ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2019 May 16; 11(5): 322-394

Published by Baishideng Publishing Group Inc

WJGE

World Journal of Gastrointestinal Endoscopy

Contents

Monthly Volume 11 Number 5 May 16, 2019

Contents

World Journal of Gastrointestinal Endoscopy

Volume 11 Number 5 May 16, 2019

AIMS AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
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EDITORIAL BOARD MEMBERS
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EDITORIAL OFFICE
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PUBLICATION DATE
May 16, 2019

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World J Gastrointest Endosc 2019 May 16; 11(5): 322-328

DOI: 10.4253/wjge.v11.i5.322

ISSN 1948-5190 (online)

EDITORIAL

Endoscopic sleeve gastroplasty: From whence we came and where we are going

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Author contributions: de Moura DTH and de Moura EGH conceptualized the study and wrote the manuscript. Thompson CC critical final review of manuscript/English review.

Conflict-of-interest statement: de Moura EGH consultant for Boston Scientific and Olympus, de Moura EGH is a consultant to Boston Scientific. Thompson CC reports fee as a consultant for Boston Scientific and Medtronic; fees as consultant and institutional grants from USGE Medical, Olympus, and Apollo Endosurgery. All other authors declare that they have no conflict of interest.

Manuscript source: Invited manuscript

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Abstract

The most effective and durable treatment for obesity is bariatric surgery. However, less than 2% of eligible patients who fulfill the criteria for bariatric surgery undergo the procedure. As a result, there is a drive to develop less invasive therapies to combat obesity. Endoscopic bariatric therapies (EBT) for weight loss are important since they are more effective than pharmacological treatments and lifestyle changes and present lower adverse event rates compared to bariatric surgery. Endoscopic sleeve gastroplasty (ESG) is a minimally invasive EBT that involves remodeling of the greater curvature. ESG demonstrated favorable outcomes in several centers, with up to 20.9% total body weight loss and 60.4% excess weight loss (EWL) on 2-year follow-up, with a low rate of severe adverse events (SAE). As such, it could be considered safe and effective in light of ASGE/ASMBS thresholds of > 25% EWL and ≤ 5% SAE, although there are no comparative trials to support this. Additionally, ESG showed improvement in diabetes mellitus type 2, hypertension, and other obesity-related comorbidities. As this procedure continues to develop there are several areas that can be addressed to improve outcomes, including device improvements, technique standardization, patient selection, personalized medicine, combination therapies, and training standardization. In this editorial we discuss the origins of the ESG, current data, and future developments.

Key words: Endoscopy; Surgery; Bariatric; Obesity; Overweight; Comorbidities; Gastroplasty; Sleeve; Endoscopic sleeve gastroplasty; Editorial

Received: March 11, 2019
Peer-review started: March 12, 2019
First decision: April 13, 2019
Revised: April 16, 2019
Accepted: April 18, 2019
Article in press: April 19, 2019
Published online: May 16, 2019

P-Reviewer: Isik A, Lee SC
S-Editor: Dou Y
L-Editor: A
E-Editor: Xing YX

Core tip: Given the worsening obesity epidemic, there is increased demand for less invasive therapies. Considering the minimally invasive nature of Endoscopic sleeve gastroplasty (ESG), the reproducibility among centers, the favorable clinical outcomes in several studies, ESG could be regarded as safe and effective in light of ASGE/ASMBS thresholds of > 25% excess weight loss and ≤ 5% severe adverse events, although there are no comparative trials to support this. As this procedure is more widely adopted, high standards of care must be maintained to guarantee satisfactory clinical outcomes. In this editorial we discuss the origins of the ESG, current data, and future developments.

Citation: de Moura DTH, de Moura EGH, Thompson CC. Endoscopic sleeve gastroplasty: From whence we came and where we are going. *World J Gastrointest Endosc* 2019; 11(5): 322-328
URL: https://www.wjgnet.com/1948-5190/full/v11/i5/322.htm
DOI: https://dx.doi.org/10.4253/wjge.v11.i5.322

ENDOSCOPIC SLEEVE GASTROPLASTY: FROM WHENCE WE CAME AND WHERE WE ARE GOING

Obesity is a disease that is characterized by inflammation of adipose tissue and increased levels of systemic inflammatory cytokines, which are associated with debilitating comorbidities. Obesity has been deemed a pandemic by the World Health Organization, effecting approximately 700 million adults worldwide with an additional 2 billion overweight. It is associated with metabolic conditions, such as type 2 diabetes, cardiovascular diseases, hyperlipidemia, fatty liver, hypertension, osteoporosis, and other diseases. Additionally, obesity is second only to tobacco as a preventable risk factor for a number of cancers[1,2]. The most effective and durable treatment for obesity is bariatric and metabolic surgery[3-5]. However, disadvantages include the irreversible nature of the procedures and the non-negligible morbidity and mortality rates[6-14]. Furthermore, less than 2% of eligible patients who fulfill the criteria for bariatric surgery undergo the procedure. The reasons for this are multifactorial and likely include perceived surgical risk, morbidity, costs, access, and patient preference[15,16].

As a result, there is a drive to develop less invasive and cost-effective therapies to combat this epidemic. It is well established that a total body weight loss (TWL) of at least 10% is most effective in improving obesity-related comorbidities[17,18]. Lifestyle modifications, diet and pharmacotherapies rarely can achieve 10% TWL, and when initially effective, weight regain is common[19]. Endoscopic bariatric therapies (EBT) are important since they are more effective than pharmacological therapy and lifestyle modification and present lower adverse event rates compared with bariatric surgery[20-23].

In 2011, a joint task force convened by the American Society for Gastrointestinal Endoscopy (ASGE) and the American Society for Metabolic and Bariatric surgery (ASMBS) defined thresholds regarding safety and efficacy for EBT[24,25]. Subsequently, a Preservation and Incorporation of Valuable endoscopic Innovations document was created by the ASGE based on this consensus[26]. The results of this process are described below: (1) For primary obesity therapies in patients with obesity class II and III a minimum of 25% excess weight loss (EWL) at 12 mo, with a statistical difference > 15% above the control group is required; (2) For non-primary EBT such as metabolic therapy, bridging to surgery, and early intervention, a minimum of 5% TWL is necessary; and (3) Serious adverse events ≤ 5% is recommended for all EBT.

An EBT that meets these criteria is considered appropriate to incorporate into clinical practice after adequate training[26].

Endoscopic sleeve gastroplasty (ESG) is an incisionless, minimally invasive technique that involves remodeling of the greater curvature, via the placement of full-thickness sutures, in an effort to reduce gastric capacity and delay gastric emptying[27,28].

ESG with full-thickness suturing has demonstrated clinical effectiveness and safety, nevertheless, the technique continues to evolve. This concept was originally inspired by two older procedures, an abandoned endoscopic technique (endoluminal vertical gastroplasty) performed by Fogel *et al*[29] that focused on emulating a vertical banded gastroplasty along the mid-proximal gastric body not involving the greater curvature, and the surgical gastric imbrication procedure. The original greater curvature ESG

performed in 2008 using a superficial suction-based suturing device had limited results due to early suture loss[30,31]. Subsequently, ESG was performed using the current full-thickness suturing device in 2012 by Thompson and Hawes[28,32]. ESG has since been the focus of many studies worldwide. These studies have demonstrated technical feasibility, safety, and efficacy for this procedure in terms of weight loss and resolution of metabolic comorbidities[28,30,31,33-39].

Although the exact mechanisms of weight loss following ESG are not clear, the procedure is performed with the intention of reducing gastric volume and altering motility[27,34,37,38]. This is achieved via a reduction in both gastric width and length. Since the first ESG report, different numbers of sutures, orientation of sutures, spacing and frequency of bites, and tightness of cinching have been reported[40]. A variety of suture patterns have been used, including "M", "Z", and "U" patterns[41,42], as the procedure has evolved, with the main focus remaining greater curvature remodeling. An important element of all suture patterns is the distal to proximal movement within each running suture that is placed along the greater curvature, contracting the stomach longitudinally to confer the intended gastric shortening while simultaneously narrowing the lumen. Another difference is the use of reinforcement sutures which may be used in an attempt to further reduce volume, minimize tension on running sutures, and potentially improve durability. Nevertheless, no one suture pattern has yet been proven to achieve better efficacy[33,35,38,40-42]. The durability of weight loss may be less related to suture retention than it is to alteration in gastric function, which may persist even after suture loss. The gastric foreshortening partly reduces fundic capacity, however, this is achieved without placing any stitches directly into the fundus. In fact, the fundus is intentionally avoided to allow formation of a small pocket proximal to the sleeve to serve as a reservoir for food which may contribute to the prolonged gastric retention and improved satiety. Furthermore, fundic tissue is particularly thin and prone to leaks, and is in proximity to the spleen. Avoiding direct suture placement into the fundus minimizes the risk of adverse events.

As with many other novel procedures, in the beginning ESG was seen with a mix of enthusiasm and caution by the medical community. ESG was considered by some as a revolutionary technique that would treat obesity with the same efficacy as bariatric surgery. However, others remembered the transient effects of procedures performed with partial-thickness suturing devices that were plagued by early suture loss, and were far more skeptical. The results of the new ESG studies were not superior or similar to bariatric surgery in terms of efficacy, although they realized significant weight loss with fewer adverse events. On long-term follow-up endoscopy the stomach appears to be similar to its original size, however, with some peripheral bridging of tissue, and questions remain regarding the durable impact this may have on gastric function and long-term weight loss.

