution might be required when adopting CSP, especially for small (6-9 mm) polyps because these polyps exhibited a higher incidence of immediate bleeding compared to the diminutive (≤ 5 mm) polyps. We observed no CSP cases involving delayed bleeding, perforation or postpolypectomy syndrome that required treatment in this trial, which is perhaps one of the greatest advantages of CSP.

Many Japanese patients who undergo polypectomy are currently hospitalized for a few days, and the number of hospitals that can perform polypectomy is insufficient to treat all of the patients with colorectal polyps. Considering this limited access to polypectomy in Japan and the fact that more than 90% of polyps are subcentimetric, it is possible that the implementation of CSP could increase the availability of a safe and easy procedure for the removal of subcentimetric polyps in outpatients, which could not only the decrease medical expenses associated with hospitalization but also shorten the waiting time for polyp removal in large groups of patients in Japan. Nonetheless, it should be noted that minor bleeding (that did not require endoscopic hemostasis) was observed in 3 patients (5%) after CSP. Although we rarely experience such minor bleeding after conventional polypectomy with electrocautery, this information is important when adopting CSP in daily practice.

Notably, we observed that CSP was associated with a retrieval failure of 12%. Deenadayalu and Rex[24] reported no cases of retrieval failure after CSP in their study, whereas Komeda *et al*[25] reported a retrieval failure of 19% after CSP. The relatively higher incidence of retrieval failure associated with CSP might be an issue of concern for endoscopists who do not currently apply CSP in clinical practice. However, because the indication for CSP is limited to subcentimetric polyps, which have low risks for invasive carcinomas, this aspect is perhaps not a major concern. Additionally, the "resect and discard" policy, which omits formal pathological examination, is now regarded as a promising strategy for decreasing the cost and labor associated with screening and surveillance colonoscopy[26,27]. Therefore, retrieval failure will not be a major obstacle for the generalization of CSP in the future especially if a "resect and discard" strategy is adopted. Of course, careful endoscopic assessment before CSP is essential to avoid removing and discarding invasive carcinomas. Magnifying narrow-band imaging may be a promising tool to secure the safety of both CSP (*i.e.*, by preventing the removal of subcentimetric invasive carcinomas) and the "resect and discard" strategy because pretreatment assessment using magnifying endoscopy allows for the selection of lesions with advanced histologies[28,29]. Therefore, we believe that the combination of CSP and the "resect and discard" strategy using magnifying narrow-band imaging could provide a more efficient (*i.e.*, simple, safe, and cost-effective) strategy for screening and surveillance colonoscopy.

Assessment of the HMs of tumor specimens that have been resected by CSP is also a potential concern for endoscopists who are skeptical about CSP because we cannot expect the thermal burn effect to eradicate

the neoplastic tissue around the electrosurgical snare during CSP. The incidence of HM 1 was only 1.1% in our trial, but the incidence of HM X was 40%. The main indication for CSP is subcentimetric polyps, and for such lesions, doctors do not usually pay attention to HM X statuses because they expect the thermal burn effect to occur and routinely confirm the absence of tumor residue *via* observations of the surrounding mucosa. Although Lee *et al*[30] reported a significantly higher rate of histologic eradication with CSP than with CFP in their prospective randomized controlled trial, the non-inferiority of CSP for tumor residues compared with conventional polypectomy warrants further investigation of the efficacy of CSP. In the meantime, although it is important to pay attention to the presence of tumor residue after CSP, care must be taken to remove the surrounding non-neoplastic mucosa as well as the targeted lesion when implementing CSP. Moreover, careful observation of the surrounding mucosa after CSP using magnifying endoscopy or chromoendoscopy, the washing out of minor bleeding after CSP, and strict surveillance colonoscopy are recommended until the evidence for tumor residue after CSP is considered to be adequate.

This was only a pilot study and therefore has some limitations. First, although the number of CSP procedures was larger than those of previous reports, the small sample size remains still a major limitation of this trial. A large-scale prospective study investigating the actual incidence of delayed bleeding after CSP should be conducted in the future. Second, we used a conventional electrosurgical snare in this trial because the snare developed for CSP was not available during the study period. The use of this snare may have affected the rates of removal failures or insufficient assessments of the HMs of the resected specimens. Finally, although the CSPs in this study were performed by nine endoscopists with no prior experience in CSP, different results might have been obtained if the endoscopists had experienced at least 20-30 CSPs. Specifically, the 70 (40%) HM X lesions should be carefully assessed.

In conclusion, we found that CSP is effective for removal subcentimetric polyps in the colon and rectum. CSP was safe and resulted in no cases of delayed bleeding or perforation and a 3.4% incidence of manageable immediate bleeding. Attention should be given to the potential risk of bleeding immediately after CSP, particularly for small (6-9 mm), lesions as well as to careful endoscopic diagnosis before CSP and the evaluation of tumor residue after CSP. Other areas of concern when implementing CSP might be retrieval failure and incomplete HM assessment. Nonetheless, we conclude that CSP for subcentimetric colorectal lesions is also a feasible procedure for implementation in Japan.

COMMENTS

Background

Although cold snare polypectomy (CSP) using snare resection without electrocautery has been reported to be a safe method for the removal of subcentimetric polyps, CSP is not currently widely used in Japan.

Research frontiers

CSP is a promising procedure, but there are no detailed data about immediate bleeding or the horizontal margins of the histological specimens from Japanese institutions.

Innovations and breakthroughs

The incidence of immediate bleeding after CSP for small polyps (6-9 mm) was significantly higher than that for diminutive polyps (≤ 5 mm). Histopathological diagnoses can be often insufficient because 12% of the resected lesions could not be retrieved for pathological examination, and tumor involvement in the lateral margin could not be histologically assessed in 70 (40%) lesions.

Applications

The authors need to be cautious in the performance of CSP for small (6-9 mm) polyps due to concerns about immediate bleeding and histopathological assessment.

Terminology

Cold forceps polypectomy is a simple procedure that uses endoscopic forceps without electrocautery. CSP is a procedure that uses snare resection without electrocautery.

Peer-review

This is an important manuscript.

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CASE REPORT

Duodenal polyposis secondary to portal hypertensive duodenopathy

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Abstract

Portal hypertensive duodenopathy (PHD) is a recognized, but uncommon finding of portal hypertension in cirrhotic patients. Lesions associated with PHD include erythema, erosions, ulcers, telangiectasia, exaggerated villous pattern and duodenal varices. However, duodenal polyposis as a manifestation of PHD is rare. We report a case of a 52-year-old man who underwent esophagogastroduodenoscopy and was found with multiple small duodenal polyps ranging in size from 1-8 mm. Biopsy of the representative polyps revealed polypoid fragments of duodenal mucosa with villiform hyperplasia lined by reactive duodenal/gastric foveolar epithelium and underlying lamina propria showed proliferating ectatic and congested capillaries. The features were diagnostic of polyps arising in the setting of PHD.

Key words: Cirrhosis; Portal duodenopathy; Polyposis; Portal hypertension

Core tip: Duodenal polyposis secondary to portal hypertensive duodenopathy (PHD) is rare. We report a case of PHD presenting as polyposis.

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INTRODUCTION

Portal hypertensive duodenopathy (PHD) is a recognized, but uncommon finding of portal hypertension in cirrhotic patients. While other associations of portal hypertension such as portal hypertensive gastropathy and portal hypertensive colopathy have been described and studied, data concerning duodenal alterations is relatively scarce. The lesions described in PHD include erythema, erosions, ulcers, telangiectasia, exaggerated villous pattern and duodenal varices[1]. Recently, there have been emerging reports of polyps as a manifestation of PHD[2-5]. Herein, we report a patient with duodenal polyposis secondary to portal hypertension, review the literature and describe the spectrum of histopathologic changes.

CASE REPORT

A 52-year-old man with compensated alcoholic cirrhosis presented for follow up esophagogastroduodenoscopy. Past medical history includes remote T1N0 colon cancer (status post right hemicolectomy 4 years), low-grade gastrointestinal blood loss, iron deficiency anemia, gastric antral vascular ectasia, portal hypertensive gastropathy and hypertension. He was diagnosed with cirrhosis 13 years ago when he presented with jaundice and ascites and had a recent history of hepatic encephalopathy. Abdominal U/S and magnetic resonance imaging showed a large heterogenous liver, recanalization of the umbilical vein, splenomegaly, splenorenal shunt, additional collateral vessels inferior to the left renal vein and scattered renal cysts. Endoscopy revealed numerous small 1-2 mm polyps extending from the duodenal bulb to the second portion of the duodenum. The three largest polyps included a 6 mm polyp in the mid duodenal bulb (Figures 1A and B), 8 mm polyp distal to this along the anterior wall, and 8 mm polyp in the second part of the duodenum (Figure 1C). The esophagus was normal and no esophageal varices were noted. The stomach showed diffuse "snake skin" appearance, an area of friable mucosa with a polypoid appearance and surface erosions in the antrum and pre-pyloric area with spontaneous oozing of blood. The three duodenal largest polyps were biopsied and histologic examination revealed polypoid fragments of duodenal mucosa with villiform hyperplasia lined by reactive duodenal and gastric foveolar epithelium. The underlying lamina propria showed proliferating ectatic and congested capillaries (Figures 2A and B, D and E). The findings were diagnostic of multiple portal hypertensive duodenal polyps.

DISCUSSION

Common gastrointestinal tract manifestations of portal hypertension include esophageal/gastric/anorectal varices and gastric antral vascular ectasia. In addition, less common features include portal hypertensive gastropathy[6-8], congestive jejunopathy[9,10], portal colopathy[11,12] and PHD[1,13]. PHD is commonly defined as the appearance of patchy or diffuse congestion of the duodenal mucosa associated with friability, erosions or ulcerations[14,15]. The prevalence of PHD in cirrhotic patients with portal hypertension ranges from 8.4%[16] to 51.4%[1]. The lesions described in PHD include erythema, erosions, ulcers, telangiectasia, exaggerated villous pattern and duodenal varices[1]. Coexistence of severe gastropathy and higher hepatic venous pressure gradients are more frequent in PHD patients and features of PHD have been reported to disappear after liver transplantation[16].

Duodenal polyps as a manifestation of PHD, an uncommon event, have been reported previously (summarized in Table 1). These include an ulcerated solitary 3 cm polyp in the descending duodenum[3], multiple sessile polyps in the first portion of the duodenum[2] and a recent report documenting two to "several" duodenal or jejuno-ileal polypoid lesions ranging in size from < 5 mm to 15 mm in 5 patients[4]. The spectrum of histopathologic findings in the polyps includes the presence of numerous capillaries with vascular ectasia/congestion/thrombi as well as fibrosis and smooth muscle proliferation. In addition gastric foveolar metaplasia, reactive atypia and ulceration may be seen. Devadason *et al*[5] reported "duodenal capillary hemagiomatous polyps" in 3 pediatric patients (aged 1, 4 and 6 years old). All these 3 patients presented with multiple duodenal polyps in either the 1st or 2nd portion of the duodenum in the setting of extrahepatic portal venous obstruction. Polyps were biopsied in two patients, both of which demonstrated lobular capillary proliferation within the polyps[5]. Although they favored the term "duodenal capillary hemagiomatous polyps", it appears from their description, as well as accompanying image, that the polyps they described share similar morphological features to the polyps in our case and other reported polyps in the setting of PHD.

To date, including our case, there are 11 documented reports of polyps associated with PHD (Table 1). There is no gender predilection (6 male and 5 female), the ages of patients ranges from 1 to 73 years and in the majority of cases (10/11), multiple polyps are seen. The etiology of portal hypertension in adult patients include alcoholic cirrhosis (37.5%, 3/8), hepatitis C cirrhosis (25%, 2/8) and cryptogenic cirrhosis (37.5%, 3/8), while extrahepatic portal venous obstruction accounts for all cases in the pediatric population (100%, 3/3).

Histologically, the PHD associated polyp surface- and crypt-lining epithelium may focally show cells with

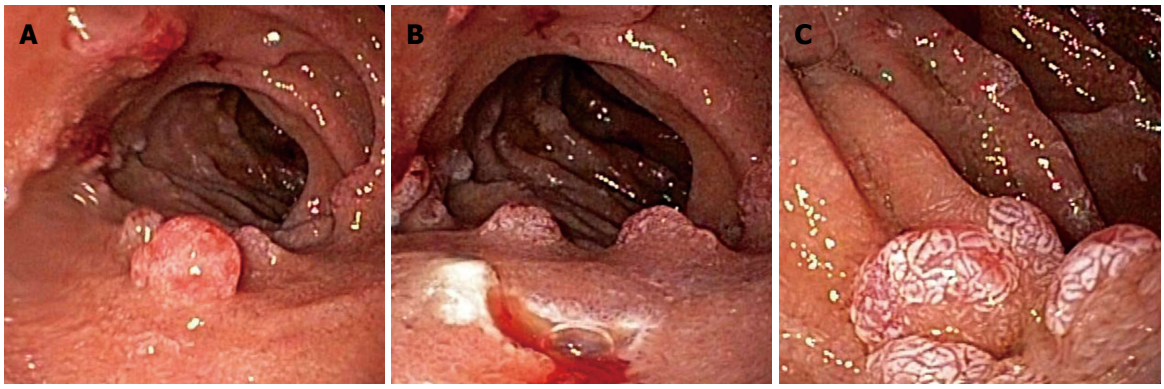

Figure 1 Duodenal polyposis under esophagogastroduodenoscopy. A 6 mm, sessile polyp was seen [prior to removal (A); immediately after removal (B)] in the mid duodenal bulb. A separate 8 mm polyp was seen along the lateral aspect of the second part of the duodenum (C).

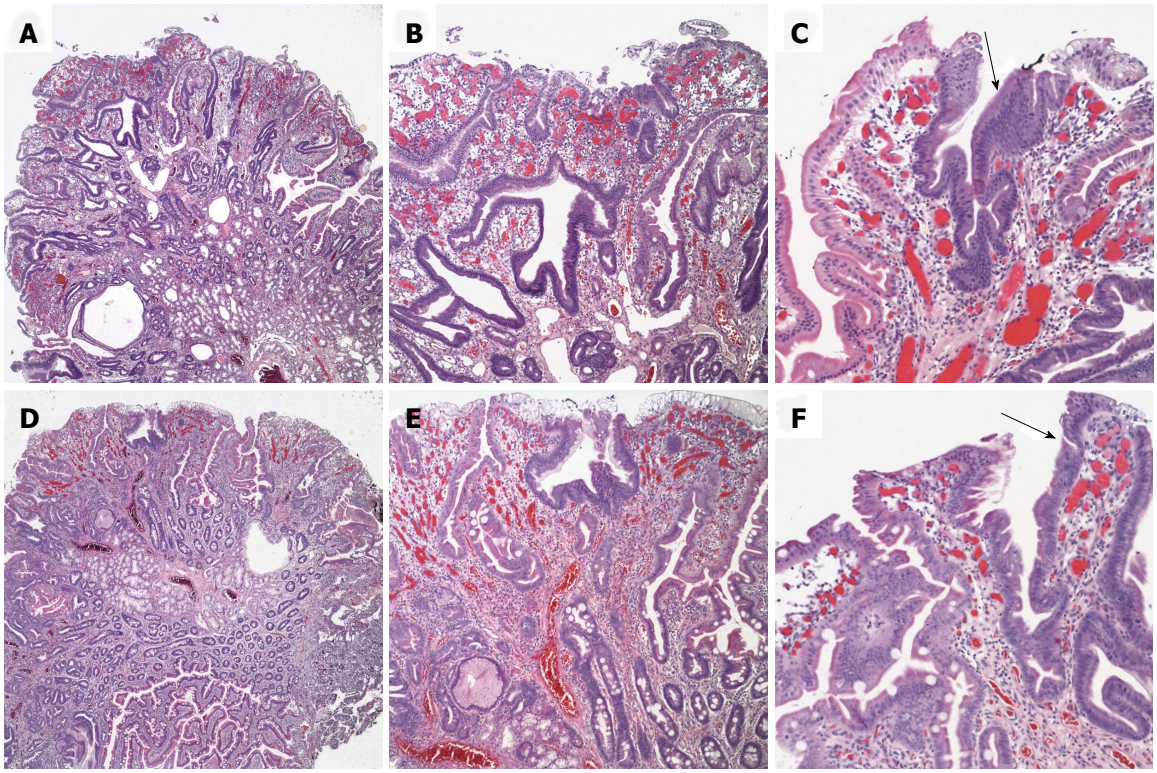

Figure 2 Histopathologic findings. Biopsies from the mid duodenal bulb polyp showed villiform hyperplasia of intestinal and gastric foveolar epithelium with numerous capillaries demonstrating congestion and vascular ectasia (A and B). Similar changes seen in the polyp from the second part of the duodenum (D-E). The epithelium lining the surface and crypts focally (arrows) showing cells with mucin depletion and slightly pencillate nuclei with hyperchromasia (C and F). Representative images of hematoxylin and eosin stained slides taken at 40 × (A, D: 4 × objective and 10 × ocular magnification), 100 × (B, E: 10 × objective and 10 × ocular magnification) and 200 × (C, F: 20 × objective and 10 × ocular magnification).

mucin depletion and contain slightly pencillate nuclei with mild hyperchromasia (Figures 2C and F). These features may mimic duodenal adenomatous polyp, a precancerous lesion in the duodenum. Our current case was previously diagnosed as "duodenal adenomas" at an outside institution. The initial diagnosis of duodenal adenoma in our patient's prior biopsy highlights the challenges that the reactive atypia may pose during histological evaluation. The differential diagnosis of polypoid lesions in the duodenum is diverse (Table 2) and we limit our discussion to more commonly seen and lesions with similar histologically features to PHD associated polyps. While duodenal adenomas with low-grade dysplasia (which are histologically similar to those seen in the colon) are typically composed of mucin depleted cells with hyperchromatic pencillate nuclei, compared to the reactive atypia seen in polyps associated with PHD, nuclei show a greater degree of enlargement, hyperchromasia and stratification. PHD polyps differ from duodenal hamartomatous polyps seen in Peutz-Jegher syndrome as polyps in the latter typically show disorganized mucosa with thick arborizing

Table 1 Reported small intestinal polyps secondary to portal hypertension (including current case)

Ref.	Age (yr)/ gender	Location(s)	Number/sizes of polyps	Pathologic findings	Etiology of portal hypertension
Current report	52/M	Duodenal bulb to second portion	Greater than 7, majority 1-2 mm, largest 8 mm	Villiform hyperplasia of reactive intestinal and gastric foveolar epithelium, proliferating ectatic and congested lamina propria vessels	Alcoholic cirrhosis
Pillai *et al*[2]	55/M	1st portion of duodenum	"multiple sessile polyps", sizes NS	Polypoid muocsa lined by small intestinal and gastric foveolar type epithelium with ectatic capillaries, fibrosis and smooth muscle proliferation of lamina propria	Alcoholic cirrhosis
Zeitoun *et al*[3]	70/M	2nd portion of duodenum	Single polyp, 3 cm	Numerous thick-walled capillaries with vascular ectasia in lamina propria	Alcoholic cirrhosis
[1]Lemmers *et al*[4]	50/F	Jueuno-ileal	"Several", > 5 mm	Lamina propria vascular dilation and thrombi without epithelial atypia	Hepatitis C cirrhosis
	73/M	Jejunal	Two "bumps", < 5 mm	Not biopsied	Cryptogenic cirrhosis
	67/M	Duodenal	"Several", 5 mm	Lamina propria vascular dilation and inflammation with epithelial atypia and ulceration	Alcoholic cirrhosis
	74/F	Antral/duodenal	"Several", 15 mm	Lamina propria vascular dilation and epithelium with crenellated glands	Hepatitis C cirrhosis
	66/F	Duodenal/jejuno-ileal	"Several", 5/< 5 mm	Not biopsied	Cryptogenic cirrhosis
Devadason *et al*[5]	6 yr/M	1st and 2nd portion of duodenum	"polyps", sizes NS	Lobular capillary proliferation in a hemagiomatous pattern in lamina propria	EHPVO
	4 yr/F	2nd portion of duodenum	"numerous", sizes NS	Lobular capillary proliferation in a hemagiomatous pattern in lamina propria	EHPVO
	1 yr/F	2nd portion of duodenum	"polyps", sizes NS	Polyp not biopsied, mucosa adjacent to polyp with ecatsia and congestion of lamina propria with smooth muscle hypertrophy	EHPVO

[1]Data obtained from Table 1 (provided by Dr. Lemmers, personal communication). EHPVO: Extrahepatic portal venous obstruction; NS: Not specified.

Table 2 Histological differential diagnosis of polyps in the duodenum

Primary	Epithelial
	Duodenal adenoma/adenocarcinoma
	Ampullary adenoma/adenocarcinoma
	Hyperplasia, heterotopias, ectopias, inflammatory
	Brunners gland hyperplasia/hamartoma
	Gastric/pancreatic hetertopia/ectopia
	IBD associated inflammatory pseudopolyps
	Inflammatory fibroid polyp
	Peutz Jegher polyps
	Juvenile polyps (JPS or PTEN associated)
	Cronkhite-Canada syndrome polyps
	Neuroendocrine/neural
	Neuroendocrine tumors
	Mixed adenocarcinoma neuroendocrine carcinoma
	Gangliocytic paranglioma
	Neurofibroma
	Ganglioneuroma
	Schwannoma
	Perinerioma
	Mesenchymal
	Gastrointestinal stromal tumor
	Leiomyoma
	Lipoma
	Hemangioma
	Granular cell tumor
	Kaposi sarcoma
	Lymphoid
	Lymphoid hyperplasia
	B and T cell lymphomas
Secondary	Metastases
Miscellaneous	Malakoplakia, mucosal prolapse related, lymphangiectasia, xanthoma

IBD: Inflammatory bowel disease.

smooth muscle fibers of the muscularis mucosa. Although there may be histologic overlap between Juvenile polyps, inflammatory bowel disease (IBD) associated inflammatory polyps and PHD associated polyps, Juvenile polyps are characterized by dilated mucin filled crypts, while IBD associated polyps tend to have prominent glandular architectural distortion in the background of IBD.

In summary, duodenal polyps secondary to PHD is uncommon. With our case, the total number of patients reported in the literature to date is 11. The finding of multiple polyps in a patient with portal hypertension should raise suspicion for this entity and careful histopathologic examination is necessary to render the appropriate diagnosis.

COMMENTS

Case characteristics

A 52-year-old man with compensated alcoholic cirrhosis presented for follow up esophagogastroduodenoscopy and multiple duodenal polyps were found.

Clinical diagnosis

Cirrhosis and duodenal polyps.

Differential diagnosis

Duodenal adenomatous polyp, polyposis syndrome, duodenal pancreatic or gastric ectopia, or other benign neoplasms.

Imaging diagnosis

Endoscopy revealed numerous small 1-2 mm polyps extending from the duodenal bulb to the second portion of the duodenum. The three largest polyps

included a 6 mm polyp in the mid duodenal bulb, 8 mm polyp distal to this along the anterior wall, and 8 mm polyp in the second part of the duodenum.

Pathological diagnosis

Portal hypertensive duodenal polyps.

Related reports

Duodenal polyps as a manifestation of portal hypertensive duodenopthy (PHD), an uncommon event, have been reported previously. The prevalence of PHD in cirrhotic patients with portal hypertension ranges from 8.4% to 51.4%. However, manifestation as multiple duodenal polyps is rare.

Term explanation

Portal hypertensive duodenal polyps are seen in patients with cirrhosis and portal hypertension. The spectrum of histopathologic findings in the polyps includes the presence of numerous capillaries with vascular ectasia/congestion/thrombi as well as fibrosis and smooth muscle proliferation. In addition gastric foveolar metaplasia, reactive atypia and ulceration may be seen.

Experiences and lessons

PHD is a recognized, but uncommon finding of portal hypertension in cirrhotic patients. Multiple duodenal polyps can be an endoscopic finding of PHD.

Peer-review

The authors reported a 52-year-old patient with cirrhosis and portal hypertension who underwent endoscopy and was found with multiple portal hypertensive duodenal polyps. This is an interesting case report and literature review. It is very well written with excellent images. The article highlights the clinical characteristics of PHD and provides information about differential diagnosis of portal hypertensive duodenal polyps.

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Contents

Biweekly Volume 7 Number 18 December 10, 2015

EDITORIAL

MINIREVIEWS

ORIGINAL ARTICLE

Observational Study

Contents

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EDITORIAL

Opinion: How to manage subepithelial lesions of the upper gastrointestinal tract?

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Abstract

Subepithelial lesions (SELs) in the upper gastrointestinal (GI) tract are relatively frequent findings in patients undergoing an upper GI endoscopy. These tumors, which are located below the epithelium and out of reach of conventional biopsy forceps, may pose a diagnostic challenge for the gastroenterologist, especially when SELs are indeterminate after endoscopy and endoscopic ultrasound (EUS). The decision to proceed with further investigation should take into consideration the size, location in the GI tract, and EUS features of SELs. Gastrointestinal stromal tumor (GIST) is an example of an SEL that has a well-recognized malignant potential. Unfortunately, EUS is not able to absolutely differentiate GISTs from other benign hypoechoic lesions from the fourth layer, such as leiomyomas. Therefore, EUS-guided fine needle aspiration (EUS-FNA) is an important tool for correct diagnosis of SELs. However, small lesions (size < 2 cm) have a poor diagnostic yield with EUS-FNA. Moreover, studies with EUS-core biopsy needles did not report higher rates of histologic and diagnostic yields when compared with EUS-FNA. The limited diagnostic yield of EUS-FNA and EUS-core biopsies of SELs has led to the development of more invasive endoscopic techniques for tissue acquisition. There are initial studies showing good results for tissue biopsy or resection of SELs with endoscopic submucosal dissection, suck-ligate-unroof-biopsy, and submucosal tunneling endoscopic resection.

Key words: Gastrointestinal neoplasm; Gastrointestinal endoscopy; Endoscopic ultrasound-guided fine needle aspiration; Endosonography; Gastrointestinal stromal tumors

Core tip: Subepithelial lesions (SELs) of the upper gastrointestinal tract include a broader differential diagnosis, which can range from non-malignant tumors to lesions with malignant potential such as gastrointestinal stromal tumors. The possibility of having a potentially malignant lesion may bring anxiety and discomfort to patients and doctors. Further investigation should be carried out for patients with high-risk lesions after risk stratification. This editorial presents the current

evidence about the diagnostic management of SELs.

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TYPES AND DIAGNOSIS OF SUBEPITHELIAL LESIONS

Expansive lesions located below the epithelium of the gastrointestinal (GI) tract pose a diagnostic challenge for the gastroenterologist. In most cases, the endoscopic aspect is not diagnostic and lesions are out of reach for conventional biopsy forceps[1].

The differential diagnosis of subepithelial lesions (SELs) encompasses non-neoplastic lesions such as varices, as well as neoplastic lesions with practically no malignant potential, including leiomyoma or lipoma. However, there are neoplastic lesions with a higher malignancy potential, for example gastrointestinal stromal tumors (GISTs) and neuroendocrine tumors[2]. Dealing with patients with SELs is a real exercise in risk stratification.

In a few circumstances, the endoscopic aspect is sufficient to define a low risk lesion, such as a pancreatic rest located at the greater curvature of the antrum, or a large and ulcerated mass like a high grade gastric GIST. The challenge is the inconspicuous SEL clearly located below the mucosa[3].

Some endoscopic maneuvers should be employed to better characterize SELs: Chromoendoscopy and conventional biopsy are useful to rule out true mucosal neoplasms that rise deep in the epithelium, such as myoblastoma and neuroendocrine tumor. Measuring the lesion is also important. Changing patient decubitus and palpation with the biopsy forceps are usually employed to differentiate a true SEL from an extrinsic compression caused by other organs. Generally, these maneuvers have low sensitivity for defining the true nature of the lesions[4].

Sometimes it is relatively easy to make a differential diagnosis using endoscopic ultrasound (EUS), for example between a small gastric carcinoid limited to the deep mucosa and a compression of the GI tract caused by other extrinsic structures, such as a giant splenic cyst. However, in many circumstances the differential diagnosis is not straightforward, even with EUS. When we are dealing with intramural lesions, the EUS image will define the layer of the GI wall where the lesion lies.

Hypoechoic SELs from the fourth layer include a broader differential diagnosis, for example GIST, leiomyoma, and schwannoma, among other mesenchymal tumors.

RISK STRATIFICATION

Thinking about risk stratification, authors looked for some EUS features predictive of SEL malignancy. Larger, heterogeneous lesions with cystic areas and irregular outer margins were proved to harbor a higher risk for malignancy. The presence of at least two of these features had an 80% sensitivity and 80% specificity for detecting malignancy[4,5].

It is noteworthy that the location of the lesion can also predict its behavior. Esophageal SELs rarely harbor any malignant potential (1%), different from gastric and duodenal lesions which have a higher risk for malignancy, in more than 20% of cases[2].

Indeed, when SELs are located in the esophagus, the risk for a potential malignant lesion, such as a GIST, is low (7%). On the other hand, when the lesion is located in the stomach or duodenum this risk is much higher, as some publications reported that subepithelial neoplasms located in the stomach and duodenum were GISTs in more than 70% and 50% of cases, respectively[6,7].

When we looked at our experience[8], we also noticed that location inside the stomach could be useful for risk stratification. From 11 lesions located in the cardia, none were GISTs, while from 17 lesions located at the gastric body, 11 (70%) were GISTs.

Our numbers were confirmed in a larger trial[9], where 144 patients with SELs were endoscopically resected by endoscopic submucosal dissection (ESD). Only 14% of the lesions located at the cardia proved to be GISTs, while 85% were leiomyomas.

EUS is an important tool for the differential diagnosis of SELs. Its features can be diagnostic of extrinsic compressions, lipomas, cysts and varices, and no further investigation is needed.

GIST: ONCOGENESIS AND HISTOLOGIC ASSESSMENT

The concept of GISTs is relatively recent, and refers to a group of mesenchymal lesions that express a transmembrane protein called KIT. This KIT protein is codified by a proto-oncogene called c-kit. In normal conditions, the stem cell factor activates two kit receptors to signal cell proliferation, by activating tyrosine kinase. In GISTs pathogenesis, oncogenic mutations in KIT result in ligand-independent activation of tyrosine kinase. C-kit mutations located at exons 11 and 9 are the most frequent ones. Around 5% of GISTs do not present c-kit mutations; in those cases mutations of the platelet-derived growth factor are seen[10].

GISTs are rare tumors that affect patients in their fifties. In the United States, the estimated incidence of GIST is 7 to 14 new cases per million in the general population[11]. The most frequent locations of GISTs are the stomach and small bowel. The colorectum and esophagus are much less frequent locations, as well as the omentum, retroperitoneum and mesenterium[11].

Histologically, most GISTs are spindle cell type (70%). In the minority of cases, they present as epithelioid (20%) or mixed (10%) types[12]. It is controversial whether the histologic type has prognostic implications. The spindle cell type is practically identical to the histology of leiomyoma. Only an immunohistochemistry panel can make a differential diagnosis between them.

Immunohistochemistry testing at least for C-kit and CD34 is recommended. It is noteworthy that up to 40% of GISTs express smooth muscle actin[12].

GISTs have been included in the 2010 TNM classification, meaning that they should be regarded as malignant neoplasms. However, not all GISTs present invasive or metastatic behavior. Small bowel GISTs present a more invasive behavior when compared to gastric ones. The overall 5-year mortality rate for small bowel GISTs reaches up to 39%, compared to 17% for gastric GISTs[13,14]. Spindle cell GISTs have a higher 5-year disease-free survival rate[15], but these results have not been replicated. In addition, mutations at exon 11 are associated with a better response to target therapy, such as oral imatinib[16].

However, the most important factors that predict GIST behavior are size and mitotic rate[17]. In fact, these features are used for the 2010 TNM classification[18]. In that classification, gastric GISTs up to 2 cm with a low mitotic rate (< 5 mitoses per 50 high-power field), are staged as Ia.

CAN EUS DIFFERENCIATE GISTS FROM OTHER MESENCHYMAL TUMORS SUCH AS LEIOMYOMAS?

The answer is no. At least up to now.

Hunt *et al*[19] found that gastric hypoechoic lesions measuring more than 4 cm, with cystic spaces and ulceration, are probably GISTs. However, most of incidental SELs do not present these features.

Another publication[20] looked at the correlation between EUS and the final histology of small (< 2 cm) resected gastric SELs. It is noteworthy that none of the 22 patients had a GIST, probably because the authors did not resect lesions from the fourth layer, where GISTs usually lie. Most lesions were pancreatic rests, and the presumptive EUS diagnosis was correct in ten of the 22 cases, less than 50%.

In our experience using EUS[8], the presence of flow detected by power Doppler and irregular outer borders had a positive likelihood ratio of 10 for GIST diagnosis. But, from 21 patients with gastric GISTs, power Doppler was positive in only five cases (25%), and irregular outer borders in seven (35%). Therefore, the absence of these features does not rule out the diagnosis of GIST, or in other words, these features have a low negative predictive value for the diagnosis of GIST.

Recently, contrast-enhanced harmonic EUS (CEH-EUS) has been employed for differential diagnosis of gastric SELs. The results were positively convincing in the study by Kannengiesser *et al*[21], but with a limited cohort (fewer than 20 patients). CEH-EUS showed hyperenhancement of gastric lesions from the fourth layer that proved to be a GIST, and no enhancement of gastric leiomyoma.

Computed tomography (CT) and magnetic resonance imaging (MRI) may also be valid tools for GIST diagnosis, especially when a cytological diagnosis is unnecessary. In fact, a meta-analysis[22] that evaluated 4534 patients with GISTs, from 46 studies, showed that CT and MRI had a pooled diagnostic yield of 73% and 91% respectively.

CAN WE PREDICT GIST BEHAVIOR BY ENDOSCOPY OR EUS?

It has been observed that high grade GISTs double in size in 9 mo, while those with benign behavior do it in 18 mo.

Onishi *et al*[23] reported that hypoechoic spots were present in 84% of gastric GISTs which grew in size, and in 52% of gastric GISTs that remained stable in size (84.2% *vs* 51.9%, $P = 0.023$). Again, this is another interesting piece of information but useful only when it is present.

A previous study[24] looked at the use of CEH-EUS to predict GIST grade. Based on enhancement of features immediately after contrast administration (the vessel phase), and a few minutes after (the perfusion phase), gastric GISTs were classified as types Ⅰ and Ⅱ. All type Ⅰ lesions revealed low grade GISTs after resection. On the other hand, all type Ⅱ lesions were high grade GISTs. Once more, this is very interesting data that needs validation in a large cohort of patients.

TISSUE IS THE ISSUE

The bite-on-bite biopsy technique has been described for tissue acquisition of hypoechoic lesions of the fourth layer. However, some reports demonstrated low diagnostic yield of around 17%[25].

EUS-guided fine needle aspiration (EUS-FNA) is the logical procedure for tissue acquisition. A study by Hoda *et al*[26] performed EUS-FNA on gastric lesions with a mean size of 28 mm. They employed a standard 22 G needle, and the diagnostic yield was 62%.

When we remember that during EUS-FNA the GI wall, including the proper muscle layer, is sampled, the first question that comes to our minds is: Is EUS-FNA diagnosis correct? Apparently, the answer is yes. Stelow *et al*[6] reported, in a study of EUS-FNA with sufficient material from 29 patients with SELs and follow-up information, that EUS-FNA diagnosis was correct in 93% of patients, and in almost all cases of mesenchymal tumors.

EUS-FNA diagnosis of SELs may be correct, but the diagnostic yield is not so high for lesions smaller than 30 mm. EUS-FNA had an overall diagnostic yield of 40% to 50% for lesions measuring up to 10 mm, and of 60%

to 70% for lesions measuring from 11 to 30 mm[26]. In conclusion, EUS-FNA has a diagnostic yield of 60% to 70%, with a lower diagnostic yield for small lesions.

The next logical development would be to employ needles that make core biopsy possible. In a prospective study[27], the authors did not find any difference between EUS-FNA and EUS-trucut core biopsy of SELs. They employed the trucut biopsy needle model that was a rigid, 19 G needle. Needle malfunction was relatively common when the scope was in a bent position.

Now, there are new models of core biopsy needle available, such as the 19 G flexible nitinol needle, and the ingenious core trap, which come in different sizes. The first results with these new needles were presented a couple of years ago. In a limited cohort of patients, the diagnostic yield reached impressive figures.

Meta-analysis of 21 studies[28] comparing standard EUS-FNA and the ProCore needle for tissue acquisition of solid masses, including pancreatic masses, lymph nodes and SELs, showed no significant difference in the rates of diagnostic yield, diagnostic accuracy or histologic yield, between the two techniques.

Another meta-analysis[29] focused on diagnostic yield, and on the complication rate of EUS-FNA and EUS-guided core needle biopsy (EUS-CNB), for patients with GIST. The authors reached the same conclusion, *i.e.*, the diagnostic yield of EUS-FNA and EUS-CNB are the same, 65%. The EUS-FNA complication rate was 0.4%, and for EUS-CNB it was 1.1%. Death is rare but may occur after EUS-FNA of GIST, so one must beware of that.

Core biopsy is necessary for GIST diagnosis, and EUS-FNA provides core biopsy in 70% of cases, especially for lesions larger than 2 cm. EUS-core biopsy needles did not prove to be better; therefore, their higher cost is not justifiable. Severe complications and mortality are rare, but may occur after EUS-FNA and EUS-core needle biopsy of SELs.

ENDOSCOPIC TECHNIQUES FOR SEL DIAGNOSIS AND RESECTION

The limited diagnostic yield of EUS-FNA and EUS-core biopsy of SELs prompted the development of more aggressive endoscopic techniques for tissue acquisition. One of them [suck-ligate-unroof-biopsy (SLUB)] consists of placing an endoloop at the base of the lesion with the aid of a cap. After unroofing, biopsies are taken. A few months later, endoscopic and EUS control confirms the complete disappearance of the tumor. Not all fourth layer SELs can be treated by SLUB. The authors suggest that the dimension should not surpass 2 cm and, very importantly, the tumor should have no exophytic growth[30].

ESD is another option for tissue acquisition and treatment of SELs located at the cardia. In a large series[31] of 143 patients, the authors obtained a 95% complete resection rate of leiomyomas and GISTs, with a 4% perforation rate, and no recurrence in 2-year follow-up.

Submucosal tunneling endoscopic resection (STER)[32] involves the creation of a submucosal tunnel in the same fashion as the peroral endoscopic myotomy procedure. The tumor is then resected, and the mucosal incision site is closed, which guarantees the safety of the procedure, even in cases of perforation.

