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CASE REPORT

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REVIEW

Role of endoscopy in acute gastrointestinal bleeding in real clinical practice: An evidence-based review

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Abstract

Although upper gastrointestinal bleeding is usually segregated from lower gastrointestinal bleeding, and guidelines for gastrointestinal bleeding are divided into two separate sections, they may not be distinguished from each other in clinical practice. Most patients are first observed with signs of bleeding such as hematemesis, melena, and hematochezia. When a patient with these symptoms presents to the emergency room, endoscopic diagnosis and treatment are considered together with appropriate initial resuscitation. Especially, in cases of variceal bleeding, it is important for the prognosis that the endoscopy is performed immediately after the patient stabilizes. In cases of suspected lower gastrointestinal bleeding, full colonoscopy after bowel preparation is effective in distinguishing the cause of the bleeding and treating with hemostasis. The therapeutic aspect of endoscopy, using the mechanical method alone or injection with a certain modality rather than injection alone, can increase the success rate of bleeding control. Therefore, it is important to consider the origin of bleeding and how to approach it. In this article, we aim to review the role of endoscopy in diagnosis, treatment, and prognosis in patients with acute gastrointestinal bleeding in a real clinical setting.

Key words: Endoscopy; Gastrointestinal bleeding; Endoscopic bleeding control; Emergency bowel preparation; Bedside endoscopy; Second-look endoscopy

Core tip: When a patient with signs of bleeding, such as hematemesis, melena, and hematochezia, presents to the emergency room, an endoscopic approach is considered together with initial resuscitation. Timely endoscopy and appropriate bowel preparation are very important in patients with acute gastrointestinal bleeding. In addition, mechanical bleeding control is an imperative part of therapeutic endoscopy. After

bleeding control, the risk classification of rebleeding is important because old age, concomitant diseases, and use of drugs (non-steroidal anti-inflammatory drug, antiplatelet, and anticoagulant drugs) are increasing. Therefore, endoscopy has a very important role in the diagnosis, therapy, and prognosis of gastrointestinal bleeding.

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INTRODUCTION

Along with abdominal pain, gastrointestinal bleeding (GIB) is one of the most common conditions in the emergency department. Upper GIB (UGIB) is a major problem that has been declining over the past 20 years but still has a mortality rate of 2.1%[1]. Lower GIB (LGIB) has a mortality rate less than 5%, but it is common in older patients and those with intestinal ischemia and comorbidity[2].

GIB usually manifests as hematemesis (vomiting of blood or coffee-ground-like material), melena (black or tarry stools), and hematochezia. UGIB appears as hematemesis in 40%-50%, and as melena or hematochezia in 90%-98%, especially hematochezia in massive UGIB[3]. However, patients with LGIB typically present with hematochezia, but right-sided colonic bleeding or small bowel bleeding may show as melena[4]. Therefore, it is frequently difficult to distinguish between UGIB and LGIB based on only the initial symptoms of the patient[5]. In real clinical practice, it is necessary to approach the patient with melena and hematochezia based on the main symptom rather than UGIB or LGIB.

Early resuscitation of acute GIB is usually performed by the physician in the emergency room, but highly skilled endoscopists are needed to determine the cause and location of bleeding. In many cases, endoscopic treatment should be performed to stop bleeding and prevent recurrence[6]. Here, we will review the diagnostic, therapeutic, and prognostic roles of endoscopy in patients with clinical signs and symptoms of GIB.

ROLE OF ENDOSCOPY IN THE DIAGNOSTIC APPROACH

Timing of upper endoscopy for patients with hematemesis or melena

There is still a debate as to when endoscopy should be undertaken in patients with suspicious acute GIB. In particular, it is difficult to clearly distinguish the cause of UGIB from clinical symptoms alone. The causes of UGIB were summarized by frequency in Table 1.

When variceal bleeding is strongly suspected, endoscopy should be performed just after proper resuscitation when the patient is hemodynamically stable[7]. The guidelines of American Association for the Study of Liver Diseases recommend that endoscopy should be performed within 12 h for acute variceal bleeding[8]. Because gastroesophageal varix can be observed in more than 50% of patients with liver cirrhosis, and the 6-wk mortality of varix bleeding is about 20%, urgent endoscopy should be considered in patients with hematemesis and liver cirrhosis[7,9].

In the case of non-variceal UGIB, a previous Asia-Pacific Working Group consensus recommended endoscopic intervention be taken within 24 h of onset of bleeding in patients at high risk of pre-endoscopic assessment (*e.g.*, Glasgow-Blatchford Score (GBS) ≥ 12; The GBS is a composite score of blood urea, hemoglobin, systolic blood pressure, pulse, history, and comorbidities)[10]. This consensus is similar to a recent cascade guideline of European Society of Gastrointestinal Endoscopy in 2018, which reported that endoscopy should be performed within 24 h after adequate initial management[11]. Therefore, it has been pointed out that, in patients who are hemodynamically unstable and presenting with massive hematemesis, endoscopy should not be done until after the patient is stabilized by resuscitation[12].

Several studies have investigated the role of emergency endoscopy within 12 h in non-variceal UGIB. A retrospective study of 361 patients found that patients undergoing emergency endoscopy had a 5-fold increase in the risk of adverse events including death, rebleeding, surgery, radiological intervention, or repeated

Table 1 Causes of upper gastrointestinal bleeding

Common causes	Other causes
Peptic ulcer disease (gastric or duodenal)	Hemosuccus pancreaticus
Gastric or esophageal varices	Cameron lesions
Erosive esophagitis	Hemobilia
Upper gastrointestinal tumors	Aortoenteric fistula
Upper gastrointestinal angioectasias	Anastomotic bleeding
Mallory-Weiss tear	Arteriovenous malformation
Gastric or duodenal erosions	Acute esophageal necrosis
Dieulafoy lesion	Atrial-esophageal fistula
	Gastric antral vascular ectasia

Data from references[109,110].

endoscopic management. In a subgroup analysis of that study, time to endoscopy was not significant as a predictor of worse outcome and was a weaker prognostic factor in patients with a high GBS score (≥ 12 points) than in patients with a low score[13]. High-risk patients are more likely to undergo fluid therapy and rapid proton pump inhibitor (PPI) therapy before endoscopy because initial bleeding symptoms are more severe. This emergency medical therapy may be the most important factor to prevent a poor outcome from UGIB regardless of time of endoscopy.

A nation-wide cohort study by Laursen *et al*[14], which included 12601 peptic ulcer patients, suggested that patients with an American Society of Anesthesiology score of 3-5 points or who were hemodynamically unstable had a reduced rate of hospital mortality if they received an endoscopic intervention within 6 h-24 h after admission[14]. However, the exact timing within the 24 h is not yet clear. Another national survey conducted in the United Kingdom, which included 4478 patients, suggested an early endoscopy of fewer than 12 h after admission and, compared to endoscopy provided within 24 h, showed no association with lower mortality rate or need for surgery[15]. According to a cohort study in Singapore, the timing of endoscopy in high-risk UGIB patients with GBS > 12 is the most important factor related to all-cause mortality in hospitals[16]. The cut-off time of endoscopy that improved the survival rate was within 13 h from the onset of symptoms. Active hemorrhagic lesions requiring endoscopic hemostasis were frequent in patients who received endoscopy within 6 h, but it did not help in prevention of rebleeding, mortality, transfusion rate, or duration of hospitalization. Therefore, emergency endoscopy is not required within 6 h for all non-variceal UGIB.

In summary, recent guidelines and recent studies suggest that emergency endoscopy should be performed within 12 h if variceal bleeding is present or the patient is hemodynamically unstable[17]. In addition, endoscopy should be preceded by appropriate and prompt medical therapy, which includes fluid therapy and intravenous PPIs.

What is the best option for patients with hematochezia: Sigmoidoscopy or colonoscopy

Unlike UGIB, which is mostly divided into variceal bleeding and non-variceal bleeding, the causes of LGIB are variable, involving various clinical manifestations. Table 2 summarizes the causes of LGIB by category. Therefore, what should be done for patients with hematochezia? In cases of hemodynamic instability, emergency upper endoscopy should be considered while performing initial resuscitation because of the possibility of UGIB as mentioned above. However, if vital signs are stable, LGIB should be considered first.

In patients with hematochezia who are less than 50 years of age, anorectal disease predominates in about 90%, whereas the prevalence of colorectal cancer increases with age. Some researchers believe that total colonoscopy is not necessary for patients with hematochezia at age 50 or younger, and sigmoidoscopy alone is sufficient[18]. On the other hand, some authors suggest that colonoscopy be performed in all patients with hematochezia because it can help to diagnose associated diseases such as colorectal cancer and polyps[19]. In addition, patients who have undergone sigmoidoscopy might believe that full colonoscopy will reveal more dangerous and fatal diseases such as cancer. However, full colonoscopy can be required complete preparation and long observation time with pain. In some situations, anesthetics and long-term hospitalization are necessary[20].

Table 2 Causes of acute small bowel and lower gastrointestinal bleeding by category

Type	Causes
Anatomic	Diverticulosis, including Meckel's diverticulum
	NSAID-induced enterocolopathy
	Antiplatelet or anticoagulant-induced enterocolopathy
	Stercoral ulceration (solitary rectal ulcer syndrome)
	Anal fissure
Vascular	Ischemic colitis
	Hemorrhoids
	Angiodysplasias (Angioectasias)
	Colorectal varices
	Postpolypectomy bleeding
	Radiation telangiectasia or proctitis
	Dieulafoy's lesion
Neoplastic	Colorectal polyps
	Colorectal and anal cancers
	Small bowel tumors, including gastrointestinal stromal tumor
	Metastatic or direct invasion from other cancer
Inflammatory	Inflammatory bowel disease
	Infectious colitis

Data from references[111-113]. NSAID: Non-steroidal anti-inflammatory drug.

Currently, there is no clear consensus on whether patients with hematochezia should undergo full colonoscopy or sigmoidoscopy alone. To summarize the opinions of several researchers, sigmoidoscopy without bowel preparation can be performed to rule out bleeding from anorectal disease. However, to investigate the combined presence of colon polyp or cancer, we suggest that full colonoscopy be performed for the entire colon investigation, regardless of the presence of bleeding and the success or failure of hemostasis in the anorectal area.

In patients with suspected lower gastrointestinal bleeding, when is the best time to perform endoscopy?

The optimal timing of colonoscopy for acute LGIB is controversial. Three recent systematic reviews with meta-analysis have attempted to address the question of whether urgent colonoscopy improves the outcome of LGIB. Seth *et al*[21] evaluated six studies including two randomized controlled trials (RCTs) and four observational studies involving 23419 patients who received urgent or elective colonoscopy. Urgent colonoscopy is one that is performed within 8 h to 24 h of observing LGIB. The use of urgent colonoscopy increased the detection rate of stigmata for recent bleeding but did not reduce rebleeding, mortality, or surgical necessity[21]. Kouanda *et al*[22] evaluated 10172 patients with urgent colonoscopy and 14224 patients with elective colonoscopy in an analysis of 12 studies. Urgent colonoscopy was associated with increased use of endoscopic therapeutic intervention. The reason for the difference in the use of endoscopic therapy is that hemorrhoid band ligation was included as an intervention. However, there was no significant difference in localization of bleeding source, adverse event rates, rebleeding rates, transfusion requirement, or mortality. Moreover, a limitation was that the definition of urgent colonoscopy varies widely in every study from within 8 h to within 24 h[22]. The third meta-analysis was performed by Sengupta *et al*[23] and involved 422 patients in the early colonoscopy group (< 24 h) and 479 patients in the delayed colonoscopy group (> 24 h). There was no statistically significant difference in blood transfusion requirement, need for surgery, or in-hospital mortality. Early colonoscopy showed a high correlation with detection rate of definite bleeding focus and endoscopic intervention[23].

The efficacy of early colonoscopy for reducing hospitalization, transfusion, and need for surgery is not clear. A timely colonoscopy is basically recommended as an initial diagnostic procedure for patients with acute LGIB because most guideline colonoscopy is highly accurate in detecting and treating the major causes of LGIB[4].

Is bowel preparation helpful before colonoscopy?

Bowel preparation is closely related to timing of colonoscopy. In urgent colonoscopy,

there is no time to perform proper bowel preparation. However, if vital signs in patients with hematochezia suggest a low probability of UGIB, bowel preparation is recommended. Proper bowel preparation is associated with successful and safe colonoscopy insertion and the ability to detect and treat lesions and to prevent rebleeding of high-risk lesions such as diverticular bleeding or angiodysplastic bleeding[4]. Generally, urgent colonoscopy of acute LGIB is done with "rapid purge" bowel preparation of a high-dose (4 L-6 L) polyethylene glycol (PEG) formulation administered over 3 h to 4 h[4,24]. Stools should be checked frequently during preparation, and PEG should be provided until the patient is properly prepared. To facilitate rapid purge[25], a nasogastric tube for PEG administration could be used for patients with low risk of aspiration[4].

Prospective trials evaluating urgent colonoscopy with PEG preparations appear to achieve adequate visualization of approximately 90% of the colon with 4 L-6 L of PEG over 3 h-4 h. In an RCT by Laine *et al*[26], the patients received 4 L of PEG solution over 3 h for urgent colonoscopy within 12 h of presentation, and no colonic preparation quality was reported; only 7% of patients required repeat colonoscopy because of inappropriate preparation. Another RCT by Green *et al*[27] reported only 8% of poor preparation cases in an urgent colonoscopy group using a similar preparation method. Because of the good efficacy of the urgent colonoscopy preparation method, the American College of Gastroenterology recommends not performing non-prepared colonoscopy in patients with acute LGIB[4]. Repaka *et al*[28] assessed the possibility of unprepared hydroflush colonoscopy in patients with severe LGIB. Only 13 procedures were included in the study, and the patients were treated with tap water enema and immediate colonoscopy without oral bowel preparation. The rate of cecal intubation was as low as 69.2%. A definite source of bleeding was found in only 38.5% of the patients, and 25% of the patients had repeated bleeding during the same hospitalization[28].

Although there are not many studies on the safety of bowel preparation in acute LGIB patients, overall bowel preparation is considered safe. Niikura *et al*[29] evaluated the safety of preparation and performance of colonoscopy in 161 patients admitted with acute LGIB compared to controls without bleeding. There was no significant difference in adverse events between the bleeding group and control group. None of the patients had volume overload, aspiration pneumonia, or loss of mental status[29]. In the guideline of the American College of Gastroenterology, precaution for aspiration is recommended for patients of old age and debilitation[4].

Approach to unknown origin gastrointestinal bleeding

Obscure GI bleeding (OBGIB) is defined as persistent or recurrent bleeding, despite of examination by esophagogastroduodenoscopy or colonoscopy[30]. OBGIB can be divided into overt bleeding with apparent gastrointestinal hemorrhage, such as hematochezia or melena, and occult bleeding, with repeated positive findings of fecal occult blood test or laboratory finding of iron deficiency anemia[30]. This OBGIB accounts for about 5% of all gastrointestinal bleeding, and it is known that more than 80% of these bleeding occur in the small intestine[31]. The development of capsule endoscopy has enabled the full examination of small intestine mucosa. The device-assisted enteroscopy has enabled therapeutic endoscopy for these lesions[32]. Details of small bowel bleeding are not covered in this review, but only the common causes of small bowel bleeding are summarized in the Table 2 together with LGIB.

Is it helpful to perform video capsule endoscopy in the emergency room?

The first attempt to use video capsule endoscopy (VCE) in evaluating UGIB patients was performed in a multicenter study after nasogastric tube and conventional endoscopy[33]. Although bloody materials were detected significantly more often by VCE than by nasogastric tube aspiration, there was no difference in the identification of inflammatory lesions between VCE and sequential conventional endoscopy. VCE may be feasible and safe method in patients with acute UGIB.

Following promising initial results, a prospective RCT was performed. Seventy-one UGIB patients were randomly assigned to receive standard care including early endoscopic evaluation within 24 h or VCE using PillCam ESO 2 in the emergency room. The need for hospitalization was determined by the findings of VCE[34]. This study showed a greater than 70% reduction rate without serious adverse events in the VCE group. Comparing the VCE results with the initial GBS, hospital admissions were significantly reduced for patients recruited to receive the VCE. Based on these results, the authors considered VCE in the emergency room to be an appropriate screening tool to distinguish patients who do not need hospitalization.

Although the initial data seem to be promising, it would be premature to use VCE as a screening tool for decisions to hospitalize. To date, there is only one small RCT that supports using VCE as a tool for patient classification. In addition to an

inappropriate duodenal visualization, the possibility of missing lesions in the fundus and other less accessible areas is a limitation of VCE. Moreover, it is difficult to train emergency doctors or specialists in for interpretation and set up of VCE in the emergency room[17].

RISK STRATIFICATION AND PRE-ENDOSCOPIC ASSESSMENT FOR GASTROINTESTINAL BLEEDING

In patients with suspected upper gastrointestinal bleeding including hematemesis or melena, treatment may be different according to the etiology of the bleeding. However, the evaluation of vital signs, hemodynamic status and appropriate fluid treatment are important in all patients[35]. If there are hypovolemic shock, rapid pulse rate, high blood urea nitrogen level, decreased urine volume at the time of presentation or previous history of acute bleeding, more aggressive initial monitoring, fluid treatment, and blood transfusion treatment are needed. However, if there is suspicion of massive bleeding, careful observation and follow up are necessary because early level of hemoglobin in acute bleeding may be normal[36].

The scoring system used when referring to the emergency department due to upper gastrointestinal bleeding can be divided into two types, one that includes endoscopic findings and the other that does not. The most commonly used scoring system is the Rockall score (RS) published by Rockall *et al*[37] In 1996. This scoring system predicts the likelihood of death within 30 d by using the five factors: Patient age, accompanying shock, co-morbidities such as heart, liver, and kidney, causative diseases of bleeding, and endoscopic bleeding stigmata. However, since there is a disadvantage that the endoscopic findings must be known, in practice, the preendoscopic RS that can be calculated with the three findings except the etiology of the bleeding and endoscopic findings is used. This is useful for predicting rebleeding and mortality risk[38].

In addition, the Glasgow-Blatchford score (GBS) developed in 1882, which was calculated from patient's symptoms, blood test, physical examination, and accompanying diseases before endoscopy, is widely used to predict the need for transfusion, endoscopic treatment, rebleeding rate and prognosis[39]. In particular, this scoring system has the advantage of being able to quickly and simply measure in the emergency room due to blood urea, hemoglobin, systolic blood pressure, pulse rate, presence of melena or syncope, liver disease, and heart failure.

Recently, AIMS65, a simpler scoring system, has also been proposed, including albumin, prothrombin time, mental state, systolic blood pressure and age over 65 years. It is easy to memorize, and it can be calculated objectively and easily[40]. In one study, mortality from AIMS65 scores ranged from 0.3% to 32%[41].

The initial treatment of patients with GI bleeding is to restore the stability of the hemodynamic circulation. In order to maintain blood vessel volume and hemodynamic stability, it is important to secure a large vein, and it is important to check whether it is accompanied by heart, kidney, and liver disease[35].

Although the nasogastric tube insertion is controversial, it can detect the need for immediate endoscopic hemostasis if blood is seen from the upper gastrointestinal hemorrhage to the nasogastric tube. However, it should be remembered that there may be a false negative due to duodenal hemorrhage[35]. One dose of antibiotic erythromycin administered 30 min-120 min before endoscopy is not recommended on a routine basis, but it is recommended to improve endoscopic visualization, reduce the need for transfusion and endoscopy, and reduce the length of hospital stay[42,43]

THERAPEUTIC ROLE OF ENDOSCOPY

In recent years, endoscopic techniques have improved the management of GIB, including peptic ulcer, variceal, diverticular, and angiodysplastic bleeding. Moreover, an increase in accessible and technologically advanced, well-trained, endoscopy center-related specialists has led to early diagnosis through endoscopic intervention[44].

Methods of endoscopic hemostasis for acute UGIB and LGIB include injection (usually diluted epinephrine or a special sclerosing agent), contact and non-contact thermal devices (unipolar or bipolar electrocoagulation, heater probes, and argon plasma coagulation), and mechanical devices (endoscopic clips and band ligation)[45]. Diluted epinephrine injections of 1:10000 to 1:20000 dilution facilitate primary hemostasis of active bleeding; to reduce the risk of rebleeding, mechanical or thermal therapy to obtain definite hemostasis should follow immediately as a secondary

method[4,46]. Randomized trials are insufficient in assessing the endoscopic hemostatic effects on acute GIB. The choice of a hemostasis method is generally determined by the cause and location of GIB, the ability to access the site, and the experience of the endoscopist.

In the following, we will discuss the most clinically relevant methods of endoscopic treatment for the four major types of GIB and describe the most effective procedure.

Peptic ulcer bleeding

Peptic ulcer bleeding, which accounts for 30%-60% of UGIB, has been the most studied. Although the classifications for peptic ulcer bleeding were created a very long time ago, an endoscopic classification called Forrest classification is widely used as a standard for endoscopic treatment. In most cases in the Forrest classification, Ia to IIa lesions have a rebleeding rate greater than 50%, in most of which active endoscopic treatment should be performed[47,48].

However, the Forrest classification is over 40 years old; recently, de Groot *et al*[49] evaluated whether this classification is useful in predicting the rebleeding and mortality of peptic ulcer bleeding and conducted a study to assess whether it could be simplified. They have simplified the Forrest classification as high risk (Forrest Ia), increased risk (Forrest Ib-IIc), and low risk (Forrest III). The rate of rebleeding in a total of 397 patients was highest (59%) in Forrest Ia peptic ulcers, but the rebleeding rates in Ib and IIc were similar. In subgroup analysis, prediction of rebleeding using the Forrest classification is more reliable for gastric ulcers than for duodenal ulcers. Simplifying this classification can reduce interobserver variability in classifying lesions but requires confirmation studies[49].

Traditionally, three endoscopic treatment methods of peptic ulcer bleeding have been used: Injection therapy, thermal therapy, and mechanical therapy. The question of whether monotherapy or combined modality therapy is more effective has been the subject of several trials and meta-analyses. The Cochrane review in 2014 evaluated 19 RCTs with 2033 patients and concluded that the second bleeding control method significantly reduced the risk of rebleeding and emergency surgery compared to epinephrine injection therapy alone[50]. Mortality was also reduced but was not statistically significant. Similar results were shown in other meta-analyses[51,52]. In a study published in 2016[52], involving 2888 patients, hemoclips alone or injection therapy combined with thermal therapy were more effective than injection therapy alone. Thus, it was concluded that epinephrine injection therapy should not be used as a monotherapy but in conjunction with a secondary therapy. After endoscopic treatment, adverse outcomes including perforation and therapy-induced bleeding can occur. They may be more common in endoscopic therapy than in medical therapy alone, but a meta-analysis showed no statistically significant difference (0.8% *vs* 0.1%)[53].

After endoscopic treatment for spurting bleeding or exposed vessel lesion, which is known to be highly rebleeding, high dose PPI is known to be an important medication to prevent rebleeding[54]. However, according to recent study, risk of rebleeding associated with Forrest Ib is very less compared Forrest IIa and IIb and may not require high dose IV PPI after successful endotherapy[55].

Variceal bleeding

Variceal bleeding is a common and very serious complication of portal hypertension. In previous studies, variceal bleeding in patients with liver cirrhosis has been reported to result in a mortality rate of up to 50%[56]. The use of vasoactive drugs, endoscopic management, and prophylactic antibiotics has improved mortality, but esophageal varix bleeding is still associated with 20% mortality within 6 wk[9]. It is important to stabilize patients prior to endoscopic treatment for variceal bleeding and to maintain an intravenous line for hemodynamic stability and a hemoglobin level of at least 7-8 g/dL through blood volume resuscitation[57]. Administration of prophylactic antibiotics such as intravenous quinolone or ceftriaxone is also necessary and could lower systemic bacterial infection and reduce mortality[58]. Vasoactive drugs such as octreotide, somatostatin, and terlipressin are recommended to be administered as soon as possible[56].

Endoscopic variceal ligation (EVL) is the treatment of choice for esophageal variceal bleeding and secondary prevention. The diagnosis of variceal bleeding in the setting of active bleeding is based on the appearance of bleeding varices, stigmata of recent bleeding including an adherent clot over varix or platelet plug called by white nipple marks, or presence of varices without definite active bleeding focus[59]. In a recent meta-analysis of 1236 cases in 14 studies reported by Dai *et al*[60], EVL is better in terms of major outcome including rebleeding, variceal eradication, and complication rate compared with endoscopic injection sclerotherapy but not in mortality. Therefore, EVL is the most effective first choice for esophageal varix bleeding. After acute

esophageal variceal bleeding, repeated endoscopy with EVL until varix eradication is recommended, usually requiring 2 to 4 sessions of therapy[61]. The optimal interval of each EVL for secondary prevention has been undefined and usually ranges from 2 wk to 8 wk in studies evaluating repeated EVLs for secondary prevention.

Post-EVL band-induced ulcer bleeding may occur as a complication of EVL. Sinclair *et al*[62] reported that the incidence was just 2.8%, but was significantly associated with mortality. A high MELD score (MELD is an abbreviation for Model for End-stage Liver Disease, which is calculated using serum bilirubin, prothrombin time, and serum creatinine) was associated with more frequent development of band-induced ulcer bleeding[62]. Transjugular intrahepatic portosystemic shunt (TIPS) or sclerotherapy can be considered as a treatment for band-induced ulcer bleeding, and pantoprazole for 10 d can reduce the ulcer size[63]. Moreover, rebleeding from band ulcers can be treated by hemostatic power or spray that used in management of peptic ulcer bleeding[64,65]. Recently, a study by Ibrahim *et al*[66] showed that immediate application of hemostatic powder is effective for early clinical course and endoscopic hemostasis in patients with acute initial variceal bleeding.

In addition, we could consider another management including esophageal balloon tamponade in patients of recurrent or refractory variceal hemorrhage despite of the most effective EVL treatment. The esophageal stent, which was mainly used for luminal GI stenosis, has been used in place of balloon in refractory variceal bleeding, showing statistically significant rate of treatment success and bleeding control[67]. As mentioned previously, TIPS treatment is used for recurrent and refractory variceal bleeding in patient with high-risk criteria (Child-Pugh B plus active bleeding at endoscopy or Child-Pugh C). However, early TIPS in a Child-Pugh B patient for recurrent variceal bleeding could be accelerating the development of acute-on-chronic liver failure and/or death. The careful decision of patients for TIPS is essential and other parameters should be considered, such as systemic inflammation, non-selective beta blocker-non-response and portal vein thrombosis[68].

Diverticular bleeding

The prevalence of colonic diverticula increases with aging, up to 30% at 50 years and 70% by 80 years[69,70]. Clinically significant bleeding occurs in 3%-15% of patients with colon diverticulosis, usually as a result of traumatic injury to the vasa recta at the neck or dome of the diverticulum. Nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, hypertension, and anticoagulants are known to be associated with diverticular bleeding[71]. Diverticular bleeding, which accounts for 20%-65% of LGIB, is known to stop spontaneously in about 75% of patients[72], and 25%-40% experience rebleeding within four years. Therefore, endoscopic treatment is required in patients with stigmata[73]. Only conservative therapy can be used in patients with a very high rate of rebleeding, and active endoscopic treatment is recommended and effective for long-term follow-up[24].

Various methods of endoscopic treatment have been used to treat colonic diverticular bleeding, including bipolar coagulation, epinephrine injection, clipping including the over-the-scope clip, and ligation such as endoscopic band ligation and endoscopic detachable snare ligation[4,22,74]. Due to lack of muscle layer in the colonic diverticulum, bipolar electrocoagulation is not recommended because of the risk of perforation. Epinephrine injection monotherapy has a high risk of rebleeding (20%)[74]. A very useful technique is to directly attach the clip to the neck of the diverticulum containing the bleeding stigmata[75]. Band ligation is a familiar method for endoscopists. Recently, many studies have reported band ligation as a safe and effective hemostatic method for diverticular bleeding[76]. Ishii *et al*[76] have reported that simple band ligation of diverticular bleeding can be performed by both endoscopic expert and trainee with similar safety, efficacy, and procedure time.

In a meta-analysis recently conducted by Ishii *et al*[74] to confirm the efficacy of endoscopic treatment for colonic diverticular bleeding, 16 studies of 384 colonic diverticular bleeding patients were analyzed. Ligation therapy was found to be more effective than clipping in terms of avoiding trans-arterial embolization. Surgery, coagulation, clipping, and ligation were equivocal in terms of effectiveness for initial hemostasis and early recurrent bleeding. However, most studies in meta-analysis have been retrospective in design and small in sample size, making them susceptible to recall and selection biases. A recent prospective study of recurrent diverticular bleeding showed that 1-year rebleeding was higher in clipping (37%) than in ligation (11.5%), suggesting that band ligation is superior to clipping for treatment and elimination of colonic diverticular bleeding[77]. However, ligation may be limited due to inadequate suction in the presence of a small orifice or a large dome, and these cases have reported a high prevalence of rebleeding. Therefore, further studies are required for its application in real clinical practice.

Angiodysplastic bleeding

The prevalence of colonic angiodysplasias have various clinical presentations; for example, 1%-2% in screening colonoscopy and 40%-50% in patients with hematochezia[78]. Studies have shown that angiodysplasias account for 3%-15% of LGIB. The incidence of angiodysplasias increases with age, and more than two-thirds of lesions are observed in patients > 70 years[46]. The cause of angiodysplasias is degenerative changes of submucosal vessels with chronic intermittent low-grade occlusion[79]. These vessels are mainly located in the right colon including the cecum and ascending colon. Colonoscopy can reveal multiple angiodysplasias, which appear as flat, red lesions ranging in size from 2 mm to a few centimeters with tree-like morphology from a central feeding vessel.

Risk factors for angiodysplasia bleeding include older age, combined morbidities, presence of multiple angiodysplastic lesions, and use of anticoagulants or antiplatelet agents[80,81]. Clinical presentation may occasionally have intermittent hematochezia, melena, or occult bleeding with anemia. The detection rate of angiodysplasias by colonoscopy is 80% based on sensitivity[82]. However, with the use of sedatives, mucosal blood flow could be reduced, and colonoscopy can make it difficult to detect these lesions[83].

Contact and non-contact thermal coagulation with argon plasma are useful for endoscopic treatment of angiodysplasias. Argon plasma coagulation can be a preferred technique due to its ease of application, the therapeutic potential of a large surface area, and predictable penetration depth of the colon wall[84]. A low power setting of 30 W to 45 W and an argon flow rate of 1 L/min are used to reduce the risk of perforation to the thin wall of the right colon. The probe should preferably be 1 mm to 3 mm from the mucosal surface and should be applied at 1-2 s[25]. In follow-up data of 100 patients with angiodysplastic bleeding (including 31% colon lesions) for a median of 16 mo, argon plasma coagulation led to significantly improved hemoglobin level and reduced blood transfusion requirement without adverse events[84].

Recent developments for endotherapy in patients with acute GI bleeding

Various endoscopic therapies have been attempted in cases of failure of hemostasis due to general endoscopic treatment. The OTSC (Over-the-scope clip, Ovesco AG, Tübingen, Germany) system, which is inserted at the upper end of the endoscope, has been widely used in fistulas and perforations. However, it can be used in cases of continuous hemorrhage due to local injection or clipping[85]. In addition, the hemostasis of the bleeding site through the nano powder (Hemospray, Cook Medical, Winston-Salem, NC, USA) or starch (EndoClot Plus Inc., Santa Clara, CA, USA) can be used when other hemostasis is not treated. Previously, it was difficult to distribute the powder or starch materials to the hemorrhagic lesion, but in recent years, disposable powder roots have been developed and can be used more easily[86,87].

ENDOSCOPY FOR CRITICALLY ILL PATIENTS WITH SUSPECTED GIB

Bedside endoscopy for intensive care unit patients

Patients in the intensive care unit (ICU) often have GIB from a variety of reasons. GIB in the ICU is an important event with serious complications that increase morbidity and mortality. Management of GIB in the ICU is difficult because most patients have complex poor prognostic factors; in most cases, they cannot be transferred to the endoscopy center. Therefore, bedside endoscopy is a good option for these patients[88,89].

In a recent study by Kim *et al*[88], 253 cases of bedside endoscopy and 69 cases of bedside colonoscopy were analyzed. The most common causes of UGIB were peptic ulcer and acute gastric mucosal lesion, and the causes of LGIB were ischemic colitis and rectal ulcer. The detection and treatment rate of bleeding focus were significantly increased in patients who underwent early upper endoscopy within 24 h. However, in patients with LGIB, early colonoscopy led to lower detection and hemostatic rate because of poor bowel preparation and bloody stool materials. Therefore, early upper endoscopy could be effective when UGIB is suspected in ICU patients, while in cases of colonoscopy, appropriate bowel preparation may first be necessary.

Prophylactic endotracheal intubation before upper GI endoscopy

Patients with UGIB have a particularly high risk of cardiopulmonary complications due to aspiration of blood and gastric contents and the presence of underlying comorbidities[90,91]. In a study in 2003 by Rudolph *et al*[92], high-risk patients with UGIB requiring ICU admission had 33.6% overall cardiopulmonary morbidity during

hospitalization and 13.6% mortality. Upper GI endoscopy-related cardiopulmonary complications were common (4.1%), and new development of pulmonary infiltration was found in 14.1% of patients[92].

Prophylactic endotracheal intubation is performed to protect the airway and prevent aspiration during upper GI endoscopy and severe UGIB. It is thought to be effective in prevention of aspiration pneumonia, but there have been few studies. In a retrospective study conducted in 2009, of 307 patients with UGIB who received upper endoscopy, 53 underwent prophylactic endotracheal intubation, but cumulative incidence of cardiopulmonary complications, ICU or hospital length of stay and mortality were similar to non-intubated patients[93]. However, in a study by Hayat *et al*[94] in 2017, 200 patients were divided into groups of 100 based on need for intubation or not. In the intubation group, unplanned cardiopulmonary events were significantly higher than in the non-intubation group, and this difference between groups did not change after adjustment for presence of esophageal varices. Therefore, prophylactic endotracheal intubation should be carefully considered before upper GI endoscopy,

THE ROLE OF ENDOSCOPY IN PROGNOSIS AFTER GIB

Is there a difference in prognosis between endoscopic and clinical findings?

Endoscopic findings of GIB are observed, and successful hemostasis can improve the prognosis and increase the survival rate. However, endoscopic hemostasis is not always successful. If we know the factors that are likely to fail in endoscopic hemostasis, decisions can be made to change the modality.

In a previous report[95], the success of endoscopic treatment of peptic ulcer bleeding was reported to be 94%, followed by that of permanent hemostasis without rebleeding (82.5%). There was failure of endoscopic treatment or rebleeding in 17.5% of endoscopic treatments. The patients had significantly higher rates of active bleeding at the time of diagnosis, shock at admission, or low hemoglobin level. However, medication history, old age, and location of gastric ulcer had no effect on the failure rate of endoscopic bleeding control. In another large study involving injection and thermal therapy of 3386 patients with peptic ulcer bleeding, 98.6% had successful initial hemostasis, but 8.2% had rebleeding. Therefore, the final failure rate of bleeding control was 9.6%. When blood pressure was low, hemoglobin was less than 10 g/dL, fresh blood was observed in the stomach, and large or active ulcers were seen, the failure rate of endoscopic bleeding control was significantly higher[96]. In a study by Thomopoulos *et al*[97], 427 patients were endoscopically treated, with a failure rate of 20.1%. Endoscopic findings of spurting bleeding and duodenal ulcer on the posterior side or anastomosis site showed significant treatment failure. In summary, signs of severe bleeding, including shock, decreased hemoglobin level, fresh blood at the time of initial presentation, or ulcer with a large surface area and spurting blood, could lead to failure of the endoscopic procedure.