The largest ESG study, including 1000 patients, was recently published[39]. This study showed satisfactory results of ESG in the management of obesity with a mean %TWL at 6, 12, and 18 mo of 13.7% ± 6.8%, 15.0% ± 7.7%, and 14.8% ± 8.5%, respectively. The mean %EWL at 6, 12, and 18 mo were 64.3% ± 56.2%, 67.5% ± 52.3%, and 64.7% ± 55.4%, respectively. There are two multicenter studies[33,43] evaluating ESG in obese patients. In the study[43] including 112 consecutive patients, the average %TWL and %EWL were 11.9% and 39.9% at 3 mo, and 14.9% and 50.3% at 6 mo follow-up, respectively. By 6 mo post-ESG, 81% and 53.8% of patients had a %TWL greater than 10% and 15 %, respectively. The proportion of patients who achieved greater than 25% EWL was 86.5% at 6 mo. The other multicenter study[33], including 248 patients, reported the longest ESG follow-up to date. At 6 mo and 24 mo, %TWL was 15.2% and 18.6%, respectively, with similar weight loss between centers. The percentage of patients achieving ≥ 10% TWL was 84.2%. Additionally, in both univariable and multivariable regression analysis, weight loss at 6 mo predicted weight maintenance at 24 mo. Achieving less than 10% TWL at 6 mo was an early predictor of poor long-term results and adjunctive therapy to enhance weigh loss in these patients may be recommended. Lopez-Nava *et al*[44], also reported results up to 2 years follow-up. At 24 mo after the procedure baseline mean body mass index (BMI) changed from 38.3 to 30.8 kg/m^2; %TWL and %EWL were 19.5% and 60.4%, respectively. In this study, 85.7% of patients achieve greater than 25% EWL.

Most studies report the success of ESG specifically for weight loss. However, some studies also analyzed comorbidities related to obesity[38,39]. Sharaiha *et al*[38] studied 91 patients with BMI higher than 30 kg/m^2 who underwent ESG, with a follow-up up to 24 mo. Patients had significant reductions in levels of hemoglobinA1c, systolic blood pressure, waist circumference, alanine aminotransferase, and serum triglycerides. In this study a mean %TWL of 14.4%, 17.6%, and 20.9% were reported at 6 months, 1 year, and 2 year follow-up. Alqahtani *et al*[39] reported 76.5% complete remission in type 2 diabetes by the third month following the procedure, with all remaining

patients showing improvement. Additionally, all patients with hypertension and dyslipidemia had complete remission at the time of last follow-up. Despite few studies evaluating obesity-related comorbidities, these results are in keeping with what would be expected with this degree of weight loss.

Procedure durability remains unclear, as the longest follow-up published to date is 2 years[33,44]. It is important to note that redo ESG is an available minimally invasive option. Combination with medical therapy is also effective and should be considered for weight maintenance as needed. Additionally, if ESG fails, bariatric surgery is not contraindicated and has been shown to be effective. A major concern regarding surgical conversion is that the suture T-tags may cause the stapler to misfire resulting in a leak. However, in most suture patterns the gastric cardia is spared, minimizing this risk in conversion to RYGB. Additionally, conversion to sleeve gastrectomy has been successfully performed without adverse events[39].

Overall ESG is well tolerated. In the literature, mild and moderate adverse events such as abdominal pain, nausea and emesis are usually not analyzed in detail because they are expected and managed conservatively with improvement after few days[34,37,41]. A recent study[39] reported 92.4% of nausea or abdominal pain controlled with medication and resolved during the first week. Of 1000 patients, 24 were readmitted with no mortality. Causes for readmission included: severe abdominal pain, postprocedure bleeding, perigastric fluid collection, and post procedure fever. Additionally, another study[45] reported 24.2% moderate abdominal pain and 31.2% nausea and emesis in the first 48 h. Compared to other endoscopic techniques, ESG appears to have favorable outcomes regarding these symptoms. Intragastric balloons and duodenal jejunal bypass sleeves are also associated with approximately 7% and 18% early removals, respectively[26], whereas ESG reversal is extremely rare[39]. In the largest series of ESG, only 0.003% of procedures required reversal due to persistent symptoms[39]. Severe adverse events (SAE) after ESG are rare[27,34-36,43]. A recent review[42], including 9 ESG studies reported a 2.3% SAE rate, including gastric leaks, perigastric fluid collections, pulmonary embolism and pneumoperitoneum with pneumothorax. In the literature there are 7 reports of gastric leaks/perigastric fluid collections and all of these cases were treated without surgical intervention[33,38,39,46]. In general, ESG is associated with a lower rate of SAE, and no mortality, compared to surgical bariatric procedures which has up to a 20% SAE rate with 0.04% mortality rate[9,47,48] Additionally, the SAE rate of less than 5% achieves the threshold set by ASGE/ASMBS position paper[24,25].

ESG studies notably demonstrate some variability in weight loss outcomes, ranging from 15% to 19% TWL at 1 year[28,39]. The reasons for this are unclear and likely multifactorial. Baseline patient characteristics, number of sutures, suture pattern, use of reinforcement sutures, post-procedure diet, concomitant weight loss medication use, intensity of life-style modification, and follow-up plan of care all may be important factors influencing these results. Number of sutures and pattern are particularly important from a financial standpoint for many centers. Using fewer sutures is less costly and reduces procedure time, which ultimately may allow broader adoption. Although there is no rigorous evidence regarding number of sutures or ideal pattern, we believe that reinforcement sutures are associated with better efficacy and should be incorporated into suture patterns when possible. Post-procedure plan of care also differs among centers with unique diet recommendations, follow-up schedules, and pharmacotherapy use, which no doubt impact clinical outcomes and likely contribute to this variability as well.

In addition to ideal technique, experience level and patient characteristics required for optimal outcomes are also not well understood. Regarding recommended experience level, a multicenter study[31] showed that 34 cases were statistically significant to achieve a satisfactory %TWL, however, no formal learning curve assessment was performed. Similarly, there are little data to guide patient selection. A univariable analysis showed that younger age was significantly associated with weight loss at 1-year follow-up. Additionally, as one proposed mechanism is prolonged gastric retention, patients with underlying gastroparesis may be poorer candidates for this procedure.

As this field continues to develop there are several areas that can be addressed to improve outcomes. We are already seeing procedure and device improvements to simplify technical aspects and enhance durability. Technique standardization is still needed and will likely occur when better data are available. Patient selection is always an important consideration for optimizing patient outcomes. Moving towards personalized medicine, several factors are being investigated including baseline demographics, gastric motility, autonomic function, bile acid metabolism, gut hormones, genetics, and microbiome. Combination therapies also hold the promise of improved efficacy. Endoscopic device combinations, applied simultaneously or sequentially, that employ different mechanisms of action and combination with

pharmacotherapies are now actively being studied. It is also time for randomized controlled trials to better address many of these questions and provide level 1A evidence to confirm satisfactory outcomes. This will also help establish best medical practices and contribute towards broader reimbursement. Finally, as use of this procedure grows, standardized training and credentialing processes will be required to ensure patient safety and maintain good clinical outcomes.

In summary, given the worsening obesity epidemic, there is increased demand for less invasive bariatric therapies. Considering the minimally invasive outpatient nature of ESG, the reproducibility among centers with different experience levels, and the favorable clinical outcomes in several studies, ESG could be regarded as safe and effective in light of ASGE/ASMBS thresholds of > 25% EWL and ≤ 5% severe adverse events, however, there are no comparative trials to date. As this procedure is more widely adopted, high standards of care must be maintained to guarantee satisfactory clinical outcomes.

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World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2019 May 16; 11(5): 329-344

DOI: 10.4253/wjge.v11.i5.329

ISSN 1948-5190 (online)

REVIEW

Role of endoscopic vacuum therapy in the management of gastrointestinal transmural defects

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Author contributions: de Moura DTH and de Moura EGH conceptualized the study and wrote the manuscript; de Moura BFBH and Ribeiro IG collected data/approved final draft of the manuscript; Bazarbashi AN contributed to responsible for figure illustration/approved final draft of the manuscript; Thompson CC, Hathorn KE and Manfredi MA contributed to critical final review of manuscript/English review.

Conflict-of-interest statement: Eduardo Guimaraes Hourneaux de Moura, consultant for Boston Scientific and Olympus Moura, E is a consultant to Boston Scientific; Christopher C Thompson, reports fee as a consultant for Boston Scientific and Medtronic; fees as consultant and institutional grants from USGE Medical, Olympus, and Apollo Endosurgery. All other authors declare that they have no conflict of interest.

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Abstract

A gastrointestinal (GI) transmural defect is defined as total rupture of the GI wall, and these defects can be divided into three categories: perforations, leaks, and fistulas. Surgical management of these defects is usually challenging and may be associated with high morbidity and mortality rates. Recently, several novel endoscopic techniques have been developed, and endoscopy has become a first-line approach for therapy of these conditions. The use of endoscopic vacuum therapy (EVT) is increasing with favorable results. This technique involves endoscopic placement of a sponge connected to a nasogastric tube into the defect cavity or lumen. This promotes healing *via* five mechanisms, including macrodeformation, microdeformation, changes in perfusion, exudate control, and bacterial clearance, which is similar to the mechanisms in which skin wounds are treated with commonly employed wound vacuums. EVT can be used in the upper GI tract, small bowel, biliopancreatic regions, and lower GI tract, with variable success rates and a satisfactory safety profile. In this article, we review and discuss the mechanism of action, materials, techniques, efficacy, and safety of EVT in the management of patients with GI transmural defects.