The first published series[32] includes fewer than 20 patients. The majority of them had SELs in the esophagus and cardia. In this paper, only three cases with gastric lesions were treated by STER. It should be remembered that most esophageal SELs are benign leiomyomas.

A word of caution is advised for those interested in these innovative procedures such as SLUB and STER. EUS is absolutely necessary to select lesions suitable for these techniques. In this scenario, a CT scan often demonstrates a smooth outer contour of gastric SELs. However, in the operative field, it is clear that the lesion may project to the serosal surface, making SLUB and STER very dangerous.

CONCLUSION

In conclusion, SELs that are indeterminate after endoscopy and EUS examinations may have a challenging diagnosis. Otherwise, as mentioned before, if the aspect is typical of a neuroendocrine tumor, a pancreatic rest, lipoma, cyst, or varices, management poses no major problems. If EUS demonstrates small hypoechoic tumors of the second and third layers, endoscopic resection is possible and quite safe. For small hyperechoic lesions of the second and third layers, endoscopic resection is a valid alternative. For larger lesions, a tissue diagnosis is necessary. For larger lesions of the fourth hypoechoic layer, EUS-FNA and core biopsy are safe and have a good diagnostic yield. Some authors advocate referring the patient directly for surgery, if the lesion is located in the stomach or in the duodenum. SLUB, STER, and ESD are techniques under investigation for SELs.

Small hypoechoic lesions of the fourth layer should be simply followed (every six months for one year, and then yearly or biannually), especially if EUS features indicate a benign lesion. Oh the other hand, if EUS features are worrisome, EUS-FNA or core biopsy should be tried, but they have a very low diagnostic yield in small lesions. Surgery is a reasonable option especially if the lesion is located in the stomach or duodenum. Again, ESD, SLUB, and STER are under investigation.

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Advanced endoscopic imaging of indeterminate biliary strictures

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Abstract

Endoscopic evaluation of indeterminate biliary strictures (IDBSs) has evolved considerably since the development of flexible fiberoptic endoscopes over 50 years ago. Endoscopic retrograde cholangiography pancreatography (ERCP) was introduced nearly a decade later and has since become the mainstay of therapy for relieving obstruction of the biliary tract. However, longstanding methods of ERCP-guided tissue acquisition (*i.e.*, biliary brushings for cytology and intraductal forceps biopsy for histology) have demonstrated disappointing performance characteristics in distinguishing malignant from benign etiologies of IDBSs. The limitations of these methods have thus helped drive the search for novel techniques to enhance the evaluation of IDBSs and thereby improve diagnosis and clinical care. These modalities include, but are not limited to, endoscopic ultrasound, intraductal ultrasound, cholangioscopy, confocal endomicroscopy, and optical coherence tomography. In this review, we discuss established and emerging options in the evaluation of IDBSs.

Key words: Cholangiocarcinoma; Bile duct diseases; Cholangiopathies; Gastrointestinal endoscopy; Pancreatic adenocarcinoma

Core tip: Indeterminate biliary strictures (IDBSs) remain a considerable challenge for endoscopists, clinicians, surgeons, and other medical professionals as well as patients. The limitations of current technologies have helped drive the search for novel techniques aimed to enhance the evaluation of IDBSs and thus improve diagnosis and clinical care. Here we review existing and emerging techniques and provide a synopsis of current understanding of their strengths, limitations, and role in the evaluation of IDBSs.

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INTRODUCTION

A substantial proportion of biliary strictures cannot be classified as benign or malignant on the basis of non-invasive imaging, endoscopic retrograde cholangiopancreatography (ERCP), and/or routine tissue sampling methods (*i.e.,* biliary brushing, intraductal forceps biopsy)[1]. Although the addition of fluorescence *in situ* hybridization (FISH) to conventional biliary cytology has been useful in assessing strictures with a higher suspicion for malignancy which may benefit from closer follow-up, sensitivity remains low. As a result, these "indeterminate biliary strictures" (IDBSs) remain a clinical challenge, especially when considering the resulting delayed diagnosis, deferred implementation of care, economic impact from repeated evaluations, and resulting angst among patients, clinicians, and endoscopists.

IDBSs may arise *de novo* or in patients with known chronic biliary disease. They typically manifest with (abrupt onset or slowly progressive) jaundice, pruritus, right upper quadrant pain, and/or cholangitis. IDBSs may also be incidentally discovered, often following abdominal computed tomography or magnetic resonance imaging performed for other indications. The differential diagnosis of IDBSs is broad (Table 1), and determination of the underlying etiology and pathobiology is often challenging. Endoscopic evaluation of IDBSs has traditionally consisted of ERCP, but several other ancillary techniques have been developed to help address this common diagnostic challenge.

In this article, we review these ancillary techniques, providing our current understanding of their strengths, limitations, and role in the evaluation of IDBSs.

ERCP

ERCP provides fluoroscopic images of the biliary tree and provides the primary portal for diagnosis and intervention. Cholangiographic features suggestive of a malignant stricture include length (> 14 mm), irregularity, abrupt shelf-like borders, presence of intraductal polypoid or nodular areas, and the presence of simultaneous common bile duct (CBD) and pancreatic duct dilation (*i.e.,* double duct sign)[2,3]. Efforts to improve the sensitivity of cholangiography have led to methods for tissue acquisition; however, conventional methods such as biliary brush cytology, intraductal biopsy, and fine needle aspiration (FNA) have yielded disappointingly low sensitivity for detecting malignancy. For example, a recent review of the literature that identified 16 studies reported an overall biliary brush cytology sensitivity of 42% with a negative predictive value (NPV) of 58%[4]. The poor sensitivity was attributed to sampling error, inadequate specimen (*e.g.,* due to desmoplastic reaction or biliary fibrosis), and/or difficult cytopathologic distinction of subtle differences between malignant and nonmalignant cells[5,6]. Biliary cytopathology interpretation is often challenging, even within high-volume centers. A recent meta-analysis by Navaneethan *et al*[7] compared the effectiveness of brush cytology and intraductal biopsy for evaluating biliary strictures; nine studies were included, and the pooled sensitivity and specificity for brushings was 45% and 99%, respectively, compared to 48% and 99% for intraductal biopsies, respectively. When the two modalities were combined, there was some incremental yield, with sensitivity improving to 59%[7]. Methods tested to potentially further increase the diagnostic sensitivity have included use of longer brush length, initial stricture dilation, and repeated brushing, with repeat brushing appearing to be most effective, albeit still with suboptimal results[8,9]. Intraductal FNA has also been associated with disappointing results, as data from five series (220 patients) demonstrated a sensitivity of 34%, in part perhaps due to technical challenges with performing intraductal FNA[10]. The suboptimal diagnostic performance of conventional tissue sampling techniques has provided the impetus for developing advanced cytologic methods such as FISH, digital image analysis (DIA), and flow cytometry, which are described further in a subsequent section.

A "dominant stricture" is a subtype of IDBS that arises in the setting of underlying primary sclerosing cholangitis (PSC) or other fibrosing cholangiopathies and may be loosely defined as a CBD stenosis of $\leqslant$ 1.5 mm or hepatic duct stenosis $\leqslant$ 1 mm in diameter[11]. Accurately detecting malignancy in the setting of PSC is especially critical given the 1560-fold increased risk of developing cholangiocarcinoma (CCA) in this cohort compared to the general population[12]. However, this imposes an even greater diagnostic challenge, as ERCP-guided approaches to tissue acquisition have performed poorly in this disease, with sensitivity ranging from 18%-40%[11,13,14]. Reasons for low sensitivity include but are not limited to periductal (or submucosal) as opposed to radial growth of some CCAs, desmoplastic reaction, and inadequate access of endoscopic devices and sampling under indirect visualization (chiefly due to the stenotic nature of the disease)[15]. Adjunctive modalities for endoscopic evaluation of IDBSs in this high-risk subset of patients may provide improved diagnostic value and are discussed below in their respective sections.

ADVANCED CYTOLOGIC TECHNIQUES FOR ERCP-ACQUIRED BILIARY BRUSHING SPECIMENS

Fluorescence in situ hybridization

FISH is a cytogenic technique that employs fluorescently labeled DNA probes to chromosomal loci of interest

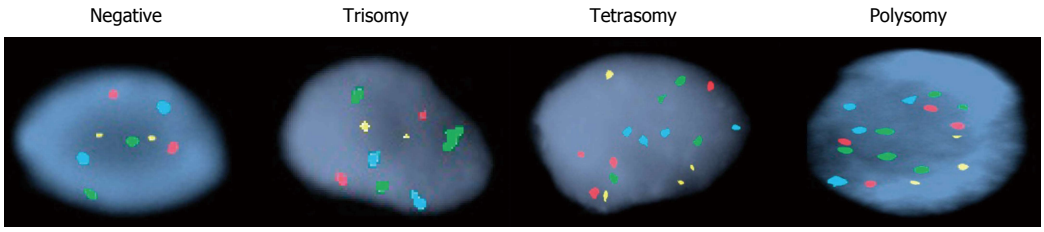

Figure 1 Representative fluorescence *in situ* hybridization microscopic image. Shown above are individual cells from biliary brushings showing distinct fluorescence *in situ* hybridization (FISH) results (arranged from lowest to highest risk of malignancy) using centromere enumeration probes (CEPs) to chromosomes 3 (red), 7 (green), 17 (aqua) and the 9p21 locus (gold). Potential FISH results include negative (two copies of each probe), trisomy 7 (≥ 10 cells with ≥ 3 CEP 7 signals and ≤ 2 signals for the other probes), tetrasomy (≥ 10 cells with four signals for all four probes), and polysomy (≥ 5 cells with ≥ 3 signals for ≥ 2 of the four probes).

Table 1 Potential etiologies of indeterminate biliary stricture

Benign
Primary sclerosing cholangitis
IgG4-associated cholangiopathy
Postoperative stricture (anastomotic, ischemic, cholecystectomy-related)
Ischemia (*e.g.*, hepatic artery thrombosis)
Infections (HIV cholangiopathy, parasites)
Pancreatitis (acute, chronic, autoimmune)
Choledocholithiasis
Mirizzi syndrome
Eosinophilic cholangitis
Vasculitis
Radiation
Portal biliopathy
Malignant
Pancreatic adenocarcinoma
Cholangiocarcinoma
Hepatocellular carcinoma
Lymphoma
Metastatic adenocarcinoma (*e.g.*, compressive lymphadenopathy)

HIV: Human immunodeficiency virus.

and thereby reveals losses or gains in these specific loci (*i.e.,* aneuploidy). Fluorescence microscopy is then used to quantify cells containing nuclei with abnormal probe signal numbers (Figure 1). The presence of ≥ 5 such cells showing gains of ≥ 2 of the (currently four) probes on FISH analysis, *i.e.,* polysomy, has been found to provide improved sensitivity compared to cytology while maintaining comparable specificity[16-20]. Recent studies have reported that incorporating 9p21 (*i.e.,* CDKN2A locus, critical in cell cycle progression and senescence[21,22]) deletion into the diagnostic criteria further improves the sensitivity to 76%-89%[23,24]. In individuals with PSC, detection of polysomy during subsequent ERCPs (*i.e.,* serial polysomy) or detection of polysomy in multiple segments of the biliary tree (*i.e.,* multifocal polysomy) appears to denote even greater risk of CCA[25,26].

DIA

DIA incorporates digital conversion and computer analysis to quantify nuclear DNA content and evaluate nuclear features; when compared to conventional cytology, it has been shown to have a higher sensitivity (39% *vs* 18%) but at the expense of lower specificity (77% *vs* 98%)[27]. In two studies comparing DIA with FISH, DIA appeared to have slightly lower sensitivity (38%-43% *vs* 44%-45%) and specificity (92%-95% *vs* 98%-100%). In one of the studies, routine cytology had a sensitivity of 15% and specificity of 100%, whereas in the other, DIA and FISH were performed only after negative cytology and histology[16,18]. Moreover, multivariable analysis of advanced cytologic methods in the evaluation of IDBSs showed FISH polysomy to be an independent predictor of malignancy, whereas DIA was not[19]. Despite the somewhat enhanced diagnostic sensitivity, the associated decrement in specificity has eliminated the use of DIA in many centers.

Flow cytometry

Flow cytometry relies on the detection of hyperploidy to identify malignant cells; it has similar sensitivity to routine cytology (42%) but has inferior specificity (77% *vs* 92%)[28]. It is not routinely used in the clinical evaluation of IDBSs.

ENDOSCOPIC ULTRASOUND

Endoscopic ultrasound (EUS) is increasingly being utilized in the evaluation of biliary strictures since reports of its first application in the mid-1980s[29,30]. Most of the hepatobiliary system can be examined with curvilinear echoendoscopy (EUS) from the gastric antrum (for visualization of the gallbladder), duodenal bulb (for visualization of the mid-CBD up to the confluence of the left and right hepatic ducts), or second portion of the duodenum (for visualization of the periampullary region)[31,32]. In addition, EUS provides other key information, including lymph node (Figure 2A), portal vein, and hepatic artery status for staging and through the detection of malignant ascites, omental deposits, and hepatic metastasis. Furthermore, EUS-guided FNA (Figure 2B) offers a minimally-invasive means for diagnostic tissue sampling (Table 2).

EUS with or without FNA may be useful in distinguishing malignant from benign biliary strictures. EUS findings of a pancreatic head mass (causing a biliary stricture secondary to extrinsic compression), an irregular outer edge of the bile duct wall, or bile duct wall thickness > 3 mm have been associated with malignancy when

Table 2 Comparison of advanced endoscopic imaging modalities

	Advantages	Disadvantages
ERCP	Widely available	Procedural risks
	Workhorse technique with numerous accessories	Fluoroscopic (and endoscopic) images only
	Facilitates other diagnostic modalities (*e.g.*, biliary brushing, biopsy, endomicroscopy) as well as therapy	Low sensitivity of conventional cytology and intraductal biopsies
EUS	Provides staging information	Limited views of the intrahepatic biliary tree (and non-visualization of the right intrahepatic ductal system)
	Permits FNA	Generally nondiagnostic in and of itself without FNA
	Can facilitate difficult biliary cannulation	Risk of tumor seeding if FNA primary tumor
IDUS	Can help direct ERCP-guided tissue acquisition	Limited depth of imaging
		Infrequently used in routine practice
Cholangioscopy	Excellent visualization of the biliary mucosa (with digital cholangioscopes)	High cost (disposable system $2000 per case)
	May improve sensitivity, specificity, and overall accuracy compared to ERCP alone	Likely higher rates of pancreatitis, cholangitis, and perforation compared to ERCP alone
		Time-consuming
		Not widely available
CLE	Excellent sensitivity and negative predictive value	Marginal interobserver agreement
	Provides imaging at a cellular and sub-cellular level (lateral resolution of 3.5 μm)	Contact imaging of a very limited regional surface
		Time-consuming
		Not widely available
OCT	High resolution	Suboptimal sensitivity
	Improved sensitivity compared to ERCP-guided tissue acquisition	Resolution not as high as CLE
	Highly specific	Not widely available
	Permits larger surfaces areas to be examined compared to CLE	Not well-validated

ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound; IDUS: Intraductal ultrasound; CLE: Confocal laser endomicroscopy; OCT: Optical coherence tomography; FNA: Fine needle aspiration.

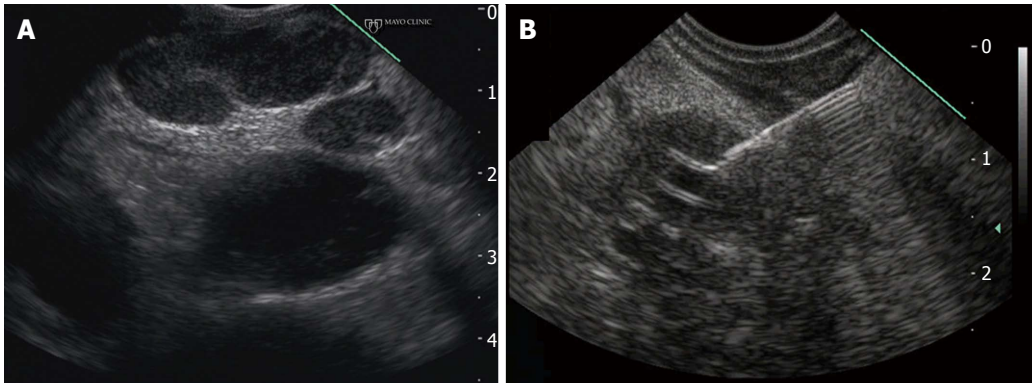

Figure 2 Endoscopic ultrasonographic findings in a patient found to have locally-advanced cholangiocarcinoma. A: Malignant lymphadenopathy; B: Endoscopic ultrasound-guided fine needle aspiration of primary cholangiocarcinoma.

evaluating IDBSs[33]. In a meta-analysis of nine studies including 555 patients, EUS without FNA was found to diagnose a malignant biliary stricture with a sensitivity and specificity of 78% and 84%, respectively[34]. The addition of FNA provides even more encouraging results, as a separate meta-analysis of 9 studies including 284 patients undergoing EUS-FNA demonstrated a sensitivity and specificity of 84% and 100%, respectively[35]. Many of these studies were performed following unsuccessful ERCP diagnosis, thus suggesting the value of EUS-FNA even among this more difficult-to-diagnose cohort.

A factor that appears to influence the sensitivity of EUS-FNA is the location of the stricture: Proximal (intrahepatic or hilar) *vs* distal (extrahepatic). In one study, the sensitivity for distal CCA was significantly higher than that for proximal CCA (81% *vs* 59%)[36]. This is perhaps explained by the greater ease of imaging and sampling of distal lesions as compared to proximal, which may be an important consideration when comparing EUS-FNA to ERCP data. Rösch *et al*[37] found EUS-FNA to be inferior to ERCP in patients with hilar biliary tumors (25% *vs* 75%) but superior for distal malignant strictures (60% *vs* 38%). Another variable that may impact performance of EUS-FNA is the presence of a bile duct stent, which results in acoustic shadowing and may occasionally interfere with sonographic imaging and FNA[38]. However, published data have not found the presence of plastic bile duct stents to lower the yield of EUS-FNA in the evaluation of IDBSs or suspected CCA[39].

A major limitation of EUS-FNA remains the concern for potential seeding of malignant cells along the needle track. This is less problematic for pancreatic head

lesions, as the path of trans-duodenal sampling would be resected during potential subsequent pancreatoduodenectomy. The concern is predominantly for proximal bile duct lesions, which require traversal of the hepatoduodenal ligament portion of the lesser omentum, which may not be resected during potential subsequent surgical intervention. In a series of 191 patients with hilar CCA receiving neoadjuvant chemoradiation followed by liver transplantation, 16 underwent transperitoneal FNA, and of the 6 (38%) that were positive for malignancy, 5 (86%) were later found to have peritoneal metastasis at operative staging *vs* 14/175 (8%) who did not undergo transperitoneal biopsy ($P < 0.01$)[40]. While nearly all patients in this study underwent FNA *via* a percutaneous route, the same concerns exists for EUS-guided FNA. Due to the potential for needle tract seeding, EUS-FNA of a primary bile duct tumor is considered a contraindication to liver transplantation; however, a recent retrospective study showed that preoperative EUS-FNA in patients with CCA did not affect overall or progression-free survival[41]. Until additional studies have further explored this area of uncertainty, biliary specimens to rule out CCA should be acquired intraductally rather than transmurally (*e.g.,* percutaneous or trans-duodenal) if liver transplantation is a consideration.

INTRADUCTAL ULTRASOUND

Intraductal ultrasound (IDUS) employs a thin (2.0-3.1 mm), high frequency (12-30 MHz) wire-guided radial ultrasound probe that is passed through the working channel of a duodenoscope and into the pancreatobiliary system during ERCP. With a radial penetration of 2 cm, IDUS allows for high-resolution characterization of IDBSs. Two to three mural layers are visualized during IDUS: (1) an inner hypoechoic layer representing mucosa, muscularis propria, and the fibrous layer of serosa; (2) an outer hyperechoic layer representing subserosal adipose tissue and serosa; and (3) sometimes an interface layer between bile and the inner hypoechoic layer[42].

IDUS features that have been associated with malignant rather than benign biliary strictures include sonographic disruption of the choledochal wall layers, wall thickening or irregularity, a hypoechoic mass with irregular margins, sessile tumor, infiltration of adjacent tissue or vasculature, or the presence of enlarged lymph nodes[43-45].

The published literature suggests that IDUS, although not often used in routine clinical practice, can be a useful ancillary technique in the evaluation of IDBSs. A retrospective review by Meister *et al*[46] of patients undergoing ERCP with IDUS demonstrated sensitivity as well as specificity of 98%, and a meta-analysis of 5 other studies found that IDUS accuracy for malignancy ranged from 84%-95%. Studies have also demonstrated that adding IDUS to ERCP-guided tissue acquisition improved sensitivity from 41%-68% to 90%-93%[47-49]. Domagk *et al*[50] found a combination of ERCP and IDUS to correctly diagnose malignancy in 88% of patients *vs* 76% and 58% of patients by ERCP alone and MRCP, respectively. Compared to EUS, IDUS has been shown to have greater sensitivity (91% *vs* 76%) and accuracy (89% *vs* 76%) in differentiating a malignant from a benign stricture[51]. IDUS was also found to have superior sensitivity (88% *vs* 63%) and specificity (91% *vs* 53%) in patients with PSC compared to ERCP alone[52].

IDUS, in a single experience reported cancer staging of T1, T2, T3/T4, N0 and N1 to be 84%, 73%, 71%, 69% and 69% accurate, respectively[46]. These results are intriguing; the low accuracy with N staging may be attributable to the limited depth of ultrasonic penetration, which limits IDUS largely to characterizing the mural features of the IDBS[51].

CHOLANGIOSCOPY

Cholangioscopy involves the use of a small-caliber, flexible endoscope to directly inspect the biliary epithelium and facilitate targeted sampling. The cholangioscope (daughter scope) is typically passed either through the working channel of a therapeutic (mother) scope during ERCP (Figure 3) or *via* direct peroral cholangioscopy following endoscopic papillotomy and percutaneous transhepatic cholangioscopy. Early cholangioscopy typically required two skilled endoscopists; this has since evolved to a single endoscopist effort with as-needed nurse assistance. In the last decade, a single-operator cholangioscopy system (SpyGlass Direct Visualization System, Boston Scientific Endoscopy, Marlboro, MA) with capability for 4-way tip deflection, a channel for insertion of a reusable fiberoptic probe, and irrigation and working channels, has been introduced. This system was severely hampered by poor image quality, but recent modifications, including the use of a video chip, has markedly improved image quality. Other cholangioscope options also exist, as alluded to above, but are currently not utilized clinically in the United States[53,54].

Cholangioscopy can help distinguish malignant from benign strictures, particularly *via* examination of epithelial vascular pattern (*e.g.,* irregularly dilated tortuous vessels, *i.e.,* "tumor vessels"), which is 100% specific and 96% sensitive when combined with targeted biopsies[55,56]. The presence of nodules, ulceration, or papillary or villous mucosal projections also suggest malignancy and warrant targeted biopsies[57].

Studies examining direct peroral or percutaneous cholangioscopy with or without biliary mucosal biopsies have demonstrated a sensitivity of 77%-100% and specificity of 79%-100%, with tissue adequacy achieved in 82%-97% of patients[58-63]. Addition of cholangioscopy to ERCP-guided tissue sampling enhances sensitivity for the diagnosis of biliary malignancy. For example, Fukuda *et al*[58] reported the sensitivity and accuracy of ERCP guided cytology and/or forceps biopsy improved from 58% and 78% to 100% and 93%, respectively. In a study by Draganov *et al*[63], sensitivity and accuracy of cytology, forceps biopsy, and cholangioscopy-guided mini-

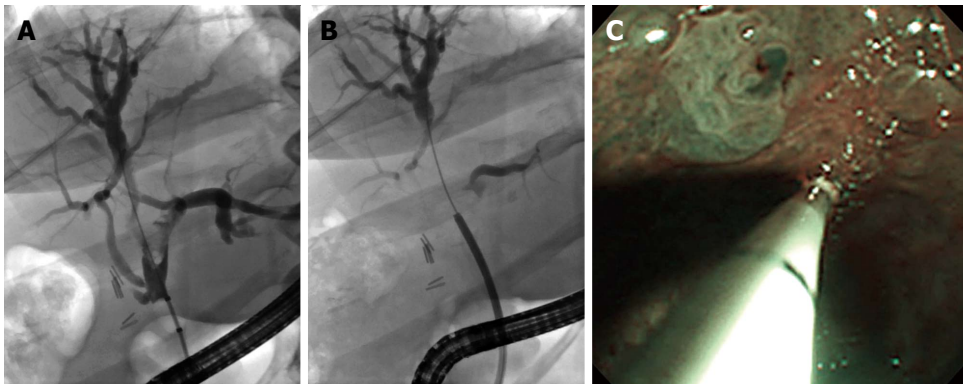

Figure 3 Passage of a SypGlass digital cholangioscope through a therapeutic duodenoscope to better evaluate hilar strictures and filling defects. A: Hilar (primarily right anterior hepatic duct) stricture and filling defects seen during endoscopic retrograde cholangiography pancreatography; B: SypGlass cholangioscope being passed through the working channel of therapeutic duodenoscope to better assess biliary stricturing and filling defects; C: SpyGlass cholangioscopy with narrow band imaging revealing villiform biliary mucosal changes; targeted biopsies were obtained and revealed low grade dysplasia concerning for early cholangiocarcinoma.

forceps biopsy were as follows: 5.8% and 39%, 29% and 54%, and 77% and 85%, respectively; mini-forceps biopsy was significantly more sensitive and accurate than cytology (P = 0.0001) or forceps biopsy (P = 0.0215) alone. Chen *et al*[64] reported the sensitivity and specificity of ERCP, cholangioscopy, and cholangioscopy-directed tissue biopsies to be 51% and 54%, 78% and 82%, and 49% and 98%, respectively, thus demonstrating much greater sensitivity and specificity for cholangioscopy with or without biopsy compared to ERCP alone.

The benefit of cholangioscopy over ERCP in patients with PSC and for distinguishing malignant from benign dominant strictures has also been demonstrated. In a study of 53 patients with PSC and dominant stricture, Tischendorf *et al*[52] used cholangioscopic findings of a polypoid or villous mass or irregularly shaped ulcer to classify malignancy before confirmation with standard tissue acquisition. This cholangioscopic finding provided greater sensitivity (92% *vs* 66%) and specificity (93% *vs* 51%) with a better NPV (97% *vs* 84%) than ERCP alone[52]. Cholangioscopy in the setting of PSC is often severely hampered by the number and severity of biliary stenosis. Cholangioscopy is performed predominantly under water immersion; alternatively, carbon dioxide gas insufflation can be used (predominantly during direct peroral cholangioscopy) and provides a distinctly different appearance to the biliary mucosa. Differences between the two imaging approaches may have individual value, *e.g.,* interpreting subtle surface mucosal change *vs* mucosal surface vascular pattern changes.

Video chip-based cholangioscopes are also equipped with narrow band imaging (NBI) (Figure 3C). NBI is based on the observation that the depth of light penetration depends on wavelength; the longer the wavelength, the deeper the penetration. Standard color video chips provide images based on sequential red-green- and blue illumination. The image is passed directly through selective band filters which highlight the red and blue bands. Blue light penetrates only superficially, whereas red light penetrates into deeper layers. The selective color imaging enhancement highlights mucosal surface detail and more so, mucosal vascular patterns[65-67]. An initial feasibility study involving 21 patients with biliary lesions found visualization of 57% of lesions to be "excellent" using NBI *vs* 9.5% using conventional white-light imaging[68]. A recent, small series of patients with PSC also led to the conclusion that NBI allowed better determination of tumor margins and increased detection of suspicious lesions compared to white-light imaging; the authors could not demonstrate an improved dysplasia detection rate, but this may have been consequent to methodological issues[69].

Relatively few studies have compared the diagnostic yield of cholangioscopy *vs* EUS. In one retrospective series of 66 patients undergoing evaluation of IDBSs with cholangioscopy combined with EUS, sensitivity and specificity for combined modalities was greater than for either modality alone[70]. In another study, 39 patients with negative brush cytology underwent EUS-FNA first and only proceeded to cholangioscopy if EUS was negative; EUS-FNA was diagnostic in 23 patients (58%), and the remainder of the patients required cholangioscopy, thus leading the authors to conclude that cholangioscopy could be reserved for cases where EUS-FNA is nondiagnostic[71].

Potential adverse events of cholangioscopy include pancreatitis, cholangitis, perforation, hemobilia, and sphincterotomy bleeding. A recent retrospective study found that patients undergoing ERCP with cholangioscopy had significantly higher rates of pancreatitis (2.2% *vs* 1.3%), cholangitis (1.0% *vs* 0.2%), and perforation (1.0% *vs* 0.3%) than ERCP alone[72]. However, multivariable analysis did not find cholangioscopy to be associated with an increased rate of adverse events compared to ERCP[73].

CONFOCAL LASER ENDOMICROSCOPY

Confocal laser endomicroscopy (CLE) is an emerging imaging modality that permits high-resolution, *in vivo* assessment of the biliary epithelium. It provides real-time contact imaging at a cellular and sub-cellular

level, offering a lateral resolution of 3.5 μm, optical slice thickness of 30 μm, and optical penetration of 40-70 μm. CLE is based upon the principle of illuminating a tissue with a low-power laser and then detecting reflected fluorescent light. The laser is focused at a specific depth, and only light which is reflected back from that plane is refocused and able to pass through the pinhole confocal aperture; the term "confocal" hence refers to the fact that the reflected light is refocused onto the detection system by the same lens through which the laser light was initially emitted. As a result, scattered light from above and below the plane of interest is not detected, thereby increasing spatial resolution. A focused, scanning light source (*i.e.,* laser) and processor then generate reconstructed grayscale images of the target area, enabling epithelial and subepithelial visualization. Notably, CLE requires administration of intravenous or topical contrast (typically fluorescein) to highlight tissue features and better differentiate normal architecture or inflammatory changes from neoplastic tissue.

A CLE imaging probe (pCLE) can be passed through various ERCP catheters or through the working channel of a cholangioscope. In the first study of pCLE for the evaluation of IDBSs, Meining *et al*[74] reported that the visualization of irregular, dilated ("angiogenic") vessels predicted malignancy with a sensitivity of 83% (compared to 50% for standard histopathology), specificity of 88%, and accuracy of 86% among 14 patients. A subsequent study with 37 patients revealed similar findings[75]. In an effort to more uniformly identify pCLE imaging findings associated with malignancy, a standardized classification system (*i.e.,* Miami classification) was proposed consisting of: (1) the presence of thick, white bands (> 20 pm); (2) thick dark bands (> 40 μm); (3) dark clumps; (4) epithelial structures; and (5) fluorescein leakage[76]. Suggested criteria for benign strictures were: (1) thin, dark (branching) bands; and (2) thin, white bands. In a blinded consensus review that validated this classification schema, combining two or more of the criteria suggestive for malignancy (except fluorescein leakage) provided a sensitivity, specificity, positive predictive value (PPV), and NPV of 97%, 33%, 80%, and 80%, respectively, compared with 48%, 100%, 100%, and 41% for standard tissue acquisition[77]. Interobserver variability was moderate for most of the criteria. A prospective, multicenter study assessing the role of pCLE in the evaluation of 89 patients with IDBSs reported a sensitivity, specificity, PPV, and NPV of 98%, 67%, 71%, and 97% for the detection of malignancy, respectively, compared with 45%, 100%, 100%, and 69% for index pathology[78]. Moreover, when combined with ERCP, pCLE was significantly more accurate than ERCP with tissue acquisition (90% *vs* 73%). Among the subset of patients with PSC, a small retrospective study found that pCLE detected malignancy with a sensitivity, specificity, PPV, and NPV of 100%, 61%, 22.2% and 100%, respectively, compared to 0%, 94.4%, 0% and 89% with standard tissue sampling[79]. Given its high sensitivity and NPV, pCLE may ideally be used to exclude malignancy in this high-risk population. The technique is limited by the need for point contact and by movement. Additional study is needed to optimize image interpretation and to determine the cost benefit.

A limitation of the Miami classification is the suboptimal interobserver agreement. In contrast to the initially reported moderate interobserver variability with most criteria, a subsequent study among 6 experienced endoscopists from 5 institutions reviewed 25 de-identified pCLE video clips of IDBSs and found interobserver agreement for individual criteria to range from poor to fair and for final diagnosis to be slight[80]. Further training and standardization is needed to improve interobserver reliability, as may be expected with most evolving techniques[81].

In an effort to improve the low specificity of pCLE, which has been attributed to inflammatory changes (*e.g.,* chronic inflammation, stent-related changes, previous endoscopic procedures), descriptive criteria (*i.e.,* Paris classification) have recently been proposed[82]. These criteria aim to distinguish benign inflammatory strictures by assessing for vascular congestion, dark glandular patterns, increased interglandular space, and thickened reticular structures, and reportedly have increased the specificity from 64% to 76%[82]. A prospective, multicenter study evaluating 112 patients with IDBSs incorporating the Paris classification found pCLE to be 89% sensitive, 71% specific, and 82% accurate compared with 56%, 100% and 72% with standard tissue sampling alone[83].

OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) is analogous to ultrasound but relies on low-intensity infrared light (700 to 1500 nm wavelength range) instead of sound to generate high-resolution, cross-sectional tissue imaging. The delay in time of light back-scattered by the various tissues is measured using a technique known as low coherence interferometry, which has a depth of penetration of 1-3 mm and lateral and axial resolution down to 10 μm. This technology provides much greater spatial resolution than IDUS and, unlike endomicroscopy, does not require contrast administration. OCT achieves visualization of layer architecture similar to histologic sections[84,85]. In doing so, OCT allows visualization of microscopic structures such as blood vessels, lymphoid aggregates, crypts, and submucosal glands and can aid in differentiating malignant from benign tissue in real-time[86-88]. Miniaturization of early OCT probes has enabled insertion into a transparent biliary catheter that can be passed through the working channel of an ERCP scope for biliary cannulation and *in vivo* imaging[89].

OCT has been shown to increase the sensitivity for detecting malignant biliary strictures as compared to biliary brushing cytology alone. Arvanitakis *et al*[90] evaluated 2 OCT criteria, namely unrecognizable layer architecture and presence of large nonreflective areas compatible with tumor vessels, for diagnosing malignant

strictures when compared to the gold standard of tissue acquisition in 35 patients undergoing ERCP for evaluation of IDBSs. Nineteen patients ultimately had malignant strictures, and these 2 OCT criteria were associated with a sensitivity, specificity, PPV, NPV and accuracy of 53%, 100%, 100%, 64% and 74%, respectively. The sensitivity of biliary mucosal brushings and/or biopsy improved from 67% to 84% when at least 1 criterion was added. In another study, the diagnostic utilities of OCT and ERCP-guided brush cytology were compared while evaluating 12 patients with main pancreatic duct stricture. Six patients ultimately had malignancy and OCT demonstrated greater sensitivity (100% *vs* 67%) than cytology while maintaining equal specificity (100%)[91]. OCT, unlike confocal imaging, permits larger surfaces areas to be examined. Improved resolution is paramount. The limited existing data are encouraging, but additional studies are awaited to better define the potential role of OCT in evaluating IBDSs, particularly among patients with high-risk conditions such as PSC.

FUTURE DIRECTIONS

Other technologies may be amenable to use in the evaluation of IDBSs. These include high-resolution endomicroscopy, Raman spectroscopy, EUS elastography, and CLE with chromocholangioscopy or autofluorescence. Each will be challenged by the need for miniaturization and must satisfy value in the face of added cost.

CONCLUSION

IDBSs pose a diagnostic challenge for which more accurate diagnostic tests are critically needed. Although ERCP offers therapeutic options for biliary obstruction, conventional methods of tissue acquisition remain generally insensitive, albeit to a lesser degree with use of advanced cytologic techniques such as FISH. EUS can be of additional benefit in evaluating distal strictures and staging, though concerns remain regarding tumor seeding. IDUS may supplement ERCP and EUS and aid in local staging but, despite its longstanding availability, is seldom employed. Cholangioscopy permits direct visualization and directed sampling; design enhancements may simplify its use and improve performance. Emerging techniques such as pCLE and OCT enable real-time, *in vivo*, endohistologic assessment, but additional study is needed to standardize interpretation, improve inter-rater reliability, and validate performance. The challenges in diagnosis often result in multimodal testing that marginally enhances diagnosis but substantially increases cost. While application of new and innovative technologies is of interest to endoscopists, their use must be tempered by the realization of only marginal improvements in diagnostic sensitivity and frequent decrement in specificity, their potential for adverse events, associated cost, and often limited availability to a small number of diagnostic centers. In addition, more research is needed to determine how to best guide important clinical decisions using these and other established and emerging modalities.

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Achieving competence in colonoscopy: Milestones and the need for a new endoscopic curriculum in gastroenterology training

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Abstract

Colonoscopy is considered to be the most effective tool for reducing colorectal cancer (CRC) morbidity and mortality. As a result, certifying trainee competence in the performance of colonoscopy is critical to maximizing CRC screening and prevention efforts. Guidelines on training and accreditation around the world have been revised to emphasize the attainment of milestones in the technical and cognitive skills necessary to perform the procedure. To meet this challenge, new evaluation systems have been developed to measure trainee competence through all aspects of colonoscopy training. These changes stem from increased recognition that procedural numbers alone do not necessarily guarantee trainees' proficiency in the performance of colonoscopy. Variability in endoscopic practice and in CRC screening outcomes also point to deficiencies in the current approach towards colonoscopy instruction. However, technological innovations hold great promise in training endoscopists to perform high quality colonoscopy. Furthermore, potential advances in the use of feedback as a training tool provide new avenues for research. This review summarizes the latest evidence on the effort to define, evaluate and promote the achievement of competence in colonoscopy among trainees.

Key words: Competence; Colonoscopy; Colorectal cancer; Core curriculum; Cecal intubation

Core tip: The certification of competence among trainees in the performance of colonoscopy is currently evolving. Recent efforts are shifting the paradigm towards formal evaluation systems that emphasize core skills. Similar innovations in technology and teaching methods provide the push to re-define the future curriculum for colonoscopy training.

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INTRODUCTION

The process of determining if medical trainees possess the requisite knowledge and skill to practice the healing arts has played a central role in the evolution of medicine. In the time of the ancient Greeks and Romans, competence was based upon the judgment of the elder physician under whom the trainee served as an apprentice[1]. In 1260, the Mongol Emperor Kublai Khan established the first system of certification based upon the completion of formal written examinations[1]. With the founding of the Royal College of Physicians in London in 1518, a further shift towards formal medical licensure took place with the advent of both written tests and objective assessments of procedural skills[1].