Variceal bleeding is affected by portal hypertension. The hepatic venous pressure gradient, which reflects portal pressure, is most important. In addition, the severity of liver disease reflected by the Child-Pugh class or MELD, encephalopathy, platelet count, history of alcoholism, and presence of portal vein thrombosis were found to be independent factors for failure of endoscopic variceal bleeding control[98,99]. Therefore, in high-risk patients with a high probability of failure of bleeding control, a preemptive TIPS should be prepared, and tamponade ballooning should be performed temporarily after retrials of endoscopic hemostasis[100]. Unlike bleeding in other diseases, variceal bleeding should be considered to be more affected by the severity of liver cirrhosis than by endoscopic findings[101].

The determinant of LGIB recurrence is the pattern used to achieve primary hemostasis. Predisposing factors of recurrent LGIB are primary hemostatic modality[102]; use of antiplatelet, anticoagulant agent, and NSAIDs; presence of chronic kidney disease or liver cirrhosis; and etiology of initial bleeding[4]. It is not clear how the proportional influence of these individual characteristics will affect the incidence of recurrent bleeding. In a retrospective study with 171 severe LGIB cases[103], the three causes of bleeding were diverticular bleeding, which was the most common cause, anorectal diseases, and angiodysplasia. In particular, 15% of the subjects were treated previously with antiplatelet agents and 9% with anticoagulants. During the mean follow-up period of 11 years, about one-third of the participants had recurrent LGIB. As noted in previous studies, LGIB is more likely to rebleed and affects older patients taking several medications. One of the most important points in diverticular bleeding and angiodysplasias bleeding, which comprise a large part of LGIB, is that they can stop spontaneously and rebleed at the same site or in other lesions.

Is routine second-look endoscopy necessary?

Recurrent bleeding occurs in 8%-15% of patients with peptic ulcer bleeding and increases mortality by 2 to 5 times. The goal of routine second-look endoscopy performed within 24 h after initial endoscopic hemostasis is to treat stigmata of peptic ulcer bleeding preemptively before rebleeding symptoms develop[17].

A meta-analysis based on eight prospective RCTs was conducted to evaluate whether rebleeding can be reduced by second-look endoscopy in very high-risk patients without high dose PPI[104]. The pooled data showed that second-look endoscopy reduced the need for surgery but not mortality. Moreover, there was no benefit in second-look endoscopy by subgroup analysis after exclusion of two trials with bleeding in high-risk patients[104,105]. In a recent randomized trial comparing second-look endoscopy and intravenous PPI infusion after endoscopic hemostasis for peptic ulcer bleeding[105], there were no differences in recurrence bleeding, need for surgery, and mortality between the two treatment strategies. In addition, second-look endoscopy did not appear to be cost-effective when offered to all patients.

The remaining problem is whether we can identify high-risk patients and obtain the benefit from second-look endoscopy with repeated endoscopic treatment for stigmata by the next day. In a study of 699 patients in Korea, use of NSAIDs, a large volume of transfused blood, and failure of second-look endoscopy were risk factors for rebleeding after endoscopic intervention[106]. A study in Taiwan, involving 316 patients who received high dose PPI after endoscopy, attempted to formulate predictive scores using endoscopic monotherapy and serum albumin level[107]. This score indicated that the receiver operating characteristic curve would help predict the need for routine second-look endoscopy, but the results were insufficient. However, a recent multicenter prospective study showed that the success of initial hemostasis, the use of NSAIDs, and the large number of blood transfusions were independent risk factors for rebleeding. Therefore, scheduled second-look endoscopy could be helpful for patient with unsatisfactory initial endoscopic hemostasis, use of NSAIDs, large amounts of blood transfusions[108].

Therefore, the risk assessment method and preemptive endoscopic treatment for selecting high-risk patients who require second-look endoscopy are not clear. However, since many clinicians are practicing prophylactic second-look endoscopy for patients with a high risk of rebleeding, further studies on risk classification and selecting the method for routine second-look endoscopy are needed.

CONCLUSION

The symptoms of bleeding in the GI tract that are encountered in real clinical practice are mainly melena, hematemesis, and hematochezia. When a patient with these symptoms presents to the emergency room, endoscopic diagnosis and treatment are considered together with appropriate initial resuscitation. For better prognosis in cases of suspected variceal bleeding, it is paramount that endoscopy is performed immediately after the patient is stabilized, and it would be sufficiently effective for endoscopy to be undertaken within 24 h from symptom development for non-variceal UGIB. In cases of suspected LGIB, sigmoidoscopy may be initially performed if there is a strong suspicion of anorectal bleeding. However, on the whole, full colonoscopy after bowel preparation is effective for distinguishing the cause and location of bleeding and treating with hemostasis.

There are three methods used to perform hemostasis by endoscopy: Injection, thermal, and mechanical therapy. Using a mechanical method or injection therapy combined with other modalities, rather than injection therapy alone, increases the success rate of bleeding control. In patients in the ICU, bedside endoscopy may be effective, but prophylactic intubation is still controversial. Proper endoscopic hemostasis can affect prognosis and prevent rebleeding. Routine second-look endoscopy does not affect the outcome of hemostasis, but it may be helpful in selected patients with a high risk of rebleeding. From the emergency room to discharge of the patient, the contents of this review are summarized in Figure 1.

In conclusion, the role of endoscopy in GIB is very important, and many guidelines have been developed about endoscopic treatment for specific bleeding diseases. However, there are still parts that have not been established. Especially, further studies on prophylactic intubated endoscopy, routine second-look endoscopy and emergency capsule endoscopy issues are needed.

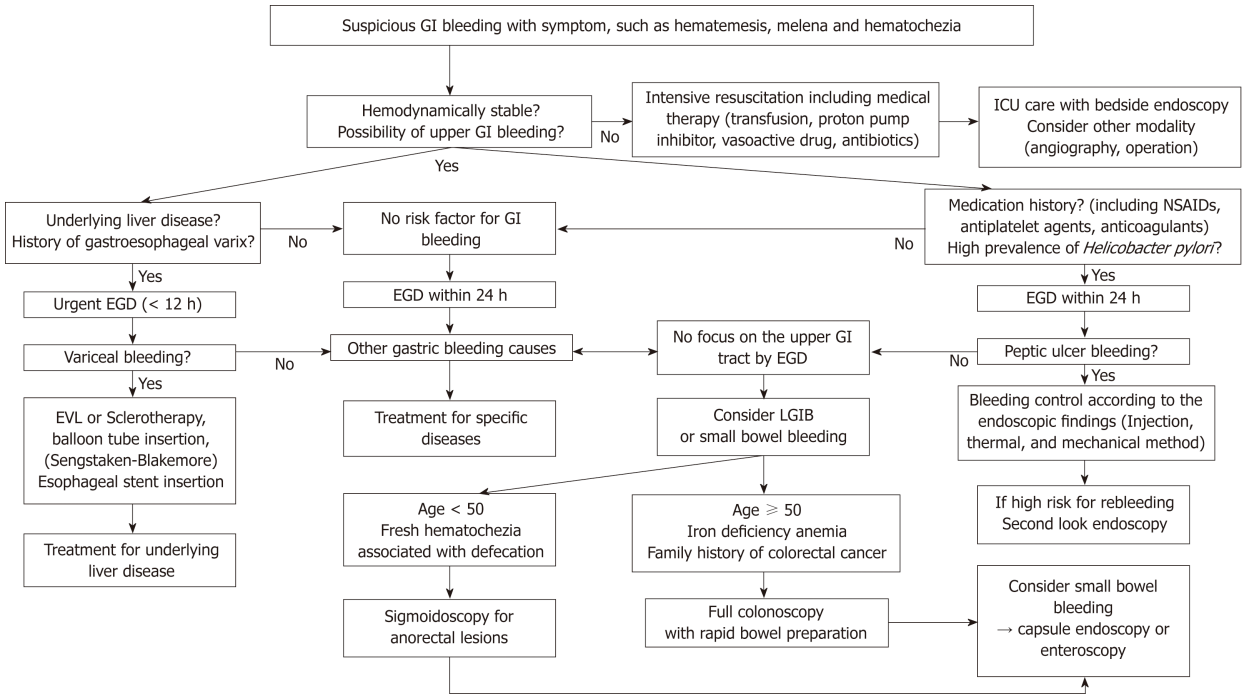

Figure 1 Flowchart of assessment and management of patients with suspicious gastrointestinal bleeding. GI: Gastrointestinal; EGD: Esophagogastroduodenoscopy; NSAIDs: Non-steroidal anti-inflammatory drugs; ICU: Intensive care unit; EVL: Endoscopic variceal ligation; UGIB: Upper gastrointestinal bleeding; LGIB: Lower gastrointestinal bleeding.

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MINIREVIEWS

Role of endoscopy in the management of primary sclerosing cholangitis

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Abstract

Primary sclerosing cholangitis (PSC) is a rare but prominent fibroinflammatory cholangiopathy which can affect individuals of essentially any age. It carries a median survival of 15-20 years, regardless of age at diagnosis, and is a foremost risk factor for cholangiocarcinoma. Given the chronic and progressive nature of PSC, its inherent risk for biliary tract and other complications, and the paucity of effective pharmacotherapies, endoscopy plays a major role in the care of many patients with this disorder. In this review, we discuss the endoscopic management of PSC, including established and evolving approaches to the diagnosis and treatment of its benign as well as malignant sequelae. Owing to the rarity of PSC and dearth of high-quality evidence, we propose pragmatic approaches based on both currently available data and expert opinion.

Key words: Bile duct diseases; Cholangiocarcinoma; Inflammatory bowel disease; Endoscopic retrograde cholangiopancreatography; Biopsy; Primary sclerosing cholangitis

Core tip: Primary sclerosing cholangitis is a chronic, inflammatory condition of the biliary tract associated with several biliary and extrabiliary complications requiring endoscopic evaluation, treatment, and surveillance.

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic, progressive cholestatic disease of unknown pathogenesis that is characterized by inflammation and stricturing of the biliary system. The incidence of PSC worldwide is heterogeneous, with studies reporting prevalence rates ranging from as low as nearly 0 to as high as 14 patients per 100000 individuals, depending on which region is studied[1,2]. The mean age at the time of diagnosis of PSC is approximately 40 years old, and 60% of patients diagnosed with PSC are male[3]. Notably, PSC is associated with inflammatory bowel disease (IBD); indeed, roughly 70% of patients diagnosed with PSC are at some point in their lives also diagnosed with IBD (before, contemporaneous with, or after the diagnosis of PSC), though this too is geoepidemiologically variable[4].

Although many patients with PSC are asymptomatic at the time of diagnosis, the long-term consequences of PSC can be severe and even lethal. The median liver transplantation-free survival for patients with PSC is approximately 15-20 years[5]. The shortened survival is in large part related to the fact that PSC is a mutagenic condition associated with several different malignancies including cholangiocarcinoma (CCA), gallbladder carcinoma, colorectal cancer, and hepatocellular carcinoma, among others. The chronic parenchymal inflammation associated with PSC over time also leads to the development of liver cirrhosis, which although a precursor for hepatocecullar carcinoma, is not required for the development of other malignancies.

Despite years of research, there remains an absence of pharmacologic therapies to safely and effectively stem the inflammatory cascade driven by PSC that results in biliary strictures and the development of malignant complications. Therefore, physicians often have to rely on endoscopy to help manage patients during the PSC disease course. This review focuses on the role of biliary as well as luminal endoscopy in the diagnosis, management, and surveillance of PSC and its complications.

DIAGNOSIS OF PSC

Approximately 50% of patients diagnosed with PSC are initially asymptomatic; therefore, clinicians must maintain an index of suspicion that their patient may have PSC if characteristic abnormalities are discovered in laboratory, imaging, cholangiographic, and histologic studies[6]. At the time of diagnosis, patients with PSC are often found to have chronically elevated serum liver tests with a cholestatic pattern of liver injury. Cholangiography will usually demonstrate diffuse intrahepatic and/or extrahepatic biliary ductal irregularities characterized by areas of alternating stricture and dilation, though a small subset of patients with PSC (approximately 10%) will have a negative cholangiogram, a phenotypic variant of PSC referred to as "small duct PSC". Liver biopsy in patients with PSC typically shows evidence of periductal fibrosis, chronic nonsuppurative cholangitis, and ductular reaction, though classic "onion skin" features are not commonly seen on biopsy specimens. Notably, with the exception of small duct PSC and rare instances, clinicians often can rely on cholangiographic and serum laboratory data to establish a diagnosis of PSC, *i.e.*, without obtaining a liver biopsy.

From a historical perspective, direct cholangiography by endoscopic retrograde cholangiography (ERC) was first described in the early 1970s and, for years, had a central role in a clinician's diagnostic approach to PSC[7]. Prior to the development of ERC, PSC was rarely diagnosed due in large part to the inability to reliably image the biliary tree. ERC in PSC demonstrates a classic "beads on a string" appearance of the intrahepatic and extrahepatic ducts, representing diffuse ductal stricturing alternating with proximal ductal dilation. The use of ERC for the diagnosis of PSC shed light on the different phenotypic variants of the disease (Table 1). For example, it permitted the recognition that there are patients with PSC with solely intrahepatic strictures, solely extrahepatic strictures or, in some cases, both intrahepatic and extrahepatic strictures. The classification of the different phenotypic variants by cholangiography and liver biopsy is key as each variant demands its own nuanced diagnostic and management approach.

In the past decade, for patients with suspected PSC, there has been a shift from ERC

Table 1 Phenotypic variants of primary sclerosing cholangitis

Phenotype	Cholangiographic features	Liver histology features
Classic PSC	Multifocal intrahepatic and extrahepatic strictures and resultant upstream (*i.e.*, proximal) ductal dilation	Typical findings of PSC (*e.g.*, non-suppurative paucicellular cholangitis, periductal fibrosis, ductular reaction, and ductopenia)
Intrahepatic PSC	Multifocal intrahepatic strictures and resultant upstream (*i.e.*, proximal) segmental ductal dilation	Typical findings of PSC
Extrahepatic PSC	Extrahepatic only strictures and resultant upstream (*i.e.*, proximal) ductal dilation	Non-diagnostic or non-specific features of cholestasis, particularly in early stage disease
Small-duct PSC	Normal	Typical findings of PSC

All of the above phenotypes will generally have a cholestatic serum biochemical profile, though a small minority of patients can have normal serum liver tests. PSC: Primary sclerosing cholangitis.

to a non-invasive diagnostic option-magnetic resonance cholangiopancreatography (MRCP). MRCP uses heavily T2-weighted image sequences to highlight the biliary system and is useful for the diagnosis of several different biliary disorders such as choledocholithiasis, CCA, and sclerosing cholangitis (including PSC). Technologic advancements (such as ultrafast T2-weighted imaging sequences and three-dimensional reconstruction *via* maximum intensity progression) have amplified the role of MRCP in the diagnosis of PSC[8]. Compared to ERC, MRCP allows for better visualization of smaller, proximal branches of intrahepatic ducts and, therefore, may be a superior modality for the diagnosis of PSC phenotypes that do not primarily involve the extrahepatic and/or perihilar ducts[9]. Over the last two decades, meta-analyses and cost-effectiveness studies have demonstrated that MRCP is at least equivalent to ERC as the initial modality to provide cholangiographic evidence of PSC[10,11].

Although the role of ERC in the initial diagnostic approach to PSC is diminishing, there are scenarios where ERC may be required. For example, in instances where MRCP is negative in the diagnosis of patients with a high pre-test probability of PSC based on other clinical features, ERC is a reasonable next step. ERC is also appropriate for patients who cannot tolerate MRCP due to contraindications (such as non-MRI compatible implanted cardiac devices) or issues such as respiratory illness (with inability to breath hold) or metallic foreign bodies that can cause image artifacts or safety concerns.

ENDOSCOPY FOR EXTRABILIARY SURVEILLANCE OF PSC

Once the diagnosis of PSC is established, the role of endoscopy expands. While the majority of this review will focus on the role of biliary endoscopy in the surveillance and management of PSC and its complications, it is also important to consider the extrabiliary role of endoscopy in PSC (Figure 1). As mentioned earlier, the majority of patients with PSC are found to have underlying IBD. Therefore, it is recommended that patients undergo a colonoscopy to evaluate for possible IBD once a diagnosis of PSC has been established. Concomitant PSC in patients with IBD has been shown to be an independent risk factor for the development of colorectal cancer, therefore it is recommended that colonoscopies be performed annually as part of dysplasia surveillance in these patients[12-16].

During dysplasia surveillance for patients with IBD, it is recommended that endoscopists obtain four quadrant biopsies sequentially while withdrawing the colonoscope after cecal intubation is achieved[17]. Recently, however, researchers have raised questions about the appropriateness of this approach given concerns that the majority of the colon is left unsampled[18]. Research has since focused on the possible benefits of chromoendoscopy for dysplasia surveillance in IBD patients (Figure 2). A recent meta-analysis demonstrated that chromoendoscopy had a dysplasia detection rate of 7% compared to 5.1% in the traditional random biopsy cohort. Future studies are needed to demonstrate a benefit to chromoendoscopy and its cost-effectiveness in PSC-associated IBD and are likely to produce clinically meaningful results that would change our approach to dysplasia surveillance for these patients[19].

Upper gastrointestinal pathology, though not as commonly recognized, is also important to bear in mind in patients with PSC. Indeed, the hepatobiliary inflammation in PSC (akin to primary biliary cholangitis) can result in focal portal tract fibrosis resulting in portal hypertension before the development of widespread

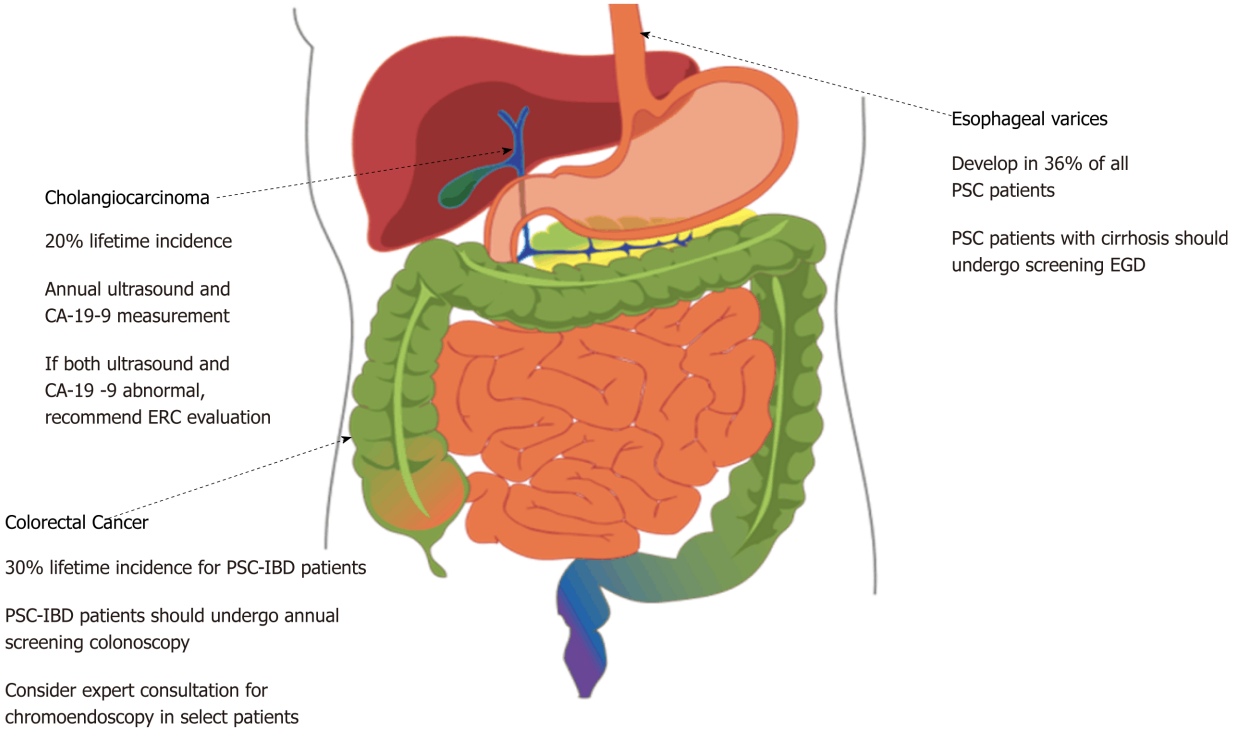

Figure 1 Overview of endoscopic surveillance of primary sclerosing cholangitis. AASLD: American Association for the Study of Liver Diseases; CA 19-9: Carbohydrate antigen 19-9 serum tumor marker; EGD: Esophagogastroduodenoscopy; PSC: Primary sclerosing cholangitis; PSC-IBD: Inflammatory bowel disease co-existing with primary sclerosing cholangitis.

cirrhosis, thus rendering patients with PSC at risk for esophageal varices and other sequelae. In a large cohort study of 283 patients with PSC from the Mayo Clinic, 36% were found to have esophageal varices, the majority of which were moderate or large in size; of the patients found to have esophageal varices, 47% were identified as not having cirrhosis on liver biopsy[20]. Practice guidelines support performing esophagogastroduodenoscopy for variceal screening in patients with PSC who develop cirrhosis[21-23]. One area of controversy, however, is whether there is a role for variceal screening in patients with PSC without cirrhosis. At this time, guidelines limit variceal screening to only those with evidence of advanced liver fibrosis; however, clinicians should be aware of the possibility of varices in patients with PSC before the development of cirrhosis[23].

DIAGNOSIS AND MANAGEMENT OF DOMINANT STRICTURES

Due to the invasive nature and potential complications associated with ERC, it should generally be limited to instances where there is concern that patients have developed complications requiring intervention and/or tissue sampling, such as choledocholithiasis, acute cholangitis, or a dominant stricture. Development of a dominant stricture is a relatively common but also feared complication of the PSC disease course. Dominant strictures are loosely defined as extrahepatic strictures of less than or equal to 1.5 mm or intrahepatic strictures greater than or equal to 1.0 mm in diameter (Figure 3)[24]. Published reports suggest that 40%-58% of patients with PSC will develop a dominant stricture during their lifetime[24-26]. This is of particular importance as patients with PSC who develop dominant strictures have a mean survival of 14 years compared to 27 years in patients who do not develop dominant strictures[27]. Moreover, the presence of a dominant stricture is itself associated with an increased risk of developing CCA[27-29]. Clinicians should become concerned about the possibility of a dominant stricture (and the potential for underlying CCA) when a patient develops subacute worsening of right upper quadrant pain or laboratory abnormalities suggestive of worsening biliary obstruction, though in many cases, a dominant stricture is found (incidentally) during routine CCA surveillance, as discussed further below[30,31].

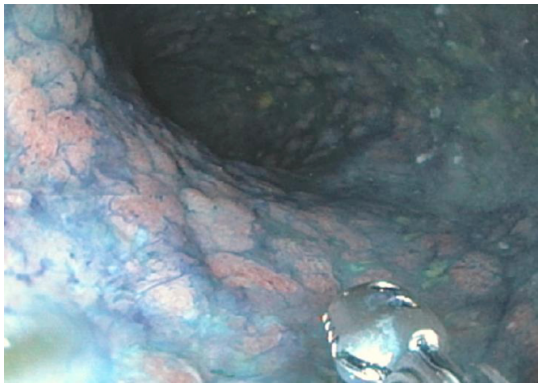

Figure 2 Example of the use of chromoendoscopy in a patient with primary sclerosing cholangitis. In this example, the colon was irrigated using a methylene blue solution. Targeted biopsies were obtained in a region of the sigmoid colon where decreased uptake of methylene blue revealed a diffusely flat, nodular region. Pathology revealed multifocal low-grade dysplasia requiring total proctocolectomy.

Once patients become symptomatic (*i.e.*, develop pruritus, jaundice, or cholangitis) or develop laboratory abnormalities consistent with worsening cholestasis and there is evidence that a dominant stricture has developed, endoscopic intervention with ERC is warranted. Once a dominant stricture has been identified, a key step (in addition to remediating the stricture) is to distinguish whether or not it is benign or malignant (*i.e.*, CCA). In one retrospective study of 20 patients with PSC with new dominant stricture formation, 35% of the patients were found to have underlying malignancy[32]. Therefore, it is of critical importance to consider and rule out the possibility of malignancy when such strictures are identified. For diagnostic evaluation of dominant strictures, a newer technology, single-operator cholangioscopy (SOC), is available to provide targeted sampling under visual guidance. Currently, an indication for SOC is to provide a definitive diagnosis for any patients with indeterminate strictures following biliary brushing or random biopsies. The mean sensitivity of biliary biopsies of all indeterminate strictures *via* SOC for diagnosing underlying malignancy is 68%, which is slightly better than random brushings and biopsies (59% and 63%, respectively)[33-40]. For patients with PSC, one would expect that the diagnostic performance of SOC is even lower, therefore, the challenge of detecting underlying malignancy is even more difficult. One of the potential limitations of SOC in patients with PSC is that SOC catheters are large in diameters (measuring 10 french) and can be difficult to insert into and through stenosed areas of the biliary system. An important benefit of SOC, at least in theory, is that in addition to directed biopsies, SOC offers direct visualization of the biliary mucosa within dominant strictures and thereby provide valuable diagnostic information. Visualization and characterization of stricture phenotypes (through advanced techniques such as narrow band imaging and probe-based methodologies) could improve how we characterize these strictures in the future; however, at present, the role of SOC in the initial evaluation of dominant strictures is still being defined through ongoing studies[41].

Another important consideration when evaluating possible malignancy in PSC is the role of endoscopic ultrasound (EUS) and fine needle aspiration/core needle biopsy (FNA/FNB). If a patient has evidence of perihilar lymphadenopathy, endoscopists should be cautious, however, with transperitoneal sampling *via* EUS. Transperitoneal sampling of tumors or malignant lymph nodes carries a risk of microscopic seeding of malignant cells. In a study of 191 patients with unresectable Klatskin tumors, transperitoneal sampling was associated with peritoneal metastases in 83% of patients compared to 8% in those who did not have EUS-FNA/FNB[42]. Therefore, protocols of liver transplantation for patients with CCA exclude those who have undergone percutaneous or transperitoneal biopsies of suspected malignancy due to concern for microscopic seeding[43].

In the last decade, an emerging modality for the evaluation of indeterminate strictures is confocal laser endomicroscopy (CLE). CLE provides real-time information to endoscopists regarding microscopic tissue composition of the biliary subepithelium. After a contrast agent (*e.g.*, fluorescein) is injected and used to stain the extracellular matrix of tissues, resultant high-contrast images allow for analysis of the subepithelial architecture of the target area and potential differentiation of neoplastic from benign tissue[44]. A study published in 2011 demonstrated that CLE had an accuracy of 81% for correctly diagnosing the underlying pathology of

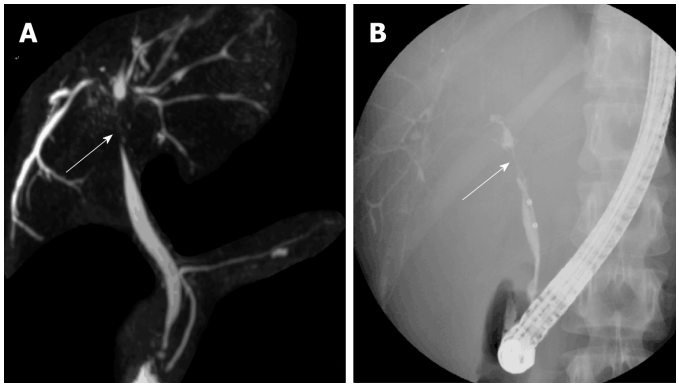

Figure 3 Examples of dominant strictures (arrow) in primary sclerosing cholangitis patients as seen on magnetic resonance cholangiopancreatography (A) and on endoscopic retrograde cholangiography (B).

indeterminate strictures and was superior in diagnostic performance compared to ERCP with random brushings[45]. Specifically when used for patients with PSC with dominant strictures, CLE has been shown to be more sensitive for the detection of neoplastic tissue compared to traditional brushings or biopsies[46]. Further study of CLE will be necessary to validate the technique and support its use in the algorithm for evaluating dominant strictures.

While ruling out underlying malignancy in a patient with a dominant stricture, a contemporaneous step is to consider what therapeutic intervention to perform to relieve worsened biliary obstruction posed by the dominant stricture. Some researchers hypothesize that decreasing episodes of cholangitis and limiting inflammation secondary to dominant strictures *via* biliary interventions may decrease the risk of CCA in patients with PSC[29,47]. When an intervention for a dominant stricture is indicated, a frequent question faced by gastroenterologists, hepatologists, and endoscopists is what specific endoscopic intervention to pursue (*i.e.*, stricture dilation or short-term stenting or both) (Figure 4). To help address this question, a randomized controlled trial was recently performed in 9 centers across Europe. In this study, patients were randomized to one of two groups - either balloon dilation alone or short-term stent placement for a maximum of 2 wk. Patients were then followed for 24 mo. The primary outcome of the study was cumulative recurrence-free patency of dominant strictures. The study was ended early after an interim analysis demonstrated futility and that there were significantly more treatment-related adverse events in the group that received short-term stenting. Specifically, the patients who received short-term stenting had higher rates of post-ERCP pancreatitis as well as acute cholangitis compared to the patients who had balloon dilation alone. But whether more tailored use of a stent for specific scenarios or use of a fully-covered self-expanding metallic stent would have resulted in more favorable outcomes with stenting is unknown. Further data are required to provide recommendations regarding whether patients should undergo balloon dilation without short-term stenting for first-line management of dominant strictures, potentially saving stenting for only those cases wherein balloon dilation alone does not result in improved biliary drainage[48].

ROLE OF ENDOSCOPY IN SURVEILLANCE FOR CCA

The development of CCA is ostensibly the most severe complication for patients with PSC. The cumulative 30-year risk of developing CCA in PSC is approximately 20%[5]. Treatment options for CCA are limited, as is reflected by the 5-year survival rate for patients following this diagnosis of less than 10%[49].

A multimodal approach is necessary to provide surveillance for CCA in patients with PSC. Currently, such an approach includes using annual serum laboratory testing and abdominal imaging (*e.g.*, *via* MRCP) in addition to routine follow-up and labwork. The former would entail measurement of carbohydrate antigen 19-9 (CA 19-9), the only available biomarker for CCA (Figure 5). Choosing a CA 19-9 cutoff value of ≥ 20 U/mL improves sensitivity to nearly 100% at the cost of low specificity and accuracy (38% and 47%, respectively). Conversely, choosing a CA 19-9 threshold of ≥ 129 U/mL increases specificity, but at the cost of decreased sensitivity[50,51]. It is also important to not completely rely on CA 19-9, as 7% of the general population have a negative Lewis Antigen and, therefore, does not produce CA 19-9[52].

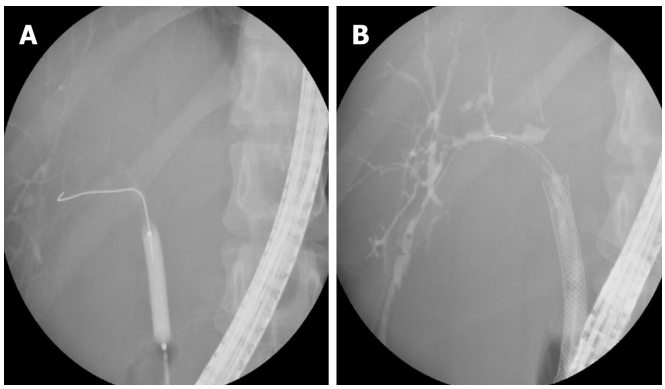

Figure 4 Examples of endoscopic management of a dominant stricture in a primary sclerosing cholangitis patient using balloon dilation (A) and short-term stenting (B).

If the combination of imaging and serum biomarkers is suggestive of findings concerning for CCA, the role of endoscopy and, particularly, ERC is to provide additional diagnostic information to help make a formal (tissue) diagnosis. This can be done by obtaining biliary brushings for cytology (which can include fluorescence in situ hybridization), acquiring targeted biopsies *via* fluoroscopy and/or cholangiosopy, or by providing a visual assessment of the stricture using cholangioscopy[53-56].

In addition to surveillance for CCA, societal guidelines also recommend that patients receive screening for gallbladder cancer. In patients with PSC, the estimated (lifetime) incidence of gallbladder cancer ranges from 3%-14%. Thus, in addition to the screening recommendations above, patients should undergo abdominal ultrasound annually to assess for gallbladder polyps and other potentially (pre-)cancerous changes[57].

COMPLICATIONS OF ENDOSCOPY IN PATIENTS WITH PSC

As has been alluded to throughout this article, although endoscopy has a very important role in the management and surveillance of patients with PSC, gastroenterologists will try to limit endoscopic interventions (especially ERC) in patients with PSC due to concerns of causing complications. In 2009, a Mayo Clinic study compared the rate of complications of over 1000 patients with and without PSC undergoing ERC. This retrospective review demonstrated no significant difference in the overall rate of complications in patients with PSC and those without PSC; there was, however, a significantly higher rate of subsequent acute cholangitis in patients with PSC compared to those without PSC (4% *vs* 0.2%, respectively). A seemingly contributing factor to the development of cholangitis in patients with PSC was the length of the ERC procedure, as patients with PSC who developed cholangitis had an average procedure length of almost 90 min compared to 50 min in those who did not develop cholangitis[58].

Different therapeutic maneuvers during ERC have varying rates of complications. For example, in one prospective study of over 500 balloon dilations of dominant strictures in 96 patients, significant adverse events such as pancreatitis (2.2%), acute cholangitis (1.4%), and bile duct perforation (0.2%) occurred rarely[47]. As mentioned previously, however, a recent randomized controlled trial suggests that short-term stenting of dominant strictures appears to carry a higher risk profile compared to balloon dilation. Short term stenting was associated with a higher rate of acute cholangitis (12%) and post-ERC pancreatitis (24%). The overall rate of complications in patients randomized to a short-term stenting protocol compared to balloon dilation was also much higher (45.4% *vs* 6.7%)[48].

The hypothesis behind the increased rate of post-ERC pancreatitis with stenting in patients with PSC is that compared to patients without PSC, the papilla in PSC is often small and retracted. Therefore, in addition to potentially more difficult cannulation, placement of a stent across such a small papilla may have a much higher chance of blocking off the pancreatic duct, thereby leading to pancreatitis. This hypothesis is supported by the fact that studies suggest that a prior sphincterotomy is protective against the development of post-ERC pancreatitis in patients with PSC[59,60]. Similarly, stenting carries an increased risk of blocking off the cystic duct or intrahepatic ducts, which can lead to cholecystitis or acute cholangitis, respectively.

