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EDITORIAL

Gastrointestinal endoscopy biopsy derived proteomic patterns predict indeterminate colitis into ulcerative colitis and Crohn's colitis

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Abstract

Patients with indeterminate colitis (IC) are significantly younger at diagnosis with onset of symptoms before the age of 18 years with significant morbidity in the interim. The successful care of IC is based on microscopic visual predict precision of eventual ulcerative colitis (UC) or Crohn's colitis (CC) which is not offered in 15%-30% of inflammatory bowel disease (IBD) patients even after a combined state-of-the-art classification system of clinical, visual endoscopic, radiologic and histologic examination. These figures have not changed over the past 3 decades despite the introduction of newer diagnostic modalities. The patient outcomes after restorative proctocolectomy and ileal pouch-anal anastomosis may be painstaking if IC turns into CC. Our approach is aiming at developing a single sensitive and absolute accurate diagnostic test tool during the first clinic visit through endoscopic biopsy derived proteomic patterns. Matrix-assisted-laser desorption/ionization mass spectrometry (MS) and/or imaging MS technologies permit a histology-directed cellular test of endoscopy biopsy which identifies phenotype specific proteins, as biomarker that would assist clinicians more accurately delineate IC as being

either a UC or CC or a non-IBD condition. These novel studies are underway on larger cohorts and are highly innovative with significances in differentiating a UC from CC in patients with IC and could lend mechanistic insights into IBD pathogenesis.

Key words: Indeterminate; Ulcerative; Crohn's colitis; The colitides; Proteomics; Diagnostic accuracy

Core tip: This Editorial is introductory, dedicated to a novel and innovative study with clinical relevance regarding precision of indeterminate colitis (IC) into accurate diagnosis of either ulcerative colitis (UC) or Crohn's colitis (CC). To date, it is very difficult to predict the clinical course of IC, whether it will evolve into UC or CC. About 90% of IC is diagnosed at the time of colectomy for fulminant colitis and subsequent management critically depends on the correct eventual diagnosis. The outcome after colectomy and pouch anastomosis may be painstaking if IC turns into CC. The undergoing studies of proteomic analysis on colon biopsy specimens, if successful will permit delineate IC into UC or CC precision which could be of great help in decision making regarding treatment indication. Although the present data is convincing and support differentiated between UC and CC, this data requires validation and confirmation on a large scale by clinical studies. Hopefully, this editorial will stimulate research into this field to trying to overcome the diagnostic accuracy challenges in inflammatory bowel diseases.

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INTRODUCTION

In endoscopic medicine, predicting the phenotypic outcomes of "indeterminate colitis (IC)", given its unpredictable clinical presentation and disease course, is challenging[1,2]. Inadequate differentiated diagnoses of the two predominantly colonic inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's colitis (CC), may lead to the inconclusive IC diagnosis even when a state-of-the-art classification system of combined clinical, endoscopic, radiologic and histologic tools[1,2] are used. Unless there is a unique and yet unclassified class of colitis, the field needs to develop supplemental molecular biomarker tools for precise and rapid distinction between UC and CC for patients that will otherwise be diagnosed with IC. Previous studies using mucosal biopsy[3,4] have been successful as prognostic indicators for IBD whether the colitis is in a quiescent or active state, but have not been able to distinguish UC from CC[3,4]. Patients with IC are significantly younger at diagnosis (M ± SEM, 9.53 ± 4.8 years)[5-8] with onset of symptoms before the age of 18 years[9-13]. IC shows an equal gender distribution[8,14,15]. In contrast, UC is predominant among males and the mean age at onset is 36-39 years[14-18]. These figures have not changed over the past 3 decades despite the introduction of newer diagnostic modalities[1,2,5,10,13,19]. Even after long-term surveillance, a substantial number of patients with IC still have an unchanged diagnosis[5,19,20], with significant patient suffering in the interim[5,19,20]. The continued presence of an IC diagnosis over a long period of time supports part of our hypothesis that IBD may represent a spectrum of diseases rather than just two entities, Crohn's disease (CD) and UC[21].

The need for IC classification into either UC or CC is important for proper care in patients suffering from IBD, with obvious therapeutic and prognostic implications[22]. Early and accurate diagnosis and sub-classification of UC and CC is therefore the cornerstone for personalized and evidence-based interventional care[23-25]. These two pathologies have differing therapeutic strategies and prognoses. Most patients with UC, or IC likely to develop UC[22], will require pouch surgery for resolution[26-30]. Pouch surgery is well-established[22] and restores gut continuity, defecation, deferral, and discrimination, but is only successful if the UC and/or IC likely to develop UC diagnosis is correct[31,32]. However, IC and UC are mistakenly diagnosed in patients with CC[1,33]. Current data show that 15% of IBD patients who undergo pouch surgery for presumed definitive UC (or IC likely to develop UC) subsequently are diagnosed with *de novo* CD in the ileal pouch[34,35]. Identifying patients with CC and positive outcomes after pouch surgery is a painstaking clinical experience[4,34,35]. Ileal pouch anal anastomosis is acceptable standard care for UC patients, and restorative proctocolectomy should be contraindicated for CC patients[4,36,37] .

Pouch complications are significantly higher in patients with CC (± 64%) and IC (± 43%) *vs* patients having UC (± 22%) ($P < 0.05$)[23,38,39]. This diagnostic dilemma holds potential morbidity from unnecessary and/or inappropriate surgery, and underscores the need for a research strategy focused on developing molecular biometrics to improve diagnosis of colitides at initial endoscopic biopsy[21,40-44]. De novo CD in the ileal pouch is the diagnosis most feared by IBD patients and doctors due to its intractable nature and associated complications which often necessitate excision of the pouch with a permanent end-ileostomy[45-49].

ADVANCES

Mass spectrometry (MS) and imaging mass spectrometry (IMS)[21] are non-invasive technologies that can measure individual molecules in complex endoscopic and surgical clinical specimens[40,41]. These analyses

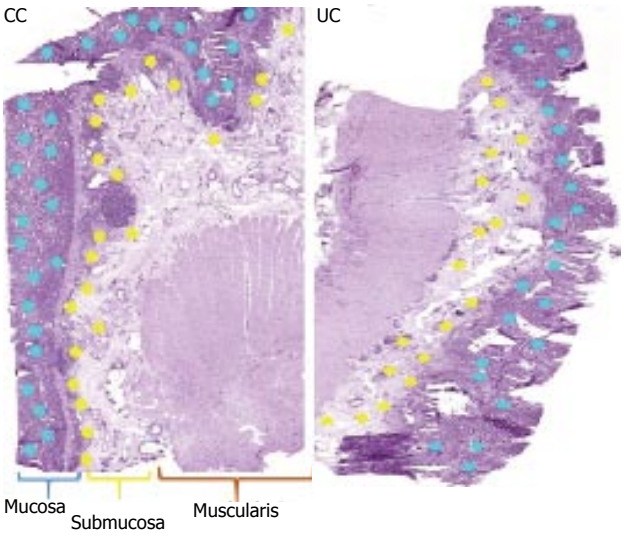

Figure 1 Illustrates histology-directed tissue compartment proteomics profiling using matrix-assisted-laser desorption/ionization mass spectrometry. Digital photomicrographs acquired form histology and matrix-assisted-laser desorption/ionization sections are used to identify and designate sites of interest for profiling. Using bioinformatics technology comparisons are performed in both the training and independent test set samples between inflamed mucosa and inflamed submucosa Crohn's colitis (CC) *vs* ulcerative colitis (UC). Tissue showing marked areas of pathological interest. Rings demonstrate matrix spots in mucosal (blue) and submucosal (yellow) layers (our unpublished data).

provide quantitative and qualitative data about cellular systems, and can differentiate diseased from normal tissue, and can identify diseases within the same organ[40,41,50]. These characteristics offer significant diagnostic and prognostic potential for clinical medicine and could supplement known clinicopathologic variables for delineating IC into UC or CC at a patient's first clinical visit. Due to the current alarming epidemiologic studies indicate that the incidence and prevalence of IBD is widening worldwide, especially in developing nations[9,21,51-60], established techniques like MS and IMS, which are affordable, non-invasive, easier, accurate and faster at screening for potential delineation of IBD, ought to be considered for clinical applications in IBD laboratories. The basic steps of the MS/IMS methodology of histology-directed proteomic patterns profiling are outlined in Figure 1.

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REVIEW

Advances in endoscopic retrograde cholangiopancreatography for the treatment of cholangiocarcinoma

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Abstract

Cholangiocarcinoma (CCA) is a malignancy of the bile ducts that carries high morbidity and mortality. Patients with CCA typically present with obstructive jaundice, and associated complications of CCA include cholangitis and biliary sepsis. Endoscopic retrograde cholangiopancreatography (ERCP) is a valuable treatment modality for patients with CCA, as it enables internal drainage of blocked bile ducts and hepatic segments by using plastic or metal stents. While there remains debate as to if bilateral (or multi-segmental) hepatic drainage is required and/or superior to unilateral drainage, the underlying tenant of draining any persistently opacified bile ducts is paramount to good ERCP practice and good clinical outcomes. Endoscopic therapy for malignant biliary strictures from CCA has advanced to include ablative therapies *via* ERCP-directed photodynamic therapy (PDT) or radiofrequency ablation (RFA). While ERCP techniques cannot cure CCA, advancements in the field of ERCP have enabled us to improve upon the quality of life of patients with inoperable and incurable disease. ERCP-directed PDT has been used in lieu of brachytherapy to provide neoadjuvant local tumor control in patients with CCA who are awaiting liver transplantation. Lastly, mounting evidence suggests that palliative ERCP-directed PDT, and probably ERCP-directed RFA as well, offer a survival advantage to patients with this difficult-to-treat malignancy.

Key words: Endoscopic retrograde cholangiopancreatography; Cholangiocarcinoma; Stents; Self-expandable metal stents; Photodynamic therapy; Photodynamic therapy; Radiofrequency ablation; Radiofrequency ablation

Core tip: Endoscopic retrograde cholangiopancreatography (ERCP) is a valuable treatment modality for patients with cholangiocarcinoma (CCA), as it enables

luminal drainage of blocked bile ducts and hepatic segments by using plastic or metal stents. While there remains some debate as to if bilateral hepatic drainage is required and/or superior to unilateral drainage, the underlying tenant of draining any persistently opacified bile ducts is paramount to good ERCP practice. Although ERCP interventions cannot cure CCA, advancements in the field of ERCP, including ERCP-directed photodynamic therapy and radiofrequency ablation, likely confer a survival advantage and improve upon the quality of life of patients with incurable disease.

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INTRODUCTION

Cholangiocarcinoma (CCA) is the second most common primary neoplasm of the liver[1]. It arises from malignant transformation of cholangiocytes, which are the epithelial cells that line the biliary tree. CCA may be classified based on location as intrahepatic, perihilar, or extrahepatic[1]. Perihilar lesions are further sub-classified depending on their proximal tumor extension according to the classification proposed by Bismuth[2]. Seventy percent of tumors present with bilateral hilar involvement - termed "Klatskin tumors" - and are unresectable cancers[2]. Although CCA is a rare malignancy with 3500 to 5000 cases diagnosed annually in the United States[3], mortality from this cancer is high due to a typically late presentation and limited curative therapies[3].

In patients with inoperable, incurable CCA, initial management usually involves drainage of malignant biliary obstruction and palliation of jaundice. Nevertheless, systemic or locoregional therapies do exist that offer the potential for tumor control, in part to mitigate the complications of further biliary obstruction. Chemotherapeutic agents and radiation therapies have been utilized to achieve this end, although their efficacy is limited, with partial response rates with chemotherapy demonstrated to be 35.9%, and with a stable disease rate of only 26.9%[4].

Over the past two to three decades, the management of CCA has evolved. While surgery remains a curative option for early disease, most cases of CCA are unresectable at the time of presentation. The typical presenting sign of CCA is jaundice. As such, decompressive biliary drainage techniques can help bridge symptomatic patients to surgery, and they can also be used for palliation by treating jaundice and pruritus and by reducing the risk of cholangitis. Various strategies have been employed for biliary drainage, including surgical drainage, percutaneous drainage, and endoscopic decompression *via* nasobiliary drainage or internal biliary stenting. Other mainly palliative modalities for treatment of CCA involve chemoradiation, transarterial chemoembolization, and ablative therapies such as brachytherapy, photodynamic therapy (PDT), and radiofrequency ablation (RFA), which can be applied intraoperatively, percutaneously, or endoscopically[5]. Herein, we will focus on endobiliary therapies for the treatment of CCA and its complications, and the majority of this review will pertain to interventions delivered *via* endoscopic retrograde cholangiopancreatography (ERCP).

BILIARY DECOMPRESSION

While surgical resection is the only treatment that offers curative intent to patients with CCA, the morbidity and mortality associated with liver resection is significantly higher in patients with obstructive jaundice than in patients with normal liver function[6]. Therefore, preoperative biliary drainage is routinely performed to reverse cholestatic liver dysfunction and reduce mortality after selective hepatectomy[7].

Historically, surgical bypass (hepaticojejunostomy or choledochojejunostomy) was the primary modality of biliary drainage prior to percutaneous and endoscopic advancements[8-11]. With advances in endoscopic therapy, particularly the development and refinement of ERCP, endoscopic decompression of obstructive jaundice due to malignant biliary stricturing from CCA should be considered the standard of care[12-16]. While adverse events are influenced by the clinical scenario, the risks associated with ERCP are well documented and uncommon. An American Society for Gastrointestinal Endoscopy guideline on "Complications of ERCP" reports a post-ERCP pancreatitis rate of about 3.5% (range 1.6%-15.7%), a rate of hemorrhage of 1.3%, and a perforation rate of 0.1%-0.6%[17]. Typically, the rate of post-ERCP cholangitis is 1% or less, but this risk does increase in situations of ERCP for drainage of malignant biliary obstruction[17].

In circumstances where biliary decompression is not possible or is incomplete by ERCP, percutaneous transhepatic biliary drainage (PTBD) can be an effective adjunctive therapy. However, PTBD is also associated with its own risks, including intra-procedural death in 1.7% of cases[18].

Many variables must be considered when endoscopic biliary drainage is pursued in patients with obstructive jaundice from CCA. Decisions include whether to use plastic stents (PS) *vs* self-expandable metal stents (SEMS) and whether to pursue unilateral *vs* bilateral biliary stenting.

UNILATERAL *VS* BILATERAL BILIARY DRAINAGE

In patients with Bismuth I perihilar cholangiocarcinoma,

which involves the extrahepatic bile duct but not the biliary confluence, a single stent that crosses the malignant stricture is usually adequate[12]. However, when considering patients with obstructive jaundice from more advanced CCAs that might involve the biliary confluence but not the second-order radicals (Bismuth Ⅱ), or for those that involve the right (Bismuth ⅢA), left (Bismuth ⅢB), or bilateral (Bismuth Ⅳ) hepatic ducts and higher-order branches, it has been suggested that drainage of as little as 25% of the liver can result in resolution of jaundice[19]. Thus, placement of a single stent into one lobe of the liver can result in sufficient biliary decompression in many cases. In some circumstances, segments of the liver that are inaccessible may be atrophied due to chronic involvement of tumor, making additional stenting unnecessary. However, in cases of Bismuth type II, Ⅲ, or Ⅳ CCA, the optimal location and number of stents remains controversial and has been addressed by a number of studies[12-16,20-31].

Deviere *et al*[12] demonstrated in 1988 that bilateral biliary stenting was associated with significantly improved survival and decreased development of cholangitis compared to unilateral stenting. However, in that study, contrast was injected into both lobes of the liver in all patients making the need for bilateral stenting more critical. In instances where one or more segments of the liver are injected with contrast, cholangitis may develop if adequate drainage is not achieved. This concept underscores an important point that - given the advancements in radiographic imaging - whenever possible, a thinly-sliced computed tomography (CT) scan performed on a multidetector scanner or a contrasted magnetic resonance imaging scan with magnetic resonance cholangiopancreatogram (MRCP) should be obtained prior to ERCP. High resolution cross-sectional imaging can identify areas of obstruction that can be selectively targeted for biliary decompression during ERCP, thereby avoiding over-opacification of the intrahepatic bile ducts[32,33].

In 1998, Chang *et al*[20] reviewed fluoroscopic images from ERCPs conducted for biliary decompression in 141 patients with hilar CCA. Those patients who had either a single lobe opacified and drained (unilateral stenting) or both lobes opacified and drained (bilateral stenting) had a significantly lower incidence of cholangitis and mortality compared with those patients who had both lobes of the liver opacified and only one side drained. These findings highlight that the decision to pursue unilateral *vs* bilateral stenting is greatly influenced by procedure-related issues, such as the extent of intrahepatic biliary opacification as well as the ease/difficulty of cannulating and subsequently draining various intrahepatic segments.

Other reports have suggested that drainage of more than 50% of the liver volume is associated with improved survival[34]. In a large retrospective review of 480 patients receiving endoscopic biliary drainage for hilar CCA, bilateral stenting (with either SEMS or PS) resulted in significantly longer overall stent patency compared with unilateral stenting [18 wk *vs* 17 wk for PS (P = 0.0004) and 27 wk *vs* 20 wk for SEMS (P < 0.0001)][26]. This finding had previously been reported in a smaller retrospective review of 46 consecutive patients undergoing palliative endoscopic biliary stent placement for malignant hilar obstruction. In a subgroup with hilar CCA, significantly greater overall stent patency was found in the group receiving bilateral stenting compared to the unilateral stenting group (P = 0.009)[27].

In 2001, De Palma *et al*[21] randomized patients in Italy with malignant hilar obstruction (about 57% from CCA) to unilateral or bilateral stenting for biliary decompression following a diagnostic cholangiogram. On intention-to-treat (ITT) analysis, patients who received unilateral 10-French (Fr) PS had significantly greater rates of successful stent insertion and drainage and also significantly lower rates of cholangitis (8.8% *vs* 16.6%, P = 0.013) compared to those who got bilateral PS. There were no significant differences between the two groups with respect to 30-d mortality, late complications, and median survival. It is important to note that successful stent insertion was significantly lower in the group randomized to bilateral PS (76.9%) as compared to the unilateral PS group (88.6%, P = 0.041). Bilateral stenting of complex hilar strictures from CCA is challenging and often requires significant device manipulation and repeated opacification of the biliary tree in order to access undrained hepatic segments using a guidewire. In fact, on per-protocol analysis (when only patients with successful unilateral and bilateral drainage were included) there was no difference in outcomes between these two groups, but this secondary analysis was underpowered to detect significant differences.

In considering these somewhat disparate data, it is probably best to be guided by the central tenet of endoscopic retrograde cholangiography, that drainage of any opacified large bile ducts or hepatic segments that do not drain spontaneously should be pursued. In a patient with complex perihilar stricturing, use of cross-sectional imaging to guide ERCP and limit contrast opacification can reduce the risk of cholangitis and other procedure-related complications. Planning an ERCP using cross-sectional imaging can also help one avoid opacifying atrophic segments that are less likely to be functional, which might also be more difficult to access and completely drain. When ERCP is performed using this type of a planned and deliberate approach, unilateral biliary stenting might be sufficient to relieve jaundice from a malignant hilar obstruction.

Lastly, effective treatment of patients with CCA requires multidisciplinary consultation. In patients with potentially resectable disease, the choice of which lobe or segments to drain may not be as simple as going after the largest volume of obstructed liver on cross-

sectional imaging. Indeed, presurgical biliary drainage of the lobe or segments of the liver that will remain after operative resection is key to avoiding atrophy of the liver remnant. If the bile ducts of the designated remnant liver are obstructed and not accessible by ERCP, drainage *via* PTBD should be pursued. In these situations, drainage of the portion of the liver targeted for resection might not be required, as atrophy of these segments is desired (and sometimes pursued by selective portal vein embolization) so as to cause hypertrophy of the future liver remnant, which reduces the risk of post-resection hepatic decompensation[35,36].

PLASTIC *VS* SELF-EXPANDABLE METAL STENTS

The issue of the most appropriate means of biliary decompression is further complicated by the decision to utilize either PS or SEMS. Plastic stents are smaller in caliber and tend to form biofilms, resulting in earlier obstruction than SEMS. On average, PS need to be exchanged at least every 3 mo, while SEMS may remain patent for 6 to 12 mo or longer. Raju *et al*[37] demonstrated median SEMS patency of 5.6 mo compared with 1.9 mo for PS, and they found SEMS to be more cost effective because of reduced need for re-intervention. The advantage of PS is that they are removable, and thus their use may be more attractive in patients with good functional status who might outlive a palliative SEMS. Metal stents are available in uncovered, partially-covered, or fully-covered versions. While fully-covered SEMS are potentially removable, their use across a perihilar stricture can be problematic as they can inadvertently obstruct other intersecting normal bile ducts due to their coating. Covered SEMS are also more prone to migration. Uncovered SEMS are less likely to migrate as tumor ingrowth keeps these stents in place, although tumor ingrowth can also lead to stent occlusion. In clinical practice, many interventional endoscopists tend to favor plastic biliary stenting in situations where the diagnosis remains in question, when surgery might still be possible, and in those patients who are likely to outlive the patency of permanent uncovered SEMS.

Multiple non-randomized and randomized trials have demonstrated greater patency with use of SEMS in patients with inoperable CCA, as compared to plastic stenting[13-16,23,25-30,38-40]. Peters *et al*[16] conducted a small prospective pilot study in 1997 to assess the efficacy of SEMS for palliation of jaundice in patients with malignant hilar strictures. Of the 17 patients included, 11 had CCA, and 9 demonstrated adequate drainage following SEMS placement as reflected by a significant decrease in bilirubin. The 2 patients who did not obtain relief from jaundice had extensive intrahepatic disease. Median stent patency was 12 mo with median survival of 10 mo. While these authors concluded that SEMS appeared to provide durable palliation for high-grade malignant biliary strictures, they cautioned against direct comparison with PS until a controlled trial comparing the two modalities had been completed.

In 2003, Kaassis *et al*[13] published a randomized study that found no significant survival difference in patients with malignant common bile duct strictures who underwent SEMS placement compared with patients who underwent PS placement. However, time to the first episode of biliary obstruction was significantly longer in the group receiving SEMS (P = 0.007). Metal stenting was also noted to be more cost-effective in patients without hepatic metastases, who had longer survival (5.3 mo *vs* 2.7 mo in patients with metastases). These authors recommended that plastic stenting was more appropriate in patients with advanced disease, signified by metastases, due to their shorter expected survival[13].

A large retrospective review of 480 patients who received endoscopic biliary drainage in the setting of hilar CCA over a 15-year period demonstrated greater functional success (defined by a decrease in bilirubin to less than 75% of pre-treatment level) with SEMS placement (97.9%) compared with PS placement (84.8%, P < 0.001)[26]. Furthermore, there were significantly greater rates of early complications (8.3% *vs* 2.0%) and late complications (56.4% *vs* 24.4%) in the group that received PS compared to the group that received SEMS. Interestingly, multivariate analysis using Poisson regression showed that SEMS placement (P < 0.01) and bilateral deployment (P < 0.01) were the only independent prognostic factors associated with stent patency[26].

In 2012, Sangchan *et al*[30] conducted an open-label randomized controlled trial in Thailand that compared PS to SEMS placement for unresectable hilar CCA. 180 patients underwent ERCP with randomization to unilateral placement of a 10-mm-wide SEMS *vs* a 7-Fr or 10-Fr PS into the hepatic duct with the largest area of obstruction based on pre-procedural CT or MRCP. On ITT analysis, the rate of successful drainage in the SEMS group was significantly greater than in the PS group (70.4% *vs* 46.3%, P = 0.011)[30]. Median survival time for the SEMS group (126 d) was also significantly longer compared with the PS group (49 d, P = 0.0021).

In 2013, a randomized controlled trial conducted in Japan compared SEMS to PS for drainage of malignant biliary strictures[15]. This study found the 6-month stent patency in the SEMS group was significantly greater (81%) compared with the PS group (20%, P = 0.0012). Kaplan-Meir analysis demonstrated a 50% patency rate of 359 d in the SEMS group as compared to 112 d in the PS group (P = 0.0002). Furthermore, the mean number of interventions for stent failure was significantly lower in the SEMS group (0.63 times/patient) compared to the PS group (1.80 times/patient, P = 0.0008). Lastly, the overall total cost for the treatment was significantly lower in the SEMS group than in the PS group (P = 0.0222).

Overall, these studies support the use of SEMS over

PS for long-term palliation of patients with malignant biliary obstruction, including from unresectable CCA. Typically, uncovered SEMS should be used for palliation when strictures are found across the biliary confluence, and these SEMS likely have even greater utility and cost-effectiveness when expected survival exceeds 3 mo, such as in those patients without metastatic disease. However, with the advent of ERCP-directed ablative therapies for unresectable CCA, a substantial proportion of patients might now expect to outlive even the patency of SEMS. In these patients, a strategy of repeated ERCPs for plastic stent revision and possibly repeated ERCP-directed ablations for locoregional tumor control is reasonable, particularly while they maintain good functional status and quality of life.

PERCUTANEOUS TRANSHEPATIC BILIARY DECOMPRESSION

Biliary decompression and stent placement for malignant biliary strictures can also be achieved by a percutaneous approach. In most centers, PTBD is performed by interventional radiologists. Decompression tubes may be inserted into dilated proximal biliary radicals to facilitate drainage of static bile above the level of obstruction. Alternatively, stenting across a malignant stricture can also be achieved by PTBD, which then allows for bile drainage internally into the duodenum. However, several studies have evaluated the use of PTBD with mixed results[14]. Complications associated with PTBD include vascular injury, risk for tumor seeding, and discomfort at the external drain site[28]. Additionally, PTBD has reported intraprocedural hemorrhage and sepsis rates of 2.5% and a death rate of 1.7%[18].

Hamy *et al*[23] evaluated 35 patients with malignant hilar obstruction (most had CCA) who received a palliative SEMS *via* a percutaneous-transhepatic route. They found a 97% rate of adequate biliary drainage with a median survival of 182 d and a 25% rate of recurrent jaundice after 180 d. These results were corroborated by a large retrospective multicenter study of 84 patients that compared the efficacy of percutaneous-transhepatic to endoscopic SEMS placement for initial malignant biliary decompression[28]. In this study, the rate of successful initial biliary decompression was higher in the percutaneous group (92.7%) as compared with the endoscopically-placed SEMS group (77.3%)[28]. However, overall stent patency and survival-once decompression was achieved-were similar between the groups, suggesting that a well-placed stent, irrespective of how it was placed, is the key to durable biliary decompression and improved survival in patients with malignant biliary obstruction.

Oftentimes, the decision to pursue biliary drainage *via* ERCP or PTBD is determined by clinical reasons, such as in patients with surgically altered gastroduodenal anatomy in whom PTBD might offer easier or more reliable access for therapeutic biliary interventions, or by local expertise. PTBD can be a valuable adjunctive therapy to drain obstructed bile ducts not accessible by ERCP, particularly in patients who might be surgical candidates and require drainage of the future liver remnant so as to prevent atrophy. In our experience, most patients favor endoscopic biliary drainage whenever possible, as it obviates the need for an external catheter for drainage or access. In general, if an experienced biliary endoscopist is available who can perform complex ERCP (as treatment of a hilar tumor is considered a level-3-complexity ERCP by American Society for Gastrointestinal Endoscopy guidelines[41]), we suggest attempting biliary decompression *via* ERCP. If adequate biliary drainage by ERCP is not achieved, then PTBD is an important adjunctive therapy in this patient population that should be pursued. Furthermore, once a PTBD track is mature (which typically requires 3-4 wk), a rendezvous-ERCP procedure can be performed to internalize biliary drainage of a previously inaccessible segment, after which the PTBD catheter can be removed.

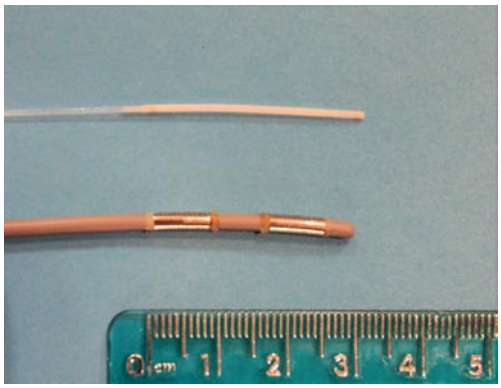

Figure 1 Endoscopic retrograde cholangiopancreatography-directed ablative therapies. Photodynamic therapy is applied *via* a laser fiber (above), whereas radiofrequency ablation is delivered using an 8-Fr catheter with two sets of bipolar rings (below).

ERCP-DIRECTED PHOTODYNAMIC THERAPY

PDT is a well-studied ablative therapy that induces tumor necrosis and apoptosis in treated portions of the biliary tree. The intravenous photosensitizer used in the United States is porfimer sodium (Photofrin, Pinnacle Biologics, Bannockburn, IL). While use of this drug for PDT in patients with CCA is done so off-label in the United States, Medicare and most private insurers in the United States do cover this procedure for palliation of unresectable CCA[42]. Porfimer sodium is typically administered intravenously, at 2 mg/kg, ideally 48 h (but possibly up to 72 h) before ERCP. At the time of ERCP, a 10-Fr bougie catheter (SBDC-10, Cook Medical, Bloomington, IL) or a choledochoscope (SpyGlass, Boston Scientific, Natick, MA) is advanced over a wire to

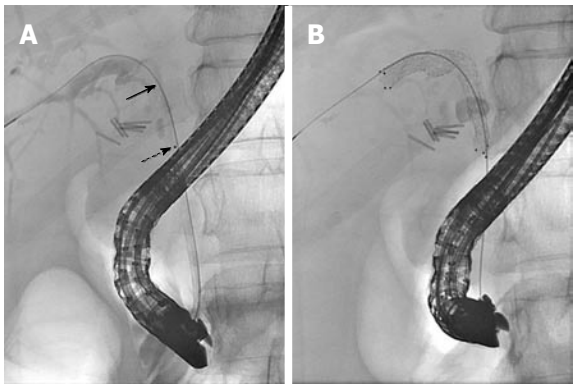

Figure 2 Endoscopic retrograde cholangiopancreatography-directed photodynamic therapy followed by unilateral metal stenting. A: Fluoroscopic view of a photodynamic therapy laser fiber delivered through a 10-Fr-bougie catheter during endoscopic retrograde cholangiopancreatography. The portion of the fiber that emits laser light is demarcated by the black dot (dashed arrow). The proximal-most tip of the fiber is not visible fluoroscopically (solid arrow) but is located near the biliary confluence; B: An 8 mm x 6 cm uncovered self-expandable metal stent was placed across a malignant stricture that involved the right hepatic duct and common hepatic duct.

the level of the malignant stricture and used to pass a laser fiber. This laser fiber (Figures 1 and 2) is then used to deliver activating light (at 630 nm for 750 s, with a light dose of 180 J/cm^2)[43]. When the photosensitizer is activated, oxygen free radicals are released that result in local tissue destruction. Since its first description for biliary tumor ablation in 1991[44], multiple studies have demonstrated that PDT can enable local tumor control and also can result in improved quality of life in this difficult-to-treat patient population[42,45-61]. Metal stent patency has also been shown to be significantly greater with PDT applied immediately prior to stent placement *vs* metal stent placement alone (median time of 244 d *vs* 177 d, respectively, $P = 0.002$)[49].

In 2003, Ortner *et al*[52] conducted a prospective, open-label, randomized, multicenter study of patients with unresectable CCA that compared PDT (using porfimer sodium) in addition to endoscopic or percutaneous stenting by using two 10-Fr endoprostheses *vs* stenting alone and demonstrated significant improvement in survival times (median 493 d *vs* 98 d, respectively, $P < 0.0001$)[52]. Improvement in cholestasis and quality of life indices were also reported. Another randomized controlled trial by Zoepf *et al*[60] in 2005 compared PDT (using Photosan-3, SeeLab, Wesselburenerkoog, Germany) and stenting *vs* stenting alone in patients with unresectable CCA. These investigators demonstrated significantly improved survival in the group that received PDT (21 mo) compared to the group that received only stents (7 mo, $P = 0.0109$). In this study, PDT was delivered *via* ERCP (transpapillary) or by percutaneous biliary access.

The survival benefit associated with PDT in patients with unresectable CCA has also been demonstrated by multiple heterogeneous cohort studies, which were mostly retrospective in nature[45,47,54,62,63]. In 2012, Leggett *et al*[50] conducted a meta-analysis that included six studies that contributed 170 patients with unresectable CCA who received PDT and biliary stenting *vs* 157 patients with CCA who underwent stenting alone. This meta-analysis found that PDT was associated with a statistically significant survival advantage (weighted mean difference of 265 d, $P = 0.01$) and significantly improved quality of life as reflected by improvement in Karnofsky score (weighted mean difference of 7.74, $P = 0.01$). While there appears to be sufficient data to support that at least one round of PDT offers a survival advantage to patients with incurable CCA, it is not clear if multiple rounds of PDT (done every few months) adds to the survival advantage[62]; nor is it clear if bilateral PDT is superior to unilateral PDT in the case of Bismuth IV tumors.

The merits of PDT are tempered somewhat by its potential side-effects. Although a study evaluating the safety and long-term efficacy of PDT using porfimer sodium reported no treatment-related mortality or grade-4 toxicity, complications including photosensitivity resulting in burns (Figure 3) and to a lesser extent bleeding, stenosis, and bile leak have been reported[46]. Cholangitis is usually the most commonly encountered problem that arises in patients with CCA who have undergone biliary intervention, and as expected cholangitis following PDT does occur. A major drawback with ERCP-directed PDT is the need for patients to avoid direct or indirect sunlight for 4-6 wk, which may significantly affect their quality of life. Efforts to limit light toxicity have also resulted in use of a newer photosensitizer meta-tetra(hydroxyphenyl)chlorin (Foscan, Biolitec AG, Jena, Germany) that has demonstrated efficacy in a small study while potentially removing the detrimental side-effects of prolonged skin photosensitivity[48]. Another major drawback of PDT is that the cost of a single-dose of porfimer sodium in a 75 kg patient is about USD $37208, which can be prohibitively high[43].

Nevertheless, PDT has several advantages including: (1) porfimer sodium preferentially accumulates in malignant cells, potentially reducing damage to non-malignant epithelium; and (2) laser light can refract through bile, which can transmit the PDT effect to malignant strictures that are not directly adjacent to (and might be inaccessible to) the laser fiber[43]. Because PDT is dependent on the transmittance of laser light, and does not require the laser fiber to directly make contact with tumor tissue, successful delivery of PDT through metal stents has been reported with appropriate adjustment of the light dose[64].