In gastrointestinal endoscopy, the task of certifying competence among trainees is also evolving from an apprenticeship model towards a more objective process based upon the achievement of milestones. With nearly 14.2 million procedures performed in the United States alone[2], colonoscopy represents the most common endoscopic procedure performed by gastroenterologists, surgeons and family practitioners. However, recent studies suggest that the detection of adenomatous polyps and the development of missed interval colorectal cancers (CRCs) may be closely related to the proficiency of the endoscopist[3-5]. Consequently, the process by which trainees are trained and certified to be competent in the performance of colonoscopy has become a high priority.

To approach this vital issue, there are several salient questions to be asked: (1) What is competence; (2) Why does competence matter; (3) How do we determine trainee competence; (4) Do trainees currently attain competence; and (5) How do we help trainees to attain competence.

WHAT IS COMPETENCE?

Competence is defined by the American Society for Gastrointestinal Endoscopy (ASGE) as the "Minimal level of skills, knowledge and/or expertise derived through training and experience that is necessary to safely and proficiently perform a task or procedure"[6]. Competence is determined to be contingent upon: (1) Technical skills to safely perform the procedure; and (2) Cognitive skills to take information gained from a procedure and to place it in the appropriate clinical context[6]. These cognitive and technical skills are further broken down into basic and intermediate competencies (Table 1)[7].

Given that the end-goal of colonoscopy is to reduce CRC-related mortality, competence among trainees can also be defined based upon their ability to surpass quality thresholds. The ASGE defines these benchmarks as: (1) adenoma detection rate (ADR) of $\geqslant$ 30% in male and $\geqslant$ 20% in female patients undergoing average-risk CRC screening; (2) A successful cecal intubation of $\geqslant$ 90% in all colonoscopies and $\geqslant$ 95% for screening colonoscopy; (3) the successful removal of polyps < 2 cm in size; and (4) A colonoscopy withdrawal time of > 6 min[8]. In the United Kingdom, the Joint Advisory Group (JAG) on gastrointestinal (GI) endoscopy requires: (1) Cecal intubation rate of > 90%; (2) > 90% of rate of completing procedures without assistance; (3) Attendance at a basic skills colonoscopy course; and (4) Procedure total of $\geqslant$ 200[9].

WHY DOES COMPETENCE MATTER?

While the answer to this question may seem largely self-evident, the process of certification is salient to many potential interests regarding colonoscopy. First and foremost, endoscopist competence has been shown to have a significant impact on the effectiveness of colonoscopy in detecting and preventing CRC. Baxter *et al*[4] recently questioned the long-standing assumption that colonoscopy decreases CRC-related morbidity and mortality when they demonstrated that the procedure was not protective for right-sided CRC (OR = 0.99, 95%CI: 0.86-1.14). To potentially explain this observation, Singh *et al*[10] in a large population based study in Manitoba, Canada found that colonoscopy with polypectomy, cecal intubation failure and procedures performed by family practitioners were associated with the development of interval CRC within 3 years of an index colonoscopy. This raises the prospect that low levels of competence in polypectomy, cecal intubation and endoscopic training limit the effectiveness of colonoscopy. Furthermore, Kaminski *et al*[11] found that endoscopists with a mean ADR of < 11% had a cumulative hazard rate for the development of interval CRC of 10.94 (95%CI: 1.37-87.01) when compared with physicians who had an ADR of > 20%. A similar study by Corley *et al*[12], found that physicians who increased their ADR from the lowest quintile to the highest quintile prevented 1 interval CRC over the course of 10 years. Furthermore, they found that every 1.0% increase in ADR predicted a 3.0% decrease in the risk of interval cancer (HR = 0.97; 95%CI: 0.96-0.98)[12]. Given that ADR is one of the primary benchmarks for both competence and quality in colonoscopy, it is clear that the process of determining endoscopist proficiency plays a pivotal role in the effort to improve CRC prevention.

Finally, the issue of establishing competence among trainees is important because of recent studies that demonstrate that physician behavior is difficult to alter once an endoscopist is no longer a trainee. Sawhney *et al*[13] found that an institutional mandate to achieve a minimum withdrawal time (time spent from cecal intubation to removal of the colonoscope from the anus) among 42 attending endoscopists failed to produce any significant change in polyp detection rate (PDR). Lin *et al*[14] performed a similar study where they provided periodic feedback of patient satisfaction scores, average withdrawal time, and PDR every 3-6 mo to 10 attending gastroenterologists who were at least 8 years removed from training. One year after the implementation of this feedback mechanism, there was no significant increase

Table 1 American Society for Gastrointestinal Endoscopy Core Curriculum list of core motor and cognitive skills required to be competent in colonoscopy[7]

Motor	Cognitive
Correctly holding the colonoscope	Anatomy
Use of the colonoscopy controls	Patient selection
Colonoscope insertion	Preparation
Colonoscope advancement	Colonoscope selection
Tip control	Informed consent
Torque	Sedation management
Lumen identification	Assessment of indication and risks
Withdrawal/mucosal inspection	Pathology identification
Loop reduction	Therapeutic device settings
Angulated turns	Integration of findings into management plans
Terminal ileum intubation	Report generation and communication
Biopsy	Complication management
Snare polypectomy	Quality improvement
	Professionalism

in either PDR (33.1% *vs* 38.1%, P = 0.04) or ADR (19.6% *vs* 22.7%, P = 0.17)[14]. These observations highlight the potential value of establishing good practices early on in the career of an endoscopist.

HOW DO WE DETERMINE TRAINEE COMPETENCE?

Traditionally, credentialing guidelines have focused primarily on the number of colonoscopies performed to determine procedural competence. In a small study of 7 trainees (4 GI fellows, and 3 surgical residents), Freeman *et al*[15] defined competence based upon independent cecal intubation. They found that trainees were able to intubate the cecum without assistance only 80% of the time after the first 50 procedures and consequently concluded that > 100 cases were likely required to achieve a 90% success rate. Using a cecal intubation time of < 15 min, a cecal intubation rate > 90%, and a 6-point technical skill score as a measure of competence, Chak *et al*[16] found that trainees did not achieve an attending-level of proficiency in colonoscopy even after 120 procedures were performed. These observations form the basis for the Accreditation Council for Graduate Medical Education (ACGME) and ASGE recommendation that a trainee perform a minimum of 140 cases before competency can be assessed in colonoscopy[6,17]. The European Board of Gastroenterology, the Canadian Association of Gastroenterology and the Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy in Australia however use the 100 case threshold[18-20]. In the United Kingdom, JAG guidelines recommend a higher threshold (200 independently completed colonoscopies)[9].

Recently, several studies have highlighted the fact that these numbers represent a minimal threshold for competence and that procedural numbers by themselves do not guarantee trainee proficiency. In a large study involving 15 tertiary care centers in South Korea, Lee *et al*[21] found that trainees were able to independently intubate the cecum > 90% of the time, and attain a cecal intubation time of < 20 min only after > 150 procedures were performed. Spier *et al*[22] defined competence as the point at which trainees were able to perform all aspects of colonoscopy (cecal intubation, polypectomy, hemostasis) without the aid of an attending > 90% of the time. Using this definition, the investigators found that all of the 11 GI fellows studied attained these objectives by 500 cases but none attained that goal by the 140 case threshold set by the ASGE/ACGME guidelines[22]. And in a multicenter study[23] of 7 first-year GI fellows at two separate training programs, our own group sought to determine the threshold number of cases at which trainees were able to achieve: (1) Independent cecal intubation rate of $\geqslant$ 90%; (2) Independent ADR of $\geqslant$ 25%; (3) Mean withdrawal time $\geqslant$ 6 min; and (4) Ability to successfully remove polyps without the aid of the attending $\geqslant$ 95% of the time. This study was unique in that nurses were asked to judge whether each of the skills (adenoma detection and removal, cecal intubation) were performed by the fellow without significant assistance by the attending. Consequently, trainees were given credit for adenoma detection only if the adenoma was determined to be independently detected and removed by the trainee in the opinion of the endoscopy nurse. Using these criteria, we found that trainees achieved all of the quality benchmarks only when 201-250 procedures were performed[23].

Recognizing the inherent shortcomings in assigning competence solely based upon procedural numbers, recent efforts have focused on developing evaluation systems that assess both the technical and cognitive skills necessary to perform colonoscopy. In the United Kingdom, the JAG group has developed the Direct Observation of Procedural Skills (DOPS) evaluation for colonoscopy as part of a national system of accreditation for GI trainees[24]. Using a 4 point scoring system ranging from 1-Accepted standards not yet met; frequent errors uncorrected to 4-highly skilled performance, assessors are tasked with grading trainees on both diagnostic and therapeutic skills in colonoscopy. In a study of 111 attending endoscopists, Barton *et al*[24] demonstrated that DOPS had good relative reliability (G = 0.81) and a good correlation with a questionnaire that assessed candidates' knowledge. While the value of DOPS as a method for determining trainee competence is yet to be validated, current JAG guidelines require a total of 10 DOPS evaluations with > 90% of them having no score less than 3 for any given skill. A similar scoring system known as the Direct Observation of Polypectomy Skills (DOPyS) has also been developed by JAG to determine competence in polyp removal using the same four point rating scale with scores of 1-2 considered as failing grades[25]. In a study by Gupta *et al*[25], DOPyS was found to have discriminatory value in differentiating experienced endoscopists with > 1000 procedures from GI trainees who had limited experience in therapeutic

colonoscopy. The added advantage of the DOPyS rating system is that it has been validated to be applied towards video-recordings of procedures.

In the United States, Sedlack[26] have made significant strides in the development of a comprehensive evaluation system for determining trainee competence with the advent of the mayo colonoscopy skills assessment tool (MCSAT). Using a rating system of 1 (Novice) to 4 (Superior), the MCSAT evaluates trainees during live cases[26]. Trainees are assessed in terms of cognitive skills such as knowledge of indication for procedure, use of initial sedation, landmark localization, and pathology identification. They are also are evaluated on procedural abilities such as safe endoscope advancement techniques, loop reduction, mucosal visualization during withdrawal, and polypectomy. In a large study of 41 GI fellows who were evaluated during 4103 procedures, the investigators determined that a mean score of $\geqslant$ 3.5 in all MCSAT parameters along with a cecal intubation rate of 85% and a mean cecal intubation time of less than 16 min best distinguished experienced endoscopists from trainees who had not yet met minimal competence thresholds[27]. Furthermore, they found that GI fellows did not reach these goals until 275 procedures were performed[27]. Because of this work, the most recent ASGE Core Curriculum has endorsed using the MCSAT as a tool for competency assessment throughout colonoscopy training[7].

DO TRAINEES CURRENTLY ATTAIN COMPETENCE?

While there are no formal studies outlining the characteristics of colonoscopy training among Gastroenterology, Surgery and Family Practice programs, it is highly probable that a large degree of variability exists in the educational approaches taken towards teaching trainees how to perform the procedure. Teaching strategies likely vary with the "See one, do one, teach one" approach on one end of the educational spectrum and more didactic and hands-on instruction by an experienced endoscopist on the other. This heterogeneity in training is highlighted by studies that compare GI trainees and surgical residents in achieving benchmarks in quality colonoscopy. In a study of 7 GI fellows and 6 surgical residents, Leyden *et al*[28] found that surgical trainees had lower cecal intubation rates (84% *vs* 93%, $P < 0.0001$), polyp detection rates (14% *vs* 21%, $P < 0.0001$) and ADR (9% *vs* 14%, $P = 0.0065$). A similar study by Spier *et al*[29] found that surgical residents only had a cecal intubation rate of 47% after a mean of 80 procedures were performed.

Even among trainees in recognized GI fellowship programs, recent studies point to potential deficiencies in the approach towards teaching colonoscopy. In an innovative tandem colonoscopy among procedures performed by GI fellows, Munroe *et al*[30] found an overall adenoma miss rate of 27%. Furthermore, the investigators found that there was a 2.2 fold decrease in the risk of missing an adenoma with each 10 fold increase in trainee experience[30]. Thus, to attain a less than 25% adenoma miss rate, a trainee would have to perform 450 procedures, a number that many GI fellows and certainly most surgical and family practice trainees may never reach in the course of training. One potential explanation for this finding is a failure to fully incorporate quality guidelines into the educational curriculum on the part of many training programs[30]. In an online survey on quality guidelines for colonoscopy, GI fellows received a mean score of 55% correct, with only 42% identifying the correct cecal intubation rate goal and 44% indicating the correct ADR benchmark[31].

Finally, feedback from GI trainees themselves highlight the need for improvements in colonoscopy instruction. In a survey of 169 GI trainees in the United Kingdom, Wells *et al*[32] found that only 36% felt that they were "fully" trained in colonoscopy. Furthermore, the respondents estimated than an attending was in the room to provide supervision in only 30% of colonoscopies that were performed[32]. Trainees also cited important aspects of effective teaching which included: (1) Close interaction with a supervisor who has good teaching skills; (2) Systematic approach towards endoscopic techniques; (3) Excellent supervision and discussion-based training; (4) Attendance of a course on quality colonoscopy; and (5) Smaller procedure schedules to allow for training time[32]. These comments point to the need for reforming our current approach toward teaching colonoscopy.

HOW DO WE HELP TRAINEES ATTAIN COMPETENCE?

Advances in both technology and teaching methods clearly point the way towards a new curriculum that is based upon establishing competence in colonoscopy. From a technological standpoint, innovations in simulation present new avenues for trainees to develop and hone cognitive and technical skills away from the time pressures and risks of performing procedures on live patients. Current simulators consist of a mannequin and a modified colonoscope with pressure sensors which mimic the resistance felt with scope advancement and loop formation. Trainers are able to assign specific modules to trainees on the simulators ranging from basic lessons meant to establish hand-eye coordination skills to more realistic scenarios in which full cases are performed on simulated patients.

Several randomized controlled trials have demonstrated a potential benefit to the use of simulation during the early phase of colonoscopy training. Cohen *et al*[33] compared simulation (Simbionix GI Mentor, Simbionix Corporation, Cleveland, Ohio) *vs* non-simulation trained GI fellows in terms of competence measures on colonoscopies performed on live patients. In particular they looked at subjective (rating scale of 1-5 on the part of the trainer) and objective measures such as successful cecal intubation and the ability to correctly identify

Table 2 Median performance scores (25%-75% interquartile range) on live-patient procedures among fellows trained on colonoscopy simulator *vs* trainees with bedside training alone[34]

Fellow performance parameters	Simulator fellow (n = 462)	Traditional teaching (n = 423)	P value
Time to reach maximum insertion (min)	20.0 (14.0-25.0)	20.0 (15.0-29.8)	0.170
Median depth of unassisted insertion (1 = rectum, 6 = terminal ileum)	5.0 (4.0-6.0)	5.0 (4.0-5.0)	0.002
% of colonoscopies completed independently	64.1% (59.7-68.5)	56.3% (51.6-61.0)	0.018
Identifies landmarks (1 = strongly disagree, 7 = strongly agree)	7.0 (6.0-7.0)	6.0 (6.0-7.0)	0.003
Inserts in a safe manner (1 = strongly disagree, 7 = strongly agree)	7.0 (6.0-7.0)	7.0 (6.0-7.0)	0.020
Adequately visualizes mucosa during withdrawal	7.0 (6.0-7.0)	6.0 (6.0-7.0)	0.009
Responds appropriately to patient discomfort	7.0 (6.0-7.0)	6.0 (6.0-7.0)	0.255
Patient-reported discomfort	1.0 (1.0-4.0)	1.0 (1.0-4.0)	0.090

cecal landmarks[33]. During the first 80 live cases, the simulator-trained group had higher objective and subjective levels of competence[33]. However after 120 cases, the advantage found with simulation was no longer present and both groups still required a total of 160 live cases to attain 90% competence[33]. In a similar study by Sedlack *et al*[34], GI fellows who received training using the AccuTouch Colonoscopy Simulator (Immersion Medical, Gaithersburg, MD) scored better on all performance measures (Table 2) except for cecal intubation time when compared with trainees who received just bedside instruction on live patients. However, the differences between the two groups also dissipated once greater than 30 procedures were performed[34]. The positive impact of simulation during the early phases of colonoscopy instruction is well summarized in a meta-analysis by Walsh *et al*[35] who found that there was a significant benefit when simulator-based training was compared to no-training at the beginning of fellowship. In contrast, the advantage of simulator-based training was less pronounced when it was pitted against usual training on live patients[35].

Along with simulation, recent advances in technologies designed to be used during live-cases also hold promise in helping trainees to achieve competency in colonoscopy. During training, the formation and reduction of loops that occur with scope advancement represent one of the most important skills that a trainee must acquire in order to safely perform colonoscopy. To assist in this task, magnetic endoscope imaging (MEI) has been developed to provide trainees with a real-time view of scope positioning. With the ScopeGuide (Olympus Corporation, Tokyo, Japan) MEI system, coils embedded within the colonoscope generate an electromagnetic field which is detected by an external receiver dish producing a 3-dimensional image of the location of the colonoscope[36]. In a randomized controlled trial comparing MEI assisted *vs* standard colonoscopy Shah *et al*[37] found that trainees who performed with MEI had a shorter duration of loop formation (median 3 min *vs* 5.4 min, P = 0.0049) and a fewer number of loop straightening attempts (5 *vs* 12, P = 0.0002). In a similar study of trainees who had experience of fewer than 200 procedures, Holme *et al*[36] observed a higher rate of cecal intubation (77.8% *vs* 56%, P = 0.022) and a lower percentage of cases which required attending assistance (18.5% *vs* 40%, P = 0.018) in the MEI group. Thus, MEI may provide a useful role in colonoscopy training if it aids trainees in acquiring the feedback response for recognizing loop formation.

Water immersion colonoscopy also represents another more readily available modality which may assist trainees in their development of procedural competence. In the early stages of training, novices often have difficulty in discerning the direction of the lumen and as a result this leads to prolonged cecal intubation time, the excessive insufflation of air into the colon, looping of the colonoscope and patient discomfort. Addressing these issues, the water immersion technique refined by Leung *et al*[38] involves filling the colonic lumen with room temperature or warm water using a pump connected to the colonoscope. The air pump is turned off during the intubation phase and 30-60 cc of water is instead used to open the collapsed lumen[38]. In a randomized controlled trial by Leung *et al*[39], trainees who used water immersion had shorter cecal intubation times (13 min *vs* 20.5 min, P = 0.0001), lower mean doses of midazolam (mean dose 2.41 mg *vs* 2.9 mg, P = 0.001) and Fentanyl (mean dose 37.9 mcg *vs* 71.7 mcg, P = 0.002) than those who utilized standard air insufflation. More importantly, a recent meta-analysis found that water immersion resulted in higher ADR (RR = 1.16, 95%CI: 1.04-1.30, P = 0.007) and would lead to an additional 68000 colonoscopies in the United States where an adenoma is detected[40].

Along with water immersion, hood-assisted colonoscopy may also aid trainees in determining the direction of the lumen with scope insertion. Because novice endoscopists often have poor control of scope movement and directionality, a significant amount of time is spent with a "redded-out" image because the scope tip is stuck against the colonic wall[41]. This leads to prolonged scope insertion time and excessive air insufflation. A transparent hood that is attached to the instrument tip may help with this problem by maintaining a proper distance between the colonoscope camera and the colonic mucosa. Furthermore, the hood may assist in mucosal inspection and polyp detection upon withdrawal since it helps with depressing and exposing colonic folds. In a randomized trial of hood colonoscopy *vs* standard colonoscopy among Italian trainees, the hood group was found to have a shorter cecal intubation time (4.4 ± 1.8

vs 7.3 ± 3.5, $P < 0.01$), and a higher rate of detecting polyps 5 mm-1 cm in size (72% *vs* 44%, $P = 0.01$)[41]. A similar randomized controlled trial in Japan, found that trainees had a higher cecal intubation rate (60.7% *vs* 37.4%, $P = 0.003$) among female patients and a 17% reduction in cecal intubation time when hood-assisted colonoscopy was used[42]. Consequently, hood-assisted colonoscopy and water immersion both hold promise as future techniques in colonoscopy training if they assist trainees in the sustained acquisition of skills in luminal orientation, safe scope advancement and polyp detection.

While technology may prove to be important in shaping the future of colonoscopy instruction, the role of feedback will remain the central foundation of the colonoscopy core curriculum. The ASGE Training Committee guidelines recommend that: "Regardless of the method ultimately used, it is recommended that some form of continuous assessment be performed and the results used ideally in a formative manner- to give feedback to trainees in areas where further work may be needed-and a summative assessment of skills that can be used for competency assessment"[7].

Despite this directive, the utility of assessment and feedback as teaching tools in colonoscopy remains poorly understood. Koch *et al*[43] developed a self-assessment form (Rotterdam Assessment Form) which asked trainees to rate their own performance after completion of individual procedures. The form consisted of objective data including successful cecal intubation, cecal intubation time, and the amount of time spent without attending assistance along with a subjective rating of various colonoscopy skills using a visual analogue scale and an action plan for improvement[43]. After the implementation of this self-evaluation system, the cecal intubation rate improved from 65% after the first 20 procedures to 85% at 200 procedures ($P < 0.001$)[43]. Cecal intubation time also improved from 13 min, 10 s at 20 procedures to 8 min 30 s after completion of 200 colonoscopies[43]. However, even with these results, it remains largely unclear if the self-evaluation system resulted in an actual improvement on the normal rate of skills acquisition or improvements in polyp detection that one would see in the regular course of training.

While the clinical evidence for using feedback as a training tool in colonoscopy remains limited, this area provides fertile ground for future research endeavors. In a study by Rex *et al*[44] the act of video-recording individual colonoscopies resulted in a 49% improvement in mucosal inspection time and a 31% improvement in withdrawal technique among experienced endoscopists. Relying upon the concept of the Hawthorne effect whereby subjects improve or modify their behavior in response to the fact that they are being studied[45], it is certainly possible that video-recordings can be used to improve technical and cognitive performance among trainees. Furthermore, the addition of the MCSAT to the colonoscopy core curriculum also affords the opportunity to use continuous feedback of competency scores and comparisons with the group average to assist novices in identifying areas that require improvement. Finally, the current JAG certification process also requires trainees to provide a formal assessment of the trainers' performance during individual procedures. Similar "train the trainer" measures that seek to improve the quality of colonoscopy instruction are vitally important from both research and educational standpoints.

CONCLUSION

While the process of certifying competence has clearly evolved away from the apprenticeship model of medical training, the future shape of colonoscopy instruction remains to be determined. With the increasing emphasis on quality benchmarks and recent data questioning the pre-eminent role of colonoscopy in CRC screening due to variability in endoscopic practice, the task of evaluating and teaching competence remains as important as ever. The movement away from concentrating on procedural numbers and towards the attainment of milestones in the development of cognitive and technical skills represents a significant shift in determining competence in colonoscopy. As first steps in this evolution, the MCSAT and the DOPS evaluation systems standout as significant contributions to the process of re-defining the core curriculum. Whether the solution lies in better technology or a feedback-based system of procedural instruction, the approach towards educating trainees will need to adapt to a curriculum that rightfully emphasizes the importance of quality colonoscopy.

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Role of virtual reality simulation in endoscopy training

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Abstract

Recent advancements in virtual reality graphics and models have allowed virtual reality simulators to be incorporated into a variety of endoscopic training programmes. Use of virtual reality simulators in training programmes is thought to improve skill acquisition amongst trainees which is reflected in improved patient comfort and safety. Several studies have already been carried out to ascertain the impact that usage of virtual reality simulators may have upon trainee learning curves and how this may translate to patient comfort. This article reviews the available literature in this area of medical education which is particularly relevant to all parties involved in endoscopy training and curriculum development. Assessment of the available evidence for an optimal exposure time with virtual reality simulators and the long-term benefits of their use are also discussed.

Key words: Virtual reality; Colonoscopy; Sigmoidoscopy; Endoscopy; Endoscopic ultrasound; Medical education; Endoscopic retrograde cholangio-pancreatography; Gastroscopy; Simulation

Core tip: There is good evidence for the use of virtual reality simulation in endoscopy training programmes, with most benefit seen amongst novice trainees. More research is needed concerning the best integration of simulators within a training programme and the optimal exposure needed. Findings are limited by the variety of simulators used and limited power of the studies. More evidence is also needed to support the benefits virtual reality simulators may have within endoscopic ultrasound and endoscopic retrograde cholangio-pancreatography training programmes.

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INTRODUCTION

Endoscopy training and skill acquisition conventionally involves observation and feedback on a trainee's performance under the supervision of an experienced endoscopist. This applies to traditional training in a variety of procedures, including oesophagogastroduodenoscopy (OGD), endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS) and colonoscopy. More recently, a variety of alternative educational tools have become available that aim to improve trainees' endoscopy skills.

Virtual reality (VR) simulators are an educational modality that has been purposely developed to facilitate endoscopy training in a controlled environment. With improving graphics and technology, medical simulation has advanced from basic mechanical models or animal models to screen-based simulators. Their use and incorporation into endoscopy training curricula has been thought to enhance the speed of trainee skill acquisition, thus improving patients' comfort and safety during candidates' initial phase of learning[1].

This review article aims to evaluate existing evidence on the role of VR simulation in endoscopy training, identify if there is an evidence-based educationally optimal method of incorporating such simulators within endoscopy training programmes and to review the impact that VR simulator training may have upon patient comfort. This article will focus on the impact of virtual reality simulator training for the most common endoscopy modalities, namely OGD, ERCP, EUS and colonoscopy.

LITERATURE STUDY

An extensive bibliographical search was performed *via* the online databases MEDLINE and EMBASE using the following keywords: Simulation, simulator, virtual reality, endoscopy, gastroscopy, OGD, colonoscopy, sigmoidoscopy, endoscopic retrograde cholangio-pancreatography, ERCP, endoscopic ultrasound, EUS. Some of these terms (simulation, simulator, virtual reality), which were relating to simulation, were searched in combination with the remaining keywords, which were relating to endoscopy (*e.g.,* "simulation and endoscopy", "simulation and colonoscopy", "virtual reality and gastroscopy", *etc.*), in order to identify all relevant papers investigating the role of virtual reality simulation in endoscopy training. The results were combined before duplicates were removed and the reference lists from the selected studies were manually examined to identify further relevant reports.

All primary research papers published in full from any year of publication were considered for inclusion in this review, regardless of their design. These papers included internationally conducted studies, but only those written or translated into English were included in the full text assessment. The participants of studies considered in this review ranged from physicians, nurses and medical students and the individuals' endoscopy experience was not taken into account in screening for studies. The intervention sought was that of VR endoscopy against traditional patient-based training methods or where there was no comparison at all.

Screening of these results removed papers which did not have an educational impact focus, as well as discussion papers, in which the title and abstract aimed to legitimise VR simulators (in comparison to traditional training) solely by expert opinion. Papers that included non-VR educational simulators which involved *ex-vivo* parts or mechanical models were also excluded. This demonstrated that a subset of 24 articles were relevant for this review (Figure 1).

RESULTS

Role of VR simulation in OGD training

Table 1 shows the methodology of the eight studies that were included.

Regarding the role of VR simulators in OGD training the available evidence demonstrates that screen-based simulators have a useful role in facilitating training of novice candidates in OGD[2-7], and potentially a place in the continued professional development of more experienced trainees[2,6,8].

Multiple studies have shown that novice trainees who underwent training that included a VR simulator had significantly better performance outcomes than candidates who were traditionally trained in OGD[3-5,7] and Table 2 summarises the various outcomes of studies investigating the role of VR simulation in OGD training. Ferlitsch *et al*[7] furthered support for early use of the VR simulators by showing that there was a continued significant difference in VR simulator-trained candidates' timing, diagnostic and technical accuracy at 60 d. The only study to report a negative outcome comparing simulator training against traditional training stated that the incidence of pain was reported as higher amongst those who used the simulator[9].

Another study showed that a significant proportion of trainees who utilised VR simulators felt that simulator practice would be most useful in early training, with those who were more advanced reporting that some of the modules were not very realistic for their stage of training[6].

Role of VR simulation in ERCP training

Although there have been several studies looking into the role of simulation in ERCP training, the majority of these have used mechanical models and only one has focused on the role of VR simulation. This study enrolled novice and expert endoscopists and aimed to determine the construct and face validity of the simulator. It concluded that the GI Mentor Ⅱ simulator was both realistic and able to differentiate novices and experts based on their performance. In addition, most participants considered it a helpful training tool[10]. Table 3 provides a summary of the design and outcomes of

Table 1 Summary of analysed oesophagogastroduodenoscopy studies and their design

Ref.	No. of participants	Participants' level of training	Design	Task	Model	Primary outcome	Secondary outcomes
Bloom *et al*[6]	35	Novice and advanced	NRSIS	Visualisation Questionnaire	5 DT gastroscope training simulator	Time to complete procedure[1]	Wall visualisation[1] Questionnaire responses
Clark *et al*[2]	13	Novice and advanced	NRSIS	Completion of monthly assignments over two years on simulator	GI Mentor Ⅰ	Objective criteria measured by simulator[1]	
Di Giulio *et al*[4]	22	Novice	MC RCT	Complete simulator or control training programme	GI Mentor Ⅰ	Competency scores[2]	Instructor assessed[2]
Ferlitsch *et al*[7]	13	Mixed novice and advanced	RCT	Comparison of novice and expert performance in simulated endoscopy. Comparison of performance of simulation-trained and control group of novices	GI Mentor Ⅰ	Competency scores from simulator[1]	
Ferlitsch *et al*[3]	28	Novice	RCT	Training on simulator against traditional training	GI Mentor Ⅰ	Competency scores from expert after 10 and 60 endoscopic examinations[2]	Pain experienced by patient
Sedlack[9]	8	Novice	RCT	6 h simulation training before 1 mo of traditional training	GI Mentor Ⅱ	Mixed competency scores from expert[2]	
Shirai *et al*[5]	20	Novice	RCT	5 h simulation training before 2 assessed endoscopies	GI Mentor Ⅱ	Mixed competency scores from expert[2]	
Van Sickle *et al*[8]	41	Mixed novice and advanced	MC NRSIS	Baseline assessment on simulator and after 8 wk of training	GI Mentor Ⅱ	Competency scores from expert[1]	

[1]Simulator-related outcome; [2]Patient-related outcome. MC: Multicentre; RCT: Randomised control trail; NRSIS: Non-randomised single-intervention study; GI: Gastro-intestinal; DT: Dimension technologies.

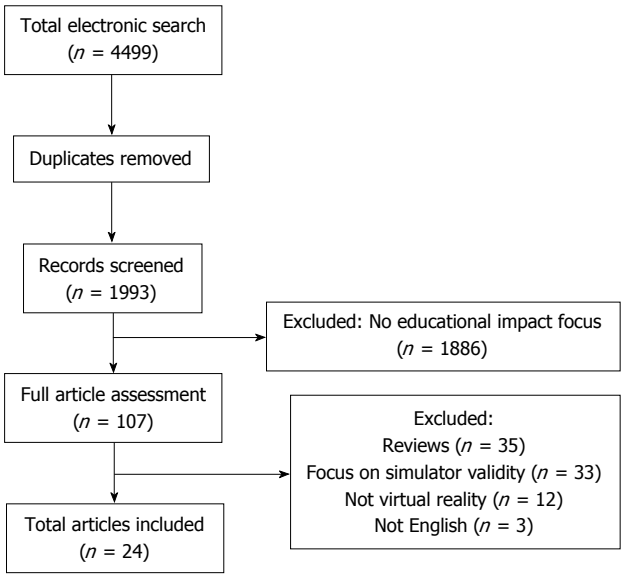

Figure 1 Article screening and selection process.

this study.

Role of VR simulation in EUS training

Only one study could be found that discusses the role of VR simulation in EUS training[11]. Eight experts compared an EUS VR simulator (EUS Mentor) to an animal model, a phantom (EUS FNA box) and a combination model and ranked them by realism, utility as an educational modality, ease of use and ease of incorporation into a training programme. They determined the phantom model to be easiest to use and incorporate into training, whereas animal models were marked as best for realism and utility as an educational tool[11].

Role of VR simulation in colonoscopy training

Table 4 shows the methodology of the thirteen studies that were included.

In assessing the role of VR simulators in colonoscopy training there is more evidence to support its use in training programmes[12-21]. In one survey, 91% of all participating candidates agreed that VR simulators would be useful in their training[12]. Several studies demonstrated that when VR simulator training was compared to traditional colonoscopy training alone, competency parameters were significantly greater amongst simulator trained candidates[13,15-18,20]. The majority of these studies adopted the same methodology, utilising the VR simulator model before candidates started traditional training, which supports the use of VR simulators in this way.

Some studies attempted to determine the amount of exposure with the simulator which is necessary to acquire an "expert" skill base - determined when learning curves plateaued on the simulator modules. While one study reported that the learning curve of novice candidates plateaued on the seventh consecutive attempt[22], another stated that learning curves consistently plateaued at or after the ninth attempt amongst novice candidates[23]. In a separate study which compared learning curves between novice residents and nurses with varying experience in endoscopy the learning curve

Table 2 Results of studies evaluating the role of simulation in oesophagogastroduodenoscopy training

Ref.	Primary outcome	Secondary outcome
Bloom *et al*[6]	Mean time to complete procedure was 224 ± 27.65 s for novice, 171.22 ± 25.43 s for intermediate and 106.40 ± 13.08 s for experienced candidates (P = 0.008) The study demonstrated the construct validity of the simulator	Mean percentage of total surface visualised was 60.56 ± 2.56 for novice, 66.56 ± 2.80 for intermediate and 72.10 ± 0.23 for experienced candidates (P = 0.005) Questionnaire responses suggested that novice and intermediate candidates considered VR simulation an important training tool
Clark *et al*[2]	Efficiency scores (total time to complete procedure divided by percentage of mucosal surface examined) of senior residents were higher than those of junior residents (85% *vs* 59%) demonstrating improved efficiency with continued use of simulator	
Di Giulio *et al*[4]	The simulator-trained group performed a higher number of complete procedures (87.8% *vs* 70%, P < 0.0001) and needed less assistance (41.3% *vs* 97.9%, P < 0.0001) compared to control group. Length of procedure was similar in the two groups	Instructor marked performance as positive more frequently in the simulator-trained group compared to the controls (86.8% *vs* 56.7%, P < 0.0001)
Ferlitsch *et al*[7]	Performance of expert candidates (compared to novices) was better in performance of J-manoeuvre during oesophagogastroduodenoscopy (P < 0.005), complications at colonoscopy (P < 0.02), insertion time (P < 0.001), identification of abnormal findings in gastroscopy and colonoscopy (P < 0.02) and skill performance (P < 0.01). Amongst novices, the simulation-trained group had a better performance compared to the controls in relation to complication rates at virtual endoscopy (P < 0.04), the insertion time during colonoscopy (P < 0.03) and skill performance (P < 0.01)	
Ferlitsch *et al*[3]	The simulation-trained group performed better than the control group in terms of time needed to reach the duodenum [239 s (range 50-620) *vs* 310 s (110-720), P < 0.0001] and technical ability (P < 0.02) in the first ten endoscopic examinations on patients. Diagnostic ability was similar in the two groups After 60 endoscopic examinations, investigation time was still less in the simulation-trained group. Technical and diagnostic ability improved during on-patient training in both groups and differences between groups were no longer seen at that stage	There were no significant differences in pain scores between the groups after 10 and after 60 endoscopies
Sedlack[9]	The control group performed better than the simulation-trained group in terms of patient discomfort (5; IQR, 4-6 *vs* 6; IQR, 5-6; P = 0.015), sedation, independence and competence scores	
Shirai *et al*[5]	The simulator-trained group achieved significantly higher scores than the control group in the following skills: oesophageal intubation, passing from the EGJ to the antrum, pyloric intubation, and examination of the duodenum and the fundus	
Van Sickle *et al*[8]	The study group showed an improvement in endoscopic skills (*e.g.*, Global Assessment of Gastrointestinal Endoscopic Skills scores) after 8 wk of VR simulation training	

IQR: Interquartile range; EGJ: Esophagogastric junction; VR: Virtual reality.

Table 3 Summary of analysed endoscopic retrograde cholangio-pancreatography study and its design

Ref.	No. of participants	Participants' level of training	Design	Task	Model	Primary outcome	Secondary outcomes
Bittner *et al*[10]	12	Mixed	NRSIS	2 simulator ERCP cases	GI Mentor Ⅱ	Time to complete procedure[1]	Time to papilla[1] Questionnaire on views

[1]Simulator-related outcome. NRSIS: Non-randomised single-intervention study; ERCP: Endoscopic retrograde cholangio-pancreatography; GI: Gastro-intestinal.

did not plateau in any group by the tenth attempt[21].

In addition, several studies evaluated the effect of VR simulation training on patient discomfort. Most studies found that this was less during the procedure in simulator trained candidates[13,14,18], but few concluded that there was no significant difference between the two groups[15,24].

Better evidence that simulator training has effective translational skills can be identified by the long-term impact that simulator training has on a candidate's skill base. It has been shown that a simulator trained candidate retains a significant advantage in competence during their first 100 colonoscopies[15] and that these skills are maintained 9 mo after the simulator intervention[19].