Key words: Gastrointestinal; Endoscopy; Endoscopic vacuum therapy; Negative pressure

Manuscript source: Invited manuscript

Received: March 8, 2019
Peer-review started: April 12, 2019
First decision: April 13, 2019
Revised: April 16, 2019
Accepted: May 1, 2019
Article in press: May 1, 2019
Published online: May 16, 2019

P-Reviewer: Gkekas I, Richardson WS
S-Editor: Ji FF
L-Editor: A
E-Editor: Xing YX

therapy; Fistula; Leak; Perforation; Defect

Core tip: Gastrointestinal (GI) transmural defects, including perforations, leaks, and fistulas, are difficult to manage and are associated with high rates of morbidity and mortality. Endoscopic vacuum therapy (EVT) has developed into a valuable tool for the treatment of these conditions. EVT has proven to be an effective and safe method in the intraluminal treatment of transmural defects, as it promotes changes in perfusion, causes microdeformation and macrodeformation, and decreases bacterial contamination, secretion, and local edema to facilitate healing. In this review, we discuss the mechanism of action, materials, techniques, efficacy, and safety of EVT in the management of patients with transmural GI defects.

Citation: de Moura DTH, de Moura BFBH, Manfredi MA, Hathorn KE, Bazarbashi AN, Ribeiro IB, de Moura EGH, Thompson CC. Role of endoscopic vacuum therapy in the management of gastrointestinal transmural defects. *World J Gastrointest Endosc* 2019; 11(5): 329-344
URL: https://www.wjgnet.com/1948-5190/full/v11/i5/329.htm
DOI: https://dx.doi.org/10.4253/wjge.v11.i5.329

INTRODUCTION AND BACKGROUND

A gastrointestinal (GI) transmural defect is defined as total rupture of the GI wall and these defects can be divided into three main categories including perforation, leaks, and fistulas. Recognition of the specific classification of the defect is essential for choosing the best treatment modality. In the past, many endoscopic techniques, including clips, cap-mounted clips, covered self-expandable metal stents (CSEMS), tissue sealants, endoscopic sutures, cardiac septal defect occluders, septotomies, and internal drainage with pig-tail stents, have been shown to be effective in reducing morbidity and mortality in the treatment of transmural defects. However, the efficacy varies in most studies[1-17] and, thus, endoscopists continue to investigate novel techniques for management of these defects.

Endoscopic vacuum therapy (EVT), also known as endoscopic negative pressure therapy, Endovac therapy, and E-Vac therapy, is an innovative endoscopic option for treating transmural GI defects[18-21]. This endoscopic approach is based on the negative pressure wound therapy for treatment of non-healing wounds. The healing effect of this technique occurs through multiple mechanisms, including changes in perfusion, microdeformation, macrodeformation, exudate control, and bacterial control[22]. Although some authors use the term "negative pressure" in their description of this technique[18,19,21], we find this to be misleading, as physical pressure always has a positive value[23,24]. Thus, in this review we will use the term EVT.

The first report of EVT[25] was in the treatment of an anastomotic leak following a rectal surgery in 2003. Since then, EVT has been used in the adult population for closure of esophageal, gastric (most commonly after bariatric surgery), small bowel, pancreatic, and colorectal defects, with success rates above 70%[26-33]. Additionally, one study demonstrated the use of EVT in the pediatric population, with a high success rate in the treatment of upper GI transmural defects[34].

In this article, we review and discuss the mechanism of action, indications, materials, techniques, efficacy, and safety of EVT in the management of patients with transmural defects.

MECHANISM OF ACTION

Vacuum therapy has been commonly used for treatment of non-healing skin wounds. In management of transmural defects, EVT is thought to promote healing *via* similar mechanisms, including macrodeformation, microdeformation, changes in perfusion, exudate control, and bacterial clearance[35,36].

Macrodeformation

Macrodeformation occurs when suction is applied to the sponge resulting in deformational forces being exerted on the defect edges, thus drawing the edges together. Studies showed that a negative pressure of 125 mmHg can decrease the volume of a reticulated open-pore polyurethane sponge by approximately 80%, resulting in substantial shrinkage of the defect[35-39].

Microdeformation

Microdeformation describes the mechanical changes that occur on a microscopic scale when suction is applied. Mechanical strain causes a deformation of the cytoskeleton which initiates signaling cascades leading to release of growth factors which promote cell proliferation and migration, increasing the expression of extracellular matrix components and contractile elements that are necessary for healing. Factors known to affect the efficiency of this mechanism include level of suction, pore size and consistency of the sponge, type of tissue being treated, and deformability of the surrounding tissues[35,40].

Changes in perfusion

Adequate blood flow is essential for healing because it delivers oxygen and vital nutrients to the tissue in addition to removing waste products. Vacuum therapy treatment results in increased microvessel density. Vacuum therapy causes temporary hypoperfusion in the defect edges resulting in localized hypoxia-inducible factor 1α and concomitant modulation of vascular endothelial growth factor expression, leading to increase angiogenesis[22,41,42]. In healthy human skin, suction levels of up to 300 mmHg applied to a reticulated open-pore polyurethane sponge cause a fivefold increase of blood flow[43]. Additionally, other studies have demonstrated that a negative pressure of 125 mmHg considerably increased the blood vessel density, reaching a maximum of 200% in contrast to the vessel density prior to treatment[44].

Exudate control

Fluid accumulation in the extracellular space and tissue edema often occur in chronic defects, inhibiting healing by compressing local cells and tissues. It has been demonstrated that wound healing is improved following fluid removal, and although the exact mechanism for this improved healing is unclear, proposed theories include local alterations in blood flow and removal of harmful substances[22,24,45,46]. Additionally, by removing fluid, there is a reduction in the compression forces acting on the microvasculature, which allows increased blood flow and perfusion of the tissue[35].

Bacterial clearance

A high bacterial load may interfere with the process of defect healing; however, there is conflicting evidence regarding the role of vacuum therapy in decreasing bacterial contamination[22]. One randomized study reported that vacuum treatment had a positive effect on wound healing because of a significant decrease in bacterial load compared with non-vacuum–treated wounds[47]. Additionally, a second study including patients with thoracic infections showed improvement in infection control prior to definitive closure[48]. However, other studies have also shown either an increase or no change in bacterial load using this technique[49,50].

INDICATIONS

EVT represents a clinical endoscopic evolution of vacuum-assisted closure therapy, a well-established treatment for open wounds[47,49,51]. Since it is still a relatively new technique, currently no standardized indications for use have been established[51].

All patients with acute or chronic GI defects are candidates for EVT. Endoscopic evaluation is always required prior to treatment to identify the wall defect, to characterize the leak or fistula tract, and to evaluate the contaminated cavity. Larger defects, including perforations, leaks and fistulas, typically associated with fluid collections, are the most common indication for EVT, and studies have shown high efficacy rates of healing associated with this technique[26-34]. When a small defect is associated with a contaminated cavity, dilation of the defect to access the cavity is needed to place the sponge extraluminally. Additionally, small defects, less than 10 mm, without an associated cavity, can be managed with intraluminal placement of the sponge[1,10,52,53].

EVT can be used throughout the GI tract for esophageal, gastric, small bowel, biliopancreatic, and colorectal defects. The most common indications with established data are defects in the esophagus (perforations, leaks and fistulas after anastomoses), stomach (mainly after bariatric surgery), and colorectal areas (anastomotic leaks and

fistulas)[26-33,51,54]. Additionally, recent data on early use of EVT in patients with anastomotic ischemic following esophagectomy has been reported with favorable results[55]. The use of EVT in GI ischemia had also been successfully reported in a case of ischemia of the blind end of the jejunal loop after Roux-en-Y gastrectomy[56].

An additional benefit is that EVT can be used in critically ill, hemodynamically unstable patients in need of infectious source control. This technique allows for control of the focus of the sepsis by removing necrotic debris, tissue, and purulent material, while promoting tissue healing and thus hopefully allowing for patient stabilization. It should be noted, however, that if the patient does not clinically respond to EVT therapy, surgical intervention may still be required[48,51,52].

Similar to alternative techniques, EVT has limited efficacy in some clinical scenarios. In defects larger than 5 cm, the sponge size may be insufficient to occlude the defect[52,57,58]. In multiloculated fluid collections, the proper placement of the sponge can be inadequate due to the septations of the collection[57]. In patients with complete dehiscence of a surgical anastomosis, EVT can be used to control sepsis; however, frequently, a second intervention, such as CSEMS or revisional surgery, is needed to restore the anastomosis and preserve continuity of the upper GI tract. Additionally, patients with anastomotic leakage after esophagectomy with necrosis of the gastric conduit usually require surgical revision[51,59]. And finally, another limitation of use of EVT occurs in patients with GI-cutaneous fistula. Mechanistically, EVT relies on the ability to create negative pressure to keep the defect and fistula tract close. Atmospheric exposure prevents this negative pressure system from occurring, and frequently results in dressing malformation and failure. While attempts to plug the fistula at the skin level with occlusive dressings or glue/tissue sealants has been used, this does not maintain an ideal negative pressure seal, which can lead to moisture buildup and eventual failure[52].