ERCP-DIRECTED RADIOFREQUENCY ABLATION

Percutaneously- and intraoperatively-directed RFA have been demonstrated by several studies to be efficacious for local tumor control in patients with

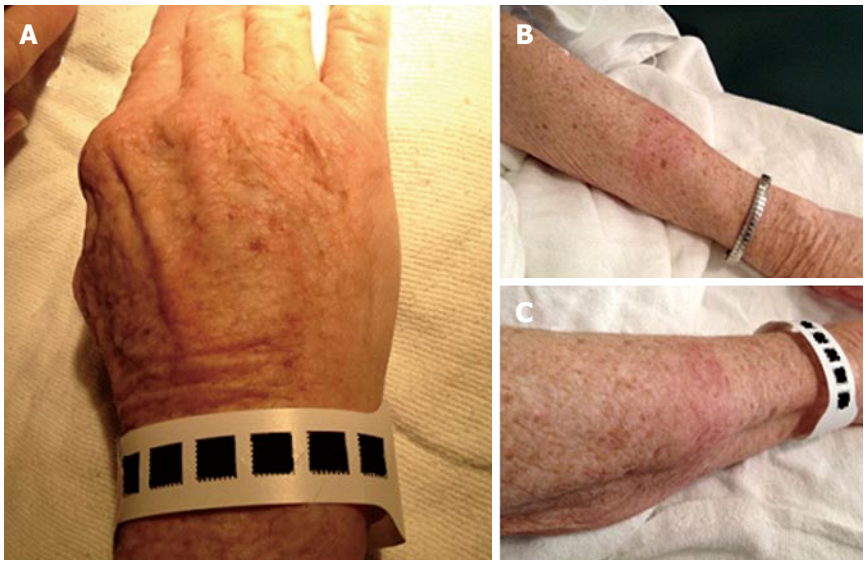

Figure 3 Photosensitivity following photodynamic therapy. A patient with unresectable cholangiocarcinoma was treated with photodynamic therapy. After 4 wk, a test dose of 10 min of exposure to direct sunlight on small areas of uncovered skin resulted in moderate burns on hands (A) and forearms (B, C). Two additional weeks of avoidance to even indirect sunlight was required.

inoperable CCA[65-70], including as an adjunct to surgery[71-73]. RFA has been used for local control of tumor recurrence following surgery in patients who may no longer be good operative candidates or for whom no other surgical intervention is possible[68,72], including those who have already undergone protocol liver transplantation for CCA[74]. However, complications following the percutaneous delivery of RFA are not trivial and have included gastrohepatic fistula[75], hemorrhage necessitating transarterial embolization[76], hepatic vein pseudoaneurysm[77], acute liver failure or abscess formation[78], and needle-tract seeding of tumor[79].

ERCP-directed RFA was developed to enable endoscopists to treat malignant biliary strictures *via* a mechanism of coagulative necrosis induced by thermal energy that is delivered *via* contact using a bipolar catheter[43]. One commercially available RFA catheter (Figure 1) is an 8-Fr device with two electrodes spaced 8 mm apart at the end of the catheter that can be passed over a guidewire (Habib EndoHPB; EMcision, London, United Kingdom)[80]. This device passed United States Food and Drug Administration 510[k] premarketing clearance in 2009. This RFA catheter can be passed through the accessory channel of a duodenoscope and into the bile duct (Figure 4). Fluoroscopic guidance is used to center the two sets of bipolar rings across a malignant stricture for RFA treatment (Figures 5 and 6).

In 2011, Steel *et al*[81] conducted a single-center open-label pilot study that demonstrated that ERCP-directed RFA could be performed safely and efficaciously in patients with malignant biliary strictures from unresectable pancreas cancer or CCA. In this initial study, all but one of 21 patients who had RFA followed by SEMS placement maintained stent patency at 30 d. One patient had asymptomatic biochemical pancreatitis, 2 patients required percutaneous gallbladder drainage, and 1 patient developed rigors. At 90-d follow-up, 3 patients had occluded biliary stents. Subsequently, in a retrospective series of 12 patients (9 with CCA) with malignant intraductal or perihilar biliary strictures, Tal *et al*[80] performed 19 successful RFA applications *via* ERCP followed by PS placement. These investigators used a setting of 8 W for treatment of intrahepatic and perihilar biliary strictures and 10 W for extrahepatic bile duct strictures using an ERBE electrosurgical generator (VIO 200D, ERBE Elektromedizin, Tübingen, Germany). However, biliary bleeding was observed at 4-6 wk in 3 patients (2 of whom died of hemorrhagic shock), and cholangitis developed in 4 patients, which was amenable to stent exchange. Finally, Figueroa-Barojas *et al*[82] reported on the use of ERCP-directed RFA in 25 patients with malignant biliary structures (11 patients had CCA). Procedures were performed using a RITA 1500X RF generator (Angiodynamics, Latham, NY) set at 7-10 W for a time period of 2 min. These investigators reported a resultant significant increase in mean bile duct diameter of 3.5 mm ($P < 0.0001$)[82]. In this series, 5 patients presented with pain after the procedure, one patient developed mild post-ERCP pancreatitis, and one patient developed cholecystitis following endobiliary RFA.

In 2014, Sharaiha *et al*[83] published a retrospective series of 66 patients with malignant biliary strictures (36 with CCA) who underwent either SEMS placement alone or RFA followed by SEMS placement. They reported 100% technical success in both groups. While these investigators found that rates of stent patency were similar between the two groups, on multivariate analysis, RFA was found to be an independent predictor of survival (HR = 0.29, 95%CI: 0.11-0.76, $P = 0.012$). Finally, RFA has been described as a means of treating tumor ingrowth of uncovered SEMS in the bile duct[84].

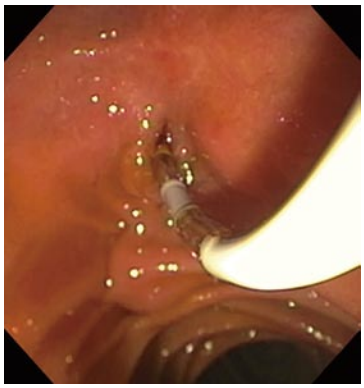

Figure 4 Endoscopic view of a radiofrequency ablation catheter being inserted into the bile duct by using a duodenoscope. A biliary sphincterotomy had been performed during a prior endoscopic retrograde cholangiopancreatography procedure in this patient with an unresectable cholangiocarcinoma to enable easier access to the bile duct. Note: this is not a depiction of radiofrequency ablation (RFA) actively being performed, as RFA is not typically applied with the bipolar coils exposed in the duodenal lumen, in order to avoid thermal injury to the duodenal wall.

Typically, the RFA catheter can be passed into a blocked stent and used under fluoroscopic guidance to ablate any tumor ingrowth, which is then removed by retrieval balloon sweep. This ablation may be followed by placement of an indwelling plastic stent or a second uncovered SEMS, in appropriate situations (Figure 6).

When compared to PDT, the advantages of endobiliary RFA include being able to provide ablative treatment without the patient having to come in 2 d in advance for infusion of a photosensitizer, easier delivery of the RFA catheter that can be done over a guidewire, and no requirement to avoid sunlight for several weeks to prevent photosensitivity. However, RFA requires direct contact with neoplastic tissue for ablation, thus it does not offer the "field effect" conferred by the laser light used in PDT, which can refract through bile to treat inaccessible blocked bile ducts.

In 2014, Strand *et al*[43] demonstrated comparable survival following ERCP-directed RFA *vs* ERCP-directed PDT. In this retrospective cohort study, 48 patients with unresectable CCA underwent RFA (n = 16) or PDT (n = 32) followed by plastic or metal biliary stenting. Overall median survival in both treatment groups was not statistically different (9.6 mo following RFA and 7.5 mo following PDT, P = 0.799). Furthermore, patients who underwent RFA had a lower mean number of plastic stents placed per month (0.45 *vs* 1.10, P = 0.001) but also had more episodes of stent occlusion (0.06 *vs* 0.02, P = 0.008) and cholangitis (0.13 *vs* 0.05, P = 0.008) per month, as compared to patients who received PDT.

In addition to the differing advantages and disadvantages of RFA *vs* PDT that were mentioned earlier, a major discriminating factor between these two ablative technologies is cost. Strand *et al*[43] noted that because both procedures required ERCP with sent exchange, the true cost differential is the difference between the cost of a dose of porfimer sodium (USD $37208) and the cost of the RFA catheter (USD $1295), which is $35913[43]. In the current environment of falling reimbursements and the need for cost-containment, this is a significant difference that favors ERCP-directed RFA.

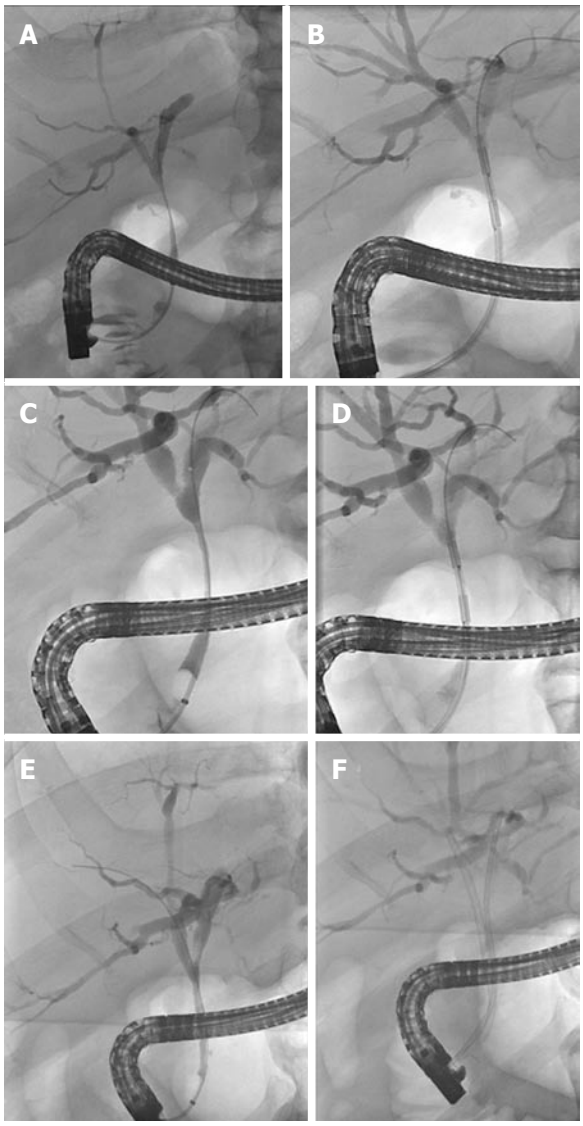

Figure 5 Effect of repeated endoscopic retrograde cholangiopancreatography-directed radiofrequency ablation on a malignant extrahepatic biliary stricture in a patient with unresectable cholangiocarcinoma. A long perihilar stricture is seen involving the extrahepatic duct (A) in a patient who had exploratory laparotomy that showed locally advanced and unresectable Bismuth I cholangiocarcinoma. A cholecystectomy had been performed at the time of laparotomy. Endoscopic retrograde cholangiopancreatography (ERCP)-directed radiofrequency ablation (RFA) was applied to this malignant stricture (B) followed by biliary stenting (not shown). Following two rounds of RFA done at about 3 mo intervals, a third ERCP showed moderate improvement in the stricture's diameter (C). Repeat ERCP-directed RFA was performed (D). After 4 rounds of RFA therapy, an ERCP 1 year later showed marked improvement of the extrahepatic bile duct with no high-grade stricture seen (E), and RFA was not repeated during this procedure. A 10-Fr plastic stent was placed into the right hepatic duct and a 7-Fr plastic stent was placed into the left hepatic duct for more durable biliary drainage (F), as this was an otherwise healthy patient with excellent functional status who would likely outlive metal stenting. While patients with Bismuth I cholangiocarcinoma often do well with a single extrahepatic biliary stent, this patient had previously had premature stent failure and cholangitis with a single plastic stent, thus two biliary stents were required.

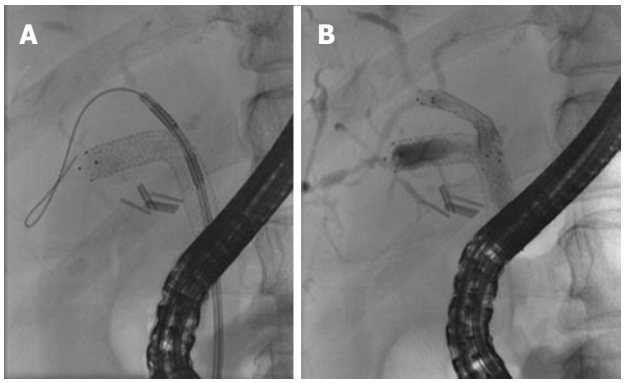

Figure 6 A patient with unresectable cholangiocarcinoma was previously treated with photodynamic therapy followed by placement of an uncovered metal stent (see Figure 2). For persistent symptomatic biliary obstruction due to undrained segments in the right liver, a wire was passed into the previously undrained segments which allowed for 6-Fr bougie dilation followed by 4-mm balloon dilation across the lattices of the existing large-cell uncovered self-expandable metal stent (SEMS) (not shown). After dilation, the 8-Fr radiofrequency ablation (RFA) catheter was deployed over the wire and through the SEMS, and RFA was applied to a malignant stricture that was obstructing drainage (A). Lastly an 8-mm uncovered SEMS was deployed through the previously placed 8-mm uncovered SEMS (B) enabling durable drainage of more of the right liver.

ERCP-DIRECTED NEOADJUVANT ABLATIVE THERAPY FOR CCA PRIOR TO LIVER TRANSPLANTATION

Experience with liver transplantation (LT) for unresectable CCA had previously been disappointing due to frequent cancer recurrence and poor 5-year survival rates[3]. To improve outcomes following LT for CCA, a protocol for neoadjuvant chemotherapy followed by LT was first developed at the University of Nebraska and then at the Mayo Clinic[3,85]. Patients who met the following criteria were included in this LT protocol: (1) perihilar location of suspected CCA; (2) a malignant-appearing stricture on cholangiography with malignant endoluminal brushing or biopsy, carbohydrate antigen 19-9 level > 100 U/mL (in the absence of cholangitis), mass on cross-sectional imaging, and/or polysomy on fluorescence *in situ* hybridization; (3) unresectable disease or disease arising in primary sclerosing cholangitis; (4) completion of neoadjuvant therapy before LT; and (5) medical suitability for LT[85]. Neoadjuvant therapy from the early "Mayo" protocol included administration of external beam radiation therapy (XBRT) and 5-fluorouracil, followed by brachytherapy[85-87]. Use of intraluminal brachytherapy and XBRT in patients with unresectable CCA has been reported for palliation of jaundice and as a treatment to temporarily obviate the need for biliary stenting[88,89]. Furthermore, a retrospective study by Darwish Murad *et al*[85] of 287 patients, 75% of whom received brachytherapy as part of neoadjuvant therapy prior to LT, demonstrated a 5-year ITT survival rate of 53% and post-transplant recurrence-free survival of 65%[85]. In this large series of patients, recurrence-free survival for patients who had received brachytherapy was similar to those who had not (HR = 1.05; 95%CI: 0.60-1.85)[85]. Other studies have also shown no mortality benefit from the addition of brachytherapy[90,91]. In an effort to mitigate side-effects associated with brachytherapy and the complexities associated with delivery of radioactive ribbons in the endoscopy or radiology suite, other endobiliary therapies for neoadjuvant locoregional CCA tumor control prior to LT have been adopted.

In particular, PDT, as mentioned previously, has been demonstrated to be a safe and potentially efficacious modality for locoregional control of perihilar CCA in palliative patients. In a proof-of-concept study performed at our institution, Cosgrove *et al*[42] reported on 4 patients with unresectable CCA who had undergone protocol-driven neoadjuvant chemoradiation followed by ERCP-directed PDT to provide endobiliary and local tumor control in patients who were awaiting LT[42]. Although the sample size of this study was small, none of the patients who received PDT had progressive locoregional disease or distant metastases during the pre-transplant period, and all patients underwent successful LT. ITT disease-free survival was 75% at a mean follow-up of 28.1 mo. Based on these data regarding PDT, as well as our comparable experience with RFA for patients with incurable CCA[43], our institution's protocol allows for the use of either PDT or RFA as an alternative to brachytherapy for locoregional tumor control in patients with inoperable CCA who are awaiting LT. Prospective trials to study these ERCP-directed neoadjuvant modalities for locoregional control in patients with CCA are indicated.

CONCLUSION

CCA is a malignancy with high morbidity and mortality due to its typically late presentation with obstructive jaundice, and its associated complications of cholangitis and biliary sepsis. ERCP is a valuable treatment modality for patients with CCA, as it enables internal luminal drainage of blocked bile ducts and hepatic segments by using plastic or metal stents. While there remains debate as to if bilateral (or multi-segmental) hepatic drainage is required and/or superior to unilateral drainage, the underlying tenant of draining any persistently opacified bile ducts is paramount to good ERCP practice and good clinical outcomes. Endoscopic therapy for malignant biliary strictures from CCA has advanced to include ablative therapies *via* ERCP-directed PDT or RFA. As chemoradiation is of limited efficacy in providing tumor control for this cancer, these endoscopic modalities, which offer the potential for locoregional control and hopefully more durable biliary drainage, are a much needed addition to our therapeutic endobiliary armamentarium. While ERCP techniques cannot cure CCA, advancements in the field of ERCP have enabled us to improve upon the quality of life of patients with incurable disease. ERCP-directed PDT has been used in lieu of brachytherapy to provide neoadjuvant local

tumor control in patients with CCA who are awaiting LT. Lastly, mounting evidence suggests that palliative ERCP-directed PDT, and probably ERCP-directed RFA as well, can offer a survival advantage to patients with this difficult-to-treat malignancy.

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REVIEW

Role of endoscopic ultrasonography in the loco-regional staging of patients with rectal cancer

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Abstract

The prognosis of rectal cancer (RC) is strictly related to both T and N stage of the disease at the time of diagnosis. RC staging is crucial for choosing the best multimodal therapy: patients with high risk locally advanced RC (LARC) undergo surgery after neoadjuvant chemotherapy and radiotherapy (NAT); those with low risk LARC are operated on after a preoperative short-course radiation therapy; finally, surgery alone is recommended only for early RC. Several imaging methods are used for staging patients with RC: computerized tomography, magnetic resonance imaging, positron emission tomography, and endoscopic ultrasound (EUS). EUS is highly accurate for the loco-regional staging of RC, since it is capable to evaluate precisely the mural infiltration of the tumor (T), especially in early RC. On the other hand, EUS is less accurate in restaging RC after NAT and before surgery. Finally, EUS is indicated for follow-up of patients operated on for RC, where there is a need for the surveillance of the anastomosis. The aim of this review is to highlight the impact of EUS on the management of patients with RC, evaluating its role in both preoperative staging and follow-up of patients after surgery.

Key words: Rectal cancer; Staging; Endoscopic ultrasonography; Accuracy; Therapeutic strategy

Core tip: In the era of tailored management of patients with rectal cancer (RC), endoscopic ultrasonography (EUS) has become crucial for the appropriate preoperative

staging of these patients. This review highlights the impact of EUS on the management of patients with RC, evaluating its role in both preoperative staging of RC and follow-up of patients after surgery. Finally, possible new application are discussed, on the basis of the technologic innovation and the evolution of the therapeutic strategies.

Marone P, de Bellis M, D'Angelo V, Delrio P, Passananti V, Di Girolamo E, Rossi GB, Rega D, Tracey MC, Tempesta AM. Role of endoscopic ultrasonography in the loco-regional staging of patients with rectal cancer. *World J Gastrointest Endosc* 2015; 7(7): 688-701 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i7/688.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i7.688

INTRODUCTION

Every year approximately 40000 patents are diagnosed with rectal cancer (RC), and the incidence of RC in the European Union is 15-25/100000 per year, with an estimated mortality of 4-10/100000 per year[1]. The prognosis of RC is strictly related to both T and N stage of the disease at the time of diagnosis[2]. This is traditionally staged according to local invasion depth (T stage), lymph node involvement (N stage), and presence of distant metastases (M stage) (Table 1)[3,4]. Staging RC is crucial for choosing the best multimodal therapy (Table 2)[2]: patients with high risk locally advanced RC (LARC) undergo surgery after neoadjuvant chemotherapy plus radiotherapy (NAT); those with low risk LARC are operated on after a preoperative short-course radiation therapy. The latter is used as a valid alternative to NAT in elderly patients, or for patients unfit for preoperative chemotherapy because of severe comorbidities. Finally, surgery alone is recommended only for early RC. Total mesorectal excision (TME) is the standard surgical approach, with or without sphincter preservation. Extended abdomino-perineal resection is performed in distal RC which requires sphincter demolition. Local excision is performed in small T1 cancers with favorable histology by means of trans anal endoscopic microsurgery (TEM) or trans anal minimally invasive surgery. Local excision is also performed in selected patients showing complete clinical response after NAT. Therefore, precise staging of patients has a pivotal role for the selection of different therapeutic options and team work among the members of the multidisciplinary team is mandatory to improve patients outcome[2].

Several imaging methods are used for staging patients with RC: computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and endoscopic ultrasound (EUS)[1]. The latter has a high accuracy for loco-regional staging of RC, since it is capable to evaluate precisely the mural infiltration of the tumor (T), especially in the early RC.

Table 1 The 2010 AJCC staging system for primary rectal cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*: Intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor directly invades or is adherent to other organs or structures
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional nodal metastasis
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (*i.e.*, liver, lung, ovary, non-regional node)
M1b	Metastases in more than one organ/site or the peritoneum

From ref.[3].

Table 2 Therapeutic strategy

cT1 cT2 cN0 cCRM-	Surgery alone
Any cT cN+	CRT
cT2 cT3 cN0 cCRM+	
cT2 cT3 cN0 cCRM-	SCRT

C: Clinical stage; CRM: Circumferential resection margin; CRT: Standard chemotherapy + radiation therapy; SCRT: Short term chemotherapy + radiotherapy. From ref.[2].

On the other hand, EUS is less accurate in restaging RC after NAT and before surgery. Recently, EUS has been used in clinical trials where patients have been selected for less invasive therapies: polypectomy for T1 RC; TEM for T1/T2-N0 cancers, and NAT + TEM for T2N0 tumors. Finally, EUS is indicated for following-up patients operated on for RC, where there is a need for surveillance of the colorectal anastomosis, which is at risk for local recurrences[2,5-7].

This review evaluates the role of EUS in the loco-regional staging of patients with RC, analyzing both accuracy and limits of this imaging method, which is part of the multidisciplinary approach for patients with RC. In particular, the aim of the review is to highlight the impact of EUS on the management of patients with RC, evaluating its role in both preoperative staging and follow-up after surgery. Finally, possible new applications are discussed on the basis of the

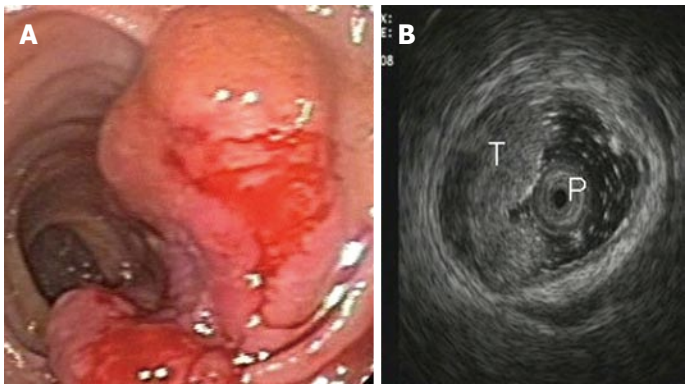

Figure 1 Stage T1 rectal cancer: (A) endoscopic and (B) ultrasonographic view. Endoscopic ultrasound with radial miniprobe (12 MHz), showing a small tumor located within the mucosa and superficial submucosal layers, and preservation of the outer layers of the rectal wall. T: Tumor; P: Radial probe.

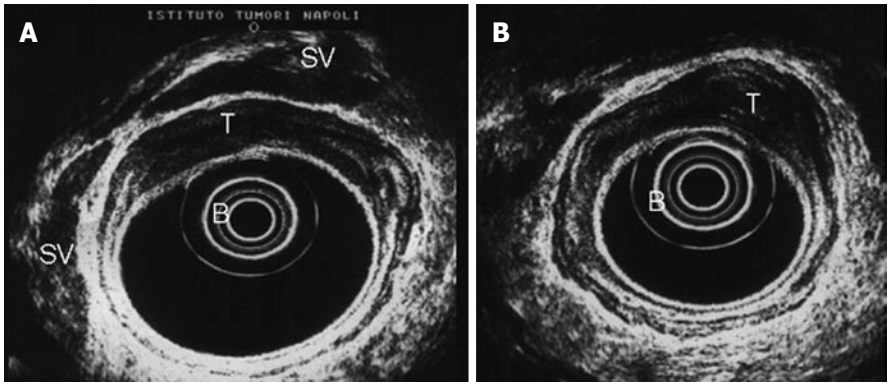

Figure 2 Stage T2 rectal cancer: Ultrasonographic view. The tumor infiltrated the entire wall, without invading the smooth outer margin of the muscularis propria (fourth layer). Endoscopic ultrasound with radial array transducer UM 20 (7.5-12 MHz). B: Ballon; T: Tumor; SV: Seminal vesicles.

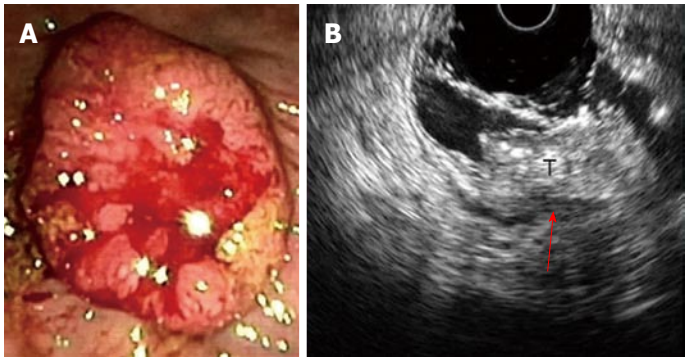

Figure 3 Stage T3 rectal cancer: (A) endoscopic and (B) ultrasonographic view. Endoscopic ultrasound with radial array transducer UM160 (5-20 MHz), showing increased wall thickness for the presence of a mass with inhomogeneous echogenicity, invading all the layers of the wall and minimal infiltration of the perirectal fat. T: Tumor; Red arrow: Infiltration of the perirectal fat.

technological innovation and the evolution of the therapeutic strategies[7-10] (Figure 1).

EUS Accuracy in staging rectal cancer T staging

At the time of EUS, RC usually appear as a hypoechoic mass, with loss of the normal echo-layers of the wall, which is inhomogeneous and irregular because of the fusion of the layers infiltrated by the tumor[5,9-11]. According to the infiltration depth, there are four different echoendoscopic T stages (uT) (Table 3, Figures 1-5). In patients with RC, EUS assesses the tumor penetration depth into the rectal wall, with an overall accuracy for T stage of about 84%, ranging from 63% to 96%, while the reported accuracy of CT and MRI are 65%-75% and 75%-85%, respectively (Table 4)[12-45]. In a systematic review of 31 articles published over a period of 20 years, Skandarajah *et al*[46] reported that EUS has an overall accuracy of 82% for T stage and it is useful for discriminating early superficial RC. In another review of 42 studies, which analyzed the accuracy of EUS in patients with RC, confirmed by pathological exam of the surgical specimen, Puli *et al*[47,48] concluded that EUS has a sensitivity of 81%-96% and a specificity of 91%-98%, showing a higher sensitivity for LARC (95%), compared with early cancer (88%). In a multicenter, prospective, study conducted in 384 hospitals in Germany over a 8-year period, Marusch *et al*[49] analyzed the diagnostic accuracy of rectal EUS in the clinical staging of 7000 patients with RC who had not received NAT. This allowed uT *vs* pT comparison, which showed a uT-pT correspondence of 65%. The latter was related to the hospital volume, with uT-pT correspondence of 63% for hospitals undertaking ≤10 EUS/year, 65% for those performing 11-30 EUS/year,

Table 3 T staging (uT) of rectal cancer at endoscopic ultrasound, according to the infiltration depth

uT1 = tumor invasion limited to the mucosa and the submucosa; this is further divided into T1m, if the tumor infiltrates the mucosa, with normal muscolaris mucosa, and T1sm, when there is submucosal invasion (Figures 1 and 7)
uT2 = tumor infiltration of the muscolaris propria, with the tumor mass extended through the first 4 layers of the rectal wall. The outer layer corresponding to the muscolaris propria is smooth, meaning that the tumor is still limited to the rectal wall (Figure 2)
uT3 = tumor invasion of the perirectal fat, with an irregular 4th layer, which means that the tumor has spread outside the rectal wall (Figures 3 and 4)
uT4 = tumor infiltration of adjacent structures and organs, which are strictly connected to the rectal hypoechoic mass (Figure 5)

From ref.[9].

Table 4 Endoscopic ultrasound accuracy of T and N stage of rectal cancer

Ref.	Pts no.	T Stage	N Stage	P/R	Tipe of EUS probe
Saitoh *et al*[13]	88	90%	75%	-	Flexible, radial, (7 MHz) Rigid, radial (5-7.5 MHz)
Feifel *et al*[14]	79	89%	-	P	Rigid, linear (3-7 MHz)
Yamashita *et al*[15]	122	78%	-	R	Rigid, linear (5.5-7 MHz)
Beynon *et al*[16]	100	93%	83%	-	Rigid
Rifkin *et al*[17]	102	72%	81%		Rigid, radial (7 MHz)
Hildebrandt *et al*[18]	113	-	78%	P	Rigid, radial (7 MHz)
Tio *et al*[19]	91	88%	-	-	Rigid
Katsura *et al*[20]	120	92%	-		Rigid, radial, (7 MHz)
Glaser *et al*[21]	154	86%	81%	P	Rigid, radial (7 MHz)
Herzog *et al*[22]	118	89%	80%	P	Rigid, radial (7 MHz)
Cho *et al*[23]	76	82%	70%	P	Flexible, radial (7 MHz)
Thaler *et al*[24]	36	88%	80%	P	Rotating wall transducer IR 1510 AKTM (Kretz) (5, 7.5, 10 MHz)
Nielson *et al*[25]	100	85%	-	-	Probe (7 MHz)
Sailer *et al*[26]	160	77%	83%	P	Rigid
Nishimori *et al*[27]	70	76%	69%		Flexible
Norton *et al*[28]	121	92%	65%	P	Flexible, radial (7.5-12 MHz)
Kim *et al*[29]	89	81%	63%		Rotating transducer (7.5 MHz)
Marone *et al*[30]	63	81%	70%	R	Flexible, radial (7.5-12 MHz)
Akasu *et al*[31]	154	96%	72%	R	Flexible, radial (7.5-12 MHz
Garcia-Aquilar *et al*[32]	545	69%	64%	P	Rigid, radial (7-10 MHz)
Harewood *et al*[12]	80	91%	82%	P	Flexible, radial (7.5-12 MHz)
Marusch *et al*[33]	422	63%	-	P	Rigid
Kauer *et al*[34]	458	69%	68%	R	Probe (7.5-10 MHz)
Vila *et al*[35]	120	83%	72%	P	Flexible, radial
Landman *et al*[36]	938	-	70%	P	Probe (10 MHz)
Halefoglu *et al*[37]	34	85%	76%	P	Probe (7-10 MHz)
Lin *et al*[38]	192	86%	78%	P	Flexible, radial (7.5-12 MHz)
Fernández-Esparrach *et al*[39]	90	95%	65%	P	Flexible, radial (5-20 MHz)
Ünsal *et al*[40]	31	80%	70%	R	Radial
Zhu *et al*[41]	110	91%	85%	-	Rigid, radial (5-10 MHz)
	4976				
Mean		84	74		
Range		63-96	63-85		

uTN stage compared with pTN stage; no previous neoadjuvant therapy (NAT). P: Prospective; R: Retrospective; Pts: Patients; EUS: Endoscopic ultrasound.

and 73% for hospitals where more than 30 EUS/year were performed. Furthermore, the poorest uT-pT correspondence was found for T2 and T4 RC, with understaging occurring in 18% of cases and overstaging in 17% of patients[49]. These results were similar to those of a previous multicenter, prospective, study conducted by the same authors who reported that EUS had overall accuracy of 63% for T staging of RC. The diagnostic accuracy was 51% for pT1 RC, 58% for pT2 lesions, 73% for pT3 tumors, and 44% for pT4 cancers, with overstaging in 24% of cases and understaging in 13% of patients[33]. According to the results of both studies, EUS staging of RC in clinical practice does not have the same accuracy reported in the literature and the authors believe that EUS is a useful tool for guiding the therapeutic strategy of RC only when it is performed by experts[33,49]. Lower accuracy of EUS was also reported in a series of 545 patients with RC, where this method showed an overall accuracy of 69% for T stage and 64% for N stage[32]. A possible limitation of this study was the exclusion from the analysis of those patient who underwent NAT. This could have affected the accuracy of EUS for T stage, especially for T3 RC which is usually visualized the best at the time of EUS. Another pitfall of the study could be the different experience of the operators, which influenced the

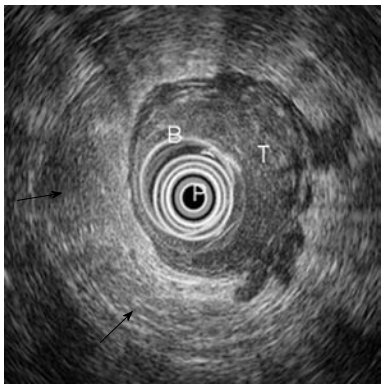

Figure 4 Stage T3 rectal cancer: Ultrasonographic view. Endoscopic ultrasound shows advanced cancer of the rectum with large hypoechoic and inhomogeneous thickening of the rectal wall, loss of the five-layered wall structure and deep infiltration of the perirectal fat. Endoscopic ultrasound with radial array transducer UM160 (5-20 MHz). B: Ballon; P: Transducer; T: Tumor; Black arrow: Perirectal fat.

accuracy of EUS, as highlighted by Marusch *et al*[33,49]. Indeed, Kauer *et al*[34] observed that there is a high inter-observer variability (61%-77%), according to the experience of the operator. These authors reported that EUS has an overall accuracy of 69% for T staging of RC, with T3 tumors better (86%) staged and T4 cancer the least (36%) accurately classified. Differentiating T1 from T2 was difficult in this retrospective series, where overstaging (19%) was much more frequent than understaging (12%)[34].

Superficial RC limited to the mucosa can be resected endoscopically. Whenever a trans anal resection is planned, it is recommended to perform a preoperative EUS staging of the tumor, as suggested by Kneist *et al*[50]. These authors evaluated the accuracy of EUS in 552 patients undergoing trans anal excision of RC and they reported that EUS has a sensitivity of 95% and a positive predictive value of 93% in staging early RC[50]. Similarly, Glancy *et al*[51] demonstrated that EUS has an overall accuracy of 95% in staging early superficial RC suitable for local treatment. This high accuracy rate was confirmed by Zorcolo *et al*[52], who reported that EUS allows a precise distinction between early and advanced RC, with sensitivity of 96%, specificity of 85%, and overall accuracy of 94%. The latter is lower in our personal series, where we reported that EUS has an accuracy rate of 81% in differentiating early (T1) from advanced RC (T2), with the same occurrence of overstaging and understaging (9%)[30]. Finally, a recent meta-analysis analyzed the results of 11 studies, which discussed the efficacy of preoperative EUS in staging patients with early RC: the sensitivity of EUS in diagnosing T0 was 97%, with a specificity of 96%[48]. These data support the conclusion that EUS accurately diagnoses T0 RC, helping physicians to choose endoscopic treatment for patients with early RC.

Several studies have shown that EUS accuracy for T stage is strictly related to the depth of infiltration and the accuracy is lower for T2 stage than for early

Table 5 Accuracy of endoscopic ultrasound for each single T stage

Ref.	Year	No.	pT1	pT2	pT3	pT4
Akasu *et al*[31]	1997	164	86%	56%	93%	75%
Marone *et al*[30]	2000	63	80%	78%	84%	80%
Lin *et al*[38]	2011	192	86%	94%	86%	65%
Fernández-Esparrach *et al*[39]	2011	90	95%	76%	76%	95%
Zhu *et al*[41]	2013	110	93%	88%	88%	96%
Range		619	80%-95%	56%-94%	76%-93%	65%-96%
Mean			88%	78.4%	85.4%	80.2%

uTN stage compared with pTN stage; No previous neoadjuvant therapy (NAT).