Such concordance advocates strong support for the use of simulators in endoscopy training. However, it is important to note the findings in Gerson *et al*[24] which

Table 4 Summary of analysed colonoscopy studies and their design

Ref.	No. of participants	Participants' level of training	Design	Task	Model	Primary outcome	Secondary outcomes
Aabakken *et al*[12]	33	Mixed	NRSIS	1 simulated colonoscopy and questionnaire	GI Mentor	User satisfaction[1]	
Ahlberg *et al*[13]	12	Novice[3]	RCT	Completion of simulator or control training programme followed by assessment on 10 colonoscopic procedures	AccuTouch	Mixed competency scores[2]	Time to caecum[2]
Buzink *et al*[14]	35	Mixed	NRSIS	4 training sessions	GI Mentor Ⅱ	Mixed competency scores[1]	
Cohen *et al*[15]	45	Novice	MC RCT	Completion of simulator or control training programme followed by assessment of first 200 colonoscopies	GI Mentor Ⅰ	Mixed competency scores[2]	Long term impact[2]
Eversbusch *et al*[22]	28	Novice[3]	RCT	10 consecutive assessments on VR simulator	GI Mentor Ⅱ	Mixed competency scores[1]	
Gerson *et al*[24]	16	Novice	RCT	Completion of simulator or control training programme followed by assessment on 5 endoscopic procedures	AccuTouch	Mixed competency scores[2]	
Haycock *et al*[16]	36	Novice	RCT	Completion of simulator or control training programme followed by simulator and patient-based assessment	Olympus Endo TS-1	Mixed competency scores[1,2]	
Kruglikova *et al*[21]	30	Mixed	NRSIS	10 repetitions of one VR simulator task	AccuTouch	Mixed competency scores[1]	
Park *et al*[17]	24	Novice	RCT	Completion of simulator or control training programme followed by assessment on one patient-based colonoscopy	AccuTouch	Mixed competency scores[2]	
Sedlack *et al*[18]	8	Novice[3]	RCT	Completion of simulator or control training programme followed by assessment of one endoscopic procedure	AccuTouch	Mixed competency scores[2]	Patient discomfort[2]
Sugden *et al*[23]	50	Mixed	NRSIS	Completion of modules on the VR simulator	Olympus Endo TS-1	Mixed competency scores[1]	
Thomas-Gibson *et al*[19]	21	Novice	NRSIS	Completion of 5 d training programme including VR simulation, with pre- and post-training assessments followed by a 9-mo follow-up assessment	AccuTouch	Mixed competency scores[1,2]	Long term outcome (9 mo)[1,2]
Thomson *et al*[20]	13	Novice	NRSIS	Completion of respective training with or without simulator use with assessments during that period	GI Mentor	Mixed competency scores[2]	

[1]Simulator-related outcome; [2]Patient-related outcome; [3]Subjects had previous oesophagogastroduodenoscopy training and knowledge. MC: Multicentre; RCT: Randomised control trail; NRSIS: Non-randomised single-intervention study; VR: Virtual reality; GI: Gastro-intestinal.

is the only reported study to find that simulator-based training was inferior to traditional teaching methods. It concluded that simulator candidates had significantly greater difficulty with insertion of the endoscope, a lower ability to reach the splenic flexure and a lower ability for accurate retroflexion, but these findings were not replicated in other studies.

DISCUSSION

This review evaluated the evidence on the use of VR simulation endoscopy training in order to determine its role within modern educational programmes. The skill base acquired during VR simulation-supported training seems to translate into useable skills for patient-based endoscopy. In addition, learning is facilitated and skills acquisition is more effective compared to training with traditional methods alone. This applies to training in OGD (where the evidence was strongest in those who had least experience in OGD), colonoscopy and ERCP despite the small volume of literature available on this topic. There is no strong evidence for the impact of EUS VR simulator use in novice candidates when compared to traditionally trained candidates.

Integration of VR simulation in endoscopy training curricula

Our literature review did not reveal a single optimal method of integrating VR simulator use in endoscopy training programmes. This is in part due to the variety of exposures candidates had with VR simulators within each study. Whilst the majority of studies controlled candidates to a one-time formal exposure with the VR simulator[2-5,14] others allowed unlimited access[8] or optional extra-access[7,15]. The timing of this controlled exposure also varied with some being integrated

within a structured training programme[14] and some randomly during a participant's training. Despite the varied integration within the education programme, study findings were in support of VR simulator use, but further research is needed to show which approach is most effective. The main issue with the available studies is that there are significant differences in their design, in terms of sample size, candidates' prior endoscopic experience, tasks included (*e.g.,* some studies included therapeutic interventions or biopsies of specific lesions as additional tasks[2,6]), training time span, type of training (*e.g.,* some studies included hard-eye co-ordination modules, such as Endobubble/Endobasket, as well as virtual endoscopies[7,14], whereas other studies included virtual endoscopies alone[13]). These differences make comparisons between studies difficult, but there was general agreement in the literature that VR simulation training was effective in improving trainees' endoscopic skills. Therefore, despite differences in the specific interventions and differences in the endpoints of the various studies, the fact that there was an overall trend suggesting an improvement in skill level was sufficient in this review and suggests that institutions can flexibly integrate VR simulation in their endoscopy training curricula.

Optimal exposure to VR simulation

Debate still exists about the optimal exposure time needed with the VR simulator, as this was not apparent within this review. Even within those studies that controlled the exposure within a formalised teaching setting, the time which candidates had with the VR simulator varied from 5-10 h[3,5,7,22], whilst only one study stated that 20 h of exposure was needed on average to reach an expert criteria within colonoscopy[13]. However, its findings were not supported by others and more research is needed to determine the length of exposure needed with the VR simulator. There may be several explanations for the differences in the length of exposure required to achieve an improvement in performance, such as differences in the level of experience of participants, differences in simulator types, differences in the tasks (*e.g.,* some studies included therapeutic interventions or biopsies of specific lesions as additional tasks[2,6]) and collateral learning (*e.g.,* some studies included bedside teaching, educational videos or didactic modules, in addition to VR simulation practice as the main intervention[5,6,24]).

Long-term benefits of VR simulation

Whilst there was some evidence of the long-term benefits of VR simulator use when compared to traditional methods alone[3], the significance of long-term or continued training and the effect on outcomes remains unknown.

Effects of VR simulation on patient comfort

When looking at the reported discomfort or pain, only four studies found that VR simulator training reduced patients' pain significantly[13,16,18,22]. Another four studies found no significant difference between VR simulator trained and traditionally trained candidates[3,15,21,24] and only one found that patients of the VR simulator trained group reported significantly more pain[25]. More evidence is needed to show the true impact that VR simulator training has on patients' reported levels of discomfort.

LIMITATIONS

There are several issues relating to the consistency of the methodology of these studies that limits the comparison and generalisability of their findings. When looking at the studies reviewed, ten of the included studies were single-group intervention studies[2,6,8,10,12,14,19-21,23] without control groups and there were very few larger randomised control trials[15,16] (more than 30 participants). This is impacted further by the variety of different VR simulator models used, as the ability to draw accurate comparisons remains difficult.

Because of the different VR simulator models used, it is hard to accurately compare the mixed competencies used to measure candidates' skills, as measurements made in different simulator models are not truly identical. Recognition of the overall trend suggesting an improvement or reduction in skill level was sufficient in this review, negating the technicalities of the different measures.

Despite the overall trend advocating the use of VR simulators, the power of these findings is also limited by the relatively small study size. Also, as mentioned in the discussion, not all studies actively used VR simulators as part of a structured training programme and it is difficult to assess the impact of each different approach.

Finally, one limitation across all these studies was the varied definition of who was a "novice" or "experienced" candidate and the selection criteria. It was not always clear in the selection criteria how one was defined as being novice, with some studies defining a novice candidate as having no prior endoscopy experience, some as having limited experience in the procedure, whilst others allowed candidates trained in other endoscopy modalities, providing it was not the one under investigation[13,18,21]. For example, having completed less than 200 colonoscopies was defined as being a novice candidate in one study[12] whilst in the majority of studies a novice candidate had to have done no prior colonoscopies. Other studies only excluded those who had prior simulator experience[6,8]. Similarly, there were no uniform criteria among different studies regarding the definition of advanced or expert level. For example, in some studies having done more than 1000 procedures was defined as being an expert[7,13], whereas in other studies having done more than 500 procedures[8,12] or more than 30 procedures in the past 5 years[6] were considered sufficient thresholds for entering the "advanced" group. Clearly using an arbitrary number of previous endoscopies to stratify a candidate's ability and not

standardising a candidate's background experience may impact on the conclusions made in these studies.

CONCLUSION

Given the limitations of the studies, there is consistent evidence advocating the use of VR simulation in endoscopy teaching, stronger still in those who are least experienced. More evidence is needed to strengthen support of VR simulators in ERCP, as many of the models that currently exist to support this field of teaching rely on *ex-vivo* simulators not included in this review. For EUS training, more research is needed into the impact that VR simulators may have.

However, there does not appear to be a clear model in how best to integrate simulators in an educational programme. This is due to the variety of simulator models used and the lack of agreement over the length of exposure needed with any one simulator to obtain a beneficial outcome. A combined curriculum of traditional teaching supplemented with virtual reality simulators is of greater benefit than one without virtual reality simulation. Other considerations, such as the cost-benefit-analysis, although not considered here, would also influence decisions about how best to integrate VR simulators into any endoscopy curriculum.

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MINIREVIEWS

Core value of laparoscopic colorectal surgery

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Abstract

Since laparoscopy was first used in cholecystectomy in 1987, it has developed quickly and has been used in most fields of traditional surgery. People have now accepted its advantages like small incision, quick recovery, light pain, beauty and short hospital stays. In early times, there are still controversies about the application of laparoscopy in malignant tumor treatments, especially about the problems of oncology efficacy, incision implantation and operation security. However, these concerns have been fully eliminated by evidences on the basis of evidence-basis medicine. In recent years, new minimally invasive technologies are appearing continually, but they still have challenges and may increase the difficulties of radical dissection and the risks of potential complications, so they are confined to benign or early malignant tumors. The core value of the laparoscopic technique is to ensure the high quality of tumor's radical resection and less complications. On the basis of this, it is allowed to pursue more minimally invasive techniques. Since the development of laparoscopic colorectal surgery is rapid and unceasing, we have reasons to believe that laparoscopic surgery will become gold standard for colorectal surgery in the near future.

Key words: Laparoscopy; Minimally invasive surgery; Core value; Laparoscopic colorectal surgery

Core tip: This article discusses problems of oncology efficacy, incision implantation and operation security in laparoscopy on the basis of evidence-basis medicine, and also analyzes new minimally invasive technologies, their challenges and their range of application. The core value of the laparoscopic technique is studied and concluded.

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HISTORY AND CURRENT STATUS

Since 21st century, minimally invasive surgery has got revolutionary successes in more and more fields of

traditional surgery, and has become mainstream of the global surgery developments. Minimally invasive surgery has been not only the belief and pursuit of modern surgeons, but also the compulsory courses as well.

In March 1987, Franch surgeon Phillipe Mouret first used laparoscopy in cholecystectomy, which has unveiled a new era in the development of minimally invasive surgery. Compared with small incision in traditional surgery, modern minimally invasive surgery has a deeper and promoted meaning. Small incision, quick recovery, light pain, beauty, and short hospital stays are all advantages of minimally invasive surgery. People begin to realize that postoperative recovery is mainly related with abdominal incision, exposure duration and extent of damage of the abdominal cavity.

In 1990, American surgeon Jacobs completed the world's first laparoscopic right colon resection. Cutting stapling device (Endo-GIA) has greatly improved the operating conditions of laparoscopic surgery, which has made the cut-off of mesenteric vessels and bowel loops inside abdominal cavity and the lower rectal anastomosis possible. In October 1990, Dennis Fowler operated the first laparoscopic sigmoid resection using Endo-GIA. In November of the same year, Patrick Leahy completed the first laparoscopic ultra-low anterior resection (Dixon) with Endo-GIA. In July 1991, Joseph Uddo completed the first laparoscopic right colon resection. Within one year, almost all types of colon surgeries have been attempted under laparoscopy. In 1992, Kokerling completed world's first abdominoperineal resection (Miles) with laparoscopy. In our country, first laparoscopic colorectal surgery was carried out in 1993, and since then, laparoscopy was gradually used in traditional colorectal cancer surgeries. In the past 20 years, with the continuous development of laparoscopic surgical techniques and the invention and perfection of all kinds of laparoscopic equipments, laparoscopic colorectal surgery has achieved encouraging achievements, and its short and long-term effects have been approved.

With the improvement of the technologies and equipments, laparoscopic colorectal surgery is developing constantly. Mainly, laparoscopic colorectal surgery includes three techniques: Laparoscopic colorectal resection, laparoscopic assisted colorectal resection, and hand assisted laparoscopic colorectal resection. Compared with traditional open surgery, laparoscopic colorectal surgery has following advantages: (1) light postoperative pain; (2) shortened wound healing time, the abdominal incision is relatively small and beautiful; (3) faster recovery of gastrointestinal function; (4) fast-returned normal activities and short hospital stays; (5) reduced complications such as ileus, incision infection; (6) improved patient's intraoperative and postoperative immunity; (7) better operative view in narrow space such as pelvic floor; and (8) precise operation under the magnified view, which is beneficial to vascular skeletonization and lymph-node dissection.

Although laparoscopic colorectal surgery has these advantages, in early time, it did not develop fastly as people expected like laparoscopic cholecystectomy. This is mainly because of the complexity and the long "learning curve" of the laparoscopic colorectal surgery. In recent years, with the development of laparoscopic surgical techniques and the invention of ultrasound knife, Ligasure, and all kinds of intracavitary cutting stapling devices, intraoperative bleeding and operation difficulties are greatly reduced, and the operation time is also notably shortened, which has vigorously promoted the development of laparoscopic colorectal surgery. Since then, laparoscopic colorectal surgery has entered into a rapid developing stage. At present, all the colorectal cancer centers in Shanghai have carried out laparoscopic colorectal surgery, and the proportion of laparoscopic surgeries is rising year by year.

EVIDENCE OF LAPAROSCOPIC COLORECTAL CANCER SURGERY

In the early developing period, laparoscopic colorectal surgery has many controversies. This is mainly because people have a lot of concerns about the application of laparoscopic surgery in malignant tumor treatments: First, whether laparoscopic surgery may increase the incidence of implantation metastasis? And whether laparoscopic surgery can achieve radical resection? Second, whether laparoscopic colorectal surgery may increase surgical complications? Third, since in early time, the learning curve and operation time of laparoscopic colorectal surgery is obviously longer, whether laparoscopic surgery can embody minimal invasion? To answer the above questions, it is necessary to resort to evidence-based medicine for help.

Oncology efficacy

At the end of last century, a series of large randomized controlled trial (RCT) studies comparing laparoscopic and open colorectal surgeries were carried out in Europe and United States (Table 1). In 1993, Lacy *et al*[1] in Spain firstly launched RCT studies comparing laparoscopic and open colon surgeries. From then on, RCT studies such as COST in United States, COLOR in Europe, and CLASICC in United Kingdom were carried out successively[2-4], Leung *et al*[5] in Hong Kong also conducted RCT studies on laparoscopic and open colorectal surgeries. In 2002, Lacy *et al*[1] first published the result of RCT studies on short and long-term effects of laparoscopic colorectal cancer surgery. Since then, the results of RCT studies above have been completed and published one after another. The research contents involve radical resection, long-term curative effects, quality of life and cost effectiveness, *etc.*, which have provided credible clinical evidences for the application of laparoscopic colorectal cancer surgery on the basis of evidence-based medicine.

Since the lack of evidence on laparoscopic rectal

Table 1 Randomized controlled trial studies comparing laparoscopic colorectal surgery and conventional colorectal surgery

Study	No. of patients (laparoscopic *vs* conventional)	Year
Lacy *et al*[1]	219 (111 *vs* 108)	1993-1998
Leung *et al*[5]	403 (203 *vs* 200)	1993-2002
COST	872 (435 *vs* 437)	1994-2001
COLOR	1248 (627 *vs* 621)	1997-2003
CLASSIC	794 (526 *vs* 268)	1996-2002
COLOR Ⅱ	1103 (739 *vs* 364)	2004-2010

cancer surgery, Colon Cancer Laparoscopic or Open Resection Study Group in Europe launched COLORII study[6]. The study began in 2004, a total of 8 countries and 30 centers participated. From January 2004 to May 2010, a total of 1103 cases entered into the group randomly, 59 patients were ruled out for various reasons or incompleted follow-up, 1044 patients were analyzed for statistics finally. In 2013, the study reported the preliminary results. According to the results, the conversion rate of laparoscopic surgery was 17% (91/536). Compared with open surgery, laparoscopic surgery has longer operation time (240 min *vs* 188 min, $P < 0.001$), but less blood loss (200 mL *vs* 400 mL, $P < 0.0001$), faster recovery of gastrointestinal function (2 d *vs* 3 d, $P < 0.036$) and shorter postoperative hospital stays (8 d *vs* 9 d, $P < 0.036$). Postoperative pathological report shows that tumor stage, tumor size, and pathological type have no significant differences between these two groups. No significant differences were also observed in margin distance, positive margin rate and the number of lymph node dissection. The 28-d postoperative complication and mortality rates were close in these two groups. The researchers concluded that for experienced surgeons, laparoscopic rectal cancer surgery can not only meet the radical standard of open surgery, but also enhance postoperative recovery at the meantime.

Implantation metastasis problems of incision

In early times, there were controversies about whether laparoscopic colorectal cancer surgery may cause incision implantation or tumor dissemination. Once upon a time, it was reported that the rate of incision implantation was higher in laparoscopic surgery, the reason may due to the lack of standardization of the operation. In Lacy *et al*[1] study, among these 111 cases, only one had implantation metastasis in trocar puncture hole. More and more reports confirmed that as long as the surgery is operated in accordance with disease-free principles, the rate of incision implantation will not increase. After analyzing 2858 laparoscopic colon cancer cases, Stocchi *et al*[7] reported that the rate of incision implantation is only 0.7% for experienced surgeons. It was also reported, the incision implantation rate is about 0%-1.3% after laparoscopic colon cancer surgery in experienced laparoscopic centers, which has no difference with open surgery[8-11]. Standardized operation can greatly decrease the rate of incision implantation, including: (1) follow the disease-free principles during the surgery and avoid cutting tumor directly using ultrasonic knives; (2) do not stretch or squeeze tumor and simply pursue small incision when removing the tumor, take the tumor out gently with an incision protector or specimen bag, and pay attention to incision flushing at the end of surgery; and (3) before taking the Trocars out, exhaust gases from the vent hole slowly first.

Operation security problems

As the laparoscopic vision is 2-dimensional, it is often difficult to distinguish anatomical structure with spatial perception during the surgery. Moreover, laparoscopic surgery is operated by equipments, as a result, there is no hand feeling, so the laparoscopic colorectal surgery is much more difficult than ordinary laparoscopic cholecystectomy. In early time, complications of laparoscopic colorectal surgery is high, generally reported about 10%-17%. But as the advancement of "learning curve" and improvement of surgical techniques and experience, current literature reports that the incidence of complications will be gradually reduced after operating more than 30 cases. The laparoscopic peculiar complications include: Air embolism and subcutaneous emphysema, *etc*. There are also two Trocar-related complications, one is Trocar infection, but it is very rare, and does not extend hospital stays, and can be treated in outpatient clinics. The other is Trocar hernia, which is also relatively rare, and can be avoided by closing the Trocar holes carefully. Generally, laparoscopic colorectal surgery does not increase mortality, which is usually caused by systemic complications rather than the surgery itself. The life-threatened complications are extremely rare.

Arezzo *et al*[12] analysed all randomized and prospective controlled studies comparing laparoscopic and open rectal cancer surgeries in the Medline and Embase database from 2000 to 2011. Twenty-three studies including 4539 patients meet the criteria. Among them, there are 8 RCT studies, including 1746 patients. Analysis showed that within 30 d after surgery, mortality in laparoscopic group was 1.0%, while in open group was 2.4% (95%CI: 0.21-0.99, $P = 0.048$). The total complication rate was 31.8% in laparoscopic group, while 35.4% (95%CI: 0.76-0.91, $P < 0.001$) in open group. The results of meta-analysis once again prove that laparoscopic surgery has lower complications and mortality rates than open surgery.

INNOVATIVE OR CONSERVATIVE?

In recent years, new technologies in laparoscopy emerge in endlessly, including traditional laparoscopic surgery, robotic surgery, 3-D laparoscopic surgery, single-port laparoscopic surgery (SPA), natural orifice transluminal endoscopic surgery (NOTES) and transanal minimally invasive surgery (TAMIS).

We take Da Vinci Robot as an example, the system not only inherits advantages of traditional laparoscopic surgery, but has many peculiar advantages as well: (1)

there are 4 mechanical arms with the ability of 7 free degrees, which makes it possible to operate precisely in narrow and small space; (2) the thrill of hand can be filtered by computer, which improves the stability of real-time operation picture, and greatly improves the accuracy of operation; (3) high resolution 3-D image gives the operator clear and real stereo visual feedbacks; (4) the good ergonomic design allows the surgeon to operate without standing, which can significantly alleviate fatigues and is more convenient for surgeons to complete complicated and long-time surgeries; and (5) long-distance operation is possible through the robot arm controlled by remote signal transmission. However, so far, the robot's force feedback components are not perfect, because in colorectal surgery, keeping good tension is very important for the quality of operation. Moreover, robots are extremely expensive, their overall cost performance is not high enough for developing countries. So, there is still a long way to go for the popularization of robots.

3-D laparoscopic surgery has the advantages of traditional laparoscopic surgery, its high resolution 3-D image makes the operation more accurate, so it can shorten the learning curves for surgeons, especially for beginners. In order to pay more attention to minimally invasive surgery, techniques such as SPA, NOTES and TAMIS were developed in recent years, the challenges we face are how to operate safely and effectively with only one hole in the case that the surgical instruments are still deficient and how to design instruments with good handling and flexibility, these challenges decide whether these techniques would be epoch-making innovations like the birth of laparoscopy 24 years ago.

In the era of rapid development of new technologies, should a colorectal surgeon be innovative or conservative? It is hard to decide sometimes. As far as I am concerned, the key point is: the feasibility of technology does not mean the rationality of treatment. When treating colorectal cancer, the reliability of radical resection is always in the first place, the second is to minimize surgical complications, finally we may consider to operate minimally invasively. So, we should not put the cart before the horse. We should not pursue less holes and result in increasing difficulties of radical dissection and decreasing of the quality of surgery. For the new techniques like SPA, NOTES and TAMIS, they are now restricted by the existing equipments, which will undoubtedly increase the difficulties of radical dissection and the risks of potential complications. As a result, such technologies should only be confined to benign or early malignant colorectal tumors presently.

As a colorectal surgeon, we should not get lost in the tide of minimally invasive surgery and simply pursue the maximization of minimally invasion. We are delighted to see that since laparoscopic colorectal surgery was developed in China, high-resolution endoscopic vision, high levels of fine anatomy and the establishment of good training plans have made young surgeons more profound in understanding colorectal surgery, which have greatly improved the surgical quality of young surgeons. Therefore, patients are getting better quality of the surgical treatments, and gaining a better survival. Based on the above understanding, we think that the core value of the laparoscopic technique is to ensure the high quality of tumor's radical resection and less complications. On the basis of this, it is allowed to pursue more minimally invasive techniques.

After hundred years of development of colorectal cancer surgery, people's concepts have been greatly changed, the early emphasis of radical resection has been substituted by function preservation and life quality improvements on the basis of radical treatment. Minimally invasive surgery meet these requirements, which reveals the irreversible developments of laparoscopic colorectal surgery. We have reasons to believe that laparoscopic surgery will become gold standard for colorectal surgery in the near future.

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ORIGINAL ARTICLE

Observational Study

Race and colorectal cancer screening compliance among persons with a family history of cancer

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Abstract

AIM: To determine compliance to colorectal cancer (CRC) screening guidelines among persons with a family history of any type of cancer and investigate racial differences in screening compliance.

METHODS: We used the 2007 Health Information National Trends Survey and identified 1094 (27.4%)

respondents (weighted population size = 21959672) without a family history of cancer and 3138 (72.6%) respondents (weighted population size = 58201479) with a family history of cancer who were 50 years and older. We defined compliance with CRC screening as the use of fecal occult blood testing within 1 year, sigmoidoscopy within 5 years, or colonoscopy within 10 years. We compared compliance with CRC screening among those with and without a family member with a history of cancer.

RESULTS: Overall, those with a family member with cancer were more likely to be compliant with CRC screening (64.9% *vs* 55.1%; OR = 1.45; 95%CI: 1.20-1.74). The absolute increase in screening rates associated with family history of cancer was 8.2% among whites. Hispanics had lowest screening rates among those without family history of cancer 41.9% but had highest absolute increase (14.7%) in CRC screening rate when they have a family member with cancer. Blacks had the lowest absolute increase in CRC screening (5.3%) when a family member has a known history of cancer. However, the noted increase in screening rates among blacks and Hispanics when they have a family member with cancer were not higher than whites without a family history of cancer: (54.5% *vs* 58.7%; OR = 1.16; 95%CI: 0.72-1.88) for blacks and (56.7% *vs* 58.7%; OR = 1.25; 95%CI: 0.72-2.18) for Hispanics.

CONCLUSION: While adults with a family history of any cancer were more likely to be compliant with CRC screening guidelines irrespective of race/ethnicity, blacks and Hispanics with a family history of cancer were less likely to be compliant than whites without a family history. Increased burden from CRC among blacks may be related to poor uptake of screening among high-risk groups.

Key words: Colon cancer; Health disparities; Screening; Fecal blood test; Colonoscopy

Core tip: It is unclear whether suboptimal screening contributes to the increased risk of cancer within families. We evaluated compliance with colon cancer screening guidelines among adults in the United States. Our study suggested that adults with a family history of any cancer had higher screening rates, but the smallest increase was noted among blacks. Overall, screening was lower among blacks and Hispanics to such an extent that screening among those with a family member with cancer was not higher than screening among whites without a family member with cancer. There is a particular need to improve screening among high risk blacks.

Laiyemo AO, Thompson N, Williams CD, Idowu KA, Bull-Henry K, Sherif ZA, Lee EL, Brim H, Ashktorab H, Platz EA, Smoot DT. Race and colorectal cancer screening compliance among persons with a family history of cancer. *World J Gastrointest Endosc* 2015; 7(18): 1300-1305 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i18/1300.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i18.1300

INTRODUCTION

Colorectal cancer (CRC) is a leading cause of cancer-related deaths in the United States[1]. There is ample evidence that screening reduces the burden from this deadly but largely preventable disease[2-4]. Unfortunately, screening rates are suboptimal among the population, particularly among racial/ethnic minorities.

A primary driving factor for the time to initiate CRC screening is the family history of CRC[5]. However, it is well known that malignancies of other organ sites are associated with syndromic CRC such as Lynch syndrome (hereditary non-polyposis colorectal cancer)[6,7]. Lynch syndrome is caused by mutations in mismatch repair gene and is associated with an increased the risk of CRC but other malignancies such as endometrial and urogenital cancers are associated with this syndrome as well.

We hypothesized that CRC awareness should be higher among families with any history of cancer, not just CRC. This awareness should in turn be associated with uptake of CRC screening. The burden of CRC is highest among blacks due to multiple factors related to poorer access, inadequate utilization of healthcare resources even when available and possible biological susceptibility differences[8-10]. Furthermore, blacks are less likely to be aware of cancer diagnosis of their family members[11,12]. We postulated that increased CRC incidence and mortality among blacks may be due to poorer uptake of CRC screening among those at a higher risk of the disease. The aim of the present study was to evaluate compliance with CRC screening guidelines among United States adults with and without a family member with any cancer and investigate differences in compliance by race/ethnicity (whites, blacks and Hispanics).

MATERIALS AND METHODS

We used data from the 2007 Health Information National Trends Survey (HINTS) and the details of the survey have been published[13]. In summary, HINTS was a national survey of adults on health-related information and practices. It was conducted by the National Cancer Institute, National Institutes of Health in the United States between January 2008 and May 2008. The survey is available online at http://hints.cancer.gov/docs/Instruments/HINTS%202007%20CATI%20Instrument%20(English).pdf and http://hints.cancer.gov/docs/HINTS2007FinalReport.pdf.

A total of 7674 people completed the HINTS telephone interview (n = 4092), or mailed survey (n = 3582). Respondents were asked to provide information

Table 1 Comparison of characteristics of respondents with and without a family history of cancer

	Family history of cancer		*P* value
Characteristics	No	Yes	
	n = 1094 (27.4%)	*n* = 3138 (72.6%)	
Mean age, yr (95%CI)	63.4 (62.7-64.2)	63.8 (63.5-64.1)	
Sex, *n* (%)			< 0.001
Male	520 (55.8)	1158 (42.5)	
Female	574 (44.2)	1980 (57.5)	
Race, *n* (%)			< 0.001
White	818 (70.4)	2560 (82.1)	
Black	107 (12.6)	244 (9.6)	
Hispanic	92 (10.0)	134 (5.2)	
Other	62 (6.9)	123 (3.1)	
Education status, *n* (%)			0.03
Less than high school	139 (19.6)	287 (14.6)	
High school	287 (25.2)	857 (28.6)	
Some college/vocation	297 (31.1)	933 (31.7)	
College graduate	365 (24.1)	1050 (25.2)	
Marital status, *n* (%)			0.01
Unmarried	406 (32.1)	1300 (37.2)	
Married	684 (67.9)	1822 (62.8)	
Insurance status, *n* (%)			0.001
Uninsured	100 (12.1)	201 (7.3)	
Insured	983 (87.9)	2886 (92.7)	
Smoking status, *n* (%)			0.31
Never	499 (44.7)	1472 (46.2)	
Former	400 (37.4)	1205 (38.7)	
Current	179 (18.0)	419 (15.1)	
Body mass index in kg/m^2			0.82
< 25	363 (31.7)	1047 (31.7)	
25-29	406 (39.0)	1160 (37.8)	
⩾ 30	316 (29.3)	905 (30.5)	
Personal history of cancer, *n* (%)			0.06
No	908 (87.8)	2536 (85.3)	
Yes	185 (12.2)	592 (14.7)	

All percentages are weighted.

on demographic and lifestyle factors, first degree family history of any type of cancer. They were also asked about colon cancer screening with fecal occult blood test, sigmoidoscopy or colonoscopy and when they had the tests. After obtaining approval (IRB-14-MED-28) from the Institutional Review Board of Howard University in Washington DC, we downloaded the dataset. For the present study, our analytical cohort consisted of 4232 respondents (weighted population size = 80161151) who were at least 50 years old and answered questions about their family history of cancer and CRC screening compliance.

Statistical analysis

Our primary outcome was the compliance to CRC screening guidelines defined as the uptake of fecal occult blood testing within 1 year, sigmoidoscopy within 5 years, or colonoscopy within 10 years. We compared the characteristics of respondents with and without family members with a history of cancer. We used survey weights in all analyses and Taylor series linearization was used for variance estimations. Logistic regression analysis was used to estimate OR and 95%CI for the association between family history of cancer and compliance with CRC screening guidelines. We also investigated this association by race/ethnicity. Our final models included age, sex, marital status, highest education achieved, race, health insurance status, smoking status and personal history of cancer. We calculated OR and 95%CI. Statistical analysis was performed by a qualified biostatistician using Stata® statistical software version 11.2 (College Station, Texas) for all analyses. All reported percentages were weighted.

RESULTS

The comparisons of the characteristics of respondents with and without a family history of any cancer are shown in Table 1. Overall, those with a family history were more likely to be female, unmarried, and have health insurance. However, there was no difference in the prevalence of cigarette smoking, body mass index, or personal history of cancer.

When compared to respondents without a family history of cancer, those who had family members with cancer were more likely to be compliant with CRC screening (64.9% *vs* 55.1%; OR = 1.45; 95%CI: 1.20-1.74). Among whites, those with family history of

Table 2 Intra-racial comparison of being up-to-date with colorectal cancer screening by racial distribution of family history of any cancer

	Family history of any cancer	Up-to-date with CRC screening		
		Wt % screened	Unadjusted OR (95%CI)	Adjusted OR (95%CI)
Overall	No (n = 1094)	55.1	Reference	Reference
	Yes (n = 3138)	64.9	1.51 (1.25-1.81)	1.45 (1.20-1.74)
By race				
White	No (n = 818)	58.7	Reference	Reference
White	Yes (n = 2560)	66.9	1.42 (1.18-1.72)	1.49 (1.24-1.78)
Black	No (n = 107)	49.2	Reference	Reference
Black	Yes (n = 244)	54.5	1.24 (0.64-2.38)	1.34 (0.61-2.94)
Hispanic	No (n = 92)	41.9	Reference	Reference
Hispanic	Yes (n = 134)	56.7	1.81 (0.84-3.89)	1.42 (0.55-3.67)

Adjusted for age, sex, education, health insurance, BMI, smoking, marital status and personal history of cancer. CRC: Colorectal cancer; BMI: Body mass index.

Table 3 Inter-racial comparison of being up-to-date with colorectal cancer screening by racial distribution of family history of any cancer

Race	Family history of any cancer	Up-to-date with CRC screening		
		Wt % screened	Unadjusted OR (95%CI)	Adjusted OR (95%CI)
White	No (n = 818)	58.7	Reference	Reference
White	Yes (n = 2560)	66.9	1.42 (1.18-1.72)	1.45 (1.21-1.74)
Black	No (n = 107)	49.2	0.68 (0.39-1.18)	0.96 (0.51-1.80)
Black	Yes (n = 244)	54.5	0.84 (0.54-1.31)	1.16 (0.71-1.90)
Hispanic	No (n = 92)	41.9	0.51 (0.27-0.95)	0.84 (0.48-1.47)
Hispanic	Yes (n = 134)	56.7	0.92 (0.57-1.48)	1.25 (0.72-2.18)

Adjusted for age, sex, education, health insurance, BMI, smoking, marital status and personal history of cancer. CRC: Colorectal cancer; BMI: Body mass index.

cancer had 8.2% absolute higher screening rates than whites without family history of cancer (OR = 1.45; 95%CI: 1.20-1.75; Table 2). Screening rates were generally lower among Hispanics and blacks. Blacks had the lowest increase in screening rates (5.3%) when a family member had a history of cancer which was not statistically different from blacks without a family member with cancer diagnosis (OR = 1.34; 95%CI: 0.61-2.94). Although, Hispanics had the lowest screening rates among those without history of cancer (41.9%), the absolute increase in screening rates was highest among Hispanics (14.7%) when a family member has had a history of cancer.

Despite increase in CRC screening rates among blacks and Hispanics with family history of cancer, their screening rates were still numerically lower than the screening rates among whites without a family history of cancer. However, there were no statistically significant differences in the comparison of interracial screening rates (Table 3).

DISCUSSION

In the present study, we evaluated compliance with CRC screening guidelines among United States adults with and without a family history of cancer overall and by race/ethnicity. Irrespective of race/ethnicity, we found that those with a family history of cancer were more likely to be compliant with CRC screening guidelines compared to those without a family history. This pattern was present among each racial/ethnic group. However, this relationship was statistically significant only among whites. Among blacks, the absolute increase in the compliance with CRC screening among those with a family history of cancer was small. We found that screening rates were so low among blacks that the higher screening rates observed among blacks with family history of cancer were still numerically lower albeit not statistically different from the screening rate among whites without a family history of cancer. This suggests that the increased CRC burden among blacks may be, in part, due to low screening rates among high risk blacks and underscores the need to increase awareness and screening rates among blacks.

Although the Hispanics in this study have the lowest CRC screening rates among those without a family history of cancer, they exhibited the highest absolute increase in CRC screening among those with a family history of cancer. This suggests an appropriate response in uptake of preventive services among Hispanics, but the screening rates were still lower than that among whites without a family history of cancer. This finding indicates that increased education about CRC screening is needed among Hispanics.

We are not aware of any other study that has examined the association of a family history of any

cancer with CRC screening for a direct comparison to our study. However, prior studies have examined the CRC screening among persons with a family history of CRC. Using data from the 2005 California Health Interview Survey (CHIS), Ponce *et al*[14] reported that screening rates were lower among Hispanics in general when compared with whites, but disparities were more pronounced among respondents with a family history of CRC (OR = 0.28; 95%CI: 0.11-0.60) as compared to disparity among those without family history of CRC (OR = 0.74; 95%CI: 0.59-0.92). However, CRC screening rate was comparable among blacks and whites among those with (OR = 0.92; 95%CI: 0.31-1.34) or without a family history of CRC (OR = 1.08; 95%CI: 0.84-1.40). In another study which used the 2009 CHIS, Almario *et al*[15] investigated CRC screening among respondents with a family history of CRC in California. The authors reported that there was no difference in overall screening rate among blacks when compared to whites (OR = 1.03; 95%CI: 0.81-1.27). However, among individuals who were 40-49 years old (when early screening should have started because of the increased risk of CRC), blacks were 71% less likely to have had a colonoscopy (OR = 0.29; 95%CI: 0.04-0.87). Taken together, these two studies suggest lower rates of appropriate CRC screening among blacks and Hispanics at an increased risk of CRC. However, the studies focused only on residents of the state of California. Nonetheless, these findings were comparable to our findings that are based on nationally representative data of United States adults.

It is unclear why the rates of CRC screening was lower among these minority populations, but we speculate that known factors such as health literacy, access and utilization differences may be playing important roles. In a previous study using the 2007 HINTS data, Orom *et al*[16] reported differences in perceived cancer risk by race. The authors reported that Hispanics were less likely to perceive themselves at higher risk of cancer even when they have family members with cancer. This disconnect may be related to health literacy or communication challenges. It is well known that blacks are less likely to discuss their chronic health problems with family members[17,18] and often hold fatalistic beliefs which negatively correlate with uptake of preventive services such as CRC screening[19].

There are some notable strengths of our study. We examined compliance with CRC screening guidelines among a nationally representative large sample of United States adults and two modes of survey was used (mail and telephone), thereby increasing the reach of the survey. Furthermore, the survey was conducted in English and Spanish to ensure broader participation. However, our study has important limitations. Although we do not suspect that respondents would have any motivation not to tell the truth, but our study was based on self reports and we could not abstract medical records to verify CRC screening uptake and the time they took place. Also, the race designation in the HINTS survey was by self-identification. Furthermore, our study did not capture other factors which may influence CRC screening compliance such as accessibility to healthcare facilities, availability of culturally sensitive care providers and type of health insurance coverage.

In conclusion, while being up-to-date with CRC screening is generally higher among those with a family history of cancer, blacks and Hispanics with a family history of cancer were less likely to be compliant with CRC screening guidelines compared with whites without a family history of cancer. There is a need to improve cancer education among blacks and Hispanics and increase CRC screening rates, especially among higher risk groups.

COMMENTS

Background

The risk of cancer is higher among families when a member has been diagnosed with cancer. The current study evaluated compliance with colorectal cancer (CRC) screening guidelines among adults with and without a family member with a history of cancer.

Research frontiers

The CRC screening rates were higher among United States adults with family members with cancer diagnosis. By race, CRC screening rates among blacks and Hispanics were lower than whites. The screening rates among blacks and Hispanics with family history of cancer did not even reach the level of screening among whites without family history of cancer.

Innovations and breakthroughs

The current study examined whether United States adults with a family history of cancer were more likely to be compliant with CRC screening guidelines. This has not been thoroughly investigated previously.

Applications

Blacks and Hispanics have lower screening rates than whites even when they have family members with history of cancer. This study suggests that the low absolute increase in CRC screening rates among blacks when a family member has a history of cancer may represent inadequate CRC screening uptake among high risk blacks. This may be playing a role in the observed CRC disparity by race in the United States.

Terminology

Screening for CRC reduces the incidence and mortality from the disease.

Peer-review

The manuscript is a well-designed observational study that addressed a major issue about health behavior among different races. The authors managed to reveal this issue through extensive research and thorough statistical analysis.