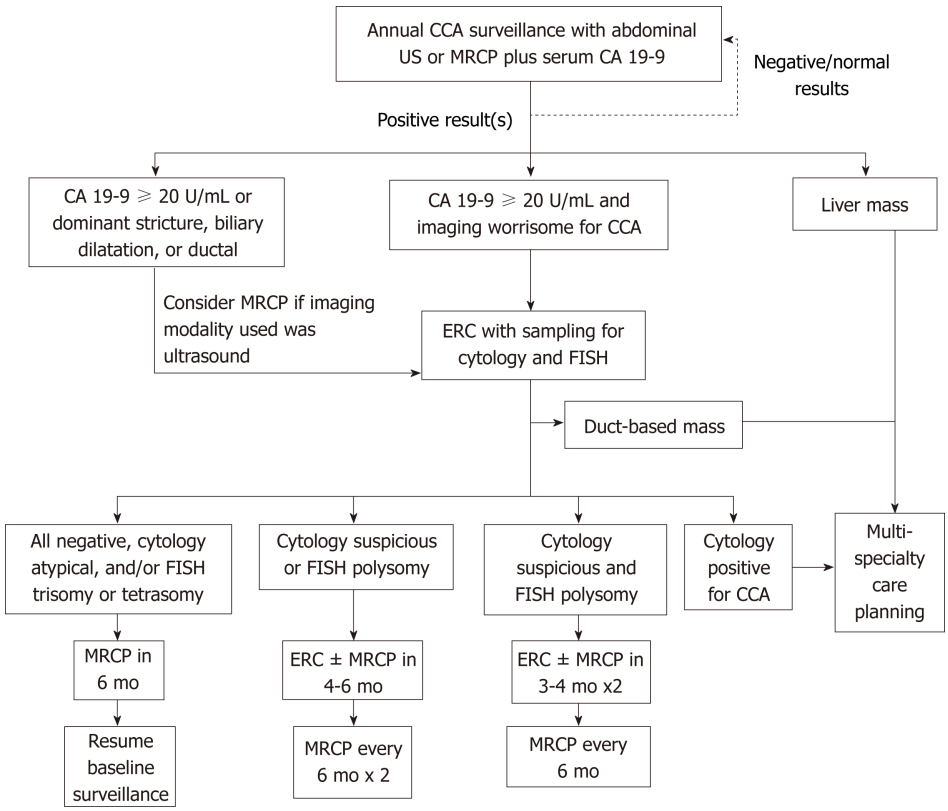

Figure 5 Proposed surveillance algorithm for cholangiocarcinoma in patients with primary sclerosing cholangitis. CCA: Cholangiocarcinoma; US: Ultrasound; MRCP: Magnetic resonance cholangiopancreatography; CA 19-9: Carbohydrate antigen 19-9; ERC: Endoscopic retrograde cholaniography; FISH: Fluorescence *in situ* hybridization.

This is of particular concern in patients with PSC compared to those without PSC because of the several strictures laden throughout the biliary tree that already result in impaired biliary drainage[61].

SYNOPSIS AND FUTURE DIRECTIONS

In this review article, we have discussed how the role of endoscopy has shifted over the past 4 decades and also highlighted important questions that still are yet to be addressed.

Originally, ERC was the premier diagnostic modality available for PSC and was central to our recognition of PSC and developing an understanding of the various PSC phenotypes. As non-invasive methods of imaging of biliary anatomy emerged, the role of endoscopy has changed, but endoscopy still remains a pillar of PSC management. We now rely on ERC for the diagnosis of PSC when a patient cannot undergo MRCP, for the surveillance of extrabiliary manifestations of, and for the management and surveillance of biliary complications of PSC.

New research continues to provide gastroenterologists guidance with how to best use endoscopic techniques to manage patients with PSC. Specifically, and for example, just within the last year a randomized controlled trial has provided us with important new data regarding how we manage dominant strictures in PSC.

Clinical questions that remain to be answered and that could change the role of endoscopy in the future management of PSC are several: (1) Is there a benefit to chromoendoscopy compared to high-definition white light colonoscopy for dysplasia surveillance in patients with PSC-IBD? (2) Do patients with PSC without cirrhosis require variceal screening? (3) What is the role of cholangioscopy in CCA surveillance? (4) In light of the increased risk of complications, when should endoscopists perform short-term stenting of dominant strictures instead of or in addition to balloon dilation? (5) Would fully-covered self-expanding metallic stents fare better in PSC, though at what (monetary) cost? And (6) What is the role of CLE and other novel techniques in the diagnostic approach to dominant strictures?

We anticipate and encourage that these questions and others be addressed collaboratively in the coming years as we continue to improve how we use endoscopy

to best manage and care for patients with PSC.

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MINIREVIEWS

Radiofrequency and malignant biliary strictures: An update

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Abstract

Malignant biliary strictures are usually linked to different types of tumors, mainly cholangiocarcinoma, pancreatic and hepatocellular carcinomas. Palliative measures are usually adopted in patients with nonresectable or borderline resectable biliary disease. Stent placement is a well-known and established treatment in patients with unresectable malignancy. Intraductal radiofrequency ablation (RFA) represents a procedure that involves the use of a biliary catheter device, *via* an endoscopic approach. Indications for biliary RFA described in literature are: Palliative treatment of malignant biliary strictures, avoiding stent occlusion, ablating ingrowth of blocked metal stents, prolonging stent patency, ablating residual adenomatous tissue after endoscopic ampullectomy. In this mini-review we addressed focus on technical success defined as deployment of the RF catheter, virtually succeeded in all patients included in the studies. About efficacy, three main outcome measures have been contemplated: Biliary decompression and stent patency, survival. Existing studies suggest a beneficial effect on survival and stent patency with RFA, but current impression is limited because most of studies have been performed using a retrospective design, on diminutive and dissimilar cohorts of patients.

Key words: Radiofrequency; Ablation; Endoscopic retrograde colangiopancreatography; Malignant biliary strictures

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Core tip: Intraductal radiofrequency ablation (RFA) represents a procedure that encompasses the use of a biliary catheter device, *via* an endoscopic approach, mainly endoscopic retrograde colangiopancreatography. Indications for biliary RFA described in literature are: Palliative treatment of malignant biliary strictures, avoiding stent occlusion, ablating ingrowth of blocked metal stents, prolonging stent patency, ablating residual adenomatous tissue after endoscopic ampullectomy. Existing studies suggest a favorable effect on survival and stent patency. Moreover, up-to-date feeling is that evidence supporting RFA is limited because most of the analyses have been achieved using a retrospective design, on diminutive and dissimilar cohorts of patients.

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INTRODUCTION

The aim of this mini-review is to assess the utility of radiofrequency ablation (RFA) in malignant biliary obstruction (MBO). Malignant biliary strictures represent a diagnostic and therapeutic open question for biliary endoscopist. MBO is usually linked to different types of tumors, mainly cholangiocarcinoma, as well as pancreatic and hepatocellular carcinomas. Traditionally palliative measures have been adopted in patients with nonresectable or borderline resectable biliary disease. Stent placement is a well-established and widely accepted treatment in patients with unresectable malignancy[1,2], with a lower rate of adverse events such as procedural complications and post-stenting occlusion than surgical decompression[3]. The use of metal stents decreases the need for re-intervention and the occurrence of cholangitis compared to plastic or polyethylene stents[4]. However, stent patency is difficult to preserve due to neoplastic in- and over-growth, epithelial hyperplasia, and sludge deposition[5].

Efforts have been ongoing to develop different palliatives interventions to prolong patency of metallic biliary stents. Some of the interventions which have been studied include photodynamic therapy (PDT), intraductal radiotherapy and RFA[6-8].

RFA is a well-recognized percutaneous approach that has widely been used in the management of hepatocellular carcinoma and metastatic hepatic malignancy, with demonstrated effectiveness[9].

Even within the bile duct, RFA can be performed by specific endo-biliary probes that enable increased precision in the delivery of thermal energy in the biliary tree resulting in decreased epithelial hyperplasia and tumor ingrowth. Several studies have confirmed the safety and feasibility of these procedures for clinical use with promising results reported for the palliative treatment of malignant biliary strictures, preventing stent occlusion, ablating ingrowth of blocked metal stents, prolonging stent patency, ablating residual adenomatous tissue after endoscopic ampullectomy[10].

TECHNICAL ASPECTS

RFA creates an electrical passage through the body of monopolar probes, between an electrode and a grounding pad placed on the patient. Additionally, it may be generated by two interstitial electrodes with bipolar catheters, by using an alternating current. Resistance heats the surrounding tissues burning up to elevated temperature (50°C-100°C) and causing protein denaturation followed by cell desiccation and coagulative necrosis. The most contiguous areas to the electrode undergo to the highest current and heat shock due to reduced electrical conductivity of tissues. On the other hand, the parts of the tumor most distant are only burnt and necrosis is not determined because thermal conduction is not sufficiently high[11,12].

Intraductal RFA represents a procedure that encompasses the use of a biliary catheter device, *via* an endoscopic approach. For biliary RF, two devices are designed to be used over a guide wire during endoscopic retrograde colangiopancreatography (ERCP): Habib™ EndoHBP and ELRA™.

The RFA catheter Habib EndoHPB (EMcision Ltd, London, UK; Boston Scientific, Marlborough, Massachusetts, USA) is a disposable device properly designed for

endoluminal delivery of RFA into the biliary system. It is an 8 Fr RFA probe, with bipolar conduction features. It is well-suited for large working channel of duodenoscopes, mostly over 0.035-inch guidewires. The catheter has two ring electrodes, 8 mm distant from each other. It provides local coagulative necrosis over a 2.5 cm length, in circular and ellipsoidal way (Figure 1). The highest energy accumulation is achieved between the electrodes, placed below and above the target. VIO 200D or 300D generator (Erbe Elktromedizin, Tubingen, Germany) are usually used, delivering high-frequency bipolar current. Generator setting mostly lies on: Power between 7 W-10 W, effect set at 8 for a duration of 30 s-90 s.

ELRA™ (EndoLuminal Radiofrequency Ablation, Taewoong Medical, South Korea) probe has been recently introduced. It allows strict control of temperature at the interface tissue-electrode. This probe has two sizes (18- and 33-mm length), with a diameter of 7 Fr. It contains four bipolar electrodes which provide linear ablation. There is no need for ground pads. The generator is VIVA (Taewoong Medical, South Korea) mostly set to two minutes interval, maximum temperature of 80°C and a power of 10 watts (Figure 2). In animal studies this represents the ideal setting to reduce the charring process, allowing more prolongated current stream and more effective tissue ablation[13,14].

To perform biliary RFA, biliary tract is cannulated as a standard ERCP procedure. Then a cholangiography is performed to distinctly visualize the location of the stricture and to define its extent and width. Though not crucial, a sphincterotomy is generally completed. In addition to this, dilation of the stricture, mostly by mean of a balloon, could be performed before RFA procedure. The probe is then inserted over the guidewire across the stricture.

RF energy is applied for the desired period, according to different RFA probe manufacturer's indications. Before withdrawn the probe, a break period of about 60 s is necessary to prevent tissues from adhering to the electrodes. Usually multiple RF applications are completed during the same session. Generally it is preferred from the proximal verge of the target to the distal one, with tiny overlap in order to decrease the risk of complications, mainly perforation.

Once the probe has been removed, coagulated tissue debris are swiped by mean of balloon, and a plastic or metal stent is positioned to guarantee biliary drainage[15,16].

MALIGNANT BILIARY OBSTRUCTION

Over the last 8 years, more than 350 patients were reported in the literature to have been undergone endoscopic biliary RFA. Indications were mainly malignant strictures and occluded self-expanding metal stents (SEMS).

Nearly in all studies, malignant strictures accounted cholangiocarcinoma or pancreatic cancer, but also other malignant strictures have been considered, such gallbladder cancer, hepatic carcinoma and metastatic cancers as well.

In this mini-review we will focus on retrospective "largest" papers including more than 40 patients (including controls group) and all prospective and randomized controlled trial studies published on topic up to August 2018. Table 1 summarizes the main characteristics of the included studies (study design, population, intervention, RFA probe, outcomes, main findings)[17-25].

Technical success defined as deployment of the RF catheter was essentially succeeded in all patients. About efficacy, main outcome measures considered are: Biliary decompression and stent patency, survival. As for stent patency and biliary drainage different outcome measures have been considered: 30- or 90-d patency rate, median time patency. Moreover, in these studies different types of procedures have been grouped in the same series (RFA before stenting, RFA without stenting, RFA in occluded SEMS, combined endoscopic and/or percutaneous RFA), dissimilar stents have been used (metallic or plastic), different stenting replacement strategies have been adopted (on demanding, 3 mo scheduled ERCP). Despite this lack of homogeneity, the results of the included studies are quite similar, with 90-d patency ranging between 80%-86%, up to 69% ad 180-d[17,24]; median patency ranged between 170 d[19] and 200 d[25]. RFA + metallic stent placement outperformed RFA + plastic stent strategy, doubling median patency rate[19]. About survival, all but one study, in which similar results have been observed between RFA and PDT[21], showed very encouraging results in patients performing one or more RFA sessions. Overall survival ranged between 226 and 396 d[22,23,25], and RFA + stent outperformed stenting alone strategy in all study comparing them.

With regard to adverse events (AE), frequency ranged between 6.3% and 33.3%. Most of these concerns the bilio-pancreatic compartment: Acute pancreatitis, cholangitis, cholecystitis, and haemobilia. Only one study report two severe adverse

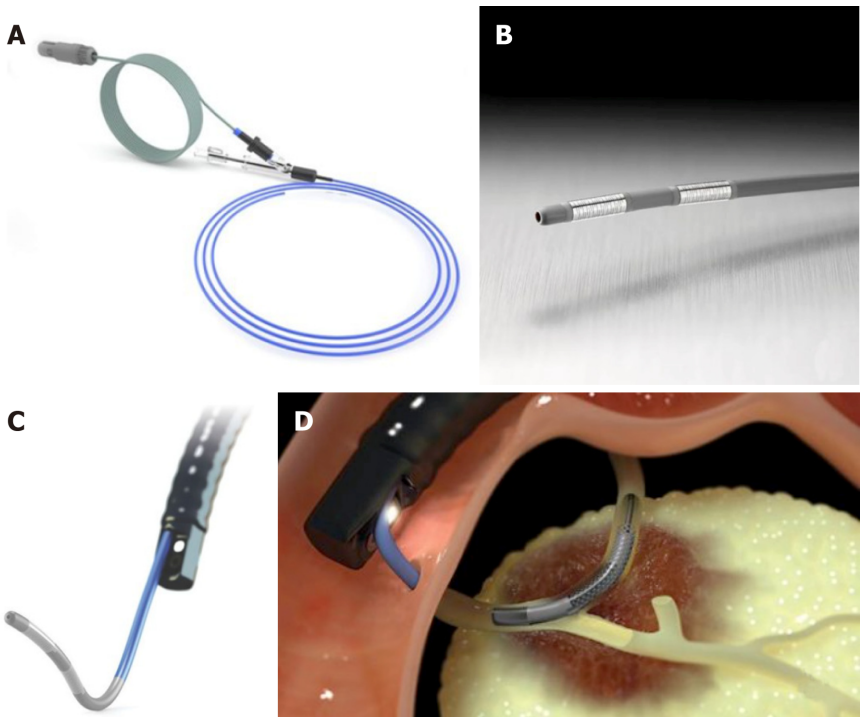

Figure 1 Habib™ EndoHPB Catheter. A, B: Radio Frequency ablation catheter; C, D: Duodenoscope and catheter in endoscopic retrograde colangiopancreatography simulation model. From: https://www.bostonscientific.com/content/gwc/en-US/products/rf-ablation/habib-endohpb-bipolar-radiofrequency-catheter.html.

events: One hepatic liver infarction and one hepatic coma[19].

OCCLUDED SEMS

Only two studies have specifically addressed biliary RFA in case of occluded metal stents. Kadayifci *et al*[26] matched endobiliary RFA to controls in which plastic stents were inserted across the stent. The study group included 25 patients treated with RFA using a Habib™ endoprobe inside the SEMS. The control group involved 25 patients treated only with placement of a plastic stent into an occluded SEMS. Biliary drainage was restored in all patients. Stent patency was evaluated at 90 d, reaching 56% and 24% in the RFA and control groups, respectively. In addition to this, stent patency was significantly longer in the RFA group compared to the control group (119.5 d *vs* 65.3 d, $P = 0.03$). 30-d mortality rate and 3- and 6-mo survival rates did not significantly differ between the RFA group and controls ($P > 0.05$).

The other study, recently published, is a feasibility prospective case series of 7 patients treated with novel temperature-controlled RFA probe ELRA™ (Taewoong, South Korea)[14]. Nine procedures were performed. Seventy percent of patients (5/7) required additional procedures and stent placement to guarantee optimal drainage. There were no procedure-related complications.

ENDOSCOPIC RADIOFREQUENCY ABLATION OF INTRADUCTAL RESIDUAL OF AMPULLARY ADENOMA

Ampullary adenomas are usually treated by endoscopic papillectomy. Nevertheless, ampullary adenomatous residuals spreading into the distal common bile duct or Wirsung represent a tricky condition.

Intraductal adenoma typically has been considered a contraindication to endoscopic management. Surgical treatment represents the gold standard in this condition. Conversely, a pancreaticoduodenectomy or a Whipple procedure are associated with high morbidity and mortality.

Firstly Valente *et al*[27] published a small series of three patients in which rescue endoscopic RFA for ampullary neoplasms with intraductal extension has been performed. They presented a long follow-up concluding that this approach may

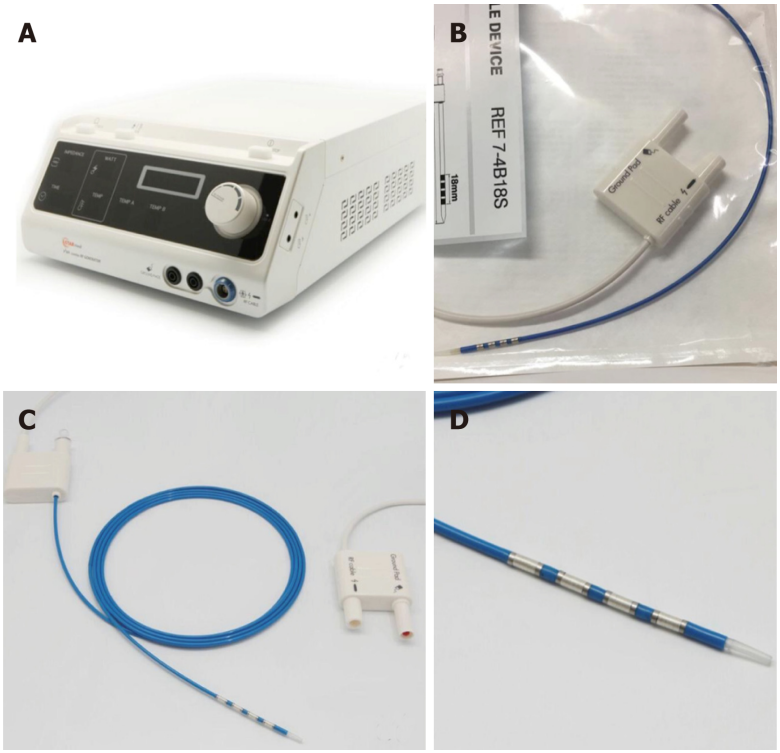

Figure 2 ELRA™ (EndoLuminal Radiofrequency Ablation, Taewoong Medical, South Korea). A: VIVA generator; B, C, D: ELRA™ catheter. Courtesy of Euromedical Srl.

represent a safe alternative in patients refusing or not suitable for surgery. It could represent a long-term, palliative strategy in high risk patients.

A retrospective study evaluated the feasibility, safety, and efficacy in 14 patients with adenoma extension into the common bile duct and pancreatic duct. These patients underwent one RFA session (range, 1-5 sessions). At a median follow-up period of sixteen months after RFA, complete intraductal ablation was obtained in about 92% of patients. Adverse events occurred in 43% of cases, mainly represented by ductal strictures and a retro-duodenal abscess[28]. Suarez *et al*[29] published another small case series of 4 patients showing similar results, with 3 patients succeeding complete ablation of the intraductal adenoma and no adverse events noted during the short follow-up period.

Finally, Camus *et al*[30] published in 2018 the results of a prospective and open-label multicenter study including 20 patients with pathological confirmed endobiliary adenoma remnant undergoing intraductal RFA. Residual neoplasia was evident in 15% and 30% of patients at 6 mo and 12 mo, respectively, achieving seventy percent possibility of dysplasia eradication at 12 mo after a single session of RFA. At least one adverse event (no one severe) occurred in 40% patients during 12 mo follow-up.

Although small in number, in these studies RFA seems to be a reasonably safe and effective approach for the treatment of residual ampullary adenomas with endobiliary extension.

CONCLUSION

RFA is an additional treatment recently impemented to the advanced bilio-pancreatic endoscopy. In the field of unresectable neoplasia and MBO, in which treatment options are very restricted, great potential has been addressed to this procedure. Available studies suggest a beneficial effect on survival and stent patency with RFA, but current suggestion is limited because most of studies have been performed using a retrospective design, on diminutive and dissimilar cohorts of patients. As for complication, safety seems to be tolerable, though serious adverse events have been reported. Only few prospective studies and one randomized controlled trial are available and confirm and enhance these two main aspects: Increased survival and reduced rates of adverse events. Further efforts are needed to increase the degree of evidence and to comply with additional therapeutic indications such as occluded SEMS or adenomatous post-ampullectomy residuals.

Table 1 Summary of the main characteristics of the included studies (study design, population, intervention, radiofrequency ablation probe, outcomes, main findings)

Author (reference), Country, Year	Patients number	Study design	Intervention	Probe	Tumour type	Control group	Outcomes	Main findings
Steel *et al*[17], UK 2011	22	Prospective	ERFA before SEMS	Habib EndoHPB	CC, PC	No	Technical and clinical success; adverse events	(1) 21/22 technical success; 18/21 stent patency at 90 d; and (2) 3 AE (1 pancreatitis, 2 cholecystitis)
Figueroa-Barojas *et al*[18], USA 2013	20	Prospective	ERFA before stenting (metallic or plastic)	Habib EndoHPB	MBO	No	30 d patency, stricture size; adverse events	(1) Significant increase of 3.5 mm CBD diameter after RFA; and (2) 2 AE (1 pancreatitis, 1 cholecystitis)
Dolak *et al*[19], Austria 2014	58	Retrospective	Miscellaneous (ERFA before stenting, ERFA for blocked SEMS, percutaneous RFA)	Habib EndoHPB	MBO (mainly CC)	No	Patency, adverse events, mortality	(1) Median stent patency 170 d (95%CI 63-277): Metal *vs* plastic stenting (218 d *vs* 115 d, P = 0.051); and (2) 12 AE (1 partial liver infarction, 5 Cholangitis, 2 hemobilia, 2 cholangiosepsis, 1 hepatic coma, 1 left bundle branch block)
Sharaiha *et al*[20], USA 2014	66	Retrospective	ERFA before stenting (26pts) *vs* stenting alone (40 pts)	Habib EndoHPB	CC, PC	Yes	Survival, stricture size; Adverse events	(1) ERFA independent predictor of survival [HR 0.29 (0.11-0.76), P = 0.012]; and (2) No differences in AE (2 RFA *vs* 3 no-RFA)
Strand *et al*[21], USA 2014	48	Retrospective	ERFA (16 pts) *vs* PDT (32 pts)	Habib EndoHPB	CC	Yes	Survival; Adverse events	Similar survival; more stent occlusions in RFA group
Kallis *et al*[22], UK 2015	69	Retrospective	ERFA before stenting (23 pts) *vs* stenting alone (46 pts)	Habib EndoHPB	PC	Yes	Survival, morbidity, and stent patency rates	Median survival in RFA group 226 d *vs* 123.5 d in controls (P < 0.01); SEMS patency equivalent
Sharaiha *et al*[23], USA 2015	69	Retrospective (multicentric registry)	Miscellaneous (mainly ERFA before stenting)	Habib EndoHPB	MBO (mainly CC)	No	Survival; Adverse events	(1) Median survival 11.46 mo (6.2 mo-25 mo); and (2) AE 10 % (1 pancreatitis 2 cholecystitis, 1 hemobilia, 3 abdominal pain)

Laleman *et al*[24], Belgium 2017	18	Prospective	ERFA before stenting	ELRA	CC, PC	No	Feasibility, safety, and biliary patency rate of a new RFA device	(1) Biliary patency 80% and 69% at 90 d and 180 d respectively; and (2) 6 AE (4 cholangitis, 2 pancreatitis)
Yang *et al*[25], China 2018	65	RCT	ERFA before stenting (32 pts) *vs* stenting alone (33 pts)	Habib EndoHPB	CC	Yes	Overall survival, biliary patency; post-ERCP AE	(1) OS RFA + stent *vs* the stent-only (13.2 mo ± 0.6 mo *vs* 8.3 mo ± 0.5 mo, $P < 0.001$); Biliary patency RFA + stent longer than stent-only (6.8 mo *vs* 3.4 mo, $P = 0.02$); and (2) Similar AE [6.3% (2/32) *vs* 9.1% (3/33), $P = 0.67$]

ERFA: Endoscopic radiofrequency ablation; CC: Cholangiocarcinoma; PC: Pancreatic cancer; MBO: Malignant biliary obstruction; SEMS: Self-expandable metal stents; AE: Adverse events; CBD: Common bile duct; HR: Hazard ratio; PDT: Photo dynamic therapy; OS: Overall survival.

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MINIREVIEWS

Endoscopic ultrasound-guided drainage of the biliary system: Techniques, indications and future perspectives

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Abstract

Over the last decade, endoscopic ultrasound-guided biliary drainage (EUS-BD) has evolved into a widely accepted alternative to the percutaneous approach in cases of biliary obstruction with failed endoscopic retrograde cholangiopancreaticography (ERCP). The available evidence suggests that, in experienced hands, EUS-BD might even replace ERCP as the first-line procedure in specific situations such as malignant distal bile duct obstruction. The aim of this review is to summarize the available data on EUS-BD and propose an evidence-based algorithm clarifies the role of the different EUS-BD techniques in the management of benign and malignant biliary obstructive disease.

Key words: Endoscopic ultrasound; Endoscopic retrograde cholangiopancreaticography; Biliary drainage; Rendez-vous; Hepaticogastrostomy; Choledochoduodenostomy

Core tip: Endoscopic ultrasound-guided biliary drainage (EUS-BD) has recently been introduced as a valuable approach case in patients with failed endoscopic retrograde cholangiopancreaticography (ERCP). Evidence suggests that EUS-BD is equally effective and safer than the percutaneous approach. EUS-BD has even been proposed as a first-line procedure (replacing ERCP) in selected indications. Various approaches for EUS-BD exist, depending on the type (malignant or benign) and location (distal or proximal) of the biliary obstruction, and the anatomy of the upper gastrointestinal tract (surgically altered or not). This review gives an overview of the technique and the available data of EUS-BD in several indications.

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INTRODUCTION

Endoscopic biliary drainage, achieved by endoscopic retrograde cholangiopancreaticography (ERCP), has been the established first-line therapy for both benign and malignant biliary obstruction since the beginning of the 1990s. However, even in experienced hands, ERCP fails in 5%-10% of cases[1] because of impossible cannulation or inaccessibility of the major papilla (for example due to tumoral invasion of the ampullary region or surgically altered anatomy). Moreover, ERCP can be complicated by pancreatitis, cholangitis, bleeding, perforation or stent dysfunction requiring reintervention[1,2]. Until recently, percutaneous transhepatic biliary drainage (PTBD) was the only non-surgical alternative to achieve biliary drainage in cases of failed ERCP. However, reported adverse rates of PTBD are high with 1 out of 4 patients suffering from bleeding, bile leak or acute cholangitis after the procedure[3].

Endosonographic-guided biliary drainage (EUS-BD) techniques have recently been introduced as an alternative to PTBD. Over the last decade, increasing operator experience reduced the number of adverse events and augmented technical and clinical success rates of EUS-guided biliary drainage. Many retrospective comparative analyses have concluded that EUS-BD is associated with fewer adverse events as compared to PTBD and should be the treatment of choice in cases of failed ERCP[4].

EUS-BD might even be considered a first-line approach in patients with distal malignant bile duct obstruction. Three randomized controlled trials that compared EUS-BD with ERCP have been published within the last year suggesting that the success-rate of both techniques is similar, but adverse events and reintervention rates might be lower for EUS-BD[5-7]. In other words, the "ERCP-first" paradigm is not sacrosanct, at least for specific indications.

In this review, we describe the different EUS techniques for biliary drainage. Contemporary evidence regarding the efficacy and safety of EUS-BD in benign as well as malignant biliary obstructive diseases is discussed. We highlight the comparison between EUS-BD, PTBD and ERCP. Finally, we provide a practical flowchart that positions EUS-BD in the current therapeutic algorithm of biliary obstruction and conclude with some future perspectives.

SEARCH STRATEGY

We searched for relevant publications using PubMed, EMBASE, and the Cochrane Library, from their inception until Dec 1, 2018. Our search algorithm included the following terms: Endoscopic ultrasound, biliary drainage, ERCP, bile duct, percutaneous, rendez-vous, hepaticogastrostomy, choledochobulbostomy, choledochoduodenostomy, hepatico-enterostomy, choledocho-enterostomy in various combinations. We critically reviewed articles published in English and gave priority to randomized controlled trials and meta-analyses.

TECHNIQUES

General technique

EUS-guided biliary drainage involves the visualization of dilated extra- and or intrahepatic bile ducts and the puncture of these ducts with a needle or a direct access device (LAMS). Puncture of dilated left intrahepatic bile ducts is usually performed from the upper part of the stomach whereas the common bile duct is best accessed from the bulbar portion of the duodenum. Aspiration of bile confirms the position within the bile duct. If necessary contrast injection provides cholangiography to plan the desired intervention. Subsequently, several procedures can be performed, depending on the clinical scenario and the puncture site.

Rendez-vous technique: This technique is mainly used for benign indications when retrograde cannulation of the bile duct fails. A prerequisite for the technique is an endoscopically accessible ampulla or anastomosis. After puncture of the bile duct, a guidewire is advanced *via* the needle through the ampullary orifice into the duodenum or the surgical anastomosis. While this might be easy in some cases, several challenges may occur. Firstly, with the trans-bulbar approach, the wire may find its way into the intrahepatic bile ducts rather than the ampulla. This can usually be overcome by moving to a long scope position, by deflecting the endoscope tip towards the ampulla or by using a guidewire with an angled tip. Secondly, the wire may not be able to pass the ampullary orifice (due to a distal stricture, impacted stone, ampullary stenosis, *etc*.). In that case, it might be necessary to insert a papillotome over the wire into the bile duct to further steer and support the wire. Advancement of a papillotome requires a prior cystogastrotomy using a 6 Fr cystogastrotome (preferred) or 4 mm balloon dilatation. Once transpapillary passage of the wire is achieved, the wire should be introduced deeply in the duodenum. The needle and the endoscope are removed leaving the wire in place. Next, a duodenoscope is introduced to visualize the wire protruding from the ampullary orifice. In most cases it is possible to cannulate the bile duct next to the wire. Occasionally, the wire needs to be retrieved using a snare into the endoscope instrument channel. In this way a papillotome can be introduced over the wire directly in the bile duct.

Choledochoduodenostomy (CDS): This technique (Figure 1A) is mainly used for malignant distal bile duct obstruction when the ampulla is not accessible or when retrograde cannulation fails. It is important to verify duodenal patency beforehand, or to place a duodenal stent or an endoscopic gastrojejunostomy if indicated. The conventional technique involves trans-bulbar puncture of the dilated common bile duct, then a guidewire is advanced upstream into an intrahepatic bile duct and the puncture tract is dilated with a cystogastrotome (6 Fr) or a dilation balloon (4 mm). Thereafter, a fully covered metallic stent can be left in place to achieve biliary drainage. Stent migration can be an issue and can be overcome in different ways: By using a long covered metal stent, a LAMS (Axios^{R}, Boston Scientific, USA; Nagi^{R} stent, Taewoong Medical, South Korea) or by placing a partially covered stent with the uncovered portion within the bile duct. However, no short partially covered biliary stents are available at the current time (minimal length is currently 8cm with an uncovered part of 3 cm or 4 cm).

The novel approach involves the use of a LAMS, with direct puncture of the dilated common bile duct using pure cut current, optional placement of a guidewire and delivery of the LAMS without a further dilation step. This technique is now favored in most centers. An 8 mm or 10 mm diameter stent is usually used, and for safe LAMS placement the diameter of the CBD should exceed 10 mm, to avoid misplacement

Hepaticogastrostomy (HGS): This technique (Figure 1B) can be used for proximal (perihilar) bile duct obstruction when the ampulla is not accessible, when retrograde cannulation fails, or when the left lobe cannot be drained by ERCP. It can also be used for malignant distal bile duct obstruction if the common bile duct is not accessible due to surgically altered anatomy (*e.g*., after Whipple procedure or roux-en-Y gastric bypass). It is the preferred technique by some experts in any distal malignant obstruction. In cases of perihilar bile duct obstruction, this route of drainage can only drain the left hepatic ducts in case of total hilar obstruction, or both liver lobes in case of left-right biliary communication. After puncture, guidewire introduction and dilatation of the puncture tract (using a 6 Fr cystogastrotome or a 4 mm dilatation balloon), a partially covered stent can be placed, with the uncovered part in the bile duct to prevent migration and the covered part bridging the bile duct and the gastric lumen (Giobor stent, Taewoong Medical, South Korea).

In benign diseases, the HGS can be created with a plastic stent to allow for removal, dilation and sequential repeat access to the bile ducts either for stricture dilatation, or stone lithotripsy.

EUS-guided antegrade transpapillary stent placement: This technique involves the same initial steps as described above for the rendez-vous technique but after placement of the guidewire, a metallic stent is advanced through the ampullary orifice in an antegrade fashion. This is technically more challenging than EUS-guided transmural drainage and does not eliminate the risk of pancreatitis. As such, the technique should be reserved for patients with benign distal bile duct strictures (*e.g*., in the context of chronic pancreatitis) in whom both the retrograde and rendez-vous approaches have failed. HGS and antegrade stent placement may be combined.

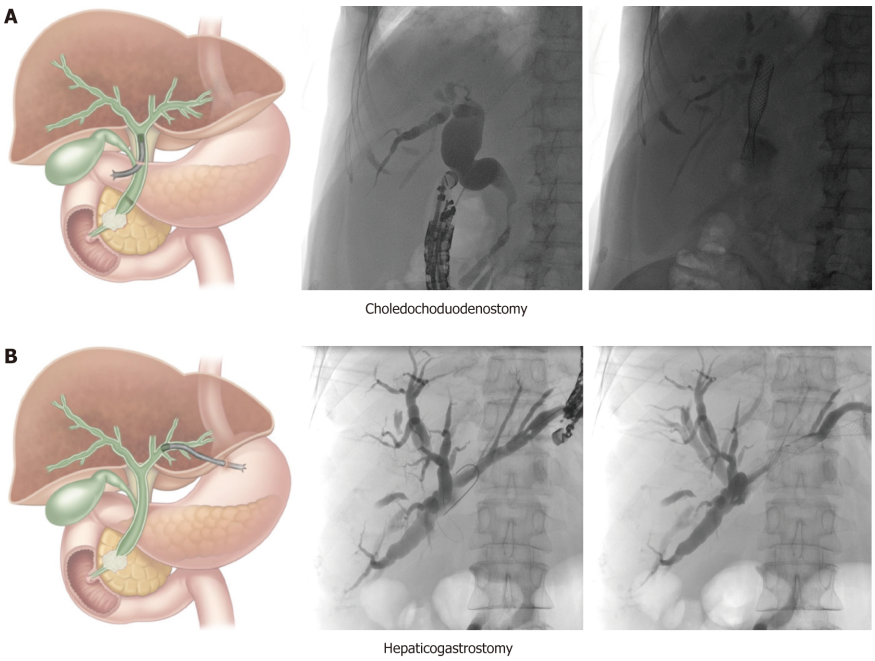

Figure 1 Schematic and case illustration of the choledochoduodenostomy (A) and the hepaticogastrostomy (B). Patient A had a distal bile duct obstruction due to a locally advanced pancreatic head carcinoma. Patient B had a large perihilar metastasis of a small cell lung carcinoma with a complete obstruction of the proximal common bile duct but preserved left-right intrahepatic bile duct communication. The choledochoduodenostomy can be combined with a duodenal stent or an endoscopic gastrojejunostomy if indicated. Adapted from Paik *et al*[5].