(T1) or advanced (T3-4) RC (Table 5)[31,30,38,39,41]. These assumptions are supported by the results of another meta-analysis which examined 42 studies, with a total number of 5039 patients: the pooled sensitivity and specificity of EUS for T1 stage was 88% and 98%, respectively; for T2 stage, EUS had pooled sensitivity and specificity of 80% and 96%, respectively; for T3 stage, the pooled sensitivity and specificity of EUS were 96% and 91%, respectively; finally, for T4 stage, EUS had pooled sensitivity of 95% and specificity of 98%, respectively. The authors of this meta-analysis concluded that EUS should be the imaging method of choice for T staging of RC[47]. Despite the high accuracy that EUS has for T stage, this imaging method is not capable of differentiating peri-tumoral inflammation and edema from neoplastic infiltration. One of the mayor limits of EUS, is overstaging T2-T3 RC, with the risk of overtreatment[30,32,53-59]. In T3 stage cancer infiltrates the rectal wall up to the perirectal fat, with different penetration depth. The precise evaluation of the infiltration depth into the perirectal fat is an important prognostic factor for T3 RC. Harewood *et al*[56] demonstrated that T3 RC are not all equal, with minimally invasive disease carrying a more favorable prognosis. In a series of 42 patients with T3 RC, who underwent surgery without receiving NAT, EUS overstaged the minimally invasive (invasion < 2 mm beyond muscolaris propria at EUS) T3 cancer in 50% of cases, in comparison with advanced (invasion > 2 mm beyond muscolaris propria at EUS) T3 RC. These were overstaged only in 4% of cases. The reported EUS accuracy for differentiating T1/T2 and T3/T4 was 88%, with an overall accuracy of 76% for T stage and 63% for N stage. Since the overstaging rate of minimally invasive T3 RC was high, the authors recommend to exclude these patients from NAT, which should be used only for patients with advanced T3 RC[56]. These data highlight the importance of proper measurement of the infiltration depth of RC at EUS, because this information is crucial for establishing the prognosis and guiding the multimodal therapy. According to Esclapez *et al*[57], an ultrasonographic maximum tumor thickness cutoff point of 19 mm could be useful to classify patients preoperatively and select them for primary surgery or

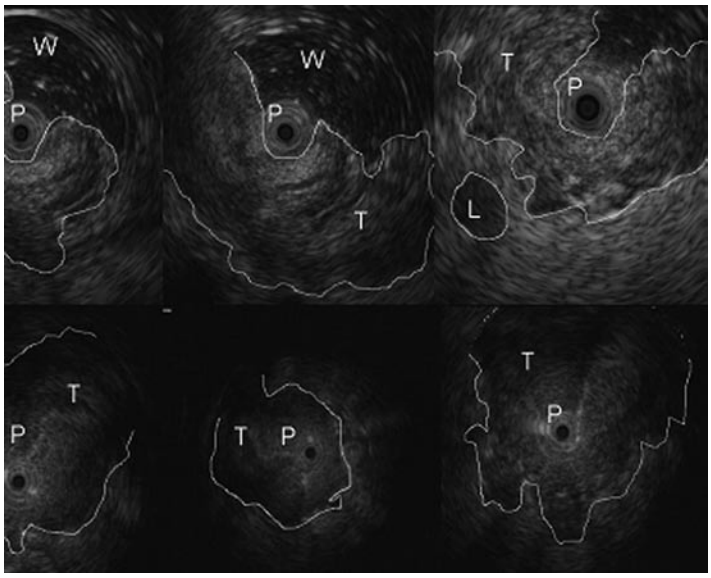

Figure 5 Stage T4 rectal cancer: Miniprobe ultrasonographic view. Endoscopic ultrasound with radial miniprobe (12 MHz) shows an advanced, stenotic rectal cancer with large hypoechoic and inhomogeneous thickening of the rectal wall, loss of the five-layered wall structure and invasion of adjacent organs. T: Tumor; P: Miniprobe; L: Metastatic lymph node; W: Water.

Table 6 N staging at endoscopic ultrasound, according to the number of metastatic lymph nodes

uN1 = 1-3 positive nodes
uN2 = More than 4 metastatic lymph nodes

From ref.[9].

NAT. Indeed, these authors showed that tumor thickness of more than 19 mm in uT3 RC was associated with a higher rate of postoperative recurrence[57].

In approximately 14% of RC there is a stricture that cannot be traversed by the echoendoscope, leading to inaccurate staging and potential errors because EUS evaluates only the distal portion of the cancer[5,50,51]. The presence of a stricture is a limitation for staging RC at EUS: this determines not only inaccurate T staging, but also incomplete N staging because perirectal lymph nodes cannot be examined. Moreover, a stricture often does not permit perpendicular position of the ultrasonographic beam and an adequate focal distance of the probe from the tumor leading to misstaging. All these pitfalls can lead to an incorrect staging of the tumor, which can then affect the therapeutic strategy[5]. Marone *et al*[60] reported that EUS has an overall accuracy of 83% in a series of 127 patients with RC, who underwent surgery without receiving NAT. When the T stages were analyzed separately, EUS showed an accuracy of 76% for T1, 72% for T2, 91% for T3 and 67% for T4 stages. Overall, EUS misstaged T in 16% of cases, with 11% of overstaging and 5% of understaging errors. The presence of a stricture lowered the accuracy rate of EUS for T stage from 93% to 56%; similarly the distance of RC from the anal verge affected the accuracy of EUS for T stage, which decreased from 92% for tumors located > 5 cm from the anal verge to 67% for cancer sites < 5 cm from the anus[60]. Therefore, the presence of a stricture and tumor distance of less than 5 cm from the anal verge are two factors limiting the accuracy of EUS in staging RC.

Recently, the capability of EUS in assessing MRF and predicting the circumferential resection margin (CRM) of RC has been evaluated by Granero-Castro *et al*[61]. In a series of 76 patients with mid-low RC, preoperative staging was performed by means of both MRI and EUS and the patients underwent surgery without receiving NAT. A comparison between preoperative (EUS and MRI) CRM status and pathologic examination after TME surgery was eventually made: overall accuracy of EUS and MRI in assessing CRM status was 84% and 92%, respectively, with similar negative predictive values (97%). When focusing on low RC, the overall accuracy of EUS increased to 87%, whereas MRI lowered its accuracy rate to 87%, with a negative predictive value of 96% for both imaging methods. These data suggest that EUS should be used together with MRI for predicting CRM involvement in low anterior RC.

N STAGING

EUS allows the assessment of perirectal lymph nodes for metastatic infiltration: these are metastatic when they appear as roundish or oval, homogeneous echo-poor nodules with a short axis of at least 5 mm (Figure 6)[5,7,9,10]. According to the number of metastatic lymph nodes, there are two different N (uN) echoendoscopic stages (Table 6).

The incidence of malignant metastatic lymph nodes in patients with RC is strictly related to T stage and varies from 6%-11% for T1, 10%-35% for T2 and 26%-65% for T4 RC[3,5,7,8]. Determination of lymph nodes involvement during EUS is difficult and less precise, with a variable accuracy of 63%-85% (Table 4)[12-45]. Kauer *et al*[34] reported that EUS has an overall accuracy of 68% in diagnosing metastatic lymph nodes associated to RC, with a sensitivity of 52% and a specificity of 82%. A recent meta-analysis of 35 published studies evaluated the accuracy of EUS in diagnosing metastatic lymph nodes of patients with RC[7]. EUS showed sensitivity of 73% and specificity of

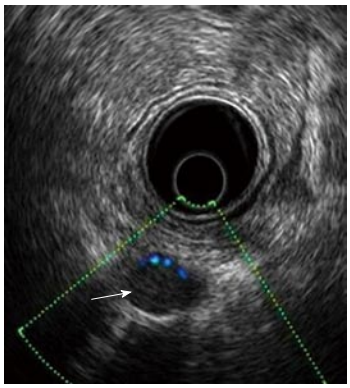

Figure 6 Perirectal metastatic lymph node: Ultrasonographic view. Endoscopic ultrasound with radial array transducer UM160 (5-20 MHz). White arrow: Perirectal metastatic lymph node.

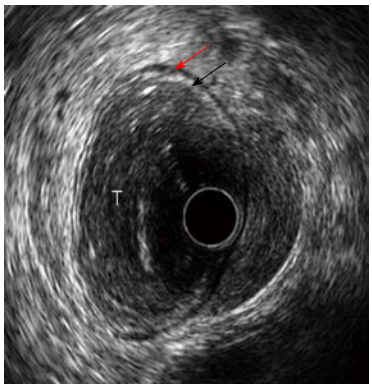

Figure 7 Stage T1 rectal cancer: miniprobe ultrasonographic view. Endoscopic ultrasound with radial miniprobe (12 MHz), showing a small tumor located within the mucosa and superficial submucosal layers, with preservation of the outer layers of the rectal wall. T: Tumor; Red arrow: Muscularis propria layer; Black arrow: Submucosa layer.

76% for N staging and the data analyzed supported the hypothesis that EUS is more accurate in excluding nodal invasion, rather than diagnosing it. Indeed, determination of nodal invasion is less accurate because of difficulty in discriminating between inflammatory and metastatic nodes, which leads to false positive diagnosis and possible overtreatment. The size of lymph nodes could be indicative of neoplastic invasion: nodes greater than 5 mm can be metastatic in 50%-70% of cases, whereas those smaller than 4 mm harbor malignancy in less than 20% of cases[16]. These data have been partly confirmed by Akasu *et al*[59], which observed that the incidence of nodal metastases is strictly related to the size of the lymph node in patients with RC: 9.5% for nodes less than 2 mm; 47% when the lymph node measures 3-5 mm and 87% for nodes larger than 6 mm. However, despite this correlation between size of the node and incidence of metastatic invasion, there are several reports of metastatic lymph nodes smaller than 5 mm in patients with RC, with an overall incidence of 18%[20,62-64]. There is a clear correlation between T stage of RC and risk of metastatic invasion of perirectal lymph nodes. The more advanced the RC, the higher the risk of metastatic lymph nodes: less than 5% with T1m and more than 80% with T3 RC[65,66]. The latter results were confirmed by Landmann *et al*[36], who reported that the accuracy of EUS for N staging decreases from 84% in pT3 RC to 48% in pT1 cancers. The low detection rate of metastatic lymph nodes in T1 RC is probably explained by the fact that in these cancers possible metastatic nodes are small, with a size variable from 0.3 to 3.3 mm. Therefore, EUS can misstage early RC where the presence of neoplastic invasion is possible even in small lymph nodes: this exposes a patient who undergoes local excision to pelvic recurrence because of misstaged early cancer. To avoid this, it was proposed to decrease the dimensional cut off of 5 mm to 3 mm, with increased sensitivity, but reduced specifity and overall accuracy for N staging at EUS. Indeed, with a 5 mm cut off, EUS has an overall accuracy of 89% for N stage in T1 RC, with sensitivity of 39% and specificity of 89%. On the other hand, reducing the cut off to 3 mm, EUS shows an increased (75%) sensitivity for N stage in T1 RC, with significantly reduced specificity (49%) and overall accuracy (53%)[31,36,45]. These data confirm that the size of the lymph node cannot be the only parameter to be used for assessing neoplastic nodal invasion in patients with RC[36,45,59,67].

EUS accuracy for N staging can be ameliorated associating other parameters to the dimensional criterion used for defining malignant lymph nodes. These ultrasound features include lymph node short axis size, echogenicity, shape, and border. Among them, those which better correlate with malignancy are: enlarged node ($\geqslant$ 1 cm in short axis), hypoechoic appearance, round shape, and smooth border[11]. The presence of two or more features is associated with EUS sensitivity of 77%, specificity of 29%, and accuracy of 54%. Three or more features give EUS a sensitivity of 68%, and a specificity of 52%, with an accuracy of 61%. Finally, with four or more features EUS shows sensitivity of 23%, specificity of 100% and accuracy of 61%. Simultaneous presence of all these features in a lymph node is related to 100% of positive predictive value, but this is a rare occurrence (less than 25% of cases)[65]. Despite all the efforts to find the right criteria, determination of lymph nodes involvement during EUS is less accurate and useful than T staging. The most important limitation is the difficulty in both discriminating between inflammatory and metastatic lymph nodes and recognizing small metastatic nodes. These limitations can be overcome by EUS-guided FNA, which allow sampling of the suspicious perirectal nodes, leading to correct N staging. However, even with EUS-guided FNA, the overall accuracy of EUS for N stage remains low, because distant metastatic lymph nodes are undetectable by EUS, since they are out of the scanning area. Indeed, incomplete evaluation of the iliac nodes is the most frequent cause of incorrect staging of patients with RC, leading to mistreatment in 6% of cases[16,45,62,63,66-70]. Recently, Kim *et al*[64] suggested that tridimensional EUS could obviate the low accuracy of

EUS for N staging. However, these results need to be confirmed.

PITFALLS IN STAGING RECTAL CANCER

Sometimes, EUS staging of RC can be incorrect and the cancer is misstaged because of overstaging rather than understaging. At EUS, hypoechoic fibrosis and/or inflammation cannot be differentiated by the hypoechoic mass of the tumor leading to overstaging. On the other hand, understaging occurs when the microscopic neoplastic invasion into the next layer is undetectable during EUS, especially when an entire layer is distended by the invading tumor which abuts into the adjacent layer, without showing clear infiltration. Moreover, a stricture which cannot be traversed limits the accuracy of EUS, while location, shape and size of the tumor can alter the direction of scanning and result in overstaging. Similarly, the T stage can influence the results of EUS staging, as in the case of T2 cancer for which EUS staging is less accurate. Finally, EUS is operator dependent and there is a substantial difference in accuracy between novice and experienced endoscopists, since the latter have learned over the time how to avoid technical problems, like oblique scans, overfilling of the balloon and inadequate water filling of the rectum[5].

MINIATURE ULTRASONIC PROBES

Dedicated echoendoscopes have some limitations due to the fact that combining endoscopy and ultrasonography in one instrument increases the diameter of such scopes (12-13 mm). Because of the large diameter, complete passage of severe strictures is often impossible. Furthermore, conventional EUS often requires a second examination, separate from the previous routine endoscopy. The miniature ultrasonic probes (diameters about 2 mm; frequencies 12-20-30 MHz) can be passed through the working channel of standard endoscopes to provide high frequency ultrasound images (Figures 1, 5 and 7). These miniprobes allow simultaneous endoscopic and ultrasonographic evaluation of the lesions, complete assessment of strictures that cannot be traversed by conventional echoendoscopes and accurate staging of superficial lesions[8]. The rarity of lymph node metastases in T1m or T1sm 1 RC supports the indication for endoscopic resection of these lesions, which require accurate preoperative staging. This has been performed by Harada *et al*[71], using a 15-MHz ultrasound miniprobe in 35 patients with submucosal invasive colorectal cancer. The accuracy of miniprobes was low (37%) in categorizing the different depth of submucosal invasion, while it was high (86%) in differentiating between mucosal/superficial submucosal infiltration (M and SM) and deep submucosal invasion (SM2, SM3, MP, and S)[71]. These data support the indication for ultrasonographic staging of early colorectal *via* miniprobes in order to plan endoscopic resection. In a prospective study of 131 consecutive patients with adenocarcinoma or broad-based polyps of colorectum, EUS accuracy for T staging with miniprobes was 96%, with 4% of overstaging and 2% of understaging[72]. The overall accuracy of N staging using miniature ultrasonographic probes was 87% (sensitivity 95%, specificity 71%, positive predictive value 87%, negative predictive value 88%). These data confirm that miniprobe ultrasonography has a high overall accuracy for both T and N staging of colorectal cancer and it may be useful for selecting patients fit for local resection. Finally, Gall *et al*[73] conducted a meta-analysis of ten studies with a total of 642 patients to evaluate the accuracy of miniprobe EUS in staging RC. The pooled sensitivity and specificity were respectively 91% and 98% for T1 cancers, 78% and 94% for T2 tumors, 97% and 90% for T3/T4 RC. Eight percent of T1/T2 cancers were upstaged to T3/T4 tumors and 5% of T3/T4 RC were downstaged. Finally, the pooled sensitivity and specificity for N staging were 63% and 82%, respectively. These data confirm that miniprobe EUS is highly effective for clinical staging of RC, allowing identification of those patients who may be suitable for nonsurgical treatments.

EUS-FNA for staging rectal cancer

According to a recent study, EUS-FNA is useful for assessing primary and metastatic rectal cancers. In this setting, EUS-FNA had sensitivity, specificity, positive and negative predictive values of 89%, 79%, 89% and 79% respectively. This technique improves staging of suspected nodal or distant metastases, but it is indicated only when cytologic results will change the therapeutic strategy[74,75]. This is the conclusion of Harewood *et al*[12], who reported that standard EUS modified therapeutic strategy of LARC in 25 patients, while only in 1 case EUS-guided FNA was crucial for choosing the correct therapy. According to Shami *et al*[76], EUS-guided FNA has a clinical impact of 19% on staging and subsequent management of patients with RC. In this cancer the incidence of lymph node metastases is strictly related to T stage, with a higher risk of nodal metastasis with more advanced T stages. Peritumoral lymph nodes are highly predictive of cancer invasion: the majority of perirectal nodes detected by EUS are metastatic in patients with RC. This is the explanation for the low clinical impact of EUS-guided FNA in staging patients with RC. Moreover, T3 RC is an indication for NAT, independently from N stage, which has no influence on the therapeutic strategy of patients with LARC[12,75]. EUS-guided FNA seems to offer the most potential for the management of T1-2 stage disease, where the presence of metastatic perirectal lymph nodes modifies the therapeutic strategy. Therefore, its use should be confined to this subgroup of patients[12,67,75,77]. This indication is confirmed by Levy and colleagues who evaluated the role of EUS guided FNA in N staging of 32 patients with RC and suspicious iliac lymph nodes[70]. In approximately 50% of cases, the sampled nodes were positive for neoplastic invasion and determined

a change in the therapeutic strategy. Of note, CT scan did not detect half of the lymph nodes which were malignant at EUS–guided FNA. These data support the need to properly investigate the iliac lymph nodes during staging of patients with RC.

EUS in comparison with CT and MRI for staging rectal cancer

In RC, EUS has been compared with digital examination, CT scan and MRI. EUS is superior to rectal digit examination, showing a higher accuracy (91%-92% *vs* 52%-60%). CT scan is unable to correctly define the single layers of the rectal wall and therefore is not indicated for T staging of RC, while it is crucial for diagnosing distant metastases[77]. EUS is more accurate than CT scan in loco-regional staging of RC, showing an accuracy rate of 87% for T stage and 62% for N stage, compared to that of CT scan (76% for T stage and 62% for N stage)[6,63,77]. Similarly, EUS was considered more precise (85% *vs* 77%) than MRI in determining the T stage of RC[77]. However, recent technology has allowed MRI to define the status of MRF and subsequently delineate the possible threatened CRM, making this imaging method crucial for loco-regional staging of RC[44]. A systematic review of 31 articles published over a 20-year period evaluated the role EUS and MRI in loco-regional staging of RC[46]. While EUS is more useful for staging early RC, with an overall accuracy of 82%, MRI is indicated for staging advanced disease, providing a better definition of both the mesorectum and the MRF. The latter is crucial for choosing the best therapeutic strategy. In another systematic review, Kwok *et al*[78] evaluated the role of CT scan, EUS and MRI in the preoperative staging of RC. In determining T stage, EUS was more accurate than CT scan and MRI. The latter, with the adjunct of an endorectal coil, has the same accuracy of EUS for T stage, while it is more precise in determining nodal metastases. Both EUS and MRI with an endorectal coil are limited by the presence of strictures when staging RC. An MRI with a pelvic phased-array coil is not invasive, has a high spatial resolution and appears to be a promising image method for loco-regional staging of RC[37,79]. Yimei *et al*[80] evaluated the reference value to surgeons of both EUS and MRI, reporting that EUS has higher sensitivity (P = 0.044) and specificity (P = 0.039) than MRI, showing elevated accuracy for early stage RC. This makes EUS staging crucial for the identification of those patients who are suitable for less invasive surgery. On the other hand, MRI is useful for the proper diagnosis of LARC which need to undergo multimodal treatment. MRI has been preferred to EUS because it is better tolerated, can be used in stenotic tumors and it can define the infiltration depth of MRF and assess the CRM. The latter is a crucial information for choosing the best therapeutic strategy. However, Cesmeli *et al*[81] point out that EUS is still important in the preoperative staging of early RC, because of its ability to delineate the different layer of the rectal wall, allowing the selection of those patients suitable for local excision. EUS can also improve N staging by performing FNA, whenever N stage can change the therapeutic strategy[81]. In a series of 49 patients, EUS and MRI showed similar accuracy (88%), in predicting pathologic CRM of low RC[82]. Therefore, EUS and MRI are complementary and should be both used for preoperative staging of patients with RC. The fact that staging accuracy is improved by combination of MRI and EUS is supported by the results of a recent study in which the authors compared feasibility and accuracy of both 1.5 Tesla MRI and three-dimensional (3D) EUS for staging patients with RC before and after preoperative chemotherapy[83]. The stage accuracy by MRI, 3D-EUS and the combination of MRI and 3D-EUS was 65%, 70% and 74%, respectively, before chemotherapy and 65%, 78% and 83%, respectively, after chemotherapy. The post chemotherapy staging by MRI alone was improved by a combination of MRI assessment of the lymph nodes and 3D-EUS assessment of the perirectal tissue penetration (P= 0.046). These results confirmed that staging accuracy is improved by combining MRI with EUS.

According to the data of the literature, EUS and MRI are superior for T- staging, while CT and PET/CT are the main stay for metastatic work-up. EUS is superior in staging early cancers and defining the infiltration of the anal sphincter, while MRI is excellent for staging T4 and clarifying both the MRF status and the infiltration of the elevator muscle; CT and EUS are complementary, rather than competitive in loco-regional and distant staging of RC[84-86]. Therefore, the best approach for RC is the combination of all different imaging methods, which are complementary: they should be utilized according to the clinical condition of the patient, the availability of each single test and the personal preference. Cost-benefit studies have demonstrated that the most cost-effective association of imaging methods is EUS plus CT scan[87].

Accuracy of eUS in staging locally advanced rectal cancer after chemoradiation

Loco-regional staging of RC after NAT is affected by local effects of the treatment which determines peritumoral inflammation, edema, necrosis, and fibrosis of the neoplastic tissue. This reduces the accuracy of EUS, leading to overstaging errors (Table 7)[88-90]. EUS staging of RC after NAT is inaccurate, as shown by Vanagunas and colleagues in a series of 82 patients with LARC[90]. After NAT, EUS correctly predicted complete response to chemoradiation in only 63% of cases and its overall accuracy for pathologic T-stage was 48%, with 14% of understaging and 38% of overstaging. These data suggest that EUS staging of RC after NAT is inaccurate, and its routine use for restaging patients should be discouraged. Similary, Marone *et al*[91] and Maor *et al*[92], demonstrated that EUS restaging of LARC after NAT has low accuracy. Both studies compared two groups of patients with LARC: one operated on without receiving NAT and another one who underwent surgery after NAT. The results of the studies were similar, showing

Table 7 Accuracy of endoscopic ultrasound in staging locally advanced rectal cancer after chemo-radiation

Ref.	Year	No.	T	Mistakes		N
				Over	Under	
Vanagunas *et al*[90]	2004	82	48%	38%	14%	77%
Mao *et al*[92]	2006	25	72%	8%	12%	80%
Radovaanovic *et al*[94]	2008	44	75%	18%	7%	68%
Marone *et al*[91]	2011	85	61%	28%	7%	59%
Mean		236	64%	23%	10%	71%
Range			48%-75%	8%-38%	7%-14%	59%-80%

uTN stage compared with pTN stage; Previous neoadjuvant therapy (NAT). Over: Overstaging; Under: Understaging.

that EUS restaging of LARC after NAT has low accuracy (60%-70%) and is able to predict a complete response in only 50% of cases. Further confirmation of this low accuracy came from a study where the authors compared sensitivity and specificity of EUS and MRI, in patients with LARC after NAT[93]. Both EUS and MRI had low accuracy (46% *vs* 44%) for T stage of LARC after NAT. Better accuracy of EUS restaging was reported by Radovanovic and colleagues who demonstrated that EUS has an accuracy of 75% for T stage after NAT, with 18% of overstaging and 7% of understaging[94]. The majority of overstaging occurred in patients with uT3 tumors, eventually found to have pT0-pT2 RC. EUS was able to correctly stage only one of the patients who had complete response after NAT. Despite the fact that EUS restaging accuracy for LARC was higher, the results of this study confirm that EUS is not useful after NAT.

EUS DIAGNOSIS OF LOCAL RECURRENCE IN PATIENTS OPERATED ON FOR RC

After surgery, local recurrence of LARC has an incidence of about 25%, which decreases to 10%, if NAT has been administered before surgery (10%). The risk of local recurrence is strictly related to T stage and it is higher for more advanced T stages, occurring mostly in the first two postoperative years[95-97]. Early identification of local recurrence and its immediate treatment could potentially improve patients survival. EUS has a high sensitivity, but low specificity in defining local recurrences. A limitation of EUS is its inability to clearly differentiate postoperative changes and benign lesions from cancer recurrence[95-97].

EUS-guided FNA increases the specificity of EUS (57% *vs* 97%). To date, there are no guidelines which define the role of EUS in the follow-up of patients operated on for RC, since there are no clear data that echoendoscopic follow-up and/or EUS-guided FNA influence patients survival after surgery for RC[95-97].

Future perspectives

The recent development of new technology for EUS generates novel applications for echoendoscopic diagnosis and staging of gastrointestinal tumors. Tridimensional EUS (3D-EUS) seems to improve the spatial visualization of RC allowing better evaluation of tumor resectability[98]. 3D-EUS is more accurate than 2D-EUS and CT scan in T staging of RC, for which the three imaging methods have an accuracy of 78%, 69% and 57%, respectively[64]. 3D-EUS visualization of the outer margin of the rectal wall is well related to neoplastic infiltration and metastatic nodal invasion diagnosed by pathological examination of the surgical specimen. Some data suggest that 3D-EUS allows correct visualization of MRF, which was not well delineated by 2D-EUS. Proper measurements of the tumoral area before and after NAT could be a useful criterion for evaluating the response of RC to NAT[98-100].

Elastography is a new technique which has been recently added to the armamentarium of EUS and allows measurement of tissue elasticity useful to differentiate normal from tumoral tissue. Preliminary data have shown that simultaneous elastography during EUS improves its accuracy for T staging of RC[98]. Finally, EUS with contrast medium administration (contrast harmonic EUS or CH-EUS) and simultaneous Doppler visualization allows the study of tumoral vascularization and irroration. These data are useful for the evaluation of both tumoral response to NAT and efficacy of anti-angiogenic treatments, because this combination of techniques shows accurately those changes in the vascular pattern of RC which reflect its response to therapy. Miyata *et al*[101] evaluated the micro-vascularization of lymph nodes by means of CH-EUS in order to differentiate benign from malignant nodes: sensitivity, specificity, and accuracy of CH-EUS for malignant lesions were 95%, 97%, and 97%, respectively. These data show that CH-EUS is accurate in detecting minimal changes of tumoral vascularization in lymph nodes which harbor neoplastic invasion. This information could address the correct use of FNA-guided EUS, whenever it is needed[101,102]. To date, there are still little data on the clinical application of simultaneous use of these new methods together with standard EUS. Therefore, further clinical trials are needed for the evaluation of indication, accuracy, clinical impact and limitation of CH-EUS and Doppler-EUS.

CONCLUSION

Prognosis of patients with RC is strictly dependent from the stage of the disease at the time of diagnosis. Multidisciplinary approach to patients with RC is the standard of care in order to reduce local recurrences and improve survival outcomes. A strong cooperation among members of a multidisciplinary team is mandatory to improve patients outcomes, because the latter are strictly dependent from the chosen therapeutic strategy. This is the results of an accurate loco-regional staging, especially if metastatic disease has been excluded. CT scan, MRI, PET are the imaging method used for staging RC and give information on both loco-regional and distant disease. In the last decades, EUS has been

used in combination with these imaging methods for staging RC in order to better define both the T stage and the involvement of loco-regional lymph nodes. EUS has significant clinical impact on patients with RC, allowing to identify those who are candidate for local excision and/or direct surgery, without receiving NAT. LARC is well defined by EUS, even if the identification of both MRF and possible threatened CRM is more precisely obtained by MRI. The latter lacks accuracy for mid - low anterior RC, which could be better staged by EUS, as recent data suggested. Therefore, EUS and MRI are complementary and they should be used simultaneously, with a significant increase of the overall accuracy for the T stage of RC. EUS is superior in identifying early cancers and infiltration of anal sphincter, while MRI is excellent in recognizing T4, in relationship to MRF infiltration of the elevator muscle. While EUS and MRI are superior for T- staging, CT and PET/CT are the main stay for metastatic work-up.

Restaging after NAT is mandatory for establishing a correct prognosis of patients with RC and choosing the most effective treatment. This should be tailored according to the results of NAT, whose experimental drugs can be tested in clinical trials and evaluated by means of restaging RC. The latter is not performed by means of EUS because this imaging method has low accuracy in restaging RC, due to the difficulty in differentiating inflammation and tissue fibrosis from actual residual cancer.

EUS has low sensitivity, but high specificity in diagnosing local recurrences in patients operated on for RC, because it is unable to differentiate perianastomotic surgical changes from recurrent cancer. In this case, EUS-guided FNA increases specificity, but its use in clinical practice has not been standardized. Probably, high resolution images and guided FNA are the best combination for improving EUS accuracy in naive and recurrent RC.

Technological improvements, like elastography, contrast medium administration, high ultrasonographic frequencies and 3D, will certainly improve EUS accuracy and broaden its clinic use; however there is a need for further studies which should confirm the potential of these new technologies.

In conclusion, accurate EUS staging is crucial for the best treatment of each single patient with RC and especially LARC, because patients can be understaged or overstaged, with subsequent mistreatments.

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REVIEW

Endotherapy of leaks and fistula

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Abstract

Perforations, leaks and fistula involving gastrointestinal (GI) tract are increasing encountered in clinical practice. There is a changing paradigm for their management with surgical approach being replaced by conservative approach including endoscopic therapy. Clips (through the scope and over the scope) and covered stent are front runners for endotherapy for GI leaks and fistula. Over the scope clips introduced recently, can treat larger defects compared to through the scope clips. Covered stents are suited for larger defects and those associated with luminal narrowing. However cervical esophagus, gastro-esophageal junction, stomach and right colonic lesions may be better for clip therapy rather than stenting. Recent developments in this field include use of endovac therapy which consists of a sponge with suction device, biodegradable stent, use of fibrin glue and some endo-suturing device. Conservative therapy with no surgical or endoscopic intervention, may be suitable for a small subset of patients. An algorithm based on location, size of defect, associated stricture, infection and available expertise needs to be developed to reduce the mortality and morbidity of this difficult clinical problem.

Key words: Fistula; Leak; Perforation; Post operative; Endoscopy; Endoscopic; Surgery; Stent; Suture; Endoclip; Clip

Core tip: Gastrointestinal (GI) leaks and fistula are increasingly recognized in our day to day practice. While these patients were earlier managed by surgical interventions, more and more such patients are now considered for endoscopic therapy. Endotherapy for GI leaks include endoclips (through the scope and over the scope), covered stents, fibrin glue, suture devices and more recently introduced endoscopic vacuum therapy using bioactive sponge. Since the experience with these modalities is limited, there are hardly any clear guidelines to treat these difficult patients. This review article deals with endotherapy of GI leaks and fistula and presents an updated experience as well some guidance to select appropriate modality.

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INTRODUCTION

Gastrointestinal (GI) leaks and fistula constitute disruption of GI wall. GI leaks and fistula can be either spontaneous due to GI pathology or may be iatrogenic. There seems to be increase in prevalence of GI leaks and this seems primarily due to increasing complexity of GI surgery and endoscopic interventions. There is a changing paradigm in management strategy of GI leaks and fistula. While majority of these complicated patients were managed by surgery 15-20 years back, non-operative treatment including endoscopy presently constitute the primary modality of therapy[1]. There is evidence to suggest that this changing paradigm in form of endoscopic therapy is associated with improved outcome and shortened length of hospital stay[1]. This review deals with endoscopic techniques and their present status in the management of GI leaks and fistula.

Management of pancreatic and bile ductal leaks is however, not discussed.

DEFINITION AND ETIOLOGY

Perforation, fistula and leaks are terms, which are often used interchangeably. However in strict terms, they are somewhat different. Perforation refers to acute full thickness defect in GI tract. Leaks are defined as disruption of surgical anastomosis resulting in a fluid collection[2]. The term fistula usually means an abnormal communication between two epithelialized surfaces[2]. Table 1 enumerates the causes of GI leaks and fistula[3-17], while Table 2 distinguishes the underlying etiology for leaks and fistula. Table 3 details the endoscopic procedures associated with increased risk of perforation[18].

Table 1 Etiology of gastrointestinal leaks and fistula

Diagnostic endoscopy including endoscopic ultrasound
Dilation: bougie, balloon, achalasia
Polypectomy/EMR/ESD
Foreign body
Endoscopic variceal therapy including ligation
POEM
Anastomotic dehiscence
Boerhaave's syndrome
Diverticulitis
Laser
PEG
Endoscopic sphincterotomy
Biliary stent migration
Ampullectomy
Appendicular abscess
Empyema

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; POEM: Peroral endoscopic myotomy; PEG: Percutaneous endoscopic gastrotomy.

Table 2 Causes of leaks and fistula

Leaks	Fistula
Iatrogenic (60%)	Malignant (50%)
Endoscopy	Benign
EVL	Stents
Dilatation	Tuberculosis
ESD/EMR	Crohn's
POEM	Iatrogenic
Spontaneous	Trauma
Boerhaave's	Surgical
Foreign body	AIDS
Surgical	
Trauma	

EVL: Endoscopic variceal ligation; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; POEM: Peroral endoscopic myotomy; AIDS: Acquired immune deficiency syndrome.

TOOLS AND TECHNIQUES

The two options for managing GI leaks and fistula include surgery and endotherapy. The choice between two is decided by size of disruption, location and accessibility of lesion, presence of contamination, time of diagnosis and availability of expertise. Whatever be the choiced option for repairing the disruption, the management needs to include bowel rest, institution of appropriate antibiotics, drainage of associated collection, pneumoperitoneum, pneumothorax and maintenance of nutrition. Proton pump inhibitors are instituted, if leaks are located in upper GI tract. As highlighted in a recently published Position Statement of European Society of Gastrointestinal Endoscopy, it is important to have a systematic approach for diagnosis and treatment of GI perforations[18]. Endoscopist must record details of findings, attending physician must evaluate the clinical profile, necessary investigations which may include a CT scan and a blood picture should be carried out, a decision should then be taken whether to perform endotherapy or surgery and finally post endotherapy monitoring must be done to evaluate success or failure of the endotherapy[18]. Table 4 lists the endoscopic modalities, which can be used for closure of GI leaks and fistula. Of these, endoclips and covered stents are the two modalities, which are most commonly used and have most consistent results.

Endoclips

Endoclips, which are more frequently used for arresting GI hemorrhage can also be used for closing the GI wall disruptions and work like surgical sutures or staples[3,4,19]. First report of endoclipping for closure of GI perforation came from Germany[20]. This report discussed successful endotherapy of a perforation after endoscopic removal of gastric leiomyoma[20]. Endoclips can either be through the scope (TTS) clips, where clip applicator with loaded clip is introduced through the biopsy channel of the endoscope or recently available over the scope (OTS) clips, which are mounted over the scope tip like variceal band ligator device and released by a similar technique. TTS clips (Figure 1) are available in various designs and sizes: Quick clip

Table 3 Endoscopic procedures in different parts of gastrointestinal tract associated with increased risk of iatrogenic perforation

Esophagus and stomach	
Dilatation	ESD
EMR	Foreign body removal
POEM	EVL
Small bowel	
Altered anatomy	DBE in altered anatomy
Dilatation in Crohn's	ESD
Dilatation of GJ stricture after gastric bypass	
Colon	
EMR	Balloon dilatation
ESD	Old age, co-morbidity
Inexperience	Inflammatory colonic disease

ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; POEM: Peroral endoscopic myotomy; EVL: Endoscopic variceal ligation; DBE: Double-balloon; GJ: Gastrojejunostomy.