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EDITORIAL

Utilisation of magnets to enhance gastrointestinal endoscopy

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Abstract

Methods to assess, access and treat pathology within the gastrointestinal tract continue to evolve with video endoscopy replacing radiology as the gold standard. Whilst endoscope technology develops further with the advent of newer higher resolution chips, an array of adjuncts has been developed to enhance endoscopy in other ways; most notable is the use of magnets. Magnets are utilised in many areas, ranging from endoscopic training, lesion resection, aiding manoeuvrability of capsule endoscopes, to assisting in easy placement of tubes for nutritional feeding. Some of these are still at an experimental stage, whilst others are being increasingly incorporated in our everyday practice.

Key words: Magnet; Endoscopy; Training; Therapeutic; Capsule; Nutrition; Child; Paediatric; Colonoscopy; Imaging

Core tip: Magnetic technology is being incorporated into many aspects of endoscopy from diagnostic procedures to assisting in therapeutic interventions. Here we summarise some of the more exciting innovations and the potential future roles magnets will play in this field.

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INTRODUCTION

Magnets were traditionally viewed with great scepticism by the endoscopy community due to the potentially hazardous consequence that ingestion of this material

led to. However the property of magnets, notably the ability to be sensed and also exert a force from a distance, began to be recognised as a solution to many emerging problems faced by an endoscopist. Magnetic technology is now incorporated within many areas of endoscopy.

Endoscopic training

Colonoscopy is undertaken worldwide, with variations in reported caecal intubation rates. Although there are several reasons for this, a common factor elucidated in quality assurance audits is the consequence of recurrent colonic looping leading to a consequent lack of advancement of the endoscope tip, and subsequent patient discomfort[1]. Measures to appreciate colonoscopic positioning in the past required fluoroscopy, however, its use was cumbersome and posed a radiation risk[2,3]. In 1993, the technique of magnetic endoscopic imaging (MEI) of the colonoscope was described by Bladen *et al*[4]. This was then further developed by Olympus® into a mobile unit known as "Scopeguide". This technology provides a real time three-dimensional image of the colonoscope as it passes through the colon. The basic principle relies on the generation of pulsed low intensity magnetic fields generated from electromagnetic generator coils positioned at regular intervals within the colonoscope. This is then picked up by a receiver dish which allows calculation of the precise position and orientation of the colonoscope. It enables loops to be visualised and loop resolution to be performed under direct vision as well as assisting in identifying the location of the tip of the scope.

It has been proposed that this device can improve caecal intubation rates, times and patient comfort. This was demonstrated in the first randomized controlled trial (RCT) of MEI on colonoscopy performance in adults[5]. However, more recent studies have demonstrated conflicting results in those with enough statistical power to show a difference in the two groups. Two studies have shown higher caecal intubation rates, one study has shown shorter intubation times and two showed patient comfort scores were better with MEI, although one of the latest studies looking into its role in unsedated colonoscopy failed to show any statistical difference in any of these outcome measures[5-8]. The largest RCT on MEI to date (n = 810) did however reveal that in less experienced endoscopists the performance, measured by caecal intubation rate, was significantly better than with standard colonoscopy without MEI[9]; also demonstrated by Chen *et al*[10] in a meta-analysis collating 8 RCT. This may lead to the conclusion that the benefit of the device may be more of a training tool for trainee endoscopist through identification of loops, as shown by similar performance improvements in this group in other cohort studies[11-13].

These devices are not in general routine practice on all endoscopy sessions, in part because they are expensive to purchase and require the use of Olympus® equipment. However, what studies have not recorded is the current trainee and trainer satisfaction with this equipment. As the dynamics of the colon can be visualised, there can be a more logical discussion between the trainer and trainee, to resolve an issue of lack of tip advancement or patient discomfort. In practice, trainees appear to be more satisfied with the use of MEI during colonoscopy. One explanation for this is that it allows the trainer to explain the decision making required to facilitate tip advancement without taking the colonoscope over from the trainee. With the growing pressure to train a greater number of generic healthcare endoscopists, the additional cost may thus be justified. With other endoscope manufacturers, such as Pentax®, incorporating MEI into their equipment in the near future it is likely this technology becomes increasingly embedded in day to day colonoscopy practice.

Therapeutic endoscopy

Going beyond the realms of basic diagnostic endoscopy, into an era where the endoscopist has now developed the proficiency to undertake therapy, comes an explosion of technology. Endoscopic polypectomy has evolved since its first undertaking by Hiromi Shinya in 1969, from the basic "lassoing" of a polyp to endoscopic mucosal resection (EMR) to endoscopic submucosal dissection (ESD) which allows en-bloc resection of large lesions[14]. ESD is however a technically demanding procedure with relatively longer procedure times compared with EMR, and significant complication rates with perforation risk as high as 18% in some series[15]. A common reason for this difficulty is the limited field within which the endoscopist, with his "one handed knife", is operating in. Current standard technique requires the use of a combination of submucosal fluid injection and utilisation of gravity. However, these methods often lead to difficulty in maintaining a safe field of dissection due to a lack of elevation to expose the submucosal plane. To overcome this issue, Gotoda *et al*[16] designed a magnetic anchor device to apply counter-traction. The anchor consisted of a small magnetic weight that was attached to an endoclip with a thread. Once the standard circumferential incision had been made for ESD, the anchor, which was loaded on the end of a standard endoscope, was deployed by attaching the clip to one end of the flap of the lesion[16]. Initially, an extracorporeal magnetic control system of a C-arm type was used to attract the anchor away from the lesion to allow sufficient counter-traction of the flap by the endoclip, which behaved as micro-forceps. The external magnet has since been miniaturised by other investigators to a smaller hand held magnet which is positioned over the torso of the patient. This method has been shown to be feasible as well as reduce procedural times, with no reported complications on 25 gastric lesions[17,18]. This is a promising method and adds to the arsenal of ways to allow possible endoluminal triangulation.

At a more endoscopic surgical level, the use of magnets has been used to create suture free anastomoses. The concept relies on a pair of identical magnetic rings being applied to each end of the intestinal segments to be joined.

When they are then brought into close proximity, the magnets align and mate together. Over a period of about 5 d the inner area necroses off while the surrounding non compressed tissue heals and remodels itself. The coupled magnets then fall off into the created lumen leaving a magnetic compression anastomosis. Initial animal model experiments have shown encouraging safety and efficacy. But unfortunately this did not transpire into the clinical setting, with reports of serious adverse events[19-21]. Further disadvantages in this technique were the inevitable delay in anastomotic formation as well as a restriction on the circumference of the anastomosis due to the initial fixed size magnets used. To get over this drawback, more recent research has looked into using "nano-magnets" delivered *via* an endoscopic catheter device. These self-assemble at the two opposing desired sites to occupy a larger perimeter. The lumen of the anastomosis is then created with the aid of a needle knife. An early proof of concept studys on live porcine models, as well as a human cadaver, has shown the successful formation of gastro-jejunostomies[22]. Although currently not commercially available, magnetic compression anastomosis seems a viable option to aid in the formation of a secure gastro-enteric anastomosis during future natural orifice transluminal endoscopic surgery, replacing the standard methods of suturing or stapling which has its associated complications of leakage and stricture formation.

Capsule endoscopy

The demand for capsule endoscopes has grown exponentially, and it is unlikely that even Paul Swain when he took it upon himself to swallow this first "pill" in 1999 would have envisaged that over 2 million of these would have been ingested worldwide subsequently. The market is well established in the small bowel, and beginning to grow in force progressively for the colon. The upper GI tract seemed to have eluded this technology, firstly due to the speed of travel down the oesophagus and secondly because the larger more capacious stomach really necessitated capsule maneuverability. This has led to several investigators trialling various methods for capsule control, with magnetic assisted capsule endoscopy (MACE) being the most promising. Four systems have been developed, all of which have incorporated magnetic inclusion bodies into the capsule endoscope and controlled externally either by a magnetic field generated by a guidance system or more simply by a fixed magnet on a hand held device. The largest comparative trial to date (n = 189) comparing MACE to standard upper GI endoscopy was undertaken in France using a system developed jointly by Olympus® and Siemens®. The mean examination time was 11 min compared to the 6 min for standard gastroscopy, with the specificity and sensitivity of 94% and 62% respectively for major lesions[23]. However, the magnetic guidance system was similar in size to that of an MRI scanner and was limited to the examination of the stomach.

A simpler system which utilises a hand held magnet has recently been developed by Intromedic Ltd®, the MiroCam-Navi, and which for the first time was capable of exploring the entire upper GI tract. Although awaiting a randomised comparison trial the first feasibility study undertaken on volunteers showed promising visualisation of all the landmarks of the upper GI tract from the GOJ, cardia, fundus, body, incisura, antrum and pylorus of 92%, 88%, 100%, 96%, 96% and 100% respectively[24]. This system even has the possibility to aid in small bowel examination by reducing gastric transit time, through manoeuvring the capsule across the pylorus. Due to the simplicity of its use and high patient acceptance this technology certainly seems a true prospect for the future of upper GI tract examination, with the possibility of accurate capsule localisation and even targeted drug delivery being a distinct likelihood in the future[25,26]. The opportunity to support a community based screening programme, if one was to ever occur for upper GI tract pathology, is an attractive proposition with this technology. This MACE system would not require the expensive set-up costs or decontamination equipment needed with standard endoscopy. However, the current cost of this capsule would need to drop considerably, which should be within the realms of the manufacturers should mass use occur.

Nutritional feeding

In recent times there has been a growing demand for endoscopically placed naso-gastric/jejunal tubes largely due to increase demand for enteral feeding in those unable to maintain an adequate oral intake[27,28]. Jejunal tube placement is often undertaken at the bedside blindly, although this approach is associated with a significant failure rate. The alternative of direct endoscopic or radiological placement requires significantly resources. To attempt to solve these issues, two "bedside magnetic" devices have been developed; the Syncro-Blue tube and the Cortrak system. The Syncro-Blue tube uses a magnetic stylet placed at the end of the feeding tube which is then maneuvered into position *via* attraction of a hand held magnet. This system was evaluated in a case series of 288 critically ill patients, with successful post pyloric placement in 89% and a mean procedure time of 15 min[29]. Each tube costs approximately 95 dollars, which is likely to be cost saving given the associated expense of endoscopic or radiologically placed tubes. The more widely used Cortrak system, which has an electromagnetic transmitting stylet and a receiver placed in the epigastrium, allows real time tracking of the feeding tube as it is passed down the upper GI tract to its desired position. Although the Cortrak system does not allow external control, a recent systematic review has shown that procedure times as well as tube related adverse events are significantly lower compared to endoscopy with similar successful insertion rates[30]. The advantage of this system over the former is that it does not need X-ray imaging to confirm its position, with studies demonstrating 99.5% correlation with X-ray positioning[31]. In addition, there is the benefit of re-inserting the tube if accidental

dislodgement to the stomach was to occur.

CONCLUSION

So it seems that magnets are truly an ally to GI endoscopy, with several establishing methods. Those that are in an experimental stage are growing in momentum with even newer concepts being conceived. With more and more collaborations being undertaken between scientists, physicians and surgeons this seems to be an innovating field and the application of magnets is and will remain an attractive proposition enhancing endoscopy.

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MINIREVIEWS

Endoscopic options for treatment of dysplasia in Barrett's esophagus

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Abstract

Recent advances in the endoscopic treatment of dysplasia in Barrett's esophagus (BE) have allowed endoscopists to provide effective and durable eradication therapies. This review summarizes the available endoscopic eradication techniques for dysplasia in patients with BE including endoscopic mucosal resection, endoscopic submucosal dissection, photodynamic therapy, argon plasma coagulation, radiofrequency ablation and cryotherapy.

Key words: Dysplasia; Barrett's esophagus; Endoscopic therapy; Endoscopic mucosal resection; Radiofrequency ablation; Endoscopy; Photodynamic therapy

Core tip: Endoscopic treatment of high-grade dysplasia in Barrett's esophagus (BE) has become the standard of care for patients with this premalignant condition. In this review, we highlight the efficacy, durability and safety of the available endoscopic therapies for BE with high-grade dysplasia.

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INTRODUCTION

Barrett's esophagus (BE) is defined by the "American Gastroenterological Association" (AGA) as "a condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus", (Figure 1)[1]. The existence of intestinal metaplasia (IM) in the esophagus predisposes to development of esophageal adenocarcinoma and BE

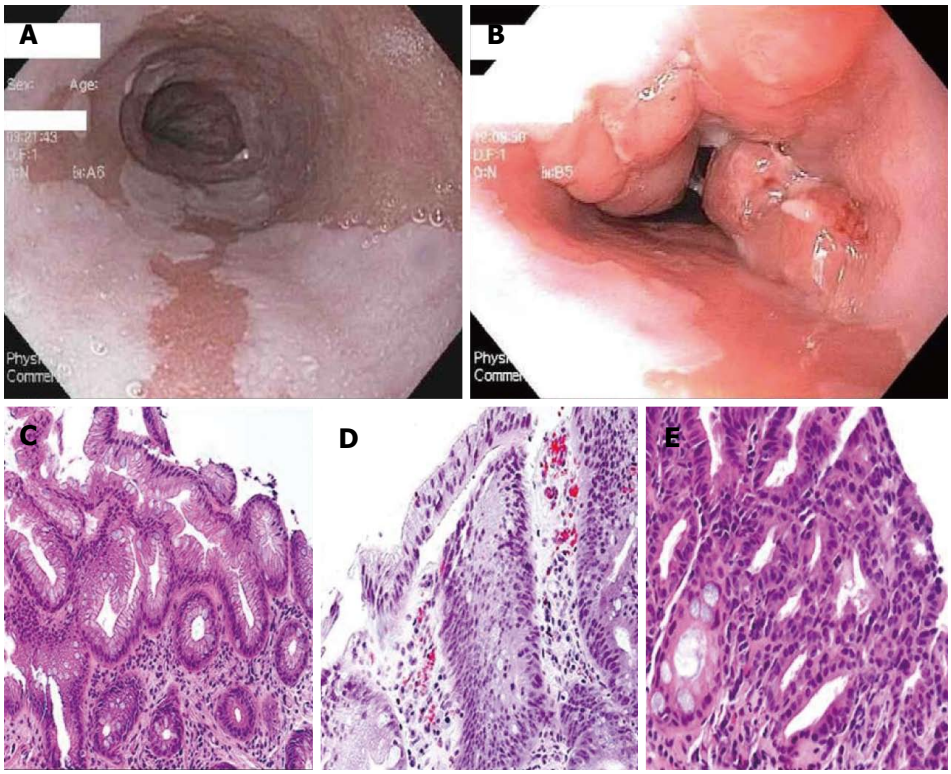

Figure 1 Histopathology pictures. A: White-light endoscopic image of long segment BE; B: White-light endoscopic image of BE with nodular mucosa found to be HGD; C: Hematoxylin and eosin (HE) stain of Barrett's mucosa; D: HE of Barrett's mucosa with LGD; E: Barrett's mucosa with HGD. Histopathology pictures courtesy of Purva Gopal, MD, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas. HGD: High-grade dysplasia; LGD: Low-grade dysplasia; BE: Barrett's esophagus.

has become a well-recognized and treatable condition. The estimates of progression of non-dysplastic BE to adenocarcinoma are variable but uniformly low, ranging from 0.12% to as high as 2.9% per year, with more recent studies reporting lower rates of progression, generally less than 0.5% per year[2,3]. However, the incidence of progression to adenocarcinoma in patients with BE with dysplasia is up to five times as high as in non-dysplastic BE[2]. The presence of high-grade dysplasia (HGD, Figure 1) in BE portends a significant risk of progression to adenocarcinoma, calculated to be up to a 6% annual risk in one meta-analysis[3].

The need for non-invasive strategies to treat dysplasia in patients with BE has become an impetus for gastrointestinal endoscopists to develop new and effective endoscopic techniques. In this paper, we review the different options for treatment of dysplasia in BE, with a focus on endoscopic treatment of HGD.

SURGICAL TREATMENTS

In the past, the gold standard of therapy for HGD was esophagectomy, a procedure with well-recognized morbidity and perioperative mortality as high as 10%[4,5]. More recently, laparoscopic approaches and techniques such as the transhiatal esophagectomy have become more common. These techniques have lower morbidity than some of the older surgical techniques, including reduced hospital length of stay, fewer major complications, and less post-operative dumping syndrome[6,7]. Surgical therapy is a valid curative option for patients in whom there is suspicion of cancer invading the submucosa or if lymph node metastases are present. In patients with early esophageal adenocarcinoma, up to 20% of patients with cancer involving the submucosa will have lymph node metastases, with the risk increasing further with growth of the tumor into the deeper submucosa. In contrast, the risk of lymph node metastases in patients with intramucosal adenocarcinoma (*i.e.*, not invading the submucosa) is much lower at less than 2%[8].

While endoscopic therapy of HGD has become increasingly common, esophagectomy is still an option for patients. The AGA and American Society of Gastrointestinal Endoscopists (ASGE) still acknowledge esophagectomy as a therapeutic option in appropriate patients with BE and HGD, while the American College of Gastroenterology (ACG) guidelines on BE state that esophagectomy is no longer the necessary treatment response to HGD[1,9,10].

ENDOSCOPIC TREATMENTS

For patients with HGD limited to the esophageal mucosa, endoscopic eradication has become the mainstay of therapy. Multiple modalities compatible with endoscopy have been studied including both mechanical removal of tissue and ablative techniques. Methods that involve tissue resection include endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD).

The ablative techniques include several older techniques such as photodynamic therapy (PDT), laser therapy with Nd:YAG (neodymium-doped yttrium aluminum garnet; Nd:$Y_3Al_5O_{12}$) or potassium titanyl phosphate (KTP) lasers, multipolar electrocoagulation (MPEC), argon plasma coagulation (APC), and newer techniques such as cryotherapy and radiofrequency ablation (RFA). These therapies are tailored to the type of HGD present, specifically whether the dysplasia is visible, raised, discolored or nodular; features which have been associated with higher rates of malignancy compared to flat mucosa[11]. It is important to note that all the endoscopic treatments described below require acid suppression therapy for success, namely proton pump inhibitor (PPI) therapy.

EMR AND ESD

EMR, initially developed in Japan for treatment of superficial squamous cell esophageal carcinoma, is now the treatment of choice for nodular HGD in the esophagus[12]. It is also considered helpful diagnostic tool to evaluate for adenocarcinoma invading the submucosa, as well as to determine whether mucosal nodules harbor dysplasia. EMR is useful in staging, as illustrated by Wani *et al*[13]'s study which found that in patients with BE and dysplasia or early cancer, EMR resulted in upstaging of the diagnosis in 10% of patients and downgrading of the diagnosis in 21%. The two main EMR techniques are use of an endoscopic resection cap (ER-cap) (Olympus, Tokyo, Japan), which varies in terms of shape and texture and a multi-band ligator (Wilson-Cook, Indianapolis, United States) used for multiband mucosectomy (MBM). A diathermic snare is used for resection in both techniques. A submucosal lift with saline or a more viscous solution such as hydroxypropyl methylcellulose (artificial tears) can also be employed prior to resection when using the ER-cap method and is sometimes used with MBM. Pouw *et al*[14] performed a randomized controlled trial comparing of ER-cap and MBM and found that MBM was less costly and resulted in fewer acute complications without any significant difference in the depth of tissue resected.

EMR has been shown to be safe and effective as monotherapy for eradication of HGD in several studies. The reported rates of remission from HGD after EMR range from 87%-96% with median follow-up of 22-28 mo[15-17]. The long term remission rate and the durability of EMR as a solo modality for treatment are not currently known; therefore, these patients should be maintained in a surveillance endoscopy program. Complications of EMR include bleeding, perforation, and most commonly stricture formation. The frequency of stricture development reported in EMR studies varies widely, from 12.5% to 88%, depending on the extent of EMR and number of sessions[15-17]. For the majority of patients, post-EMR strictures are easily treated with endoscopic dilation techniques. In general, the smaller the area of resection, the lower the likelihood of stricture formation[17].

ESD is a safe and effective therapy for early gastric cancers and large dysplastic colon polyps[18,19]. Technically, the procedure differs from EMR in that a specialized ESD knife is used to access the submucosal space and dissect the superficial lesion away from the submucosa. As with EMR, a cushion of fluid is first injected to lift the lesion of interest and protect the esophageal wall from deeper penetration of the ESD knife. This fluid typically contains a viscous agent to allow for a sustained lift and a dye to help identify tissue planes for appropriate dissection[20]. The rationale for using ESD is that this technique can allow for a larger and more precise area of dysplastic tissue removal than EMR can safely target.

ESD has recently been evaluated in the management of BE with HGD and early adenocarcinoma. A German group reported a 77% curative resection rate in a small group of patients with a recurrence rate of 5.9% in two years follow-up. The complication rate was 27% for this group of patients and included one perforation and three strictures[21]. A retrospective analysis of 70 Belgian patients who underwent ESD reported a curative resection rate of 64% for patients with HGD and 85% for patients with early adenocarcinoma. At a median follow-up of 20 mo, 92% of patients retained remission from neoplasia. Strictures formed in 60% of patients and these were managed endoscopically[22]. The technique of ESD requires specific training and is only safe in qualified hands in high volume centers. At this time, the ASGE is the only major United States GI society that recognizes ESD as a potential treatment for visible HGD[10].

PDT

PDT is a technique for endoscopic ablation using either 5-aminolevulinic acid or porfimer sodium as a photosensitizing agent followed by exposure to laser light, which causes a photochemical reaction, damaging both mucosal and deeper tissues. The largest study of PDT was a randomized clinical trial evaluating PDT plus omeprazole *vs* omeprazole alone, which showed that patients treated with PDT had a HGD eradication rate of 77% compared to 39% in the omeprazole-alone group. With 5-year follow-up 15% of patients treated with PDT had progressed to cancer, compared to 29% in the omeprazole group[23]. In one longer-term follow-up study of 66 patients with HGD and early adenocarcinoma who underwent PDT, in the calculated 5-year survival was 97% in patients with HGD and 80% in those with early adenocarcinoma without significant long-term complications[24]. Currently, all three major United States societies mention PDT as an option for ablating HGD in BE[1,9,10].

LASER THERAPIES

Nd:YAG and KTP laser-derived thermal therapies have also been evaluated as a treatment tool for HGD in BE. Both Nd:YAG and KTP are crystals that when used in lasers produce wavelengths of light that can damage

tissue, such as dysplastic BE. These lasers have typically been studied in tandem with one another or combined with another mode of therapy. Sharma *et al*[25] reported a series of seven patients with BE and HGD who were not surgical candidates who underwent combination therapy with Nd:YAG laser and monopolar electrocautery. The dysplasia was eradicated in all seven with only residual metaplasia in three patients over a mean follow-up of 3.4 years. Nd:YAG-enhanced KTP laser was also shown to be safe and effective in pilot study of 10 patients with 100% eradication of dysplasia on follow-up esophageal biopsies and no recurrence on average follow-up of 10 mo[26]. Laser treatment is rarely used at this time as other therapies have become more popular.

APC AND MULTIPOLAR ELECTROCOAGULATION

APC is another form of endoscopic thermal therapy using the medium of argon gas to conduct electrical current leading to tissue destruction. The therapy is performed *via* a catheter that fits through the endoscope working channel. MPEC utilizes electrical current through an endoscopic catheter to cause localized tissue destruction. One prospective trial compared APC and MPEC for treatment of dysplastic BE and found no statistical difference in either endoscopic or histologic eradication of dysplasia[27]. However, MPEC required significantly fewer endoscopic therapy sessions with a trend toward better histologic eradication. There were no serious adverse events but 8% of patients treated with MPEC and 13% of patients treated with APC experienced transient upper GI symptoms. While APC is not typically used as a solo modality for treatment of BE and dysplasia, APC can be used to treat small areas of residual BE. In one study of patient with BE and HGD who underwent mucosectomy, treatment of residual disease with APC was found to prolong recurrence-free survival[28].

CRYOTHERAPY

The goal of this endoscopic therapy is to use freeze-thaw cycles for the destruction of tissue. Cryotherapy is performed using low-pressure liquid nitrogen (CSA Medical, Maryland, United States) or carbon dioxide (GI Supply, Pennsylvania, United States) delivered *via* spray catheter. One of the earlier prospective studies of cryotherapy found a 94% eradication rate for HGD with complications including chest pain and dysphagia, as well as one gastric perforation[29]. Recently, a prospective cohort study of 96 patients (two-thirds of whom had HGD) underwent cryotherapy, resulting in a complete eradication rate of 81% for HGD. Only three patients developed a stricture in the 37 mo of follow-up[30]. The durability of cryotherapy in preventing disease recurrence has come into question. Halsey *et al*[31] published data suggesting that up to 30% of patients treated with cryotherapy experienced disease recurrence at a median of 6.5 mo, and 10% had a second recurrence. However, a more recent single center retrospective cohort reported a HGD eradication rate of 100% with sustained remission in 97% of patients with previous HGD over a range of 24-57 mo[32]. At this time, only in the ASGE guidelines is cryotherapy specifically mentioned as a treatment option for dysplasia in BE[10].

RFA

RFA has emerged as the ablative technique of choice for BE with HGD because of the quality of evidence to support the ease of its administration, its efficacy, and safety profile. The procedure involves the direct application of radiofrequency energy to the esophageal mucosa, using either a balloon for circumferential treatment and more focal treatment through an attachment to the end of the endoscope or a small catheter that can pass through the working channel (Barxx/Covidien, Dublin, Ireland). With these tools, RFA can be applied to the mucosa circumferentially or focally. In the landmark multicenter sham-controlled randomized controlled trial by Shaheen *et al*[33], RFA resulted in eradication of dysplasia in 81% of patients with HGD. The treatment also decreased the progression of dysplasia to cancer. Complications were rare in this study, with only a 6% rate of stricture formation over 12 mo of follow-up[33]. RFA has also been shown to be successful in eradicating persistent dysplasia after initial therapy with PDT. In one study, RFA used as rescue therapy after PDT treatment successfully eradicated residual HGD in 86% of patients[34].

For some patients with BE, multiple endoscopic therapies are required for treatment. RFA is most effective on smooth BE mucosa, and is not adequate treatment for nodular dysplasia. As a result, endoscopists have been combining endoscopic eradication therapies, most commonly EMR and RFA. With combination therapy, visible or nodular dysplasia can be precisely removed with EMR, and any residual dysplasia or metaplasia can be systematically treated with RFA, typically performed after the EMR site has healed. One retrospective study of combination therapy reported an 86% complete eradication rate of HGD, but complete eradication of only 62% of nondysplastic intestinal metaplasia[35]. More recently, a multicenter prospective trial in Europe (EURO Ⅱ) evaluated the efficacy and safety of such a treatment strategy. EMR was performed on visible abnormalities within the BE segment and the remaining visible Barrett's mucosa was treated with RFA 6 wk later. Patients underwent a median of two RFA sessions. This combination of procedures achieved a 92% complete eradication rate for HGD and neoplasia and complete eradication of intestinal metaplasia in 87% of patients. At 36 mo of follow-up, only 4% of patients had recurrence of neoplasia. There were no major complications from the procedures and the rate of esophageal stenosis rate was 6%[36].

The existing evidence for treatment of low-grade dysplasia (LGD, Figure 1) in BE (most often with RFA) is

less abundant than studies of patients with BE and HGD. However, a recent randomized clinical trial (the SURF trial) showed a significantly lower rate of progression of LGD to either HGD or adenocarcinoma over three years after RFA[37]. Complicating the decision to ablate LGD is the fact that there is significant disagreement between pathologists on the definition of LGD. Several studies have highlighted the discrepancy in pathologist interobserver agreement when evaluating specimens with LGD. In one such study, expert pathologist confirmed only 15% of previously diagnosed LGD[38]. The AGA recommends RFA as therapy for BE with LGD based on high quality evidence while the ASGE dictates that RFA should be considered as therapy for LGD, and ACG acknowledges the effectiveness of RFA for LGD[1,9,10].

RISK OF RECURRENCE AFTER ENDOSCOPIC THERAPY

Recurrence after endoscopic therapy is a concern for gastroenterologists treating patients with dysplastic BE and the rates of recurrence vary widely depending on the study. Gupta *et al*[39] noted that IM returned in up to 33% of patients at 2 years after endoscopic therapy including RFA. A smaller percentage of recurrent IM was dysplastic (22%). The investigators were unable to identify any predictors for recurrence in this particular population of patients[39]. Other groups have tried to define predictors for recurrence of IM after definitive ablative therapy. In one recent large retrospective analysis, researchers found a slightly lower recurrence rate of 20% at 2.4 years for either IM or dysplasia. These investigators were able to identify risk factors for recurrence of BE and neoplasia, which included a worse pre-treatment histology, older age, and longer BE segments[40]. A single-center retrospective analysis of patients who achieved complete eradication of both IM and dysplasia with RFA found the one-year recurrence rate of IM to be 25% while dysplasia recurred in 8.5% of patients[41]. In contrast, a systematic review and meta-analysis of prospective and retrospective studies of RFA found that recurrence of dysplasia and IM was much lower after RFA treatment, with a 0.9% pooled recurrence rate for dysplasia and a 13% rate of recurrence for IM with an average follow-up of 1.5 years. There was wide range of IM recurrence rates reported in this study, ranging from 8% to 21%[42].

ENDOSCOPIC THERAPY OF NON-DYSPLASTIC BE

The debate rages on in the world of BE whether ablation of non-dysplastic Barrett's esophagus (NDBE) should be performed. Endoscopists advocating ablation of NDBE extrapolate the success of RFA in patients with HGD and LGD, applying these findings to non-dysplastic metaplasia. Another argument favoring ablation of NDBE is the lack of randomized controlled trials showing that surveillance of BE reduces mortality from esophageal adenocarcinoma, and thus other interventions should be considered[43,44]. Endoscopists who argue against ablation of NDBE focus on the lack of high quality evidence available to support such a notion and the very low rates of progression to cancer reported for non-dysplastic BE. Other issues proposed in the argument against ablation of nondysplastic BE include issues related to subjecting large numbers of patients to multiple endoscopic procedures, and the associated costs of the procedures and risk of complications[45]. One other argument against ablation of non-dysplastic BE is the possibility of missing subtle nodularity or mucosal changes that would be optimally treated with EMR, and instead burying it with suboptimal RFA therapy[45,46]. More prospective randomized controlled trials are needed to study the utility of RFA and other endoscopic therapies to treat NDBE. The AGA and ASGE mention that RFA could be considered for selected patients with NDBE thought to be at increased risk of progression to HGD and cancer[1,10].

CONCLUSION

The treatment options for HGD in BE have evolved into less-invasive therapies. There are now highly effective endoscopic therapies that are less morbid than esophagectomy. Most patients are treated with a combination of endoscopic resection and RFA with good outcomes. However, it is the job of the gastrointestinal endoscopist to be vigilant in surveillance for possible dysplasia recurrence in these patients. We have not yet reached the point where a patient can be told he or she has experienced complete eradication with no possibility of recurrence, and all patients should remain in surveillance. Until that time comes, we will continue to sharpen the endoscopic tools that will help us along the way to a durable cure.

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Endoscopic incisional therapy for benign esophageal strictures: Technique and results

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Abstract

Benign esophageal strictures refractory to the conventional balloon or bougie dilatation may be subjected to various adjunctive modes of therapy, one of them being endoscopic incisional therapy (EIT). A proper delineation of the stricture anatomy is a prerequisite. A host of electrocautery and mechanical devices may be used, the most common being the use of needle knife, either standard or insulated tip. The technique entails radial incision and cutting off of the stenotic rim. Adjunctive therapies, to prevent re-stenosis, such as balloon dilatation, oral or intralesional steroids or argon plasma coagulation can be used. The common strictures where EIT has been successfully used are Schatzki's rings (SR) and anastomotic strictures (AS). Short segment strictures (< 1 cm) have been found to have the best outcome. When compared with routine balloon dilatation, EIT has equivalent results in treatment naïve cases but better long term outcome in refractory cases. Anecdotal reports of its use in other types of strictures have been noted. Post procedure complications of EIT are mild and comparable to dilatation therapy. As of the current evidence, incisional therapy can be used for management of refractory AS and SR with relatively short stenosis (< 1 cm) with good safety profile and acceptable long term patency.

Key words: Endoscopic incisional therapy; Esophageal strictures; Anastomotic strictures; Needle knife; Radial incision and cutting

Core tip: Benign esophageal strictures refractory to conventional balloon or bougie dilatation can be subjected to endoscopic incisional therapy. The technique entails the use of needle knife or scissors for radial incision and cutting off of the stenotic rim. Adjunctive therapies with balloon dilatation or intralesional steroids may be needed for prevention of re-stenosis. Current evidence suggests use of incisional therapy for refractory short segment (< 1 cm) anastomotic strictures and Schatzki's rings with good safety profile and acceptable long term patency.

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INTRODUCTION

Benign esophageal strictures are a frequent challenge for the endoscopist. Peptic injury secondary to chronic acid exposure accounts for 80% of all benign esophageal strictures[1]. However, the remaining 20%-30% may be associated with Schatzki's rings (SR), esophageal webs, post radiation injury, anastomotic strictures (AS) and caustic ingestion. Based on anatomical complexity the strictures are classified as either simple or complex[2]. Simple are those with short, straight strictures, usually allowing passage of normal diameter endoscopes and are easy to treat (webs, rings and peptic strictures). The difficult to treat complex strictures are longer (> 2 cm), angulated or with severely stenosed lumen, a consequence of fibrosis with cicatricial narrowing. AS, caustic strictures and radiation strictures are known to be complex strictures[2]. Dilatation by bougie or balloon dilators has been the age old technique for management of benign esophageal strictures and generally the simple ones respond adequately to 1-3 dilatations[3]. The more difficult ones require more sessions of dilatations or the need for additional modes of treatment. Henceforth, Kochman *et al*[4] have defined strictures as: (1) refractory, when there was a persisting dysphagia score of 2 or more, as a result of inability to successfully achieve a diameter of 14 mm over 5 sessions at 2 wk intervals; and (2) recurrent, when there was inability to maintain a satisfactory luminal diameter for 4 wk once the target diameter of 14 mm had been achieved.

Although dilatation is a time tested, safe and effective mode of therapy for esophageal strictures, 10% of patients may require repeated dilatations[4,5] and 90% of those who have a single recurrence will eventually develop further recurrence. Moreover, dilatation failure group will require adjunctive modes of therapy. The various endoscopic options (Table 1) besides dilatation are intralesional steroid injection[6-8] or topical mitomycin C[9,10], esophageal stenting (self-expanding metal stents[11-13], self-expanding plastic stents[14,15] and biodegradable stents[16-19]), rendezvous procedure (antegrade and retrograde dilatation)[20,21] and incisional therapy.

Limited literature exists on endoscopic incisional therapy (EIT) and this review will deal with indications, techniques and the outcome of this modality in the management armamentarium of benign esophageal strictures.

DESCRIBED USES OF EIT

After the first description of its utility by Raskin *et al*[22] for Schatzki's ring in 1985, incisional therapy has been found to be useful in a number of other causes such as AS[23-25], strictures after esophageal endoscopic sub mucosal dissection (ESD) or endoscopic mucosal resection (EMR)[26,27], corrosive strictures[28], upper esophageal webs[29] and a host of other benign strictures.

Table 1 Endoscopic options of esophageal stricture management

Dilatation
Balloon
Bougie
Dilatation with injection therapy
Intralesional triamcinolone
Topical mitomycin C
Incisional therapy
Stent placement
SEMS
SEPS
Biodegradable stents
Rendezvous procedure

SEMS: Self expanding metal stents; SEPS: Self expanding plastic stents.

TECHNICAL DETAILS OF INCISIONAL THERAPY

Pre procedure assessment

Before subjecting a patient to EIT a proper assessment of the indication, the suitability of the procedure and the safety of the patient has to be done. The baseline symptom profile including the grade of dysphagia has to be recorded. Usually, strictures refractory to conventional modes of therapy are subjected to EIT as use of EIT for naive strictures (without prior dilatation therapy) has not been found to be superior to the conventional dilatation[30]. Active inflammation or underlying malignancy has to be ruled out with histology. Contrast esophagography and cross sectional imaging are needed for proper delineation of the stricture anatomy. The diameter of the stricture can be roughly estimated on endoscopy as: (1) size of 10 mm or more if a standard endoscope tip can be passed (GIF-H180 with insertion tube diameter of 9.8 mm; Olympus Medical Systems, Tokyo, Japan); (2) size of 5-10 mm if standard ultrathin scope can be passed (GIF-N180 with insertion tube diameter of 4.9 mm); (3) size of 2-5 mm if the ultrathin scope cannot be passed; and (4) less than 2 mm (pin point strictures) if the outer sheath of the needle-knife catheter (1.7-mm needle diameter) (Wilson Cook Medical Inc, Winston-Salem, NC) can just be passed or not pass through. The depth of the lesion is assessed by comparing with the length of the needle knife (approximately 4 mm). This documentation will help in outcome assessment post therapy. Finally, patients with bleeding diathesis, respiratory failure, severe or unstable cardiac disease and anastomotic leakage or infection need correction of these risk factors before therapy.

Instruments required

EIT has been carried with a host of electrocautery and mechanical devices including polypectomy snares and

Table 2 Instruments for incisional therapy

	Distal tip outer diameter (Fr)	Knife length (mm)	Knife diameter (mm)	Min. channel size (mm)	Working length (cm)
Needle knives					
Olympus (Tokyo, Japan)					
Triple lumen needle knife	5	5	0.2	2.8	195
Hook knife	Hook length 1.3 mm	4.5	0.4	2.8	165/230
Needle knife (require handle)					
KD-10Q-1.B	NA	3	0.4	2.0	195
KD-11Q-1.B	NA	3	0.7 (flat)	2.0	195
IT-Knife-L	Ceramic tip with diameter 2.2 mm	4	0.4	2.6	
Boston scientific (Natick, Mass)					
RX needle knife	5.5	5			200
Microknife™XL triple lumen knife	7-5.5				200
Cook medical (Winston Salem, NC)					
Fusion needle knife	6	4		4.2	200
Zimmon needle	5	7		2.0	200/320
Scissors					
Surgical scissors FS-3L-1 (Olympus): Min. channel size - 2.8 mm Working length - 165 cm					
Heiss-Device flexible endoscopic scissors (Telemed Systems, Hudson, Mass): 1.7 mm blade diameter × 2.5 mm blade length 1.7 mm shaft diameter 180 cm shaft length Single-action blade					
SB knife Jr (Sumitomo Bakelite Co., Tokyo, Japan): Width 4.4 mm × Length 3.5 mm Rotatable monopolar scissors					

Fr: French; NA: Not applicable; IT knife: Insulated tip knife.

argon plasma coagulation[31]. However, the most widely used are the needle knives that are nothing but "naked" diathermy wires[32]. The standard needle knife designed for endoscopic retrograde cholangio-pancreaticography is a diathermy wire that protrudes out of the catheter sheath by a handle mechanism and electrocautery is done powered by electrosurgical generators. This free hand technique is a cause of concern for fear of perforation. To minimize this risk, a modification has been made with the addition of an insulated ceramic tip (insulated tip needle knife, IT knife) allowing only cutting at the side. Other modifications such as the hook tip knife can also be used[32].