To date, contraindications to EVT remain unclear. However, it is recommended that EVT should be avoided in patients with defects in close vicinity of major vessels or those on therapeutic anticoagulants due to the risk of major bleeding[26,60-62]. Additionally, it should be avoided in patients with defects in connection to the tracheobronchial system[18].

PROCEDURE

The procedure can be performed in the operating room, endoscopy suite, or at the bed side. In those patients with upper GI defects, anesthesia with endotracheal intubation is recommended for safe airway management during the passage of the sponge. However, during exchanges, deep sedation may be preferred in certain patients. In those patients with lower GI defects, deep sedation is likely safe depending on other clinical factors. Once the patient is adequately sedated, endoscopic evaluation is required to identify and characterize the wall defect and to evaluate the contaminated cavity. Once adequately evaluated, endoscopic irrigation and debridement is recommended.

A meticulous evaluation of the cavity (with or without fluoroscopy) is performed to choose the correct sponge size; estimation of the size of the sponge can be based on the size of the endoscope or endoscopist prior experience. After these steps, the endoscope is removed, and the sponge system is prepared[18,34,52,57].

For the purposes of this review, we will explain the detailed technique for use of EVT in upper GI defects. Lower GI defects can be managed with few modifications to this technique. A silicon 16 or 18-Fr (10 to 16 Fr in children) nasogastric tube (NGT) is introduced into the patient's nares and advanced to the posterior pharynx. Then, the NGT is retrieved though the mouth by using a finger or grasper instrument[18,34,52,57].

A custom EVT sponge is assembled using a polyurethane foam (PUF). The custom sponge is cut to size based on the defect size. Of note, the sponge size is limited to the diameter of the esophagus and overestimation of the sponge size may hinder your ability to visualize the perforation, as there is limited working space with the relatively small diameter of the normal esophagus. In general, the standard size of the sponge is 3 to 7 cm in length and 2-3 cm in diameter. After the sponge is cut to the appropriate size and positioned at the tip of the NGT, the sponge is secured using either silk ties or permanent suture (such as 2-0 or greater prolene or nylon). Finally, a stitch is placed through both the tubing and the sponge at both the proximal and distal ends. To facilitate endoscopic placement and retrieval, a permanent suture is driven to the distal part of tube and tied into a small loop[18,34,52,57].

After the customized sponge system is created, a grasper should be placed through the working channel of the endoscope before insertion into the patient mouth. Then, the short suture loop is grasped with the device. Some authors like to soak the sponge

with water-soluble contrast to allow fluoroscopic-assisted placement, however, this is an optional technique. Then, the sponge and the endoscope are lubricated and inserted into the mouth. Due to the size of the system and the endoscope, introduction into the upper esophageal sphincter can be difficult and careful attention should be paid to avoid trauma during insertion[18,34,36,57].

Depending on the size of the perforation, the endoscope should either be driven to the perforation site (if smaller than 10 mm) or should be driven through the perforation into the cavity (if larger than 10 mm) (see topic below: intracavitary and intraluminal EVT). Once inside the cavity, the grasper can be advanced while the endoscope is withdrawn to the GI lumen. Then, the suture loop is released from the grasper. After placement, under endoscopic visualization, the sponge can be pushed or pulled with the grasper to ensure proper position[18,34,36,57].

Once the sponge is in proper position, the NGT is secured to the nose. The suction tubing is hooked up to the vacuum therapy unit and canister. The NGT with the sponge is then attached to the canister tubing using a custom adapter. The vacuum therapy setting frequently used in the GI tract is 125 mmHg of pressure at continuous moderate intensity, however, some authors also describe the use of a higher pressure, to 175 mmHg. If the patient is uncomfortable, or if the patient experiences pooling of secretions above the sponge on the continuous suction setting, the settings can be changed to intermittent suction (5 min on, 2 min off) at the same pressure[18,34,52,57]. It should be mentioned that in patients with a gastrostomy, the procedure described above can be performed *via* a retrograde fashion through the gastrostomy[34].

There is limited data regarding oral fluid intake in patients during EVT treatment. While the administration of oral fluids may be controversial, in our experience, low volume of clear fluid (for example, 50 cc of water) administered four times daily for comfort need did not impact treatment course.

Intracavitary and Intraluminal EVT

The two techniques of EVT placement, intraluminal (Figure 1A) and intracavity (Figure 1B), are based on where the sponge system is placed[53,58]. In intracavitary placement, a short sponge is typically placed into the extraluminal cavity as a long sponge would be more likely to fold on itself rendering it less effective. With continuous EVT, the cavity ultimately is drained and collapses onto the lumen, which then seals the defect, preventing further contamination. In intraluminal EVT, the sponge system is placed into the GI lumen. In this approach, frequently a long, cylindrical sponge systems is used. When the vacuum is applied, the lumen collapses over the defect zone, and the EVT system keeps the tract dry by draining GI secretions, allowing the defect to seal avoiding contamination[20,53,58]. Independent of where the sponge system is placed, the most important mechanisms of action of EVT are the simultaneous drainage and closure of the defect.

Sponge system exchanges

The sponge system should ideally remain in place for approximately 3 to 5 d at a time. No more than 7 d is recommended. The sponge embeds into the surrounding tissue, and thus, the longer the sponge remains in place, the more difficult it will be to remove. To exchange the sponge, continuous suction should first be turned off. Then, the endoscope is used to drive between the tissue and the sponge interface to dislodge the sponge from the granulation tissue. If the sponge does not dislodge easily with gentle traction, water or saline can be infused into the NGT to disconnect the sponge from the tissue.

It is important to understand that NGT manipulation should be performed carefully because if the NGT is dislodged from the sponge, retrieving the sponge becomes very challenging. This can drastically increase procedure time and risks associated with prolonged procedures. A grasper can also be used to manipulate the sponge and to grab the loop suture in the distal part of the sponge system to remove it. Similar to insertion, the diameter of the sponge is too large to be removed through the nares with the NGT. Thus, the sponge must be removed from the mouth. Once the sponge is outside the mouth, the NGT can be cut with a blade or scissors[18,34,52,57].

Open-pore polyurethane sponge and open-pore film drains

Several open-pore polyurethane sponge drains (OPDs) (Figure 2) and open-pore film drains (OFDs) (Figure 3) have been developed with different advantages[19,20,53,63-67]. In general, short systems (< 5 cm) are used for intracavitary EVT and long systems (> 5 cm) are used for intraluminal therapy[53]. OPDs are more frequently used in EVT compared to OFDs[19,20,53].

The only commercially available OPD for EVTis the Endosponge® (B. Braun Melsungen AG, Melsungen, Germany) which is marketed for use in the esophagus. However, no electronic pump system has been approved for GI endoscopy therapies

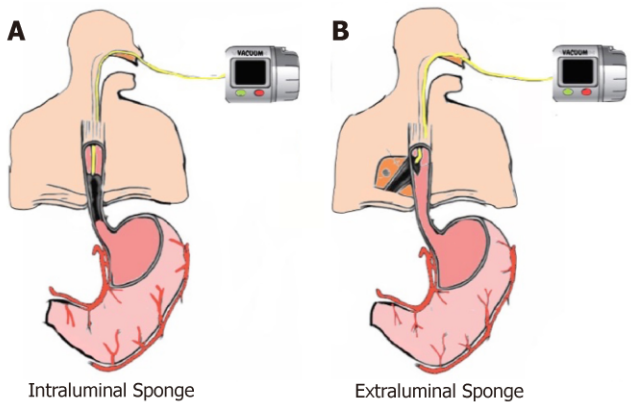

Figure 1 Sponge placement. A: Intraluminal endoscopic vacuum therapy (EVT); B: Intracavitary EVT.

yet[53].

OFDs are newer compared to OPDs and have been developed using a very thin open-pore, double-layer, drainage film (Suprasorb® CNP Drainage Film, Lohmann and Rauscher International GmbH and Co; Rengsdorf, Germany), which is approved for vacuum therapy in wound skin defects[19]. The film is wrapped around the openings in the NGT instead of the PUF[53]. These new drains have the advantage of a very small diameter facilitating their introduction through the nares and placement into small wall defects[65]. These drains also have the advantage to adhere well to the intended defect but adhere less tightly to the normal mucosa surrounding the defect during EVT[53]. A combination of the tools, with PUF wrapped with the open-pore film was also reported in some studies[64,66]. Nutritional support is imperative to wound healing, and thus, for EVT in upper GI defects a double lumen drain has been developed with an additional jejunal feeding tube to allow for enteral feeding access[67,68].

Notably, in our experience, we used gauze coated with perforated sterile plastic drain instead of OPDs or OFDs. This technique, described by Dr. Flaubert Sena de Medeiros, is feasible with a lower cost and non-inferior results to other drains systems[69] (Figure 4).

Timing and costs

The initial endoscopic vacuum system placement takes approximately 30 to 60 min, including diagnostic endoscopy, evaluation (with or without dilation), irrigation, and placement of the sponge system. Subsequent sponge system exchanges take approximately 30 min of procedural time[57]. One study evaluated the cost of EVT use and demonstrated that for an average treatment span of 25 d, including 8 sponge exchanges per patient, the total cost per patient was approximately $10118.00[57].