INDICATIONS

Malignant biliary obstructive disease

In 2001, Giovannini *et al*[8] first reported a successful EUS-guided CDS procedure in a patient with pancreatic carcinoma and distal malignant biliary obstruction after failed ERCP. Two years later Burmester *et al*[9] published a one-step method without the need for switching from the ERCP to the EUS scope. This was followed by the publication of several small case series and studies demonstrating technical and clinical feasibility of EUS-guided BD for malignant indications after ERCP failure with an acceptable safety profile[10-21]. Due to the small size of the individual studies, the overall efficacy and adverse event profile of EUS-BD had not yet been established. A meta-analysis of Moole *et al*[22] pooled 16 studies (until January 2016, n = 528)[13,15,18-20,23-30] and reported a 90.9% success rate for rescue EUS-guided BD with an overall procedure related adverse event rate of 16.5%. Khan *et al*[31] showed very similar results in their meta-analysis that pooled 20 studies (until 2015, n = 1186, 6 studies overlap with Moole *et al*[22])[21,32-35]. The technical success and post-procedure adverse event rate were 90% and 17%, respectively. Both meta-analyses included studies that evaluated EUS-BD both in benign and malignant indications. In Table 1 all published case series or studies investigating exclusively malignant biliary obstruction are listed (case reports with less than 10 cases are not considered). From this table it is evident that inclusion criteria were not homogenous, different techniques and materials were used and the definition of technical and clinical success was diverse. Some studies examined subpopulations such as patients with altered biliary anatomy[36] or ascites[37]. More recent publications have larger patient cohorts, but the majority are retrospective and single center[29,37-44]. Khashab *et al*[45] published a larger (n = 96), prospective, multicenter study and demonstrated excellent efficacy and safety of EUS-BD for malignant distal biliary obstruction. It is generally advised that the procedure should be performed by experts in biliopancreatic endoscopy and advanced endoscopic ultrasound.

CDS *vs* HGS: The meta-analysis by Uemura *et al*[46] in 2018 (10 studies until April 2017, n = 434 patients)[21,32,35,44,45,47-51] did not demonstrate superiority in terms of technical success (CDS: 94.1% *vs* HGS: 93.7%) and clinical success (CDS: 88.5% *vs* HGS: 84.5%) comparing EUS-CDS and EUS-HGS in patients with malignant biliary obstruction (only 2 studies included distal obstruction). They also found both procedures to be equivalent in terms of safety. This is contrary to previously published studies that concluded EUS-HGS was associated with more adverse

Table 1 Outcome of endoscopic ultrasound-guided biliary drainage

First Author, Yr	Type of study	Type of malignant obstruction	Number patients	Technical Success rate	ClinicalSuccess rate	Adverse events
Kanno *et al*[40], 2018	(1) Retrospective, single center; and (2) Failed ERCP/inaccessible papilla	Unresectable	99	98%	93%	Overall: 10%
Rai *et al*[38], 2018	(1) Retrospective, single center; and (2) Failed ERCP or duodenal obstruction	(1) Unresectable; and (2) Distal	30	93.3%	93.3%	(1) Overall: 10%; and (2) 83% stent patency (3 mo)
Alvarez-Sánchez *et al*[37], 2018	(1) Retrospective, single center; and (2) Failed ERCP	(1) With/out ascites; and (2) Distal or proximal	31; Ascites: 11	100%	(1) No ascites: 95%; and (2) Ascites: 64%	(1) No ascites: 20%; and (2) Ascites: 9%
Iwashita *et al*[36], 2017	(1) Prospective, single center; and (2) Altered anatomy	Unresectable	20	95%	95%	20%
Minaga *et al*[52], 2017	(1) Retrospective, single center; and (2) Failed ERCP	(1) Unresectable; and (2) Hilar obstruction	30	96.7%	75.9%	(1) Early: 10%; and (2) Late: 23.3%
Makmun *et al*[41], 2017	(1) Retrospective, single center; and (2) Failed ERCP	Distal and proximal	24	100%	79.1%	16.7%
Ogura *et al*[53], 2017	(1) Retrospective, single center; Failed ERCP	Hilar obstruction	10	100%	90%	0%
Lu *et al*[42], 2017	(1) Retrospective, single center; and (2) Failed ERCP	Distal and proximal	24	95.8%	100%	13%
Cho *et al*[51], 2017	(1) Prospective; and (2) Failed ERCP		54	100%	94.4%	16.6%
Amano *et al*[48], 2017	Prospective		20	100%		15%
Kunda *et al*[43], 2016	(1) Retrospective, single center; and (2) Failed ERCP	(1) Unresectable; and (2) Distal	57	98.2%	94.7%	7%
Nakai *et al*[61], 2016	(1) Retrospective, multicenter; and (2) Primary EUS	(1) Unresectable Distal and proximal	33	100%	100%	9%
Guo *et al*[44], 2016	(1) Retrospective, single center; and (2) Failed ERCP		21	100%	100%	19%
Khashab *et al*[45], 2016	(1) Prospective, multicenter; and (2) Failed ERCP	Distal	96	95.8%	89.5%	(1) 10.5%; and (2) 86% stent patency (1 yr)
Ogura *et al*[49], 2016	Retrospective, single center		39			(1) CDS: 6%; and (2) HGS: 2%
Dhir *et al*[34], 2015	(1) Retrospective, multicenter; and (2) Failed ERCP		104	95.%	90.9%	6.8%
Park *et al*[47], 2015	(1) Prospective, randomized; and (2) After failed ERCP	Distal and proximal	22	(1) CDS: 92%; and (2) HGS: 100%	(1) CDS: 92%; and (2) HGS: 100%	(1) Early CDS: 25% *vs* HGS: 0%; and (2) Late CDS: 8.3% *vs* HGS: 25%
Artifon *et al*[50], 2015	(1) Prospective, randomized, single center; Failed ERCP	Distal	49	(1) CDS: 91%; HGS: 96%	(1) CDS: 77%; HGS: 91%	(1) CDS: 12.5%; and (2) HGS: 20%
Dhir *et al*[33], 2014	(1) Retrospective, multicenter; and (2) Failed ERCP	Distal and proximal	68	95.6%		20.6%
Kawakubo *et al*[32], 2014	(1) Retrospective, multicenter; and (2) Failed ERCP	Unresectable Proximal and distal	64	95%		19%
Song *et al*[21], 2014	(1) Prospective, single center; and (2) Failed ERCP	Proximal and distal	27	100%	96.3%	18.5%

Prachayakul *et al*[35], 2013	(1) Retrospective, single center; and (2) Failed ERCP	Proximal and distal	22	95.2%	90.5%	9.5%
Hara *et al*[62], 2013	(1) Prospective , single center; and (2) First line	Distal	18	95%	95%	11%
Khashab *et al*[45], 2013	(1) Retrospective, multicenter; and (2) Failed ERCP	Distal	35	97%	94%	12%
Kim *et al*[27], 2012	(1) Retrospective, single center; and (2) Failed ERCP	Proximal and distal	13	92.3%	91.7%	
Iwashita *et al*[30], 2012	(1) Retrospective, single center; and (2) Failed ERCP		40	73%		13%
Song *et al*[21], 2012	(1) Prospective, single center; and (2) Failed ERCP	Distal	15	86.7%	100%	23.1%
Hara *et al*[19], 2011	(1) Prospective, single center; and (2) Failed ERCP	Distal	18	94%	100%	17%
Ramírez-Luna *et al*[18], 2011	(1) Prospective, single center; and (2) Failed ERCP or PTC		11	91%	90%	*n* = 2
Fabbri *et al*[16], 2011	(1) Prospective, single center; and (2) Failed ERCP	Proximal and distal	16	100%	75%	6.3%
Park *et al*[11], 2009	(1) Prospective, single center; and (2) Failed ERCP	Distal	14	100%	100%	

EH: Extrahepatic; IH: Intrahepatic; AG: Antegrade; CDS: Choledochoduodenostomy; HGS: Hepaticogastrostomy; RV: Rendezvous; GG: Gastro-gallbladder; HES: Hepaticoesophageostomy; SEMS: Self-expandable metal.

events[31,33]. The authors proposed that the choice of approach may be selected based on patient anatomy and the presence of bile duct dilatation. For example, EUS-CDS is not suitable for proximal (hilar) biliary obstruction, where an intrahepatic EUS-BD approach is required. In the specific situation of hilar malignancy EUS-guided HGS was found to be safe and effective[52,53], although the duration of efficacy was limited[40] and lower clinical success rates were demonstrated than for distal obstruction[41].

EUS *vs* PTBD: Two meta-analyses compared EUS-BD and PTBD after failed ERCP or an inaccessible papilla for malignant biliary obstruction (Table 2). In the meta-analysis by Moole *et al*[22], 3 studies were included[34,54,55]. The pooled odds ratio for successful biliary drainage was higher in EUS-PD versus the PTBD group and the difference for overall procedure related complications was lower. Other studies found EUS-BD to be superior[55] or have comparable efficacy[54] with lower[54] or comparable[54] adverse event rates, need for reintervention and costs. Sharaiha *et al*[56] included 6 studies[34,54-59] in their meta-analysis (2 studies were published only in abstract form). There was no difference in technical success rates between the two procedures but EUS-BD was associated with better clinical outcomes, fewer post-procedural adverse events and a lower rate of reintervention. They found no difference in length of hospital stay after the procedures, but EUS-BD was more cost-effective[4]. In 2018, a retrospective showed similar results with the additional finding of a shorter hospital stay for EUS-BD[60].

When ERCP fails to achieve biliary drainage, EUS-guided BD seems preferable over PTBD if the required expertise and logistics are available. The additional advantages are the avoidance of external drainage catheters and the option of performing the procedure under the same sedation as the attempted ERCP.

EUS *vs* ERCP: A limited number of studies reported results for primary EUS-guided BD without prior ERCP (Table 3). Nakai *et al*[61] performed EUS-HGS in 33 patients with gastric outlet obstruction, surgically altered anatomy or history of ERCP-related adverse events. The procedure appeared safe and effective. These findings have also been confirmed for primary EUS-CDS[62]. Kawakubo *et al*[63] found comparable technical success rates with ERCP for EUS-CDS as a first-line treatment for patients with distal malignant biliary obstruction, and a significantly decreased rate of acute pancreatitis in the CDS group.

In 2018, the results of 3 prospective, randomized trials comparing primary EUS-

Table 2 Studies comparing endoscopic ultrasound-guided biliary drainage and percutaneous transhepatic cholangiography

Author, Yr	Type of study	Type malignant obstruction	Number patients	Technical Succes rate	Clinical Succes rate	Complications, EUS *vs* PTC
Téllez-Ávila *et al*[60], 2018	(1) Retrospective; and (2) Failed ERCP	(1) Malignant 56.4%; and (2) Distal	(1) Total: 62; (2) EUS: 30; and (3) PTC: 32	(1) EUS: 90%; and (2) PTC: 78.1%	(1) EUS: 96%; and (2) PTC: 63%	Overall: 6% *vs* 28.1%
Sportes *et al*[57], 2017	(1) Retrospective, multicenter; and (2) Failed ERCP or altered anatomy	(1) Unresectable; and (2) Distal	(1) Total: 51; (2) EUS: 31; and (3) PTC: 20	(1) EUS: 100%; and (2) PTC: 100%	(1) EUS: 86%; and (2) PTC: 83%	(1) Overall: 16% *vs* 10%; and (2) Reintervention: 6.5% *vs* 105%
Lee *et al*[58], 2016	(1) Randomized, multicenter; and (2) Inaccessible papilla	(1) Unresectable; and (2) Distal	(1) Total: 66; (2) EUS: 34; and (3) PTC: 32	(1) EUS: 94.1%; and (2) PTC: 96.9%	(1) EUS: 87.5%; and (2) PTC: 87.1%	(1) Overall: 8.8% *vs* 31.2%; and (2) Reintervention: 25% *vs* 54.8%
Torres-Ruiz, 2016; Abstract	Failed ERCP	Distal and proximal	(1) Total: 66; (2) EUS: 35; and (3) PTC: 31	(1) EUS: 81%; and (2) PTC: 90.3%	(1) EUS: 90%; and (2) PTC: 68.7%	(1) Early: 10.8% *vs* 9%; (2) Late: 16.6% *vs* 54%; and (3) Reintervention: 8.5% *vs* 45.1%
Sharaiha *et al*[56], 2016	(1) Retrospective, single center; and (2) Failed ERCP	Malignant: 83.3%	(1) Total: 60; (2) EUS: 47; and (3) PTC: 13	(1) EUS: 93.3%; and (2) PTC: 91.6%	(1) EUS: 62.2%; and (2) PTC: 25%	(1) Late: 6.6% *vs* 53.8%; and (2) Reintervention: 6.6% *vs* 53.8%
Bill *et al*[59], 2015	(1) Retrospective, single center; and (2) Failed ERCP	Distal	(1) Total: 50; (2) EUS: 25; and (3) PTC: 25	(1) EUS: 76%; and (2) PTC: 100%	(1) EUS: 96%; and (2) PTC: 80%	(1) Early: 16% *vs* 12%; (2) Late: 12% *vs* 5%; and (3) Reintervention: 15.8% *vs* 60%
Giovannini, 2015; Abstract	(1) Randomized, multicenter; and (2) Failed ERCP or impossible	Malignant: 90.2%	(1) Total: 41; (2) EUS: 20; and (3) PTC: 21	(1) EUS: 95%; and (2) PTC: 100%	(1) EUS: 95%; and (2) PTC: 85%	Overall: 35% *vs* 60%
Khashab *et al*[45], 2015	(1) Retrospective, multicenter; and (2) Failed ERCP	Distal	(1) Total: 73; (2) EUS: 22; and (3) PTC: 51	(1) EUS: 86.4%; and (2) PTC: 100%	(1) EUS: 86.4%; and (2) PTC: 92.2%	(1) Overall: 18.2% *vs* 39.2%; and (2) Reintervention: 15.7% *vs* 80.4%
Bapaye *et al*[55], 2013	(1) Retrospective, single center; and (2) Inaccessible papil	Unresectable	(1) Total: 51; (2) EUS: 25; and (3) PTC: 26	(1) EUS: 92%; and (2) PTC: 46%	(1) EUS: 92%; and (2) PTC: 46%	Overall: 20% *vs* 46%
Artifon *et al*[54], 2012	(1) Prospective, randomized; and (2) Failed ERCP	Unresectable	(1) Total: 25; (2) EUS: 13; and (3) PTC: 12	(1) CDS: 100%; and (2) PTC: 100%	(1) CDS: 100%; and (2) PTC: 100%	Overall: 15.3% *vs* 25%

EH: Extrahepatic; IH: Intrahepatic; AG: Antegrade; CDS: Choledochoduodenostomy; HGS: Hepaticogastrostomy; RV: Rendezvous; GG: Gastro-gallbladder; HES: Hepaticoesophageostomy; SEMS: Self-expandable metal stent.

guided BD with ERCP were published. All of them described similar technical success rates and clinical outcomes. Paik *et al*[5] found lower rate of adverse events in the EUS-guided BD group, including post-procedural pancreatitis. This study did not exclude patients with duodenal obstruction or altered anatomy and also performed EUS-HGS. The study demonstrated a lower need for reintervention and higher rate of stent patency in the EUS-guided BD group. The latter finding was attributed to lower risk of tumor ingrowth and/or overgrowth with transmural stenting bypassing the site of malignancy[5]. Bang *et al*[6] and Park *et al*[7] reported similar rates of adverse events, reinterventions and stent patency. In the EUS-guided BD group stent occlusion was commonly caused by migration[63] or food impaction[6]. Paik *et al*[5] reported that the median procedure time and length of hospital stay was shorter with EUS-BD. Park *et al*[7] found no difference in procedure time between the techniques.

Taking these studies together it would be reasonable to consider EUS-BD as the primary biliary drainage approach in certain situations where the risk of ERCP failure or adverse events is substantial.

Benign biliary obstructive disease

The first report on EUS-BD for benign biliary obstructive disease was published in 2005[64]. In this report, a "neopapilla" was created under endoscopic ultrasound guidance near to the original papilla to extract bile duct stones. After this report, several case series describing the EUS-ERCP rendez-vous technique included patients with benign diseases such as bile duct stones or ampullary stenosis[26,65,66]. A

Table 3 Studies comparing primary endoscopic ultrasound-guided biliary drainage and endoscopic retrograde cholangiopancreaticography

First Author, Yr	Type of study	Type malignant obstruction	Number patients	Technical Success rate	ClinicalSucess rate	Adverse events; EUS *vs* ERCP
Paik *et al*[5], 2018	Prospective randomized multicenter	Unresectable; Distal	Total: 125; CDS: 32; HGS: 32; ERCP: 61	EUS: 93.8%; CDS: 90.6%; HGS: 96.9%; ERCP: 90.2%	EUS: 90.0%; ERCP: 94.5%	Overall: 6.3% *vs* 19.7%; Pancreatitis: 0% *vs* 14.8%; Reintervention: 15.6% *vs* 42.6%; Stent patency: 85.1% *vs* 48.9%
Bang *et al*[6], 2018	Prospective randomized single center	Pancreatic cancer; Distal	Total: 67; CDS: 33; ERCP: 34	CDS: 90.9%; ERCP: 94.1%	CDS: 97%; ERCP: 91.2%	Overall: 21.2% *vs* 14.7%; Reintervention: 3.0% *vs* 2.9%
Park *et al*[7], 2018	Prospective randomized single center	Unresectable; Extrahepatic; Distal	Total: 30; CDS: 15; ERCP: 15	CDS: 92.8%; ERCP: 100%	CDS: 100%; ERCP: 92.8%	Overall: 0% *vs* 0%; Stent dysfunction: 15.4% *vs* 30.8%
Kawakubo *et al*[63], 2016	Retrospective single center	Distal	Total: 82; CDS: 26; ERCP: 56	CDS: 96.2%; ERCP: 98.2%		Overall: 26.9% *vs* 35.7%; Pancreatitis: 0% *vs* 16.1%; Reintervention (1 yr): 16.6% *vs* 13.6%

CDS: Choledochoduodenostomy; HGS: Hepaticogastrostomy; SEMS: Self-expandable metal stent.

hepaticogastrostomy has been proposed as a technique to obtain biliary access for antegrade interventions (stone extraction, dilatation of the bilioenteric anastomosis, *etc*.) in patients with surgically altered anatomy (roux-en-y gastric bypass, Whipple intervention, *etc*.)[67,68].

COMPLICATIONS

Despite the fact that procedure-related complications of EUS-BD appear to be lower than for PTBD and potentially also than for ERCP in selected indications (see above), it remains an invasive procedure with potentially serious adverse events. These may include a pneumoperitoneum (always perform the procedure under CO2 insufflation), bile peritonitis, biliary gastritis, haemorrhage, cholangitis, stent obstruction and (life-treatening) stent migration. Procedure-related deaths have been reported[22,69]. The adverse event rate tends to decrease with the learning curve[22]. For this reason, we believe that EUS-BD should only be performed in referral centres with high volume experience in EUS and ERCP.

CONCLUSION

In patients with malignant bile duct obstruction, EUS-BD is a viable option in cases where ERCP has failed, in the context of surgically altered anatomy or in patients with an inaccessible papilla due to tumoral invasion. Based on the results of three randomized studies, EUS-BD might be a reasonable alternative to ERCP as the first-line procedure in patients with distal malignant bile duct obstruction.

The role of EUS in establishing biliary drainage where obstruction is due to a benign aetiology is rather limited (less than 5% in most case series)[22]. A rendez-vous approach can be particularly useful in patients with an accessible duodenum in whom the papilla cannot be identified or cannulated (*e.g*., in the case of a large duodenal diverticulum). Temporary transmural drainage with a choledochoduodenostomy or hepaticogastrostomy and subsequent antegrade treatment after the fistula tract has matured has been described (especially in patients with altered anatomy due to previous surgery) but should be reserved for cases in which less invasive alternatives have failed.

In Figure 2, we propose a practical flowchart that suggests roles for EUS-BD within the current management algorithm of benign and malignant biliary obstruction.

Given the development of EUS-BD over the last few years, it is anticipated that novel dedicated endoscopic devices and tools will be released. New LAMS allowing

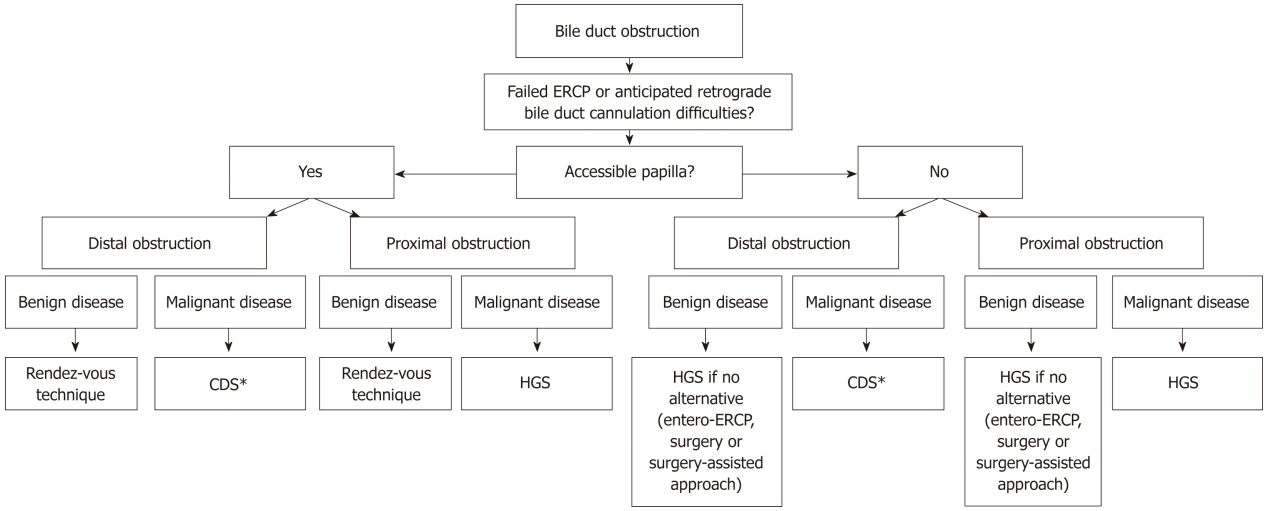

Figure 2 Proposed algorithm that positions endoscopic ultrasound-guided biliary drainage in the current management of biliary obstructive disease. *The choledochoduodenostomy can be combined with a duodenal stent or an endoscopic gastrojejunostomy if indicated. CDS: Choledochoduodenostomy; HGS: Hepaticogastrostomy; ERCP: Endoscopic retrograde cholangiopancreaticography.

puncture, tract dilatation and stent delivery in one step, provide significant advantages over needle/guidewire/dilation and stent delivery techniques. A steerable wire specifically designed for EUS-BD is being developed (oral communication, Boston Scientific, Massachusetts, USA). A 4 cm partially covered stent for CDS is expected mid 2019 (oral communication, Taewoong Medical, South Korea). A one-step dedicated stent introducer with a push-type dilator without the need for pre-dilatation or use of electrocautery has recently been described and will, when it becomes available, further facilitate EUS-guided transmural biliary drainage[5].

Future studies should address whether EUS-BD should be the first-line therapy (rather than ERCP or PTBD) in patients with malignant bile duct obstruction with preserved left-right intrahepatic bile duct communication.

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MINIREVIEWS

Spectrum of gastrointestinal involvement in Stevens - Johnson syndrome

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Abstract

Stevens - Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is a severe adverse drug reaction associated with involvement of skin and mucosal membranes, and carries significant risk of mortality and morbidity. Mucus membrane lesions usually involve the oral cavity, lips, bulbar conjunctiva and the anogenitalia. The oral/anal mucosa and liver are commonly involved in SJS or TEN. However, intestinal involvement is distinctly rare. We herein review the current literature regarding the gastrointestinal involvement in SJS or TEN. This review focuses mainly on the small bowel and colonic involvement in patients with SJS or TEN.

Key words: Stevens - Johnson syndrome; Toxic epidermal necrolysis; Lyell's syndrome; Gastrointestinal involvement; Colon; Ileum

Core tip: The oral/anal mucosa and liver are commonly involved in Stevens -Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). However, intestinal involvement is distinctly rare. We herein review the current literature regarding the gastrointestinal (GI) involvement in SJS or TEN. The extent of the GI involvement, clinical presentations, endoscopic and histopathological features, treatment options, and prognosis are described in this article.

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INTRODUCTION

Stevens - Johnson syndrome (SJS) comprises a widespread, cutaneous eruption with features resembling erythema multiforme in combination with constitutional symptoms such as fever and malaise, and mucosal lesions classically affecting the eyes, mouth, and genitalia[1]. Toxic epidermal necrolysis (TEN) is defined by involvement of at least 30% of total body surface area (TBSA) of the skin, and frequently involves at least two mucus membranes[2]. The skin involvement in SJS and SJS/ TENS overlap is < 10% and 10%-30% of TBSA, respectively. Fuchs syndrome or atypical SJS a very rare entity is defined as SJS-like mucositis without skin involvement[3].

Extracutaneous manifestations of the SJS or TEN can occur and may involve the conjunctiva, buccal mucosa, trachea, gastrointestinal (GI) tract, and genitourinary tract. Mucus membrane lesions usually involve the oral cavity, lips, bulbar conjunctiva and the anogenitalia. The mucosal lesions may go parallel, may follow or even precede the rash[4,5]. We herein review the current literature regarding the GI involvement in SJS or TEN. This review focuses mainly on the small bowel and colonic involvement in patients with SJS or TEN, which are distinctly rare.

ETIOPATHOGENESIS

SJS or TEN have been postulated to be a hypersensitivity reaction triggered by a variety of stimuli[4,6]. The most common precipitants are drugs followed by infections with mycoplasma, herpes and cytomegalo virus[7]. Beta lactam/sulfonamide antibiotics, NSAIDs (diclofenac, ketorolac, sulindac, piroxicam, and oxyphenbutazone), chlormezanone, and aromatic anticonvulsant are the most common drugs responsible for SJS or TEN.

The pathogenesis of SJS or TEN appears to be an immune mediated process. Damage of keratinocytes and mucosal epithelium is mediated by a cell-mediated and cytotoxic immune process. Activated T-cells stimulate extensive apoptosis by direct cell-cell interactions (*via* CD95 and Fas ligand-mediated signaling pathway), and by secretion of factors such as perforin, granulysin and cytokines (TNFa)[8-10]. The skin and other tissues appears to be affected by common mechanism of the Fas-ligand and the perforin-granulysin pathways. The mechanism by which SJS or TEN affects the intestine is identical to one that causes skin lesions. The pathologic features of both the skin and GI lesions are similar to acute graft-*vs*-host disease such as full-thickness epithelial necrosis and detachment, epithelial crypt cells necrosis, and a relative sparing of lamina propria. However, lymphomononuclear cell infiltrations of lamina propria can be present in some patients[11,12]. The colonic mucosa is found to constitutively express CD95[13]. The mechanism of delayed and/or persistent intestinal inflammation is not clear.

SPECTRUM OF GASTROINTESINAL INVOLVEMENT

Extent of Disease

GI complications are not uncommon in SJS or TEN and are usually mild. Some of the GI manifestations can be observed in about 10% of patients with SJS or TEN[4,14]. Severe GI involvement of SJS or TEN is rare but potentially life-threatening. In a study by Yamane *et al*[14], GI involvement noted in 9 (10%) of patients with SJS or TEN (n = 87). Common GI symptoms were diarrhea, intestinal bleeding, and severe appetite loss. One patient was expired due to perforation of intestine, DIC and pneumonia[14]. The oral/anal mucosa and liver are frequently involved in patients with SJS or TEN[14,15]. Esophageal involvement in patients with SJS or TEN is not so rare. Esophageal ulcer and chronic esophageal stricture formation have been described in SJS or TEN[16-20]. Small bowel and colonic involvement are distinctly rare. We were able to find detailed reports of about 25 cases [age (range) 8-81 years; male: female ratio of

7:18] of SJS or TEN with GI involvement (Table 1 and Table 2)[11,12,21-39]. Details of patients with small bowel and colonic involvement are summarized in Table 2. Small bowel and colonic lesions are often associated with lesions in the other parts of GI tract. Isolated involvement of the small bowel and colon does occur but is quite uncommon. The "skip" involvement of the GI tract has been described in SJS or TEN with the distal stomach and small and/or large bowel involvement, and sparing of the esophagus and proximal stomach[37].

Clinical presentation

GI manifestations usually reveals within two weeks of cutaneous lesions, but it can present many weeks after initial cutaneous symptoms. Symptoms may persist for months after disappearance of skin lesions, and duration of as long as 9 mo have been described (Table 1 and Table 2). Passage of a tubular mass of necrotic epithelium and fibrinous exudates in the stool was reported after 25 d of skin lesion[35].

The usual presenting symptoms include GI bleeding (hemetemesis, melena, and hematochezia), diarrhea, abdominal pain, abdominal distension and dysphagia. Diarrhoea is usually profuse and watery. Patients may also present with blood mixed in with the stool. Inflammation of GI tract such as esophagitis, gastritis, duodenitis, jejunitis, ileitis and colitis are common GI lesions (60%). Ulcers in the colon, small bowel, esophagus and stomach are responsible for GI bleeding in these patients (36%). Patients can be diagnosed with ulcers in multiple locations. Large bowel is most common site of ulcer followed by small bowel and stomach. Intestinal perforation and strictures (single or multiple) have been reported in three (12%) and two (8%) patients, respectively. Mesentric ischaemia, intestinal infarction, intraabdominal abscess, ileoileal intussusceptions, and subacute intestinal obstruction (one patient each) have also been described in SJS. Patients can also presents with protein-losing enteropathy, malabsorption syndromes, and hypoalbumenia. Evaluation of a patient presented with diarrhea, protein-losing enteropathy and malabsorption syndrome revealed multiple ileal strictures, pseudodiverticular sacs and pseudomembranes formation. Stricture, intestinal wall edema, intussusception and luminal stenosis caused by erosion and sublation of intestinal mucosa are the reasons for intestinal obstruction in these patients[31,36,39]. Laprotomy and necropsy of a patient presented with subacute intestinal obstruction showed hemorrhage, petechie, ecchymosis, and congestion in the stomach, small bowel, proximal large bowel and gall bladder[39]. Heye *et al*[40] showed an association between perforation of sigmoid diverticulitis and SJS, though the casual relationship was unclear.

SJS or TEN is mostly treated with prolonged antibiotic course and immunosuppressive drugs and the GI symptoms may appear late in the course of illness. The differential diagnosis in such clinical scenario often includes infective colitis especially viral, antibiotic associated diarrhea, pseudomembranous colitis and first episode of inflammatory bowel disease.

Endoscopic and histopathological features

There are various endoscopic findings observed in patients with SJS/TEN. These include the hyperemia, erythema, congestion, friability, erosions, superficial or deep ulcerations and necrotic plaque formation with mucosal sloughing (Figure 1) (Table 1). Ulcer may be irregular, friable and covered with white fibrin-like exudates[21]. Whitish plaques and pseudomembrane formation over the damaged mucosa are the other endoscopic findings in SJS or TEN. Although colonic pseudomembrane has not been reported yet, ulcerations with adherent pseudomembrane have been described in the esophagus and ileum[16,36].

Histopathological (HPE) features of biopsy or autopsy specimen include mucosal ulceration with epithelial necrosis and lymphomononuclear cell infiltrations in early stage, and severe necrotic ulcerations, lymphomononuclear infiltration of the lamina propria and inflamed granulation tissue, later in the course[11,12,37]. Lamina propria is relatively spared in these patients. HPE of healing colonic ulcer showed marked crypt architectural distortion and significant crypt loss, suggesting injury to the crypt stem cell population[21].

HEPATIC AND PANCREATIC MANIFESTATIONS

Hepatic complications of SJS or TEN includes asymptomatic hepatic enzymes elevation, hepatitis, cholestastic hepatitis, and hepatic failure. In a study by Yamane *et al*[14], hepatitis was the most common complication in seen in 47% of patients with SJS or TEN. Cholestatic liver disease, which may precede the skin manifestations of SJS or TEN, has been reported in nearly 12 cases of SJS or TEN[41-45]. Acute liver failure also has been described in association with SJS or TEN; however the exact casual

Table 1 Reported cases of Stevens - Johnson syndrome or toxic epidermal necrolysis with gastrointestinal involvement

Ref.	Age (yr), Sex	TBSA (%)	GI Symptoms	Extent of GI involvement/Complications	Treatment	Outcome
[21]	71, F	30	GI bleed, D	(1) Ileus, Intraabdominal abscess, Jejunal perforation, Gastiric/colonic ulcer; (2) LA grade C esophagitis	(1) Steroid, IVIg; (2) Plasmapheresis; (3) Surgery	Survived (LOS-2 mo)
[14]	74, M	40	-	Intestinal perforation	Steroid, IVIg	Expired (after 31 d)
[22]	44, F	0	GI bleed	Gastric/rectal erosions	Steroid	Survived (LOS-31 d)
[23]	62, F	> 30	AP, V	Intestinal infarction	Intestinal resection	Expired (after few days)
[24]	28, M	90	AD	Mesentric ischaemia	(1) IVIg; (2) Jejeunal-ileal resection	Survived (LOS-10 d)
[25]	56, F	60	D, Hypoalbumenia	Esophageal/duodenal/ileocolonic erosions	Steroid, IVIg, TPN	Survived
[26]	61, F	-	Odynophagia, GI bleed	Esophageal/recto-sigmoid ulcers	Steroid	Survived (LOS-1 mo)
[27]	23, M	-	AP,D, GI bleed	Colonic ulcers	Steroid, Probiotics	Survived (DOI-2 mo)
[28]	8, M	40	V, AD, D	Ileoileal intussusception	Surgery	Survived (LOS-15 d)
[29]	71, F	95	AD, D, GI bleed	Esophageal/gastric/sigmoid colonic erosions	IVIg	Expired (after 24 h)
[30]	30, F	61	D, GI bleed	Jejunal/colonic ulcers	Steroid, TPN, PE	Survived (DOI-5 mo)
[31]	52, F	> 30	D, GI bleed	Ileocolonic stenosis	Ileo-cecal resection	Survived
[32]	17, M	73	D, GI bleed	(1) Microscopic duodenitis; (2) Ileocolonic ulcerations	Steroid, TPN, EN, Probiotics	Survived (DOI-6 mo)
[33]	62, M	70	Massive GI bleed	Confluent esophago-gastroduodenal ulceration	Steroids	Expired (after 21 d)
[34]	81, F	40	Jaundice	Mucosal erosions in upper GI tract	IVIg	Survived (LOS-14 d)
[35]	46, F	> 75	D, GI bleed	Mucosal sloughs/ulcers (autopsy)	Steroids, Cyclophosphamide	Expired (LOS-9 mo)
[36]	48, F	40	D, malabsorption, protein-losing enteropathy	(1) Gastritis; (2) Multiple ileal strictures; (3) Multiple pseudodiverticular sacs; (4) Pseudomembranes formation	TPN, Ileal resection	Survived (LOS > 9 mo)
[12]	69, F	37	AP, GI bleed	(1) Sigmoid colon ulcers; (2) Perforations (sigmoid colon, cecum); (3) Ileal necrosis	Steroids, Ileal resection/colectomy	Survived (LOS-5 mo)
[11]	4 cases (mean 42 (3F:1M)	Mean 37	AP and GI bleed in all	(1) Duodenitis (2 cases); (2) Oesophagitis (1 case); (3) Procosigmoiditis (4 cases); (4) Jejunoileal involvement (1 case)	Ileal resection (1case)	Expired (3 cases), Survived (1 case)

[37]	41, F	> 70	AP, D, GI bleed	(1) Gastroduodenitis; (2) Sigmoiditis	Steroid	Expired (after 15 d)
[38]	53, F	> 75	AP, D	Small bowel ulcers	Steroid	Expired (after 17 d)
[39]	48, F	-	AP, D, GI bleed	Subacute intestinal obstruction	Steroid	Expired (after 8 hrs)

TBSA: Total body surface area; GI: Gastrointestinal; M: Male; F: Female; TPN: Total parenteral nutrition; LOS: Length of stay; D: Diarrhea; V: Vomiting; AP: Abdominal pain; AD: Abdominal distension; IVIg: Intravenous immunoglobulin; PE: Plasma exchange; EN: Enteral nutrition; DOI: Duration of illness.

relationship was not established[46].