Mechanical devices that have been used are the Heiss-Device flexible endoscopic scissors (Telemed Systems, Hudson, Mass) and the FS-3L-1, endoscopic suture scissors (Olympus America Corp, Melville, NY).

A combined mechanical and electrocautery device, originally devised for ESD, known as SB Knife Jr (Sumitomo Bakelite Co., Tokyo, Japan) has also been used. It is a scissor-type knife with rotatable monopolar scissors and insulated coating for enhanced incision power while protecting surrounding tissues. A comprehensive table of the various instruments with their specifications has been depicted in Table 2 and Figure 1.

The technique

First applied to SR, the most commonly used incisional therapy is the needle knife electroincision and will be dealt with in detail here. Although most commonly the standard needle knife is used, with the advent of various modifications, the IT-knife is preferred for short strictures[32]. The basic principle of this modality is the same as dilatation, *i.e.*, disruption or displacement of the fibrotic tissue to help restore a satisfactory lumen diameter and prevent the reorganization of the fibrotic tissue.

The electroincision requires use of radial incisions with the knife attached to an electrosurgical unit such as UES-30 generator (Olympus, Tokyo, Japan) or more commonly ERBE generator (Elektromedizin GmbH, Tübingen, Germany) with software controlled fractionated cuts either in the pure cut or blended cut modes.

The technique used has been essentially the application of radial incision of the stricture area and was rechristened with the term of "radial incision and cutting" (RIC) method by Muto *et al*[25] RIC is carried out in the following steps (Figure 2): (1) The stricture area is incised under direct vision with the needle knife in a radial fashion parallel to the longitudinal axis of the esophagus. Usually a virtual line connecting the cranial and the caudal sides of the lumen is presumed and the incision line is guided accordingly. Precise movement is imperative for appropriate use of needle knife and can be achieved better with the endoscope tip movement rather than the needle itself; (2) The length and the number of incisions are guided by the need to completely remove the rim of stenosis. On an average, 8-12 radial incisions are needed[24]. The incision depth is assessed using the needle-knife length as a comparator; (3) While for short segment strictures, the

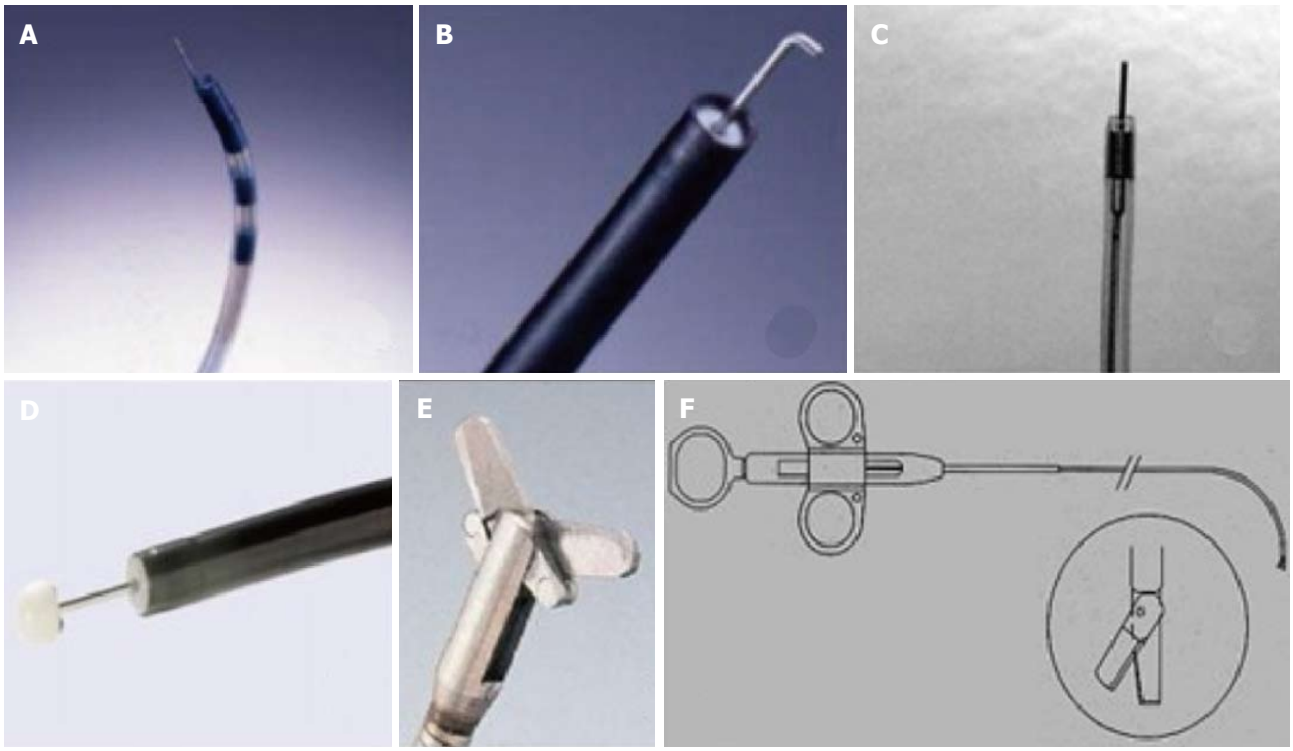

Figure 1 Accessories for incisional therapy. A: Triple lumen needle knife; B: Hook knife; C: Needle knife (KD 10Q); D: Insulated tip knife; E: Endoscopic surgical scissors (Image courtesy of Olympus); F: Heiss-Device flexible endoscopic scissors (image courtesy of Telemed systems).

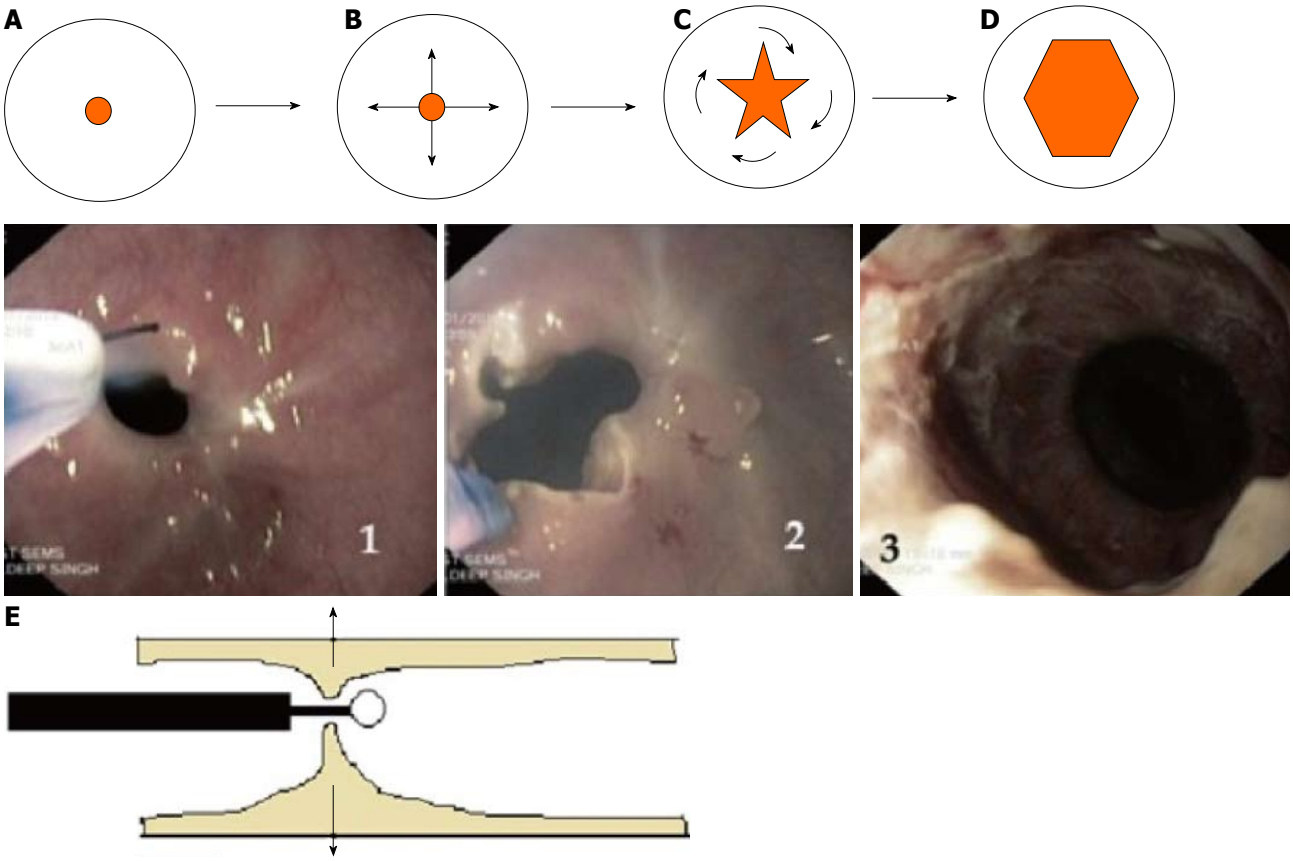

Figure 2 The technique of endoscopic incisional therapy procedure. A-D: Schematic front view of stricture site; B: Arrows depict the radial direction of incision; C: Curved arrows depict the slicing off of the intervening areas; D: Final outcome at the end of procedure; E: Lateral view of stricture site depicting the transverse working domain of the needle knife (arrows); 1: Use of needle knife for incision; 2: After radial incision; 3: At the end of EIT and balloon dilatation. EIT: Endoscopic incisional therapy.

technique is pretty straight forward, but for long segment ones, many times an opening needs to be created with multiple, short radial incisions before the scope can be negotiated for distal segments. Thus, technically difficult as it is for long segment ones, complete removal of the stenosed rim may not always be feasible; and (4) The parts of the strictured site in between the incision lines are then sliced off using the knife and the procedure is usually terminated once the scope can be easily passed across the strictured segment.

A modification to the technique proposed by Lee *et al*[24] was the use of a transparent hood attached to the scope tip for better visualization of the work field.

Post-procedure the patients are observed for immediate complications such as pain, significant bleeding or perforation. Once these have been ruled out, the patients can be discharged and assessed on a regular basis for recurrence of symptoms, grade of dysphagia or weight loss for which repeat assessment and redo of the therapy may be needed. Similar to the needle knife used for EIT various other devices such as the polypectomy snare[31] or scissors[28,33] have also been used.

Adjunctive measures

In the post-procedure phase, when the tissue has been freshly incised and chances of re-formation of stenosing fibrotic scar are high, various adjunctive measures have been described. Endoscopic balloon dilatation (EBD) with CRE balloon dilators (Boston Scientific, Natick, MA) have been done post-procedure and repeated frequently till the scarring of the cut surface[23,25,27]. Nonaka *et al*[28] have described the use of oral steroids for the prevention of re-stenosis. Yamaguchi *et al*[34] also demonstrated prevention of stricture after ESD with prednisolone. It has already been established in literature that use of intralesional steroids can prevent stricture recurrence[6-8]. The study of the efficacy of the same after EIT is currently being carried out in a large multi-center randomized control trial in Japan (UMIN Clinical Trials Registry: UMIN000014017). Argon plasma coagulation use has also been described along with incision for stepwise reduction of the scar tissue[31].

Evaluation of the treatment outcome

Recurrence of symptoms with dysphagia more than grade Ⅱ or the inability to pass a standard endoscope (9.5 mm) across the stricture site is considered as recurrent stenosis. If this condition arises even after 5 sessions of EIT, it is considered as treatment failure[30]. Post-procedure relief of symptoms, need for repeat procedure and the long term patency are factors assessed for the efficacy assessment of the procedure.

OUTCOME OF INCISIONAL THERAPY

The incisional therapy has been an alternate modality for the management of benign refractory strictures. The average time required for the procedure ranges from 6-14 min[24,25]. The majority of the published studies describe its use primarily in SR and AS. Anecdotal case reports have been found of its use in other conditions.

SR

After the first description of electrosurgical incision of SR by Raskin *et al*[22] in 1985, various studies have used it. When used as the initial intervention modality for SR (*i.e.*, without prior dilatation therapy), Guelrud *et al*[35] produced excellent results with 14 out of 17 patients (82.4%) becoming asymptomatic after a single session of EIT during a follow up of 46 mo. In the dilatation unresponsive group, Burdick *et al*[36] showed improvement in dysphagia in 6 out of 7 patients (85.7%) after a single session of EIT over a 36 mo follow-up, however later studies failed to replicate a similar outcome. DiSario *et al*[37] conducted EIT on 11 patients, who had a median of 3 dilatations prior to incision, out of whom 4 (36%) remained symptom free but 7 (64%) required further incisions or dilatations during a median follow-up of 55 mo. However, they found that there was a significant increase in the mean duration of improvement immediately after incision as compared with that of dilatation (17 mo *vs* 5 mo; $P = 0.034$).

In a prospective randomized study, comparing bougie dilatation with EIT as the initial therapy for symptomatic SR, Wills *et al*[38] demonstrated that both modalities had similar efficacy in symptom control, dysphagia and GERD, during a 12 mo follow-up period. However, the EIT group had longer symptom free survival time compared with the bougie dilatation group (7.99 mo *vs* 5.86 mo; $P = 0.03$).

AS

The most common esophageal stricture variant where EIT has been studied is the anastomotic stricture, mostly esophago-gastric anastomosis. Esophageal AS develops in 5%-46% of patients after surgical resection[2,39] and is secondary to post-operative complications such as bleeding, fistulization, leak development, anastomotic site infection and ischemia of the gastric anastomosis[2,39,40]. The success of balloon dilatation ranges from 70%-90% while 40% require more than 3 dilatations for optimal result[39-41]. A viable alternate management option has been the use of EIT as demonstrated in various studies (Table 3).

In cases of treatment naïve patients, after a single session of EIT, recurrence free course over a 6-24 mo follow up has been found to be 80.6% to 93%[24,30,31]. Thus, it is quite an effective therapy compared to dilatation without the need for repeated sessions for a considerable period of time. In fact, in a comparative trial with bougie dilatation, Hordijk *et al*[30] demonstrated that both EIT and dilatation were equally efficacious (80.6% *vs* 67.7%) at 6 mo follow-up.

In the more difficult group of refractory strictures, the symptom free rate dropped to 60% to 65%[25,42] with 44% requiring re-treatment. However, when

Table 3 Various studies of incisional therapy in esophageal anastomotic stricture

Ref.	Type of stricture	No. of patients	Length of stricture	No. of pre-procedure dilatations[1]	Follow-up duration (mo)	Outcome of single session
Schubert *et al*[31], 2003	Treatment naive	15	6.1 mm (3-10 mm)	NA	23	No recurrence - 14/15 (93%)
Simmons *et al*[23], 2006	Refractory	9	--	6	3-14	No dysphagia - 4/9 (44.4%) No response - 1/9 (11%)
Hordijk *et al*[42], 2006	Refractory	20	< 1 cm - 12 cm > 1 cm - 8 cm	8	12	No dysphagia - 12/20 (60%) Recurrence - 8/20 (40%) Treatment failure - 2/20 (10%)
[2]Hordijk *et al*[30], 2009	Treatment naive	EIT arm - 31	EIT arm - 1.35 cm	N/A	6	No difference in the success rate (80.6% *vs* 67.7%)
		SB arm - 31	SB arm - 0.55 cm (mean)			Treatment failure- EIT arm - 1; SB arm - 5
Lee *et al*[24], 2009	Treatment naive	24	< 1 cm - 21 cm > 1 cm - 3 cm	N/A	24	No recurrence - 21/24 (87.5%) Restricture - 3/24 (12.5%)
Muto *et al*[25], 2012	Refractory	EIT - 32	⩽ 5 mm - 49 mm	10	EIT - 14.8	Short term - 93.8% improvement
		EBD - 22	> 5 mm - 5 mm		EBD - 17.2	Long term - EIT better than EBD

[1]Mean number of dilatations; [2]Randomized prospective study. Treatment naïve: No previous dilatation; EIT: Endoscopic incisional therapy; SB: Savary bougienage; EBD: Endoscopic balloon dilatation; NA: Not applicable.

compared to continued dilatation therapy, EIT performed better than dilatation with significantly higher patency rates at 6 mo (65.3% *vs* 19.8%, $P < 0.005$) and 12 mo (61.5% *vs* 19.8%, $P < 0.005$) follow-up[25].

The other most important contributor of EIT response is the length of the stricture. Hordijk *et al*[42] had demonstrated that while patients with stricture length less than 1 cm had recurrence free course, all patients with stricture length greater than 1 cm had recurrence. Similar finding has been shown by Lee *et al*[24] wherein only 4.8% patients with stricture < 1 cm had re-stricture as compared to 66.7% in the group with stricture > 1 cm. This has been attributed to the increased amount of fibrosis in the longer strictures and hence decreased response.

Other strictures

In a retrospective study of 8 patients with post chemo-radiotherapy, ESD or EMR induced strictures, EIT improved dysphagia in all patients in the immediate post-procedure phase but 3 mo lumen patency was seen in only 3 (37.5%) patients[26].

Anecdotal case reports of use of endoscopic scissors have been used for management of corrosive strictures[28] and fibrous scar in proximal esophagus[33]. Stricture after surgery for esophageal atresia in a 4-year-old child has also been reported to be managed with EIT along with stenting[43].

Author's experience

A total of 14 patients with benign esophageal strictures (AS 5, corrosive strictures 4) have been subjected to incisional therapy along with balloon dilatation. Incisional therapy was done with Microknife™ XL Triple lumen knife (Boston Scientific, Natick, United States) followed by balloon dilatation with CRE™ Balloon Dilator (Boston Scientific, Natick, United States). Successful dilatation was achieved in 11 of the 14 after 3-9 sessions. No complications were noted.

COMPLICATIONS

Complications of EIT include pain, bleeding or perforation. Perforation is the most dreaded complication and can occur because of inability to gauge the depth of the esophageal wall or the length of the stricture during the incision therapy. Bleeding is usually self-limited and lesser known complication as the fibrotic strictures subjected to incisional therapy are relatively avascular. The complication rate of EIT appears to be mild comparable to dilatations with bougies or balloons, which can have perforation or significant hemorrhage at a rate of 0.1% to 0.4%[3]. For EIT, the reported perforation rate ranges from 0%-3.5%[24,25,30,37,42] with no reported evidence of significant bleeding. Perforation can be managed essentially with conservative treatment and if it fails, can be subjected to stent placement or surgery. Bleeding can be easily managed with methods such as balloon tamponade. Thus, EIT is a safe therapeutic option for stricture management.

CURRENT STATUS OF INCISIONAL THERAPY

As of the current evidence, EIT can be used as a treatment modality for refractory SR and AS with relatively short stenosis (< 1 cm). A suggested algorithm for the management of benign strictures has been shown in Figure 3.

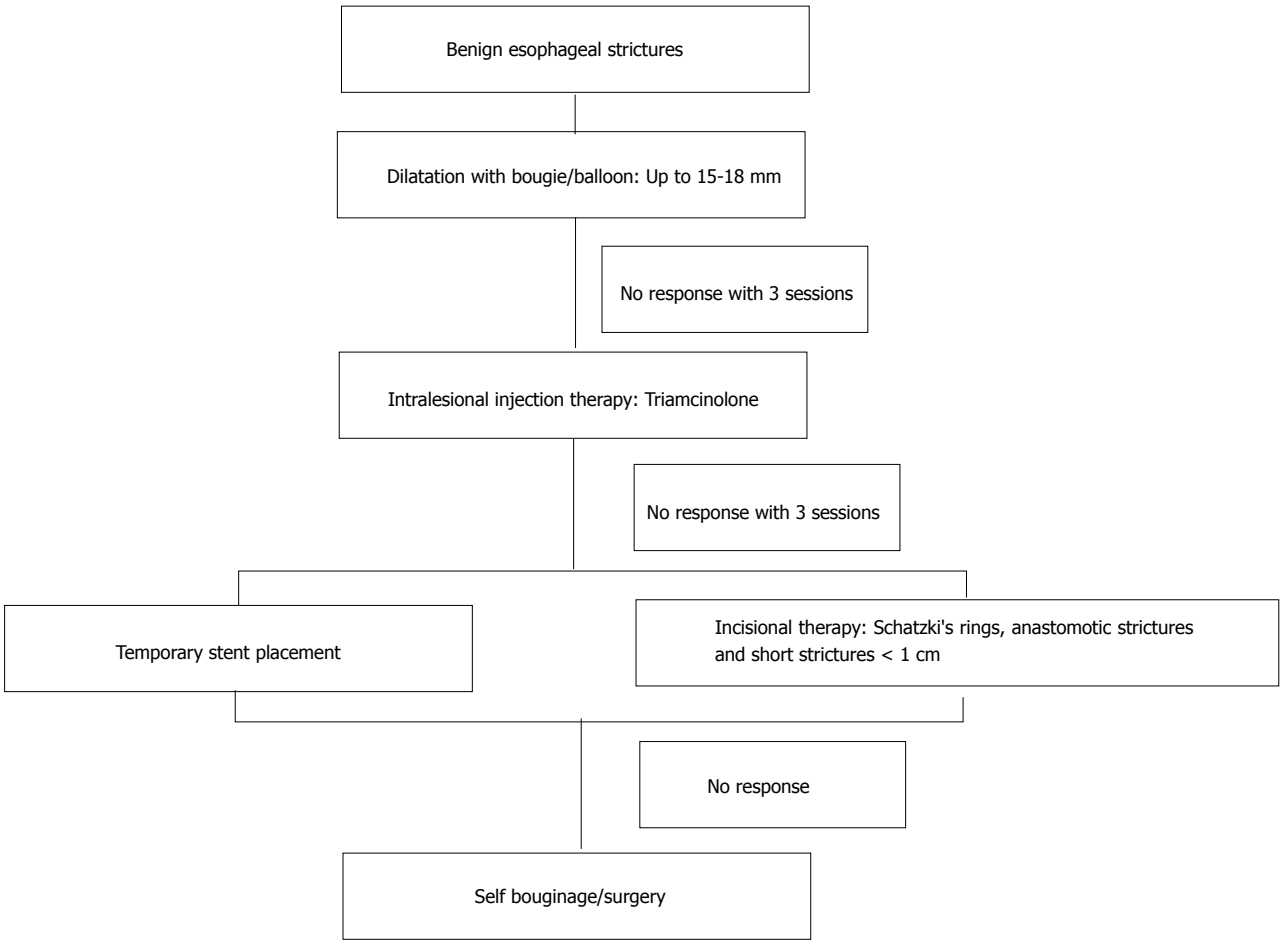

Figure 3 Algorithm for the management of benign esophageal strictures.

AREAS OF FUTURE RESEARCH

A number of questions need to be answered through larger trials before a standardized recommendation can be made regarding the use of incisional therapy in esophageal stricture management: (1) it can be used for all refractory strictures; (2) number of balloon or bougie dilatations before considering EIT; (3) cumulative risk of the procedure; (4) efficacy and applicability of instruments other than needle knife; (5) the choice of adjunctive therapy to prevent re-stenosis; (6) cost effectiveness of the therapy in the long run; and (7) technical expertise and applicability issues in day-to-day practice.

CONCLUSION

EIT is a feasible, safe and effective treatment modality for benign short refractory esophageal strictures with established evidence in SR and AS. It has good immediate symptom improvement with acceptable long-term patency.

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ORIGINAL ARTICLE

Retrospective Study

Feasibility of single-incision laparoscopic cholecystectomy for acute cholecystitis

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Abstract

AIM: To assess the safety of single-incision laparoscopic cholecystectomy (SILC) for acute cholecystitis.

METHODS: All patients who underwent SILC at Sano Hospital (Kobe, Japan) between January 2010 and December 2014 were included in this retrospective study. Clinical data related to patient characteristics and surgical outcomes were collected from medical records. The parameters for assessing the safety of the procedure included operative time, volume of blood loss, achievement of the critical view of safety, use of additional trocars, conversion to laparotomy, intraoperative and postoperative complications, and duration of postoperative hospital stay. Patient backgrounds were statistically compared between those with and without conversion to laparotomy.

RESULTS: A total of 100 patients underwent SILC for acute cholecystitis during the period. Preoperative endoscopic treatment was performed for suspected choledocholithiasis in 41 patients (41%). The mean time from onset of acute cholecystitis was 7.7 d. According to the Updated Tokyo Guidelines (TG13) for the severity of cholecystitis, 86 and 14 patients had grade Ⅰ and grade Ⅱ acute cholecystitis, respectively. The mean operative time was 87.4 min. The mean estimated blood loss was 80.6 mL. The critical view of safety was obtained in 89

patients (89%). Conversion laparotomy was performed in 12 patients (12%). Postoperative complications of Clavien-Dindo grade Ⅲ or greater were observed in 4 patients (4%). The mean duration of postoperative hospital stay was 5.7 d. Patients converted from SILC to laparotomy tended to have higher days after onset.

CONCLUSION: SILC is feasible for acute cholecystitis; in addition, early surgical intervention may reduce the risk of laparotomy conversion.

Key words: Acute cholecystitis; Single-port access surgery; Single incision laparoscopic cholecystectomy; Single incision laparoscopic surgery; Laparo-endoscopic single-site surgery

Core tip: Single-incision laparoscopic cholecystectomy (SILC) has attracted attention as a minimally invasive procedure. A scar-less operation can be achieved by making a skin incision at the umbilicus. However, the safety of this procedure for acute cholecystitis has not been established. We reported 100 consecutive cases of SILC for acute cholecystitis and their surgical outcomes. SILC was safely performed in approximately 80% of cases in this series. We believe that the results of this study indicate the feasibility of SILC for acute cholecystitis.

Ikumoto T, Yamagishi H, Iwatate M, Sano Y, Kotaka M, Imai Y. Feasibility of single-incision laparoscopic cholecystectomy for acute cholecystitis. *World J Gastrointest Endosc* 2015; 7(19): 1327-1333 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i19/1327.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i19.1327

INTRODUCTION

Cholecystectomy is widely performed as a basic treatment for acute cholecystitis. In the Updated Tokyo Guidelines issued in 2013 (TG13), early cholecystectomy is recommended as the first treatment choice, except for severe cases with organ failure[1]. Laparoscopic cholecystectomy (LC) is now a mainstream procedure. When performed by skilled surgeons, LC is considered a safe procedure even for acute cholecystitis[2].

In recent years, single-incision laparoscopic surgery (SILS) has attracted attention as a minimally invasive procedure. In SILS, multiple devices are inserted from a single skin incision into the abdominal cavity to reduce the length and number of incisions. In particular, scarless operations can be achieved by making skin incisions at the umbilicus[3]. Because cholecystectomy is performed in a nearly fixed visual field and because it does not require wide-range maneuvers, SILS is easily incorporated into cholecystectomy. SILC is becoming established as a procedural option.

However, there are limited reports on surgical outcomes of SILC for acute cholecystitis. Because maneuverability is limited in SILC compared with that in conventional LC, the safety of this procedure for acute cholecystitis has not yet been established. If SILC is as safe as conventional LC, SILC will become the procedure of choice for patients who desire better aesthetic outcomes. Although successful completion of SILC is a prerequisite for better aesthetic outcomes, data on acute cholecystitis are limited. At our hospital, we have focused on SILC and cases of acute cholecystitis. Thus, in order to address these clinical questions, we conducted a retrospective study of past cases. The objectives of this study were to assess the safety of SILC for acute cholecystitis and to investigate requirements for successful completion of SILC.

MATERIALS AND METHODS

This study included all patients who underwent SILC for acute cholecystitis at Sano Hospital (Kobe, Japan) between January 2010 and December 2014. Although SILC is, in principle, performed for all patients requiring cholecystectomy, four patients for whom laparoscopy had not been selected at the discretion of their attending physicians and one patient suspected to have concomitant gallbladder cancer were excluded. According to TG13[4], acute cholecystitis was diagnosed in patients who met all the following diagnostic criteria: (1) local inflammatory signs; (2) systemic inflammatory findings; and (3) characteristic imaging findings. Data were collected from medical records and analyzed. The parameters used to assess the safety of the surgery included operative time, volume of blood loss, achievement of the critical view of safety, use of additional trocars, conversion to laparotomy, intraoperative and postoperative complications, and duration of postoperative hospital stay.

Surgical technique

We performed SILC using a standard technique with conventional trocars and instruments. A 20-mm incision was first made at the umbilicus. An optical port, a 5-mm trocar, and 5-mm forceps were inserted in the incision. These three instruments were placed in a triangle to maximize their spacing. In addition, a 3- or 5-mm instrument was inserted beside the optical port. We did not use any devices specialized for SILS.

It is feasible to perform nearly the same surgical procedure as conventional LC because the potential interference of each device is minimized by direct insertion of two instruments without trocar. We made every effort to create the critical view of safety, as described by Strasberg. To prevent bile duct injury, we converted to open surgery when we could not create the critical view of safety or could not identify the cystic duct.

Drainage tubes were not routinely placed, even in

Table 1 Patient characteristics

	Acute cholecystitis (n = 100)
Mean age (yr ± SD)	66.8 ± 14.4
Sex	
Male	51
Female	49
Mean BMI (kg/m^2 ± SD)	23.9 ± 3.3
History of abdominal surgery	26 (26%)
Suspected choledocholithiasis	41 (41%)
Mean time from onset (d ± SD)	7.7 ± 4.1
TG13 severity grading	
Grade Ⅰ (mild)	86 (86%)
Grade Ⅱ (moderate)	14 (14%)

SD: Standard deviation; BMI: Body mass index; TG13: Updated Tokyo Guidelines.

Table 2 Surgical outcomes

	Acute cholecystitis (n = 100)
Mean operative time (min ± SD)	87.4 ± 39.3
Mean estimated blood loss (mL ± SD)	80.6 ± 162.4
Achievement of critical view of safety	89 (89%)
Additional trocar insertion	9 (9%)
Conversion to laparotomy	12 (12%)
Postoperative complication	4 (4%)
Bile leakage	(2)
Stone passage into the CBD	(2)
Mean duration of postoperative hospital stay (d ± SD)	5.7 ± 5.1

SD: Standard deviation; CBD: Common bile duct.

cases of severe inflammation. However, we placed a drainage tube from the right lateral abdomen to the liver bed in cases of suspected remnant abscess or bile leakage.

Statistical analysis

The *t* test was used to assess differences in patient age, body mass index (BMI), and days from onset. The Fisher exact test was used to assess differences in all other factors. All tests were two-sided, and *P*-values less than 0.05 were considered to indicate a statistically significant difference. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria)[5].

RESULTS

Patient characteristics

During the study period, 100 patients underwent SILC for acute cholecystitis. Their mean age was 66.8 years. The male-to-female ratio was 51:49. Their mean BMI was 23.9 kg/m^2. A history of some type of abdominal operation was found in 26 patients (26%). Choledocholithiasis was suspected in 41 patients (41%), based on imaging studies, and endoscopic lithotomy was performed before SILC. The mean time from the onset of acute cholecystitis to cholecystectomy was 7.7 d. According to TG13[4] guidelines for the severity of cholecystitis, 86 patients and 14 patients had grades I and II acute cholecystitis, respectively (Table 1).

Table 3 Histological diagnoses of resected gallbladder for acute cholecystitis

	n = 100
Edematous cholecystitis	9
Necrotizing cholecystitis	8
Suppurative cholecystitis	5
Chronic cholecystitis	74
(Acute on chronic cholecystitis)	(61)
Xanthogranulomatous cholecystitis	1
Adenocarcinoma	3

Surgical outcomes

The surgical outcomes are shown in Table 2. The mean operative time was 87.4 min, and the mean estimated blood loss volume was 80.6 mL. The critical view of safety was achieved in 89 patients (89%), although anterograde dissection of the gall bladder starting from the fundus was required for 42 of these patients. Additional trocar insertion was required in 9 patients (9%). SILC was converted to laparotomy in 12 patients (12%). A drainage tube was placed in 13 patients (13%), including 4 patients with necrotizing cholecystitis. Postoperative complications of Clavien-Dindo grade III or greater were observed in 4 patients (4%). The complications included leakage of bile from the stump of the cystic duct and passage of stones into the common bile duct in two patients each. These complications were resolved in all four patients using only endoscopic treatment. The mean postoperative hospital stay was 5.7 d.

Histological diagnosis

Histological diagnoses of the resected gallbladders included acute-on-chronic cholecystitis in 61 patients, edematous cholecystitis in 9 patients, necrotizing cholecystitis in 8 patients, suppurative cholecystitis in 5 patients, and xanthogranulomatous cholecystitis in 1 patient. Incidental adenocarcinomas were founded in 3 patients (Table 3).

Comparison of patients with and without conversion to laparotomy

The results of comparison between patients with and without conversion to laparotomy are shown in Table 4 and Figure 1. Despite the lack of statistical significance, the number of days after onset tended to be higher in patients who were converted from SILC to laparotomy.

Learning curve

The mean operative times of every five consecutive cases of SILC performed by a chief surgeon are shown

Table 4 Comparison of patients with and without conversion to laparotomy

	Without conversion (n = 88)	With conversion (n = 12)	P value
Mean age (yr ± SD)	66.1 ± 14.5	71.6 ± 13.3	NS
Sex			
Male	44	7	NS
Female	44	5	
Mean BMI (kg/m^2 ± SD)	23.9 ± 3.1	24.1 ± 4.7	NS
History of abdominal surgery	22 (25%)	4 (33.3%)	NS
TG13 severity grading			
Grade I (mild)	82 (93.2%)	4 (33.3%)	P < 0.001
Grade II (moderate)	6 (6.8%)	8 (66.7%)	
Mean time from onset (d ± SD)	7.5 ± 4.0	9.1 ± 4.4	NS

SD: Standard deviation; NS: Not significant; BMI: Body mass index; TG13: Updated Tokyo Guidelines.

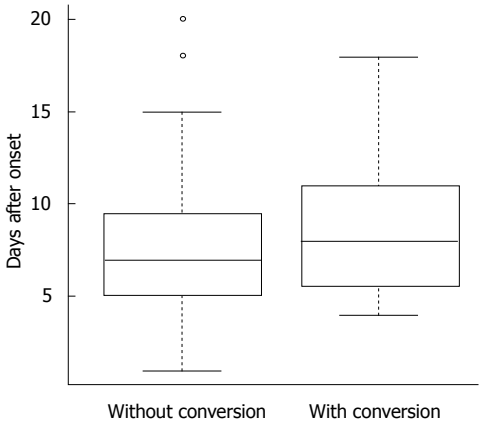

Figure 1 Time after onset of acute cholecystitis. Patients with conversion to laparotomy show a tendency toward increased preoperative days from onset.

in Figure 2. There were no obvious trends suggestive of a learning curve.

DISCUSSION

Although Navarra *et al*[6] first reported SILC in 1997, it did not initially attract much attention. However, SILC has been rapidly adopted since 2009, with improvements to platforms and devices dedicated for SILS[7-11]. Since then, SILS has been increasingly used, mainly because of its excellent aesthetic outcome; it has been widely applied not only to cholecystectomy, but also to appendectomy, colectomy, gastrectomy, urologic procedures, and gynecologic procedures[12-16]. LC in particular is relatively easy to perform with SILS, and SILC is routinely performed. The reasons for this include: (1) the surgical field is limited to the liver bed; (2) the direction of scopes and devices remains almost constant; (3) the procedure is mainly indicated for benign conditions; and (4) many patients undergoing the procedure are young. However, the drawbacks of SILS include: (1) the limited maneuverability of scopes and devices that may interfere with one another; and (2) difficulty in setting devices at different angles, as all devices are oriented in the same direction. Compared with conventional LC, SILC is technically more difficult. Because advanced endoscopic surgical techniques are required to perform SILC, it is a difficult procedure for less experienced surgeons. However, these obstacles have been gradually eliminated owing to advances such as the innovation of techniques appropriate for SILS, development of dedicated platforms, and introduction of pre-bending forceps[7,17-20].

Several randomized controlled trials (RCTs) have revealed that SILC is as safe as conventional LC[21-23]. However, to our knowledge, no RCT has assessed only patients with acute cholecystitis, for which SILC is technically more difficult, and the safety of SILC for acute cholecystitis has not been established. Thus, we reviewed 100 consecutive cases of SILC performed for acute cholecystitis and reported their surgical outcomes. The operative time tended to be longer in patients with cholecystitis; this likely reflects the difficulty of operative maneuvers. Moreover, the volume of intraoperative blood loss also tended to be higher; this may be attributable to the facts that (1) the gallbladder and its surrounding tissue affected by acute inflammation are more likely to bleed because they are congested and become edematous; and (2) the hepatic parenchyma is easily damaged because of inflammatory adherence of the gallbladder to the liver bed. These findings suggest that SILC for acute cholecystitis involves some level of difficulty. Thus, application of SILC should require careful consideration.

However, we performed SILC in all patients with acute cholecystitis who were judged to require cholecystectomy, and SILC was successfully completed without additional trocars in approximately 80% of cases. These findings indicate that SILC is applicable to many patients, even those with acute cholecystitis. Moreover, because the complication rate in this study is not higher than that reported in another study[23], we believe that SILC for acute cholecystitis is as safe as other surgical procedures under the conditions described in this study. In other words, the results of our study suggest that SILC can be performed in patients with acute cholecystitis without compromising safety. At minimum, there appears to be no need to exclude patients with acute cholecystitis from SILC.

New procedures typically have learning curves. However, there was no evidence of a learning curve for SILC

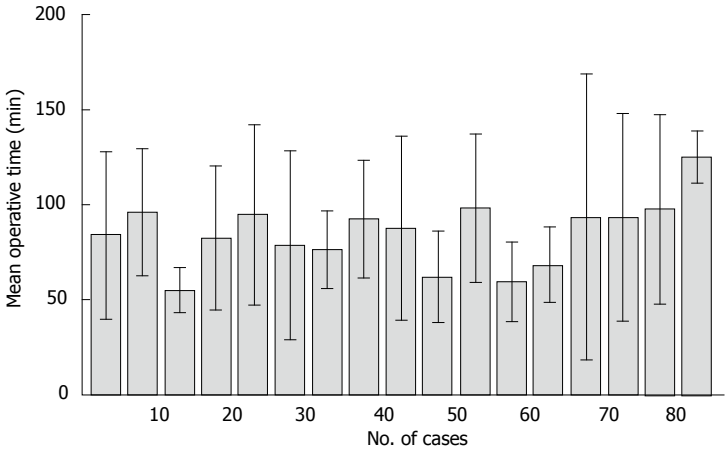

Figure 2 Mean operative time for every five consecutive cases of single-incision laparoscopic cholecystectomy for acute cholecystitis. All 85 cases performed by a chief surgeon are shown above. The standard deviation of each group is also shown. There are no obvious trends suggestive of a learning curve.

for acute cholecystitis in this study. This observation may be owing to the quality of the surgeons in our study. All surgeons who participated in this study were experienced and skilled in laparoscopic surgery and had each experienced more than 10 cases of SILC. Moreover, our SILC surgical procedure can be learned in a short time because of its similarity to conventional LC. However, the learning curve may be more obvious in less experienced surgeons.