Table 4 Modalities for endotherapy of leaks/fistula

Closure
Endoclips
Suture
Sealant: Fibrin, cyanoacrylate
Diversion
Covered stents

(Olympus, America Inc., Center Valley PA, United States), Resolution clip (Boston Scientific Inc., Natick, United States) and Instinct clip (Cook Medical Inc.; Bloomington, IN, United States). Some of these are rotatable and re-openable, making them convenient to appropriately align the disrupted tissue. Figure 2 shows an esophageal tear treated by TTS clips.

OTS clips (Figure 3) from Ovesco Endoscopy GmbH (Tuebingen, Germany) are nitinol, super elastic, biocompatible clips with teeth designed in the shape of a bear trap and can produce a full thickness closure. OTS clips are available in various shapes and sizes and selection of a particular size depends upon the size of the defect. For larger defect, one can use accessories like anchor and twin grasper, which can pull the defective mucosa into the OTS cylinder or reduce the gap of the defect respectively (Figure 3). One should carefully avoid capturing twin grasper or anchor while releasing the clip. Figure 4 illustrates the use of OTS clips in a patient with two defects in gastric wall located diagonally opposite one another following a Whipple's surgery. Two OTS clips were placed with the help of anchor and twin grasper through a double channel endoscope. Follow-up CT scan confirmed the complete closure of defects.

In general, it is believed that OTS clips cover a larger defect and one OTS clip can be compared with results obtained with 5 TTS clips. In large defects, such as after Endoscopic Submucosal Dissection (ESD), multiple TTS clips can be used to fix an endoloop at the margin of the defect and then pulling the loop and closing it can obliterate the defect. There are case reports of OTS clips

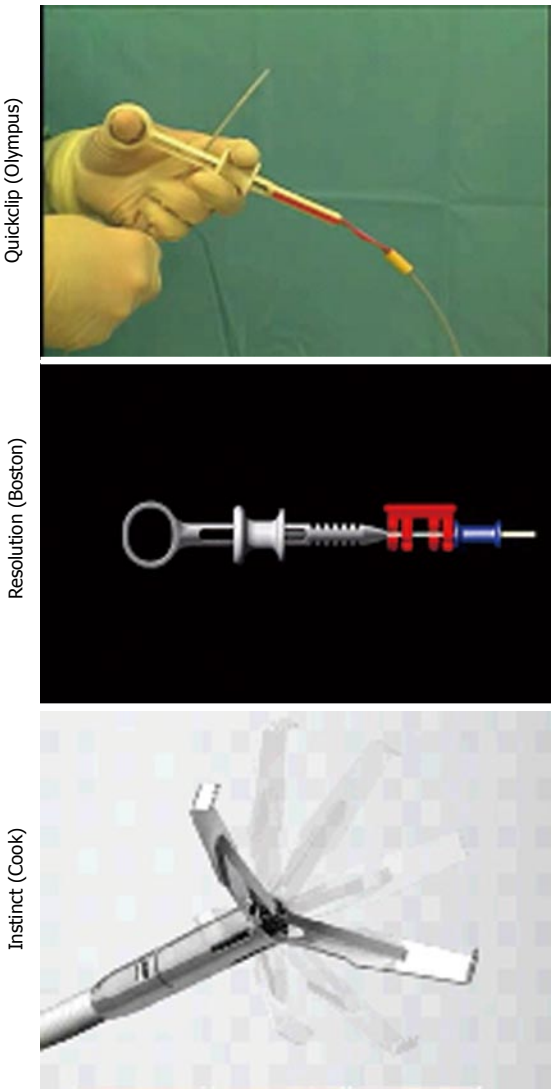

Figure 1 Through the scope clips.

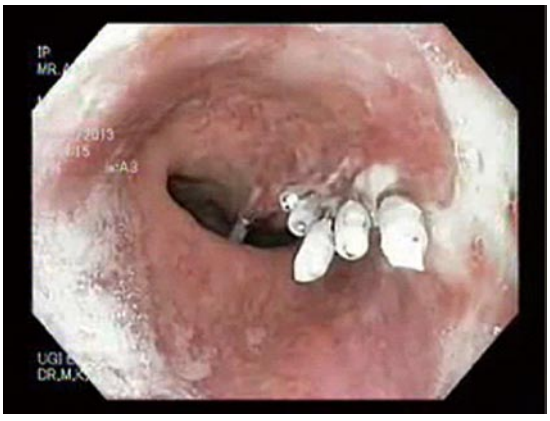

Figure 2 Endo clips (Through the scope) used to close an esophageal defect due to Boerhaave's syndrome.

applied under laparoscopic control in order to achieve greater success[21].

Both TTS and OTS clips have been used to close fistula and leaks located in esophagus, stomach as

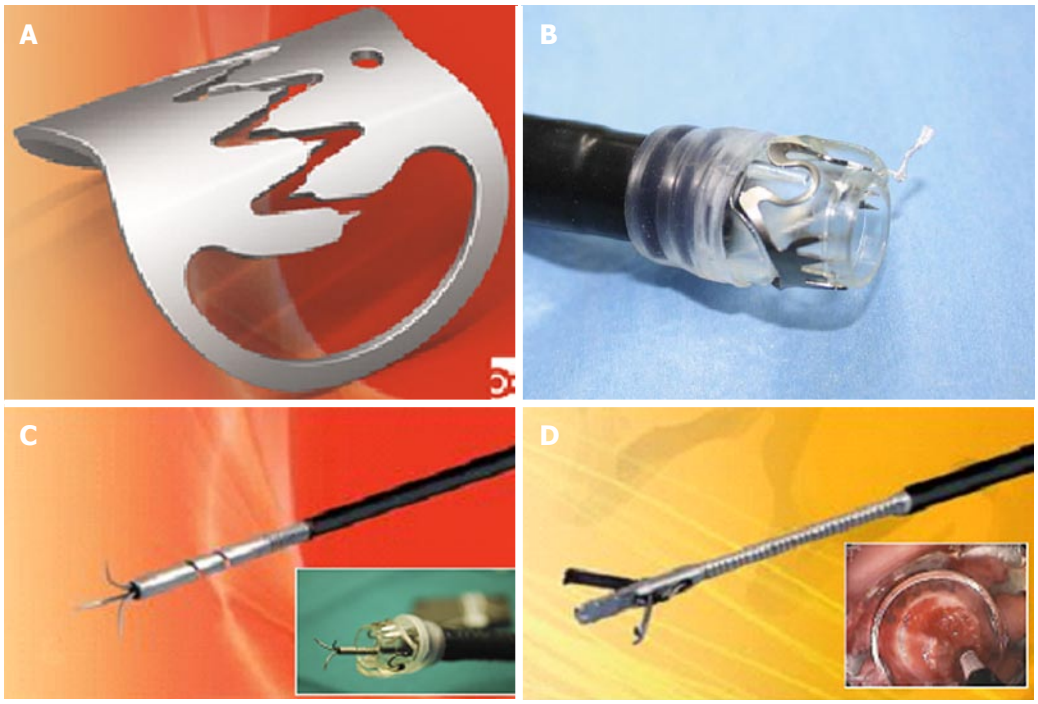

Figure 3 Over the scope clips (ovesco) (A) clip, (B) clip mounted on the endoscope, (C) anchor, (D) twin grasper.

well as colon[20,22-30]. While most of these studies involve small number of patients, large series have reported results of clips to close leaks following ESD and endoscopic mucosal resection (EMR)[23,31]. Minami *et al*[23], in a series of 117 patients with gastric leak following EMR, demonstrated a success rate of 98.3% with TTS clips. Interestingly, they found a similar recovery rate for patients with perforation treated by clips and non perforated patients[23]. Of the 39 patients with perforations following ESD reported by Jeon *et al*[32] managed by endoclip, there was no failure. Overall success rate is higher for esophagus and stomach and somewhat moderate for colonic leaks. Voermans *et al*[22] reported their experience of OTS clips in 36 patients with iatrogenic perforations (esophageal: 5, gastric: 6, duodenal: 12, colonic: 13). Overall success rate of OTS clips was 89% with only one patient having endotherapy related complications. A large muti-center retrospective study by Chavez *et al*[33] involved 188 patients with GI leaks and fistula treated with OTS clips. 27 patients were lost during follow-up. Of the remaining patients, OTS was used as primary treatment in 97 patients and as rescue therapy in 64 patients. The success rate was 75% in first group and 47% in second group. Overall success rate was 64% (103 out of 161 patients). The result was better for perforation (95%) and leaks (80%), compared to fistula (45%).

In general clips are preferred over stents, if the leak is located in proximal esophagus or in distal most esophagus as well as for stomach and right colon[34]. While TTS clips are effective for leaks smaller than 10 mm[35], OTS clips are preferred if defect is larger than 20-30 mm. Prior ablation at edges of defect to make it raw, may help in clip placement[36]. While closing a large leak, it may be worthwhile to attempt to include adjacent omental patch within the clip, akin to surgical practice[37]. Because of possibility of leakage of air during the procedure, it may be a good idea to use CO_2 insufflation during endotherapy of leaks and fistula[18]. In order to get best results, it is important to apply endoclips early after detection of leaks and perforations[35]. There is no reported risk of peritoneal dissemination or tumor recurrence after endoclips used for perforations following ESD or EMR performed for early cancers[38,39].

Luminal stenting

A large variety of stents are available to close luminal defects (Figure 5). These stents are covered (at least partially), so as to seal the defect and avoid contamination of the disrupted area. Mostly these stents are self - expanding metallic stent except for a single design of plastic stent (Polyflex, Boston). Fully covered stents, because of their ease at removability, are generally preferred particularly in the setting of benign disease. Figure 6 shows a patient with leak following gastrojejunostomy done for distal duodenal obstruction. One of the major issues with use of covered stent for closing of the GI defects is the risk of migration in absence of any obstructive pathology. This can be reduced by using large sized stents (Mega stents by Niti or Danis stent by Ella Figure 7), modified stents designs with extra covering in the shaft of stent (Figure 8) or by anchoring the stent by using endoclips or externalised threads (Figure 9)[40].

Stents have been used mostly in esophagus, duodenum and colon. Van Boeckel *et al*[41] reported the

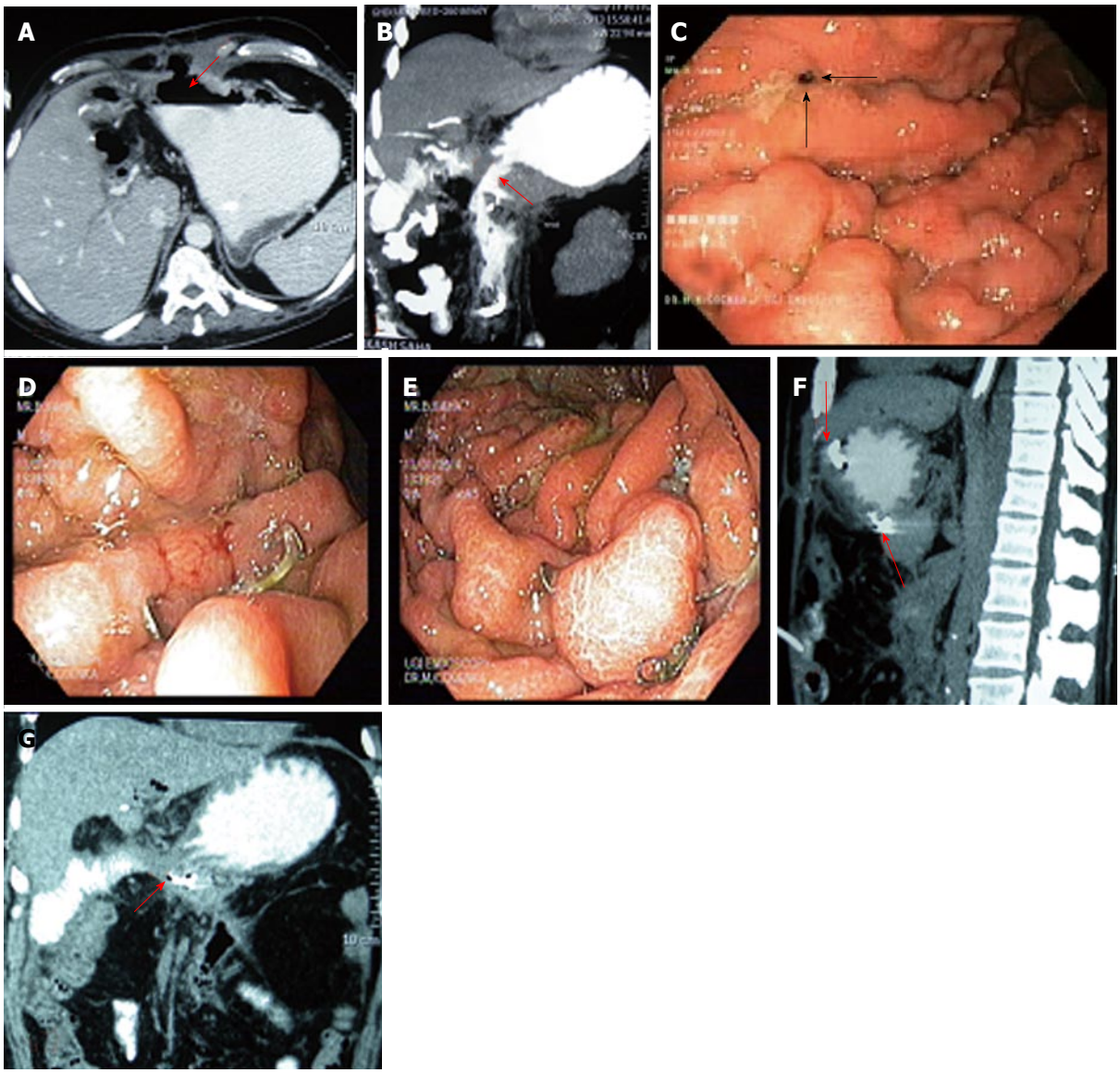

Figure 4 Dual gastric leak following Whipple's Surgery treated by over the scope clips. A and B: Anterior and posterior defects (arrows); C: Endoscopic view showing leak on anterior gastric wall (arrows); D and E: The OTS clips placed on anterior and posterior defects respectively; F and G: Follow-up CT scan showing the clips (arrows) with demonstration of closure of leaks. OTS: Over the scope.

results of 25 studies with luminal stent for iatrogenic esophageal leaks. In the cumulative data involving 267 patients, they reported a clinical success of 85% for closure of leak with no difference between plastic stent, fully covered or partially covered metal stents (84%, 85% and 86% respectively P = 0.097). Overall complication rate was 34%. Migration rate was somewhat higher for plastic stents compared to fully covered and partially covered stents (31% *vs* 26% *vs* 12% respectively). There was however, no difference in other complications such as tumor in-growth or over-growth. Freeman *et al*[42] recently reported that factors associated with failure of leak closure with stent placement include leak at cervical esophagus and esophagogastric junction, injury greater than 6 cm and additional distal leak. Tables 5 and 6 gives details of results of case series with endotherapy in esophageal and gastric iatrogenic perforation respectively[22-24,39,43-56]. As shown most of the series with gastric perforation have used clips, while both clips and stents have been used for esophageal perforation.

Bariatric surgery is not uncommonly complicated by leaks and fistula. In a retrospective study, over a period of 6 years involving 1499 bariatric surgery, Spyropoulos *et al*[57] reported a 2% incidence of luminal leak. Leaks were noted in sleeve itself, at staple line or at anastomosis site (gastrojejunostomy or enteroenteral). Of the 30 patients with leak, stents were used in 9, while surgery was performed in 3 patients and conservative approach was followed in 18 patients. Another recent study by EI Mourad *et al*[58] reported success of stent to close leaks following bariatric surgery in 41 out of 47 patients. Mega stents with a diameter of 30 mm are best suited for these indications.

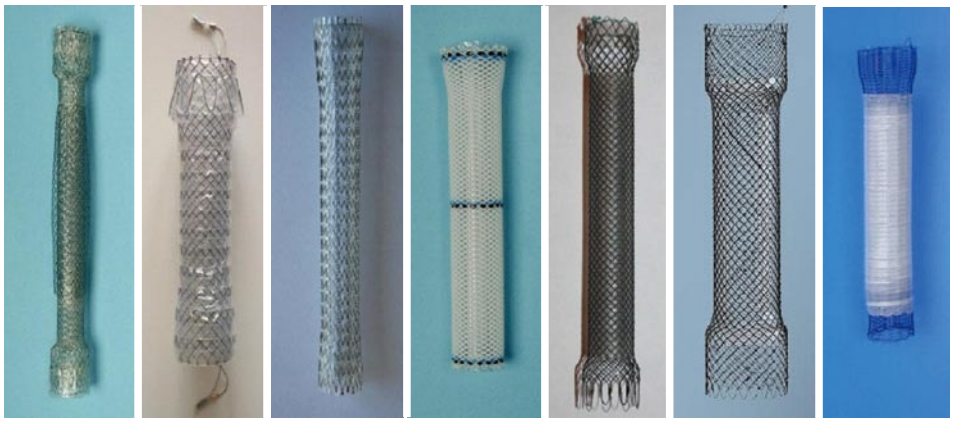

Figure 5 Stents for gastrointestinal leaks/fistula.

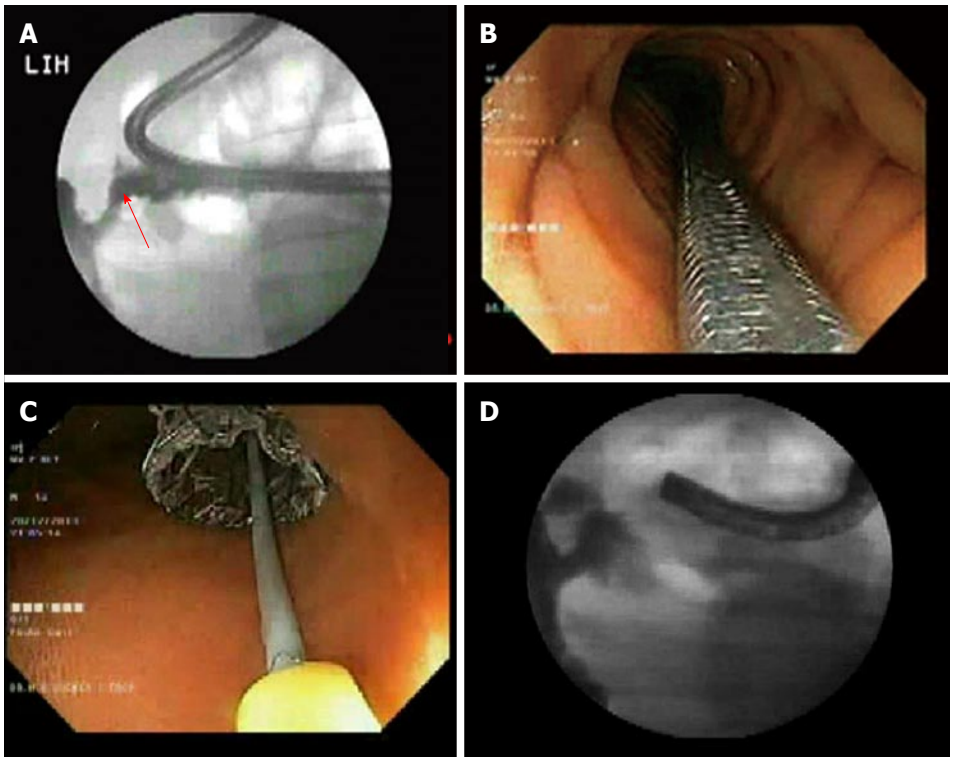

Figure 6 Leak after duodeno-jejunostomy managed by luminal stenting. A: Contrast introduced through the surgical drain site shows the leak (arrow); B: Stent being deployed; C: Fully deployed covered stent; D: Contrast through the surgical drain shows the closure of the leak.

Suturing and sealants

While suturing and use of sealants have been used to close GI leaks and fistula, results are mixed and experience is limited. Some of the suturing devices include EndoCinch suturing device (C.R. Bard, Inc, Boston, Mass, United States) Sefestitch (Safestitch, Medical Inc, Miami, Florida), Medical Power System (Power Medical Interventions, Longtrome, Pennsylvania), ESD Flexible Endoscopic Suturing devices by Wilson-Cook Medical (Winston- Salem, North Carolina) and Eagle Claw (Olympus Corporation, Tokyo, Japan)[59]. All these devices are either being still investigated or have not stood the test of time. Apollo Overstitch system (Figure 10) introduced recently, has been shown to have encouraging results[60,61]. This device is front-loaded onto a double - channel endoscope and allows continuous or interrupted stitches to be made with a cinching device. The merits of this approved device include the ability to reload the device inside the body eliminating the need to remove it between stitches as well as predictability of tissue needle penetration due to it being not suction based. Moreover, the device allows one endoscopic channel to be free to allow passage of grasping forcep for better tissue apposition[61].

Sealants which have been used to obliterate GI leaks and fistula include Cyanoacryate and Fibrin glue[62,63].

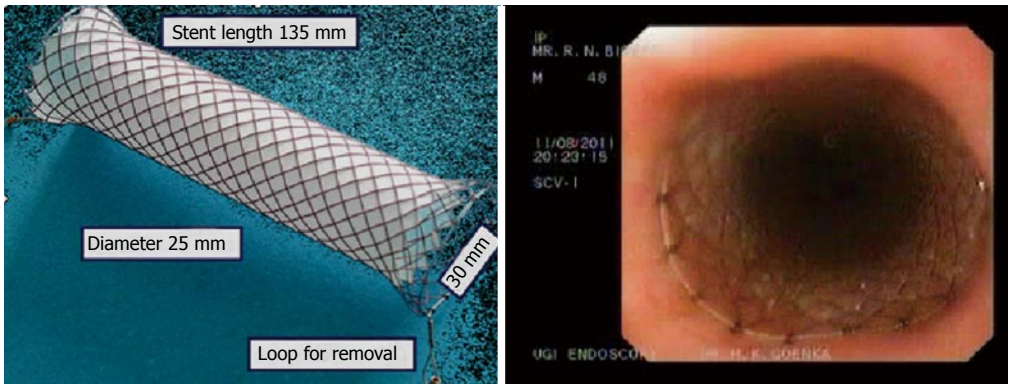

Figure 7 Danis stent.

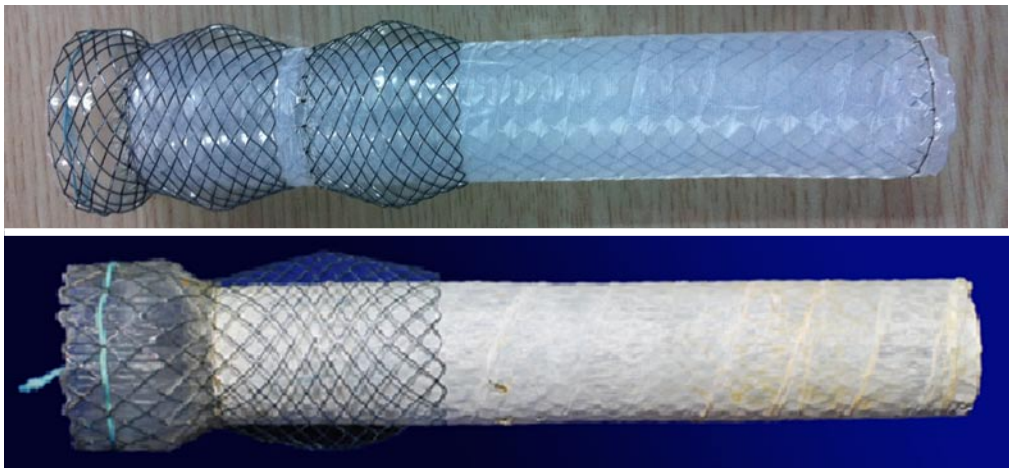

Figure 8 Modified stent design to prevent stent migration.

In a study by Rábago *et al*[62], 15 patients with post operative GI fistula were treated with Fibrin glue (combination of thrombin with fibrinogen). Complete sealing was obtained in 86.6% with a mean 2.5 sessions (range: 1 to 5) and a mean healing time of 16 d (range 5-40 d). Cyanoacrylate has been successfully used to close an esophagojejunal anastomotic leak after failed conservative therapy[63].

LIMITATIONS AND COMPLICATIONS

While endotherapy is exciting and results are encouraging, it has limitations in situations such as large perforation, difficult endoscopic position, fibrosis at the edge of the defect, evidence of abscess or fecal contamination *etc*[64]. Additional procedures or surgical alternatives should be considered in these circumstances. It is important to identify patients with failed clip closure as surgery should be promptly instituted in these patients in order to avoid sepsis and its consequences[65]. Monitoring should therefore be done by clinical profile and repeated blood counts. While endotherapy is safe if performed judiciously, complications such as perforation and bleeding are known. In particular, one must be careful while introducing endoscopes loaded with OTS clips, since the bigger insertion diameter can lead to iatrogenic perforations[22].

RECENT DEVELOPMENTS

Some of the recent techniques used to close GI leaks and fistula include Endovac therapy, Plugs and grafts, Biodegradable stents and Cardiac septal occluder. Endoscopic vacuum assisted closure sponge or Endovac therapy has been used in setting of leaks associated with infections (Figure 11)[66-69]. Ahrens *et al*[68] reported 5 patients with post esophageal surgery anastomotic leaks treated by endovac therapy. Polyurethane sponges with a drainage tube fixed to it allowing continuous suction was positioned endoscopically in the wound cavity and sponge was changed at regular interval. All 5 patients had closure of leak after a median of 9 sponge changes, median duration of drainage being 28 d. Two patients did require bougie dilatation for esophageal stenosis and one of them had fatal outcome due to aortoanastomotic fistula after dilatation. Loske *et al*[67] reported success in 13 out of 14 patients with esophageal leak treated by Endovac therapy with sponge being placed in the esophageal lumen (intraluminal method) or in the extraluminal

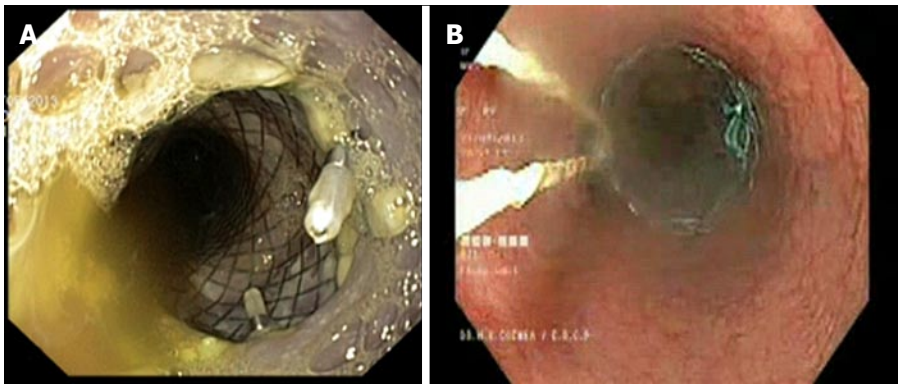

Figure 9 Anchoring of stent using (A) clip and (B) externalized thread.

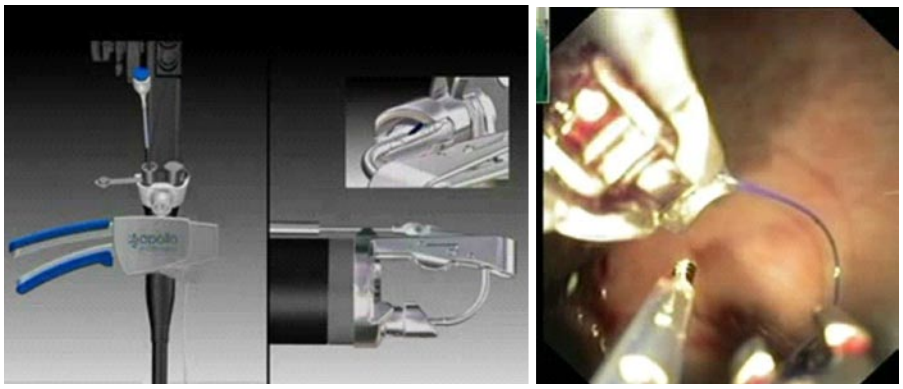

Figure 10 Apollo overstitch device.

Table 5 Result of endotherapy for iatrogenic esophageal perforation[1]

Ref.	Type of treatment	Patients (*n*)	Technical success (%)	Complications (%)
[2]Freeman *et al*[43]	SEPS	19	100	24
Vallböhmer *et al*[44]	SEMS	12	100	8
[2]van Heel *et al*[45]	SEMS/ SEPS	31	100	33
Schimdt *et al*[46]	SEMS ± clip (1)	22	100	NA
Swinnen *et al*[47]	SEMS	23	100	NA
D'Cunha *et al*[48]	SEMS/ SEPS	15	95	13
Biancari *et al*[49],	Stents ± clip (1)	12	100	25
Schweigert *et al*[50]	SEMS/ SEPS	13	100	85
[2]Heits *et al*[51]	Vaccum therapy	10	100	20
Biancari *et al*[52]	SEMS/clip	67	100	34

[1]Only studies with 10 or more patients have been included; [2]Study design was prospective, rest were all retrospective. NA: Not available; OTSC: Over-the-scope clip; SEMS: Self-expandable metal stent; SEPS: Self expandable plastic stent.

Table 6 Result of endotherapy for iatrogenic gastric perforation

Ref.	*n*	Additional procedures	Success rate (%)
TTS			
Tsunada *et al*[53]	7	Omental patch (1 case)	100
Fujishiro *et al*[39]	11	-	100
Minami *et al*[23]	121	> 1 cm: omental patch	98.3
Shi *et al*[54]	20	Endoloop	100
Zhong *et al*[55]	14	Endoloop	100
OTS			
Kirschniak *et al*[24]	7[2]	-	100
[1]Voermans *et al*[22]	6	-	100
Nishiyama *et al*[56]	7	-	86

Only studies with 5 or more patients are included. [1]All studies were retrospective except Voermans *et al*[22]; [2]13 OTS clips were placed in 7 patients.

wound cavity (intracavitary method). Similar technique has also been used for colonic anastomotic leaks with success in 28 out of 29 patients.

Plugs and grafts used include Vicryl plug and Surgisis. Surgisis soft tissue graft (Cook Biotech Inc, West Latayette, Ind) is an acellular bioactive prosthetic biomatrix produced from sheep intestinal submucosa[70]. In contrast to synthetic prosthetic material which has inherent risk of foreign body reaction, sepsis and secondary fistula formation, surgisis has been shown

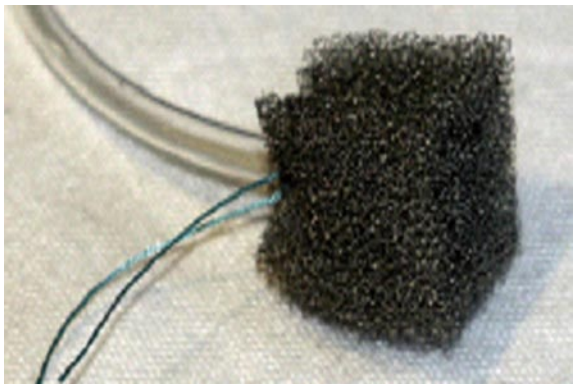

Figure 11 Endoscopic vacuum-assisted closure sponge (Endovac Therapy).

to be safe in contaminated tissues. It has been used successfully to treat complicated infected fistula after surgical resections including bariatric surgeries[71-73]. Vicryl mesh in combination with fibrin glue (covering the mesh as well as injected into the submucosa at the edge of the defect) used by Böhm *et al*[74] has also shown success in 13 out of 15 patients with leaks or fistula in upper GI tract following surgery for cancer. One to four sessions were used for this purpose.

Biodegradable stents have been used in a small series of 5 patients with esophageal leaks[75]. Four out of these 5 patients responded, inspite of 3 stents migrating during follow up. Cardiac septal occluder (Amplatzer Occluder, AGA Medical Corp, Plymouth, MN) used for cardiac septal defects have been used successfully by Repici *et al*[76] to close esophago - tracheal fistula. More data is however, required with these modalities before they are included in routine clinical practice.

CONSERVATIVE TREATMENT

While majority of patient with GI wall disruptions are candidates for either surgery or endotherapy, a small selected group of patients with iatrogenic perforation can be managed by conservative approach[18]. This subset includes stable patients who have perforations in cervical esophagus or a small number of patients with gastric or duodenal perforation, which are diagnosed late (> 12 h), are asymptomatic, have no signs of peritonitis and do not show free fluid or contrast extravasation at CT scan[18]. Somatostatin and its analogue octreotide, which decrease intestinal secretions, have also been used to improve the results of this conservative approach both in adults as well as children[77-79]. However, their role has been primarily considered for post-operative dehiscence, particularly after pancreatic surgery[78,79].

In conclusion, leaks and fistula involving GI tract are increasingly encountered in our routine practice. In a small select group of patients, there is a scope for conservative treatment of perforation and leaks. However, majority of patients are treated by surgery or endoscopic therapy. Techniques such as Endoclips (TTS and OTS) and covered metal stents have made endotherapy a preferred method to treat GI leaks and fistula. In general small leaks (< 10 mm) can be managed by traditional TTS clips, larger leaks require covered stents or OTS clips. Leaks and fistula associated with luminal strictures should be managed by luminal stenting. Recent developments with use of Endovac, Plugs and Graft and Biodegradable stents are encouraging. In particular, use of Endovac in the setting of sepsis seems promising. In view of multiple endoscopic modalities available with us, an algorithm based on location, size and associated features need to be developed to use these techniques judiciously.

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MINIREVIEWS

Current status of laparoendoscopic rendezvous in the treatment of cholelithiasis with concomitant choledocholithiasis

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Abstract

The current evidence in favor of the laparoendoscopic rendezvous is promising and demonstrates the main advantages of this technique in regard to shorter hospital stay and selective cannulation of the common bile duct (CBD), avoiding thus the inadvertent cannulation of the pancreatic duct. In addition, in the rendezvous technique the contrast medium is not injected retrogradely as during the traditional endoscopic retrograde cholangiopancreatography (ERCP), when the medium accidentally could be injected under pressure into the pancreatic duct. The RV technique minimizes that risk. Both these main advantages of the RV technique over the classic ERCP, are related with a significant lower incidence of hyperamylasemia and post-ERCP pancreatitis, compared with the traditional two stage procedure. Choledocholithiasis is present in 10% to 15% of patients undergoing cholecystectomy. To date, the ideal management of CBD stones remains controversial. Prospective randomized trials have shown that laparoscopic management of the CBD stones, as a single stage procedure, is the most efficient and cost effective method of treatment. Laparoendoscopic rendezvous has been proposed as an alternative single stage approach. Several studies have shown the effective use of this technique in the treatment of CBD stones by improving patient compliance and clinical results including shorter hospital stay, higher success rate and less cost. The current evidence about the use of this technique presented in this review article is promising and demonstrates the main advantages of the procedure.

Key words: Common bile duct stones; Laparoendoscopic rendezvous; Endoscopic retrograde cholangiopancreatography; Cholecysto-choledocholithiasis; Laparoscopic cholecystectomy

Core tip: This is a review article for the laparoendoscopic rendezvous technique - a promising single stage procedure in the treatment of patients with cholecysto-

choledocholithiasis. In this article we highlight the main advantages of the procedure compared to the traditional two stage approach [preoperative endoscopic retrograde cholangiopancreatography (ERCP) followed by laparoscopic cholecystectomy]. These advantages include the selective cannulation of the common bile duct and the avoidance of high pressure injection of the contrast medium into the pancreatic duct. Both factors are directly related with the pathogenesis of post-ERCP pancreatitis. The current evidence demonstrated in this paper is in favor of the laparoendoscopic rendezvous, however, this technique is still not widely accepted.