EFFICACY

EVT efficacy in the treatment of transmural GI defects is well reported in case series, cohort studies and systematic reviews. To date, no randomized control trials have been published comparing EVT versus other surgical or endoscopic techniques. In this section, the efficacy of EVT will be discussed with regards to management of transmural GI defects, including those involving the esophagus, stomach (post-bariatric complications), small bowel, biliopancreatic, and lower GI tract.

Upper GI defects

The successful use of EVT in upper GI defects was first published in 2008[70]. In this report, two patients with intrathoracic anastomotic leaks after esophagectomy and gastrectomy were successfully treated with a mean of 5 sponge exchanges over a mean of 15 d, without adverse events. After this report, different centers published on the use of EVT in upper GI transmural defects. To date, the most common use of EVT in the upper GI tract has been for closure of esophageal defects[20,57-59,62,71-74]. The inspiration and expiration respiratory movements associated with EVT facilitate the extraluminal transport of even small amounts of fluids[53].

In acute perforations, EVT has shown satisfactory results in several studies. Loske *et al*[75] demonstrated in a series with 10 patients, including iatrogenic perforations from the cricopharyngeal to the gastroesophageal junction, that all patients were

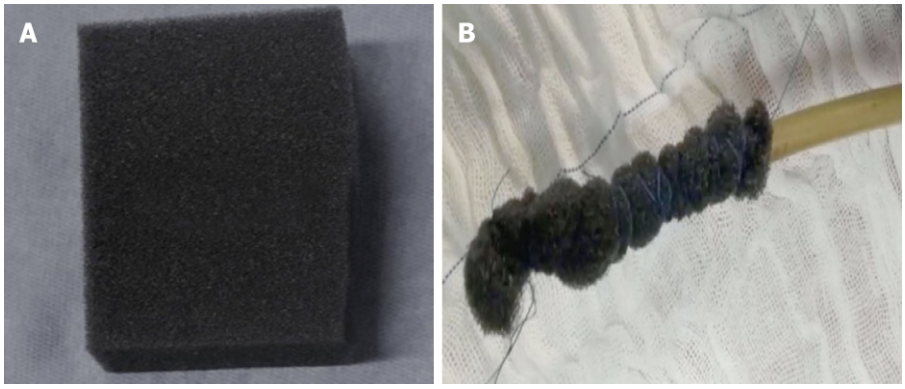

Figure 2 Open-pore polyurethane sponge drain. A: Open-pore polyurethane sponge; B: Open-pore polyurethane sponge drain for endoscopic vacuum therapy.

successfully treated within a median of 3 to 7 d without any associated adverse events or need for adjunctive therapy. Kuehn *et al*[60] demonstrated a similar clinical success rate of 100% in a separate series including 10 patients with acute perforation (8 iatrogenic and 2 Boerhaave). And finally, Heits *et al*[76] published their study which evaluated the efficacy of EVT in esophageal acute perforations (iatrogenic, spontaneous, and foreign body-associated), showing a primary clinical success of 90% with a mean sponge exchange of 5.4 (2 to 12) and a period of 19 ± 14.26 d.

The majority of studies on the use of EVT in upper GI endoscopy are related to the treatment of intrathoracic leaks, including the use of EVT as primary or as a rescue therapy (Figure 5). In these studies, the efficacy rate of EVT varies from 66.7% to 100%[58,59,73,77,78], with two of these studies demonstrating an efficacy of 100% without any adverse event[77,78].

There are several cohort studies comparing the use of EVT with other techniques in the management of esophageal leaks[27,79-83]. In one retrospective analysis comparing EVT versus self-expandable stents (metal and plastic stents), overall closure rate was 84.4% for EVT versus 53.8% for the stent group. Additionally, a multivariate analysis showed successful defect closure was independently associated with EVT[79]. The superiority of EVT compared to SEMS was confirmed in two other comparative studies[81,82]. Additionally, Manfredi *et al*[34] showed the superiority of EVT compared to stents in pediatric patients (mean age 24 mo) showing successful closure in 88% of patients who underwent EVT versus 63% of patients who had stent placement. The largest series comparing EVT versus other approaches in the management of leak after esophagectomy showed that EVT is superior to surgical revision, stent placement, and conservative management[80]. These results were confirmed in a recent systematic review and meta-analysis[83], showing that the esophageal defect closure rate is significantly higher in EVT than SEMS, with a shorter treatment duration, lower major complication rate, and lower in-hospital mortality.

The indications for use of EVT in the upper GI tract are expanding to different applications. A recent series[55] demonstrated the use of EVT in the management of anastomotic ischemia, without active leak, after esophageal resections. This study showed interesting results; 75% of the patients developed complete mucosal recovery, while the other 25% of patients developed a leak during the use of EVT. However, these leaks were ultimately successfully treated with EVT. With the increase in the use of EVT, a recent study[28] evaluating patients who underwent EVT in the treatment of esophageal transmural defects concluded that EVT is well tolerated with a satisfactory long-term quality of life.

Post-bariatric surgery complications

Obesity is a pandemic and bariatric and metabolic surgery is the most effective treatment. Despite satisfactory clinical results, the number of adverse events, including leaks and fistulas, after bariatric surgery has increased[1,84-90]. Therefore, the use of EVT in the post-bariatric surgery setting is increasing. While older management algorithms published in 2015 and 2016, did not cite the EVT approach[91,92] as a management option, those from more recent years have proposed the use of EVT in both early and chronic settings[1,93].

A recent study[94], demonstrated the use of EVT in patients with early infradiaphragmatic leakage after bariatric surgery, including laparoscopic sleeve gastrectomy (LSG) and RYGB. In this series, some cases were performed with EVT alone and others with EVT with stent (stent-over-sponge). In 80% of patients, the leak

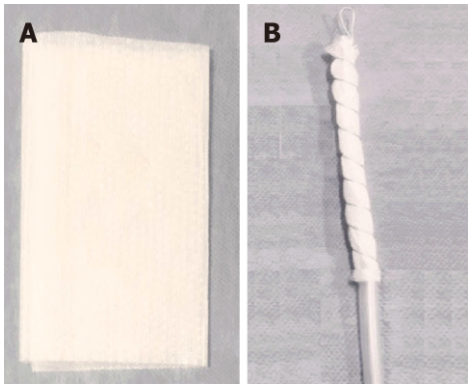

Figure 3 Open-pore film drain. A: Open-pore film; B: Open-pore film drain for endoscopic vacuum therapy.

was connected to abscess cavities. Clinical success, defined as no signs of persistent leakage, was achieved in all patients studied.

In a study including patients with acute, early, late, and chronic leaks after sleeve gastrectomy, the use of EVT was associated with 100% resolution of leaks confirmed by upper GI series, with an average of 10.3 sponge exchanges over an average of 50 d[95]. The satisfactory results of EVT in the management of post-LSG leaks was confirmed in other reports[30,96]. However, in contrast to those results, one report demonstrated a case in which the EVT failed to heal a staple line leak after a revisional bariatric surgery (adjustable gastric band to LSG)[97].

In terms of the RYGB subgroup, one group performed a study in a porcine model, performing 10 RYGB. The gastrojejunal anastomoses were fashioned, and a 2 cm defect was created across the staple line. Seven of the ten pigs received EVT and three were included in the control group that did not receive any therapy. All porcine treated with EVT had complete healing of the defect and all control porcines had persistent leak, demonstrating that EVT can be effective in the management of gastrojejunal anastomotic leaks[98]. In humans, while there is limited data for the use of EVT for gastrojejunal leaks, one case report demonstrated the successful use of EVT in the treatment of a post-RYGB leak which had failed prior endoscopic attempt with CSEMS[99]. Additionally, a case report[56] showed a complete reperfusion and epithelization of an ischemic blind jejunal loop after RYGB with EVT management.

Small bowel and biliopancreatic defects

There are several reports of the use of EVT in the management of duodenal wall defects[100-103], including leaks and perforation[29,64,100-103]. Depending on the location of the defect, the sponge system can be placed either *via* nasal/oral or *via* percutaneous stoma, such as gastrostomy and jejunostomy, in cases where the defect is located distal to the duodenum[92,100,104].

The use of EVT has been successfully reported in treatment of duodenal iatrogenic perforations during endoscopic procedures such as ERCP[100] and post argon plasma coagulation, after endoscopic mucosal resection of an adenocarcinoma[102], and in the management of post-surgical complications[29,101,102].

The successful use of EVT has also been reported in the management of post-surgical duodenal leaks[64,103]. Loske *et al*[64] reported the treatment of a duodenal leak with EVT using the pull-through technique along an intestinal-cutaneous fistula. In this case, the sponge was placed in the internal opening of the duodenal fistula. The EVT application resulted in closure of the defect next to the tube and internal drainage of the GI/pancreatobiliary secretions, immediately stopping external drainage. After 3 sponge exchanges over the course of 14 d, the EVT was removed, and at 3-mo follow-up, the defect was completed healed.