Pancreas involvement is rarely described in patients with SJS or TEN. A few cases of asymptomatic pancreatic enzymes elevation and acute pancreatitis are described in SJS or TEN[47-49]. In a study by Dylewski *et al*[47], enteral nutrition was tolerated by all patients of TEN with asymptomatic pancreatic enzymes elevation. Therefore, in the absence of symptomatic pancreatitis, patients with SJS or TEN can be supported with enteral nutrition[47].

MANAGEMENT

Treatment of SJS or TEN is still controversial. Withdrawal of offending drugs and admission in a burn intensive care unit is recommended. Disease severity and prognosis can be assessed with the SCORTEN criteria[50].The treatment of SJS or TEN is largely supportive. Supportive care include the management of airway, fluid and electrolyte balance, monitoring of renal function, nutritional supplementation, adequate analgesia, care of skin and mucosal surfaces, and prevention of infection. Currently used medical therapy comprised of systemic corticosteroids, intravenous immunoglobulins (IVIg), cyclosporine, plasmapheresis, plasma exchange, antitumor necrosis factor drugs and N-acetylcysteine, but none has been established as the most effective therapy. Systemic steroids are used as standard of care for treatment of SJS or TEN. A few case series have reported favorable outcomes in patients treated with corticosteroids and immunoglobulin[8,51,52]. But, data does not support use of steroid as sole therapy, and are no longer recommended[53]. A meta-analysis showed no survival benefit among SJS or TEN patients treated with intravenous immunoglobulin[54].

Patients of SJS or TEN with GI involvement may be treated conservatively or may require surgery. Conservative treatment consists of supportive measures, systemic steroids, intravenous immunoglobulin, probiotics, plasma exchange, and supplemental nutrition. Role of steroid in patients with SJS or TEN with GI involvement is trickier. Steroids may exacerbate mucosal sloughing, GI bleeding and perforation in SJS or TEN. Huang *et al*[54] showed decreased rates of GI complications of SJS or TEN after steroids were removed from their treatment protocol. Therefore, the choice of treatment depends on the available guidelines and the experience of the treating physician. A multidisciplinary approach is warranted, and treatment should be determined on an individual basis. Out of 25 patients, surgery was performed in eight (32%) cases. It is worth mentioning that in the patients who required a surgical intervention (8 patients) for GI manifestations, all but one patient was survived (Table 1).

PROGNOSIS

Patients with SJS or TEN and intestinal involvement have a poor prognosis. Nearly half (44%) of reported cases had fatal outcome (Table 2). Patients who survived have increased risk of late GI complications. These include strictures of the esophagus, ileum and anal canal as well as ileal pseudodiverticulae[15,17,36].

CONCLUSION

GI complications are not uncommon in SJS or TEN and are usually mild. Severe GI involvement of SJS or TEN is rare but potentially life-threatening. GI manifestations usually reveal within two weeks of cutaneous lesions, but these symptoms may be delayed. These patients may be treated conservatively or may require surgery. The conservative treatment is mainly supportive and current data does not support use of steroid or IVIg. A multidisciplinary approach is warranted and treatment should be

Table 2 Spectrum of gastrointestinal involvement in Stevens - Johnson syndrome or total parenteral nutrition

Total reported cases	25
Age (range)	8-81 yr
M:F (ratio)	7:18
TBSA (%)	0%-95% (all patients except one had > 30% of skin involvement)
Time of appearance of GI symptoms	0 wk-7 wk (usually within two weeks) after appearance of rash/mucosal lesions
Chief symptoms	GI bleeding-17 (68%) Diarrhoea-13 (52%) Abdominal pain-10 (40%) Abdominal distension-3 (12%) Vomiting-2 (8%)
Complications/ Extent of GI involvement	Luminal erosions/inflammation-15 (60%) Ulcer (Single or multiple)-9 (36%) [Large bowel (6). Small bowel (3), Esophageal (3), Gastric (2)] Perforation-3 (12%) (small bowel/colon) Strictures-2 (8%) (ileal/ileo-colonic) Mesentric ischaemia/ Intestinal infarction/ Ileoileal intussusceptions,/ Pseudodiverticular sacs/ Intraabdominal abscess,/ Pseudomembranes formation/ Subacute intestinal obstruction-One each Malabsorption/ Hypoalbumenia/ Protein-losing enteropathy- One each
Treatment	Medical [Steroids (14), IVig (4), TPN (4), Probiotics (2), PP (1), PE (1), EN (1)] Surgery-8 (32%)
Outcome	Survived- 14 (56%) [LOS (range)- 10 d -9 mo, DOI (range)-1-6 mo] Expired-11 (44%)

TBSA: Total body surface area; GI: Gastrointestinal; M: Male; F: Female; TPN: Total parenteral nutrition; LOS: Length of stay; IVIg: Intravenous immunoglobulin; PE: Plasma exchange; EN: Enteral nutrition; DOI: Duration of illness.

determined on an individual basis.

FUTURE DIRECTIONS

Pathogenesis of SJS or TEN is still not clear. Mechanism of patchy/skip involvement of GI tract are unknown. Better understanding of pathogenesis may help to develop a new and effective therapy for this dangerous disease. Because of rarity of disease, the randomized controlled trials regarding the efficacy of various drugs are difficult to perform. Therefore, multicentre randomized controlled trials are warranted to compare the efficacy of available treatment options.

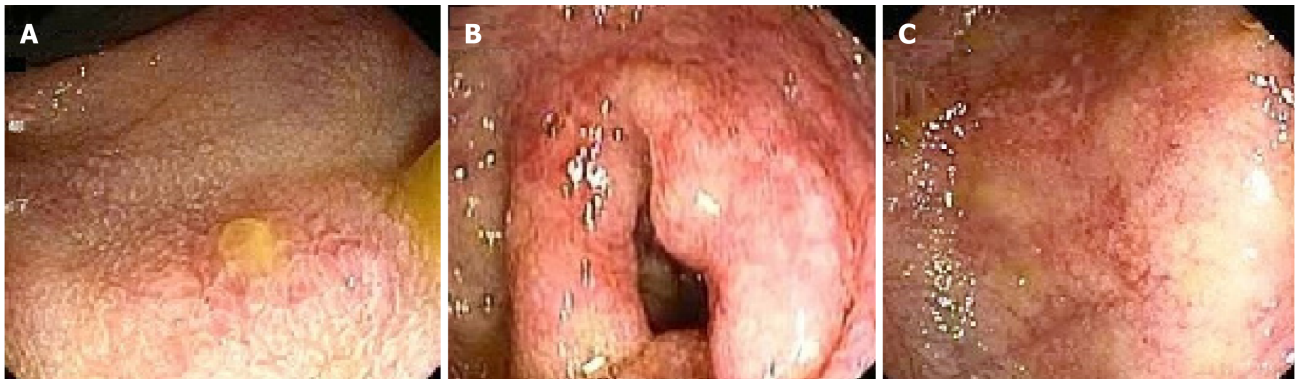

Figure 1 Colonoscopy images. A-C: Colonoscopy images showing erythema, congestion and exudates.

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ORIGINAL ARTICLE

Retrospective Cohort Study

No significant difference in clinically relevant findings between Pillcam® SB3 and Pillcam® SB2 capsules in a United States veteran population

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Author contributions: Aasen T designed the research; Aasen T, Wilhoite D, Rahman A, Devani K performed the data collection; Aasen T, Devani K performed the statistical analysis; Young M, Swenson J participated in project guidance and supervision; Aasen T wrote the paper.

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Abstract

BACKGROUND

Capsule endoscopy (CE) allows for a non-invasive small bowel evaluation for a wide range of gastrointestinal (GI) symptoms and diseases. Capsule technology has been rapidly advancing over recent years, often improving image frequency and quality. The Pillcam® SB3 (SB3) capsule is one such technology that offers an adaptive frame rate advantage over the previous versions of the capsule the Pillcam® SB2 (SB2). Some have proposed that this improvement in capsule technology may lead to increased diagnostic yields; however, real world clinical data is currently lacking.

AIM

To evaluate the clinically relevant findings of SB3 and SB2 capsules in a population of United States veterans.

METHODS

A retrospective analysis of 260 consecutive CE studies was performed including 130 SB3 and 130 SB2 capsule studies. Recorded variables included: age, gender, type of capsule, body mass index, exam completion, inpatient status, opioid use, diabetes, quality of preparation, gastric transit time, small bowel transit time, indication, finding, and if the exam resulted in a change in clinical management. The primary outcome measured was the detection of clinically relevant findings between SB3 and SB2 capsules.

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RESULTS

Mean age of the study population was 67.1 ± 10.4 years and 94.2% of patients were male. Of these 28.1% were on opioid users. The most common indications for capsule procedure were occult GI bleeding (74.6%) and overt GI bleeding (14.6%). Rates of incomplete exam were similar between SB3 and SB2 groups (16.9% *vs* 9.2%, $P = 0.066$). The overall rate of clinically relevant finding was 48.9% in our study. No significant difference was observed in SB3 *vs* SB2 capsules for clinically relevant findings (46.2% *vs* 51.5%, $P = 0.385$) or change in clinical management (40.8% *vs* 50.0%, $P = 0.135$).

CONCLUSION

Our study found no significant difference in clinically relevant findings between SB3 and SB2 capsules.

Key words: Capsule Endoscopy; Veterans; Retrospective studies; Capsules; Gastrointestinal diseases; SB3; SB2

Core tip: Capsule endoscopy is a commonly employed diagnostic procedure to evaluate a variety of gastrointestinal symptoms and diseases. The Pillcam® SB3 is a commonly used capsule that has largely replaced previous versions of the capsule. Data evaluating the effect of improvements in capsule technology on diagnostic yields is limited, particularly in the veteran population. This paper compared the diagnostic yields between Pillcam® SB3 and Pillcam® SB2 capsule groups amongst United States veterans and no significant difference in clinically relevant findings or change in clinical management was observed. Further prospective research is warranted to confirm the results of our study.

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INTRODUCTION

Capsule endoscopy (CE) offers a non-invasive form of small bowel evaluation for a variety of gastrointestinal (GI) symptoms and diseases[1,2]. Common indications for CE include the evaluation obscure GI bleeding, suspected or known Crohn's disease, surveillance of polyps or masses, and evaluation of suspect malabsorption syndromes[1,2]. Since the first wireless capsule was approved for use in 2001, multiple capsule enhancements and upgrades have been made in attempt to improve diagnostic accuracy and expand the clinical indications of CE[3,4].

Several commercial CE products are currently available and the preference of capsule often is determined by institutional policy and price; however, the Pillcam® SB3 (SB3) (Medtronic, Minneapolis, MN, United States) is currently one of the most widely used capsules[5]. Over time, advances in capsule technology have aimed to improve image capture quality, battery life, viewing angle, and rate of image capture[3-5]. In 2013, the SB3 capsule was introduced and it has largely replaced the previous version of the capsule Pillcam® SB2 (SB2) in clinical practice. The SB3 capsule offers an adaptive framerate technology which adjusts the image capture rate based on how fast the capsule is moving[6]. Additionally, in a clinical validation study, images from the SB3 capsule were rated superior to the SB2 capsule by physicians[7]. Some have proposed that this improvement in capsule technology may lead to increased diagnostic yields; however, real world clinical data is currently lacking[8]. Small studies evaluating diagnostic yields between SB3 and SB2 capsules have had mixed results, with some suggesting an improvement in diagnostic yield and others showing no benefit[9-11]. Additionally, limited data exists evaluating if capsule upgrades will alter clinical management. Data specific to the veteran population is particularly limited. This study aimed to evaluate the clinically relevant findings of SB3 and SB2 capsules in a population of United States veterans.

MATERIALS AND METHODS

Study population

This was a retrospective study conducted at the Mountain Home Veterans Affairs Medical Center after obtaining institutional review board approval. The study period included patients undergoing CE from January 2014 to January 2017. All patients undergoing CE during the study period were included. During the study period from January 2014 through December 2015, the SB2 capsule was being utilized at our institution while from December 2015 through January 2017 the SB3 capsule was being used. A total of 130 SB3 and 130 SB2 capsule studies were included. No studies were excluded. There was no financial support for this study.

Variables and outcomes

Charts were retrospectively accessed and pertinent demographic and study characteristics were recorded. Recorded patient demographics included age, gender, body mass index (BMI) and comorbidities such as history of diabetes and current opioid use. CE related variables such as indication, finding, exam completion, inpatient status, quality of preparation, gastric transit time (GTT), small bowel transit time (SBTT) were recorded. Incomplete CE examination was defined as the failure of the capsule to reach the cecum within the recording period of the study. Capsule retention was defined as evidence of capsule persistence within the body two weeks after capsule ingestions. Indications for the procedure were recorded as occult GI bleeding, overt GI bleeding, polyp or mass evaluation, inflammatory bowel disease, or other indication. Iron deficiency anemia and occult positive stool samples were included in the occult GI bleeding indication group. Clinically relevant capsule findings included the following categories: Evidence of inflammatory bowel disease, polyps/masses, and identification of a bleeding source. Findings of ulcerative disease, erosive disease, arteriovenous malformations, and gross blood in the lumen were considered positive for bleeding source identification. The primary outcome of the study was to evaluate clinically relevant findings in SB3 and SB2 capsule groups. The secondary outcome aimed to analyze if the capsule procedure resulted in a change in clinical management. A change in clinical management following the CE study was defined as those studies that lead to the ordering of an endoscopic procedure, ordering of a diagnostic study, or an addition or change of dose in the patient's medication regimen.

Capsule procedure

Standard preparation for CE at our institution included 2 liters of polyethylene glycol solution the evening before the procedure and 160 milligrams of simethicone one hour prior to capsule ingestion the morning of procedure. Patients were instructed to eat nothing by mouth starting midnight prior to procedure. After capsule ingestion patients could begin clear liquids two hours post ingestion and could eat a regular diet four hours after capsule ingestion. The capsule studies were read by gastroenterology fellows under the supervision of an experienced attending physician with expertise in CE. Studies were read using RAPID® Reader software. The preparation was considered to be inadequate if less than 50% of the small bowel was seen during the study.

Statistical analysis

Continuous variables were reported as means ± standard deviation. Categorical variables were reported as frequencies and their respective percentage. Unpaired *t*-test was used for normally distributed continuous variables and Mann-Whitney test for non-normally distributed continuous variables. For categorical variables, Pearson Chi Square was used or Fischer Exact Test when appropriate. Statistical significance was defined as two-tailed P value < 0.05. Statistical calculations were performed using GraphPad software under the guidance of a biostatistical expert.

RESULTS

Total of 260 patients undergoing consecutive CE studies were included during the study period. Of these, 130 patients utilized Pillcam® SB3 capsules and another 130 used Pillcam® SB2 capsules. Baseline characteristics of the patient population are as shown in Table 1. Overall mean age of the veterans included was 67.1 ± 10.4 years 94.2% of the patients were male. Mean BMI of the study population was 30.3 kg/m^2, 45.85% of patients were diabetic, and 28.1% were on opioid therapy. Incomplete capsule exams occurred in 13.1% of examinations, and inadequate preparation was seen in 12.7% of studies.

Table 1 Baseline demographics

	Total	Pillcam® SB3	Pillcam® SB2	*P* value
Patients	260	130	130	
Age (yr)	67.1 ± 10.4	68.3 ± 11.1	65.9 ± 9.5	0.061
Male gender	245 (94.2%)	122 (93.8%)	123 (94.6%)	0.790
BMI (kg/m^2)	30.3 ± 6.3	30.1 ± 6.1	30.5 ± 6.4	0.618
Inpatient status	32 (12.3%)	19 (14.6%)	13 (10.0%)	0.257
Diabetes	119 (45.8%)	69 (53.1%)	50 (38.5%)	0.018
Opioid use	73 (28.1%)	31 (23.8%)	42 (32.3%)	0.129
GTT (min)	39.6 ± 47.4	37.7 ± 40.4	41.4 ± 53.4	0.971
SBTT (min)	220.4 ± 85.7	233.1 ± 82.4	208.8 ± 87.3	0.554
Inadequate preparation	33 (12.7%)	15 (11.5%)	18 (13.8%)	0.576
Incomplete exam	34 (13.1%)	22 (16.9%)	12 (9.2%)	0.066

BMI: Body mass index; GTT: Gastric transit time; SBTT: Small bowel transit time.

No significant difference was observed in patient characteristics between SB3 and SB2 capsules for age, gender, BMI, opioid use, and inpatient status: Age (68.3 ± 11.1 *vs* 65.9 ± 9.5, $P = 0.061$), male gender (93.8% *vs* 94.6%, $P = 0.790$), BMI (30.1 ± 6.1 kg/m^2 *vs* 30.5 ± 6.4 kg/m^2, $P = 0.618$), opioid use (23.8% *vs* 32.3%, $P = 0.129$), and inpatient status (14.6% *vs* 10% $P = 0.257$). A significant difference for diabetes as a comorbidity was seen between SB3 and SB2 groups (53.1% *vs* 38.5%, $P = 0.018$). There was also no significant difference in incomplete exam and inadequate preparation between SB3 and SB2 groups: Incomplete exam (16.9% *vs* 9.2% $P = 0.066$), inadequate preparation (11.5% *vs* 13.8%, $P = 0.576$). No capsule retentions were observed and no capsule malfunctions were seen within the cohort. Mean GTT was 39.6 ± 47.4 min and mean SBTT was 220.4 ± 85.7 min for the cohort. No significant difference in GTT or SBTT was observed between SB3 and SB2 capsule groups: GTT (37.7 ± 40.4 min *vs* 41.4 ± 53.4 min, $P = 0.971$), SBTT (233.1 ± 82.4 min *vs* 208.8 ± 87.3 min, $P = 0.554$).

CE indications and findings are presented in Table 2. The most common indication for CE examination was occult GI bleeding (74.6%), followed by overt GI bleeding (14.6%), mass polyp evaluation (3.5%), inflammatory bowel disease (IBD) (2.7%), and other (4.6%). Other indications included diarrhea, celiac disease evaluation, and abdominal pain. Overall clinically relevant finding rate was 48.9% which included bleeding source identification (38.5%), mass/polyp (6.9%), and IBD (3.5%). No significant difference was observed in SB3 *vs* SB2 capsules for clinically relevant findings (46.2% *vs* 51.5%, $P = 0.385$). Additionally, 45.4% of CE studies resulted in a change in clinical management and no significant difference in changes in clinical management were seen between SB3 and SB2 capsule groups (40.8% *vs* 50.0%, $P = 0.135$).

DISCUSSION

CE has now become a routine part of clinical practice for gastroenterologists and can be used as a non-invasive means to investigate a variety of GI symptoms[1,2]. Though many capsule enhancements have been made since CE was first introduced, there is limited data to suggest that recent improvements in capsule technology enhance diagnostic yield of the examinations. Our study demonstrated no significant difference in clinically relevant findings detected between SB3 and SB2 capsules. As a secondary outcome, we also found no significant difference for changes of clinical management between the two capsule groups. This study represents one of the largest studies to evaluate clinically relevant findings between SB3 and SB2 capsules, and to our knowledge is the largest that exclusively looks at a veteran population.

Over time, multiple enhancements in capsule technology have been made; however, a clear impact on improvements in capsule technology on key clinical endpoints has not clearly been demonstrated. Improving capsule viewing angle has been investigated, including one study that showed no significant difference in diagnostic yields between SB2 capsules and a 360° viewing capsules[12]. Alternatively, Rahman *et al* studied the effect of increasing capsule battery life on diagnostic yields of CE studies and found that the Pillcam® SB2-ex (SB2-ex), which increased battery life from eight hours to twelve hours, lead to higher study completion rates when

Table 2 Indications and findings of Pillcam® SB3 *vs* Pillcam® SB2 capsule studies

	Total	Pillcam® SB3	Pillcam® SB2	*P* value
	n (%)	*n* (%)	*n* (%)	
Indication				
Occult GIB	194 (74.6)	92 (70.8)	102 (78.5)	0.154
Overt GIB	38 (14.6)	24 (18.5)	14 (10.8)	0.079
Mass/Polyp	9 (3.5)	4 (3.1)	5 (3.8)	0.999
IBD	7 (2.7)	2 (1.5)	5 (3.8)	0.447
Other	12 (4.6)	8 (6.2)	4 (3.1)	0.237
Finding				
Bleeding source[1]	100 (38.5)	47 (36.1)	53 (40.8)	0.444
IBD	9 (3.5)	3 (2.3)	6 (4.6)	0.500
Mass/Polyp	18 (6.9)	10 (7.7)	8 (6.2)	0.625
Change in clinical management	118 (45.4)	53 (40.8)	65 (50.0)	0.135
Clinically relevant finding	127 (48.9)	60 (46.2)	67 (51.5)	0.385

[1]Blood in lumen, ulcerative disease, erosive disease, arteriovenous malformation. IBD: Inflammatory bowel disease; GIB: Gastrointestinal bleeding.

compared to SB2 capsules; however, no improvement in diagnostic yield was seen with the capsule upgrade and in fact the SB2 capsule outperformed the SB2-ex for diagnostic yields in this study[13]. Given these findings, some have suggested that improving battery life may not be the key to improving diagnostic yields[8]. Alternatively, it was proposed that rapid transit times in the duodenum and jejunum may lead to missed lesions during CE; therefore, it was suggested that the adaptive frame rate of the SB3 capsule may enhance diagnostic yields[8]. The SB3 adaptive frame rate technology was designed to combat CE limitations during periods of rapid transit[6]. The SB3 capsules will perform a traditional image capture rate of two frames per second (FPS) during periods of slow transit, and image capture rates will automatically increase to six FPS during periods of rapid transit[6]. The SB3 capsule also offers superior image quality in comparison to the SB2 capsule and representative images from our cohort are presented in Figure 1[6].

In theory, improving image quality and optimizing image capture rate may improve overall quality of CE examinations and improve its clinical usefulness. The SB3 capsule has been shown to provide improved image quality over the SB2 capsule and images were preferred by gastroenterologists in a feasibility study[7]. Whether this improvement in image quality along with the adaptive frame rate technology of the SB3 capsule results in improved diagnostic yields are more uncertain. Studies have previously aimed to evaluate if SB3 capsules lead to improved diagnostic yields in comparison to SB2 capsules, though most are retrospective in nature and come with significant limitations. Dunn *et al*[9] reported increased diagnostic yields of SB3 capsules in comparison to SB2 capsules; however, their study is limited by small sample size and is only published in abstract form. Monteiro *et al*[8] reported a possible increase in diagnostic yields in favor of SB3 capsules over SB2 capsules. Likewise, the study was limited to small retrospective cohort and major duodenal papilla detection rate was used as a surrogate indicator of diagnostic yield[8]. These data were further expanded upon by the same group and Xavier *et al*[10] subsequently published the largest retrospective series comparing diagnostic yields of SB3 and SB2 capsules and found no significant difference. More recently, Kunihara *et al*[14] reported that SB3 capsules improved the detection of small esophageal varices in comparison to SB2 capsules; however, overall rate of variceal detection was not significantly different between the two capsules. In our cohort, there was no significant difference of clinically relevant findings between SB3 and SB2 capsules. These results may also be supported by previous studies that failed to establish a significant effect on diagnostic yield by increasing the FPS from 2 FPS to 3 or 4 FPS[15,16].

CE continues to play a key role in clinical practice and CE studies often provide diagnostic information and impact clinical management. Prior investigations have suggested that diagnostic yields of CE may range from 39%-69% depending on procedure indications and definitions of pertinent findings[17-20]. The overall rate of clinically relevant finding in our study was 48.9% and no difference in clinically relevant findings was observed between SB3 and SB2 groups. CE has previously been shown to significantly impact clinical management of patients undergoing the

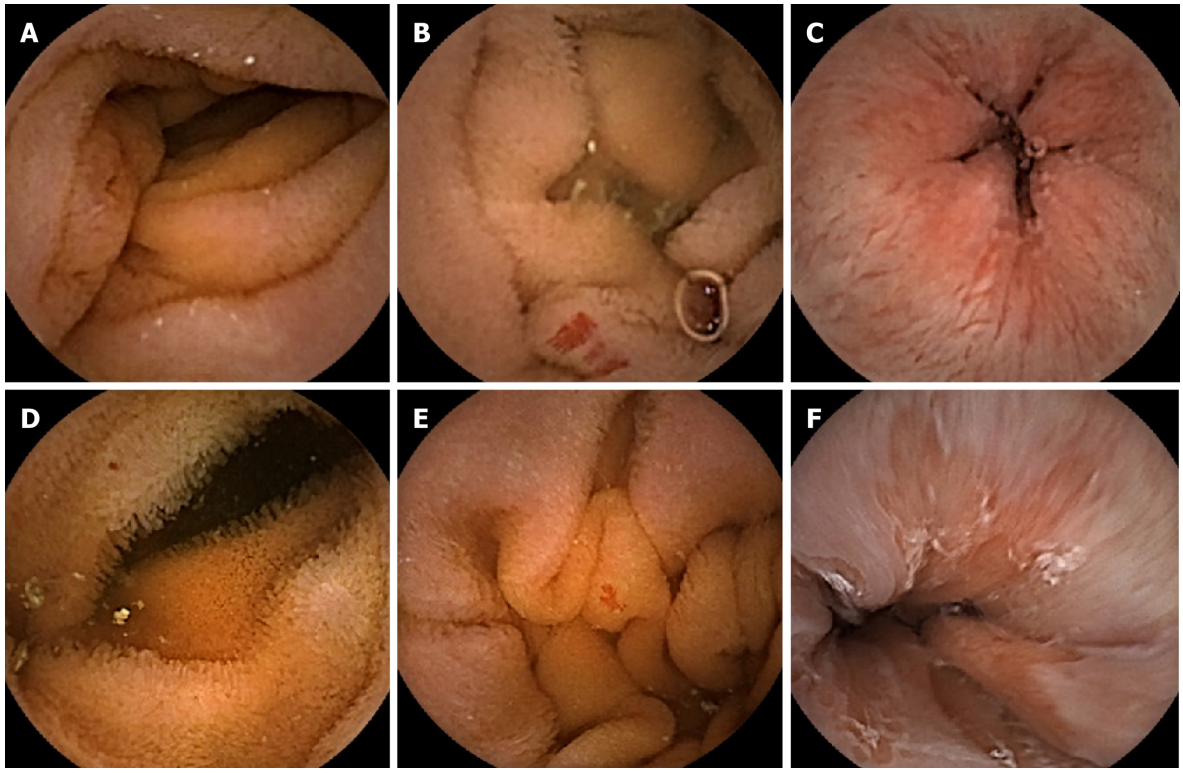

Figure 1 Image quality comparison between Pillcam® SB3 and Pillcam® SB2 capsules for selected clinical findings. A: Normal small intestinal lumen visualized with SB2 capsule; B: Vascular malformation visualized with SB2 capsule; C: Z-line visualized with SB2 capsule; D: Normal small intestinal lumen visualized with SB3 capsule; E: Vascular malformation visualized with SB3 capsule; F: Z-line visualized with SB3 capsule.

investigation, with changes in clinical management reported ranging from 26%-67%[19-22]. Our study found that 45.4% of CE studies resulted in a change in clinical management, and there was no significant difference was observed between SB3 and SB2 groups. These findings may suggest that both capsules have a strong role in clinical practice.

Our study, like others investigating this topic, is limited by the retrospective study design. Additionally, our study examined a unique population of United States veterans and may not be directly comparable to other studies investigating this area. The cohort in our study was almost entirely male (94.2%) which reflects the overall demographics of our institution. Data regarding the diagnostic yields of CE in the veteran population is extremely limited, though one study reported higher than average diagnostic yields in the veteran population[23]. The most common indication in our study was occult GI bleeding (74.6%), which represents a larger portion of studies for this indication than large CE cohorts have previously suggested[18,24]. This is likely explained by a below average use of CE for crohn's disease evaluation and management at our institution. Our study included consecutive endoscopy examinations before and after SB3 capsules became the standard capsule at our institution. Although no significant changes in how capsules were read at our institution were made during this time, it is difficult to control for variations and changes in practice patterns over time or any learning curves when the new capsule was implemented. Our CE studies were also read by trainees under the supervision of experienced providers which may introduce inter-observer variability; however, this method of reading may be reflective of real-world clinic practice. Group characteristics between SB3 and SB2 groups in our study were mostly similar, however the SB3 group had an overall higher age and great portion of patients with diabetes which previous studies have shown may potentially increase CE findings or lead to prolonged transit times[25-27]. Diabetes has been shown to be a risk factor for poor colon preparations, though the effects of diabetes on CE preparation are poorly characterized[28]. Likewise, our study included a large percentage of current opioid users at 28.1%; however opioid use has not clearly been shown to be associated with altered exam completion rates or diagnostic findings[29,30].

The failure of our study to show a significant improvement in clinically relevant findings between SB3 and SB2 capsules may potentially suggest that there is a plateau of diagnostic yield during CE studies. There is a possibility that the adaptive frame rate technology of the SB3 capsule may lead to the detection of non-clinically relevant

findings, or that the improved image quality of this capsule may lead to better visualization of lesions that would have still been detected by previous capsule versions. If a diagnostic yield plateau was exist, then potential cost savings may be created by using the most affordable capsule option under most circumstances. However, it remains to be seen if better capsule technology may result in improved diagnostic yields within particular subgroups of study indications; therefore, studies evaluating SB3 *vs* SB2 capsules or other similar improvements in capsule technology for more specific procedural indications may better elucidate if capsule enhancements would improve clinically relevant findings within these groups. Additionally, future investigation to evaluate the effect of capsule enhancement on diagnostic yield will be warranted. The principle indications for CE procedures in our study were primarily overt and occult GI bleeding. Future direction of research may seek to explore only these indications, and a post hoc analysis including only these principle indications may be beneficial to confirm the results obtained by the same total group. Likewise, studies investigating findings for procedures with the specific indication of IBD, polyp or mass evaluation, or other indications may be required to further evaluate the effect of capsule upgrades within these groups.

In conclusion, our study found no significant difference in clinically relevant findings between SB3 and SB2 capsules. Additionally, no significant change in clinical management was observed. Further prospective randomized research is needed to determine if this capsule improvement enhances clinical findings or impacts clinical management.

ARTICLE HIGHLIGHTS

Research background

Capsule endoscopy (CE) is frequently used in clinical practice to evaluate a wide spectrum of gastrointestinal symptoms and diseases. Capsule technology has advanced over time; however, it remains unclear if upgrades in capsule technology enhance clinically relevant findings during the procedure.

Research motivation

The Pillcam® SB3 capsule is a commonly used capsule that provides superior image quality and an adaptive frame rate advantage over the previous versions of the capsule the Pillcam® SB2. It has been proposed that these improvements may result in improved diagnostic yields of the CE study.

Research objectives

To assess clinically relevant findings of SB3 and SB2 capsules in a population of United States veterans.

Research methods

A retrospective analysis of 260 consecutive CE studies was performed including 130 SB3 and 130 SB2 capsule studies. The primary outcome measured was the detection of clinically relevant findings between SB3 and SB2 capsules. Whether the capsule study resulted in a change in clinical management was evaluated as a secondary measure.

Research results

The overall rate of clinically relevant finding was 48.9% in our study. No significant difference was observed in SB3 *vs* SB2 capsules for clinically relevant findings (46.2% *vs* 51.5%, $P = 0.385$) or change in clinical management (40.8% *vs* 50.0%, $P = 0.135$).

Research conclusions

Our study found no significant difference in clinically relevant findings between SB3 and SB2 capsules.

Research perspectives

Improvements in capsule technology should be critically analyzed to determine their impact on clinical practice. Further prospective research is warranted to confirm the results of our study.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Age, socioeconomic features, and clinical factors predict receipt of endoscopic retrograde cholangiopancreatography in pancreatic cancer

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Abstract

BACKGROUND

Endoscopic retrograde cholangiopancreatography (ERCP) is the recommended technique for biliary decompression in pancreatic cancer. Previous studies have suggested racial, socioeconomic and geographic differences in diagnosis, treatment and outcomes of pancreatic cancer patients.

AIM

To examine geographic, racial, socioeconomic and clinical factors associated with utilization of ERCP.

METHODS

Surveillance, Epidemiology and End Results and linked Medicare claims data were used to identify pancreatic cancer patients between 2000-2011. Claims data were used to identify patients who had ERCP and other treatments. The primary outcome was receipt of ERCP. Chi-squared analyses were used to compare demographic information. Trends in use of ERCP over time were assessed using Cochran Armitage test. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for receipt ERCP were calculated using logistic regression,

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controlling for other characteristics.

RESULTS

Among 32510 pancreatic cancer patients, 14704 (45.2%) underwent ERCP. Patients who had cancer located in the head of the pancreas (aOR 3.27, 95%CI: 2.99-3.57), had jaundice (aOR 7.59, 95%CI: 7.06-8.17), cholangitis (aOR 4.22, 95%CI: 3.71-4.81) or pruritus (aOR 1.42, 95%CI: 1.22-1.66) and lived in lower education zip codes (aOR 1.14, 95%CI: 1.04-1.24) were more likely to receive ERCP. In contrast, patients who were older (aOR 0.88, 95%CI: 0.83, 0.94), not married (aOR 0.92, 95%CI: 0.86, 0.98), and lived in a non-metropolitan area (aOR 0.89, 95%CI: 0.82, 0.98) were less likely to receive ERCP. Compared to white patients, non-white/non-black patients (aOR 0.83, 95%CI: 0.70-0.97) were less likely to receive ERCP. Patients diagnosed later in the study period were less likely to receive ERCP (aOR 2004-2007 0.85, 95%CI: 0.78-0.92; aOR 2008-2011 0.76, 95%CI: 0.70-0.83). After stratifying by indications for ERCP including jaundice, racial differences persisted (aOR black patients 0.80, 95%CI: 0.67-0.95, nonwhite/nonblack patients 0.73, 95%CI: 0.58-0.91). Among patients with jaundice, those who underwent surgery were less likely to undergo ERCP (aOR 0.60, 95%CI: 0.52, 0.69).

CONCLUSION

ERCP utilization in pancreatic cancer varies based on patient age, marital status, and factors related to where the patient lives. Further studies are needed to guide appropriate biliary intervention for these patients.

Key words: Pancreatic cancer; Endoscopic retrograde cholangiopancreatography; Socioeconomic disparities; Racial disparities; Jaundice; Outcomes research

Core tip: The use of endoscopic retrograde cholangiopancreatography for pancreatic cancer patients varies nationally by non-clinical factors. Further studies and guidelines are needed to guide appropriate biliary interventions for these patients.