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INTRODUCTION

Choledocholithiasis is present in 10%-15% between patients undergoing cholecystectomy. The overall incidence of unsuspected common bile duct (CBD) stones is approximately 4%[1,2]. Once discovered, CBD stones should be removed in order to prevent several complications, such as acute pancreatitis, jaundice and acute ascending cholangitis and hepatic abscess. The obvious aim in the treatment of patients with choledocholithiasis is to achieve ductal clearance with the less number of interventions and least morbidity[3].

Over the past few decades, there have been significant improvements in both the diagnosis and treatment of patients with gallstone disease and CBD stones. Before the introduction of laparoscopic cholecystectomy, patients with cCBD stones underwent CBD exploration by open surgery. Although a high success rate of CBD clearance was achieved, the significant morbidity and mortality of a major abdominal surgery remained. Since then, many alternative treatment modalities have been developed. Especially, the introduction and evolution of endoscopic retrograde cholangiopancreatography with endoscopic sphincterotomy, which gradually became the gold standard for the treatment of biliary duct stones[1,4].

Nowadays, laparoscopic cholecystectomy (LC) is the treatment of choice for patients with symptomatic cholelithiasis. The introduction of LC as a minimal invasive procedure, has also changed the therapeutic strategies for the management of choledocholithiasis. To preserve the minimal invasive concept of management, a number of options have been proposed, including two and single step management. Thus, the therapeutic approaches today vary, depending on availability experience and expertise and include open or laparoscopic CBD exploration, various combinations of LC and endoscopic retrograde cholangiopancreatography (ERCP) and combined laparo-endosopic procedures[5].

Due to this wide variation of treatment options the ideal management of cholelithiasis and concomitant choledocholitthiasis remains controversial. In the open surgery era, prospective studies compared the use of ERCP and endoscopic sphincterotomy (ES) before open cholecystectomy to open cholecystectomy with surgical exploration of the CBD. In these trials, a shorter hospital stay for patients underwent preoperative ES was reported, as well as, lower mortality and morbidity rates in patients over 60 years of age after ES[6,7]. In the era of LC, the combination of preoperative ERCP and LC is considered the treatment of choice for concomitant cholecysto-choledocholithiasis and remains the most frequently applied strategy at most hospital centers[8].

LAPAROSCOPIC CBD EXPLORATION

Since its introduction, ERCP has mainly been used preoperatively for the diagnosis of choledocholithiasis. However, a high incidence of negative ERCPs was recorded, raising the fear of major complications in patients who do not actually need the procedure. In addition to morbidity many patients were dissatisfied because of the need to have two procedures, an endoscopic for the clearance of CBD and a laparoscopic one for the removal of gallbladder. Thus, there was a desire from many surgeons to provide a single stage approach for the treatment of choledocholithiasis[4,9]. The evolution of laparoscopic surgery stimulated the application of laparoscopic approach for the management of CBD stones. Skilled laparoscopic surgeons proposed LCBD exploration as an effective alternative for the treatment of choledocholithiasis.

Prospective randomized trials comparing LCBD exploration with two stage procedures, have shown that laparoscopic management of the CBD stones, as a single stage procedure, is associated with equivalent success rate and patient morbidity but shorter hospital stay and lower cost[10,11].

Two, recently published meta-analyses, included studies comparing one stage vs two stage management of CBD stones. One stage procedures included LC and LCBDE or intraoperative ERCP, while two stage procedures included LC preceded of followed by ERCP. These meta-analyses showed that both clinical practices have similar clinical outcomes[12,13]. Two studies in the meta-analysis published by Alexakis *et al*[12] reported cost analysis. Both found a significantly higher costs for the two stage management.

Laparoscopic CBD exploration is a logical extension of LC. However it has not gained popularity amongst the surgical community. LCBDE, either through the transcystic route or through choledochotomy, is a technically demanding procedure and requires clinical experience in the open technique and advanced laparoscopic skills[2,10]. Thus, it has remained a procedure for experienced and/or enthusiastic laparo-

scopic surgeons. Apparently, scientific data from centers of excellence cannot not always be extrapolated into everyday clinical practice.

LAPAROENDOSCOPIC RENDEZVOUS FOR THE TREATMENT OF CHOLEDOCHOLITHIASIS

Despite the evidence from prospective randomized trials suggesting the superiority of the so-called one-stage management of cholecysto-choledocholithiasis in regards to the hospital stay and cost effectiveness, two-stage techniques, mainly preoperative ERCP followed by LC, are currently being used by most clinicians in their daily practice[10,11].

ERCP is associated with a failure rate to cannulate the ampula of Vater ranging from 4%-18% of cases while post ERCP pancreatitis is a major complication which can follow inadvertent pancreatic cannulation and contrast injection[14-16]. The laparoendoscopic rendezvous (LERV) procedure, which is a single stage combined laparoscopic and endoscopic approach to CBD stone treatment, represents an effective alternative to the sequential treatment which, in addition, minimizes the risk of inadvertent pancreatic duct cannulation and subsequently the risk of pancreatitis. Several studies during the past decades have shown the effectiveness of this technique as a single stage procedure in the treatment of CBD stones by improving patient compliance and leading to shorter hospital stay, higher success rate and lower cost. However, organization and technical problems have not facilitated the diffusion of this method[5,9,17,18].

The combined laparoendoscopic treatment was first described by Deslandres *et al*[19] in 1993. However, the method didn't encountered wide interest immediately. After the years, many authors used this approach in their practice. In 2009, La Greca *et al*[20] published the first review of original papers and case reports including a total number of some 800 patients, describing the results and comparing the LERV treatment with the other two main available treatment options. The overall effectiveness of the LERV technique was 92.3%. The duration of the endoscopic part of the procedure ranged from 8 to 82 min (mean 35 min), while the time of the whole LERV procedure was 40 to 360 min with a mean time of 104 min. The conversion rate to open surgery was 4.7%. The overall mortality and morbidity rates were 0.37% and 5.1% respectively. The mean hospital stay of patients treated with the LERV procedure was 3.9 d (range from 2 to 51 d)[20].

The advantages of the LERV approach were outlined by most authors of the reviewed studies. The most important suggested advantages compared with the LCBD exploration, which represents the single stage management rival, were the reduced operation time and lower technical difficulties. On the other hand, the main clinical advantages in comparison with the more popular two stage treatment (ERCP followed by LC) is the lower incidence of complications (especially pancreatitis), the higher success rate and the reduced hospital stay[20].

LAPAROENDOSCOPIC RENDEZVOUS AND POST-ERCP PANCREATITIS

The incidence of the post-ERCP pancreatitis ranges between 1% to 14%[21,22]. Multiple cannulation attempts have been described as an iatrogenic risk factor for post-ERCP pancreatitis. One of the most important technical factors in the concept of the LERV technique is that it facilitates the endoscopic procedure by the insertion of a guide-wire through the cystic duct and CBD into the duodenum ensuring thus elective CBD cannulation and avoiding the inadvertent cannulation of the pancreatic duct. This technical advantage provided by laparoendoscopic RV is of paramount importance, especially in cases with anatomical variations and difficult papilla cannulation[1,8].

Another important mechanical factor related to the pathogenesis of post-ERCP pancreatitis is the volume and high pressure of contrast medium injected by the endoscopist inadvertently into the pancreatic duct, during canulation of the papilla of Vater. Using the LERV technique the contrast medium is injected by the surgeon through the cystic duct avoiding thus the direct injection into the pancreatic duct[15,16].

In a recent study, LERV has been compared with standard ERCP at the same stage after the completion of LC. In this prospective randomized trial no case of post-ERCP pancreatitis was reported in either arm. However, during standard ERCP the risk of inadvertent pancreatic duct cannulation still exists, since selective cannulation of the bile duct is not ensured by the insertion of the guide-wire, as in the case of LERV[23].

Two CRTs in which LERV compared with the traditional two stage procedure reported lower serum amylase levels in patients treated with the LERV technique[8,24]. A statistically significant higher medium amylase value recorded by Tzovaras *et al*[24] in their study for the group of patients who underwent therapeutic ERCP followed by LC. La Greca *et al*[25] recorded a statistically significant reduction in serum amylase levels, in patients treated with rendezvous technique compared to ERCP/ES treatment. The authors concluded that the effectiveness and safety of the RV technique is mostly depended on the antegrade injection of the contrast medium by the surgeon through the cystic duct[25].

A statistically significant lower incidence of acute post-ERCP pancreatitis was recorded in two controlled randomized trials comparing the laparoendoscopic technique with the traditional two stage treatment[1,26]. All three meta-analyses, published to date confirmed the statistical significance of the lower post-ERCP pancreatitis rates in favor of the LERV technique[27-29]. The assessment of the overall ERCP/ES related complications in two of three meta-analyses, also confirmed

a statistically significant difference favoring the RV approach. However, when these complications were separately assessed in a subgroup analysis, no differences were found in the incidences of bleeding, perforation, cholangitis, cholecystitis and gastric ulcer.

EFFECTIVENESS OF THE LAPAROENDOSCOPIC RENDEZVOUS TECHNIQUE

It has been demonstrated that the LERV technique is an attractive option for the treatment of patients with CBD stones. It offers an advantage in selective cannulation of the CBD especially in cases of difficult papilla cannulation and where ERCP has already failed to provide a reliable therapeutic solution.

Tzovaras *et al*[30] used the LERV technique for the treatment of 22 patients who had at least one failed attempt of ERCP because of the presence of anatomic variations, mainly papillary diverticula or deemed unable to cooperate for a classic ERCP. Selective CBD cannulation achieved in all but two in whom the guidewire could not advance through cystic duct, however, the procedure completed using the classic retrograde way of ERCP intraoperatively[30].

In their controlled randomized study, Morino *et al*[8], proceeded with the rendezvous technique in 9 patients, initially randomized to the two stage approach, in whom ERCP failed to be performed. The treatment completed successfully in 8 patients using the laparo-endoscopic approach, indicating the use of the LERV technique as a safe and relatively easy way to cannulate selectively the CBD in patients in whom ERCP has failed[8].

La Greca *et al*[20] reported a higher overall effectiveness of the LERV technique regarding the CBD clearance compared to either preoperative ERCP or laparoscopic CBD exploration[20]. In controlled randomized trials comparing the LERV technique with the two stage treatment, the success rates of CBD stones clearance were similar for both treatment approaches[1,8,24,26]. However, as reported by Wang *et al*[29] in their meta-analysis, the success rate of CBD cannulation was significant higher for the rendezvous technique than the sequential treatment (RR = 2.54, 95 %CI: 1.23-5.26; $P = 0.01$)[29].

LAPAROENDOSCOPIC RENDEZVOUS TECHNIQUE AND TOTAL HOSPITAL STAY

Obviously, the laparoendosopic rendezvous as a single stage procedure is related with shorter hospital stay, comparing with the traditional two stage treatment. Four RCTs recorded statistically significant reduced hospital stay for patients treated with the LERV technique, comparing with the two stage approach[1,8,24,26]. Two meta-analyses confirmed the total hospital stay was significantly shorter with the RV technique compared with the sequential treatment[27,29]. This is mainly because a minimum of 24-48 h waiting period is required to ensure that no post-ERCP complication has occurred, before proceeding to LC in the two stage approach. It is difficult if not impossible this time interval to be reduced and this is a clear disadvantage of the two stage approach.

DISCUSSION

The LERV technique is a combined surgical and endoscopic procedure and it has been proposed as an alternative, single stage approach, for the treatment of patients with cholecysto-choledocholithiasis. This technique, did not reach wide acceptance immediately, because it requires the availability of surgical and endoscopic teams in the operating room. La Greca *et al*[20] presented the main disadvantage of the LERV technique to be logistics and organizational problems for an operation requiring the presence of two teams. Lella *et al*[1] considered this technique even more difficult to perform in the emergency setting. However, Tzovaras *et al*[24] concluded that the LERV could be effective and safe even in the urgent setting, including emergency cases in their study[24]. Obviously, in the era of minimal invasive surgery, any possible logistic problems should be resolved making the LERV technique available in the treatment of cholecysto-choledocholithiasis and its complications improving clinical results and patient's discomfort.

In comparing the laparoendoscopic approach with the sequential treatment, it should be mentioned that this technique ensures elective CBD cannulation, avoiding thus the inadvertent cannulation of the pancreatic duct. In addition, in the LERV technique the contrast medium is not injected retrogradely as during the traditional ERCP, when the medium accidentally could be injected under pressure into the pancreatic duct. The LERV technique minimizes that risk. Both these main advantages of the LERV technique over the classic ERCP, are related with a significant lower incidence of hyperamylasemia and post-ERCP pancreatitis, compared with the traditional two stage procedure[27-29].

The CBD clearance rate is an important outcome for the treatment of patients with CBD stones, leading in reduction of conversion rates to open surgery, which is associated with higher morbidity. The LERV technique is associated with at least equally high rates regarding overall CBD clearance compared to the traditional two stage approach, although it is associated with significantly higher success rate of CBD cannulation and lower number of procedures required for complete clearance. This technical advantage could be applied in clinical practice, especially in difficult papilla cannulation making it much easier for the endoscopist.

LERV is related with an additional operating time of approximately 30-45 min to be performed compared with the single laparoscopic cholecystectomy stage of

the sequential treatment. However, it saves more or less similar time in the endoscopic suite, where ERCP is performed as a separate procedure in a sedated but usually not anesthetized patient. Moreover, the extra time which represents the additional time needed for the performance of cholangiography and insertion/advancement of the guide wire into the duodenum would be balanced in case that intraoperative cholangiography is routinely used during LC[24].

Despite the aforementioned advantages of LERV there is some concern about the distention due to insufflation of the stomach and small intestine during the endoscopic part of the procedure. The use of a special bowel desufflator to decrease bowel distention or a laparoscopic small bowel clump placement across the first loop of jejunum, have been proposed to overcome this problem. It has been also suggested to perform as much as possible dissection of the gallbladder during the laparoscopic part before the beginning of the endoscopic part of the procedure[8,24].

Laparoendoscopic rendezvous is an attractive alternative for the treatment of patients with cholecysto-choledocholithiasis. The current evidence in favor of the LERV is promising and demonstrates the main advantages in regard to shorter hospital stay and selective cannulation of the CBD. The concept of the RV technique contributes in avoiding the main mechanisms of iatrogenic pancreatic damage, leading in lower incidence of post-ERCP pancreatitis. LERV requires basic laparoscopic equipment and skills; The only additional laparoscopic skill is the ability to perform an intraoperative cholangiogram, however, at an extra cost of increased operating time[24]. Despite the general improvement of skills in the last years, LERV is still considered as the least invasive approach for the treatment of cholecysto-choledocholithiasis[31]. However, the availability of the LERV nowadays is limited in most hospital centers, where the choice of the best approach for the treatment of patients with CBD stones is based on the institutional availability and expertise of their surgical and endoscopy teams. It seems that the lack of cooperation between the two teams, still does not facilitate the diffusion of the LERV procedure.

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Endoscopic mucosal resection and endoscopic submucosal dissection in the treatment of sporadic nonampullary duodenal adenomatous polyps

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Abstract

Although uncommon, sporadic nonampullary duodenal adenomas have a growing detection due to the widespread of endoscopy. Endoscopic therapy is being increasingly used for these lesions, since surgery, considered the standard treatment, carries significant morbidity and mortality. However, the knowledge about its risks and benefits is limited, which contributes to the current absence of standardized recommendations. This review aims to discuss the efficacy and safety of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) in the treatment of these lesions. A literature review was performed, using the Pubmed database with the query: "(duodenum or duodenal) (endoscopy or endoscopic) adenoma resection", in the human species and in English. Of the 189 retrieved articles, and after reading their abstracts, 19 were selected due to their scientific interest. The analysis of their references, led to the inclusion of 23 more articles for their relevance in this subject. The increased use of EMR in the duodenum has shown good results with complete resection rates exceeding 80% and low complication risk (delayed bleeding in less than 12% of the procedures). Although rarely used in the duodenum, ESD achieves close to 100% complete resection rates, but is associated with perforation and bleeding risk in up to one third of the cases. Even though literature is insufficient to draw definitive conclusions, studies suggest that EMR and ESD are valid options for the treatment of nonampullary adenomas. Thus, strategies to improve these techniques, and consequently increase the effectiveness and safety of the resection of these lesions, should be developed.

Key words: Polyps; Duodenum; Adenoma; Resection; Endoscopy

Core tip: Widespread use of endoscopy leads to increase detection of sporadic nonampullary duodenal adenomas. Due to significant morbidity and mortality of surgical treatment in this setting, endoscopic treatment with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), has been progressively used for the resection of these lesions. This extensive and detailed review discusses the efficacy and safety of EMR and ESD in this context. We conclude that EMR and ESD are valid options for the treatment of sporadic nonampullary duodenal adenomas. Strategies to improve these techniques, and consequently increase their effectiveness and safety should be developed.

Marques J, Baldaque-Silva F, Pereira P, Arnelo U, Yahagi N, Macedo G. Endoscopic mucosal resection and endoscopic submucosal dissection in the treatment of sporadic nonampullary duodenal adenomatous polyps. *World J Gastrointest Endosc* 2015; 7(7): 720-727 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i7/720.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i7.720

INTRODUCTION

We searched Medline (PubMed) for all published manuscript up to 2014. The search terms used were "(duodenum OR duodenal) (endoscopy OR endoscopic) adenoma resection". The search was restricted to English language and was extended by carefully reviewing the bibliographies of the pertinent manuscripts on this subject. Of the 189 retrieved articles, and after reading their abstracts, 19 were selected due to their scientific interest. The analysis of their references, led to the inclusion of 23 more articles for their relevance in this subject.

Duodenal adenomatous polyps are a rare disease in the general population, reported as incidental findings in up to 0.1%-0.34% of the patients undergoing upper gastrointestinal endoscopy[1,2]. The evolution and widespread of this exam contributed to the increase in smaller sized polyps early diagnosis[3-5]. Adenomas are the histologic subtype that constitutes the majority of the duodenal lesions that need resection[2,6]. For this reason, they must be distinguished from non-adenomatous polyps, namely the ones that originate in the mucosa (gastric metaplasia) or submucosa (carcinoid tumors, leiomyomas, lipomas, inflammatory fibroid polyps and gastrointestinal stromal tumors), hamartomatous polyps (Brunner glands hyperplasia and Peutz-Jegher polyps, among others), and metastatic polyps[1,5,6]. One of the goals of the treatment, common to all duodenal adenomas, is the elimination of the tumoral progression risk, which correlates with the size of the lesion and is similar to that of colorectal adenomas[6,7].

These lesions are classified, according to its location, in ampullary (if they involve the duodenal bulb major - ampulla of Vater - or minor) or not ampullary. In both circumstances, they may occur as part of a genetic syndrome associated with the development of polyps, as the Familial Adenomatous Polyposis, or sporadically[8,9].

Sporadic nonampullary adenomatous polyps have similar incidence in both sexes and are mostly diagnosed accidentally between the sixth and eighth decades of life[5,6]. Typically, these lesions are solitary, with sessile or flat morphology, more than 10 mm, located in the second portion of the duodenum and asymptomatic[9-14]. However, depending on their size, location and histological characteristics, they can cause dyspepsia, abdominal pain, bleeding and bowel obstruction[5].

The traditional therapeutic approach for duodenal polyps is local surgical excision or radical surgery, respectively characterized by high rates of recurrence and significant morbidity and mortality[15,16]. In 1973, Haubrich described the first endoscopic excision of a duodenal adenoma, which, since then, has been pointed out by several publications as a safe and effective alternative to surgery[3,4,10,11,17-19]. In a retrospective analysis of 62 patients with duodenal nonampullary polyps, the morbidity of the surgical therapy was significantly superior to the one of the endoscopic resection (33% *vs* 2%)[20].

The use of endoscopic techniques in the duodenum is still controversial, since it represents a diagnostic and technical challenge[3,6]. The duodenum has several peculiarities that make the endoscopic resection complications risk higher than the one described elsewhere in the gastrointestinal tract[21]. Indeed, its narrow lumen and retroperitoneal fixation hampers the maintenance of an adequate vision field during the procedure[22]. On the other hand, this organ has the thinnest wall of the digestive tract and shows a thick fibrous submucosa, even in a non-pathological situation, which can limit the protrusion of the mucosa achieved by the submucosal saline injection[22].

The scientific evidence of the risks and benefits of the endoscopic treatment and its long-term outcomes in the resection of nonampullary polyps, both sporadic and associated with genetic syndromes, is limited[23,24]. This reality contributes, along with the fact that this type of lesions is infrequent and has a natural history and clinical importance that is not fully understood, to the absence of a specific set of criteria for clinical guidance[5,24,25]. Consequently, the therapeutic strategies are usually considered taking into account the patient's condition, the characteristics of the lesion and the experience of who performs the endoscopic technique[5,7,24].

In 2010, a review published by the National Institute of Clinical Excellence highlighted the lack of published material that addressed this topic[23]. Although the number of clinical trials has increased since then, the best treatment of nonampullary adenomas remains

subject of discussion[9]. The purpose of this work is to review the scientific literature regarding endoscopic resection of sporadic duodenal nonampullary adenomatous polyps, highlighting the benefits and drawbacks of EMR and ESD based on the analysis of different outcomes obtained with their practice.

INITIAL ASSESSMENT

Before endoscopic resection, it is essential to characterize the size of the polyp, duodenal folds and lumen extension involvement[6]. It should be ensured that it doesn't involve the ampulla of Vater (which would imply a different diagnostic and therapeutic approach) with a side-viewing endoscope or with endoscopic ultrasound[5,6,25].

The endoscopic appearance of duodenal adenomas cannot always distinguish them safely from non-adenomatous polyps and thus, all lesions considered suspicious should be biopsied[25]. It is also important to determine the resectability of the lesion and detect any signs that suggest submucosal invasion, and that influence the treatment, such as tumors with depression (IIc in the Paris Classification), type Ⅴ pit pattern classification described by Kudo, presence of bleeding, induration, ulceration or irregularities on the surface of the polyp and non-lifting sign after submucosal saline injection[5,6,26,27].

The exact role of endoscopic ultrasound in the evaluation of nonampullary adenomas remains uncertain[24]. When it's impossible to establish the relationship of the polyp with the pancreaticobiliary tree with a forward and side-viewing endoscopy, endoscopic ultrasound is an alternative technique, obviating the need of an endoscopic retrograde cholangiopancreatography[5]. Some researchers advocate its use in the evaluation of the depth of duodenal polyps larger than 20 mm[7,24]. However, according to Al-Kawas, the routinely use of endoscopic ultrasound, apart from not bringing great benefit, would have a considerable cost[7].

Newer techniques such as magnification endoscopy, endoscopy with narrowbanding imaging or chromoendoscopy (with a non absorbable dye such as indigo carmine) allow better delineation of the margins of the lesion and can be used in the initial evaluation of duodenal adenomas, potentially reducing incomplete resection rates[6,21]. Although there is little information regarding the use of magnification chromoendoscopy in the duodenum, this technique showed a reduction of local neoplastic recurrence from 8.7% to 0.5% when associated with EMR of flat colonic lesions bigger than 2 cm[28]. Shinoda *et al*[29] found that magnification endoscopy with narrowbanding imaging or indigo carmine is more accurate than endoscopic ultrasound in the evaluation of the gastric and oesophageal mucosal cancer depth. Future research will be essential for the determination of these techniques' role in the duodenum[13].

EMR

This technique was developed to remove sessile or flat tumors that are confined to the superficial layers (mucosa and submucosa) of the GI tract wall. Classically, it's used for *en bloc* or piecemeal resection, if the diameter is less or more than 2 cm, respectively[30]. The lesion is initially elevated by the injection of a saline substance into the submucosa that causes its protrusion into the duodenal lumen. Depending on the size of the polyp, the volume of injected solution can vary between 5 and 50 mL, and it may be necessary to repeat this procedure if the cushion created by the injected fluid dissipates before the resection is complete[30]. There are several solutions currently available, but isotonic saline (0.9% NaCl) is the most frequently used[30]. However, scientific evidence suggests that hypertonic solutions originate a better and longer-lasting elevation[6,31]. This procedure allows the isolation of the mucosa involved, facilitating its resection with an endoscopic snare, and reduces the risk of thermal and mechanical injury of the deepest layers. The non-lifting sign enables the identification of polyps that are likely to have submucosal invasion, and that don't usually have an indication for endoscopic treatment[6,19,31]. The inclusion of adrenaline in the injected solution reduces the haemorrhagic risk and provides better visibility[6]. As a diagnostic tool, and differently from ablative therapy, it holds an important role in obtaining samples for histological analysis[31]. When compared to snare or forceps polypectomy, EMR allows resection of a larger area, as well as access to deeper levels, through the excision of the medium or deep submucosal layer[31]. It thus facilitates histological assessment of the entire lesion and thereby identifies foci of malignancy that cannot be included in the surface sample obtained by forceps or snare biopsy[18] (Figure 1).

Efficacy

The predominantly retrospective published clinical trials report an EMR complete resection rate of nonampullary adenomas of 79%-100%[4,10-14,18,19,32,33]. In the studies that indicate the type of resection, it appears that in 64% of the cases it was possible to remove the polyp *en bloc*, having the remaining been excised with piecemeal resection[4,10,12,13,18,32-35]. The latter is more frequent in lesions larger than 20 mm, hardly removed safely *en bloc*, and seems to be associated with higher rates of recurrence and residual lesion[13,18,19,33]. The execution of the technique is a critical factor in minimizing these potential risks[19].

Kedia *et al*[12] studied the relationship between the adenomatous polyp size, the extent of duodenal lumen involved, and the efficacy of EMR. He concluded that although there is a significant association between the proportion of duodenal lumen involved and complete endoscopic resection, the same doesn't happen between the latter and the size of the lesion. The complete resection rate achieved in tumors involving less than

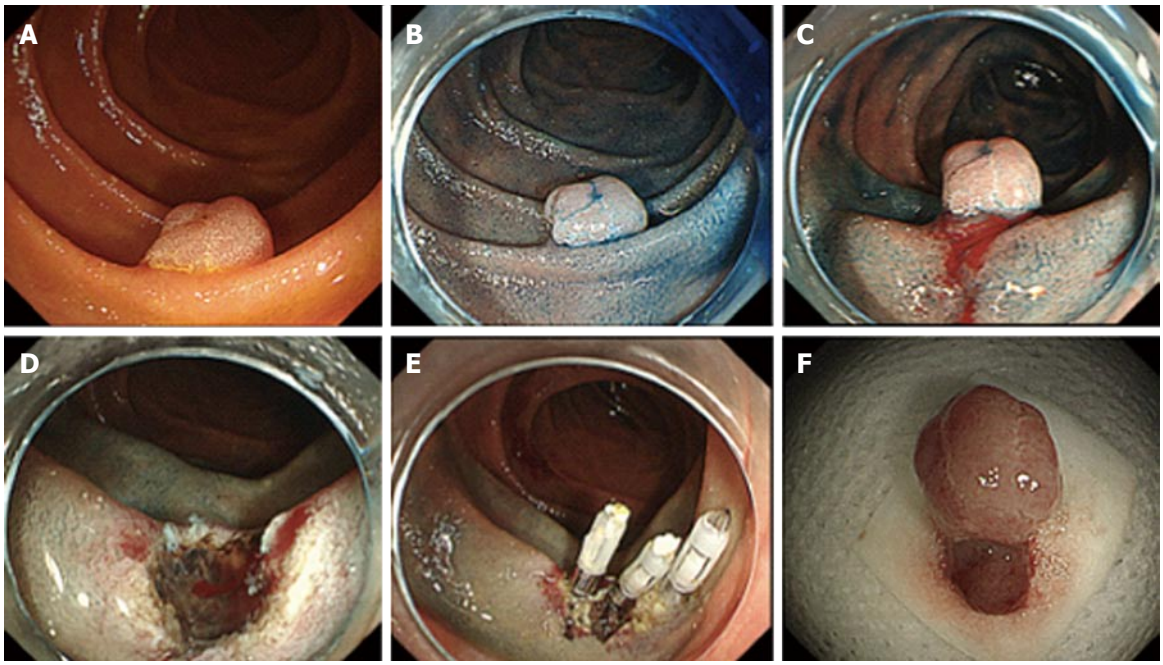

Figure 1 Endoscopic resection of a sporadic neoplastic lesion in the duodenum using endoscopic mucosal resection technique. A: Sessile lesion in the descending duodenum seen with white light (type 0 - Isp of the Paris classifi-cation); B: Same lesion after chromoendoscopy with indigo carmine; C: Same lesion after subepithelial injection of diluted adrenalin; D: Resected area after endoscopic mucosal resection; E: Closure of the resected area with clips; F: Lesion resected *en bloc*. Histology revealed a well-differentiated tubular adenocarcinoma limited to the mucosa, with 7 mm × 8 mm, without lymphatic or vascular invasion.

one quarter of the luminal circumference was 94.7%, compared to 45.5% in those involving one quarter to half of the circumference. In lesions where more than half of the luminal circumference was involved no lesion was resected successfully. Thus, this author suggests that the strongest clinical predictor of a successful polyp excision is the luminal extension that it involves. The American Society for Gastrointestinal Endoscopy (ASGE) guidelines indicate that surgery should be considered in adenomas involving more than 33% of the circumference of the lumen[24].

In the studies that report the number of sessions required to achieve complete resection, 80% of the cases it was possible with one session, 17% with two sessions and only 3% in three sessions[6]. In all situations, the purpose of who performs the EMR should be to remove the entire polyp in one session, without compromise of security[21]. Areas with residual adenoma and fibrosis are more difficult to resect during subsequent interventions, which are associated with increased risk of complications[6,9,21].

The recurrence rate varies widely between 0% and 36%, and all described recurrent lesions were treated with polypectomy snare or ablative therapy[6,9,13,18,19,36]. This high rate reinforces the need of a detailed resection of all adenomatous tissue, possibly with use of adjuvant therapy, and a rigorous follow-up period, especially in larger adenomas or with piecemeal resection[6,12,19].

Safety

Bleeding, which is associated with duodenal abundant vascularization, occurs during EMR (immediate bleeding) in 9% of procedures[6]. As there is no standardized definition of immediate haemorrhage, it's hard to know whether the reported cases were clinically significant or had comparable gravity. However, Lepilliez *et al*[18] does not consider it a true complication, since it can often be controlled by application of endoscopic clips, using ablative therapy or adrenaline injection adrenaline. None of the described cases needed blood transfusion[3,4,6,10,11,18,19].

Late bleeding rate ranges from 0 to 12%[1,4,10,12,13,18,19,33]. A recent study, that included 50 nonampullary adenomas, showed that the risk of delayed haemorrhage is significantly higher in lesions which diameter was bigger than 30 mm[35]. In all cases, bleeding occurred within the first 48 h after resection and was mostly approached conservatively or with endoscopic mono or bipolar electrocautery, epinephrine injection, haemostatic clips or a combination of these[1,4,10,12,13,18,19,33].

The proceeding method regarding the presence of visible non-bleeding vessels and the closure of the resected area as a preventive measure of late haemorrhage, are questions that don't gather a consensus answer[35]. Kim *et al*[13] defends that primary closure with clips is preferable to ablative therapy, since it does not increase the risk of tissue injury. Although closure of primary defects smaller than 2 cm is usually possible, it will probably be unnecessary, except in cases where there is potential risk of late bleeding[35]. On the other hand, areas bigger than 2 cm cannot be safely closed because of the difficulty in opposing margins of the defect[13,18,35]. In the study of Lépilliez *et al*[18], the difference found between late haemorrhage rate of the

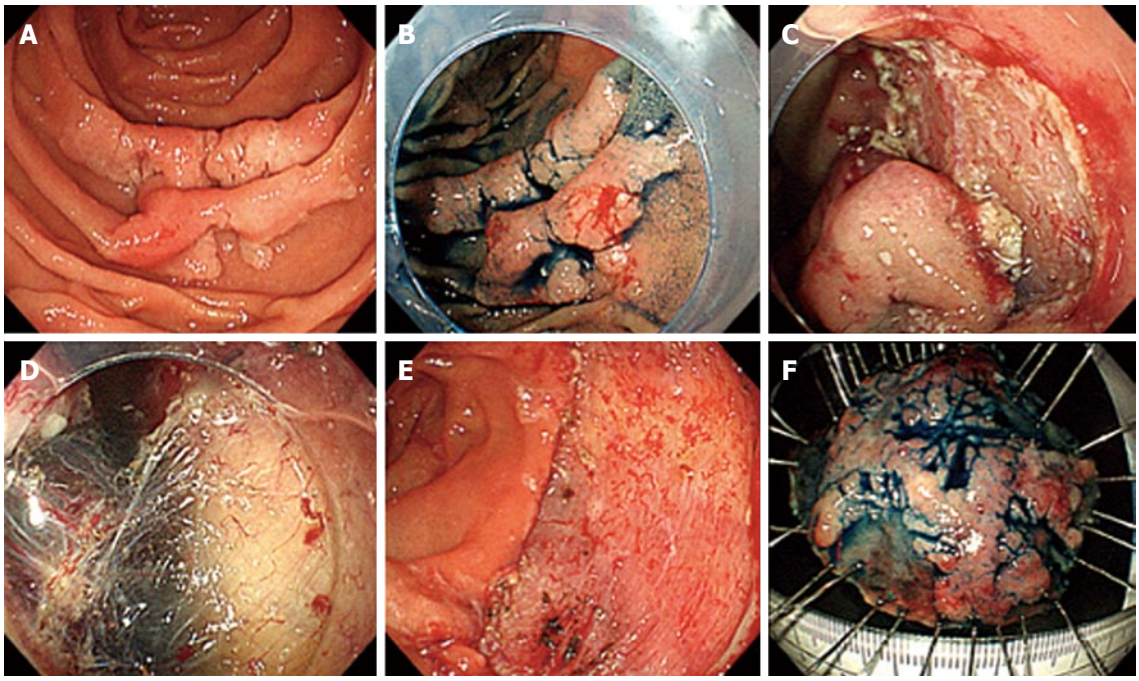

Figure 2 Endoscopic resection of a sporadic neoplastic lesion in the duode-num using endoscopic submucosal dissection technique. A: Flat lesion in the descending duodenum seen with white light (type 0-IIa of the Paris classi-fication); B: Same lesion after chromoendoscopy with indigo carmine; C: Partial dissection with endoscopic submucosal dissection; D: Dissection plan where the submucosal layer and the partially dissected lesion can be seen; E: Dissected area; F: *En bloc* dissected lesion. Histology revealed a well-differentiated adenocarcinoma limited to the mucosa, 40 mm × 32 mm, without lymphatic or vascular invasion.

cases that had haemorrhagic prevention systematically done (with ablative therapy or clips) or bleeding treatment was required during the procedure, and cases that didn't have bleeding prevention or immediate haemorrhage occurred, was statistically significant. In the first group, consisting of 14 patients, there was no late haemorrhage, while in the second 5 bleedings occurred in 23 patients (22%).

EMR has a perforation risk of the duodenal wall of 0.6%[6,35]. Registered perforations were managed with endoscopy or surgery conversion[18,35]. Resection limited to the adenomas that lifted after the submucosal injection may be a way of preventing this complication[36].

ESD

This technique is widely used for *en bloc* resection of gastrointestinal lesions[5]. Despite its growing use in the stomach, colon and oesophagus, its use in the duodenum is less frequent[37]. This fact is probably due to its retroperitoneal fixation, thin wall and narrow lumen, which make the intervention at this location technically difficult[14,29]. The low prevalence of duodenal lesions may be one of reasons that can explain the ESD long learning curve in the duodenum[14]. The published studies that performed this technique are few and include a small number of patients with short follow-up periods[14,29,33,38,39].