The use of EVT has also been reported in the treatment of biliopancreatic conditions including infected pancreatic fluid collections and post-pancreatic surgery[32,66,105-107]. Several case reports[66,105,106] have described the successful multi-step use of EVT in infected pancreatic collections. First, an endoscopic drainage with stent is performed. Then, after at least 1 wk, the stent is removed, followed by dilation of the tract and placement of the EVT system. However, despite the favorable results of EVT in the management of pancreatic fluid collections shown in these reports, there is a theoretical risk of massive hemorrhage when performing this technique in the region of the celiac trunk and portal venous system[66]. Due to this risk, we recommend endoscopic drainage with stents as a first approach and EVT as a rescue therapy in selected cases[108-110].

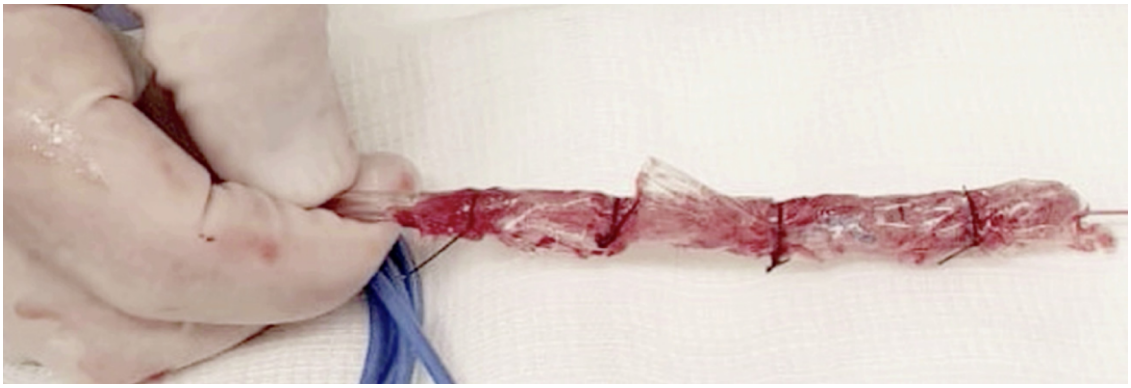

Figure 4 A low cost modified endoscopic vacuum therapy drain system made with a gauze coated with perforated sterile plastic.

EVT has also been described in the management of complications after biliopancreatic surgery[32,106,107]. Loske *et al*[107] described the treatment of a dehiscence of the biliojejunal and pancreaticojejunal anastomoses with EVT in a patient with a previous gastroenterostomy. A separate report[106] showed the feasibility and efficacy of EVT using a long sponge (12 cm in length) placed in the stomach for the treatment of a pancreatic-gastric anastomosis dehiscence. Additionally, a third case report demonstrated the successful use of EVT with a two-sided sponge using the pull-through technique in the treatment of a pancreaticgastrostomy[32].

Lower GI defects

Anastomotic leak is the most significant adverse event after colorectal surgery, with a range of occurrence between 1.5% to 23%, and is considered the major cause of postoperative morbidity and mortality[111,112]. The best approach for the treatment of anastomotic leaks has not been identified yet, especially in lower anastomoses[113]. The management decision in this population must be based on the clinical condition of the patient, including operative intervention for unstable patients (*i.e.*, those with peritonitis), and more conservative modalities for stable patients[111,112].

Endoscopic modalities, including stents, fibrin glue, clips, cap mounted clips, and double pigtail catheter drainage show variable success in the management of lower GI defects[112-117]. In 2003, Weidenhagen *et al*[25] described the first use of EVT in the lower GI tract for sepsis control caused by an anastomotic leak after a rectal surgery, showing a successful outcome. After this favorable report, the use of EVT in the management of lower GI defects increased and several studies were published showing a high efficacy and safety profile[113,118-120].

The first study evaluating EVT in the treatment of anastomotic leak after low anterior resection (LAR)[113] included 29 patients and showed 90.3% successful closure with a mean of 11.4 ± 6.3 sponge exchanges and a duration of 34.4 ± 19.4 d. In this study, most of patients had a protected stoma created at the primary surgery. In a retrospective study[118] including anastomotic leak after rectal resection, Hartmann's stump insufficiency, and rectal perforation, EVT demonstrated an 83% closure rate overall. For those patients with anastomotic leak, the closure rate success was 90%, similar to several other studies[121-123]. The German multicenter study[120] using EVT in the treatment of anastomotic leakage after colorectal surgery, including patients with rectal cancer and ulcerative colitis, analyzed the use of EVT after anastomotic leakage after colorectal surgery in two groups. One group were those patients whom underwent treatment within 6 wk post-operatively and the second group after 6 wk post-operatively. Patients whom underwent the procedure within 6 wk post-surgery had a higher closure rate (75% *vs* 38%). In this study, closure was achieved in a median of 40 d with a mean of 13 sponge exchanges.

One concern in the use of EVT in lower GI tract is that the feces may block the vacuum system, and thus, in some centers, physicians limit the use of EVT to those patients with fecal diversions. However, several studies have included patients without fecal diversion, and have shown efficacy of the method, suggesting that the lack of fecal diversion is not an exclusion criteria for EVT[119,124-127]. A study comparing the use of EVT in patients with and without stoma is needed to confirm this hypothesis.

Recently, a systematic review[112] including 14 studies (case series and cohort studies) with a total of 197 patients with anastomotic leakage treated with EVT showed an overall successful closure rate of 88.8%, with very low rates of adverse events.

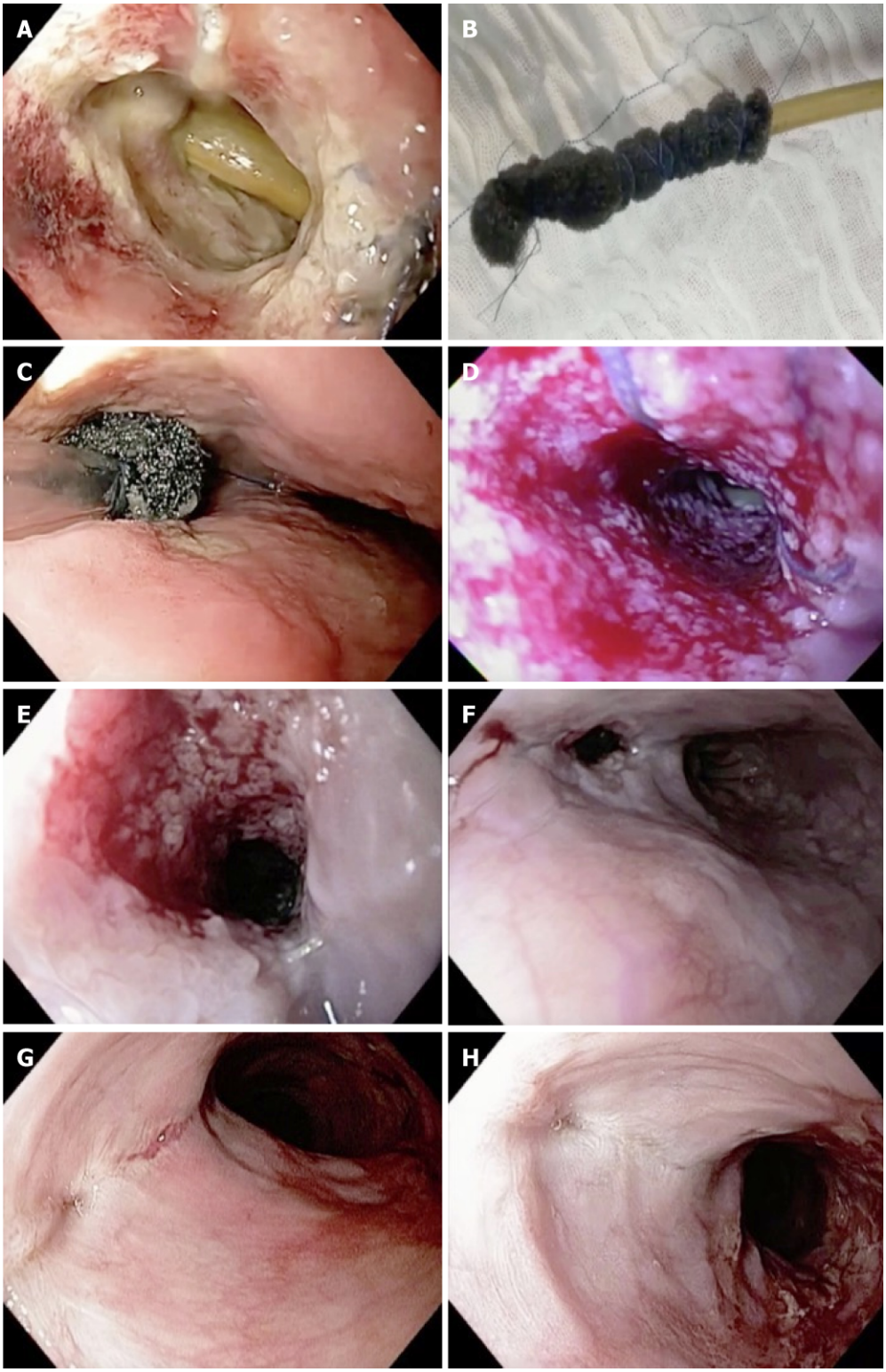

Figure 5 Endoscopic vacuum therapy in the management of an esophageal defect. A: Complete dehiscence of the esophageal leak and the mediastinal drainage; B: Open-pore polyurethane foam drain; C: Intracavitary sponge placement; D: Granulation tissue after second sponge exchange; E: Granulation tissue after fourth sponge exchange; F: Reduction of the defect size after seven sponge exchanges; G: Complete closure after nine sponge exchanges; H: Scar after esophageal closure with endoscopic vacuum therapy.