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INTRODUCTION

Pancreatic cancer is the fourth most common cause of cancer death in the United States[1]. Endoscopic retrograde cholangiopancreatography (ERCP), especially prior to widespread use of endoscopic ultrasound (EUS), served both diagnostic and therapeutic roles in the evaluation and management of pancreatic cancer[2,3]. ERCP is recommended to relieve biliary obstruction in pancreatic cancer[3,4].

Although pancreatic cancer outcomes are poor for the general population, several studies have shown that racial and sociodemographic factors impact use of treatment and overall survival[5-12]. A recent retrospective study of the Surveillance, Epidemiology and End Results (SEER)-Medicare population found that sociodemographic factors were associated with receipt of pancreatic cancer-directed surgery, but that only geographic location was independently associated with survival[13]. Other studies suggest black patients fare worse than white patients in both utilization of pancreatic cancer treatment modalities and survival[7,10-12].

Since previous studies have demonstrated racial, socioeconomic, geographic and clinical disparities in pancreatic cancer-directed surgery, chemotherapy and radiation, we hypothesized similar variations may be seen in the use of ERCP. The aim of this study is to evaluate racial, socioeconomic, geographic and clinical factors associated with use of ERCP among patients with pancreatic cancer. A secondary outcome was

receipt of ERCP in the setting of jaundice, cholangitis or pruritus.

MATERIALS AND METHODS

Patient selection and treatment

The SEER database of the National Cancer Institute is a national registry of patients diagnosed with cancer that collects data on cancer incidence and survival[14]. This database is linked with the patient's Medicare claims from time of Medicare eligibility until death. The claims were used to identify patients' clinical and procedural data. Patients in this study population are aged 65 and older because this is the age of enrollment in Medicare coverage in the United States. Patients with secondary insurance were excluded so that all claims were captured in this dataset. Patients with primary pancreatic cancer diagnosed between 2000 and 2011 were identified; those patients with more than one primary cancer were excluded to eliminate the effect of other cancers on morbidity and mortality[15].

Sociodemographic information was obtained from both the SEER and Medicare-linked databases. Comorbid conditions were controlled for using the Deyo adaption of the Charlson co-morbidity index[16-18]. Both inpatient and outpatient hospital claims (Medicare Provider Analysis and Review, Outpatient Standard Analytical File) as well as diagnoses on claims submitted by individual physicians (Carrier file) were included[18,19].

Education and income information was obtained from census data. Patients' zip codes were cross-referenced with census data to obtain median incomes for the zip code. Similarly, zip codes and census data were used to identify the proportion of residents in the zip code who had not completed high school, graduated from high school, attained some college and graduated from college. Patient level income and education data are not available.

ERCP, surgery, chemotherapy, radiation, jaundice, pruritus and cholangitis were identified from claims data using International Classification of Disease, 9th Edition and Healthcare Common Procedure Coding System codes (Table 1)[20-23]. SEER-Medicare claims have been shown to accurately capture patients who have been treated with chemotherapy[23]. SEER historic stage was used for patient stage because American Joint Committee on Cancer stage was only available from 2004 to 2011. Patients of all stages were included in this analysis because all of these patients are evaluated for and receive these procedures.

Statistical analysis

Categorical variables were compared using chi-squared analyses to test for associations between patients' racial, socioeconomic, geographic and clinical characteristics and use ERCP. Statistical significance was noted as P value < 0.05. Trends in use of ERCP over time were assessed using Cochran Armitage test. Adjusted odds ratios and 95% confidence intervals (CIs) for receipt ERCP were calculated using logistic regression, controlling for other characteristics, including age, race, marital status, education, income, metropolitan area, region of the United States, symptoms and conditions, Charlson comorbidity scores, cancer site, stage and use of other therapies including surgery, chemotherapy and radiation. All statistical analyses were performed using SAS 9.3 and 9.4 (Cary, NC). The study was approved by both the local Institutional Review Board and the National Cancer Institute.

RESULTS

Between 2000 and 2011, a total of 32510 patients were diagnosed with pancreatic cancer and met inclusion criteria (Figure 1 and Table 2). Among these patients, 14704 (45.2%) underwent ERCP. Patients who underwent ERCP were more often younger (46.9% *vs* 43.9%, P < 0.01), married (46.3% *vs* 44.2%, P < 0.01), and white (45.8% white *vs* 42.3% of black patients *vs* 42.7% of non-white/non-black patients, P < 0.01) (Table 2). ERCP was used less often later in the study period (Table 3, Cochran-Armitage trend P < 0.01). More patients in the Northeast underwent ERCP (46.5%) compared to Southeast (45.4%), Midwest (43.3%) or West Coast (45.1%), P < 0.01 (Table 2). More patients with jaundice (78.1%), cholangitis (87.4%) and pruritus (70.8%) underwent ERCP than those without these symptoms, P for all < 0.01. Patients who underwent other cancer directed therapies including chemotherapy, radiation and surgery also received ERCP more often.

To better assess the differences in receipt of ERCP, logistic regression was used to evaluate the impact of race, sociodemographic and clinical factors (Table 4). Patients

Table 1 International Classification of Disease, 9th Edition and Healthcare Common Procedure Coding System codes for claims data

	ICD-9	HCPCS
Endoscopic ultrasound	NA	76975, 43231, 43232, 43237, 43238, 43242, 43259
Endoscopic retrograde cholangiopancreatography	51.10, 51.11, 51.84-51.87, 51.99, 52.13, 52.93	74328-74330, 43260-43269, 43271, 43272
Surgery	52.51, 52.6, 52.7	48150, 48152, 48153, 48154, 48155
Jaundice	782.4	NA
Cholangitis	576.1	NA
Pruritus	698.9	NA

NA: Not applicable; ICD-9: International Classification of Disease, 9th Edition; HCPCS: Healthcare Common Procedure Coding System.

who were older (aOR 0.88, 95%CI: 0.82-0.95), not married (aOR 0.90, 95%CI: 0.85-0.97), or lived in a non-metropolitan area (aOR 0.87, 95%CI: 0.79-0.97) were less likely to receive ERCP. Compared to white patients, non-white/non-black patients (aOR 0.83, 95%CI: 0.70-0.97) were less likely to receive ERCP.

Clinical factors including cancer site, stage of cancer and use of other therapies were also associated with receipt of ERCP. Patients with cancer originating in the head of the pancreas had greater odds of receiving ERCP (aOR 3.27, 95%CI: 2.99-3.57) (Table 4). Compared to those with localized disease, patients with distant disease were less likely to receive ERCP (OR 0.52, 95%CI: 0.46-0.58). Finally, those who received chemotherapy (aOR for 1.39, 95%CI: 1.28-1.51) and radiation (aOR 1.21, 95%CI: 1.11-1.33) had increased odds of receiving ERCP. Those who underwent surgery were less likely to receive ERCP (aOR 0.82, 95%CI: 0.73-0.92). Charlson score did not impact receipt of ERCP.

ERCP may not always be indicated in pancreatic cancer, and receipt of biliary decompression may not always suggest appropriate management. To address this, we performed a stratified analysis for receipt of ERCP in the setting of jaundice, cholangitis and pruritus (Table 5). After stratifying by indications for ERCP, racial differences became apparent. Compared to white patients, black patients (aOR 0.80, 95%CI: 0.67-0.95) and non-white/non-black (aOR 0.73, 95%CI: 0.58-0.91) were less likely to undergo ERCP in the presence of jaundice (Table 5). Among patients with jaundice, patients who underwent surgery were less likely to undergo ERCP (aOR 0.60, 95%CI: 0.52-0.69).

The use of ERCP decreased over time: 4955 (47.7%) of patients received ERCP in 2000-2003, 4949 (44.5%) in 2004-2007, and 4800 (43.7%) in 2008-2011 (P-value for trend < 0.05, Table 3). Compared to those diagnosed early in the study, patients diagnosed in 2008-2011 were less likely to undergo ERCP (aOR 0.90, 95%CI: 0.83-0.97) (Table 4).

DISCUSSION

To our knowledge, this is the first study to evaluate race, income, education, geographic location and other clinical and sociodemographic characteristics in receipt ERCP in pancreatic cancer. While not curative, endoscopic procedures aid with diagnosis and staging, alleviate morbidity and facilitate other curative treatments including surgery and chemotherapy[3]. Given the dismal prognosis associated with pancreatic cancer, it is important to ensure that all patients have access to procedures that can aid in diagnosis, staging and management to reduce disparities in outcomes.

While other analyses have focused on racial disparities in PC, our study is unique in its ability to capture other sociodemographic data, such as income and education[5-10,13,24,25]. When controlling for these factors, we found no differences in overall receipt of ERCP for black patients. In our analyses stratified by ERCP indications, black patients received ERCP less often for jaundice, but not cholangitis or pruritus. In contrast, non-white/non-black patients received ERCP less often for the indications of jaundice and cholangitis, but not pruritus. Given the relatively small number of patients with pruritus (n = 146 for black patients and n = 120 for non-black/non-white patients), it is possible the sample is not sufficient to detect differences in use of ERCP for pruritic patients. Further studies are warranted to investigate these racial discrepancies.

Interestingly, patient age, marital status, and factors related to where the patient lives, including metropolitan area, were also associated with receipt of ERCP in pancreatic cancer. The relationship between surgical resection and sociodemographic factors including younger age and being married has previously been shown; our

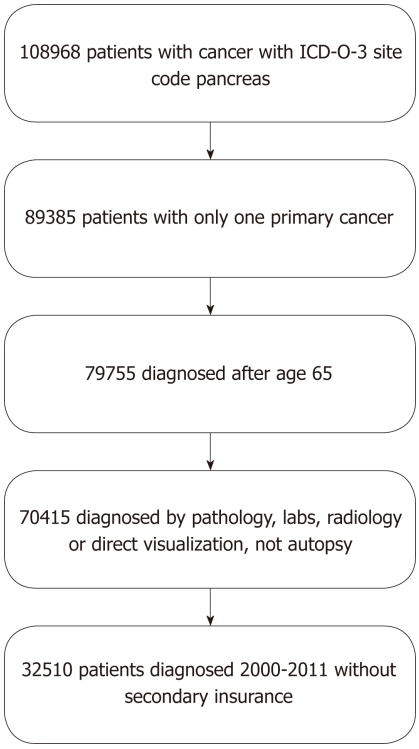

Figure 1 Patient selection.

findings suggest the same is true for ERCP[13]. Differences in utilization may be explained by access to experts available to perform these procedures and regional practice differences. It should be noted that geographic differences shown in this study may not be representative of all regions in the country, since the SEER registry includes a selected 19 urban and rural regions throughout the United States. The Charlson score was not associated with use of ERCP, suggesting patient comorbidities do not deter endoscopists from pursuing these procedures.

The use of ERCP in pancreatic cancer patients fell during this time period. This may reflect two trends: One is the use of EUS for diagnosis and staging generally supplanted ERCP during this time[3]. The second may have been a large randomized controlled trial that suggested that ERCP performed prior to surgical resection increased postoperative complications and surgical morbidity[26]. Both trends may have had an effect of decreasing the use of ERCP in pancreatic cancer.

Patients with advanced stage disease received ERCP less often than those without metastatic disease. These findings may be expected in patients pursuing palliative options or who chose to forego further diagnostic work up and treatment. In contrast, patients with regional disease were more likely to pursue ERCP, which may be consistent with a plan of care to pursue cure with other cancer directed therapies[27]. Multivariable analysis also showed that those who received chemotherapy and radiation were more likely to receive ERCP. ERCP can facilitate these treatments through biliary decompression and normalization of bilirubin. In contrast patients who underwent surgery were less likely to receive ERCP. During this time period, studies suggested that preoperative ERCP may increase postoperative complications, which may have impacted practice patterns[21,26].

There are several limitations to this study. There is variation in use of ERCP for malignant obstruction which may be guided by physician preference or protocols at different centers, which could not be measured through this database[28]. The use of ERCP in pancreatic cancer patients with resectable disease is controversial[29]. Additionally, receipt of ERCP in pancreatic cancer may not accurately reflect access to expert care or appropriate clinical care. To address this, we performed additional analyses stratified by clinical indications (jaundice, cholangitis and pruritus) for ERCP. Racial, socioeconomic and geographic disparities identified here point to the need for future studies on how best to use ERCP in the management of PC as well as how to ensure that all patients have access to high quality care.

This is an analysis of a retrospective claims database and therefore patients are not randomized. However, our goal with this study was to examine how care is delivered in the real world. As with any claims database the information are limited to

Table 2 Characteristics of patients with pancreatic cancer by receipt of endoscopic retrograde cholangiopancreatography *n* (%)

	Total	Received ERCP	No ERCP	*P* value
Total	32510 (100.0)	14704 (45.2)	17806 (54.8)	
Sex				0.49
Male	14147 (43.5)	6368 (45.0)	7779 (55.0)	
Female	18363 (56.5)	8336 (45.4)	10027 (54.6)	
Age				< 0.01
65-75	14205 (43.7)	6665 (46.9)	7540 (53.1)	
76+	18305 (56.3)	8039 (43.9)	10266 (56.1)	
Marital status				< 0.01
Married	15928 (49.0)	7370 (46.3)	8558 (53.7)	
Not married	16582 (51.0)	7334 (44.2)	9248 (55.8)	
Race				< 0.01
White	27399 (84.3)	12534 (45.8)	14865 (54.3)	
Black	3349 (10.3)	1418 (42.3)	1931 (57.7)	
Other	1762 (5.4)	752 (42.7)	1010 (57.3)	
Year of diagnosis				< 0.01
2000-2003	10388 (32.0)	4955 (47.7)	5433 (52.3)	
2004-2007	11134 (34.3)	4949 (44.5)	6185 (55.6)	
2008-2011	10988 (33.8)	4800 (43.7)	6188 (56.3)	
Residence				0.06
Metropolitan	27161 (83.6)	12346 (45.5)	14815 (54.6)	
Non-metropolitan	5346 (16.5)	2356 (44.1)	2990 (55.9)	
SEER registry region				< 0.01
Northeast	7153 (22.0)	3326 (46.5)	3827 (53.5)	
Southeast	8128 (25.0)	3688 (45.4)	4440 (54.6)	
Midwest	4243 (13.1)	1835 (43.3)	2408 (56.8)	
West Coast	12986 (39.9)	5855 (45.1)	7131 (54.9)	
Income (zip code)				0.96
High income	7948 (25.0)	3591 (45.2)	4357 (54.8)	
Low income	23841 (75.0)	10780 (45.2)	13061 (54.8)	
Education (zip code)				0.02
Low education	10188 (32.0)	4702 (46.2)	5486 (53.9)	
High education	21638 (68.0)	9687 (44.8)	11951 (55.2)	
SEER historic stage				< 0.01
Localized	3042 (9.4)	1806 (59.4)	1236 (40.6)	
Regional	9178 (28.2)	5946 (64.8)	3232 (35.2)	
Distant	16846 (51.8)	5170 (30.7)	11676 (69.3)	
Unstaged	3400 (10.5)	1758 (51.7)	1642 (48.3)	
Region of pancreas				< 0.01
Head	16670 (71.2)	10710 (64.3)	5960 (35.8)	
Body/Tail	6744 (28.8)	1080 (16.0)	5664 (84.0)	
Symptoms				
Jaundice	14189 (43.7)	11076 (78.1)	3113 (21.9)	< 0.01
Cholangitis	3970 (12.2)	3471 (87.4)	499 (12.6)	< 0.01
Pruritus	1832 (5.6)	1297 (70.8)	535 (29.2)	< 0.01
Charlson Comorbidity score				0.12
0	14423 (46.6)	6616 (45.9)	7807 (54.1)	
1	9049 (29.3)	4181 (46.2)	4868 (53.8)	
2	3964 (12.8)	1760 (44.4)	2204 (55.6)	
3+	3487 (11.3)	1550 (44.5)	1937 (55.6)	
Therapeutic treatment				
Chemotherapy	13235 (40.7)	6679 (50.5)	6556 (49.5)	< 0.01
Radiation	7298 (22.5)	4198 (57.5)	3100 (42.5)	< 0.01

Surgery	3259 (10.0)	2368 (72.7)	891 (27.3)	< 0.01

Some lines do not sum to 100% due to rounding or missing data. Other race: Neither white nor black race. Not married includes single, divorced and widowed. Metropolitan area defined as counties in metropolitan areas with population of 250000 or more; urban area defined as counties with populations of 2500 or more, both adjacent to metropolitan areas and not adjacent to metropolitan areas; rural defined as counties either completely rural or with populations < 2500. High income defined as > 75th percentile of income, or $74147. Low income defined as < 75th percentile or $74147. High education defined as living in a zip code where > 50% of the population has completed some college or more. Low education is defined as living in a zip code where > 50% of the population has no college education. ERCP: Endoscopic retrograde cholangiopancreatography; SEER: Surveillance, Epidemiology and End Results.

procedures and diagnoses as submitted by physicians. Previous studies suggest the accuracy of procedure coding (*e.g.*, for endoscopy and surgery) is high[30-32]. However, important clinical information that impacts recommendations for surgery and procedures, including smoking status and laboratory values (*e.g.*, bilirubin level, carcinoembryonic antigen, cancer antigen 19-9), is not available.

Despite these limitations, this is the first study of a large population dataset that describes racial, sociodemographic and geographic disparities in use of ERCP for patients with pancreatic cancer. Since appropriate staging and prompt referral for surgery is crucial for potential of cure for these patients, it is possible that differences in the use of endoscopic procedures may partially explain previously described racial disparities in survival as well. ERCP utilization in pancreatic cancer varies based on patient age, marital status, and factors related to where the patient lives. Further studies are needed to guide appropriate biliary intervention for these patients.

Table 3 Use of endoscopic retrograde cholangiopancreatography over time using Cochran Armitage trend *n* (%)

	Total	ERCP	*P* value
Year of diagnosis			< 0.01
2000-2003	10388	4955 (47.73)	
2004-2007	11134	4949 (44.45)	
2008-2011	10988	4800 (43.68)	
Total	32510	14704 (45.2)	

ERCP: Endoscopic retrograde cholangiopancreatography.

Table 4 Multivariable analysis of use of endoscopic retrograde cholangiopancreatography

	Adjusted OR of receiving ERCP (95%CI)
Sex	
Male	1.00 (REF)
Female	1.03 (0.96-1.11)
Age	
65-75	1.00 (REF)
76+	0.88 (0.82-0.95)
Marital status	
Married	1.00 (REF)
Not married	0.90 (0.85-0.97)
Race	
White	1.00 (REF)
Black	0.92 (0.82-1.04)
Other	0.83 (0.70-0.97)
Education (zip code)	
> 50% high school only	1.14 (1.04-1.24)
> 50% some college	1.00 (REF)
Income (zip code)	
< 75th percentile	1.10 (1.00-1.20)
> 75th percentile	1.00 (REF)
Year of diagnosis	
2000-2003	1.00 (REF)
2004-2007	0.85 (0.78-0.92)
2008-2011	0.76 (0.70-0.83)
Metropolitan area	
Metropolitan area	1.00 (REF)
Non-metropolitan area	0.87 (0.79-0.97)
United States region	
Southeast	1.00 (REF)
Northeast	1.07 (0.96-1.20)
Midwest	0.96 (0.86-1.09)
West Coast	1.03 (0.93-1.13)
Comorbid conditions	
Charlson score 0	1.00 (REF)
Charlson score 1	1.06 (0.98-1.15)
Charlson score 2	0.96 (0.86-1.07)
Charlson score 3+	0.99 (0.88-1.11)
Cancer site	
Body or tail	1.00 (REF)
Head of the Pancreas	3.27 (2.99-3.57)
Symptoms[1]	
Jaundice	7.59 (7.06-8.17)

Cholangitis	4.22 (3.71-4.81)
Pruritus	1.42 (1.22-1.66)
SEER historic stage	
Localized	1.00 (REF)
Regional	1.01 (0.89-1.14)
Distant	0.52 (0.46-0.58)
Unstaged	0.85 (0.73-1.00)
Cancer directed therapies[1]	
Chemotherapy	1.39 (1.28-1.51)
Radiation	1.21 (1.11-1.33)
Surgery	0.82 (0.73-0.92)

[1]Referent category is not having those symptoms, conditions or treatments. Other race is neither white nor black race. Not married includes single, divorced and widowed. Metropolitan area defined as counties in metropolitan areas with population of 250000 or more. High income defined as > 75th percentile of income, or $74147. Low income defined as < 75th percentile or $74147. High education defined as living in a zip code where > 50% of the population has completed some college or more. Low education is defined as living in a zip code where > 50% of the population has no college education. OR: Odds ratio; CI: Confidence interval; Endoscopic retrograde cholangiopancreatography.

Table 5 Analysis stratified by symptoms/conditions

	Adjusted OR of receiving ERCP (95%CI), amongst patients with Jaundice	Adjusted OR of receiving ERCP (95%CI), amongst patients with Cholangitis	Adjusted OR of receiving ERCP (95%CI), amongst patients with Pruritus
Sex			
Male	1.00 (REF)	1.00 (REF)	1.00 (REF)
Female	1.17 (1.05-1.30)	0.99 (0.77-1.27)	1.00 (0.75-1.33)
Age			
65-75	1.00 (REF)	1.00 (REF)	1.00 (REF)
76+	0.98 (0.88-1.09)	0.86 (0.67-1.10)	0.97 (0.73-1.29)
Marital status			
Married	1.00 (REF)	1.00 (REF)	1.00 (REF)
Not married	0.85 (0.76-0.94)	0.97 (0.75-1.26)	0.94 (0.70-1.26)
Race			
White	1.00 (REF)	1.00 (REF)	1.00 (REF)
Black	0.80 (0.67-0.95)	0.87 (0.58-1.28)	0.88 (0.52-1.51)
Other	0.73 (0.58-0.91)	0.64 (0.42-0.98)	1.00 (0.59-1.70)
Education (zip code)			
> 50% high school only	1.00 (0.88-1.13)	0.79 (0.59-1.06)	1.23 (0.88-1.71)
> 50% some college	1.00 (REF)	1.00 (REF)	1.00 (REF)
Income (zip code)			
< 75th percentile	1.13 (0.99-1.30)	1.50 (1.12-2.01)	0.84 (0.60-1.17)
> 75th percentile	1.00 (REF)	1.00 (REF)	1.00 (REF)
Year of diagnosis			
2000-2003	1.00 (REF)	1.00 (REF)	1.00 (REF)
2004-2007	0.97 (0.86-1.10)	0.94 (0.70-1.26)	0.96 (0.67-1.39)
2008-2011	1.00 (0.88-1.13)	1.02 (0.76-1.37)	0.76 (0.54-1.06)
Metropolitan area			
Metropolitan area	1.00 (REF)	1.00 (REF)	1.00 (REF)
Non-metropolitan area	0.79 (0.68-0.91)	1.30 (0.87 -1.95)	0.83 (0.56-1.24)
United States region			
Southeast	1.00 (REF)	1.00 (REF)	1.00 (REF)
Northeast	0.94 (0.80-1.11)	1.23 (0.83-1.83)	0.73 (0.46-1.14)
Midwest	0.91 (0.76-1.07)	1.09 (0.71-1.69)	1.01 (0.61-1.67)
West Coast	0.95 (0.82-1.09)	1.02 (0.72-1.43)	0.75 (0.51-1.11)
Comorbid conditions			
Charlson score 0	1.00 (REF)	1.00 (REF)	1.00 (REF)

Charlson score 1	1.06 (0.94-1.20)	1.24 (0.92-1.67)	1.24 (0.90-1.70)
Charlson score 2	0.93 (0.80-1.09)	0.69 (0.50-0.96)	0.77 (0.52-1.16)
Charlson score 3+	0.98 (0.83-1.16)	0.84 (0.58-1.21)	1.14 (0.72-1.80)
Cancer site			
Body or tail	1.00 (REF)	1.00 (REF)	1.00 (REF)
Head of the pancreas	3.82 (3.23-4.50)	2.92 (1.98-4.31)	8.03 (5.57-11.56)
SEER historic stage			
Localized	1.00 (REF)	1.00 (REF)	1.00 (REF)
Regional	0.85 (0.71-1.01)	0.79 (0.52-1.21)	1.21 (0.80-1.82)
Distant	0.51 (0.43-0.60)	0.44 (0.29-0.66)	0.83 (0.54-1.28)
Unstaged	0.75 (0.60-0.94)	0.46 (0.28-0.77)	0.88 (0.47-1.65)
Cancer directed therapies[1]			
Chemotherapy	1.68 (1.48-1.90)	1.578 (1.20-2.07)	0.91 (0.66-1.26)
Radiation	1.21 (1.06-1.39)	1.25 (0.94-1.67)	1.19 (0.86-1.64)
Surgery	0.60 (0.52-0.69)	0.48 (0.35-0.67)	0.84 (0.5-1.20)

[1]Referent category is not undergoing these treatments. OR: Odds ratio; CI: Confidence interval; Endoscopic retrograde cholangiopancreatography.

ARTICLE HIGHLIGHTS

Research background

Endoscopic retrograde cholangiopancreatography (ERCP) is an important therapeutic procedure in the management of pancreatic cancer; before endoscopic ultrasound use was widespread, it also served an important diagnostic role. Variations in its use by patient and sociodemographic factors have not previously been described.

Research motivation

Variability in diagnosis, management and survival of pancreatic cancer by patient factors such as race are well described. However, national trends and variations in use of endoscopic procedures such as ERCP for pancreatic cancer have not previously been described. We hypothesized that there would be variations that may partially explain some of the disparities in outcomes.

Research objectives

We sought to describe variations in receipt of ERCP by patient factors including sociodemographic status, regional location in the country, clinical factors such as stage and comorbidities, and receipt of cancer directed therapies.

Research methods

This is a retrospective cohort study of Medicare claims data. Logistic regression was used to identify patient characteristics associated with the use of ERCP.

Research results

Fourteen thousand seven hundred and four patients diagnosed with pancreatic cancer underwent ERCP between 2000 and 2011. After multivariable analysis, we found multiple factors were associated with receipt of ERCP, including marital status, age, race, living in a non-metropolitan area, year of diagnosis. Even amongst patients with an indication for ERCP (jaundice, cholangitis, pruritus) there were racial differences in use of ERCP. Whether or not these differences contribute to differences in outcomes is a future area of study.

Research conclusions

These findings suggest that use of ERCP in this country varies with non-clinical factors, such as patient race and marital status. This is similar to previous studies which suggest that there are disparities in stage at diagnosis, use of surgery and chemotherapy by sociodemographic factors. It is unclear what impact, if any, this may have on important patient outcomes such as survival.

Research perspectives

Further studies are needed to identify whether use of endoscopy in pancreatic cancer impacts outcomes, such as survival, and to guide appropriate use of biliary interventions in patients with pancreatic cancer.

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ORIGINAL ARTICLE

Observational Study

Narrow band imaging evaluation of duodenal villi in patients with and without celiac disease: A prospective study

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Abstract

BACKGROUND

Duodenal biopsies are commonly obtained during esophagogastroduodenoscopy (EGD) but are very often histopathologically normal. Therefore, a more strategic method for evaluating the duodenal mucosa and avoiding unnecessary biopsies is needed.

AIM

To examine the clinical utility of narrow band imaging (NBI) for evaluating duodenal villous morphology.

METHODS

We performed a prospective cohort study of adult patients at Mayo Clinic Rochester from 2013-2014 who were referred for EGD with duodenal biopsies. A staff endoscopist scored, in real-time, the NBI-based appearance of duodenal villi into one of three categories (normal, partial villous atrophy, or complete villous atrophy), captured ≥ 2 representative duodenal NBI images, and obtained mucosal biopsies therein. Images were then scored by an advanced endoscopist and gastroenterology fellow, and biopsies (gold standard) by a pathologist, in a masked fashion using the same three-category classification. Performing endoscopist, advanced endoscopist, and fellow NBI scores were compared to histopathology to calculate performance characteristics [sensitivity, specificity,

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positive and negative, negative predictive value (NPV), and accuracy]. Inter-rater agreement was assessed with Cohen's kappa.

RESULTS

112 patients were included. The most common referring indications were dyspepsia (47%), nausea (23%), and suspected celiac disease (14%). Duodenal histopathology scores were: 84% normal, 11% partial atrophy, and 5% complete atrophy. Performing endoscopist NBI scores were 79% normal, 14% partial atrophy, and 6% complete atrophy compared to 91%, 5%, and 4% and 70%, 24%, and 6% for advanced endoscopist and fellow, respectively. NBI performed favorably for all raters, with a notably high (92%-100%) NPV. NBI score agreement was best between performing endoscopist and fellow ($\kappa = 0.65$).

CONCLUSION

NBI facilitates accurate, non-invasive evaluation of duodenal villi. Its high NPV renders it especially useful for foregoing biopsies of histopathologically normal duodenal mucosa.

Key words: Endoscopy; Digestive tract; Mucosa; Celiac disease; Minimally-invasive imaging; Esophagogastroduodenoscopy

Core tip: Duodenal mucosal biopsies are frequently obtained during upper endoscopy to assess villous architecture but are largely negative (*i.e.*, histopathologically normal); thus, a method to better evaluate the duodenal mucosa and avoid unnecessary biopsies is needed. Narrow band imaging (NBI) permits superior inspection of mucosal surfaces *via* filter separation of conventional white light into only green and blue components. Based on the findings of this prospective study, NBI appears to have excellent diagnostic performance in evaluating duodenal villous morphology and can facilitate targeting of biopsies; its high negative predictive value renders it particularly useful in avoiding biopsies that are likely to reveal histopathologically normal mucosa.

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INTRODUCTION

The incidence, prevalence, and costs of digestive tract disorders warranting small intestinal mucosal evaluation are substantial and rising in the United States and worldwide[1-5]. Celiac disease alone, for example, occurs in 1 in 140 (*i.e.*, over 2000000) individuals in the United States[1,4] and is associated with thousands of dollars per person-year in increased direct medical costs compared to the general population. It is not an overstatement, therefore, that these disorders, taken together, embody a major gastroenterological (GI) and public health burden.

Esophagogastroduodenoscopy (EGD) with evaluation of the duodenal mucosa is indicated for suspected and known celiac disease as well as other inflammatory and malabsorptive digestive tract disorders. While endoscopic inspection of the duodenal mucosa during EGD is expedient, white light endoscopy (WLE) is not considered (and has been established to not be) sufficiently sensitive to confidently rule out certain mucosal abnormalities, and in particular, those involving duodenal villous morphology[6]. As a result, biopsies of the duodenal mucosa are required for histopathological evaluation; although obtaining and microscopically evaluating duodenal mucosal biopsies is considered the gold standard, it is a time- and resource-intensive approach[7]. Moreover, with anticipated healthcare reform (*e.g.*, bundled payment), it is likely that histopathology costs will ultimately be deducted from EGD reimbursements. This is a problematic prospect considering that a large proportion of duodenal biopsies are histopathologically normal[7,8]. Therefore, methods to avoid

unnecessary biopsies would be timely and clinically useful.

Narrow band imaging (NBI) is an ancillary endoscopic imaging modality which offers an enhanced capability to delineate mucosal surfaces and underlying vasculature and is readily available on contemporary endoscopes[9]. Fundamentally underpinning this capability is the principle that depth of light penetration depends on wavelength, *i.e.*, the longer the wavelength of light, the deeper the penetration[10]. NBI technology filters light from the xenon source into green and blue components. Upon illumination of the mucosa, blue light penetrates only superficially, whereas green light penetrates into deeper mucosal layers. This separation of light permits better visualization and more detailed inspection of the mucosa with NBI as compared to WLE alone[9,11-13]. NBI also offers advantages compared to biopsy-based techniques in that it: (1) is non-invasive (*i.e.*, does not add to the risks inherent to EGD); (2) can be rapidly performed by the endoscopists and yield real-time results; (3) does not involve histopathology charges; and (4) allows for wide field inspection and thus may be less prone to sampling error.

With these advantages in mind, and considering the aforementioned unmet clinical needs, we hypothesized that NBI would have high accuracy and clinical utility in the evaluation of duodenal villous morphology. Here, we prospectively and comprehensively examined the performance characteristics of NBI among patients referred for EGD with duodenal mucosal biopsies.

MATERIALS AND METHODS

This study was approved by the Mayo Clinic Institutional Review Board (IRB# 13-005715).

Patients

Adult (age ≥ 18 years) patients consecutively referred to our outpatient endoscopy center between August 2013 and August 2014 for EGD with an a priori request for duodenal mucosal biopsies were included. This cohort included patients referred for a broad variety of clinical indications, including investigation of celiac disease (suspected or known) as well as other disorders and/or symptoms (Table 1).

Endoscopic approach

Informed consent was obtained in all patients. Moderate to deep sedation was induced for all procedures with intravenous nurse-administered fentanyl and midazolam or anesthetist-administered propofol. EGD was performed by a senior staff endoscopist (JP, JAM, or KAP) with a diagnostic gastroscope (GIF-H180 or GIF-H190, Olympus America, Center Valley, PA) in the conventional manner with standard accessories. NBI was actuated intraprocedurally by the button on the gastroscope (which electronically places the NBI filter between the RGB filter and the light source) and used to evaluate the duodenal mucosa. At least four biopsies were obtained from the second portion of the duodenum using single-use radial jaw forceps (Boston Scientific, Natick, MA) per hospital standard of practice.

Scoring of duodenal villi

The performing staff endoscopist subjectively scored, in real-time during EGD, the NBI-based appearance of duodenal villi as normal, partial villous atrophy, or complete villous atrophy[14]. These three categories were expected to correspond to a Marsh classification score of 0-2, 3a-3b, and 3c, respectively. The performing endoscopist then captured at least two representative NBI images (one of which had to be either close-up or using near focus) in the second portion of the duodenum and obtained biopsies therein. Duodenal biopsies were sent to the laboratory for staining with hematoxylin and eosin and scored histopathologically (gold standard) by a masked staff GI pathologist using the same three category classification. In cases of heterogeneity in the degree of villous atrophy in the biopsies from a given patient, the most severe score was recorded.

The representative endoscopic NBI images obtained by the performing endoscopist from the second portion of the duodenum were retrospectively reviewed in a masked fashion by an experienced advanced endoscopist (CJG) and a GI fellow (JHT) and classified using the same three category convention (Figure 1). The advanced endoscopist had approximately three decades of clinical experience, and the GI fellow was in his final two years of fellowship during the study and had performed approximately 350 EGDs at the start of the study.

All scores were entered into standardized data collection forms and then aggregated into one dataset for analytical purposes.

Table 1 Indications for upper endoscopy with duodenal biopsies and corresponding histopathology scores for each indication

Indication[1]	Patients, *n* (%)	Histopathology, *n* (%)		
		Normal	Atrophy	
			Partial	Complete
Dyspepsia	47 (42.0)	44 (93.6)	2 (4.3)	1 (2.1)
Nausea or vomiting	26 (23.2)	25 (96.2)	1 (3.8)[2]	0
Weight loss	26 (23.2)	19 (73.0)	3 (11.5)	4 (15.4)
Iron-deficiency anemia	16 (14.3)	14 (87.5)	1 (6.3)	1 (6.3)
Diarrhea	15 (14.0)	13 (86.7)	0	2 (13.3)
Rule out Celiac disease	15 (14.0)	13 (86.7)	1 (6.7)	1 (6.7)
Follow up Celiac disease	12 (10.7)	4 (33.3)	0	8 (66.7)
Other[3]	3 (2.7)	2 (66.7)	1 (33.3)	0
Total	112	94 (84)	12 (11)	6 (5)

[1]Column total not additive as some patients had more than one presenting symptom or indication for EGD.
[2]Patient had focal erosive duodenitis with a peptic (*i.e.*, non-Celiac) pattern.
[3]Of the three patients referred for an "other" indication, two were referred to rule out upper gastrointestinal Crohn's disease, and a third for unexplained gastroesophageal reflux.