ESD is generally performed in several stages. After marking the margins of the lesion, by electrocauterization, and lifting it by submucosal injection, a circumferential incision is made in this layer, and the lesion is dissected from the underlying layers by using dissection knives[30] (Figure 2).

Efficacy

Complete resection rate of sporadic adenomatous nonampullary polyps by ESD ranges from 86% to 100%[14,22,29,33,38,39]. No recurrence was described[14,22,33,38,39]. The choice of ESD instead of piecemeal EMR may be a way of reducing the recurrence associated with this last technique[13].

In a study by Honda *et al*[14], in which 15 non ampullary adenomas were resected by endoscopy (9 by ESD and the rest by EMR), found that the average diameter of the lesions removed by ESD was 24 mm (the largest lesion had 39 mm), and that those removed by EMR had an average size of 8 mm. The mean time of the interventions was also registered. ESD and EMR procedures took respectively 85 and 16 min in average. The inclusion of larger and more challenging lesions, as well as duodenal more difficult haemostasis in duodenum, are possible explanations given by the author for the time consumed by ESD.

Obtaining en bloc resection with negative margins is a well-known ESD advantage[40]. According to Endo *et al*[33], ESD should be the procedure of choice for lesions larger than 10 mm, and when it is desirable to obtain en bloc resection (including lesions whose biopsy or magnification endoscopy are suggestive of carcinoma). In their study, all adenomas larger than 10 mm resected by EMR revealed positive margins. All adenomas resected by ESD had negative margins (the

biggest lesion diameter was 30 mm).

Safety

In three clinical trials, ESD was associated with a bleeding rate between 8% and 22%[14,22,41]. All cases were managed with endoscopic haemostatic clips, without requiring blood transfusion. The reported duodenal perforation rate is 31%[14,22,33,38,39]. This percentage is higher than the one obtained in the oesophagus, stomach and colon, and is associated to the anatomical peculiarities of the duodenum[22]. Duodenal perforation may have a difficult approach and contribute to increased morbidity and mortality of the patient, hospitalization period and health care costs[40].

Late perforation is a very serious complication that, according to a retrospective study published in 2013, is significantly associated with the endoscopic technique that was used and the location of the lesion[41]. In this study, that included lesions resected by EMR or ESD, all late perforations occurred after ESD or piecemeal EMR, which according to the authors, may be due to electrocautery overloading. It was also found that all perforations were distal to the ampulla of Vater, which seems to happen because of the proteolysis or chemical irritation caused by exposure of the duodenal wall to the pancreatic juice and bile enzymes, which can be decreased with the administration of protease inhibitors[14,39]. Given that there are several factors that may be associated with perforations, it is difficult to clarify which ones are more likely to relate to their origin[22]. Jung suggests that ESD is itself a perforation risk factor and, therefore, it should be performed only in selected patients[39]. The most appropriate prophylactic intervention and approach to late perforation in the duodenum have not been established yet[41].

FOLLOW-UP

The guidelines published by the ASGE emphasize that all patients who have undergone endoscopic resection of a sporadic duodenal adenoma should be considered for a follow-up program for the detection and treatment of any recurrence[24]. However, because of the lack of information, formal recommendations regarding surveillance intervals have not been defined. These should be applied on a patient-basis adjusted on the characteristics of the polyp, adequacy of the initial resection, eventual occurrence of complications and comorbidities of the patient[22]. According to a review article, most authors recommended a follow-up endoscopy 3-6 mo after resection, followed by surveillance endoscopies each 6 to 12 mo[6].

CONCLUSION

Analysis of the literature on this topic reveals a reduced number of reviews and studies, that generally include a small sample of patients and short follow-up periods, which hinders drawing consistent conclusions about the endoscopic resection long-term effectiveness of sporadic nonampullary adenomas[13,19,26,34]. Some of the results obtained in clinical trials exhibit considerable variability, which doesn't have a clear justification, but may be associated, for example, to inconsistencies in outcome definitions by different authors, as well as the length of the follow-up period[7]. Moreover, most studies have a retrospective character, which can introduce selection bias and underestimate the complication rate[34].

Although most of the analysed studies and endoscopic techniques mentioned in this review were predominantly developed in Asian countries, it is important to note that this reality may not reflect the Western context[6]. After comparing these two populations, Min *et al*[34] states that Western studies show a lower complete resection rate, and suggests that this discrepancy can be clarified by the smaller sized lesions included in Asian studies, since the diagnosis of smaller adenomas has increased in these countries due to gastric cancer screening programs and subsequent widespread of the endoscopy[12,18,19,34]. Local recurrence rates are higher in Western countries, which again may be explained not only by the difference in the lesions size, but also by the follow-up period after resection, that seems to be shorter in Asia (6-29 mo *vs* 13-71 mo)[34]. Authors, however, rarely address this divergence.

EMR is an alternative to surgery in patients with less invasive superficial duodenal adenomas, entailing shorter hospital in-stay, lower costs, and providing a reasonable complication rate that can usually be controlled by endoscopy[13]. Resection is most likely to be complete in adenomas involving less than half of the luminal circumference[12]. It requires a tight monitoring period, especially after big adenomas or piecemeal resection, so that early detection and treatment of residual or recurrent lesions is possible[6,13]. ESD, although potentially providing en bloc resection with negative margins, has higher haemorrhagic and perforation risks in the duodenum when compared to EMR[9]. Therefore, when choosing the appropriate endoscopic technique, the risks of the procedure must be balanced against its benefits[40].

Although the scientific evidence level in this area is limited, the results obtained in these last years are encouraging. However, prospective studies with larger samples and extended follow-up periods will be necessary. Future development of techniques and tools that contribute to the prevention and early detection of recurrence, and increase the efficacy and safety of endoscopic resection in the duodenum, will be essential for a better therapeutic approach to these patients.

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ORIGINAL ARTICLE

Basic Study

Feasibility and safety of endoscopic cryoablation at the duodenal papilla: Porcine model

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Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at mihir.wagh@medicine.ufl.edu. No additional data is available.

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Abstract

AIM: To assess the feasibility and safety of liquid nitrogen spray cryoablation at the duodenal papilla in a porcine model.

METHODS: This prospective study protocol was approved by the University of Florida Institutional Animal Care and Use Committee. Six pigs underwent liquid nitrogen spray cryotherapy at the duodenal papilla. Freeze time of 20-s was applied per cycle (4 cycles/session). Survival animals (n = 4) were monitored for adverse events. Hemoglobin, white blood count, liver tests, and lipase were obtained at baseline and post-treatment. EGD was performed on day#7 to evaluate the papilla and for histology. All animals were euthanized and necropsy was performed at the end of the one-week survival period. Feasibility was defined as successful placement of the decompression tube in the duodenum, followed by delivery of spray cryotherapy to the duodenal papilla. Safety was determined by monitoring post-treatment blood tests and clinical course. Treatment effect was defined as endoscopic and histologic changes after cryotherapy. This was established by comparing endoscopic and histologic findings from mucosal biopsies prior to cryotherapy and on post-operative day (POD)#7. Full-thickness specimen was obtained post-mortem to assess depth of injury.

RESULTS: Spray cryotherapy was feasible and successfully performed in all 6/6 (100%) animals. Cryospray with liquid nitrogen (four 20-s freeze-thaw cycles) at the duodenal papilla resulted in white frost formation at and around the target region. The mean procedural

time was 54.5 min (range 50-58 min). All six animals studied had stable blood pressure, heart rate, and pulse oximetry measurements during the procedure. There were no significant intra-procedural adverse events. There were no significant differences in hemoglobin, white cell count, liver tests or lipase from baseline to post-cryotherapy. Survival animals were monitored daily post-operatively without any clinical ill effects from the cryotherapy. There was no bleeding, infection, or perforation on necropsy. Endoscopic on POD#7 showed edema and ulceration at the duodenal papilla. On histology, there was loss of crypt architecture with moderate to severe necrosis and acute mixed inflammatory infiltration in each specimen following cryotherapy. The extent of cryogen-induced tissue necrosis (depth of injury) was limited to the mucosa on full-thickness specimen evaluation.

CONCLUSION: Endoscopic liquid nitrogen spray cryotherapy is feasible and safe for ablation at the duodenal papilla in a porcine model.

Key words: Liquid-nitrogen cryotherapy; Cryoablation; Duodenal adenoma; Ampullectomy; Papillectomy

Core tip: With advances in therapeutic endoscopy, endoscopic resection is commonly performed for the management of ampullary adenomas. However, endoscopic papillectomy can still carry significant morbidity, especially in elderly patients with comorbidities. Hence, less invasive effective endoscopic ablative modalities would be desirable. In this study, we demonstrate that endoscopic liquid nitrogen spray cryotherapy is feasible and safe for ablation at the duodenal papilla in a porcine model. These preliminary findings suggest a potential role of cryotherapy as an adjunct endoscopic treatment for residual/recurrent ampullary lesions or as a primary modality in patients who are not optimal candidates for surgery or endoscopic resection.

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INTRODUCTION

Ampullary adenomas are dysplastic glandular lesions that arise from the major duodenal papilla. These lesions can occur sporadically or arise in the context of genetic syndromes such as familial adenomatous polyposis. If not removed, ampullary adenomas can potentially undergo malignant transformation to ampullary cancer with a reported incidence from 25% to 85%[1-3]. Based on this risk, these lesions have been treated historically with pancreatoduodenectomy, a highly invasive surgical intervention associated with high morbidity and mortality[4,5]. With advances in therapeutic endoscopy, there has been a shift towards endoscopic resection, with consideration of surgery only for locally advanced lesions. While endoscopic approaches for the treatment of ampullary adenomas are less invasive than surgery, adverse events associated with endoscopic papillectomy still carry a reported morbidity and mortality rate of 23% and 0.4% respectively[6]. Hence a less invasive modality for endoscopic ablation of ampullary lesions would be helpful, especially in elderly asymptomatic patients with comorbidities.

There has been a growing interest in endoscopic mucosal ablative techniques for the management of different gastrointestinal pathologies, ranging from adenomatous lesions, dysplasia and/or intramucosal carcinoma, to bleeding mucosal lesions in the GI tract[7]. Currently, the role of endoscopic ablative techniques (argon plasma coagulation, laser therapy, monopolar o bipolar coagulation) for ampullary adenomas is limited to destruction of residual or recurrent adenomatous tissue following resection[8].

Cryotherapy is a mucosal ablative technique that employs non-contact delivery of either low-pressure liquid nitrogen or compressed carbon dioxide (CO_2) gas for tissue destruction.

There are currently two commercially available endoscopic cryotherapy systems for the gastrointestinal tract. One device delivers low-pressure liquid nitrogen (at -196 ℃) (CryosprayAblation, CSA Medical Inc, Baltimore, MD) whereas the other system is based on the Joule-Thompson effect, in which highly compressed CO_2 gas produces cooling upon rapid expansion and decrease in pressure (Polar Wand; GI Supply, Camp Hill, PA)[9]. Most of the current clinical experience with endoscopic cryotherapy as a mucosal ablative technique is primarily related to the data on ablation of Barrett's esophagus, where this method has been shown to be efficacious and well tolerated[10]. The use of cryotherapy in other extra-esophageal sites, besides treatment of bleeding in the stomach and colon[11], has been limited to some degree by the concern of gas expansion and high risk of barotrauma and perforation in other regions of the GI tract. We recently reported preliminary data suggesting that liquid nitrogen cryotherapy is a safe technique even in patients with altered post-surgical gastric anatomy when appropriate measures are taken for cryogen gas decompression[12]. The aim of our study was to investigate the feasibility and safety of endoscopic liquid nitrogen spray cryotherapy at the duodenal papilla in a porcine model.

MATERIALS AND METHODS

Study

This prospective study protocol was approved by the

University of Florida Institutional Animal Care and Use Committee. Six female pigs (sus) weighing 80-100 lbs were obtained from the University of Florida Swine Unit. The aim of this study was to prospectively assess the feasibility and safety of endoscopic liquid nitrogen spray cryotherapy at the duodenal papilla in a porcine model.

Animal care and use

The animal protocol in this study was designed to minimize pain or discomfort to the animals. Pigs were housed and maintained in the University of Florida Animal Care Services unit. The animals were acclimatized to laboratory conditions (23 ℃, 12h/12h light/dark, 50% humidity, *ad libitum* access to food and water) for 7-10 d prior to experimentation. All animals were euthanized by barbiturate overdose (intravenous injection, 150 mg/kg pentobarbital sodium) for necropsy.

Outcomes and definitions

Primary outcomes: (1) feasibility was assessed by the technical success of cryotherapy in this porcine model. Technical success was defined as successful placement of the cryotherapy decompression tube past the papilla in the second portion of the duodenum, followed by delivery of liquid nitrogen spray to the duodenal papilla; and (2) safety was determined by monitoring peri-procedural blood tests and clinical course. Endoscopic adverse events were defined based on previously established criteria[13] and post-operative signs of distress, behavior changes, and/or loss of appetite. Elevation of liver tests and lipase post-cryotherapy to more than 3 times the upper limit of normal was considered abnormal.

Secondary outcome: Treatment effect was defined as endoscopic and histologic changes after cryotherapy. This was established by comparing endoscopic and histological findings from mucosal biopsies prior to cryotherapy and on post-operative day (POD)#7. The degree of intestinal injury was graded as previously described by Park *et al*[14]. Full-thickness specimen was obtained post-mortem to assess depth of injury.

Endoscopes and accessories

A single-channel gastroduodenoscope (GIF-140 Olympus Medical Systems, Tokyo, Japan) was used for the study. A pediatric colonoscope (PCF-140, Olympus Medical Systems, Tokyo, Japan) was used as needed, to overcome the J-shaped porcine gastric anatomy in order to have adequate length of the scope available to access the distal duodenum. Endoscopic biopsy forceps (Boston-Scientific, Natick, MA) were used for endoscopic tissue acquisition.

Cryotherapy

Liquid nitrogen spray cryotherapy (CryoSpray Ablation system, CSA Medical Inc, Baltimore, MD) was used for the study. This cryotherapy system, consists of (1) a console with a liquid nitrogen holding tank and a foot pedal for the release of low-pressure (3 to 6 psi) liquid nitrogen (temperature -196 ℃); (2) a 7-French cryocatheter, which is inserted through the working channel of an endoscope; and (3) a modified orogastric cryode compression tube (CDT) placed alongside the endoscope prior to starting cryotherapy. This special decompression tube has two channels, one for passive venting and another for active suction, attached to a separate suction machine to evacuate the rapidly expanding evaporated cryogenic gas during the procedure.

Freeze time was defined as the time interval from the visualization of white frost (ice formation) along the entire surface of the papilla until the cryospray was stopped. Procedure time was defined as the time from endoscope insertion to withdrawal.

Pre-operative care and anesthesia

Animals were not fed for 24 h prior to the procedure. Animals were pre-anesthesized with intramuscular (IM) injection of 4 mg/kg Telazol, ketamine 2 mg/kg, xylazine 2 mg/kg, and atropine (0.04 mg/kg) or glycopyrrolate (0.001 mg/kg). Induction was performed with isoflurane 3%-5% *via* mask delivered with a precision vaporizer prior to intubation. General endotracheal anesthesia was administered with Isoflurane 1%-3.5%. An intravenous (IV) line was placed in the marginal ear vein. Pigs were intubated and placed on mechanical ventilation.

Blood tests

In survival studies, blood specimens to evaluate hemoglobin (Hb), white blood count (WBC), liver tests (AST, ALT, alkaline phosphatase and bilirubin), and lipase were obtained prior to endoscopic treatment (day 0) and post cryotherapy (day 1 and on day 7).

Endoscopic procedure

The intended treatment site (duodenal papilla) was identified by endoscopic visualization. The pediatric colonoscope (Olympus Medical Systems, Tokyo, Japan) was introduced past the second portion of the duodenum and a 0.035 inch, 350 cm length guide-wire (Jagwire, Boston Scientific, Natick, MA) was placed. The endoscope was exchanged over the guidewire and the CDT was placed distal to the papilla. Adequate positioning of the CDT (tip of tube past the papilla in the second portion of the duodenum) was confirmed by re-inserting the endoscope, and the guide-wire was removed. The CDT was connected to active high suction controlled by a foot pedal during cryotherapy.

For survival animals, two peri-ampullary endoscopic biopsies were obtained as baseline prior to initial cryotherapy. The cryocatheter was introduced through the accessory channel of the endoscope and oriented to directly target the duodenal papilla. The freeze time was established as the period from ice formation along the entire surface of the papilla until the cryospray was stopped. The liquid nitrogen dosimetry of 4 cycles of 20-s freeze time was based on published dosing from previous animal studies[15,16]. There was complete

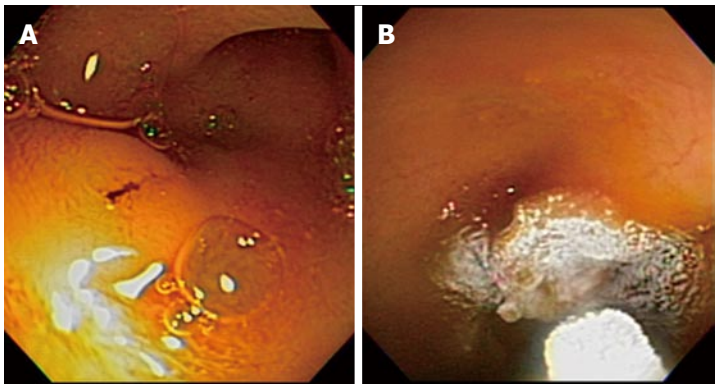

Figure 1 Endoscopic view of porcine duodenal papilla. A: Normal porcine duodenal papilla prior to treatment; B: Frost formation at the porcine duodenal papilla following liquid nitrogen cryotherapy.

thawing of ice between freeze cycles. Expanding liquid nitrogen gas was continuously suctioned via the CDT and through the endoscope between freeze cycles. Continuous monitoring for abdominal distention was performed by anesthesia personnel during the procedure.

Post-operative care, follow up and necropsy

The first two animals were used exclusively to evaluate the feasibility of liquid nitrogen cryotherapy at the duodenal papilla, and thus, were not survived. The animals were euthanized upon completion of the endoscopy, and necropsy performed. At necropsy, the peritoneal cavity and cryotherapy site was visually inspected for perforation, bleeding or damage to surrounding structures.

In survival experiments, pigs were extubated and recovered from general anesthesia. The pigs were monitored daily for any post-treatment adverse events, based on signs of distress, behavior changes, and/or loss of appetite. Oral feedings with standard chow were started the same day after recovering from anesthesia (day 0). Blood specimens were obtained at baseline (day 0), post-cryotherapy day 1 and day 7. Endoscopy was repeated on day 7 after cryotherapy to assess treatment effect at the duodenal papilla and biopsies were obtained at the cryotherapy site. At the end of the procedure, animals were euthanized and necropsy performed to rule out intra-abdominal adverse events associated with cryotherapy, such as transmural injury, bleeding, bowel perforation or abscess formation. Full-thickness duodenal specimen was obtained for histologic examination from one of the survival animals following necropsy.

Histologic examination

Biopsy specimens from all survival animals were obtained at the cryotherapy site on day 7 to assess the degree of intestinal injury. To evaluate the depth of the treatment effect, a full-thickness specimen containing the duodenal papilla was harvested from one of the survival animals following necropsy. All specimens were fixed in 10% neutral buffered formalin for at least 48 h, embedded in paraffin and stained with standard hematoxylin and eosin. The degree and depth of intestinal injury was graded by a single experienced pathologist as previously described in the text.

Statistical analysis

Summary data was expressed as the mean ± SD, and range. One-way analysis of variance (analysis of numerical data) was performed (GraphPad Prism version 6.00 for Windows, GraphPad Software, San Diego California, United States). The statistical methods of this study were reviewed by [Name, division, organization].

RESULTS

Endoscopic liquid nitrogen spray cryotherapy was performed at the duodenal papilla in 6 animals (2 non-survival and 4 survival studies).

Feasibility and safety of liquid nitrogen spray cryotherapy at the duodenal papilla

The duodenal papilla was identified in all 6 cases. The distal end of the CDT was successfully placed past the papilla into the second portion of the duodenum (Figure 1A) in all 6 animals. Cryospray with liquid nitrogen at the duodenal papilla resulted in white frost formation at and around the target region (Figure 1B). Four 20-s freeze-thaw cycles were applied with thawing between each session. Technical success was initially confirmed in the two non-survival animals and also subsequently achieved in all four survival swine studies (6/6; 100%). The mean procedural time was 54.5 min (range 50-58 min). All six animals studied had stable blood pressure, heart rate and pulse oximetry measurements during the procedure and there were no intra-procedural adverse events.

In survival studies, all 4 animals were recovered from general anesthesia and transferred to their housing facility, where they resumed regular feeding the same day of the procedure. The swine were monitored daily without any clinical ill effects from the cryotherapy (no change in activity, feeding habits and bowel and bladder elimination functions). There were no significant changes in Hb, WBC, liver tests or lipase on day 1 and 7 following cryoablation when compared to baseline (Table 1). There was no evidence of bleeding, infection (abscess), or bowel perforation on necropsy in any of

Table 1 Laboratory findings from survival animals (n = 4) at baseline (prior to liquid nitrogen cryospray application), on post-cryotherapy day #1 and #7

Lab	Mean (range)			*P* value
	Baseline	Day 1	Day 7	
Hemogloobin, g/dL	11.2 (10.2-12.3)	11.8 (11.1-12.3)	11 (9.9-11.6)	0.36
White blood count, K/μL	16.6 (12.9-17.4)	19.8 (14.1-22)	17.4 (15-21.9)	0.53
Alkaline phosphatase, U/L	98.8 (90-112)	102 (93-112)	84.5 (72-100)	0.15
Alanine transaminase, U/L	44.3 (32-52)	57.5 (47-80)	53.5 (45-57)	0.25
Aspartate transaminase, U/L	22.8 (16-31)	117.3 (24-385)	22.3 (17-29)	0.37
Total bilirubin, mg/dL	0.2 (0.1-0.3)	0.2 (0.1-0.2)	0.1 (0.1-0.2)	0.53
Lipase, U/L	5.5 (4-8)	9.3 (6-11)	4.8 (2-9)	0.06

Table 2 Histology findings

Swine	Baseline[1]		Day 7[2]	
	Crypt architecture	Inflammation	Crypt Architecture	Inflammation
1	Normal	None	Moderate necrosis	Moderate
2	Normal	None	Moderate necrosis and extensive debris	Moderate to severe
3	Normal	None	Severe necrosis and moderate debris	Severe with dense fibrosis
4	Normal	None	Moderate necrosis and extensive debris	Moderate

[1]Mucosal biopsies of duodenal papilla prior to cryotherapy; [2]Mucosal biopsies obtained from cryotherapy site at duodenal papilla 7 d following liquid nitrogen cryospray application.

the animals.

Liquid nitrogen cryotherapy effects on the duodenal papilla

At 7 days after cryotherapy, survival animals underwent a follow up endoscopy for evaluation of treatment effect on the duodenal papilla. Edema, erythema and ulceration of the papilla were seen on endoscopy (Figure 2). Mucosal biopsies from the papilla were obtained and compared to baseline. The histologic findings of each animal are summarized in Table 2. There was loss of crypt architecture with moderate to severe necrosis and acute mixed inflammatory infiltration in each specimen obtained from the duodenal papilla on day 7 following cryotherapy. The extent of cryogen-induced tissue necrosis (depth of injury) was limited to the mucosa, with the application of four 20-s freeze-thaw cycles of liquid nitrogen (Figure 3).

DISCUSSION

Endoscopic papillectomy has been increasingly used for the treatment of ampullary adenomas and early cancers. While this approach is less invasive than surgery, it is still associated with significant risks and is mainly performed by experienced endoscopists. As such, alternative endoscopic ablative therapies would be helpful, especially for the treatment of elderly asymptomatic patients with multiple comorbidities.

Endoscopic cryotherapy has been primarily used for the management of dysplastic Barrett's esophagus and early esophageal cancer. The clinical application of this mucosal ablative technique in extra-esophageal gastrointestinal tract has been limited by the potential risk of perforation from barotrauma. When liquid nitrogen is delivered to the lumen, it undergoes phase transformation into a gaseous state as energy is delivered to the target tissue[16]. If not evacuated properly, the rapidly expanding nitrogen gas can be a risk for gastrointestinal perforation. Previous reports have evaluated the feasibility of liquid nitrogen cryotherapy in the stomach[17]; however, its application in the small intestine has not been evaluated.

The present study demonstrates the feasibility and safety of endoscopic liquid nitrogen spray cryotherapy at the duodenal papilla in a porcine model. The commercially available CDT could be successfully placed, with the tip of the tube in the second portion of the duodenum in all 6 animals in this study. This step was crucial as it allowed for adequate suction of the nitrogen gas during cryospray application at the duodenal papilla. There were no apparent adverse effects associated with the cryotherapy based on daily post-treatment monitoring, lab data and necropsy 7 d following treatment. There was no evidence of changes in hemoglobin, WBC, liver tests or lipase from ablation at the duodenal papilla.

Our study validated cryogen treatment effect at the duodenal papilla on endoscopy and histology 7 d following treatment. The dosimetry of 4 cycles of 20-s freeze in this study was based on previous reports in animal studies as well as the commonly applied dosimetry for liquid nitrogen spray cryotherapy used in the treatment of BE with high-grade dysplasia or adenocarcinoma[18-20]. Endoscopic appearance of lesions at the duodenal papilla on day 7 ranged from mild erythema and edema to superficial erosions. These results are similar to the endoscopic findings reported by Johnston *et al*[15] in swine esophagus on day 7 following liquid nitrogen cryospray application.

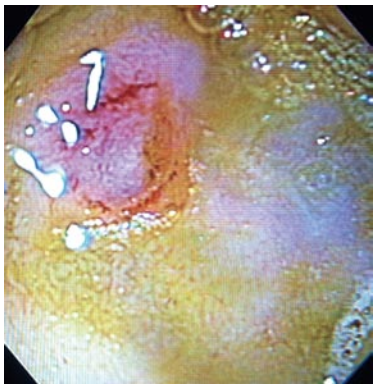

Figure 2 Endoscopic view of duodenal papilla 7 d following liquid nitrogen cryospray application.

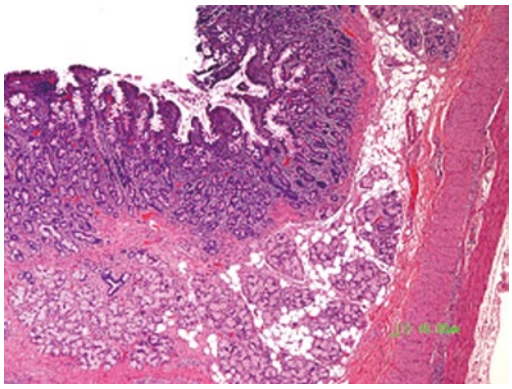

Figure 3 High-power microscopic view (HE x 40) of porcine duodenal papilla 7 d after application of a liquid nitrogen cryospray dose of 20 secfor 4 freeze-thaw cycles. There is severe blunting and loss of villar tips, infiltration of fibrous tissue and influx of mixed inflammatory cells into the lamina propria and loss of crypt architecture extending through the mucosa. The submucosa and muscularis propria are intact.

Our results demonstrate the effect of cryospray on histology based on the mucosal biopsies from the duodenal papilla on day 7. Histology on day 7 (4/4 animals) revealed loss or blunting of villous tissue and tips, crypt architectural distortion with necrosis and debris, and a mixed moderate to severe inflammatory infiltrate. This is a marked change from the normal histology obtained at baseline from the duodenal papilla and confirms treatment effect from the liquid nitrogen cryospray. We also demonstrate from a full-thickness specimen that the depth of injury was reserved to the mucosa, with inflammation and necrosis limited to the lamina propria and intact submucosa and muscularis propria. Previous animal studies have demonstrated dose-dependent injury to the esophagus, with necrosis involving the submucosa and even transmural damage with short exposures (15-30 s)[15,21]. In contrast, Shin and colleagues revealed that average grades of injury in the stomach across various doses were lower when compared with the esophagus[7]. We can speculate that the depth of tissue injury at the duodenal papilla from 4 cycles of 20-s of freeze time followed by thawing was associated with less injury compared to other studies because of differences in anatomical location in the gastrointestinal tract and mode of delivery (liquid nitrogen *vs* carbon dioxide). Further studies are needed to evaluate the relationship of cryogen dosimetry and depth of tissue injury in the small bowel.

We acknowledge the limitations of this study. First, our experiments were performed in a porcine model. While this animal model has been commonly used for experimental endoscopic studies, there are some important differences between human and porcine GI tract anatomy. The distal common bile duct and pancreatic duct in swine are not confluent at the duodenal papilla in pigs. In fact, while the biliary orifice is situated proximally in the duodenum at the papilla the pancreatic duct orifice is located separately several centimeters distal to the site of the biliary orifice. Since the primary aim of this pilot study was to evaluate the feasibility and safety of cryoablation at the duodenal papilla, we did not investigate treatment effect at the separate pancreatic duct orifice. This anatomical difference theoretically confers a decreased risk for pancreatic adverse events, including pancreatitis, when the duodenal papilla or biliary tract is manipulated in the porcine model. Thus, while there were no significant changes in serum lipase levels in our study to suggest pancreatitis following cryotherapy, we cannot definitively assess for this adverse event. Future studies are needed to evaluate the treatment effect and safety of cryotherapy at the pancreatic orifice. For this same reason, a pancreatic stent was also not placed after cryotherapy at the biliary orifice/papilla in this study, though this would need to be placed in human patients as is routinely done after endoscopic ampullectomy.

Second, as opposed to a side-viewing endoscope that is used in humans for endoscopy therapy at the papilla, a forward viewing endoscope (or pediatric colonoscope to overcome the J-shaped porcine gastric anatomy) was used to advance to the distal duodenum for adequate placement of the cryotherapy decompression tube. This technical hurdle may not be an issue with the human anatomy. Interestingly, the side-viewer may pose another challenge not encountered with the forward viewing endoscope used in this study. Use of the elevator of the side-viewing duodenoscope may theoretically kink the cryo catheter and not allow cryotherapy. However, the recently available, second generation of the cryotherapy device (truFreeze G2 spray cryotherapy device, CSA Medical Inc, Baltimore, MD) has a stainless steel reinforced catheter that enables 180 degree retroflexion and this upgrade may overcome the potential problem with the elevator. Additional studies in humans would be needed to evaluate the technical feasibility of placing the decompression tube side-by-side with a duodenoscope and performing cryotherapy with use of the elevator.

Third, in the absence of an animal model for ampullary lesions, cryotherapy was performed on normal porcine tissue. Thus, the extent of cryogen-induced effects may differ in humans with pathology (adenoma/carcinoma) at the duodenal papilla. Furthermore, our

study was limited to small numbers of animals and findings on depth of injury need to be confirmed in larger human protocols. Lastly, the study follow-up was relatively short (7 d); therefore, long term cryo ablative effects at the duodenal papilla were not evaluated.

Despite these shortcomings, our feasibility data shows that there were no adverse events from cryotherapy at the papilla. Specifically, there was no evidence of GI tract perforation, bleeding, cholangitis or bile duct injury despite directly spraying liquid nitrogen (that transforms to gaseous state with major increase in volume) at the open biliary orifice and therefore up the bile duct. Hence it appears that cryotherapy may be a viable option for treating ampullary lesions but further studies are needed to examine optimal dosimetry, effects on the pancreas and ablation of actual neoplastic tissue.

Our preliminary findings suggest that endoscopic liquid nitrogen cryotherapy at the porcine duodenal papilla is both feasible and safe. This data may serve as starting point for assessing the potential role of cryotherapy as an adjunct endoscopic treatment for residual/recurrent ampullary lesions or as a primary modality in patients who are not optimal candidates for surgery or endoscopic resection. Further studies are needed to determine the relationship between dosimetry and tissue injury at the duodenal papilla, with specific testing for effects on the pancreatic duct.

COMMENTS

Background

There is a growing interest in endoscopic mucosal ablative techniques for the management of different gastrointestinal pathologies, ranging from adenomatous lesions, dysplasia and/or intramucosal carcinoma. The role of endoscopic ablative techniques for the management of ampullary adenomas has not been fully elucidated.

Research frontiers

Cryotherapy is an emerging endoscopic mucosal ablative technique. Most of the current clinical experience with endoscopic cryotherapy is primarily related to data on ablation of Barrett's esophagus. The use of cryotherapy in other extra-esophageal sites has been limited to some degree by the concern of gas expansion and high risk of barotrauma and perforation in other regions of the GI tract.

Innovations and breakthroughs

The authors had previously reported preliminary data suggesting that liquid nitrogen cryotherapy is a safe technique even in patients with altered post-surgical gastric anatomy when appropriate measures are taken for cryogen gas decompression. This is the first study that has evaluated the feasibility and safety of endoscopic liquid nitrogen spray cryotherapy at the duodenal papilla in a porcine model.

Applications

This study demonstrates that spray cryotherapy was feasible and successfully performed in all animals. Survival animals thrived without adverse events. Follow-up evaluation one week post-treatment confirmed cryotherapy-induced tissue necrosis limited to the mucosa. These preliminary findings suggest a potential role for cyrotherapy as a primary or adjunct modality for patients who are not optimal candidates for surgery/endoscopic resection or in those with residual/recurrent disease.

Terminology

Endoscopic cryotherapy: mucosal ablative technique that employs non-contact deliver of either low-pressure liquid nitrogen or compressed carbon dioxide gas for tissue destruction. Technical success was defined as the successful placement of the cryotherapy decompression tube past the papilla followed by the delivery of liquid nitrogen spray to the target. Treatment effect was defined as endoscopic and histologic changes after cryotherapy. Freeze time was defined as the time interval from the visualization of white frost (ice formation) along the entire surface of the papilla until the cryospray was stopped.

Peer-review

Well designed, elegant animal study. The primary aim of the study was to assess the safety of a new therapeutic modality. The first acquired data proved the feasibility and safety during the short term follow-up period. The data are important and could be used in human studies.

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ORIGINAL ARTICLE

Retrospective Study

Obtaining research biopsies during pediatric colonoscopy: Safety and adverse events

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Conflict-of-interest: None of the authors have a conflict of interest.
Data sharing: Consent for data sharing was not obtained. All data was collected in a de-identified and anonymous manner.

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Abstract

AIM: To investigate the safety profile of acquiring additional intestinal biopsies for research purposes in children undergoing a medically indicated colonoscopy.

METHODS: A retrospective review of 122 pediatric patients who underwent colonoscopy over a 9 mo time period was completed. 38/122 participants consented to a research study in which 4 additional biopsies were obtained, in addition to routine biopsies. The outcomes after colonoscopy were measured in the research participants, and compared to 84 control participants who did not consent for the study. Groups were compared with regard to number of biopsies obtained, underlying diagnosis, and both serious and minor adverse outcomes. Data was collected including: age, gender, race, indication, diagnosis, number of biopsies obtained per case and post procedure adverse events. Medical records were reviewed and a questionnaire was completed by each of the ten gastroenterologists who performed procedures during the study. Physicians were asked about individual patient outcomes to ensure that all adverse events, such as perforation, excessive bleeding, infection, and minor gastrointestinal outcomes, were captured and included.

RESULTS: The research group had more biopsies obtained (mean = 13.58 ± 4.21) compared to controls (mean = 9.33 ± 4.40), $P \leqslant 0.0001$, however there was no difference in adverse events. Serious outcomes, defined as perforation, bleeding and infection, did not occur, in either group. As such, the relationship between serious adverse events and number of biopsies obtained was not determined. Minor gastrointestinal outcomes, such as abdominal pain, diarrhea or vomiting, were reported in 21 patients (8 research participants and 13 control participants) however the incidence of minor gastrointestinal outcomes between the two groups did not vary significantly, $P = 0.45$. Additionally, the mean

number of biopsies obtained in patients who had a minor outcome (mean = 12.1 ± 0.77), compared to those with no adverse outcome (mean = 10.34 ± 0.5), revealed no statistical difference between the groups (P = 0.12), suggesting that number of biopsies is not associated with incidence of minor adverse events.