SAFETY

In general, EVT is a safe procedure with a low rate of adverse events. The most common complaint from patients during EVT treatment is related to the NGT, as this can cause significant patient discomfort, including pain, nausea, and emesis, especially in those patients with an additional nasoenteral tube. Additionally, patients have reported distress over having to undergo numerous repeat procedures for

sponge exchanges[26,51,62].

The most frequent adverse events are sponge dislocation, minor bleeding after sponge exchange due to ingrowth of granulation tissue into the sponge, and anastomotic strictures. However, major bleeding events have also been reported[26,51,60,62].

One major concern regarding EVT in the upper GI tract is the risk of major bleeding, due to the risk of development of a fistula between the cavity and the aorta (or aortic branches), as well as formation and rupture of pseudoaneurysm involving vessels or heart chambers due to the ongoing inflammatory process of EVT[51,62]. Unfortunately, several studies have reported major bleeding events. A prospective study[26] including 52 patients with upper GI defects treated with EVT reported 4.1% minor adverse events, including sponge dislocations and minor bleeding after sponge removal. Minor bleeding was usually self-limited and more frequent sponge exchanges could potentially mitigate this risk.

However, more notably, in this study, two patients died due to major bleeding related to EVT. One patient died from acute hemorrhage 56 d after initial EVT placement. The other patient died 12 d after initial EVT placement due to a non-manageable hemorrhage after sponge removal during the third sponge exchange. In this case, authors believe that a rupture of the descending aorta occurred. In a case series[60] including 5 patients that were successfully treated with EVT, two anastomotic strictures were reported. In both cases dilation with bougies were performed. One of these patients had two dilations without adverse events. The other patient had severe bleeding after dilation and unfortunately died, with cause of death on autopsy being identified as an aortoesophageal fistula leading to hemorrhagic shock. In a retrospective study[62] including 21 patients, two bleeding events (10%) were reported. One bleeding event occurred from the pancreas during treatment of a posterior gastric perforation and the other bleeding event occurred from an aortic branch during treatment of an esophageal anastomotic leak. In these two cases, fresh blood was seen in the EVT output fluid and the EVT was terminated immediately. Both patients underwent surgery for aortic stenting.

Based on these major bleeding reports, if a significant bleed occurs during treatment, EVT should be stopped and a triple-phase CT performed to direct possible management. Additionally, the CT scan should be reviewed prior to starting EVT in the upper GI tract to exclude vascular issues.

CONCLUSION

EVT is a new option in the management of GI transmural defects. EVT use has been increasing and appears to be effective in the treatment of this condition as a first line therapy, as well as a salvage procedure when other options have failed. The most experience with EVT is in the treatment of esophageal transmural defects, showing better results than any other therapy. However, due to the major bleeding risks associated with this technique, patients should undergo this procedure in experienced centers and be monitored closely for adverse events.

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World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2019 May 16; 11(5): 345-353

DOI: 10.4253/wjge.v11.i5.345

ISSN 1948-5190 (online)

MINIREVIEWS

Endoscopic ultrasound-guided biliary drainage: A change in paradigm?

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Author contributions: Both EL Leung Ki and Napopleon B contributed to the writing, editing, and final approval of the manuscript.

Conflict-of-interest statement: Dr En-Ling Leung Ki EL declares no conflicts of interest. Dr Bertrand Napoleon declares educational fees and non-financial support from Boston Scientific, educational fees from Maunakea Technology, educational fees from Ipsen Pharma, educational fees from Cousin Endosurg, educational fees and non-financial support from Olympus, outside the submitted work.

Manuscript source: Invited manuscript

Received: March 18, 2019
Peer-review started: March 20, 2019

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Abstract

Endoscopic ultrasound-guided biliary drainage (EUS-BD) has been developed as an alternative means of biliary drainage for malignant biliary obstruction (MBO). Compared to percutaneous transhepatic biliary drainage, EUS-BD offers effective internal drainage in a single session in the event of failed endoscopic retrograde cholangiopancreatography and has fewer adverse events (AE). In choosing which technique to use for EUS-BD, a combination of factors appears to be important in decision-making; technical expertise, the risk of AE, and anatomy. With the advent of novel all-in-one EUS-BD specific devices enabling simpler and safer techniques, as well as the growing experience and training of endosonographers, EUS-BD may potentially become a first-line technique in biliary drainage for MBO.

Key words: Endoscopic ultrasound-guided biliary drainage; Endoscopic ultrasound-guided choledochoduodenostomy; Endoscopic ultrasound-guided hepaticogastrostomy; Lumen-apposing metal stents; Electrocautery-enhanced lumen-apposing metal stents

Core tip: Endoscopic ultrasound-guided biliary drainage (EUS-BD) has been developed as an alternative means of biliary drainage for malignant biliary obstruction. EUS-BD must replace percutaneous transhepatic biliary drainage as the salvage procedure of choice in failed endoscopic retrograde cholangiopancreatography when endoscopic expertise is available. The advent of novel all-in-one EUS-BD specific devices, as well as the growing experience and training of endosonographers are promising for the development of EUS-BD as a first-line technique.

Citation: Leung Ki EL, Napoleon B. Endoscopic ultrasound-guided biliary drainage: A change

First decision: May 8, 2019
Revised: May 11, 2019
Accepted: May 13, 2019
Article in press: May 14, 2019
Published online: May 16, 2019

P-Reviewer: Yakoot M
S-Editor: Dou Y
L-Editor: A
E-Editor: Xing YX

in paradigm? *World J Gastrointest Endosc* 2019; 11(5): 345-353
URL: https://www.wjgnet.com/1948-5190/full/v11/i5/345.htm
DOI: https://dx.doi.org/10.4253/wjge.v11.i5.345

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is the current first-line approach for drainage of malignant biliary obstruction (MBO)[1-3]. Although success rate is high, difficult cannulation or access due to surgically altered anatomy, prior duodenal obstruction or stenting, periampullary diverticulum, and large tumors account for a failure rate of 5%-10%[1-3].

Percutaneous transhepatic biliary drainage (PTBD) is the conventional salvage procedures for failed ERCP. However, it is associated with significant morbidity, discomfort, and re-interventions[1-3].

ERCP and PTBD have proven their usefulness over 40 years of experience. Since the first report by Giovannini *et al*[4] in 2001, endoscopic ultrasound-guided biliary drainage (EUS-BD) has been developed as an alternative means of biliary drainage. Several methods have been described. Rendez-vous technique and antegrade stenting (AGS) are alternative means to achieve trans-papillary drainage. However, choledocoduodenostomy (EUS-CBD), and hepaticogastrostomy (EUS-HGS) are newer approaches which achieve extra-papillary drainage by trans-mural stenting.

Initially, EUS-BD was considered an advanced technique performed by experts in referral centers. Significant morbidity limited its indications despite its efficacy.

The last published guidelines accept the following indications for EUS-BD drainage[1-3,5]: (A) failed ERCP performed by a referral center with high expertise; (B) altered anatomy or malignant obstruction precluding papillary access; (C) failed cannulation due to occluding tumor; and (D) contraindication to percutaneous access such as large volume ascites.

Expert consensus and guidelines agree that specialized pancreaticobiliary endoscopists should perform EUS-BD[1-3,5]. Surgical and interventional radiology back up must be available due to potential severe adverse events (AE).

With the growing experience in EUS-BD and new EUS specific tools, overall improvement in efficacy, and safety are apparent. A growing body of evidence suggests that EUS-BD may not only be feasible as salvage to failed ERCP but also as a first-line technique for biliary drainage in MBO[6]. Compared to ERCP it confers two important theoretical advantages: (1) it avoids papillary trauma and subsequent risk of pancreatitis; and (2) it does not traverse the malignant stricture hence reducing the risk of tumor ingrowth that ultimately leads to stent dysfunction and re-intervention.

Our review aims to present the evolving data on EUS-BD that could potentially change the current algorithm by making it the first-line technique for biliary drainage. As data in benign conditions remains scarce and its role is uncertain[7], we will focus on extra-papillary drainage in MBO.

TECHNIQUES, EFFICACY AND ADVERSE EVENTS OF EUS-BD

Techniques and material

EUS-BD can be performed through intra-hepatic (transgastric-transhepatic) or extra-hepatic (transenteric-transcholedochal) approaches. For the intrahepatic route, the echoendoscope is positioned in the distal esophagus, gastric cardia or lesser curvature, which enables left intra-hepatic access. For the extra-hepatic route, the echoendoscope is frequently positioned in the duodenal bulb and sometimes the pre-pyloric antrum.

Until recently, EUS-BD was performed using devices borrowed from ERCP. It was first demonstrated using a plastic stent for EUD-choledocoduodenostomy (EUS-CDS)[4]. Plastic stents present the risk of bile leak, bile peritonitis, and occlusion[1,2,5]. SEMS have largely superseded them. Partially covered (PC) and fully covered (FC) SEMS are preferred over uncovered (UC) SEMS to prevent bile leak [1-2], however, conventional designs still lack anti-migratory property.