SILC was introduced in our hospital in 2009. It was performed only in select patients during the early period after introduction while accumulating knowledge and standardizing the techniques used during the surgical procedure. Since January 2010, SILC has been applied to all patients, except those with gallbladder cancer. When the procedure is performed, we place the most emphasis on safety. Our policy is to convert SILC to laparotomy without hesitation when any difficulties present during the laparoscopic operation. The rate of conversion to laparotomy in the present study was slightly higher in patients with acute cholecystitis, likely owing to this policy. Consequently, no serious complications occurred, and excellent safety was demonstrated. Although the incidence of complications related with the bile duct was slightly high, this is likely because our institution specializes in endoscopic treatment. Many patients with suspected common bile duct problems seek treatment at our hospital. In fact, 41% of patients in this study were recommended to our facility for suspected choledocholithiasis and they underwent endoscopic treatment before cholecystectomy. This factor may have contributed to the increased incidence of these complications. Although bile leakage occurred in two patients with acute cholecystitis, it was not caused by damage during a laparoscopic operation, as neither case had been converted to laparotomy. While the common bile duct was not damaged in any of the patients, leakage was resolved by endoscopic biliary drainage after surgery. To maintain the safety of SILC, surgeons should never perform reckless operative maneuvers and convert to laparotomy before performing risky maneuvers.

However, a desire to avoid conversion to laparotomy is reasonable without compromising safety in terms of aesthetic outcome. In this study, SILC was converted to laparotomy in 12 patients (12%). The main reason for conversion was difficulties during the laparoscopic operation because of severe inflammatory fibrosis (10 patients). Operation difficulties owing to inflammation are reported related to the elapsed time between disease onset and operation[24]. The results of this study indicate that the number of preoperative days after onset tended to be higher in patients who were converted from SILC to laparotomy. Based on these findings, SILC performed as early as possible may permit resection before development of inflammatory fibrosis, and thus reduce the risk of laparotomy conversion. Avoiding laparotomy results in a less invasive procedure, less postoperative pain, and shorter postoperative hospital stay, making the merits offered by SILC more attractive. The TG13 recommends performing cholecystectomy within 72 h[25]. Unfortunately, we could not perform early surgery in many cases because of the lack of smooth cooperation with the first-contact physicians, limited availability of operation theater space, and lack of anesthetist availability. Despite our efforts to overcome these issues, some patients were unable to undergo early cholecystectomy. Conversely, in patients for whom early operation is not feasible, conservative treatment and elective SILC after complete suppression of inflammation may be preferable.

In conclusion, the results of this study suggest that SILC is feasible for acute cholecystitis and that early surgical intervention may reduce the risk of conversion to laparotomy. Although an aesthetic outcome is important, the decision to convert to laparotomy should be made based on other factors. We hope that SILC will be considered a safe procedure and be more widely used.

COMMENTS

Background

Cholecystectomy is widely performed as a basic treatment for acute cholecystitis. Laparoscopic cholecystectomy (LC) is considered a safe procedure and widely performed for acute cholecystitis.

Research frontiers

Recently, single-incision laparoscopic cholecystectomy (SILC) has been rapidly

adopted over conventional LC. SILC is considered a less invasive procedure with better aesthetic results. However, the safety of this procedure for acute cholecystitis has not yet been established.

Innovations and breakthroughs

In this study, the authors reviewed 100 consecutive cases of SILC for acute cholecystitis and reported their surgical outcomes. The authors focused on SILC as well as accumulated cases of acute cholecystitis. This study is based on single-institution and consecutive experiences.

Applications

The results of this study suggest the safety and difficulty of SILC for acute cholecystitis. SILC is feasible for acute cholecystitis. However, surgeons should not hesitate to convert to laparotomy when difficulties arise.

Terminology

SILC is also called single-port access surgery or laparo-endoscopic single-site surgery. It is a minimally invasive surgical procedure with a single skin incision. Scarless operations can be achieved by making a skin incision at the umbilicus. However, SILC is technically more difficult because of the limited maneuverability. Advanced laparoscopic surgical skills are required for SILC.

Peer-review

The authors retrospectively assessed the safety of SILC for acute cholecystitis. They concluded that SILC is feasible for acute cholecystitis and that early surgical intervention may reduce the risk of conversion to laparotomy. This article is of interest for further clinic practice.

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ORIGINAL ARTICLE

Observational Study

Cap-assisted endoscopic sclerotherapy for hemorrhoids: Methods, feasibility and efficacy

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Abstract

AIM: To evaluate the methodology, feasibility, safety and efficacy of a novel method called cap-assisted endoscopic sclerotherapy (CAES) for internal hemorrhoids.

METHODS: A pilot study on CAES for grade Ⅰ to Ⅲ internal hemorrhoids was performed. Colon and terminal ileum examination by colonoscopy was performed for all patients before starting CAES. Polypectomy and excision of anal papilla fibroma were performed if polyps or anal papilla fibroma were found and assessed to be suitable for resection under endoscopy. CAES was performed based on the requirement of the cap, endoscope, disposable endoscopic long injection needle, enough insufflated air and sclerosing agent.

RESULTS: A total of 30 patients with grade Ⅰ to Ⅲ internal hemorrhoids was included. The follow-up was more than four weeks. No bleeding was observed after CAES. One (3.33%) patient claimed mild tenesmus within

four days after CAES in that an endoscopist performed this procedure for the first time. One hundred percent of patients were satisfied with this novel procedure, especially for those patients who underwent CAES in conjunction with polypectomy or excision of anal papilla fibroma.

CONCLUSION: CAES as a novel endoscopic sclerotherapy should be a convenient, safe and effective flexible endoscopic therapy for internal hemorrhoids.

Key words: Sclerotherapy; Hemorrhoids; Cap-assisted endoscopic sclerotherapy; Colonoscopy; Colon; Papilla fibroma; Hemorrhoidal disease

Core tip: Sclerotherapy is the most effective therapy for grade Ⅰ or Ⅱ internal hemorrhoids. Traditional sclerotherapy may cause iatrogenic risk due to misplaced injections. We designed a novel technique called cap-assisted endoscopic sclerotherapy (CAES) for hemorrhoids by flexible endoscopy. Our study demonstrated that CAES is a safe, effective and convenient endoscopic therapeutic strategy for grade Ⅰ, grade Ⅱ and partial grade Ⅲ internal hemorrhoids. The colon preparation and colonoscopy before CAES brought more benefits for patients, including possible polypectomy and excision of anal papilla fibroma under colonoscopy. This study implies the future contribution of endoscopists on hemorrhoidal disease.

Zhang T, Xu LJ, Xiang J, He Z, Peng ZY, Huang GM, Ji GZ, Zhang FM. Cap-assisted endoscopic sclerotherapy for hemorrhoids: Methods, feasibility and efficacy. *World J Gastrointest Endosc* 2015; 7(19): 1334-1340 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i19/1334.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i19.1334

INTRODUCTION

Hemorrhoidal disease is one of the most common anorectal disorders that affects mainly adults of any age and sex[1-4]. The etiology of hemorrhoids remains controversial. Nowadays, the most widely accepted theory is that hemorrhoidal disease is the abnormal dilatation and distortion of the vascular channel, together with destructive changes in the supporting connective tissue of the anal cushion[5]. The submucosal vascular cushions are a normal anatomical structure of the anal canal and their existence with symptoms such as bleeding, prolapse, pain, thrombosis, mucus discharge and pruritus indicates hemorrhoidal disease[6]. The true incidence of hemorrhoids is difficult to estimate as many patients are reluctant to seek medical suggestions for various personal, cultural and socioeconomic reasons[7]. Approximately 50% of individuals require treatment for hemorrhoids in their 50s or older, and 10%-20% of patients need surgical therapies[8].

Hemorrhoids have been well described for thousands of years. However, the treatment of hemorrhoids has only substantially evolved during the past few decades[1]. The current therapies for hemorrhoids can be grouped into conservative management, office-based procedures and surgical treatment[8-10]. Increased fiber intake, medical therapies and lifestyle changes are included in the conservative treatment options for non-thrombosed hemorrhoids[10]. If conservative management is unsuccessful, several office-based modalities could be options, including rubber-band ligation, injection sclerotherapy, laser photocoagulation, bipolar diathermy, cryotherapy, Dopplerguided hemorrhoidal artery ligation and infrared coagulation[8,9,11]. When an office-based therapy is still ineffective, patients may consider further intervention, such as hemorrhoidectomy, thrombectomy of external hemorrhoids and stapled hemorrhoidectomy[7,9].

As an crucial component of many non-surgical practices, sclerotherapy is most effective for grade I and Ⅱ internal hemorrhoids, especially for patients who have an increased risk of bleeding[2]. However, traditional sclerotherapy is performed by physicians through an anoscope. This method may cause iatrogenic risk and complications due to misplaced injections[2]. Therefore, there is scope for improvement in the field of sclerotherapy for hemorrhoids.

With the development of interventional flexible endoscopy and in order to solve the problems above, we designed a novel method called cap-assisted endoscopic sclerotherapy (CAES) for internal hemorrhoids. This article presents our pilot study on the methodology, feasibility, safety and clinical findings using CAES for internal hemorrhoids.

MATERIALS AND METHODS

Patient inclusion and exclusion criteria

This observational study was carried out in the Second Affiliated Hospital of Nanjing Medical University. All eligible patients with symptoms and signs of grade Ⅰ, grade Ⅱ or grade Ⅲ internal hemorrhoids requiring further interventional procedures after failure of conservative treatment were included in the study. Internal hemorrhoids are graded based on protrusion and reducibility (grade Ⅰ, hemorrhoids characterized by prominent vasculature with engorgement but no prolapse; grade Ⅱ, hemorrhoids prolapse only with straining but spontaneously reduce; grade Ⅲ, hemorrhoids prolapse beyond the dentate line with straining and require manual reduction; grade Ⅳ, hemorrhoids prolapse beyond the dentate line with straining but cannot be reduced manually)[12,13]. All included cases for analysis were followed up for at least four weeks.

Acute thrombosed hemorrhoids with anal pain, stricture, fissure, fistula, fecal incontinence, ulcerative colitis, Crohn's disease and any bleeding risk condition were excluded. Patients with acute diarrhea in the last

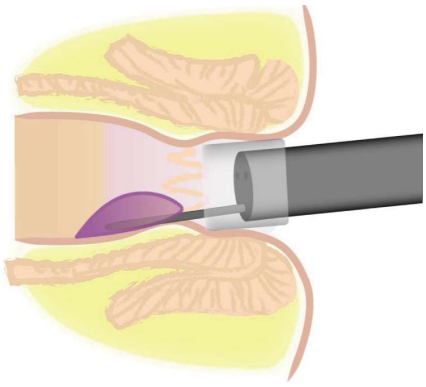

Illustration: Jacob Peichuan Ji

Figure 1 Illustration of cap-assisted endoscopic sclerotherapy.

12 h, severe complications, cancer, stroke, pregnancy, puerperium, mental disorders and portal hypertension were also excluded. Colon and terminal ileum examination by colonoscopy was performed for all patients before starting CAES. Polypectomy was performed if polyps were found and assessed to be suitable to be resected under endoscope. Informed consent was obtained from all participants.

Concept and methods of CAES

As shown in Figure 1, the regular cap used in endoscopic submucosal dissection was fixed on the top of the colonoscope. This cap is used to maximize visibility of the endoscopic view with enough insufflated air through the channel within the endoscope. A disposable endoscopic long injection needle (*e.g.,* the specially designed long needle: DT-EN-W322, 10/15/20 mm length, 22 g, Detian Medical, Changzhou, China) through the operating channel is used for the injection of the sclerosing agent. The needle is advanced into the submucosa of the targeted area of the hemorrhoids. The injecting points are above the dentate line. The sclerosing agent (Lauromacrogol injection, Tianyu Pharmaceutical, Xi'an, China), 1-2 mL for each injecting point, is injected while retracting the needle slowly. During the procedure, enough air is given for exposure of the endoscopic view. Before the complete retrieval of the needle from the tissue, as a suggestion, it is found to be helpful if you do not withdraw and stop the needle from moving for 5 s to prevent bleeding. The same procedure is performed for each targeted site under endoscopic view. Before taking out the endoscope, enough suction of air in the colon and visible rectal contents should be carried out to avoid or relieve abdominal distention and the feeling of defecation after the procedure.

Preparation and education

Although antibiotic prophylaxis was suggested for predisposing valvular heart disease because of the possibility of bacteremia after sclerotherapy[14], antibiotics were not used before and after CAES in this study. Besides, for safety considerations and observational requirements in this study, patients were required to rest in bed on the first night after the procedure. All individuals were required to follow medical instructions for avoiding constipation and diarrhea. Medicines were prescribed to soften the stools after the procedure if the patient had constipation.

Safety and satisfaction survey

Complications were recorded during and four weeks after CAES. The intensity of CAES and the relationship between the complications and CAES were described using the Common Terminology Criteria for Adverse Events (version 3.0). Intensity of complications was classified as mild, moderate, severe and disabling. The relationship between the complications and CAES was categorized as unrelated, possible, probable and definitely related to CAES. All patients were required to have a face to face communication at the doctor's office for the assessment of safety, efficacy and degree of satisfaction of the CAES. The level of satisfaction was classified into two degrees: positive, satisfied and pleased to introduce the CAES to other patients; negative, not satisfied and did not like this procedure. The second colonoscopy would be performed if the patient had bleeding or any other anorectal symptoms.

RESULTS

Patient characteristics

Table 1 shows the characteristics of the patients, including gender, age, classification of the internal hemorrhoids, grade of prolapse, previous hemorrhoidectomy history and other related information. A total of 30 patients with grade Ⅰ, grade Ⅱ or grade Ⅲ internal hemorrhoids was included for analysis in this study.

Clinical findings

Colon and terminal ileum examination by colonoscopy before CAES was performed in all patients for differential diagnosis of other possible diseases related to intestinal bleeding. No complications were observed during the procedure. However, we have to highlight that the needle could not be retrieved immediately when the injection was finished. It is suggested to keep the needle stable within the tissue for 5 s. If the needle was taken out from the tissue too quickly, bleeding would occur and the endoscopic view was affected by the blood. Figure 2 shows the procedures of CAES for internal hemorrhoids and the excision for anal papilla fibroma.

The patients were required to stay in hospital for 12 h after the procedure for safety considerations in this pilot observational study. No complications were observed during and after the procedure of polypectomy, CAES, excision of anal papilla fibroma and biopsy of polyps on the hemorrhoid lesion. All patients could return to normal activities after they were discharged from hospital. One (3.33%) patient claimed mild tenesmus within four days after CAES. This adverse event was finally confirmed as the result of one injection site that was chosen below the dentate line by an endoscopist who performed this procedure for the first time. One hundred percent

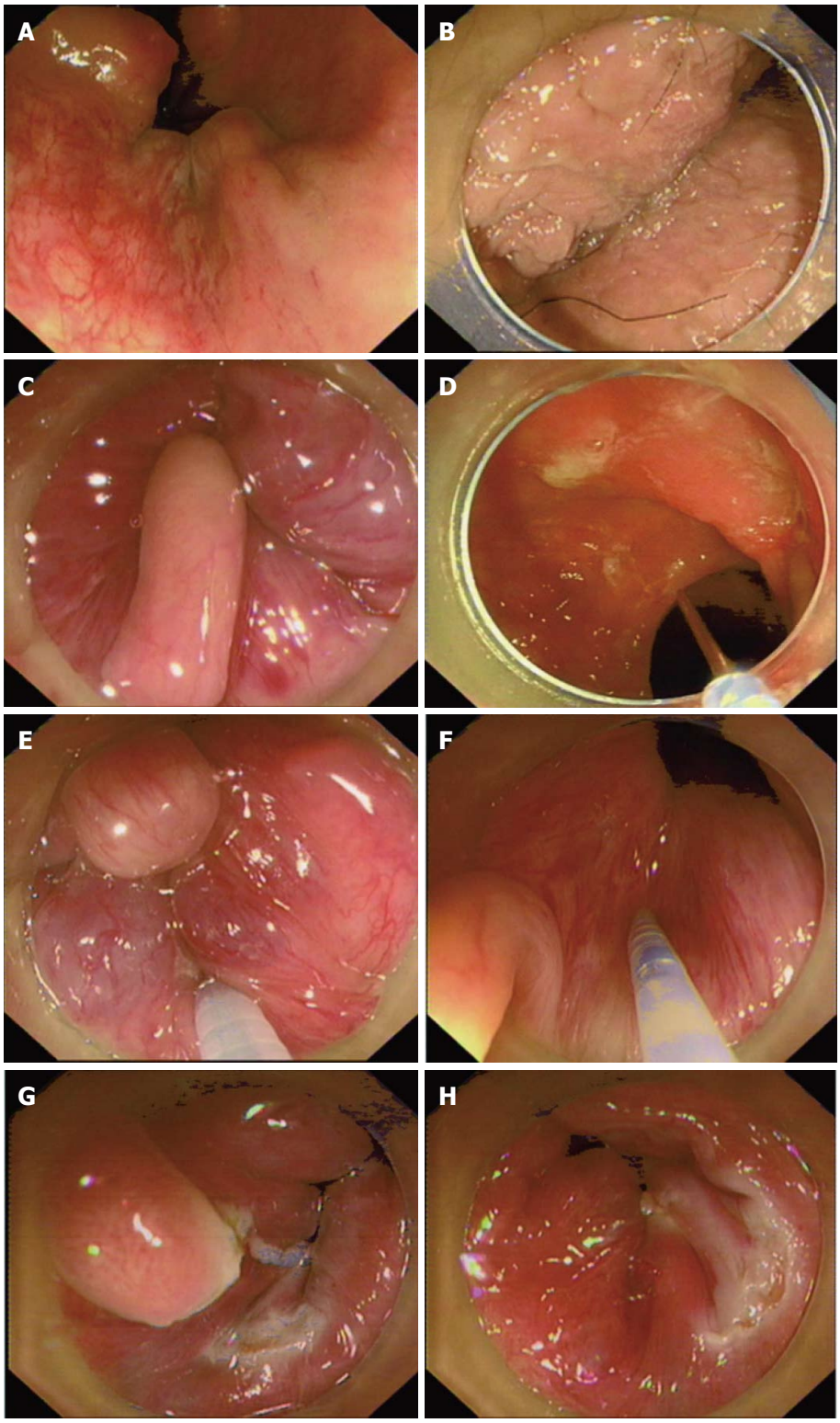

Figure 2 Procedures of cap-assisted endoscopic sclerotherapy for internal hemorrhoids and the excision for anal papilla fibroma. A: Internal hemorrhoids with retroflection of the endoscope; B: The anal region under cap-assisted endoscopic view; C: Internal hemorrhoids and anal papilla fibroma under cap-assisted endoscopic view with enough insufflated air; D: The disposable endoscopic long injection needle through operating channel; E: Injection of lauromacrogol into submucosa of internal hemorrhoids with the cap-assisted endoscopic view; F: Injecting of lauromacrogol into submucosa of internal hemorrhoids close to papilla fibroma before dissection; G: Dissection of anal papilla fibroma (confirmed by the followed pathology) after cap-assisted endoscopic sclerotherapy (CAES); H: No bleeding after CAES and dissection of anal papilla lesion before ending all procedures.

of patients were satisfied with this novel procedure. Those patients who underwent CAES in junction with polypectomy or excision of anal papilla fibroma expressed strong feeling of satisfaction for the therapeutic strategy.

DISCUSSION

Sclerotherapy dates back at least one century[15] and has been regarded as traditional therapy for grade Ⅰ and Ⅱ internal hemorrhoids. A variety of sclerosing agents, including ethanolamine, quinine, hypertonic saline solution, 5% phenol in oil, aluminum potassium sulfate and tannic acid, have been used in injection sclerotherapy for treating hemorrhoids[16-19]. Traditionally doctors had to use an anoscope during the sclerotherapy procedure. Misplacement of the sclerosing injection may result in potential complications, including pain, impotence, prostatitis, mucosal ulceration or necrosis

Table 1 Patient demographics and clinical results

Patient demographics	*n* (%)
Total included cases	30
Classification of internal hemorrhoids	
Grade Ⅰ	7 (23.33)
Grade Ⅱ	21 (70.0)
Grade Ⅲ	2 (6.67)
Grade Ⅳ	0
Male	22 (73.33)
Age (mean ± SD)	45.5 ± 4.2
With hemorrhoidectomy history	6 (20.0)
With rectal mucosal prolapse	4 (13.33)
With polyps on hemorrhoid lesions	1 (3.33)
With external hemorrhoids	0
Colon and terminal ileum examination before CAES	30 (100)
Polypectomy during colonoscopy before CAES	7 (23.33)
Excision of anal papilla fibroma after CAES	1 (3.33)
Biopsy for the polyps on hemorrhoids before CAES	1 (3.33)
Complications during and post-CAES	0
Post-CAES rectal bleeding	0
Post-CAES rectal mild pain or tenesmus	1 (3.33)
Positive satisfaction on CAES	30 (100)

Data are frequency counts (percentage of total) or the mean ± SD. CAES: Cap-assisted endoscopic sclerotherapy.

and prostatic abscess[10]. These complications emphasize the importance of precise placement of the injection with the sclerosing agent. In order to avoid the above complications, this prospective study was designed to evaluate the feasibility and efficacy of CAES for internal hemorrhoids under colonoscopy.

The preliminary results based on 30 cases demonstrated that CAES should be an effective interventional flexible endoscopic therapy for selected candidates with grade Ⅰ to grade Ⅲ internal hemorrhoids. After CAES, 100% of patients achieved the expected clinical response. The follow-up within 4 wk showed sustained clinical efficacy. No severe or obvious complications were observed and none of the suffered complications were definitely related to CAES in the study. These results indicated that CAES was safe and helpful to prevent iatrogenic risk from misplaced injections. The length of a common commercial endoscopic injection needle was not suggested in CAES because of its short length (*e.g.,* 4 or 5 mm), which seems to require more sites for injection and induce more mucosal injury and potential inflammation. Our specially designed needle, with a 15-20 mm length, is an important tool for enough submucosal injection with the sclerosing agent. Based on our experience, this CAES technique with the transparent cap is able to treat all hemorrhoids in a forward view fashion. There might be no need to have retroflection for the CAES procedure. Importantly, it is impossible for endoscopist to have retroflection in all cases.

In the present study, a high level of patient satisfaction (100%) and the convenience from adequate medical health or psychophysical protection for doctors also provide evidence to support CAES to be promising for the future. Actually, CAES brought additional benefits for patients, such as colonoscopy, possible polypectomy, excision of anal papilla fibroma and biopsy of polyps on hemorrhoid lesions under endoscopy.

Another advantage of doing an endoscopic procedure before CAES to that of using a plain disposable anoscope is that bleeding and other anorectal symptoms related to different colorectal diseases could be better differentiated[20]. A population-based study in the United States[21] reported in the hematochezia cohort showed significantly higher rates of diverticulosis, polyp or multiple polyps, mucosal abnormality/colitis, tumor and solitary ulcers on colonoscopy findings. Anorectal diseases, including hemorrhoids, are frequent in patients with intestinal disease. Hemorrhoids have been reported to occur in 20% of patients with UC[22] and approximately 7% of patients with CD[23]. In these selected cases, lesions in the colon and terminal ileum were observed during the examination by colonoscopy before CAES, which should be an effective way to have an early diagnosis of CD and UC with hemorrhoids. Therefore, colon preparation and colonoscopy is important when dealing with hemorrhoids as it would save the related medical cost and colon preparation for patients.

The cap, endoscope, air, long needle, sclerosing agent and endoscopic view should be the key points for the endoscopist to perform the CAES. This CAES technique is simple but the possible risk should be considered for physicians. One patient claimed mild tenesmus within four days after CAES. This complication was finally confirmed as the result of one injection site chosen below the dentate line by an endoscopist who performed this procedure for the first time. This lesson highlighted the importance of training for CAES. With the necessary training, the angle, direction and depth of injection under endoscopic view could be controlled very well and it would be easy to avoid the risk of injuring deeper tissues or injecting outside of the hemorrhoid.

All cases were required to be hospitalized for bed rest on the first night after the procedure, according to the design of this observational study. However, this hospitalization would not be required if the patient has no other condition except hemorrhoids. For prevention of recurrence of hemorrhoids, medicines and health education are important to maintain soft defecation within the first week after CAES if necessary.

There are some limitations in the present study. The sample size of this pilot study was small but a larger prospective study based on these preliminary results is ongoing. This was not a controlled study with the comparison of other traditional interventional therapies. Therefore, a rigorous randomized clinical trial should be designed to provide more evidence for the practice of CAES. Although CAES and the required preparation of colon and colonoscopy showed advantages and low medical costs for the diagnosis and therapy of anorectal diseases related to hemorrhoidal disease, a cost-effective analysis is needed for further study.

In conclusion, CAES is an innovation of endoscopic

sclerotherapy. It should be a convenient, safe and effective flexible endoscopic therapy for internal hemorrhoids. Traditionally, hemorrhoids are commonly treated by surgeons. However, the present study implies the future contribution of endoscopists for hemorrhoidal disease.

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COMMENTS

Background

The current therapies for hemorrhoids can be grouped into conservative management, office-based procedures and surgical treatment. As a crucial component of many non-surgical practices, sclerotherapy is most effective for grade I and II internal hemorrhoids. However, traditional sclerotherapy is performed by physicians using an anoscope. This method may cause iatrogenic risk and complications due to misplaced injections. Additionally, an anoscope has the limitation of only being used within the anus. Therefore, there is scope for improvement in the field of sclerotherapy for hemorrhoids.

Research frontiers

With the development of interventional flexible endoscopy, the authors designed a novel method called cap-assisted endoscopic sclerotherapy (CAES) for internal hemorrhoids. This article presents the authors' pilot study with the methodology, feasibility, safety, clinical findings and their experience using CAES for internal hemorrhoids.

Innovations and breakthroughs

This study demonstrated CAES is a safe, effective and convenient endoscopic therapeutic strategy for grade Ⅰ, grade Ⅱ and partial grade Ⅲ internal hemorrhoids. The colon preparation and colonoscopy are the steps before the final sclerotherapy. The colon preparation and colonoscopy before CAES brought more benefits for patients, including possible polypectomy and excision of anal papilla fibroma under endoscopy. Besides, in these selected cases, lesions in the colon and terminal ileum were observed before CAES during the colonoscopy itself, which should be an effective way to have an early diagnosis of Crohn's disease and Ulcerative colitis with hemorrhoids. Therefore, it would save the related medical cost and colon preparation for patients. This study implies the future contribution of endoscopists on hemorrhoidal disease.

Applications

This pilot study based on 30 cases demonstrated that CAES should be an effective interventional flexible endoscopic therapy for selected candidates with grade Ⅰ to grade Ⅲ internal hemorrhoids. After CAES, 100% of patients achieved the expected clinical response. The follow-up within 4 wk further showed the sustained clinical efficacy. No severe or obvious complications were observed and none of the suffered complications were definitely related to CAES in the study. These results indicated that CAES was safe and helpful in preventing iatrogenic risk from misplaced injections. The authors' specially designed needle, 10/15/20 mm in length, is an important tool to ensure enough submucosal injection with the sclerosing agent. Based on the authors' experience, this CAES technique with the transparent cap is able to treat all hemorrhoids in a forward view fashion. There may be no need for retroflection for the CAES procedure. Importantly, it is impossible for endoscopist to have retroflection in all cases. In the present study, a high level of patient satisfaction (100%) and the convenience of adequate medical health or psychophysical protection for doctors also provide evidence for supporting CAES to be promising for the future. Actually, CAES brought additional benefits for patients, such as colonoscopy, possible polypectomy, excision of anal papilla fibroma and biopsy of polyps on hemorrhoid lesions under endoscopy.

Terminology

The concept and methods of CAES: The regular cap used in endoscopic submucosal dissection was fixed on the top of the colonoscope. This cap is used to maximize visibility of the endoscopic view with enough insufflated air through the channel within the endoscope. A disposable endoscopic long injection needle through the operating channel is advanced into the submucosa of the targeted area of the hemorrhoids. The injecting points are above the dentate line. The sclerosing agent for each injecting point is injected slowly while retracting the needle slowly. During the procedure, enough air was given for exposure of the endoscopic view. Before the complete retrieval of the needle from the tissue, as a suggestion, it is helpful if you do not withdraw and stop the needle from moving for 5 s to prevent bleeding. The same procedure is performed for each targeted site under endoscopic view.

Peer-review

The authors describe a modification of the band ligation technique of hemorrhoid therapy by using ESD caps with sclerotherapy. The use of a cap mounted on the tip of an endoscope was useful to stabilize its position for precise injection of a sclerosing agent through a long needle. Overall, the model is elegant and the results seem to be promising. In addition to a novel technique, their analysis is rigorous, including the use of a post-procedure questionnaire. The images and diagram are also excellent.

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SYSTEMATIC REVIEWS

Systematic review and meta-analysis on the prophylactic role of non-steroidal anti-inflammatory drugs to prevent post-endoscopic retrograde cholangiopancreatography pancreatitis

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Abstract

AIM: To critically appraise the published randomized, controlled trials on the prophylactic effectiveness of the non-steroidal anti-inflammatory drugs (NSAIDs), in reducing the risk of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis.

METHODS: A systematic literature search (MEDLINE, Embase and the Cochrane Library, from inception of the databases until May 2015) was conducted to identify randomized, clinical trials investigating the role of NSAIDs in reducing the risk of post-ERCP pancreatitis. Random effects model of the meta-analysis was carried out, and results were presented as odds ratios (OR) with corresponding 95%CI.

RESULTS: Thirteen randomized controlled trials on 3378 patients were included in the final meta-analysis. There were 1718 patients in the NSAIDs group and 1660 patients in non-NSAIDs group undergoing ERCP. The use of NSAIDs (through rectal route or intramuscular route) was associated with the reduced risk of post-ERCP pancreatitis [OR, 0.52 (0.38-0.72), P = 0.0001]. The use of pre-procedure NSAIDs was effective in reducing approximately 48% incidence of post-ERCP pancreatitis, number needed to treat were 16 with absolute risk reduction of 0.05. But the risk of post-ERCP pancreattis was reduced by 55% if NSAIDs were administered after procedure. Similarly, diclofenac was more effective (55%) prophylactic agent compared to indomethacin (41%).

CONCLUSION: NSAIDs seem to have clinically proven advantage of reducing the risk of post-ERCP pancreatitis.

Key words: Non-steroidal drugs; Pancreatitis; Diclofenac; Indomethacin; Endoscopic retrograde cholangiopancreatography

Core tip: Current meta-analysis of 13 randomized controlled trials on 3378 patients successfully demonstrates the usefulness of non-steroidal anti-inflammatory drugs (NSAIDs) in the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Post-procedure use of NSAIDs by any route has clinically proven advantage of reducing 55% risk of post-ERCP pancreatitis. Diclofenac (55%) compared to indomethacin (41%) was more effective prophylactic agent.

Sajid MS, Khawaja AH, Sayegh M, Singh KK, Philipose Z. Systematic review and meta-analysis on the prophylactic role of non-steroidal anti-inflammatory drugs to prevent post-endoscopic retrograde cholangiopancreatography pancreatitis. *World J Gastrointest Endosc* 2015; 7(19): 1341-1349 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i19/1341.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i19.1341

INTRODUCTION

Since its introduction into the field of gastroenterology, hepatology and hepato-pancreatico-biliary surgery, the endoscopic retrograde cholangiopancreatography (ERCP) has advanced to be an important and essential diagnostic and therapeutic tool. The introduction of magnetic resonance cholangiopancreatography and endoscopic ultrasound with several technological developments has sidelined ERCP into a largely a therapeutic tool in the management of sphincter of Oddi disorders, choledocholithiasis, pancreatic duct pathologies, and benign or malignant strictures of the common bile duct. However, ERCP carries significant risk, with post-ERCP pancreatitis being the most frequent and dreaded of these. The reported prevalence of post-ERCP pancreatitis is as high as 10%[1-4] in the medical literature. Nevertheless, it may exceed up to 30% in certain high-risk cluster of female patients with sphincter of Oddi dysfunction[5]. Post-ERCP pancreatitis may result in prolonged hospital stay, pancreatic oedema, pancreatic necrosis, pancreatic pseudocyst, systemic inflammatory response syndrome and mortality up to 1% in addition to adding a significant financial burden on health-care resources[6].

Considering the morbidity, mortality and financial burden related to post-ERCP pancreatitis, it is vital to consider every preventive strategy to reduce its incidence. Risk-benefit analysis and then right patient selection may be the best way to avoid un-necessary ERCP and its subsequent complications. Several studies have reported promising modalities of prophylaxis including pancreatic duct stenting of patients with sphincter of Oddi dysfunction, administration of NSAIDs of various types by various routes and other diverse measures. The evidence of these prophylactic measures is conflicting and so far has failed to demonstrate the accurate effectiveness[7-11]. Based upon the available evidence, NSAIDs are the most commonly used modality for post-ERCP pancreatitis prevention. The possible advantages of NSAIDs use are cost-effectiveness, easily accessible and effortlessly administrable. The aim of this systematic review is to critically appraise the published randomized, controlled trials in the clinical effectiveness of the NSAIDs in reducing the risk of post-ERCP pancreatitis.

MATERIALS AND METHODS

Electronic medical databases such as the Medline, EMBASE, Cochrane Colorectal Cancer Group Controlled Trial Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library and Science Citation Index Expanded were explored until May 2015 to find published randomized, controlled trials. The MeSH terms related to the NSAIDs and post-ERCP pancreatitis were retrieved from the search engine of PubMed and were used to search electronic databases. Attempts to include additional studies were also made by the hand searching of the citations of published studies. The statistical analysis of the extracted data was conducted according to the guidelines provided by the Cochrane Collaboration including the use of RevMan 5.3® statistical software, random-effects model analysis, heterogeneity testing by χ^2 test, heterogeneity quantification by I-squared test and the use of forest plots for the graphical display of the combined outcomes[12-18]. The critical appraisal tool to score the quality of included trials was adopted from the published guidelines of Jadad *et al*[19] and Chalmers *et al*[20]. The short summary of the resulting evidence was presented in a tabulated form by using tool GradePro®[21], provided by the Cochrane Collaboration.

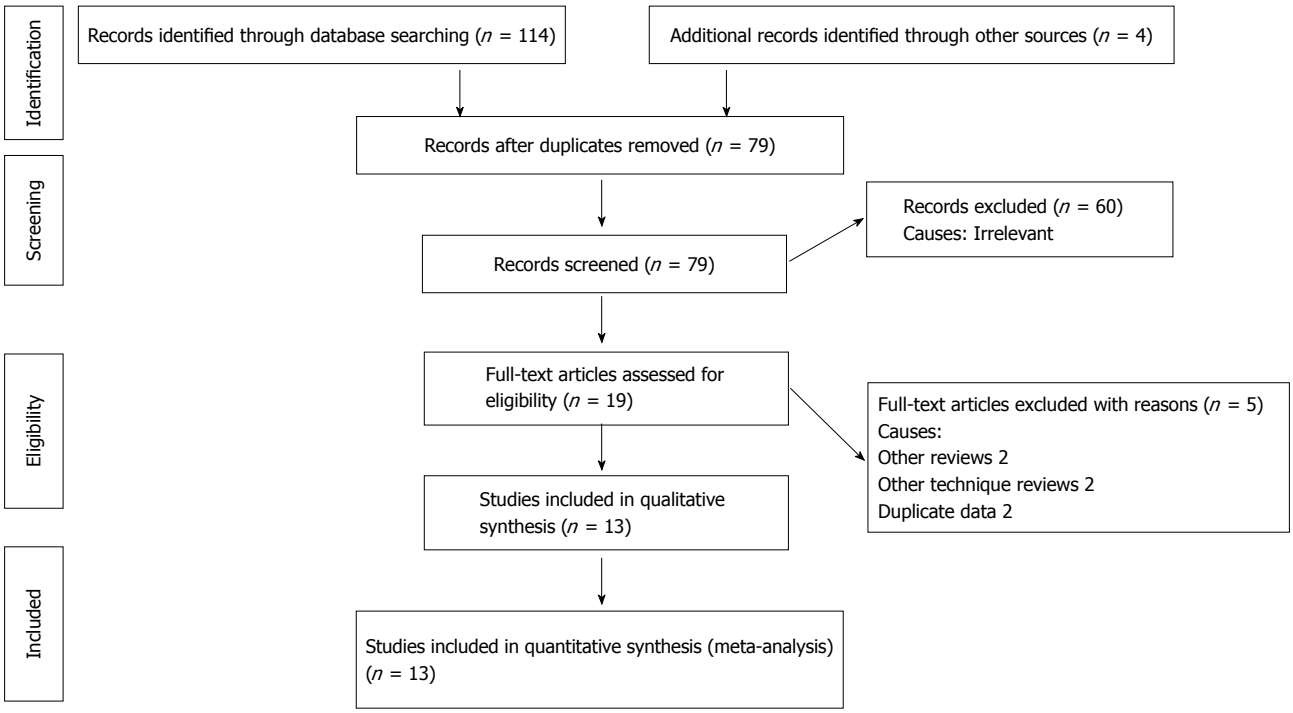


Figure 1 PRISMA flow chart.

RESULTS

Number of studies on first hit in search engines and their subsequent shortlisting is given in the PRISMA flow chart (Figure 1). Thirteen randomized, controlled trials[22-34] on 3378 patients undergoing ERCP were analysed in this study. Some 1718 patients were assigned in NSAIDs group whereas 1660 patients were in no-NSAIDs group. The characteristics of included studies are given in Table 1. The short summary on the quality of evidence generated from the combined analysis of trials used in this meta-analysis is given in Table 2. The study quality based scores of included trials were graded adequate based upon the reporting of four quality indicator variables, *i.e.*, optimum randomization technique, power calculations, concealment and intention-to-treat analysis.