CONCLUSION: Patients participating in research requiring acquisition of additional biopsies for research purposes alone, are not at an increased risk of adverse outcomes.

Key words: Pediatric colonoscopy; Outcomes; Research; Safety; Intestinal biopsy

Core tip: Acquiring biopsies for research purposes during a colonoscopy may facilitate translational research in the field of gastroenterology. However, the safety profile of acquiring research biopsies has not been established. Our study is the first to conclude that acquiring additional biopsies for research during a colonoscopy does not pose additional risk to the pediatric patient. This manuscript may serve as a reference to researchers applying for IRB approval in biological specimen studies. Additionally, our study is additive to the body of literature on outcomes after pediatric colonoscopy, in that minor gastrointestinal symptoms were the only reported adverse event after colonoscopy.

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INTRODUCTION

Colonoscopy with biopsies is a common procedure in children for the evaluation and diagnosis of gastrointestinal disease. Serious complications, such as perforation and bleeding are routinely discussed during the consent process, however, these events are rare[1-3]. Several adult studies have sought to measure the incidence of adverse outcomes during routine procedures[2,4,5], and this data has largely been applied to the pediatric population[6]. In adults, colorectal perforation is presumed to occur in 0.09% of the general population[7,8], while it remains unclear as to whether patients with pre-existing inflammatory bowel disease (IBD) are at an increased risk for serious outcomes, such as perforation[7,9,10]. The incidence of bleeding after colonoscopy is thought to occur infrequently during routine procedures[8].

There is limited data on serious adverse events in children, such as bleeding. Although one study found that 38.6% (34/86) of all reported complications were related to gastrointestinal bleeding, bleeding was not defined[3]. Other pediatric studies did not include bleeding in their outcome analysis[6]. Infection, similarly regarded as a serious and uncommon outcome after colonoscopy, has not been widely studied in pediatrics[11]. Likewise, minor post-procedure gastrointestinal symptoms, such as bloating and abdominal pain, are not well described in the pediatric literature[12].

The current pediatric studies are limited in number and do not quantify the number of routine biopsies obtained per procedure which may be a risk factor for adverse events. Additionally, these studies have not addressed whether obtaining additional biopsies solely for research purposes imposes additional risk to the patient. To our knowledge, this issue has not been addressed in the pediatric or adult literature. It is critical to establish the safety profile of collecting additional biopsies for research during routine procedures, so that investigators seeking institutional review board (IRB) approval are able to proceed with important research questions. The absence of this risk assessment may explain why studies involving the collection of pediatric biological specimens are difficult to pursue. Such IRB protocols pose a challenge to both author and reviewer, in that the lack of prior safety data serves as an obstacle for IRB approval. To address this gap, we performed a retrospective review for all children undergoing routine medically indicated colonoscopies and measured adverse events. Thirty-one percent of the participants had previously consented for a research study involving the acquisition of four additional intestinal biopsies designated for research purposes. By comparing adverse events in the research study participants to patients who did not consent, the controls, we established that acquiring additional biopsies for research alone is safe.

MATERIALS AND METHODS

We performed a retrospective review of all pediatric patients undergoing a medically indicated routine colonoscopy from June 5, 2013-March 5, 2014. Anesthesia was provided by pediatric anesthesiologists.

Patients who had previously provided written and oral consent for a biological specimens study were identified (n = 38); these participants consented to have four additional intestinal biopsies taken for research purposes alone. This research-consented cohort was then compared to non-study participants (n = 84), who had only routine biopsies obtained during the procedure.

Data was collected including: age, gender, race, indication, diagnosis, number of biopsies obtained per case and post procedure adverse events. Post-procedure adverse events were defined as events occurring within one week of the procedure. Medical records were reviewed for patient phone calls, general practitioner and gastroenterology clinic appointments, emergency department visits and hospital admissions within one week post-procedure. For those patients who were admitted to the hospital prior to their colonoscopy, the

Table 1 Participant demographics

	Research group (n = 38)	Control group (n = 84)	P value[1]
Sex			
Male, n (%)	20 (52.6)	48 (57.1)	0.64
Female, n (%)	18 (47.4)	36 (42.9)	
Age in years, n (%)			
0-5	1 (2.6)	16 (19.0)	0.05
6-12	10 (26.3)	19 (22.6)	
13-21	27 (71.1)	49 (58.3)	
Race			
White, n (%)	5 (13.2)	26 (31)	0.04
Non-white, n (%)	33 (86.8)	58 (69)	
Diagnosis			
IBD[2], n (%)	17 (44.7)	21 (25)	0.03
Normal histology, n (%)	21 (55.3)	63 (75)	
IBD diagnosis			
CD[3], n (%)	11 (28.9)	10 (11.9)	0.23
UC[4], n (%)	5 (13.2)	11 (13)	
IC[5], n (%)	1 (2.6)	0	
History of IBD			
Yes	8	12	0.54
No	9	9	

[1]All P values calculated to significance level of 0.05, [2]Inflammatory Bowel Disease, [3]Crohn's disease, [4]Ulcerative colitis, [5]Indeterminate colitis.

Table 2 Minor gastrointestinal outcomes

	Research group (n = 38)	Control group (n = 84)	P value[1]
Gastrointestinal symptom after Procedure, n (%)			
Yes	8 (21.1)	13 (15.5)	0.45
No	30 (78.9)	71 (84.5)	
Mechanism of reporting			
Phone call	6	6	0.14
PGI[2] clinic visit	0	1	
ED visit	2	1	
Inpatient	0	5	
Management			
Outpatient	5	6	0.81
Admission to hospital	1	1	
Referral to ED	2	1	
Continued admission	0	5	
Gastrointestinal symptom[3] (%)			
Abdominal pain only	2 (5.3)	4 (4.8)	0.82
Abdominal pain + diarrhea and/or vomiting	3 (7.9)	5 (6.0)	
Rectal bleeding	3 (7.9)	2 (2.4)	
Other	2 (5.3)	3 (3.6)	
Number of Biopsies			
Mean ± SD[4]	13.6 ± 4.2	9.3 ± 4.4	< 0.0001

[1]All P values calculated to a significance level of 0.05, [2]pediatric gastroenterology, [3]In research group, 1 patient with both abdominal pain and rectal bleeding, 1 with both rectal bleeding and constipation and in control group, 1 patient with rectal bleeding and diarrhea; [4]standard deviation.

inpatient record was reviewed.

We administered a questionnaire to the ten gastroenterologists who performed procedures during the aforementioned time period regarding individual patient outcomes to ensure that all adverse events, such as perforation, excessive bleeding, infection, and minor gastrointestinal outcomes, were captured and included. This study was approved by the Office of the Human Research Protection Program, Institutional Review Board at Albert Einstein College of Medicine, Bronx, NY.

Statistical analysis

Differences in participant demographics between groups were compared using analysis of variance or t tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables. All analyses were performed using GraphPad Prism version 6 (San Diego, CA). All tests for significance were two-sided, and a value of $P < 0.05$ was considered significant.

RESULTS

A total of 122 colonoscopies were performed during the study period: 38 patients consented to have additional biopsies obtained for research during the medically indicated procedure, compared to 84 non-research related cases. One thousand two hundred and ninety biopsies were obtained, including 136 intestinal biopsies for research alone. The average number of biopsies obtained per case was significantly higher in the research cohort, 13.6 compared to 9.3 in the control group, (P < 0.0001) (Table 1). Participant demographics are detailed in Table 1. Of note, statistical differences in race and age were observed in the research compared to the control groups, P = 0.04 and P = 0.05, respectively. One patient (2.6%), age 0-5, participated in the research study, compared to 16 (19%) who underwent routine colonoscopy alone (P = 0.05). No statistical difference in gender distribution was observed when comparing research to control participants.

The research cohort consisted of 38 patients, 17/38 (44.7%) of whom had IBD, compared to 21/84 (25%) of the patients in the control group (P = 0.03) (Table 1). IBD diagnosis type, such as Crohn's disease (CD) or ulcerative colitis (UC), did not vary significantly between the two groups, P = 0.23.

There were no cases of perforation, infection or hemorrhage in the research or the control group. Given that no serious outcomes occurred in our cohort, the relationship between number of biopsies and serious adverse events was not measured. Minor gastrointestinal outcomes, however, did occur in 8/38 research participants, and 13/84 control participants (Table 2). The incidence of minor gastrointestinal outcomes was not statistically different when comparing the research and control groups, P = 0.45, although the research group had significantly more biopsies obtained per procedure, P < 0.0001. Additionally, the mean number of biopsies obtained in patients who had a minor outcome (mean = 12.1 ± 0.77), compared to those with no adverse outcome (mean = 10.34 ± 0.5), revealed no statistical difference between the groups

Table 3 Indications for colonoscopy

Indication (%)	Research (n = 38)	Control (n = 84)	P value[1]
Abdominal pain	50	50	1
Diarrhea	44.7	36.9	0.41
Rectal bleeding	36.8	34.5	0.8
Weight loss	44.7	20.2	0.01
Loss of appetite	34.2	10.7	0.002
Constipation	18.4	15.5	0.68
Vomiting	15.8	14.3	0.83
Fatigue	23.7	3.57	0.001
Fever	7.89	3.57	0.31
Joint pain	10.5	1.19	0.02
Rash	5.26	0	0.03

[1]All P values calculated to a significance level of 0.05.

(P = 0.12), suggesting that number of biopsies is not associated with incidence of minor adverse events.

When comparing mechanism of reporting and management of adverse minor events no statistical differences were noted when comparing research participants to controls. Likewise, gastrointestinal symptoms reported as minor events were similar between the two groups.

Overall, during this time period, 38 children with IBD underwent colonoscopy: 47.4% (18/38) of this group were newly diagnosed patients, 11 with CD, 6 with UC, and 1 with indeterminate colitis, while 52.6% (20/38) had been previously diagnosed with IBD. Minor outcomes occurred in 21% (8/38) of patients with IBD. The incidence of minor adverse events in IBD versus non-IBD patients, did not vary significantly between the two groups, P = 0.45.

The most common indication for colonoscopy was abdominal pain, occurring in 50% of patients, while diarrhea was the second most common indication (Table 3). Weight loss, loss of appetite, fatigue, joint pain and rash occurred more often in the research group, P = 0.01, P = 0.002, P = 0.001, P = 0.02, and P = 0.03, respectively.

DISCUSSION

To our knowledge, no studies to date have evaluated the safety profile of taking additional intestinal biopsies for research purposes. Obtaining intestinal biopsies for research may facilitate investigations that will further our understanding of pediatric gastrointestinal illnesses. Our study shows that participation in research during a medically indicated colonoscopy does not place the patient at an increased risk for bleeding, perforation, infection, or minor gastrointestinal outcomes, which is in line with prior pediatric studies, as complications during routine colonoscopy are rare[3,6,7,9,11,13], and can be applied to studies involving biological specimens.

Adverse events after pediatric colonoscopy, particularly in regard to IBD, have not been well studied, as subjects with pre-existing disease are often excluded from the cohort[6]. Our data suggests that patients with IBD are not at increased risk for perforation or bleeding, which refutes prior findings[10]. A larger percentage of IBD patients (8/38, 21%) sustained minor adverse outcomes compared to non-IBD patients (13/84, 15.5%), however this difference was not found to be statistically significant. Our findings support a prior study by Tam *et al*[9] that evaluated pain indices in children with IBD, pre and post procedure, and found that patients with functional bowel disease report more pain, compared to children with IBD[9].

Interestingly, our research-consented cohort consisted of a larger percentage of IBD patients, 44.7% compared to 23.8% in the control group. From this, we may conclude that parental concern is greater in children more likely to have IBD, which may explain a greater willingness to participate in studies or to benefit from research. Alternatively, selection bias may impact the recruitment of children most likely to have IBD. In this study, however, all children undergoing colonoscopy during the aforementioned time period were asked to participate.

Given that serious adverse events did not occur in our cohort, we were unable to correlate number of biopsies obtained with incidence of serious adverse events. However, we did observe that of the patients who reported minor gastrointestinal outcomes, most (71.4%) reported the same symptom with which they presented for colonoscopy. Therefore, minor gastrointestinal events occurring after a procedure may be secondary to the primary gastrointestinal complaint, rather than the procedure. In regard to the consent process and clinical practice, clinicians may reassure parents that minor symptoms after a procedure are most commonly related to underlying symptoms on presentation, and not to the colonoscopy itself.

There are few studies in the current pediatric literature that discuss minor adverse outcomes after colonoscopy. Our study found that 17.2% of our population reported minor symptoms after colonoscopy, which is consistent with prior data, for example, Steiner *et al*[12] found that post-procedure symptoms occur in 14%-17% of patients; sore throat, diarrhea and excessive gas occurred in 6% of patients, while abdominal pain occurred in 3%[12]. In our study 1.6% of participants were admitted post procedure for observation, while Steiner et al. admitted 1.1% patients, suggesting that the general concern level regarding minor symptoms is low. Of the 17 patients who reported symptoms, 1 was under the age of 5, suggesting either that minor symptoms are more common in older children, or that underreporting is at play in younger age groups. On a similar note, only 1 patient between the ages 0-5 participated in the research study, compared to 16 children in the control group under the age of 5, suggesting that parents of very young children are less likely to consent for studies requiring the collection of biological specimens. In one study, children 0-5 years of age were the most likely group to have a complication, $P \leqslant 0.001$[3]; this supports the notion that very young

patients may have an increased risk for complications after colonoscopy and that children over the age of 5 may be more suitable candidates for research studies involving acquisition of additional biopsies.

The limitations of our retrospective study include small sample size, limited duration of the study, and selection bias, as underlying gastrointestinal symptoms may have affected study outcome. Additional studies with larger groups of pediatric patients undergoing colonoscopy for medical reasons, while participating in research, are warranted in order to further attest that no additional risk is imposed to the patient. This will allow researchers to pursue questions that will enhance our current knowledge of chronic gastrointestinal problems in children, specifically IBD.

COMMENTS

Background

Colonoscopy with biopsies is a common procedure in children for the evaluation and diagnosis of gastrointestinal disease. There is limited data on serious adverse events in children, such as bleeding, infection and perforation. Likewise, minor post-procedure gastrointestinal symptoms, such as vomiting and abdominal pain, are not well described in the pediatric literature. Current pediatric studies have not addressed whether obtaining additional biopsies solely for research purposes imposes additional risk to the patient. It is critical to establish the safety profile of collecting additional biopsies for research during routine procedures, so that investigators may proceed with studies involving biological specimens. The lack of safety data may explain why studies involving the collection of pediatric biological specimens are difficult to pursue.

Research frontiers

Institutional review board (IRB) protocols involving biological specimen collection pose a challenge to both author and reviewer, in that the lack of prior safety data serves as an obstacle for IRB approval. In order to address key research questions using translational research methods, safety data must be available for reference.

Innovations and breakthroughs

To date, the incidence of adverse events occurring when collecting additional biopsies for research during medically indicated colonoscopies has not been addressed in the pediatric or adult literature.

Applications

The study results suggest that acquiring additional biopsies for research during medically indicated colonoscopies is safe.

Terminology

Serious adverse events after colonoscopy include bleeding, perforation and infection. Minor events after colonoscopy include abdominal pain, diarrhea and vomiting.

Peer-review

This is a small retrospective study in which the authors assessed the safety profile of acquiring additional intestinal biopsies for research purposes during medically indicated colonoscopies. The results indicate that it is safe to acquire such biopsies in children for the purposes of facilitating translational research. The publication of this study may serve as a reference for researchers seeking IRB approval in biological specimen studies, and suggests the need for larger studies in the future.

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ORIGINAL ARTICLE

Retrospective Study

Endoscopic features of early-stage signet-ring-cell carcinoma of the stomach

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Author contributions: All the authors contributed to this work.

Ethics approval: This study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1964, as revised in 2013. Retrospective review of pathologic specimens is exempt from formal approval according to the policies and procedures of the Institutional Review Board (IRB) of Showa University Northern Yokohama Hospital, Yokohama, Japan.
Informed consent: All study participants, or their legal guardian, provided pre-operative informed written consent for the endoscopic or surgical procedures, as well as the collection and analysis of pathologic specimens.
Conflict-of-interest: Dr. Inoue has received fees for serving as an advisory committee member for Olympus Corporation, Tokyo, Japan. The other authors have no conflicts of interest or financial ties to disclose.
Data sharing: Technical appendix and dataset are available from the corresponding author at haruinoue777@yahoo.co.jp. Consent was not obtained but the presented data are anonymized and the risk of identification is low.

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Abstract

AIM: To identify the features of early signet ring cell gastric carcinoma using magnification endoscopy with narrow band imaging (NBI).

METHODS: A retrospective review was conducted of 12 cases of early signet ring cell gastric carcinoma who underwent treatment in a single institution between January 2009 and April 2013. All patients had magnification endoscopy with NBI and indigo carmine contrast to closely examine the mucosal architecture, including the microvasculature and arrangement of gastric pits. Histologic examination of the final endoscopic submucosal dissection or gastrectomy specimen was performed and compared with the endoscopic findings to identify patterns specific to signet ring cell carcinoma.

RESULTS: Twelve patients with early signet ring cell gastric carcinoma were identified; 75% were male, and average age was 61 years. Most of the lesions were stage T1a (83%), while the remainder were T1b (17%). The mean lesion size was 1.4 cm^2. On standard endoscopy, all 12 patients had a pale, flat lesion without any evidence of mucosal abnormality such as ulceration, elevation, or depression. On magnification endoscopy

with NBI, all of the patients had irregularities in the glands and microvasculature consistent with early gastric cancer. In addition, all 12 patients exhibited the "stretch sign", an elongation or expansion of the architectural structure. Histologic examination of the resected specimens demonstrated an expanded and edematous mucosal layer infiltrated with tumor cells.

CONCLUSION: The "stretch sign" appears to be specific for signet ring cell carcinoma and may aid in the early diagnosis and treatment of this aggressive pathology.

Key words: Signet ring cells; Early gastric cancer; Magnification endoscopy; Narrow band imaging; Stretch sign; Endoscopic submucosal dissection

Core tip: With aggressive screening, gastric cancer can be detected in the early stages, leading to the possibility of successful minimally invasive treatments, such as endoscopic submucosal dissection. A rare type of gastric cancer, signet ring cell carcinoma, has aggressive biological features, but patients treated in the early stages may actually fare better than those with adenocarcinoma. Here we present findings specific for signet ring cell carcinoma that can be identified on magnification endoscopy, potentially securing a diagnosis in the early stages of the disease without the need to rely on random biopsies.

Phalanusitthepha C, Grimes KL, Ikeda H, Sato H, Sato C, Hokierti C, Inoue H. Endoscopic features of early-stage signet-ring-cell carcinoma of the stomach. *World J Gastrointest Endosc* 2015; 7(7): 741-746 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i7/741.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i7.741

INTRODUCTION

Gastric cancer can be detected in the early stages by aggressively screening asymptomatic patients. In Japan, where such rigorous screening is conducted, half of gastric cancers are now diagnosed in the early stages of the disease[1]. Early detection affords the opportunity for less invasive treatment options, such as endoscopic submucosal dissection (ESD). However, signet ring cell carcinoma, an unfavorable subtype of gastric cancer that may require more aggressive treatment, has been reported in up to 29% of gastric cancer patients in the United States[2] and over 10% in Japan[3]. If treated early, signet ring cell carcinoma has a better prognosis than other subtypes; however, advanced signet ring cell carcinoma has a prognosis that is even worse than undifferentiated adenocarcinoma[4]. Early diagnosis of signet ring cell carcinoma is therefore critical to guide optimal treatment, but the typical presentation during conventional endoscopy is a pale, flat lesion that can easily be missed even by experienced endoscopists.

Advanced endoscopy using a magnifying endoscope and narrow band imaging (NBI) technology may play an important role. Previous studies have reported fine mucosal patterns of gastric pits and microvasculature that can be identified and classified using magnification endoscopy with NBI[5-7], and that it is possible to predict the depth of invasion of early gastric carcinomas prior to histologic assessment[8,9]. We postulate that magnification endoscopy and NBI can be further applied to the early detection of signet ring cell carcinoma.

The purpose of this study was to review our experience with magnification endoscopy with NBI in 12 cases of early signet cell gastric carcinoma, and to identify specific endoscopic patterns that may predict the final pathologic diagnosis.

MATERIALS AND METHODS

Patient selection

A retrospective chart review was performed to identify patients who underwent endoscopic and/or surgical intervention for signet ring cell gastric carcinoma in a single institution (Showa University Northern Yokohama Hospital). We identified 12 cases of signet ring cell gastric carcinoma during the study period from January 2009 to April 2013.

Magnification endoscopy

Diagnostic procedures were performed following the ingestion of 5 cc of viscous 2% lidocaine and administration of light intravenous sedation. Magnification endoscopy was performed in a single center utilizing high-resolution magnifying upper endoscopes (Olympus Evis Lucera Spectrum, GIF-H260Z, Tokyo, Japan) with 10.8 mm diameter tips and color charge-coupled-device (CCD) optical lenses with a 140 degree field of view. A distal attachment with 3 mm depth (MB-162, Olympus, Tokyo, Japan) was utilized as described by Yao *et al*[10], and images were recorded with NBI both before and after administration of 0.3% indigo carmine dye. Endoscopic images were reviewed by expert endoscopists and assessed for irregularity of the gastric pits and/or microvasculature.

Histopathology

Histologic examination of the final specimen following ESD or laparoscopic-assisted partial or total gastrectomy was performed by pathologists specializing in gastrointestinal pathology, and lesions were classified according to the Japanese classification system[11]. Pathologists did not have access to the endoscopic findings.

Table 1 Demographic data and tumor characteristics of 12 patients with signet ring cell early gastric carcinoma

No.	Age	Sex	Location of tumor	Size (mm)	Depth	Operation	F/U (mo)
1	64	F	Lower body/posterior	10 × 9	T1a	ESD	54
2	77	M	Pyloric/lesser curve	5 × 4	T1a	ESD	45
3	46	M	Mid body/posterior	5 × 5	T1a	LATG	41
4	87	F	Mid body/greater curve	20 × 16	T1b	ESD	38
5	39	M	Lower body/posterior	12 × 6	T1a	ESD	38
6	46	M	Pyloric/greater curve	10 × 8	T1a	ESD	35
7	60	M	Pyloric/greater curve	6 × 6	T1a	ESD	26
8	72	F	Pyloric/greater curve	22 × 19	T1a	ESD	18
9	71	M	Pyloric/greater curve	11 × 10	T1a	ESD	16
10	48	M	Pyloric/lesser curve	20 × 11	T1a	LADG	14
11	82	M	Pyloric/greater curve	20 × 14	T1b	ESD	13
12	44	M	Pyloric/lesser curve	10 × 3	T1a	ESD	10

F/U: Follow-up; ESD: Endoscopic submucosal dissection; LATG: Laparoscopic-assisted total gastrectomy; LADG: Laparoscopic-assisted distal gastrectomy.

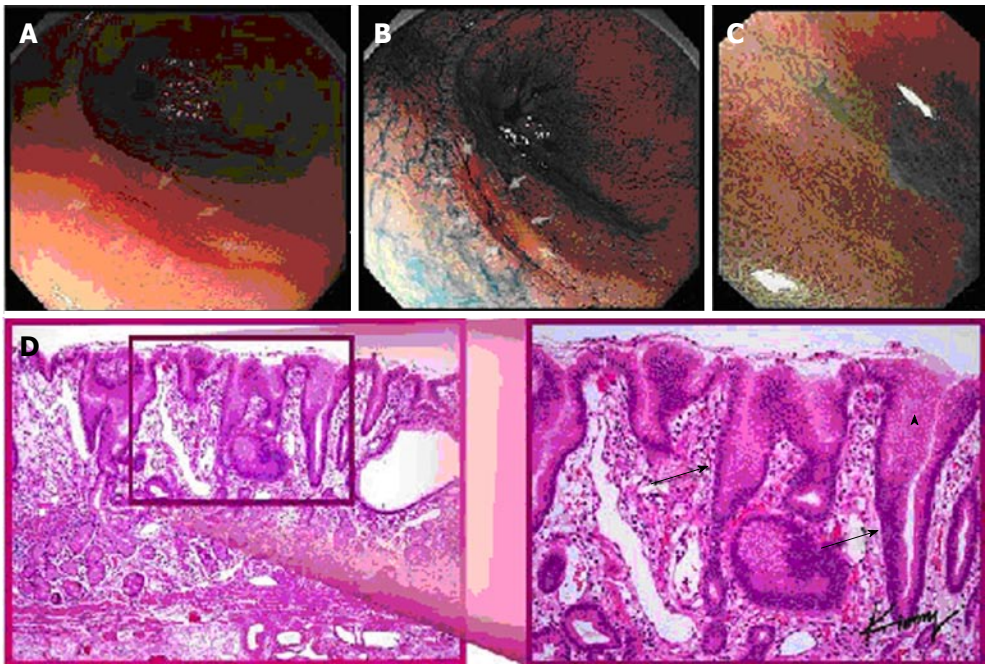

Figure 1 Multiple views of a signet ring cell gastric carcinoma in a single patient: (A) standard white light endoscopy, (B) chromoendoscopy, (C) magnification endoscopy, and (D) histopathology demonstrating elongated gastric glands (arrows) infiltrated with tumor cell (arrowhead).

Biostatistics

The data presented are a qualitative analysis of a single cohort. No statistical tests were performed.

RESULTS

Patient demographics and clinical outcomes

Patient demographic data are summarized in Table 1. Of the 12 patients with signet ring type early gastric cancer, mean age was 61.3 (range 39-87), and 75% were male; the lesions had a maximum dimension of 1.3 cm on average (range 0.5-2.2 cm) with a mean area of 1.4 cm^2 (range 0.2-4.2 cm^2); 83% of lesions were T1a, and 17% were T1b. ESD was performed in 83% of cases; laparoscopic-assisted distal gastrectomy or laparoscopic-assisted total gastrectomy was performed in the remaining 17% due to pre-operative suspicion of lymph node metastases. There was 100% disease-free survival at a median follow-up of 2.5 years.

Endoscopic findings

On standard white light endoscopy, all 12 patients with signet ring early gastric cancer had pale, flat lesions without gross mucosal abnormality such as ulceration, elevation, or depression. On magnification endoscopy, each of the patients had irregularities in the glands and microvasculature, consistent with early gastric cancer; however, in addition, the architecture appeared to be expanded or elongated, as if it had been "stretched", within a portion of the lesion for all 12 patients (Figures 1 and 2).

Pathologic correlation

On histologic examination, patients with signet ring early gastric cancer demonstrated an expanded and edematous mucosal layer infiltrated with tumor cells

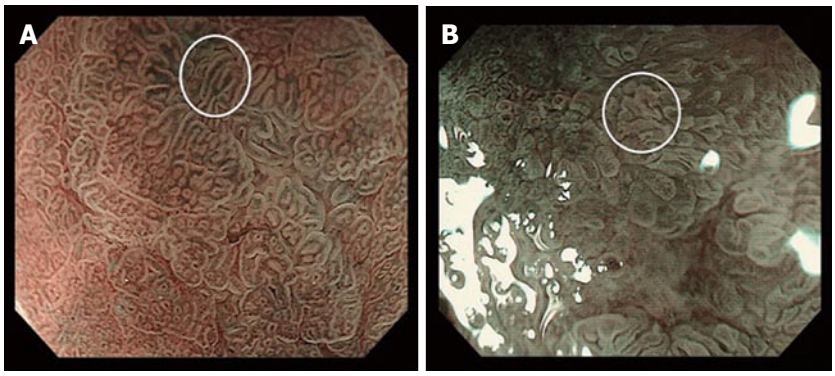

Figure 2 Magnification endoscopy of the stomach: (A) normal polygonal architecture (bottom left, underlying "a") and a signet ring cell gastric carcinoma demonstrating an elongated or "stretched" gastric gland (white circle); (B) a non-signet ring cell adenocarcinoma demonstrating irregular (non-polygonal) but non-elongated glands (white circle).

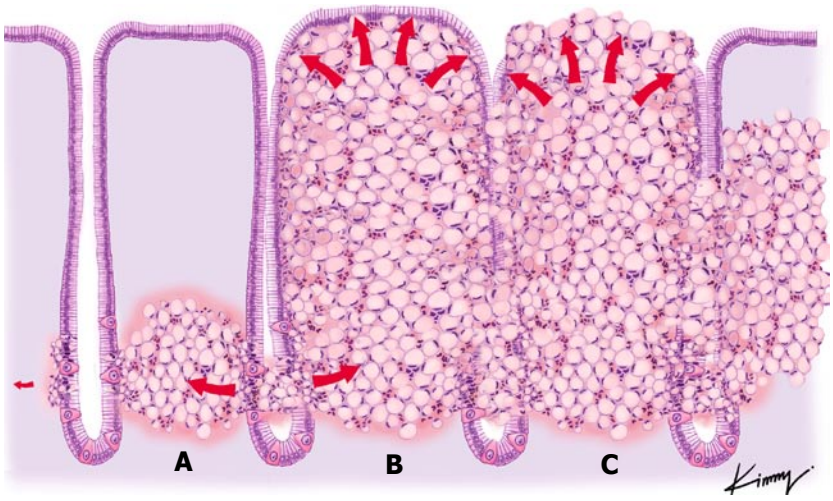

Figure 3 Theoretical view of the pathophysiology of signet ring cell differentiation: (A) tumor cells originating in the neck of the gland and spreading to the submucosal space; (B) an increasing number of tumor cells being packed together, resulting in a barrel shape; and (C) the previously non-exposed tumor becoming exposed through necrosis and formation of an ulcer.

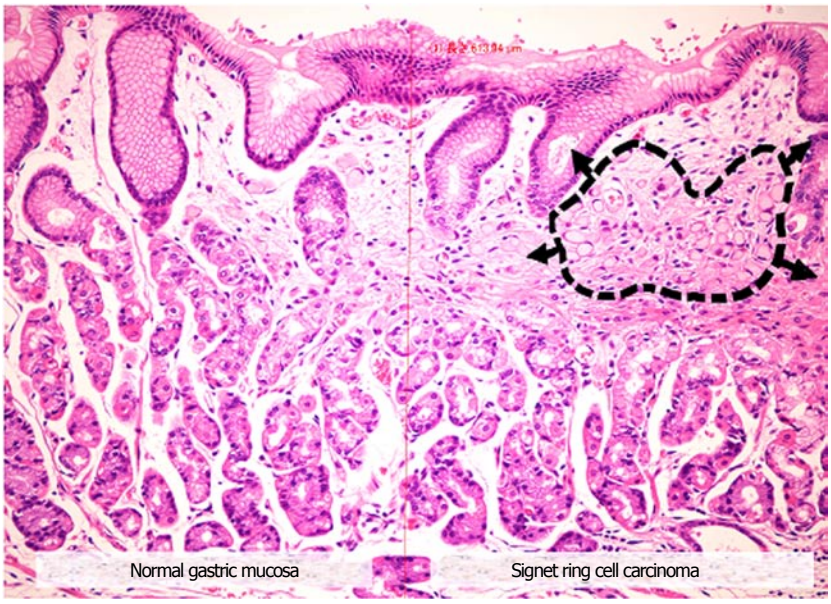

Figure 4 Microscopic view of a signet ring cell gastric carcinoma, demonstrating: (1) normal appearing gastric mucosa (left); and (2) signet ring cells (black dashed circle) causing distortion of the gastric glands (right), consistent with the endoscopic finding of the "stretch sign."

(Figure 1).

DISCUSSION

In all 12 cases of signet ring-type early gastric cancer in our institution, we identified the "stretch" sign - elongation of the architecture of the submucosa. Anecdotally, we do not note any architectural elongation in our non-signet ring early gastric cancer patients.

All 12 of our signet ring early gastric cancer patients underwent either endoscopic or surgical resection and are doing well at 2.5 years median follow-up; however; the optimal treatment for this subgroup of patients has not yet been determined. The current Japanese guidelines recommend ESD for non-ulcerated pT1a undifferentiated gastric cancer with tumor size $\leqslant$ 2 cm, but while some studies have shown only a 4% rate of lymph node metastases for tumors limited to the mucosa (as compared with 92% for tumors with submucosal spread)[12].

In an animal study, signet ring cells originated from the lamina propria at the level of the gland neck and spread through the mucosal[13]. We postulate that this proliferation of signet ring cells along the lamina propria results in clusters of tumor cells, causing the "stretched" appearance of the gastric pits and microvasculature that we observe on magnification endoscopy (Figures 3 and 4).

Our study is limited by its retrospective design and the small numbers associated with the relative rarity of early stage signet ring cell gastric cancer.

Additional studies are needed to further identify unique microendoscopic features of signet ring cell gastric cancer and to more accurately determine the sensitivity and specificity of the "stretch sign". Given that ESD is still considered an investigational treatment in the presence of signet ring cells due to the more aggressive biology and unfavorable prognosis[11,14], the presence of the "stretch sign" may help to identify patients with signet ring cells and perhaps guide more aggressive treatment, such as wider margins during ESD or earlier progression to formal surgical resection.

In conclusion, we found that signet ring cell carcinoma can be identified by the expansion or "stretching" of the gastric pits and microvasculature. This may allow for the diagnosis of signet ring cell carcinoma in the early stages using magnification endoscopy, reducing the impact of sampling error if random biopsies are taken, and perhaps guiding more aggressive treatment.

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COMMENTS

Background

Gastric cancers are aggressive tumors of the stomach that are often asymptomatic in the early stages. By the time patients develop symptoms, the tumors are often advanced and may be incurable. Aggressive screening regimens have been introduced in countries with a high prevalence of gastric cancer, such as Japan, leading to more gastric cancers being diagnosed in the early stages.

Research frontiers

Signet ring cell carcinoma, a rare subtype of gastric cancer, is unique in its biology and progression. Compared to "standard" adenocarcinoma, patients with early stage signet ring cell carcinomas have a better prognosis; meanwhile, patients with later stage signet ring cell carcinomas have a much worse prognosis than those with adenocarcinoma. Identifying and treating signet ring cell carcinoma in its early stages is therefore critical.

Innovations and breakthroughs

Early gastric cancers can be examined with magnification endoscopes using a narrow band imaging to reveal the architecture of the most superficial layers of the stomach, the mucosa and submucosa. This reveals the shapes of the gastric glands and the organization of the tiny submucosal blood vessels. In this study the authors present 12 patients with signet ring cell carcinoma; all of the patients have unique changes to the architecture of the glands and blood vessels (specifically, "stretching") that the authors have only seen when signet ring cells are present.

Applications

Use of the "stretch sign" during magnification endoscopy can potentially be used to identify patients who have signet ring cell carcinoma, allowing their prognosis and treatment to be tailored to the more aggressive biology of their cancer.

Terminology

Magnification endoscopes are upper endoscopes with a special tip and image processing equipment that can zoom in to see the organization of groups of cells. Narrow band imaging uses a small range of light (rather than the full "white light" spectrum) to highlight borders between normal and abnormal areas of the stomach. The "stretch sign" is the authors' term for elongation or "stretching" of the usual architecture of the gastric glands and the tiny submucosal vessels.

Peer-review

It is a concise and easy to read paper which brings a new progress in the field of early gastric cancer diagnosis.

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ORIGINAL ARTICLE

Clinical Trials Study

Management of liver transplantation biliary stricture: Results from a tertiary hospital

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Abstract

AIM: To review results of endoscopic treatment for anastomotic biliary strictures after orthotopic liver transplantation (OLT) during an 8-year period.