Study outcomes and variables

The primary outcome of the study was the diagnostic performance of NBI-based duodenal villous morphology scoring compared to histopathological scoring of biopsies from the second portion of the duodenum. The secondary outcome was inter-observer agreement on NBI-based scores.

In addition to NBI-based and histopathological scores of duodenal villi, the following covariates were abstracted from the electronic medical record using a standardized data collection form: Age, sex, indication for EGD, celiac disease status (rule out *vs* known), changes of peptic duodenitis, duodenal Crohn's disease, and endoscopic image adequacy (yes or no). Of note, cases wherein NBI evaluation suggested regions of normal villi intermixed with regions of atrophy were recorded (but scored overall as atrophic).

Statistical analyses

Duodenal villous morphology scores from each of the NBI raters (performing endoscopist, advanced endoscopist, and GI fellow) were compared pairwise to histopathological scores (gold standard) to generate a c-statistic (*i.e.* area under receiver operating curve for nominal outcomes). In addition, diagnostic performance characteristics of NBI, specifically specificity, sensitivity, positive and negative (NPV) predictive values, and overall accuracy were calculated. NBI scores from each of the three raters were then compared pairwise using Cohen's kappa to assess inter-observer agreement across a broad range of training and expertise. Analyses were performed using JMP statistical software version 10 (SAS Institute, Cary, NC) with support from the Mayo Clinic Division of Biomedical Statistics and Informatics. All tests were two-tailed, and a $P < 0.05$ was considered statistically significant.

RESULTS

General cohort characteristics

A total of 112 consecutive patients were included in the study, among whom the median age was 51 years (interquartile range 37-64 years) and 35.2% were male. The most common referring indications included dyspepsia (47%), nausea (23%), and suspected celiac disease (14%), as shown in Table 1.

Histopathological findings

Among the 112 patients, 94 (84%) had normal duodenal mucosa, 12 (11%) had partial atrophy, and 6 (5%) had complete atrophy based on histopathological evaluation. The highest incidence of abnormal duodenal histopathology was among patients referred for follow up of known celiac disease or for investigation of unexplained weight loss (66.7% and 27.0%, respectively), while the lowest incidence of abnormal

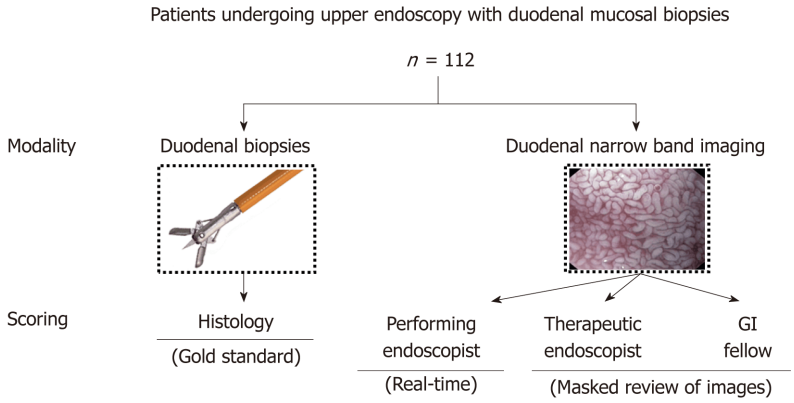

Figure 1 Study overview and flow diagram. A total of 112 patients were included in the study, all of whom underwent esophagoduodenoscopy with duodenal biopsies and duodenal narrow band imaging (NBI) evaluation by a staff endoscopist. Duodenal villi were scored as normal, partial atrophy, and complete atrophy based on real-time NBI appearance by the performing staff endoscopist, and representative duodenal NBI images were scored post-procedure using the same scoring convention by an advanced endoscopist and a gastroenterology fellow in a masked fashion. Duodenal biopsies were evaluated by an experienced pathologist in a masked fashion and compared with NBI scores.

histopathology was among those referred for nausea/vomiting (3.8%). Additional details are provided in Table 1.

NBI scoring characteristics

With respect to NBI-based evaluation, performing endoscopists' NBI scores were 79% normal, 14% partial atrophy, and 6% complete atrophy as compared to 91%, 5%, and 4% and 70%, 24%, and 6% for advanced endoscopist and GI fellow scores, respectively. As shown in Table 2, NBI scores had excellent agreement with histopathology scores (gold standard). Additional performance characteristics are provided in Table 3; as can be seen, sensitivity was highest for the GI fellow, while specificity was highest for the advanced endoscopist. Overall accuracy was highest for the performing endoscopist and advanced endoscopist (both 93%). Importantly, negative predictive values (NPVs) were particularly high for all three raters, ranging from 93%-100%.

Notably, 4 of 7 (57%) and 11 of 16 discordant cases (69%) which were scored as normal by histopathology but non-normal on NBI by the performing endoscopist and GI fellow, respectively, were recorded as having regions of normal villi present intermixed with regions of villous atrophy endoscopically; there were no cases scored as normal by histopathology but non-normal on NBI by the advanced endoscopist (specificity 100%). In addition, it should be mentioned that there were 7 cases which were reported as having normal villous architecture histopathologically but increased intraepithelial lymphocytes (30-70/high power field); of these 7, two were scored as partial villous atrophy by the performing endoscopists, and three were scored as partial villous atrophy by the fellow (all 7 scored as normal by the advanced endoscopist). Whether these cases represented true discordance (*i.e.*, false positive NBI) or early cases of Celiac disease or other duodenopathy is uncertain[15].

There did not appear to be any confounding of NBI scores by the presence of peptic duodenitis (n = 8 cases) or duodenal Crohn's disease (n = 1 case) with the exception of one case of peptic duodenitis scored as partial atrophy by the GI fellow but normal by the other two raters and by histopathology.

NBI score inter-rater agreement

To further understand the performance characteristics of NBI scoring, agreement was calculated between the three NBI raters. Agreement was found to be moderate between performing endoscopist and advanced endoscopist (κ = 0.55), good between performing endoscopist and GI fellow (κ = 0.65), and fair between advanced endoscopist and GI fellow (κ = 0.37). The suboptimal agreement between advanced endoscopist and GI fellow appeared to be a result of the relatively frequent designation of atrophy by the latter compared to more conservative scoring by the advanced endoscopist; this is supported by the high PPV of advanced endoscopist NBI scoring in contrast to the high NPV of GI fellow NBI scoring.

Table 2 Agreement between narrow band imaging - based evaluation and histopathology scores

		Histopathology[1]		C-statistic
		Normal	Atrophy	
Performing endoscopist	Normal	87	2	0.82
	Atrophy	7	16	
Advanced endoscopist	Normal	94	8	0.83
	Atrophy	0	10	
GI Fellow	Normal	76	0	0.86
	Atrophy	16	18	

[1]All discordant cases in which histopathology were rated as atrophy and narrow band imaging (NBI) findings were rated as normal were cases of partial villous atrophy (*i.e.*, not complete villous atrophy); there were no cases of histopathologically-proven complete villous atrophy which were rated as normal by NBI.

DISCUSSION

Disorders of the duodenal mucosa affect millions of individuals in the United States and lead to a large but uncertain number of diagnostic tests annually, in particular EGD with endoscopic biopsies and histopathology thereof[4]. In addition to incurring costs, duodenal biopsies are also not without risk, and albeit uncommon, serious complications have been reported[16]. Therefore, a quick, cost-effective, less invasive, and evidence-based technique for evaluating duodenal mucosa would be timely and useful. In this regard, we hypothesized that the inherent properties of NBI would permit clinically useful inspection of mucosal surfaces and specifically duodenal villous morphology. The results herein demonstrate that NBI has excellent diagnostic performance, with its high NPV rendering it particularly useful in avoiding biopsies which are likely to reveal histopathologically normal mucosa.

NBI has an inherently enhanced capability to delineate mucosal surfaces compared to WLE (Figure 2)[10]. In addition, NBI has advantages over tissue biopsies in that it is less invasive, and possibly less prone to sampling error. Moreover, it may be a less costly method of inspecting the duodenal mucosa in populations with low disease prevalence. At our institution alone (Mayo Clinic, Rochester, MN), an average of 8000 patients undergo duodenal mucosal biopsies annually, with some patients requiring two separate biopsy specimen bottles for the bulb and second portion of the duodenum (Mayo Clinic Department of Revenue Recognition. Rochester MN, United States). Each biopsy specimen bottle incurs a charge of approximately $500 for associated processing and histopathological examination (Mayo Clinic Department of Laboratory Medicine and Pathology, Rochester MN, United States). This amounts to over $6000000 annually at our institution, not including the cost of EGD, biopsy forceps, or extra endoscopy suite time and labor needed to obtain and prepare biopsy specimens. It is worth mentioning that anticipated healthcare reforms (*e.g.*, bundled payment or capitation) may lead to these costs being deducted from endoscopist reimbursements, a problematic prospect given that a considerable proportion of duodenal biopsies are performed in low-risk groups who ultimately have normal histopathology results.

The findings of our study extend the findings of earlier, smaller studies and suggest that NBI is sufficiently accurate compared to histopathology to be clinically useful and has favorable inter-observer agreement among individuals with different levels of endoscopic experience. Furthermore, we believe that with brief formal instruction (*e.g.*, training video on scoring of NBI findings), the overall diagnostic performance of NBI, even among GI trainees and junior endoscopists, could be further improved compared to the results seen herein. Given its excellent NPV, it may be particularly useful as an alternative to tissue biopsy in patients with normal appearing duodenal villi by NBI inspection and who have a low pre-test probability of duodenal mucosal pathology, *e.g.*, patients referred for nausea, vomiting, or functional dyspepsia without diarrhea or iron deficiency. Additionally, although not directly studied here, NBI can be used to target duodenal biopsies, thereby facilitating accurate diagnosis (*i.e.* by decreasing false negatives secondary to sampling error associated with random biopsies and/or in conditions with patchy or ultra-short disease involvement)[17,18]. In a similar vein, an enhanced, real-time ability to recognize villous abnormalities using NBI may identify patients who would benefit from duodenal biopsies but in whom duodenal mucosal disease (*e.g.*, celiac) was not suspected (and thus biopsies were not specifically requested prior to referral for EGD)[6]. These

Table 3 Performance characteristics of narrow band imaging for distinguishing between normal mucosa and villous atrophy (partial or complete) as compared to histopathology

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Performing endoscopist	89	93	70	98	93
Advanced endoscopist	56	100	100	93	93
Gastroenterology fellow	100	83	53	100	86

PPV: Positive predictive value; NPV: Negative predictive value.

represent currently understudied but potentially valuable applications of NBI.

The present study has several limitations and other features which merit consideration. First, this was a single center study based in an academic, tertiary-care referral setting. Second, we used a simplified classification system for histopathological and NBI scoring; while less detailed than alternative classification systems, this system has been shown to have satisfactory inter-observer agreement and is readily applicable to clinical practice, recognizing though that it may not be sufficiently granular in some scenarios [*e.g.*, cases where the presence of isolated increased epithelial lymphocytes with preserved villous architecture (*i.e.*, Marsh classification 1-2) is regarded a clinically significant finding] (Table 4)[14]. Third, sample size was, nevertheless relatively sizable in that it represents the largest known published cohort of NBI-based duodenal villous inspection with histopathological correlation. Part of the reason why the sample size was limited was that we only included EGDs with an a priori (*i.e.*, "special") request for duodenal biopsies; in doing so, however, we believe the cohort was enriched for abnormal findings, thus certain diagnostic performance characteristics, *e.g.*, specificity and NPV, may be even higher if applied to all comers (*e.g.*, a non-enriched cohort and/or non-tertiary referral setting). Fourth, we did not have a WLE control arm; though this may have clarified the incremental gain of NBI over conventional WLE, given the latter has been found to be unreliable in accurately assessing villous morphology, we deemed this to generally not be clinically relevant. Fifth, biopsies of the duodenal bulb were not included pro forma as they are not uniformly a part of the practice at our institution and are more susceptible to nonspecific chemical (*e.g.*, peptic) injury. Sixth, magnification endoscopy (*i.e.*, "near focus") was not specifically studied here, though it likely has the potential to further improve the diagnostic performance of NBI for this application[13,19,20]. Lastly, alternative modalities exist which may similarly help avoid the need for unnecessary duodenal biopsies, such as the water immersion technique (which can be coupled with NBI) and confocal endomicroscopy; however, the former may be less desirable in patients with an unprotected airway while the latter is time-consuming and costly.

In summary, NBI appears to be a promising tool for non-invasive evaluation of duodenal villous morphology, and in addition, is readily available during routine EGD. Its high NPV makes it especially useful in avoiding biopsies which are likely to reveal histologically normal mucosa. Conversely, it can facilitate targeting of duodenal tissue acquisition so as to avoid false negative biopsies due to sampling error or patchy disease. The use of NBI for the evaluation of duodenal villi may therefore result in improved diagnostic accuracy, avoidance of unnecessary biopsies, and potential cost savings.

Table 4 Interobserver agreement on narrow band imaging - based duodenal scoring

	Performing endoscopist	Advanced endoscopist	GI Fellow
Performing endoscopist	-	-	-
Advanced endoscopist	0.55	-	-
GI Fellow	0.65	0.37[1]	-

[1]The fair agreement between advanced endoscopist and gastroenterological (GI) fellow appeared to be driven by the relatively frequent designation of atrophy by the GI fellow and the more conservative scoring by the advanced endoscopist, as supported by their respective negative and positive predictive values.

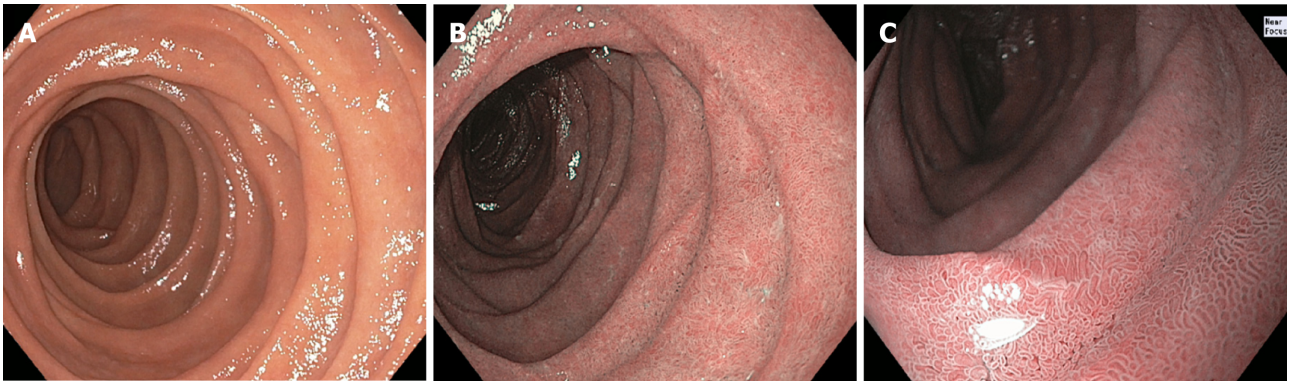

Figure 2 Representative endoscopic images of duodenal villi evaluation by white light endoscopy and narrow band imaging. A: High-definition white light endoscopy image which shows a "wet sugar" appearance but, as expected, without clear or detailed delineation of villous morphology; B: High-definition NBI image of the same patient and segment of duodenum exhibiting improved delineation and appreciation of villous morphology, without grossly evident villous blunting or denudation; C: High-definition NBI image with near focus feature of the same patient and same segment of duodenum clearly demonstrating normal duodenal villous height and density (confirmed histologically).

ARTICLE HIGHLIGHTS

Research background

Duodenal mucosal biopsies are routinely obtained during upper endoscopy (EGD) but very often are histopathologically normal.

Research motivation

To decrease unnecessary biopsies, a more strategic method for examining the duodenal mucosa is needed.

Research objectives

The primary aim of this study was to examine the clinical utility of narrow band imaging (NBI) for evaluating the morphology.

Research methods

We performed a prospective cohort study of patients at Mayo Clinic Rochester who were referred for EGD with a request for duodenal biopsies. The performing staff endoscopist scored, in real-time during EGD, the NBI-based appearance of duodenal villi into one of three categories (normal, partial villous atrophy, or complete villous atrophy), captured ≥ 2 representative duodenal NBI images, and obtained duodenal mucosal biopsies. NBI images were then scored by an advanced endoscopist and fellow, and biopsies (gold standard) by a pathologist, in a masked fashion using the same three-category classification. Performing endoscopist, advanced endoscopist, and fellow NBI scores were compared to histopathology scores to calculate performance characteristics [sensitivity, specificity, positive and negative (NPV) predictive values, and accuracy]. Inter-rater agreement was assessed with Cohen's kappa.

Research results

A total of 112 patients were included in the study. The most common referring indications for EGD with duodenal biopsies were dyspepsia (47%), nausea (23%), and suspected celiac disease (14%). Histopathology scores of duodenal biopsies were: 84% normal, 11% partial atrophy, and 5% complete atrophy. Performing endoscopist duodenal NBI scores were 79% normal, 14% partial atrophy, and 6% complete atrophy compared to 91%, 5%, and 4% and 70%, 24%, and 6% for advanced endoscopist and GI fellow, respectively. Diagnostic performance was favorable for all three raters compared to histopathology, and NPV was particularly high (92-100%). NBI score agreement was best between performing endoscopist and fellow ($\kappa = 0.65$).

Research conclusions

NBI inspection during EGD facilitates accurate, non-invasive evaluation of duodenal villi. It's particularly high NPV may render it most useful for foregoing biopsies of duodenal mucosa likely to be histopathologically normal.

Research perspectives

We believe NBI should routinely be applied to the duodenum during EGD prior to obtaining duodenal biopsies in order to help determine their likely histopathological yield and better target (rather than randomly approach) their acquisition.

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SYSTEMATIC REVIEWS

Role of pancreatoscopy in management of pancreatic disease: A systematic review

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Abstract

BACKGROUND

Per-oral pancreatoscopy (POP) plays a role in the diagnosis and therapy of pancreatic diseases. With recent technological advances, there has been renewed interest in this modality.

AIM

To evaluate the efficacy and safety of POP in management of pancreatic stone disease and pancreatic ductal neoplasia.

METHODS

To determine the safety and efficacy of POP in the management of pancreatic diseases, a systematic search was conducted in MEDLINE, EMBASE and Ovid. Articles in languages other than English and case reports were excluded. All published case series were eligible. Data specific to POP were extracted from studies, which combined cholangiopancreatoscopy. Ten studies were included in the analysis of POP therapy for pancreatic stone disease, and 15 case series satisfied the criteria for inclusion for the role of POP in the management of pancreatic ductal neoplasia. The examined data were subcategorized according to adjunctive modalities, such as direct tissue sampling, cytology, the role of intraoperative POP, intraductal ultrasound (IDUS) and POP combined with image-enhancing technology.

RESULTS

The success rate for complete ductal stone clearance ranged from 37.5%-100%. Factors associated with failure included the presence of strictures, multiple stones

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and the inability to visualize the target area. Although direct visualization can identify malignant and premalignant conditions, there is significant overlap with benign diseases. Visually-directed biopsies provide a high degree of accuracy, and represent a unique approach for tissue acquisition in patients with ductal abnormalities. Addition of pancreatic fluid cytology increases diagnostic yield for indeterminate lesions. Protrusions larger than 3 mm noted on IDUS are significantly more likely to be associated with malignancy. The rate of adverse events associated with POP ranged from 0%-35%.

CONCLUSION
Current evidence supports wider adoption of pancreatoscopy, as it is safe and effective. Improved patient selection and utilization of novel technologies may further enhance its role in managing pancreatic disease.

Key words: Pancreatoscopy; Cholangiopancreatoscopy; Chronic pancreatitis; Pancreatic duct stones; Intraductal papillary mucinous neoplasm; Pancreatic cancer; Pancreatic duct stricture

Core tip: This updated review focuses on the current evidence regarding the use of per oral pancreatoscopy (POP) in the management of complex pancreatic ductal diseases. Traditionally, treatment of pancreatic stone disease has been performed by endoscopic retrograde cholangiopancreatography; POP may fill a void, offering durable relief while avoiding surgery in certain scenarios. POP also plays a complementary role to endoscopic ultrasonography in the evaluation of pancreatic ductal abnormalities with suspicion of neoplasia. With rapid advancements in imaging technology, POP may play a wider therapeutic role in the treatment of pancreatic ductal neoplasia.

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INTRODUCTION

Evaluating the pancreatic duct (PD) is challenging due to its anatomy, which occasionally limits visualization by cross-sectional imaging, relative inaccessibility to available endoscopic devices, and certain unique obstructive disease entities. These may limit diagnostic and therapeutic endeavors under fluoroscopic guidance. Evaluation of these entities has relied heavily on various radiologic modalities including computed tomography (CT) scans, magnetic resonance imagings (MRIs), endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography (EUS)[1]. ERCP-guided brushings of pancreatobiliary strictures for cytological examination has a diagnostic yield ranging from 30%-57%[2-4]. Even with the addition of endobiliary biopsy forceps and endoscopic needle aspiration, the diagnostic yield and negative predictive value remains low[5]. Stone extraction from the PD may be limited by stone impaction at side branch take-offs, or a narrow proximal PD, which may limit balloon extraction. Furthermore, non-endoscopic interventions of the pancreas are associated with significant morbidity and mortality.

For these reasons, direct visualization of the pancreatic ductal system is helpful in evaluating and managing certain pancreatic diseases. Attempts at direct visualization of the PD with per-oral pancreatoscopy (POP) were initially described in the 1970s using a mother-baby system[6]. However, there were drawbacks, including the need for two endoscopists, scope fragility and poor image resolution, which limited its adoption for mainstream use.

The recent development of catheter-based systems, primarily developed for bile duct use (single operator cholangioscopy), has addressed some of these limitations, thus promoting widespread application of this modality for both biliary and pancreatic ductal use. Features, such as four-way tip deflection, dedicated irrigation, accessory channels, and digital image acquisition with significant improvement in

image quality, field-of-view and ability to add image-enhancing technology, have made these systems more user-friendly. They have also resulted in diagnostic and therapeutic advances in the management of complex pancreatic diseases.

We present an updated review of the current literature on POP for the management of pancreatic diseases.

MATERIALS AND METHODS

To determine the safety and efficacy of POP in the management of pancreatic diseases, a systematic search was conducted in MEDLINE, EMBASE and Ovid. We used the key words "pancreatoscopy", "cholangiopancreatoscopy", "IPMN", "chronic pancreatitis" and "pancreatic stone disease" to identify relevant articles. Articles in languages other than English and case reports were excluded. All published case series were eligible. Data specific to POP was extracted from studies that combined cholangiopancreatoscopy. The subject population was heterogeneous among the studies reviewed. Ten studies were included in the analysis of POP therapy for pancreatic stone disease (Table 1). Fifteen case series satisfied the inclusion criteria for the role of POP in the management of pancreatic ductal neoplasia (Table 2). The examined data were subcategorized according to the adjunctive modality, such as direct tissue sampling, cytology, role of intraoperative POP, intraductal ultrasound (IDUS) and POP combined with image-enhancing technology.

RESULTS

Endoscopic pancreatic ductal stone therapy

Chronic pancreatitis is characterized by ongoing inflammation that leads to fibrotic changes in the pancreas, resulting in diminished exocrine and endocrine function. Chronic abdominal pain is the main symptom, which may be severe enough to limit quality of life. Several mechanisms, such as outflow obstruction leading to ductal hypertension from strictures/stones and perineural inflammation, have been implicated in the pain pathogenesis of chronic pancreatitis. Continued ductal obstruction may eventually lead to parenchymal atrophy and loss of exocrine and endocrine function, which may cause other symptoms including anorexia, malabsorption and weight loss. Therefore, relief of pancreatic ductal obstruction is a cornerstone in the management of this disease.

Options for therapy depend on ductal morphology and the presence of PD stones and/or strictures. Pancreatic ductal stones, which can occur in up to 90% of patients, represent a significant target for therapeutic intervention[7]. Stone predominant disease, associated with a uniformly dilated PD, is often seen in patients with idiopathic or genetic etiologies, as compared to the complex ductal morphology with strictures seen in patients with chronic alcoholic pancreatitis[8].

Traditional ERCP techniques using extraction balloons and stone extraction baskets have a limited success rate of around 50%, even in expert hands[9]. The complication rate of pancreatic mechanical lithotripsy is three-fold higher than biliary lithotripsy, including trapped and broken baskets that occur in up to 10%[10]. Extra corporeal shockwave lithotripsy (ESWL) is an important adjunct to managing pancreatic ductal stones, with a success rate of 60% for pain relief[11]. However, the limited availability, cost, need for multiple sessions, along with concomitant ERCP to remove stone fragments and treat downstream strictures, have limited widespread use[9]. Furthermore, ESWL also requires a radiopaque target such as a calcified stone or the tip of a stent, thus limiting applicability with radiolucent stones. The management of radiolucent stones is more demanding, as it may require ultrasound guidance or contrast injection through a nasopancreatic catheter[12]. In addition, ESWL is less effective in patients with dense or multiple stones[13].

POP-guided intraductal lithotripsy has the potential to combine the advantages of endoscopy and ESWL. POP-guided intraductal lithotripsy was initially described by Howell *et al*[14], and significant advances have been achieved since then. Intraductal lithotripsy under direct visualization can be achieved by either electrohydraulic therapy (EHL) or laser lithotripsy (LL). The EHL probe consists of two coaxially insulated electrodes attached to a generator producing high voltage electrical impulses at a frequency of 1 to 20 Hz, with power settings between 50%-100%[15]. Sparks at this site produce high amplitude hydraulic pressure waves during water immersion, which help in stone fragmentation[16]. Neodymium: yttrium-aluminum-garnet lasers have been used for pancreatobiliary stone fragmentation by transforming optical energy into mechanical energy in the form of shockwaves *via*

Table 1 Per oral pancreatoscopy-guided pancreatic ductal stone therapy

Year	Ref.	Patients, *n*	Design	Device	EHL/LL	Success rate	AE %	Follow-up in mo
1999	Howell *et al*[14]	6	R/M	M-B	EHL	83	0	6
2009	Fishman *et al*[51]	6	R/M	Spyglass®	EHL	50	0	NA
2011	[2]Maydeo *et al*[21]	4	P/S	Spyglass®	LL	100	13.3	1
2013	Alatawi *et al*[12]	5	P/S	Spyglass®	LL	80%	0	21
2014	Attwel *et al*[19]	46	R/S	Olympus M-B (31) *vs* Spyglass® (15)	LL/EHL[1]	68 *vs* 73 (scope type)	10	18
2014	Ito *et al*[23]	8	R/S	Spyglass®	EHL[1]	37.5	25	NA
2015	Attwell *et al*[9]	28	R/M	Spyglass®	LL[1]	79	29	13
2016	[2]Navaneethan *et al*[52]	5	R/M	Spyglass®	LL	80	0	NA
2017	Bekkali *et al*[53]	6	R/S	Spyglass®	EHL	83	0	30
2017	Parbhu *et al*[22]	20	R/M	Spyglass®	EHL/LL	85	7.3	NA

[1]Combined with ESWL.
[2]Combined study of patients with biliary and pancreatic ductal stones.
EHL: Electro hydraulic lithotripsy; LL: Laser lithotripsy; P: Prospective; R: Retrospective; S: Single-center; M: Multicenter; AE: Adverse events; M-B: Mother baby.

local plasma formation[17].

Pancreatoscopy-guided lithotripsy

Ten published studies were selected for review based on the inclusion criteria. Only two prospective studies with a total of 9/134 patients were identified. There were no prospective randomized studies. Only three published studies had more than ten patients, however, they are all retrospective in nature. A majority of the included patients had chronic pancreatitis due to excessive alcohol use.

Based on the available data, the success of POP-guided PD stone therapy ranges between 37.5%-100% (Table 1) as compared to the success rate of ESWL, which ranges between 59%-76%[18]. Only one study retrospectively compared single-operator pancreatoscopy with traditional mother daughter technique. This study showed no significant differences in success rate, although there was a trend towards better success with the catheter-based system, with a complete clearance rate of 68%-73%[19]. Dorsal duct POP-guided endotherapy *via* minor papilla access was successfully attempted in cases in which the duct immediately upstream of the major papilla was inaccessible[9,19]. This can be performed in patients with pancreatic divisum or acquired obstruction of the ventral duct (pseudo-divisum) from strictures or stones. Brauer *et al*[20] reported 80% clinical success *via* minor papilla in five patients with painful pancreatolithiasis.

Most studies included patients who had failed conventional ERCP techniques[12,21,22] or ERCP with ESWL[9,14,19,23]. Median reported PD stone size ranged from 5 mm[22]-15 mm[9]. Some studies[9,19] reported 23 h observation after index POP procedure or pancreatic sphincterotomy. Most studies reported the placement of plastic PD stents for drainage after POP-guided therapy, necessitating multiple procedures. Shin *et al*[24] placed a self-expanding fully covered metal stent for downstream PD stricture prior to successful POP-guided EHL lithotripsy of a 1.1 cm large PD stone.

Parbhu *et al*[22] reported a 50% success rate in 20 patients using only balloon or basket sweeps due to better visualization with POP. Complete clearance in a single procedure was reported in 100% patients by Maydeo *et al*[21] and 61% by Attwell *et al*[9]. The majority of patients required multiple procedures to achieve clinical success.

Attwell *et al*[9] attained better technical success of complete clearance in patients who had stones in the head/neck (92%) as compared to the body/tail (67%). The same study demonstrated better success for patients with single stone (87%) *vs* patients with multiple stones (69%). Factors predicting the failure of therapy include multiple strictures, multiple stones and direct visualization failure.

POP was also reported to have an adjunctive intraoperative role with POP-guided EHL during lateral pancreatojejunostomy, having shown reduced rates of subsequent hospitalization and surgeries[25].

The risk of side effects ranges between 0%-29% (Table 1), without any reported mortalities. Broad-spectrum antibiotic prophylaxis was used before POP[9,19], although no clear study to date has evaluated its benefit. Side effects include post-procedure pain and pancreatitis, which was mild in most of the patients using the Cotton criteria. A single study reported perforation with guidewire[13], which was managed

Table 2 Role of per oral pancreatoscopy in pancreatic ductal neoplasia

Year	Ref.	*N*	Design	Key findings	Adjunct modalities/success	AE%	Follow up
1997	Uehara *et al*[42]	11	P	Made early diagnosis of CIS missed by other modalities	Cytology in all (with secretin)	NR	34 mo
1998	Jung *et al*[39]	18	P	Visual differentiation - IPMN, Cancer, Chr pancreatitis	Cytology in all	6	2 yr
1998	Mukai *et al*[47]	25	R/S	Papillary lesions > 3 mm, trend towards malignancy	IDUS (> sensitive than POP) for detecting protrusions > 3 mm	4	NA
1998	Tajiri *et al*[54]	52	P	Visual intraductal findings to differentiate Chr pancreatitis and neoplaisa	81% success	3.8	NA
2000	Yamaguchi *et al*[27]	41	R/S	Villious/vegetative lesions with red marks correlate with atypical adenoma/cancer	73.2% success	NA	38.5 mo
2002	Kodama *et al*[37]	42	P	POP correctly identified all stenosis due to Chr pancreatitis	75% success	1.8	NA
2002	Hara *et al*[33]	60	R/S	POP + IDUS 88% accuracy in differentiating benign *vs* malignant POP better for MD type, IDUS better for SB type	IDUS in 40 patients Cytology in 36 patients - Low Sens 13%	7	38.4 mo
2003	Yamao *et al*[41]	115	R	Protrusion, friability 100% spec for malignant stenosis	83% success (lower for pancreatic tumor > 2 cm)	12	2 yr
2005	Yamaguchi *et al*[43]	103	R/S	Cytology has better diagnostic value when collected by POP *vs* catheter Better for MD type *vs* SB type	Cytology in 32 with POP, 71 *via* catheter	NR	18 mo
2005	Yasuda *et al*[36]	26	R	IDUS 100% Sens for lesions > 3 mm, POP Sens 67% No carcinoma in protrusions < 3 mm Biopsy Sens 50% for cancer	IDUS	0	NA
2010	Miura *et al*[48]	21	R/S	Protrusions and vascular patterns seen better with NBI as compared to white light	Narrow Band imaging (NBI) Technical success 90%	0	2 yr
2014	Arnelo *et al*[34]	44	P/S	Spyglass Sens 84%, spec 75% Acc for MD type 76% Acc for BD type 78%	Obtained - Brushings in 88% Biopsy in 41%	17	2.3 yr

2014	Nagayoshi *et al*[35]	17	R/S	Sens for detecting malignancy Irrigation Cytology Sens 100% Biopsy Sens 25%	Cytology	35 - mild	18.8 mo
2017	Parbhu *et al*[22]	16	R/M	Accuracy Biopsy 63.7% Biopsy + Visual 100%	Technical success for biopsy 100%	7.3	6 mo
2017	El Hajj *et al*[38]	79	R/S	Accuracy Visual 87% Visual + tissue 94% (combination)	Technical success 97% Tissue acquisition was combination of brushings, POP assisted and POP directed biopsy	12	12 mo (minimum)

POP: Per oral pancreatoscopy; IDUS: Intraductal ultrasound; P: Prospective; R: Retrospective; S: Single-center; M: Multicenter; AE: Adverse events; CIS: Carcinoma in situ; MD: Main duct; SB: Side branch; Sens: Sensitivity; Spec: Specificity; Acc: Accuracy.

conservatively. There is a risk of ductal wall injury if the high energy produced is directed towards it[26], although none were reported in the evaluated studies. Two studies with more than 25% risk of side effects[9,23] had combined use of ESWL and LL/EHL, likely related to patients having more complex stone disease. In the study by Ito *et al*[23], POP-guided EHL was used as a rescue therapy in patients who failed ESWL.

The overall safety profile is similar as compared to ESWL, which so far has only one reported mortality, along with a few rare complications that include splenic rupture, bowel perforation and liver trauma[18].

Even though there are many published case series evaluating the efficacy of POP-guided therapy for pancreatolithiasis, there is lack of robust randomized prospective data. In addition, most of these studies are from tertiary care centers, and therefore may not be generalizable to the community. PD stone therapy remains challenging, and new prospective data will be needed to better define indications of POP-guided therapy for pancreatic stones. We feel a multidisciplinary consensus meeting between pancreatic endoscopists, pancreatic surgeons and radiologists may help determine the best approach for these patients.

DISCUSSION

Role of POP in pancreatic ducal neoplasia

Ohashi *et al* first described mucin-producing tumors of the pancreas (MPTP) in 1982[27]. Mucin-producing tumors are comprised of two separate entities: Intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN). IPMN is characterized by papillary proliferation of mucin-producing neoplastic epithelium, which causes cystic dilation of the PD[28]. The entity is comprised of a spectrum of epithelial changes ranging from hyperplasia to carcinoma[29]. IPMN accounts for up to 7% of clinically-diagnosed pancreatic neoplasms, and up to 50% of incidentally-diagnosed pancreatic cysts[30].

Diagnosis of IPMN has increased in recent decades, mainly due to the widespread use of high-resolution cross-sectional abdominal imaging[31]. Since IPMN has malignant potential in 65%-70% of patients[29], the differentiation between benign and malignant tumors is crucial to plan the appropriate therapy, along with timing and extent of surgery if needed.