Incidence of post-ERCP pancreatitis in NSAIDs vs placebo trials

As shown in Figure 2A, there was minimal and non-significant heterogeneity [Tau^2 = 0.11, χ^2 = 18.60, df = 12, (P = 0.10); I^2 = 35%] among trials. In the random effects model (OR, 0.52; 95%CI: 0.38, 0.72; Z = 4.02; P < 0.0001) analysis, the risk of post-ERCP pancreatitis was significantly lower (48% lower) following the use of NSAIDs. The NNT was 16 with absolute risk reduction of 0.05.

Incidence of post-ERCP pancreatitis in per rectal NSAIDs vs placebo trials

As shown in Figure 2B, there was no heterogeneity [Tau^2 = 0.11, χ^2 = 9.86, df = 7, (P = 0.20); I^2 = 29%] among trials. In the random effects model (OR, 0.43; 95%CI: 0.28, 0.67; Z = 3.77; P = 0.0002) analysis, the risk of post-ERCP pancreatitis was significantly lower (57% lower) following rectal administration of NSAIDs.

Incidence of post-ERCP pancreatitis in diclofenac vs placebo trials

As shown in Figure 2C, there was significant heterogeneity [Tau^2 = 0.38, χ^2 = 14.49, df = 6, (P = 0.02); I^2 = 59%] among trials. In the random effects model (OR, 0.45; 95%CI: 0.24, 0.83; Z = 2.55; P = 0.01) analysis, the risk of post-ERCP pancreatitis was significantly lower (55% lower) following the use of diclofenac.

Incidence of post-ERCP pancreatitis in indomethacin vs placebo trials

As shown in Figure 2D, there was no heterogeneity [Tau^2 = 0.00, χ^2 = 3.81, df = 4, (P = 0.43); I^2 = 0%] among trials. In the random effects model (OR, 0.59; 95%CI: 0.39, 0.88; Z = 2.61; P = 0.009) analysis, the risk of post-ERCP pancreatitis was significantly lower (41% lower) following the use of indomethacin. Based upon this finding it seems like diclofenac is more effective NSAIDs compared to indomethacin for the prevention of post-ERCP pancreatitis.

Incidence of post-ERCP pancreatitis if NSAIDs are administered before procedure

As shown in Figure 2E, there was no heterogeneity [Tau^2 = 0.05, χ^2 = 5.96, df = 5, (P = 0.31); I^2 = 16%] among trials. In the random effects model (OR, 0.52; 95%CI: 0.34, 0.80; Z = 2.93; P = 0.003) analysis, the risk of post-ERCP pancreatitis was significantly lower (48% lower) if NSAIDs are administered before the

Table 1 Characteristics of included trials

Ref.	Year	Country	Time of administration	Route	Dose	Type of NSAIDs used
Cheon *et al*[22]	2007	United States	Before ERCP	Oral	50 mg	Diclofenac
Döbrönte *et al*[23]	2012	Hungary	Before ERCP	Rectal	100 mg	Indomethacin
Döbrönte *et al*[24]	2014	Hungary	Before ERCP	Rectal	100 mg	Indomethacin
Elmunzer *et al*[25]	2012	United States	After ERCP	Rectal	100 mg	Indomethacin
Khoshbaten *et al*[26]	2008	Iran	After ERCP	Rectal	100 mg	Diclofenac
Montaño Loza *et al*[27]	2006	Mexico	Before ERCP	Rectal	100 mg	Indomethacin
Montaño Loza *et al*[28]	2007	Mexico	Before ERCP	Rectal	100 mg	Indomethacin
Murray *et al*[29]	2003	United Kingdom	After ERCP	Rectal	100 mg	Diclofenac
Otsuka *et al*[30]	2012	Japan	Before ERCP	Rectal	50 mg	Diclofenac
Park *et al*[31]	2014	United States South Korea	After ERCP	Intramuscular	90 mg	Diclofenac
Senol *et al*[32]	2009	Turkey	After ERCP	Intravenous infusion	75 mg	Diclofenac
Sotoudehmanesh *et al*[33]	2007	Iran	Before ERCP	Rectal	100 mg	Indomethacin
Zhao *et al*[34]	2014	China	After ERCP	Intramuscular	75 mg	Diclofenac

NSAIDs: Non-steroidal anti-inflammatory drugs; ERCP: Endoscopic retrograde cholangio-pancreaticography.

Table 2 Summary and strength of the evidence from trials analysed on GradePro®

Author(s): Sajid *et al*

Date: 20/10/2015

Question: NSAID's are an effective modality to reduce the incidence of post-ERCP pancreatitis?

Settings: All patients undergoing booth elective or emergency ERCP in endoscopy department for any indication by an experienced gastroenterologist/ endoscopists

Bibliography: Adapted from the Cochrane Database of Systematic Reviews [2015, Issue (Is)]

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAID's *vs* placebo	Control	Relative (95%CI)	Absolute		
Incidence of overall pancreatitis (follow-up mean 3 mo; assessed with: Odds ratio)												
14	Randomised trials	Serious	No serious inconsistency	No serious indirectness	No serious imprecision	Strong association	138/1900 (7.3%)	248/1878 (13.2%)	OR 0.49 (0.36 to 0.67)	63 fewer per 1000 (from 40 fewer to 80 fewer)	High	Critical
								15.7%		73 fewer per 1000 (from 46 fewer to 94 fewer)		

NSAIDs: Non-steroidal anti-inflammatory drugs; ERCP: Endoscopic retrograde cholangio-pancreaticography.

procedure of ERCP compared to placebo.

Incidence of post-ERCP pancreatitis if NSAIDs are administered after procedure

As shown in Figure 2F, there was minimal heterogeneity [Tau^2 = 0.21, χ^2 = 10.30, df = 5, (P = 0.07); I^2 = 51%) among trials. In the random effects model (OR, 0.45; 95%CI: 0.27, 0.77; Z = 2.90; P = 0.004) analysis, the risk of post-ERCP pancreatitis was significantly lower (55% lower) if NSAIDs are administered after the procedure of ERCP compared to placebo.

DISCUSSION

Summary of main results

Results of this meta-analysis demonstrate that the use of NSAIDs (by any route of administration) meaningfully reduces the incidence of post-ERCP pancreatitis; rectal administration is slightly more effective; diclofenac seems to be clinically better than indomethacin and post-ERCP administration has shown superior results. The use of pre-procedure NSAIDs was effective in reducing approximately 48% but the risk of post-ERCP pancreatitis was reduced by 55% if NSAIDs were administered after the procedure.

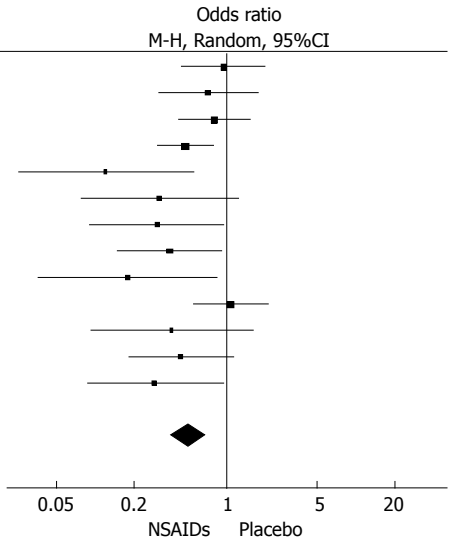
Overall completeness and applicability of evidence

The findings of current study are pertinent to only those groups of patients which may require either therapeutic or diagnostic ERCP and fit enough to undergo the procedure. Despite the reporting of several systematic reviews and meta-analysis[35-46] evaluating the role of NSAIDs in reducing

A

Study or subgroup	NSAID'S Event	Total	Placebo Event	Total	Weight	Odds ratio M-H, Random, 95%CI
Cheon *et al*[22]	17	105	17	102	10.4%	0.97 [0.46, 2.02]
Döbrönte *et al*[23]	11	130	11	98	8.4%	0.73 [0.30, 1.76]
Döbrönte *et al*[24]	20	347	22	318	12.3%	0.82 [0.44, 1.54]
Elmunzer *et al*[25]	27	295	52	307	15.0%	0.49 [0.30, 0.81]
Khoshbaten *et al*[26]	2	50	13	50	3.5%	0.12 [0.03, 0.56]
Montaño Loza *et al*[27]	3	61	8	56	4.3%	0.31 [0.08, 1.23]
Montaño Loza *et al*[28]	4	75	12	75	5.5%	0.30 [0.09, 0.96]
Murray *et al*[29]	7	110	17	110	7.8%	0.37 [0.15, 0.94]
Otsuka *et al*[30]	2	51	10	53	3.5%	0.18 [0.04, 0.85]
Park *et al*[31]	22	173	20	170	11.9%	1.09 [0.57, 2.09]
Senol *et al*[32]	3	40	7	40	4.1%	0.38 [0.09, 1.60]
Sotoudehmanesh *et al*[33]	7	221	15	221	7.9%	0.45 [0.18, 1.12]
Zhao *et al*[34]	4	60	12	60	5.4%	0.29 [0.09, 0.94]
Total (95%CI)		1718		1660	100.0%	0.52 [0.38, 0.72]
Total events	129		216			

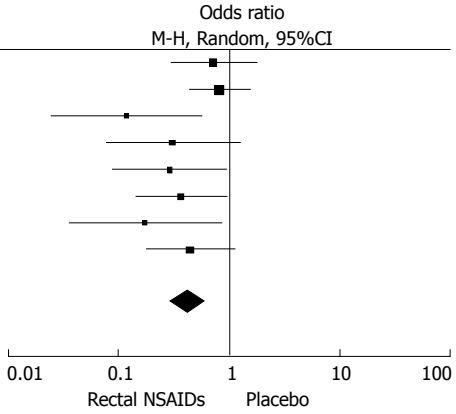
Heterogeneity: Tau^2 = 0.11; χ^2 = 18.60, df = 12 (P = 0.10); I^2 = 35%
Test for overall effect: Z = 4.02 (P < 0.0001)



B

Study or subgroup	Rectal NSAID'S Event	Total	Placebo Event	Total	Weight	Odds ratio M-H, Random, 95%CI
Döbrönte *et al*[23]	11	130	11	98	15.7%	0.73 [0.30, 1.76]
Döbrönte *et al*[24]	20	347	22	318	23.1%	0.82 [0.44, 1.54]
Khoshbaten *et al*[26]	2	50	13	50	6.7%	0.12 [0.03, 0.56]
Montaño Loza *et al*[27]	3	61	8	56	8.1%	0.31 [0.08, 1.23]
Montaño Loza *et al*[28]	4	75	12	75	10.3%	0.30 [0.09, 0.96]
Murray *et al*[29]	7	110	17	110	14.7%	0.37 [0.15, 0.94]
Otsuka *et al*[30]	2	51	10	53	6.5%	0.18 [0.04, 0.85]
Sotoudehmanesh *et al*[33]	7	221	15	221	14.9%	0.45 [0.18, 1.12]
Total (95%CI)		1045		981	100.0%	0.43 [0.28, 0.67]
Total events	56		108			

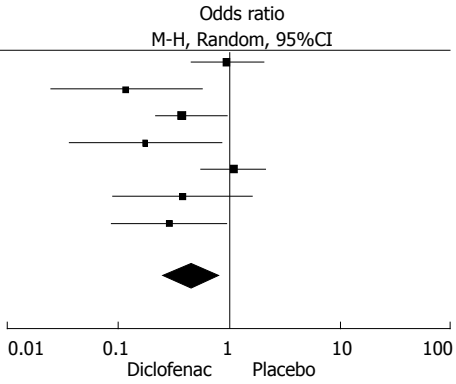
Heterogeneity: Tau^2 = 0.11; χ^2 = 9.86, df = 7 (P = 0.20); I^2 = 29%
Test for overall effect: Z = 3.77 (P = 0.0002)



C

Study or subgroup	Diclofenac Event	Total	Placebo Event	Total	Weight	Odds ratio M-H, Random, 95%CI
Cheon *et al*[22]	17	105	17	102	19.2%	0.97 [0.46, 2.02]
Khoshbaten *et al*[26]	2	50	13	50	9.9%	0.12 [0.03, 0.56]
Murray *et al*[29]	7	110	17	110	16.6%	0.37 [0.15, 0.94]
Otsuka *et al*[30]	2	51	10	53	9.7%	0.18 [0.04, 0.85]
Park *et al*[31]	22	173	20	170	20.4%	1.09 [0.57, 2.09]
Senol *et al*[32]	3	40	7	40	10.9%	0.38 [0.09, 1.60]
Zhao *et al*[34]	4	60	12	60	13.3%	0.29 [0.09, 0.94]
Total (95%CI)		589		585	100.0%	0.45 [0.24, 0.83]
Total events	57		96			

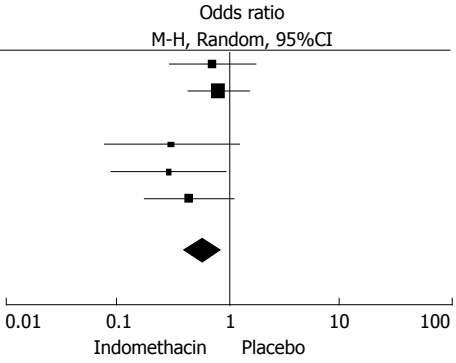
Heterogeneity: Tau^2 = 0.38; χ^2 = 14.49, df = 6 (P = 0.02); I^2 = 59%
Test for overall effect: Z = 2.55 (P = 0.01)



D

Study or subgroup	Indomethacin Event	Total	Placebo Event	Total	Weight	Odds ratio M-H, Random, 95%CI
Döbrönte *et al*[23]	11	130	11	98	20.6%	0.73 [0.30, 1.76]
Döbrönte *et al*[24]	20	347	22	318	40.7%	0.82 [0.44, 1.54]
Elmunzer *et al*[25]	27	295	523	307		Not estimable
Montaño Loza *et al*[27]	3	61	8	56	8.4%	0.31 [0.08, 1.23]
Montaño Loza *et al*[28]	4	75	12	75	11.4%	0.30 [0.09, 0.96]
Sotoudehmanesh *et al*[33]	7	221	15	221	18.9%	0.45 [0.18, 1.12]
Total (95%CI)		1129		1075	100.0%	0.59 [0.39, 0.88]
Total events	72		591			

Heterogeneity: Tau^2 = 0.00; χ^2 = 3.81, df = 4 (P = 0.43); I^2 = 0%
Test for overall effect: Z = 2.61 (P = 0.009)



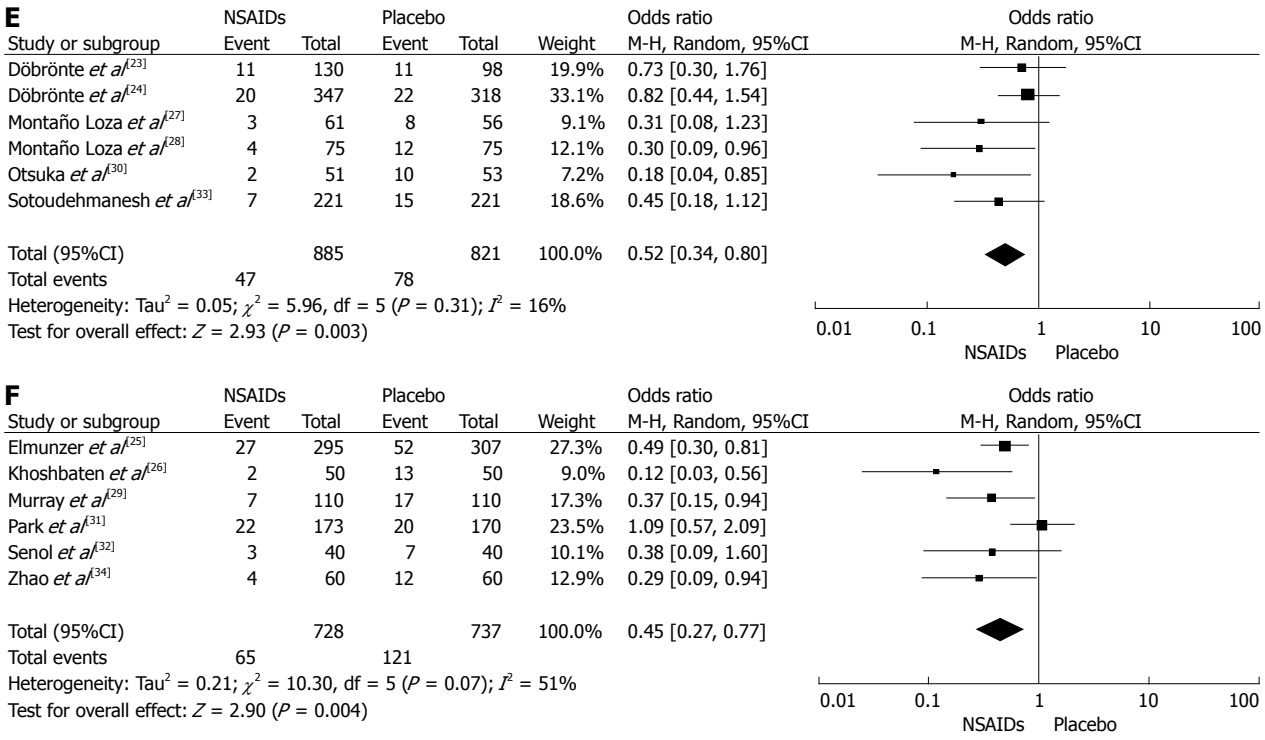


Figure 2 Forest plot for incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis. A: In non-steroidal anti-inflammatory drugs *vs* placebo groups; B: In rectal non-steroidal anti-inflammatory drugs *vs* placebo groups; C: In diclofenac *vs* placebo groups; D: In indomethacin *vs* placebo groups; E: In pre-endoscopic retrograde cholangiopancreatography non-steroidal anti-inflammatory drugs *vs* placebo groups; F: In post-endoscopic retrograde cholangiopancreatography non-steroidal anti-inflammatory drugs *vs* placebo groups. Odds ratios are shown with 95%CIs.

the risk of consequent pancreatitis resulting from ERCP, this is the only study providing evidence on the role of NSAIDs, route of NSAIDs administration, type of NSAIDs being more effective and the timing of the NSAIDs administration to reduce the incidence of post-ERCP pancreatitis.

Quality of evidence

This study reports a total of 3378 participants from 13 randomized, controlled trials undergoing ERCP reporting post-ERCP pancreatitis as primary outcome preferentially. The risk of bias in the included trials was low to moderate when scores against the standard quality guidelines and therefore, the quality of resulting evidence may be considered adequate (Table 2). The variable experience of endoscopists might have influenced the outcomes. Other confounding factors which might have influenced the final outcome of the ERCP include the use of different endoscopes, type and dosage of sedation, variable use of scope-guide technique, indications of ERCP, sundry patient selection and diverse biochemical measuring tools for the diagnosis of post-ERCP pancreatitis.

Potential biases in the review process

Authors adopted the standard Cochrane Collaboration methodology to perform the statistical analysis, interpretation as well as to present the quality of evidence. The quality of included (Table 3) randomized, controlled trials was assessed for risk of bias in one of the six domains (blinding) and at unclear risk of bias in another domain (allocation concealment). The low risk of bias was mainly attributable to the presence of blinding in all the trials and presence of allocation concealment in the majority of the studies. Presence of adequate randomization technique and optimum utilization of the power calculations in all included trials provided adequate strength to generate higher level of evidence to support the conclusion. There are no trials comparing pre-procedure *vs* post-procedure prophylactic use of NSAIDS. This inference was made based upon their comparisons against placebo. Same limitation also applies on the effectiveness of diclofenac *vs* indomethacin. However, the conclusion in terms of an individual agent *vs* other agent effectiveness and timing of NSAIDS administration may reluctantly be drawn from the available studies comparing effectiveness against placebo.

Agreement and disagreement with other published evidence

The findings of current meta-analysis are in accordance with the conclusions of the previously published reviews[35-46]. However, this study provides up to date, comprehensive and cumulative evidence on the use of NSAIDs (by any route of administration) meaningfully reducing the incidence of post-ERCP pancreatitis, suggesting the rectal administration of NSAIDs being more effective, indomethacin proven to be clinically better than diclofenac and pre-ERCP administration of NSAIDs showing superior results.

Implications for practice and research

This study quite successfully validates that NSAIDs may

Table 3 Reported quality variables in included studies

Ref.	Randomization	Power calculations	ITT	Blinding	Concealment
Cheon *et al*[22]	Yes	Yes	Yes	Yes	Yes
Döbrönte *et al*[23]	Yes	Yes	No	Yes	Yes
Döbrönte *et al*[24]	Yes	Yes	No	Yes	Yes
Elmunzer *et al*[25]	Yes	Yes	Yes	Yes	Yes
Khoshbaten *et al*[26]	Yes	Yes	No	Yes	Yes
Montaño Loza *et al*[27]	Yes	Yes	No	Yes	Yes
Montaño Loza *et al*[28]	Yes	Yes	No	Yes	Not reported
Murray *et al*[29]	Yes	Yes	No	Yes	Yes
Otsuka *et al*[30]	Yes	Yes	No	Yes	Yes
Park *et al*[31]	Yes	Yes	No	Yes	Yes
Senol *et al*[32]	Yes	Yes	No	Not reported	Not reported
Sotoudehmanesh *et al*[33]	Yes	Yes	No	Yes	Yes
Zhao *et al*[34]	Yes	Yes	No	No	Not reported

routinely be used to prevent the post-ERCP pancreatitis. However, the aforementioned confounding factors influencing the final outcomes must be acknowledged and attempts must be made to generate less biased evidence by removing these limitations. This study categorically reports the superiority of rectal administration of NSAIDs, diclofenac over indomethacin and post-ERCP administration of NSAIDs to reduce post-ERCP pancreatitis. However, these results cannot be generalized because the preventative strategy for post-ERCP pancreatitis in group of patients with known peptic ulcer disease, asthma, and allergy to NSAIDS needs also to be formulated. In addition, NSAIDs cannot be used in patients with chronic kidney disease. Other measures to prevent post-ERCP pancreatitis must not be completely abandoned and may be applicable in these situations. In addition, there are no reported trials comparing pre-procedure *vs* post-procedure prophylactic use of NSAIDS. This inference was made based upon their comparisons against placebo. Same limitation also applies on the effectiveness of diclofenac *vs* indomethacin. Trials targeting these questions must be considered for a validated conclusion from direct evidence instead of the presented indirect inference. Current review is unable to quantify the potential complication of bleeding following the prophylactic use of NSAIDs in ERCP patients, especially in patients undergoing sphincterotomy simultaneously. Although this is beyond the scope of this study but reported incidence of bleeding is almost negligible. Neither the length of incision nor the pre-procedure use of aspirin or other NSAIDs appear to be important predictors of ERCP-sphincterotomy linked bleeding[47].

COMMENTS

Background

Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis can be a serious complication resulting in increased mortality and morbidity in already sick patients. Therefore, the preventative strategies for post-ERCP are vital to reduce its consequences. The use of non-steroidal anti-inflammatory drugs (NSAIDs) is simple, economical and reported to be effective to reduce the incidence of post-ERCP pancreatitis. This article highlights the evidence in the form of meta-analysis to define the role of NSAIDs.

Research frontiers

Other preventive measures to reduce the incidence of post-ERCP pancreatitis include sphincterotomy of the sphincter of Oddi and pancreatic duct stenting. However, the use of NSAIDs seems to be less invasive and most economical. Several studies have reported its effectiveness and current study is an attempt to advance this evidence further.

Innovations and breakthroughs

Current meta-analysis of 13 randomized controlled trials on 3378 patients successfully demonstrates the usefulness of NSAIDs in the prevention of post-ERCP pancreatitis. Post-procedure use of NSAIDs by any route has clinically proven advantage of reducing 55% risk of post-ERCP pancreatitis. Diclofenac (55%) compared to indomethacin (41%) was more effective prophylactic agent.

Applications

Based upon the findings of this study the use of NSAIDs has clinical advantage in the reduction of post-ERCP pancreatitis and may routinely be used.

Terminology

ERCP: Endoscopic retrograde cholangiopancreaticography; NSAIDs: Non-steroidal anti-inflammatory drugs; MRCP: Magnetic resonance cholangio-pancreaticography.

Peer-review

The manuscript is overall well written.

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CASE REPORT

Challenges of banding jejunal varices in an 8-year-old child

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Abstract

Endoscoic variceal ligation (EVL) by the application of bands on small bowel varices is a relatively rare procedure in gastroenterology and hepatology. There are no previously reported paediatric cases of EVL for jejunal varices. We report a case of an eight-year-old male patient with a complex surgical background leading to jejunal varices and short bowel syndrome, presenting with obscure but profound acute gastrointestinal bleeding. Wireless capsule endoscopy and double balloon enteroscopy (DBE) confirmed jejunal varices as the source of bleeding. The commercially available variceal banding devices are not long enough to be used either with DBE or with push enteroscopes. With the use of an operating gastroscope, four bands were placed successfully on the afferent and efferent ends of the leads of the 2 of the varices. Initial hemostasis was achieved with obliteration of the varices after three separate applications. This case illustrates the feasibility of achieving initial hemostasis in the pediatric population.

Key words: Endoscopic variceal ligation; Endoscopic hemostasis; Pediatrics; Gastrointestinal hemorrhage; Varices; Variceal banding

Core tip: Banding jejunal varices in the pediatric population is feasible, safe and can achieve initial hemostasis in complex surgical patients.

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INTRODUCTION

Ectopic varices are defined as large porto-systemic venous collaterals occurring anywhere in the abdomen except in the cardio-esophageal region[1].

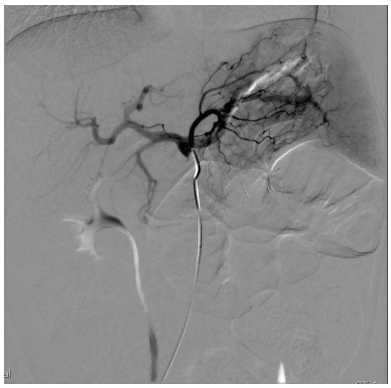

Figure 1 Computed tomography angiography with multiple serpiginous vessels in the left side of the bowel mesentery.

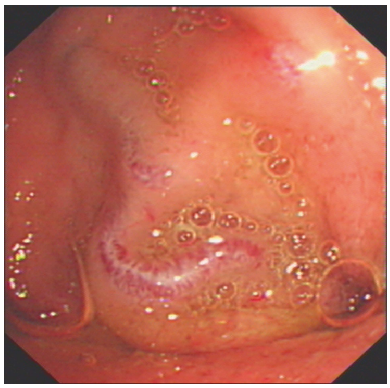

Figure 2 Suspicion of varices.

They account for up to 5% of all variceal bleeding[2]. Ectopic varices have been reported to occur at numerous sites, including 18% in the jejunum or ileum, 17% in the duodenum, 14% in the colon, 8% in the rectum, and 9% in the peritoneum[3]. Jejunal variceal bleeding, although rare, can be life threatening. There are only a few reports on the managements of jejunal varices in the paediatric population[4]. We present a rare case of severe and recurrent gastrointestinal bleeding secondary to jejunal varices in an 8-year-old patient. The management strategies including the use of endoscopic variceal ligation (EVL) are discussed.

CASE REPORT

An 8-year-old male patient was transferred from another tertiary hospital for assessment for obscure but profound acute gastrointestinal bleeding (AGIB).

He had a complex background of gastroschisis at birth associated with duodenal and colonic atresia. He had a repair of gastroschisis on day 1 of life and subsequently underwent a duodenojejunal anastamosis with right hemicolectomy and ileostomy formation, followed by ileo-colonic anastamosis and closure of the stoma. He had short gut syndrome and received nutritional supplementation *via* a balloon gastrostomy.

He had had multiple episodes of GI bleeding since he was 18 mo of age, which were thought to be associated with a superior mesenteric vein thrombosis. These were intermittent in nature and managed conservatively. The patient had a period of two years without a GI bleed prior to this presentation.

In 2014 however, the patient had 17 episodes of AGIB. Seven episodes were significant, mainly of hematochezia with clots or large melena. His lowest recorded hemoglobin was 22 g/L. The patient had multiple blood transfusions and was given 4 weekly iron infusions. He underwent computed tomography (CT) angiography which revealed distorted adjacent vascular structures around the pancreas with the splenic vein looping over the superior edge of the pancreas.

Normal enhancement was noticed in the portal vein, its left and right branches, the splenic vein (SV) and the superior mesenteric vein (SMV). However; there is unusual prominent venous structure draining in to the right side of the confluence of the SMV and the SV. There were multiple serpiginous vessels in the left side of the bowel mesentery with in particular a clump of varices/collaterals in the small bowels mesentery (Figure 1). All connections from these apparent varices couldn't be established, however; there was at least a connection to a looping vessel which extends into the left side of the SMV. Further looping vessels were seen in the anterior aspect of the mesentery from a proximal loop of the jejunum. Theses dilated blood vessels and collaterals around the mesentery of the small bowel raised the suspicion of mesenteric varices in the upper abdomen, but no active bleeding source was recognised. The patient was put intermittently on octreotide infusion but wasn't given primary or secondary prophylaxis as it was felt that the varices were more confined to some areas and secondary to mesenteric venous obstruction/abnormalities rather than strong evidence of generalised portal hypertension.

On arrival to our hospital in the same year, upper GI endoscopy revealed no esophago-gastric varices but identified portal gastropathy. Ileo-colonoscopy was normal apart from an erythematous ileo-colonic anastamotic rim. WCE identified a suspicious area (around 50 cm from the pylorus) of nodular shaped lesions with bluish discoloration, suspicious of varices. Two days later, further profound hematochezia occurred and therefore octreotide infusion (5 mcg/kg per hour) was commenced. Trans-oral double balloon enteroscopy (DBE) confirmed a normal esophagus, mild evidence of portal gastropathy, a normal duodenum, and jejunal examination revealed 4 moderately large isolated jejunal varices around 40-50 cm post-pylorus (Figures 2 and 3). Four bands were placed successfully on the afferent and efferent ends of the leads of the 2 of the varices using an operating gastroscope (Figure 4). The commercially available variceal banding devices are not long enough to be used either with DBE which was initially used diagnostically. Trans-anal DBE was performed and showed a small potential varix

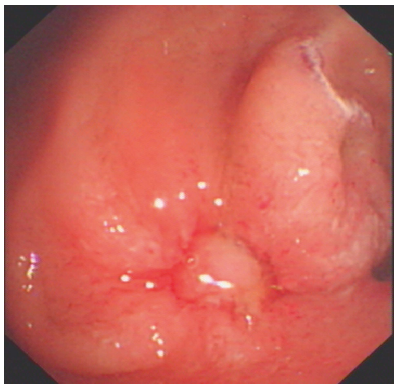

Figure 3 Appearance of jejunal varices using the double balloon enterosocpy.

approximately 120 cm proximal to the ileo-colonic anastamosis and this was not considered a risk and was not bleeding therefore was not banded. This area was marked for future reference with methylene blue tattoo injection. One week later a further endoscopy revealed the 2 banded varices to be thrombosed and now absent and sloughing within the bands was noted which were beginning to fall off the mucosa. The remaining 2 variceal vessels were then also banded. Two weeks subsequently the patient was well with no further bleed and a further endoscopy revealed friable variceal beds but no active bleeding. One further varix was banded at that time with hemostasis identified.

However the patient developed recurrence of bleed two weeks later possibly from an ileo-colonic source. The patient had shunting procedure few weeks later (mesenterico-caval shunt).

DISCUSSION

Our patient presented with the classical clinical signs reported previously in the literature for jejunal varices, evidence of abnormal vasculature in the mesentery with or without portal hypertention, a history of abdominal surgery, and hematochezia with or without hematemesis[5].

The exact pathology for developing jejunal varices in our case is not fully understood. It is likely to be a combination of superior mesenteric vein thrombosis (subsequently re-canalised however) and adhesions. A history of abdominal surgery appears to predispose to the development of ectopic varices around adhesions[6]. It seems that small-bowel anastomotic and adhesion-related varices can form within adhesions in the setting of mesenteric venous obstruction with or without portal hypertension[5].

Collateral formation within adhesions from previous surgery is the usual mechanism for the development of ectopic varices[3], with a likely mechanism that adhesions bring the parietal surface of the viscera in contact with the abdominal wall and portal hypertension results in the formation of varices below the intestinal mucosa[7].

The mainstay for the diagnosis of jejunal varices in our case was a combination of CT angiography and

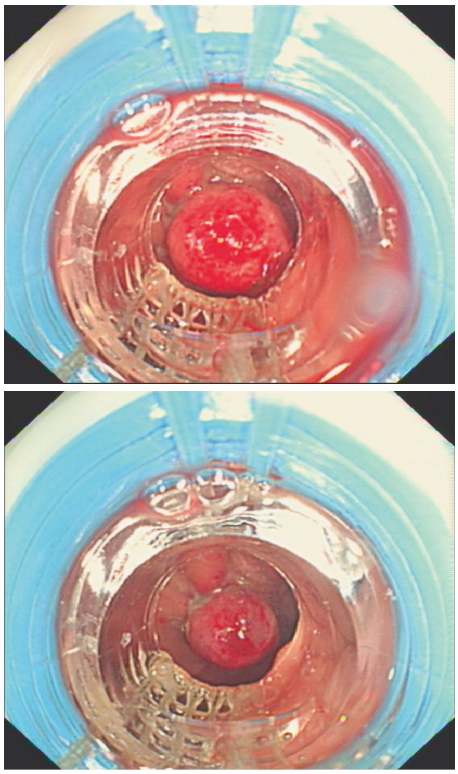

Figure 4 Banding of the jejunal varices using the operative gastroscope.

wireless capsule endoscopy.

Jejunal varices in wireless capsule endoscopy appear as serpiginous or nodular shapes, with or without a bluish discoloration. The variceal mucosa appears mosaic-like, shining, or normal compared with surrounding mucosa[8].

Capsule endoscopy is invaluable for the diagnosis of small-bowel varices. It is highly sensitive for detecting fresh blood in the small bowel. Clinical suspicion, capsule endoscopy image recognition, and alertness during capsule endoscopy interpretation are keys to diagnosis[8].

Several approaches for the treatment of jejunal varices have been described including surgery[9], portal venous stenting[10-12], percutaneous embolisation[13,14] and thne endoscopic options[5,15-18].

Surgical treatment options for small bowel variceal bleeds include resection of the afferent area of bowel and re-anastomosis[13]. However this can be challenging in patients with short gut and multiple adhesion as in our case.

Transjugular intrahepatic portal-systemic shunt or a decompressive shunting procedure is recommended in patients with overt systemic portal hypertension[13,19,20]. With the addition of coil or embolization has been reported to be particularly useful for ectopic varices, as these can continue to bleed despite successful portal pressure reduction[21].

The effectiveness of beta-blockers for primary prophylaxis and octreotide treatment for acute hemorrhage of anastomotic and segmental varices is uncertain[5].

It has been reported that endoscopic treatment including sclerosing agents can be used for treatment

of actively bleeding duodenal or jejunal varices or to prevent re-bleeding from focal varices with hemorrhage. However, while hemostasis is feasible, ulceration and re-bleeding rates can be high[5]. The use of N-butyl-2-cyanoacrylate (Histoacryl®) injection has been described in several case reports, for hemostasis of actively bleeding duodenal varices[15,22,23]. In one series all the varices had developed around the anastamotic sites and only two had elevated systemic portal pressure[18]. Another case report describes successful treatment of bleeding jejunal varices using cyanoacrylate sclero-therapy *via* enteroscopy in an adult patient[16].

EVL has a theoretical increased risk of complications in the small bowel because of its thin wall, *e.g.*, perforation. However, there are several reports of successfully treated duodenal varices by EVL in adults without complications. In a review of 19 cases (all adults) with duodenal EVL only 3 (15.8%) rebled after treatment with no deaths reported due to complications or rebleeding[16]. In a report of 4 patients with duodenal EVL, 2 achieved complete resolution of varices after one treatment session, one had remaining varices on surveillance endoscopy but no bleeding in a 9 mo period and one case required surgical resection after several banding sessions[17].

The standard ligation balloon devices available are too short to be adapted for an enteroscope or a colonoscope but are applicable to standard upper GI endsocopes. The operating gastroscope (GIF-2TQ260M) allowed 3 way tip deviation and is stiffer than conventional upper GI endsocopes allowing successful banding to occur.

In this case, EVL was used successfully to achieve initial hemostasis with obliteration of the varices after three separate applications, however bleeding subsequently occurred from an ileo-colonic source.

Frequently ectopic variceal bleeding is difficult to manage and traditionally surgery or shunting is required depending on the underlying disease and the patency of the portal vein.

Endoscopic treatment as a minimally invasive approach is feasible and safe in this case and represents a viable alternative.

To the best of our knowledge, this is the first reported case in the literature describing EVL in the management of jejunal variceal bleeding in the pediatric population.

This case illustrates the technical feasibility and apparent safety of EVL in the management of jejunal variceal bleeding in children.

COMMENTS

Case characteristics
Recurrent severe gastrointestinal bleeding.

Clinical diagnosis
Jejunal varices.

Differential diagnosis
Upper gastrointestinal endoscopy ruled out esophageal and gastric variceal bleeding. Ilio-colonosconoscopy and wireless capsule ruled out other diagnosis like polyps or other vascular malformation. Wireless capsule showed features suggestive of ectopic varices.

Laboratory diagnosis
Extensive investigations including complete blood count, Lipase, liver enzymes, kidney function, radiological images with computed tomography (CT) angiography. The diagnosis was confirmed with wireless capsule endoscopy and endoscopy of the affected small bowel.

Imaging diagnosis
Imaging study using CT scan demonstrated thickening and irregularity of the mesentery surrounding in keeping with the diagnosis of mesenteric panniculitis.

Pathological diagnosis
Variceal bleeding was the diagnosis as per the wireless capsule endoscopy and the endoscopic finding.

Treatment
The patient was treated with pharmacological agents including octreotide. Blood transfusion was needed frequently to stabilise the patient. Endoscopic variceal ligation was successfully applied to achieve initial hemostasis.

Related reports
Clark *et al* reported successful endoscopic ectopic variceal ligation: A series of 4 cases and review of the literature in adult population.

Experiences and lessons
Jejunal varices is a rare disorder that can present with recurrent severe gastrointestinal bleeding in complex surgical paediatric patient, the authors describe a novel intervention in paediatric using endoscopic variceal ligation to achieve initial hemostasis.

Peer-review
In this case report the authors present the case of an 8-year-old child treated with endoscopic band ligation for jejunal varices. This kind of pathology is rare and the therapeutic options could be challenging.

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