METHODS: This is a retrospective review of all endoscopic retrograde cholangiopancreatographys (ERCPs) performed between May 2006 and June 2014 in deceased OLT recipients with anastomotic stricture at a tertiary care hospital. Patients were divided into 2 groups, according to the type of stent used (multiple plastic or covered self-expandable metal stents), which was chose on a case-by-case basis and their characteristics. The primary outcome was anastomotic stricture resolution rate determined if there was no more than a minimum waist at cholangiography and a 10 mm balloon could easily pass through the anastomosis with no need for further intervention after final stent removal. Secondary outcomes were technical success

rate, number or ERCPs required per patient, number of stents placed, stent indwelling, stricture recurrence rate and therapy for recurrent anastomotic biliary stricture (AS). Stricture recurrence was defined as clinical laboratorial and/or imaging evidence of obstruction at the anastomosis level, after it was considered completely treated, requiring subsequent interventional procedure.

RESULTS: A total of 195 post-OLT patients were assessed for eligibility. One hundred and sixty-four (164) patients were diagnosed with anastomotic biliary stricture. ERCP was successfully performed in 157/164 (95.7%) patients with AS, that were treated with either multiple plastic (n = 109) or metallic billiary stents (n = 48). Mean treatment duration, number of procedures and stents required were lower in the metal stent group. Acute pancreatitis was the most common procedure related complication, occurring in 17.1% in the covered self-expandable metal stents (cSEMS) and 4.1% in the multiple plastic stent (MPS) group. Migration was the most frequent stent related complication, observed in 4.3% and 5.5% (cSEMS and MPS respectively). Stricture resolution was achieved in 86.8% in the cSEMS group and in 91% in MPS group. Stricture recurrence after a median follow up of 20 mo was observed in 10 (30.3%) patients in the cSEMS and 7 (7.7%) in the plastic stent group, a statistically significant difference (P = 0.0017). Successful stricture resolution after secondary treatment was achieved in 66.6% and 62.5% of patients respectively in the cSEMS and plastic stents groups.

CONCLUSION: Multiple plastic stents are currently the first treatment option for AS in patients with duct-to-duct anastomosis. cSEMS was associated with increased pancreatitis risk and higher recurrence rate.

Key words: Biliary stricture; Benign; Liver transplant; Endoscopic retrograde cholangiopancreatographys; Endoscopic treatment; Plastic stent; Self-expandable metal stent

Core tip: Endoscopic treatment is effective and safe in the management of post liver transplant biliary complications, mainly for anastomotic strictures. Progressive dilation and multiple plastic stenting have been demonstrated as the best endoscopic therapeutic modality with high success rates and low recurrence. Fully covered stent-expandable metal stents may be an option for endoscopic therapy potentially reducing the number and procedures lowering the costs, however their complication rate needs to be further evaluated.

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INTRODUCTION

Biliary complications have been considered for a long time the "Achilles' heel" of orthotopic liver transplantation (OLT), due to its elevated incidence, need for long-term therapy and major impact on graft survival and quality of life. Despite the advances in surgical techniques, organ selection, preservation and immunosuppression, the biliary tract remains the most common site for postoperative complications[1-4].

The incidence of biliary complications varies from 6% up to 40% of patients and includes strictures, leakages, stones, casts, sludge and sphincter of Oddi dysfunction[1-5].

Among the risk factors enrolled in the development of biliary complications the most important are: type of liver transplant procedure, reconstruction technique, organ preservation, technical factors during surgery, reperfusion injury, infection, prolonged cold and warm ischemia, hepatic artery thrombosis or stenosis, chronic rejection, ABO incompatibility, underlying disease, donation after cardiac death and older age donor[2-4,6-8].

Diagnosis of biliary complications after liver transplantation is challenging. Patients usually present asymptomatic elevations of bilirubin, alkaline phosphatase, gamma-glutamyl transferase and/or liver enzymes. Non-specific symptoms such as anorexia, fever, pruritus, jaundice and rarely pain (due to immunosuppression and hepatic denervation) can be observed.

The evaluation should start with an abdominal ultrasound (US) with Doppler of hepatic vessels. If hepatic artery thrombosis or stenosis is suspected, angiography should be indicated for specific treatment (Figure 1). If bile duct dilation, stones and/or leakage are identified by US the patient should be referred to therapeutic endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous trans-hepatic cholangiography (PTC)[7,9-13]. In case of normal abdominal US, a liver biopsy should be performed to exclude rejection. Finally, in patients with normal US and rejection ruled out by liver histology, a magnetic resonance cholangiopancreatography (MRCP) should precede more invasive procedures (Figure 1)[14]. Those patients who have a stricture or leakage confirmed by MRCP will be referred to therapeutic ERCP or PTC according to the type of biliary reconstruction.

Concerning management, although surgical repair used to be the standard treatment in the past, non-operative therapy of biliary complications has become the first line option in the last two decades[3,6]. Endoscopic approach is well established as the preferred therapeutic modality for patients with duct-to-duct anastomosis[15].

This paper will summarize the results of endoscopic treatment for anastomotic biliary strictures after

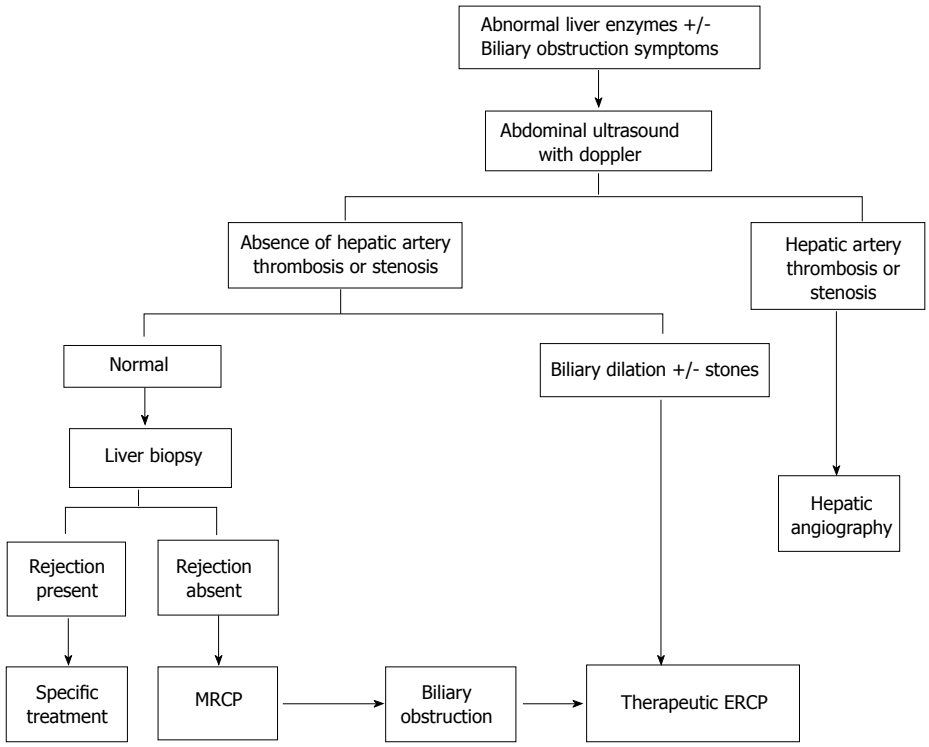

Figure 1 Algorithm for evaluation of suspected biliary obstruction after orthotopic liver transplantation in patients with duct-to-duct reconstruction. MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatographys.

deceased OLT in a tertiary center during an 8-year period and review the literature with future therapy considerations.

MATERIALS AND METHODS

Hospital Israelita Albert Einstein, São Paulo, Brazil, is a tertiary care hospital where around 120 liver transplantations are carried out annually. The study was reviewed and approved by the Hospital Israelita Albert Einstein Institutional Review Board. We retrospectively evaluated all ERCPs performed between May 2006 and June 2014 in deceased orthotopic liver transplant recipients with duct-to-duct anastomosis and suspected biliary complications. This paper reports our overall experience in such patients. All study participants, or their legal guardian, provided informed written consent prior to study enrollment. Procedures were performed under monitored care anesthesia.

Anastomotic biliary stricture (AS) was defined as a dominant short narrowing at the anastomotic site. Patients with AS were individually treated according to standardized protocols either with multiple plastic or single metal stents.

Briefly, plastic stents were initially placed after sphincterotomy and stricture balloon dilation. ERCP was repeated at 3-mo intervals for stent exchange, following a progressive balloon dilation and increasing number of stents protocol at each session, until 12 mo of therapy.

Covered self-expandable metal stents (cSEMS) were deployed with or without sphincterotomy and removed after a 3-mo period if a partially covered metal stent-expandable metal stents (PCSEMS) was used or after 6 mo in case of a fully covered stent-expandable metal stents (FCSEMS). In our early experience, biliary SEMS were placed without sphincterotomy, which we started to perform after recognizing a high rate of pancreatitis in these patients. PCSEMS were also used in our early experience, when fully covered SEMS were not available in Brazil.

Complications after ERCP (pancreatitis, cholangitis, hemorrhage, perforation) were defined by established criteria[16].

Initial technical success was the ability to obtain a cholangiogram and accomplish stent placement at ERCP alone or with a trans-hepatic *rendezvous* procedure. The investigators determined successful stricture resolution if there was no more than a minimum waist at cholangiography and a 10 mm balloon could easily pass through the anastomosis with no need for further intervention after final stent removal. All patients were followed at the institution transplant clinic through a combination of routine laboratory testing and clinical examination protocol. Stricture recurrence was defined as the return of clinical symptoms and/or elevated liver function tests with imaging evidence of obstruction at the anastomosis level causing biliary flow impairment requiring a subsequent interventional procedure in a patient previously considered successfully treated.

The primary outcome was anastomotic stricture resolution rate. Secondary outcomes were technical success rate, number or ERCPs required per patient,

Table 1 Summary of patients characteristics

	Multiple plastic stents	cSEMS
n	109	48
Sex		
Male	76 (69.7%)	36 (75.0%)
Female	33 (30.3%)	12 (25.0%)
Age (yr)		
Mean (± SD)	48.8 (± 14.5)	54.5 (± 12.9)
Median	50	56.8
Range	10-75	17-73
Time of anastomotic stricture after orthotopic liver transplantation (d)		
Mean (± SD)	214.2 (± 411.4)	221.6 (± 263.3)
Median	72	115.5
Range	6-2663	8-1339
Hepatic artery associated lesions		
Stenosis	3 (2.8%)	3 (6.3%)
Thrombosis	8 (7.3%)	1 (2.1%)
Associated biliary lesions		
Anastomotic fistula	5 (4.6%)	2 (4.2%)
Non-anastomotic fistula	1 (0.9%)	0 (0.0%)
Non-anastomotic stricture	1 (0.9%)	0 (0.0%)
Cholangitis	2 (1.8%)	0 (0.0%)
Stones	2 (1.8%)	0 (0.0%)

cSEMS: Covered self-expandable metal stents.

number of stents placed, stent indwelling, follow-up duration, stricture recurrence rate and therapy for recurrent AS.

Descriptive statistics were used to summarize data. Data was reported as the mean, standard deviation and range. Recurrence data was analyzed by the Kaplan-Meier method. Statistical data analysis was performed by the author (Martins FP) and reviewed by Hospital Israelita Albert Einstein Statistics Department.

RESULTS

A total of 195 post-OLT patients were referred to our Endoscopy Unit with a suspected biliary complication between May 2006 and June 2014. One hundred and sixty-four (164) patients were diagnosed with anastomotic biliary stricture (Figure 2).

Patients were divided into 2 groups, according to the type of stent used (multiple plastic or covered self-expandable metal stents), which was chosen on a case-by-case basis (Table 1). Both groups were similar concerning gender, age, time from OLT to anastomotic stricture and associated biliary or hepatic artery lesions.

Among the 164 patients with confirmed post-OLT anastomotic biliary stricture, initial technical success was obtained in 157 (95.7%); 109 individuals being treated with plastic stents and 48 with cSEMS (16 PCSEMS and 32 FCSEMS). Percutaneous trans-hepatic cholangiography was required in 11 (7.0%) patients to achieve access due to high-grade stricture or sharp angulation at the anastomosis. After percutaneous approach cSEMS were used in 7 and plastic stents in 4 cases.

Seven patients failed initial ERCP: 3 were referred to surgery (hepatic-jejunal anastomosis), 2 received external trans-hepatic biliary drainage, one was referred to re-transplantation and one died due to multiple organ failure after an episode of severe acute pancreatitis.

Table 2 Summary of treatment characteristics *n* (%)

	Multiple plastic stents	cSEMS
Total number of ERCP	271	70
Stent treatment duration (d)		
Mean (± SD)	282.7 (± 135.4)	124.2 (± 67.9)
Median	322	107.5
Range	3-767	9-269
Number of ERCP per patient		
Mean (± SD)	3.9 (± 1.5)	2.0
Median	4	2.0
Range	1-7	-
Number of stents per ERCP session		
Mean (± SD)	2.9 (± 1.5)	1
Median	3.0	1
Range	1-10	-
Total number of stents per patient		
Mean (± SD)	10.0 (± 7.2)	1
Median	10	1
Range	1-30	-
Complications	26 (9.6)	17 (24.3)
Acute pancreatitis	11 (4.1)	12 (17.1)
Bleeding	7 (2.6)	0 (0.0)
Perforation	2 (0.7)	0 (0.0)
Cardiorespiratory	2 (0.7)	0 (0.0)
Bacteremia	4 (1.4)	1 (1.4)
Pain	0 (0.0)	4 (5.7)
Stent related complications		
Migration	15 (5.5)	3 (4.3)
Occlusion	5 (1.8)	0 (0.0)

cSEMS: Covered self-expandable metal stents; ERCP: Endoscopic retrograde cholangiopancreatographys.

A total of 341 ERCPs were performed. Ten patients in the cSEMS group and 9 in the plastic stent group still have the stents in place and were excluded from analysis. Mean treatment duration, number of procedures and stents required were lower in the metal stent group (Table 2).

Acute pancreatitis was the most common procedure related complication, occurring in 17.1% in the cSEMS and 4.1% in the plastic stent group (Table 2). Other 4 patients (5.7%) presented abdominal pain without pancreatitis, requiring hospital admission to receive intravenous analgesics. Among stent related complications, migration was the most frequent, observed in 4.3% and 5.5% of patients with metal and plastic stents respectively.

There was one death (0.3%) related to severe acute pancreatitis in one patient who was also a technical failure.

There was no lost of follow-up until the primary outcome. Stricture resolution was achieved in 86.8% in the cSEMS group (Figure 3) and in 91% in the multiple plastic stents group (Figure 4). There were 5 failures in the cSEMS group, two of them presented spontaneous distal stent migration (Figure 5).

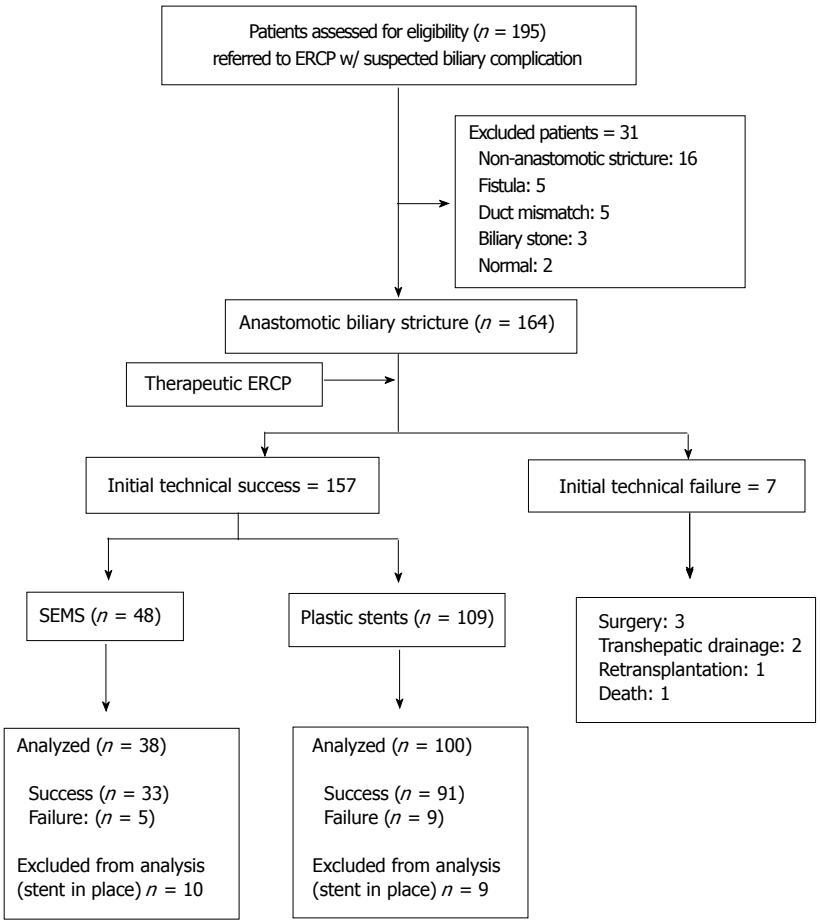

Figure 2 Flow chart of patients in the study. ERCP: Endoscopic retrograde cholangiopancreatographys; SEMS: Stent-expandable metal stents.

Table 3 Summary of the patients outcomes *n* (%)

	Multiple plastic stents	cSEMS
n	100	38
Stricture resolution rate		
Success	91 (91.0)	33 (86.8)
Failure	9 (9.0)	5 (13.2)
Follow-up (d)		
Mean (± SD)	690.8 (± 632.6)	620.3 (± 540.7)
Median	538	479
Range	0-2823	0-1615
Recurrence rate	7 (7.7)	10 (30.3)
Time to recurrent anastomotic stricture (d)		
Mean (± SD)	296.9 (± 259.5)	310.0 (± 348.4)
Median	240	124
Range	73-667	27-975
Re-treatment after failure or recurrent anastomotic stricture		
Success	10 (62.5)	10 (66.6)
Failure	6 (37.5)	1 (6.7)
In treatment	0 (0.0)	3 (20.0)
Lost of follow-up	0 (0.0)	1 (6.7)

cSEMS: Covered self-expandable metal stents.

Late stricture recurrence was observed in 10 (30.3%) patients in the cSEMS and 7 (7.7%) in the plastic stent group (Table 3). A Kaplan-Meier analysis (Figure 6) disclosed a statistically significant difference in the recurrence rate between both groups ($P = 0.0017$).

In the cSEMS group, 8 patients received re-treatment with multiple plastic stents, 2 received another cSEMS, 4 were referred to surgery and 1 lost of follow-up. In the multiple plastic stents group, secondary treatment consisted of cSEMS in 9 patients, multiple plastic stents in 4, surgery in 2 and PTC in 1 (choice of treatment in patients who failed initial treatment was decided by the referring physician). The results are summarized in Table 3.

DISCUSSION

Bile duct strictures after OLT are the most common biliary complication and have been classified according to their location into anastomotic strictures and non-anastomotic. They will be discussed separately in this paper as they differ in pathogenesis, presentation, natural history and response to treatment.

Anastomotic strictures present as a thin, short, localized and isolated narrowing in the area of biliary anastomosis as a result of fibrotic healing arising from ischemia at the end of both the donor and recipient bile duct[4,6,17]. They occur in 5% to 15% of patients after deceased OLT and 19% to 32% after living donor liver transplantation (LDLT)[3,4,6,18,19]. Early presentation

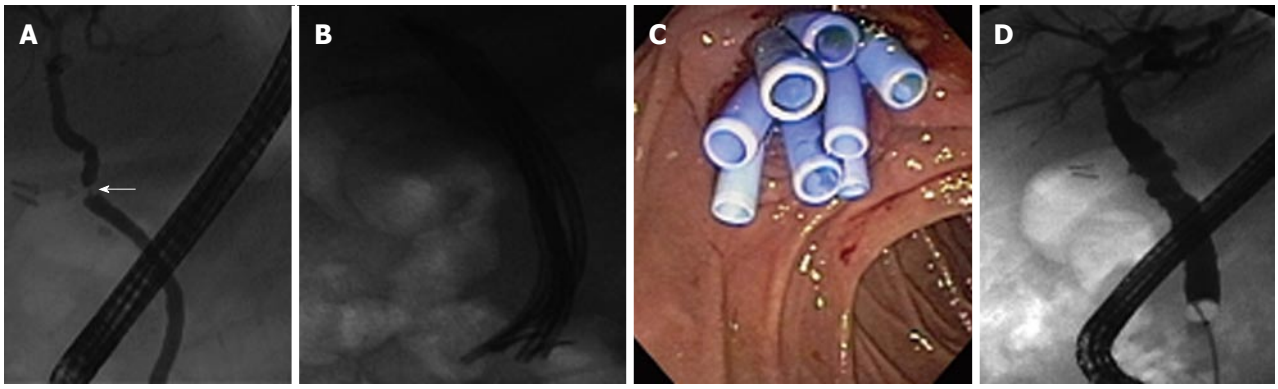

Figure 3 Patient with post-orthotopic liver transplantation anastomotic stricture from index endoscopic retrograde cholangiopancreatographys. A: Retrograde cholangiogram demonstrating post-OLT anastomotic stricture (arrow); B: Patient was treated with progressive multiple plastic stents; C: Patient was treated with progressive multiple plastic stents; D: Final cholangiogram revealing complete stricture resolution. OLT: Orthotopic liver transplantation.

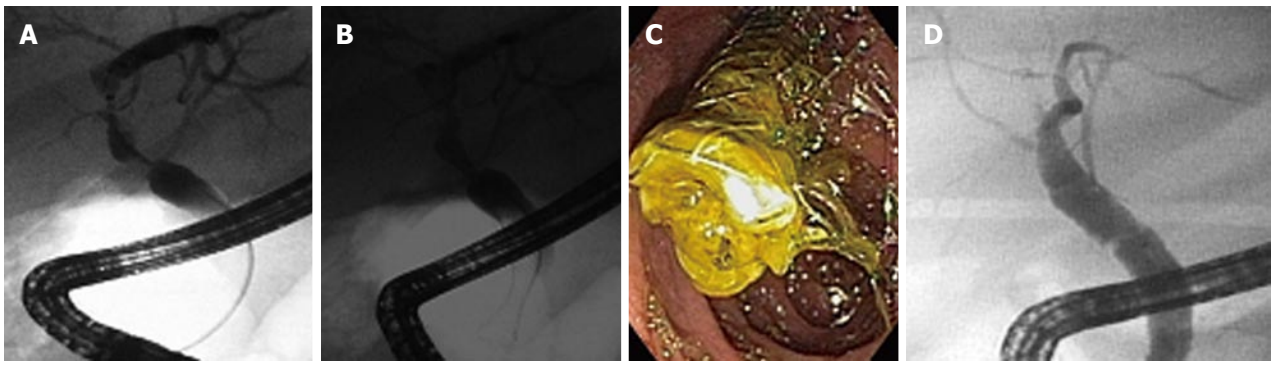

Figure 4 Patient with post-orthotopic liver transplantation anastomotic stricture. A: Post-OLT anastomotic biliary stricture; B: Placement of a fully covered SEMS across the stricture as a primary therapy option; C: Endoscopic view of the FCSEMS after 6 mo in place; D: Fluoroscopic image revealing enlargement of the common hepatic duct after SEMS removal. OLT: Orthotopic liver transplantation; FCSEMS: Fully covered stent-expandable metal stents.

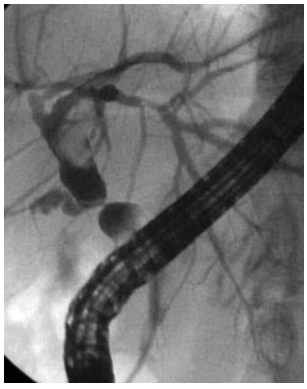

Figure 5 Recurrent anastomotic stricture after fully covered stent-expandable metal stents distal migration.

(within 12 wk) of anastomotic strictures have been related to technical issues, such as, small caliber of bile ducts, mismatch in size between donor and recipient ducts, inappropriate surgical techniques including suture material, tension at the anastomosis and excessive use of electrocautery[20]. The presence of bile leak has been reported as an independent risk factor for the development of AS; the underlying process may be related to the inflammation and subsequent fibrosis as a local effect caused by the bile itself or it may be a marker of poor vascularity in those patients in whom the leak is not originated from the cystic stump[8,21]. Late strictures are mainly due to vascular insufficiency, ischemia and problems with healing and fibrosis[12,22].

The majority of anastomotic stricture develops within the first year after OLT. In our series, the mean time between OLT and biliary stricture presentation was about 7 mo. Patients usually present asymptomatic or may have non-specific symptoms with abnormalities in liver function chemistries. Clinical suspicious must be confirmed by imaging diagnostic tools and patients are then referred to treatment, accordingly to the algorithm presented above.

There has been a transition over the past two decades in the primary management of benign biliary strictures from surgery to minimally invasive *via* ERCP. Endoscopic therapy presents a lower complication rate and shorter hospital stay when compared to surgery, not compromising the option of operation in case of failure[23,24]. Percutaneous therapy is still considered a second line option for patients with duct-to-duct anastomosis, though reserved to failed endoscopic

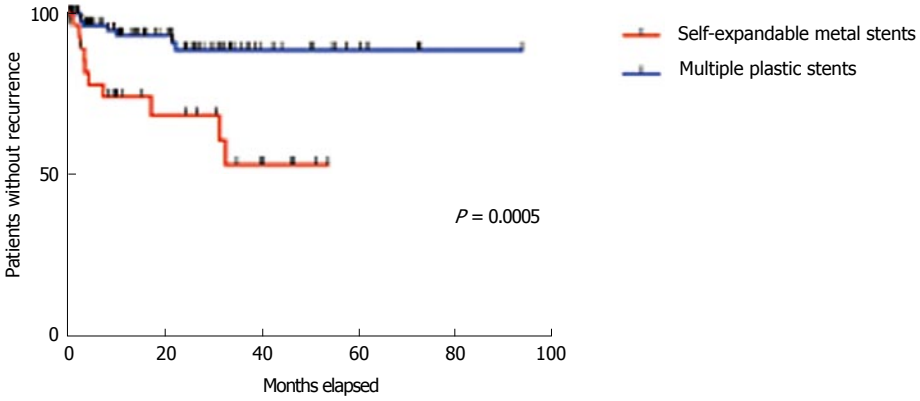

Figure 6 Stricture recurrence after resolution.

access to the anastomotic stricture, and patients with hepaticojejunostomy or choledochojejunostomy reconstruction. Currently surgical revision is confined for patients who have failed endoscopic and percutaneous therapy with re-transplantation being the final option.

Most patients with anastomotic stricture require multiple endoscopic interventions at 3-mo intervals for 12 to 24 mo with balloon dilation and long-term stenting[4,6,7,19,25-29]. The rational for multiple biliary stents placement through the stricture is to maintain the maximal expansion in luminal diameter achieved during balloon dilation, possibly promoting the re-modelation of bile ducts over the stents and preventing duct narrowing when stents are still in place[27,30]. In addition, the use of multiple stents may reduce complications related to stent occlusion, such as obstructive jaundice and cholangitis by adding biliary drainage through interstent channels[27,30,31].

A recent systematic review showed that stricture resolution rates were 78.3% for stent indwelling of less than 12 mo, compared with 97% for those longer than 1 year. The corresponding recurrence rates were 14.2% and 1.5% respectively[32].

In our center, we adopted an aggressive multiple plastic prophylactic stent exchange protocol over 1 year period, achieving a stricture resolution rate of 91%, which compares favorably with literature results. Recurrence rate after a mean follow-up of approximately 2 years is as low as 7.7%, reinforcing the benefits of extending the treatment up to 1 year.

A recent multivariate regression analysis was published assessing the outcome of endoscopic treatment of biliary complications after OLT[5]. Patients who received a graft from living donor or from a donor after cardiac death and those who had a reoperation for a non-biliary indication within the first month after liver transplantation were less likely to respond to endoscopic therapy[5]. Another factor apparently associated to stricture recurrence is the presence of a biliary leakage at initial ERCP[33]. On the other hand, early onset strictures seem to respond better and this finding may be related to the fact that those with late-onset are likely to be more fibrotic and therefore tighter and more resistant to therapy[8,27,33,34]. However, in case of recurrence, patients appear to respond well to repeated endoscopic treatment[8,27,30,35].

The major drawbacks of endoscopic treatment with balloon dilation and multiple plastic stents placement are the need of multiple procedures. Partially or fully covered SEMS were introduced on the market and became a very appealing option for benign biliary strictures due to their removability[36-49].

Post OLT biliary strictures offer an anatomical advantage for the placement of SEMS, which is the presence of the graft duct, permitting enough space above the stenosis to accommodate the metal stent distant from the hepatic confluence. Kahaleh *et al*[44] have been pioneer in the use of SEMS for benign biliary strictures of different etiology. Firstly, by describing metallic stent removability[44] and afterwards testing partially and fully covered SEMS in different clinical and technical settings[42,43,50-52].

Temporary placement of FCSEMS in patients with post-OLT anastomotic strictures refractory to conventional endoscopic therapy reached 87.5% to 100% initial success rate with a 4.5% to 7.4% recurrence. The major drawback of FCSEMS use was migration; occurring in 27.2% to 37.5%, even though with no clinical consequences[36,40,46].

In a systematic review that included 21 studies, multiple plastic stents were compared with metal stents in post liver transplant anastomotic stricture. There was significant heterogeneity in stent protocols, types of SEMS used, the use of balloon dilation or plastic stents before SEMS placement, primary outcome and stent free follow-up. There were no randomized controlled trials or non-randomized studies comparing these two modalities. Two hundred patients treated with SEMS were analyzed and stricture resolution rate was 80% to 94% when stent indwelling was longer than 3 mo, very similar to a 94% to 100% rate seen with multiple plastic stent for at least 12 mo. Moreover SEMS were used as a second line therapy for refractory strictures in 125 of these patients, what can be considered a

selection bias for more difficult strictures. The main problem with SEMS was stent migration, occurring in 16% of cases[32]. The rate of stricture resolution is lower in patients with FCSEMS migration[32,46,48].

In our study, we analyzed 38 post OLT patients with anastomotic stricture treated with cSEMS as a first line approach, reaching a stricture resolution of 86.8% after a mean stent indwelling of 124.2 d. Although the initial success was comparable with the currently standard multiple plastic stent treatment, there was a 30.3% recurrence rate after a mean of 310 d. We wonder if this higher recurrence rate was due to the shorter stent indwelling or the smaller final diameter of a 10 mm (30 French) cSEMS compared with the maximum number of plastic stents (up to 90 French per ERCP session) achieved in the other group.

We presented a mid-term evaluation of our randomized controlled trial comparing cSEMS with multiple plastic stents at DDW 2013. Although success rate was similar between groups, mean treatment duration and number of procedures required were statistically lower in cSEMS group ($P < 0.001$ for both comparisons). Moreover in our prospective trial, the mean total diameter for plastic stent group was 59 French (range 20 to 104.5 French)[47].

In summary, temporary placement of FCSEMS has been demonstrated effective and safe in the treatment of post OLT anastomotic strictures and should be considered for patients with refractory strictures[36,40,42,43,49]. On the basis of the current data, FCSEMS may allow anastomotic biliary stricture resolution with fewer procedure sessions possibly reducing treatment global cost, with the initial high price of a SEMS being compensated by the reduction in the number of ERCPs and the total number of plastic stents used during the 12-mo treatment period[53].

Questions remain about the optimal stenting interval and ideal metal stent. Concerning the first question, FCSEMS may be left in place for longer periods than partially covered ones, but prospective randomized studies with long-term follow-up are necessary to confirm this concept. The pursue for the ideal SEMS is still ongoing, it should be fully covered with an inert and resistant coating and have no fins, which seem to be associated to significant tissue reaction.

Concerning complications rate, in our study, the rate of post procedure acute pancreatitis in the plastic stent group was 4.1%, which compares favorably with the literature reports[54,55]. However, the rate of pancreatitis in the cSEMS group was 17.1%, which is exceedingly high even for a high-risk population.

Biliary sphincterotomy is usually not performed before SEMS placement in malignant biliary obstructions and therefore in the first 16 cases in our study cSEMS were deployed without one. The high incidence of acute pancreatitis (50% in the first 16 cases) came to our attention raising a debate over the impact of the sphincterotomy preceding metal stent deployment in a benign biliary stricture. Moreover, the severity of the event after cSEMS placement without sphincterotomy was also alarming, since 1 case was severe, 5 moderate and 2 mild.

The main hypothesis was that placing a trans-papillary metal stent in a native papilla without prior sphincterotomy was the main reason for the high rate of post procedure pancreatitis. Differently from patients with malignant obstruction that probably have already pancreatic parenchymal atrophy secondary to insidious pancreatic distal obstruction and therefore do not present acute pancreatitis after trans-papillary SEMS[56] Currently in our practice, all cSMES are placed after a biliary sphincterotomy in the post-OLT anastomotic stricture what drastically decreased acute pancreatitis rate to 12.5% (4/32) and all events were mild.

Although advances in surgical technique, organ preservation and selection have been made, biliary complications remain a significant source of morbidity in post liver transplant patients. Endoscopic treatment is already established as standard first line therapy. Progressive balloon dilation and multiple plastic stenting have been considered the first treatment option for biliary stricture in patients with duct-to-duct anastomosis. Our study shows encouraging results regarding placement of biliary cSEMS as the therapeutic endoscopic choice aiming to reduce the number of procedures and thus have a positive impact in cost, morbidity and quality of life of these patients, however their complication rate needs to be further evaluated.

COMMENTS

Background

Biliary complications have been considered for a long time the technical "Achiles heel" of orthotopic liver transplantation (OLT), with biliary strictures incidence up to 40% of patients. The standard strategy for post OLT biliary strictures in patients with duct-to-duct anastomosis has been balloon dilation followed by insertion of multiple plastic stents. Recently, covered self-expandable metal stents (cSEMS) has been increasingly used in the management of benign biliary strictures.

Research frontiers

The major drawback of conventional endoscopic treatment with multiple plastic stents placement is the need of multiple procedures. cSEMS have removability previously demonstrated in published studies and longer patency. In the area of benign biliary lesions, the current research hotspot is to evaluate the effectiveness and adverse events related to cSEMS.

Innovations and breakthroughs

Current evidence does not suggest a clear advantage of SEMS use over multiple plastic sten. In the study although success rates were similar, mean treatment duration and number of procedures required were statistically lower in cSEMS group. On the basis of the current data, fully covered stent- EMS may allow anastomotic biliary stricture resolution with fewer procedure sessions possibly reducing treatment global cost, with the initial high price of a SEMS being compensated by the reduction in the number of endoscopic retrograde cholangiopancreatographys and the total number of plastic stents used during the 12-mo treatment period.

Applications

Conventional endoscopic treatment with progressive balloon dilation and multiple plastic stenting has been considered the first option for post-OLT biliary stricture for decades. The study shows encouraging results regarding placement of biliary cSEMS as the therapeutic endoscopic choice aiming to reduce the number of procedures and thus have a positive impact in cost, morbidity and quality of life of these patients, however the complication rate

needs to be further evaluated.

Terminology

Anastomotic biliary strictures in the post-OLT scenario present as a short narrowing at the area of choledochal anastomosis. Endoscopic therapy can be performed by standardized protocols either with multiple plastic or single metal stents. Multiple plastic stents are placed after sphincterotomy and stricture balloon dilation, exchanged at 3-mo interval, until 12 mo of therapy. cSEMS are deployed at the index procedure and removed after approximately 6 mo.

Peer-review

This is a good descriptive study in which the authors analyzed the effectiveness and safety of endoscopic therapy in the management of post-OLT anastomotic biliary stricture. The results are interesting and suggest that cSEMS is a potential therapeutic option to multiple plastic stents that could be used for reducing the number of procedures and overall costs.

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