Various modalities have been employed to assess these lesions. A number of factors, such as main duct diameter, cyst diameter, and the presence or absence of septa and nodules, have been useful in identifying lesions with a higher risk of malignant transformation. However, these features are less prominent in uncharacteristic or early lesions. The multicentric nature of IPMN poses an additional challenge, and may lead to recurrence even after surgical resection with negative margins. Sauvanet *et al*[32] reported the limitation of using frozen sections by the existence of discontinuous ("skip") lesions that range from 6%-19% of IPMN in surgical series, and can lead to reoperation in up to 8% of cases. Direct pancreatoscopy has been shown to be useful in differentiating benign mucin-producing tumors of the pancreas from more dysplastic lesions[27].

Role of POP visual impression and POP-guided biopsy

In 2000, Yamaguchi *et al*[27] investigated the efficacy of POP in differentiating between benign and malignant MPTP by comparing findings in 41 patients with surgical pathology, and characterized them according to the shape of the intraductal elevations and the color features on the lesions. They reported a technical success rate of 73.2%, where failure of examination was associated with branched ductal-type lesions. They classified elevated lesions as sessile, semi-pedunculated, villous and vegetative, and color markings were reported as white or red (spotty/linear). Red color markings were noted only over semi-pedunculated or villous-type lesions. The correlation of POP findings with surgical pathology indicated that villous and vegetative tumors were observed only in patients with severely atypical adenoma and adenocarcinoma. Red color markings were also characteristic of this group, with a sensitivity of 87.5% compared with 16.7% for the group, including hyperplasia and mild/moderately atypical adenoma. In this series, 23% of the patients underwent segmental pancreatic resection with favorable outcomes. Pancreatoscopy also helped identify synchronous lesions at different sites, which were missed by other modalities in three patients, helping to determine the location of surgical resection.

Similar conclusions were noted in a retrospective study of 60 patients who underwent POP (IDUS performed in 40) by Hara *et al*[33]. They found protruding lesions by POP in 67% of the patients, with better yield in main ductal-type lesions as compared to branching ductal-types. A fish egg appearance with vascular patterning and villous and vegetative lesions were significantly more likely to be malignant as compared to granular appearance or fish eggs without vascular markings.

Arnelo *et al*[34] prospectively studied the utility of POP in evaluating IPMN in 44 patients with a technical success rate of 93%. They reported additional diagnostic information provided by POP-affected clinical decision-making in 76% of the patient cohort. With operated cases as a reference, the sensitivity of POP was 84% and specificity was 75% in identifying malignant lesions. A classic fish eye papilla was noted in only 35% of the patients with a final diagnosis of MD-IPMN. POP-guided biopsy was diagnostic in 13 of the 17 patients, with inadequate tissue acquisition in four. Nagayoshi *et al*[35] evaluated 17 patients with radiological diagnosis of IPMN. They used the Spyglass® optical probe inserted into a regular ERCP catheter to inspect lesions in patients with non-dilated MPD or severe angulation, with success in 4/5 patients. Ten patients with protruding lesions were identified, but biopsies could only be obtained in seven due to insufficient angulation of the probe. Targeted biopsies had a sensitivity of 25% and a specificity of 100%. Yasuda *et al*[36] reported that targeted biopsies had 50% sensitivity and 100% specificity for detecting malignant IPMN in 11 patients. Targeted biopsies may be more challenging in pancreatoscopy as compared to cholangioscopy due to smaller MPD diameter, more tortuous course and the inability to adequately visualize side branch lesions. The diagnostic accuracy could also be affected by the quality of images obtained.

Pancreatoscopy findings in pancreatic cancer may include findings similar to the above, along with erythema, friability, erosions, infiltrative strictures (with near occlusions of the lumen) with irregular margins, or signs of extrinsic compression with normal mucosa. In a series by Kodama *et al*[37], 5/8 cases of pancreatic cancer were seen adequately, and all had stenosis with a ductal cut-off of MPD.

Parbhu *et al*[22] studied the impact of POP in 16 patients who had EUS suggestive of IPMN, but definitive diagnosis could not be achieved. They achieved 100% success in obtaining biopsies with a diagnostic accuracy of 75%. Four patients in this cohort had negative biopsies, but strong visual impression led the authors to recommend surgery, with a postoperative diagnosis of IPMN.

El Hajj *et al*[38] investigated the role of POP in 79 patients with suspected pancreatic ductal neoplasia, with a technical success of 97%. In the subset of patients with confirmed neoplasia (n = 33), POP-guided tissue sampling with the index procedure could confirm diagnosis in 88%. The sensitivity, specificity and accuracy of POP was 87%, 86%, 87%, respectively, whereas it was 91%, 95% and 94%, respectively, for POP plus targeted tissue sampling. The diagnostic yield reported here may be higher due to more extensive methods employed - a minimum of three passes with either POP-guided direct biopsy, POP-assisted fluoroscopic-guided biopsy or POP-guided brushings; a combination of the above was employed in eight patients.

POP-directed tissue acquisition has been shown to be very useful in distinguishing benign from malignant PD strictures. Jung *et al*[39] prospectively evaluated 18 patients who had indeterminate ductal abnormalities using POP with brush cytology and biopsy (EUS used in three patients only). They confirmed neoplasia in seven and chronic pancreatitis in eight. Macroscopic features of strictures in chronic pancreatitis include white-gray smooth narrowing without superficial vessels. These visual impressions may be critical in distinguishing various etiologies of unexplained pancreatic ductal abnormalities (Table 3). Other findings may include turbid pancreatic juice, protein plugs, indistinct vascular markings, erythema or rough

surfaces[40]. Similar findings were noted by Yamao *et al*[41], where benign stenotic lesions in the PD demonstrated smooth mucosa without protrusions, friability or tumor vessels.

Parbhu *et al*[22] were successful in dilating 100% strictures in five patients in their study, and were able to obtain targeted biopsies in 80%. Dorsal ductal pancreatoscopy (DDP) *via* minor papilla can be considered in patients with true or pseudo-divisum presenting with indeterminate strictures, which may be inaccessible *via* major papilla. Brauer *et al*[20] attempted DDP in five patients, with technical success of 80%. One failure reported was the inability to obtain biopsies due to acute angulation. These studies suggest the possible role of POP in patients with indeterminate PD strictures.

POP with cytology

Uehara *et al*[42] reported the early diagnosis of pancreatic carcinoma in situ (CIS) in their study of 72 patients using POP with cytology. Of these, 11 patients had presented with minimal symptoms and abnormal imaging, showing dilated PD without any localizing signs seen by other modalities such as EUS/ERP/CT. A combination of POP with pancreatoscopic cytology was useful in diagnosing and locating CIS, with 100% recurrence-free post-operative survival up to a median of 34 mo. Cytology with POP assistance had a better diagnostic yield compared to catheter-assisted collection (100% *vs* 60%). Hara *et al*[33] assessed the value of pancreatic juice cytology in 36 out of 60 patients, with low sensitivity of 13% and accuracy of 44% in identifying malignant lesions. K-Ras point mutations were noted in 31 out of 36 patients with high conversion regardless of histologic grade, which manifests as low specificity. Similar results were elicited from a retrospective study of 103 patients by Yamaguchi[43], who found a suboptimal impact of pancreatic juice cytology in differentiating between benign and malignant IPMN. The sensitivity was higher for main PD tumors as compared to branch type (57.9% *vs* 47.4%) with better results when the pancreatic juice was collected by POP as compared to catheter. In this study, there was a small additional benefit of cytology, even when no high-risk lesions were seen on POP, as 4/7 patients with no malignant stigmata on POP exams had positive cytology. Nagayoshi *et al*[35] also compared regular pancreatic cytology with irrigation cytology, with reported sensitivity and specificity of 67% and 100%, respectively.

The exact cytological discrimination between benign and malignant lesions is difficult, and results from different studies are variable due to diverse reasons that include observational bias and location of tumors. For this reason, the use of pancreatic juice cytology remains controversial, although supplementary benefits with other modalities can be appreciated. EUS-FNA has the advantage of sampling mural nodules and a superior ability to assess branch-type lesions, which is clearly advantageous in certain settings.

Intraoperative POP

The specific utility of POP to guide surgical therapy in patients with MPTP has been studied prospectively by Kaneko *et al*[44] in 24 patients. Using surgical pathology as the standard, they reported that the sensitivity, specificity and overall accuracy of intraoperative pancreatoscopies were 100% as compared to 43.8%, 100%, and 60.9% for endoscopic retrograde pancreatography, and 47%, 100%, and 62.5% for endoscopic ultrasonography, respectively. Ten patients were noted to have intraductal MPT that were missed by ERCP and EUS. Five out of these ten patients had multicentric lesions, with three requiring an extension of the planned surgical margin. The overall accuracy to identify lesions was 100% for intraoperative POP *vs* 60.9% for ERCP and 62.5% for EUS. Similar findings were demonstrated by Navez *et al*[45] from a retrospective review of 21 patients with suspected IPMN who underwent intraoperative POP, revealing eight occult lesions. Five of these eight patients underwent modified surgery, with 90.5% disease-free survival at a mean of 93 mo. Tyberg *et al*[46] outlined the role of POP in guiding surgical therapy for lesions in the PD. Out of 13 patients who underwent POP, the initial surgical plan was altered in eight (62%), with an overall correlation of 88% between pancreatoscopy and final surgical histology.

This confirms that intraoperative pancreatoscopy is safe and effective in evaluating main ductal IPMN, with the specific advantage of diagnosing multicentric lesions. These may be missed on ERCP or EUS, thus highlighting its complimentary nature to these modalities. Preoperative thorough direct examination of the PD may be limited due to the acute angle noted at the junction of the duct of Wirsung and Santorini, and intraoperative POP helps in overcoming this problem.

IDUS with POP

Mukai *et al*[47] evaluated mucin-producing tumors in 25 patients with POP and IDUS. They concluded that papillary tumor height of more than 3 mm implied more

Table 3 Per oral pancreatoscopy visual findings for pancreatic ductal abnormalities

	IPMN	Adenocarcinoma	Chronic pancreatitis
Uehara *et al*[42]	Papillary projections, irregular/nodular mucosa		
Jung *et al*[39]	Papillary projections; Villous protrusions	Tumor vessels; Erosions	Smooth narrowing; White/gray mucosa; Blurred blood vessels
Tajiri *et al*[54]	Papillary projections; Salmon eggs	Protrusions; Tumor vessels; Friability, erosions	Protein plugs/stones; Edema, erythema, scar
Yamaguchi *et al*[27]	(1) Hyperplasia/Mild atypia; sessile or semi pedunculated with white color markings; (2) Severe atypia/adenocarcinoma semi pedunculated or villous or vegetative with red color markings		
Kodama *et al*[37]	Papillary projections; Nodular/villous; White/spotty/red marks	Duct cut off; Friability/erosions	Stones, proteins plugs; Scar, erythema; Blurred vessels
Hara *et al*[33]	CIS/Invasive carcinoma; salmon eggs with vascular pattern; Villous/vegetative protrusions		
Yamao *et al*[41]	Coarse, granular papillary projections with mucus	Papillary projection with tumor vessels; Protrusion/friability	Coarse erythema
Miura *et al*[48]	(1) High risk - villous/vegetative with tumor vessel; (2) Low risk - sessile / semi pedunculated		
El Hajj *et al*[38]	(1) Invasive - villous/vegetative papillary projections; (2) Noninvasive - granular projections with erythema	Protrusion with tumor vessel; Ulceration; Infiltrative stricture	Coarse, blurred vessels, scarring, erythema and edema

advanced dysplastic lesions. The sensitivity of detecting lesions more than 3 mm was 29% for US, 21% for CT, 86% for EUS, 100% for IDUS and 83% for POP. Adequate examination of papillary lesions using POP was technically successful in 60% of the total patients. The sensitivity for detecting protrusions more than 3 mm was 100% for IDUS and 67% for POP in a study of 26 patients by Yasuda *et al*[36]. In this study, out of the six patients with adenocarcinoma, none had protrusions less than 3 mm on the resected pathological specimen. The same study demonstrated the suboptimal diagnostic capability of cross-sectional imaging for protruding lesions, with 16 % for CT scan and 20% for MRI.

In the study performed by Hara *et al*[33], 88% of the lesions with villous projections more than 4 mm on IDUS were malignant. The diagnostic accuracy of POP alone in differentiating benign/malignant was 88% and 67% for main duct and branch duct, respectively, as compared to IDUS with an accuracy of 63% and 88%. Their study confirmed that adding IDUS to POP improves the evaluation of branch ductal-type lesions. The combined accuracy rate for different modalities such as CT, EUS, POP and IDUS was 55%, 65%, 75% and 78%, respectively, with the highest rate of 88% for POP plus IDUS combined. Surgical pathology served as the gold standard in this study. Most malignant tumors had POP visual morphology types III, IV or V (as per the Yamaguchi classification). The benefit of using this combined modality was evident in the fact that reduced operations were performed in 33 out of 60 patients, with only one positive resection margin that was due to infiltrative parenchymal changes. Critically, management based on these criteria culminated in an extraordinary 95% 3-year cumulative survival rate and a 93% disease-free survival rate.

IDUS is particularly useful to visualize branches distant from the probe and the parenchyma, and plays a crucial complementary role to POP. IDUS also has better efficacy for early lesions like CIS, due to higher resolution and probe location as compared to EUS.

POP with image-enhancing technology

Miura *et al*[48] assessed POP-guided NBI (narrow band imaging) in 21 patients with IPMN. They used a small diameter videoscope CHF-BP260 (Olympus medical systems) with an outer diameter of 2.9 mm, and achieved technical success of 90%. Vascular patterns and protrusions were detected more clearly in NBI images as compared to examination under white light. Similar findings were observed by Ito *et al*[49]. NBI identified skip tumor lesions in the tail of the pancreas, which were not

detected by conventional POP.

Other adjuvant imaging modalities utilizing POP are also being evaluated. Meining *et al*[50] prospectively studied the role of probe-based confocal laser endomicroscopy (pCLE) in assessing indeterminate pancreatobiliary strictures. The accuracy of the combination of ERCP and pCLE was significantly higher compared with ERCP, with tissue acquisition (90% *vs* 73%, $P = 0.001$) having higher specificity in the exam when the probe was delivered *via* cholangiopancreatoscopy as compared to a standard catheter.

The risk of pancreatitis in these series, which ranged between 0%-35%, seemed to be higher in patients without dilated MPD, and also depended on the level of experience of the operator[34,35]. Arnelo *et al*[34] recorded one fatal case of post-POP pancreatitis. They postulated that reducing the flow rate could help in minimizing the risk of it, however this needs further evaluation.

The role of POP for intraductal pancreatic neoplasia has evolved over time with the availability of longitudinal data and rapid technological improvements. Prospective multicenter studies of POP with selected adjunct modalities may eventually address the true value of POP in the evaluation and management of pancreatic ductal neoplasia. POP will continue to serve a crucial complementary role for such patients, in addition to cross-sectional imaging and EUS. Appropriate application will likely be restricted to high volume tertiary care centers where multidisciplinary approaches will guide the treatment of such rare diseases.

In conclusion, this review illustrates the crucial role POP may play in the management of pancreatic disease by providing direct macroscopic assessment, targeted tissue acquisition and the opportunity for guided endotherapy. The application of this technology has been largely limited to high volume expert centers due to the procedural complexity, the morbidity of the conditions being treated, technical challenges, and cost. There is significant heterogeneity in the available data, with variable patient follow-up, lack of control arms and retrospective designs. Innovations like larger fields-of-view, higher image resolution, integrated image enhancements, and larger working channels may augment the capability of the procedure. Well-designed and powered prospective trials would refine the role of POP in the management of pancreatic disease.

ARTICLE HIGHLIGHTS

Research background

Pancreatoscopy has been used for over 30 years in the diagnosis and management of pancreatic diseases; however, its use remains limited to large volume referral centers. Data regarding its efficacy and safety are limited and have been available mainly from single or multicenter retrospective case series. Well-designed large randomized controlled trials are lacking and may be difficult to conduct due to a heterogeneous patient population. With this study, we have compiled a systematic review of available data, thus highlighting the valuable role of per oral pancreatoscopy in managing pancreatic diseases.

Research motivation

The main aim of our study was to systematically analyze available data regarding the therapeutic potential of pancreatoscopy in managing difficult pancreatic stone disease and pancreatic ductal neoplasia. It appears to be safe, with rare serious side effects, and serves a crucial complementary role to other pancreatic endoscopic modalities.

Research objectives

The main objective of the study was to gather data related to the safety and efficacy of pancreatoscopy. We wanted to identify the success rates and factors associated with treatment failure for pancreatoscopic management of stone disease. We also aimed to analyze the pancreatoscopic visual findings associated with pancreatic ductal neoplasia, and how it can be differentiated from benign pancreatic duct strictures. The diagnostic potential of adjunctive techniques like POP guided/assisted biopsy, pancreatic juice cytology and intraductal ultrasound (IDUS) was evaluated separately.

Research methods

This is a systematic review of available studies published in English. We performed an extensive medical database search to identify relevant publications. Case reports and stand-alone abstract publications were excluded from the final analysis. Data regarding safety and efficacy were extracted and presented. Studies addressing the role of POP in management of pancreatic ductal neoplasia with adjunctive modalities were examined separately.

Research results

Pancreatoscopy is overall safe, with rare reported serious side effects. The success rate ranges between 37.5%-100% for treating pancreatic stone disease. Factors associated with failure include the presence of multiple stones, stones in side branches causing failure of visualization, and the

presence of stricture. Visual impression during pancreatoscopy provides important information in patients with indeterminate pancreatic ductal strictures. The key finding in our study was the association between villous projections with red color markings, which is associated with high-risk advanced neoplastic lesions across multiple studies. Smooth narrowing with the presence of coarse mucosa, protein plugs or stones, and blurred mucosal vessels are seen in patients with strictures caused by chronic pancreatitis. POP-assisted tissue acquisition, as well as adjunctive techniques such as cytology, narrow band imaging and IDUS, greatly enhance the diagnostic potential and help in treatment planning.

Research conclusions

Pancreatoscopy is an overall safe and effective diagnostic and therapeutic modality. It serves as an important bridge for patients with pancreatolithiasis who fail conventional Endoscopic retrograde cholangiopancreatography or ESWL. Patients with multiple stones in body/tail, or those with pancreatic strictures, may have risk of decreased success with POP-guided therapy; the recognition of these factors may help in treatment planning. POP visual impression provides a plethora of information regarding etiology in patients with indeterminate pancreatic ductal strictures, although there is an overlap between benign and malignant conditions. POP-guided tissue acquisition has been shown to greatly enhance the diagnostic yield, but limitations persist due to technical challenges. The addition of newer imaging technology may further augment the potential of POP in managing such scenarios.

Research perspectives

Appropriate future action may involve multicenter prospective studies to identify patient characteristics, which may make them amenable to POP-guided endotherapy for pancreatic diseases. Continued improvement in imaging technology, such as narrow band imaging and probe-based confocal laser endomicroscopy, need to be evaluated extensively before mainstream use is implemented.

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CASE REPORT

Safety and efficacy of over-the-scope clip-assisted full thickness resection of duodenal subepithelial tumors: A case report

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Abstract

BACKGROUND

Over-the-scope clip-assisted endoscopic full thickness resection (eFTR) of subepithelial tumors is a novel and promising endoscopic technique. Recently, there have been prospective studies investigating its use for colonic masses, but data regarding its use and efficacy in the duodenum are limited to a few reports.

CASE SUMMARY

A 65-year-old African American female presents for evaluation of persistent gastroesophageal reflux disease not responsive to medical treatment. A 1 cm nodule was incidentally found in the duodenum and biopsies revealed a low grade well differentiated neuroendocrine tumor. The nodule was removed using over-the-scope clip-assisted eFTR and pathology revealed clear margins. We review the available literature with a discussion on the efficacy and safety of clip-assisted eFTR s of subepithelial lesions in the duodenum.

CONCLUSION

Clip assisted eFTR appears to be a safe and efficacious treatment approach to duodenal subepithelial lesions. Further prospective studies are needed to investigate the long-term utility and safety of clip-assisted eFTR in the management of subepithelial duodenal lesions.

Key words: Case report; Duodenum; Carcinoid; Endoscopic full thickness resection

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Core tip: Over-the-scope clip-assisted endoscopic full thickness resection (eFTR) of subepithelial tumors is a novel endoscopic technique, but has not been extensively studied in duodenal tumors. We present a case of a duodenal carcinoid tumor resected with clip-assisted eFTR that was complicated by bleeding. We explore the safety and efficacy of this procedure in light of the available literature.

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INTRODUCTION

Endoscopic full thickness resection (eFTR) is a promising endoscopic procedure useful for resection of masses arising from any layer of the gastrointestinal wall, particularly for subepithelial tumors. Increasingly, eFTR is being used with the assistance of over the scope (OTS) clips such as the OTSC® (OVESCO Endoscopy AG, Tübingen, Germany) and more recently, the Padlock Clip (Padlock Pro-Select®, Aponos Medical Corporation, Kingston NH, United States). Traditionally, endoscopic resection of duodenal lesions was *via* endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), procedures which are technically challenging and associated with significant adverse events such as bleeding and perforation. However, several reports have demonstrated the efficacy of OTS clip-assisted eFTR. We report on a case of carcinoid tumor in the duodenum that was resected with an OTSC clip that was complicated by bleeding, and discuss the efficacy and safety of duodenal OTS clip-assisted eFTR in light of the available literature.

CASE PRESENTATION

Chief complaints

A 65-year-old African American female presents for evaluation of persistent gastroesophageal reflux disease (GERD) not responsive to medical treatment.

History of past illness

She had a medical history of a hiatal hernia, GERD and a benign peptic stricture. The patient was not on anticoagulation, antiplatelet agents or non-steroidal antiinflammatory drugs.

Personal and family history

There was no personal or family history of gastrointestinal cancer.

Physical examination upon admission

Physical examination was unremarkable and revealed a comfortable lady without any abdominal tenderness on examination.

Laboratory examinations

Complete blood count, complete metabolic panel and prothrombin time/international normalised ratio were all within normal limits.

Imaging examinations

An esophagogastroduodenoscopy (EGD) was performed which revealed a normal esophagus and mild gastritis in the antrum. A single large subepithelial nodule was found in the duodenal bulb and was biopsied.

FINAL DIAGNOSIS

Pathologic examination revealed nests of neuroendocrine cells diffusely positive for synatophysin and chromogranin consistent with a low grade well-differentiated neuroendocrine tumor (WDNET)/carcinoid (Figure 1). After evaluation by

Hematology/Oncology and Surgery, the patient returned for endoscopic intervention.

TREATMENT

During endoscopy an approximately 1 cm subepithelial mass was seen (Figure 2) which was felt to be very superficial given the mucosal biopsies positive for carcinoid tumor on her previous endoscopy. The endoscope was mounted with the OTSC, the lesion was suctioned into the cap slowly and the clip was deployed at the base of the nodule leading to serosa-to serosa apposition, mimicking a pseudo-polyp with the nodule above the closed clip. The nodule was subsequently resected en bloc using electrocautery with a flexible 13 mm snare resecting the tissue above the clip. Despite the presence of the OTSC, the patient started bleeding profusely with active spurting of blood, which was quickly controlled with a hot forceps biopsy. The mass was successfully removed.

OUTCOME AND FOLLOW-UP

Pathologic examination revealed a 9 mm submucosal WDNET with clear margins (R0). Immunohistochemistry confirmed an intermediate grade tumor (G2 with a Ki67 index of 3.5%). There was no lympho-vascular or perineural invasion identified. A subsequent follow up EGD two months later revealed the OTSC in place with hyperplastic mucosa protruding through the clip. Multiple biopsies were taken with no evidence of neuroendocrine tumor cells.

DISCUSSION

The optimal treatment for subepithelial tumors of the duodenum remains controversial, and the overall data on the safety of endoscopic resection of small bowel carcinoids are limited[1]. If duodenal carcinoids are isolated lesions < 10 mm in size, are low grade, do not infiltrate the muscularis and do not show angioinvasion, EMR is considered by many to be the treatment of choice as they have a very low risk of metastasis, between 6%-10%[2,3]. Current Consensus Guidelines recommend endoscopic removal for small duodenal SET < 10 mm, and consideration of surgical resection for tumors > 20 mm[4]. Tumors between 10 mm-20 mm can be removed either endoscopically or surgically since the risk of metastases noticeably increases when tumor size is ≥ 2 cm[2], and the approach is currently not standardized[4]. However, surgical techniques for duodenal SET resection usually results in a Whipple's procedure or the more complex pylorus preserving pancreaticoduodenectomy, both associated with significant morbidity and mortality[5]. Endoscopic resection of tumors in the duodenum is usually achieved by EMR or ESD, which is controversial in the duodenum due to the high incidence of adverse events and technical difficulty[6]. Although ESD achieves a greater en bloc resection rate compared to a complete resection (R0) of only 50% with EMR, EMR is preferred over ESD since the risk of perforation is greater than 30% with ESD[5]. The duodenum has a thin wall compared to other parts of the gastrointestinal tract rendering it more prone to perforation. Furthermore, the base of post-ESD ulcer is continually exposed to bile and pancreatic enzymes leading to an increase in delayed perforation[6]. The duodenum is narrow, which along with its C-loop makes endoscopic procedures technically challenging. It has abundant blood vessels in the submucosal layer making it more prone to bleeding[7], in part from the electrosurgical snaring which may cause deep coagulation necrosis and damage[7] with a risk of delayed bleeding of 12%[8]. Furthermore, many lesions cannot be lifted due to scarring from pre-procedural biopsy sampling[9], rendering resection of non-lifting SET arising from layers deeper than the submucosa extremely challenging[1-3,8,10].

Over the past several years eFTR, an endoscopic method allowing for full thickness resection has been described. The benefits of using eFTR over EMR and ESD include the ability to resect the entire lesion and achieve R0; avoiding immediate and delayed perforation and bleeding by placement of the OTS clip; and avoiding the technical difficulty of ESD in the duodenum.

There are two types of eFTR, "free-hand" or "exposed" eFTR where full thickness excision is carried out using usual ESD techniques and the GI wall defect is subsequently closed, typically via endoscopic wall suturing; and device assisted (*i.e.*, OTS clip-assisted) eFTR where an endoscopic clip is first deployed after which the full thickness excision is carried out[11]. Recently, there has been increasing interest in over

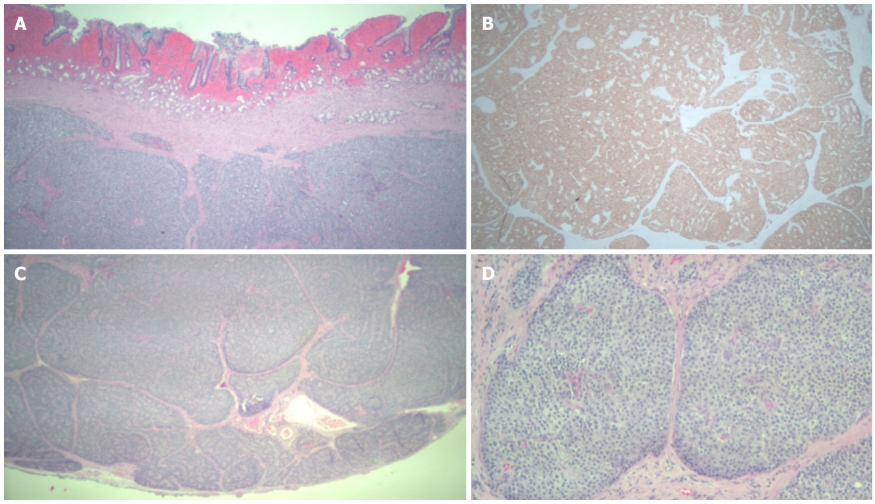

Figure 1 Pathology of duodenal mass. A: Well differentiated neuroendocrine tumor, hematoxylin and eosin (HE) stain, 25 ×; B: The tumor cells are immunoreactive for synaptophysin (immunohistochemical stain, 25 ×); C: Well differentiated neuroendocrine tumor with negative deep margin (R0, HE stain, 25 ×); D: Well differentiated neuroendocrine tumor (HE, 100 ×).

the clip assisted eFTR. It has successfully been used in the stomach for gastric epithelial lesions[12], as well as lesions in the colon[13], particularly after the approval of a dedicated full thickness resection device (FTRD®; OVESCO Endoscopy AG, Tübingen, Germany) for lower gastrointestinal use[14,15]. However, as of now there are only a handful of reports describing clip-assisted eFTR of duodenal lesions (Table 1)[8,13,16-19]. In our review, out of all cases of duodenal OTC clip-assisted eFTR, 85% achieved R0 resection (17/20). In comparison, one series of eFTR of colonic masses demonstrated an R0 of 76.9% of cases[15]. The majority of cases used a curved clip, the OTSC mounted on a flexible endoscope, similar to what was used in our patient. In these cases, the authors reported R0 in 8/10 of all cases, and technical success in all. There were no reported side effects, including bleeding. One study by Schmidt *et al* attempted to perform duodenal nodule resections using the new FTRD that was approved for lower gastrointestinal tumors[8]. The authors reported only two episodes of minor bleeding and an R0 in 3/4 of the patients. Most recently, Kappelle *et al*[5] published a case series of 6 patients with SET where they attempted to perform device assisted eFTR with a new flat clip (Padlock Pro-Select®, Aponos Medical Corporation, Kingston NH, United States). Of the 6 patients, 4 of them had micro-perforation or perforation, and one had significant gastrointestinal hemorrhage, although R0 was achieved in all[5].

In our case although we used the OTSC, there was a spurting arterial bleed during the resection which was quickly controlled with a hot biopsy forceps. Although OTSC is commonly used to stop bleeding and has been used as first line and salvage therapy in gastric and duodenal ulcers[20,21], the technical difficulties of endoscopic therapies in the duodenum remain, and endoscopists should keep in mind the anatomical considerations as well as the extensive blood supply in the duodenum and its proclivity for bleeding. However, in our opinion, despite the possibility of bleeding the use of OTSC before endoscopic resections appears to be a good option for duodenal SET, particularly given the high incidence of clinically significant bleeding with alternate techniques.

CONCLUSION

Based on the available data, clip assisted eFTR appears to be a safe and efficacious treatment approach to duodenal SET. Further prospective studies are needed to investigate the long-term utility and safety of clip-assisted eFTR in the management of subepithelial duodenal lesions, as well as the safety profile of different clips used.

Table 1 Duodenal lesions resected with over the scope clip assisted endoscopic full thickness resection

Ref.	Year	*n*	Age	Sex	Location	Histology	Complication	R0	Size (mm)	Clip
Kappelle *et al*[5]	2018	6	51	M	Bulb	Brunneroma	No	Yes	13	Padlock Pro
			44	M	D2	NET	Microperforation	Yes	4	Padlock Pro
			60	M	D2	Ectopic Pancreas	Hemorrhage	Yes	10	Padlock Pro
			44	M	D2	NET	Microperforation	Yes	9	Padlock Pro
			40	M	D2	NET	Perforation	Yes	10	Padlock Pro
			61	F	D2	NET	Microperforation	-	5	Padlock Pro
Al-Bawardy *et al*[17]	2017	4	66	M	Bulb	NET	No	Yes	9	Padlock
			78	M	Bulb	NET	No	Yes	9	OTSC
			76	M	Bulb	NET	No	Yes	10	OTSC
			59	M	D2	Pancreatic Heterotopia	No	Yes	18	OTSC
Milano *et al*[19]	2016	1	49	M	Bulb	NET	No	Yes	10	OTSC
Schmidt *et al*[8]	2015	4	74	F	Bulb	Inflammatory polyp	No	Yes	22	OTSC
			77	M	D3	Adenoma HGD	Minor bleed	Yes	15	OTSC
			35	F	D2	NET	No	Yes	10	OTSC
			57	F	D2	Adenoma HGD	Minor bleed	No	30	OTSC
Fähndrich *et al*[13]	2015	1	68	F	D	NET	No	Yes	20	OTSC
Sarker *et al*[16]	2014	4	71	F	D2	NET	No	Yes	18	OTSC
			66	M	D	NET	No	Yes	9	OTSC
			58	M	D	NET	No	Yes	10	OTSC
			66	M	D	NET	No	Yes	15	OTSC
Mönkemüller *et al*[18]	2014	1	71	F	D2	NET	No	No	30	OTSC

Bulb: Duodenal bulb; D: Duodenum, unspecified location; D2: Second part of duodenum; D3: Third part of duodenum; EFTR: Endoscopic full thickness resection; F: Female; HGD: High grade dysplasia; M: Male; NET: Neuroendocrine tumor; OTSC: Over the scope clip (OVESCO®); R0: Microscopic tumor-free vertical and horizontal margins in specimen.

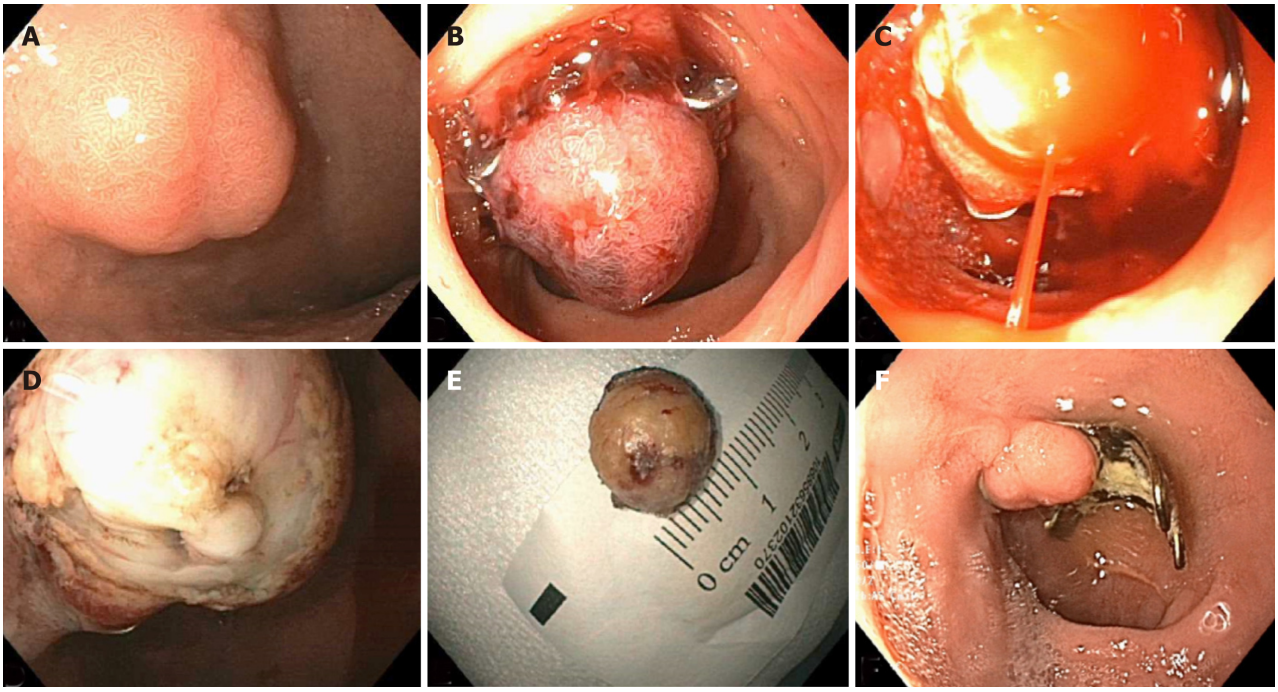

Figure 2 Endoscopic view of duodenal lesion. A: Duodenal nodule prior to intervention; B: Pseudopolyp lesion after deployment of over the scope clip; C: Arterial spurting of blood from the lesion during resection; D: Post-resection defect; E: *En bloc* resected specimen; F: Follow up upper endoscopy revealing over the scope (OVESCO®) clip, scar and granulation tissue.

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