Device-related shortcomings have led to the development of specifically designed EUS-BD stents including lumen-apposing metal stents (LAMS), hybrid metal stents (distal covered and proximal UC portions with anti-migratory properties), and one-

step dedicated devices with pre-mounted hybrid stents[8].

The most data and extensive experience are on LAMS. LAMS are a recently developed, revolutionary device, designed for EUS trans-luminal drainage[9]. They are short dumbbell-shaped FC metallic stents with wide flanges to allow anchoring across non-adherent structures (Figure 1). LAMS were initially designed for drainage of pancreatic fluid collections. Indications have expanded to EUS-CDS for distal MBO. The newer version of dedicated LAMS have integrated an electrocautery-enhanced delivery system (ECE-LAMS) to allow puncture and release of the stent in a single step procedure hence decreasing the number of accessory exchanges, and reducing the potential of complications[10-12]. There are several different LAMS available with different lengths and diameters. The AXIOS stent with diameters of 6 and 8 mm and saddle length of 8 mm is custom designed for EUS-CDS.

Efficacy and AE

Four meta-analyses reported a technical success rate of EUS-BD of 90%-94.7%, clinical success rate of 87%-94%, and AE rate of 16%-29%[7,13-15]. MBO was the most frequent indication.

AE of EUS-BD depend on the route, the device used, type and extent of disease and operator experience. Overall AE rate for EUS-BD is 16.5%-23.3%[7,13,14]. The most frequent AE are bleeding, bile leak, pneumo-peritoneum, cholangitis, stent migration, abdominal pain, and peritonitis. Although these complications are often self-limited and can be treated conservatively or with endoscopic re-intervention, some complications such as stent migration into the peritoneal cavity may be fatal[8].

In EUS-CDS, the most frequent complications are pneumo-peritoneum and biliary leak predominantly occurring with plastic or UCSEMS[16]. In EUS-HGS, needle puncture into the peritoneal cavity increases the risk of pneumo-peritoneum and bile leak. Smaller intra-hepatic duct caliber precluding the placement of a wider metallic stent may also predispose to these complications due to incomplete sealing of the bilio-enteric fistula. Finally, the movement of the liver during respiration may lead to stent migration, resulting in biliomas and trauma to the bilio-enteric tract.

AE progressively decrease as experience grows and with the development of new stents. In a more recent prospective international multicenter study on efficacy and safety of EUS-BD, by Khashab *et al*[17] (n = 96), 10.5% (10/96) AE occurred: 2 pneumo-peritoneum, 1 sheared wire, 1 bleeding, 3 bile leaks, 2 cholangitis, and 1 perforation. 4 AE were graded mild, 4 were moderate, 1 was severe, and 1 was fatal due to unintended perforation. 91.3% of inserted stents were SEMS (44 FC, 26 PC, 14 UC) as oppose to plastic stents. The necessity for track dilation with the use of plastic stents or SEMS was a likely predisposing factor for bile or air leakage.

The advent of LAMS for EUS-CDS confers the theoretical advantage of decreasing migration and bile leak. ECE-LAMS also removes the need for tract dilation, and numerous guide-wire exchanges, potentially reducing complications. Data on LAMS show excellent efficiency and safety profile in short series[6]. Two larger trials have been published for the use of LAMS in distal MBO: (1) A multicenter, retrospective study by Kunda *et al*[10] (n = 57) showed that EUS-CDS with LAMS or ECE-LAMS, had a technical success rate of 98.2% (56/57) and clinical success rate of 94.7% (54/57). Mean procedure time was 22.4 min. Overall AE rate was 7% with 2 duodenal perforations, 1 bleed, and 1 transient cholangitis. During follow-up, 9.3% (5/54) with clinical success required re-intervention for 1 stent migration and 4 sump syndromes; (2) A recent multicenter, retrospective study by Jacques *et al*[11] (n = 52), showed that EUS-CDS with ECE-LAMS had a technical success of 88.5% (46/52), and clinical success rate of 100% (46/46). Mean procedure time was 10.2 min. 3.8% (2/46) patients presented short-term complications (1 bleed and 1 cholangitis due to obstructive bezoar). Long-term AE were 13.5% including 6 (11.5%), recurrent jaundice due to 4 tumor obstructions and 2 sump-syndromes. One patient experienced stent migration at 6 wk. In univariate analyses, a small common bile duct diameter and not following the recommended procedure technique were significant risk factors for technical failure. Median survival time without biliary complications was 135 d. Interestingly, expert and non-experts performed the procedure however no difference in technical or clinical success was found in the two groups. Finally, 2 patients underwent pancreaticoduodenectomy with no interference of the stent on the procedure.

Choice of EUS-BD technique

Currently, there is no established consensus for the choice of EUS-BD technique, and data remains conflicting[1,7,18]. Subgroup analyses from 2 meta-analyses compared extra-hepatic and intra-hepatic routes for EUS-BD[7,13]. Technical and clinical success rates were similar although AE were less frequent with the extra-hepatic compared to the intra-hepatic approach (OR = 0.40, 95%CI: 0.18-0.87, P = 0.022)[13]. A multicenter retrospective study by Dhir *et al*[18] compared success and complication rates in

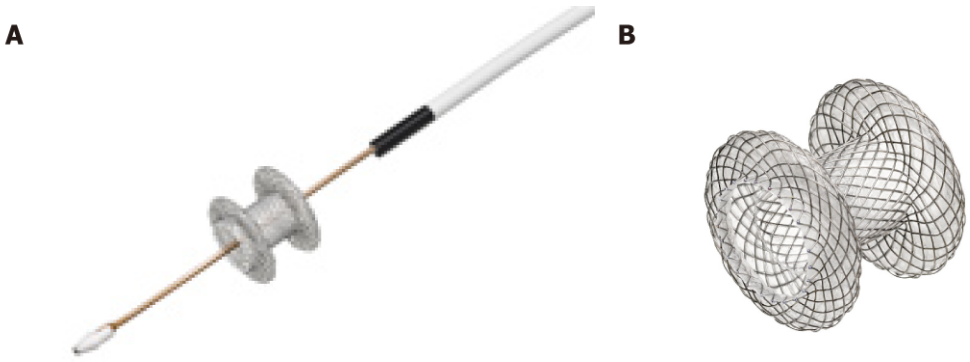

Figure 1 Hot AXIOS deployed. Image provided courtesy of Boston Scientific. ©2019 Boston Scientific Corporation or its affiliates. All rights reserved. With permission.

patients undergoing EUS-BD *via* different methods. This study showed that success rates of different techniques were comparable, but that AE rates were higher for trans-hepatic *vs* trans-duodenal route (30.5% *vs* 9.3%, $P = 0.03$). A systematic review by Alvarez-Sanchez *et al*[16] also showed that AE rates were higher for intra-hepatic (18%) compared to the extra-hepatic (14%) approach. On the other hand, a systematic review and meta-analysis by Uemura *et al*[19] of 10 studies ($n = 434$), concluded that EUS-HGS and EUS-CDS had equal efficacy and safety.

In summary, AE in EUS-BD are non-negligible. The more recent data shows an overall lower rate of AE in EUS-BD compared to older publications, which could reflect increasing experience and the development of EUS-BD specific devices.

In choosing which technique to use for EUS-BD, a combination of factors appears to be important in decision making; technical expertise, the risk of AE, and anatomy[12]. It is also generally admitted that EUS-HGS is technically more challenging than EUS-CDS. In general, in patients with distal common bile duct obstruction and adequate duct dilatation, the trans-duodenal and trans-hepatic approaches for EUS-BD have similar efficacy, but extra-hepatic route may be a safer option. Future trials will probably rapidly confirm that LAMS specifically designed for EUS-CDS further reduce complications of this route of drainage and simplify the technique. Hence EUS-HGS will probably be reserved to patients where EUS-CDS is not possible.

COMPARISON EUS-BD WITH PTBD

PTBD has a high success rate (87%-100%). However, the external drainage catheter causes discomfort to the patient, and AE are non-negligible, reaching 30%, including pneumothorax, bleeding bile leak, and infection. PTBD is also contraindicated in the presence of ascites or multiple liver metastases[20-23]. EUS-BD offers drainage in a single session in the event of failed ERCP; provides internal drainage with less physical discomfort; allows better nutritional absorption; and avoids electrolyte loss.

The result of randomized controlled trials and meta-analyses comparing EUS-BD to PTBD after failed ERCP show comparable technical and clinical success of 90%-100% with higher complication rates in PTBD[20-23]. Sharaiha *et al*[23] performed a systematic review and meta-analysis of 9 studies ($n = 483$), which showed no difference in technical success between EUS-BD and PTBD (OR = 1.78, 95%CI: 0.69-4.59, $I2 = 22\%$) after failed ERCP. EUS-BD was associated with better clinical success (OR = 0.45, 95%CI: 0.23-0.89, $I2 = 0\%$), fewer post-procedure AE (OR = 0.23, 95%CI: 0.12-0.47, $I2 = 57\%$), and lower re-intervention (OR = 0.13, 95%CI: 0.7-0.24, $I2 = 0\%$). There was no difference in length of hospital stay with a pooled standard mean difference of -0.48 (95%CI: -1.13-0.16). EUS-BD was more cost-effective.

An interesting multicenter survey by Nam *et al*[24] ($n = 313$) examined patient perception and preference of EUS-BD and PTBD. After explaining the procedure and AE, patients were asked to choose between 2 simulated scenarios. 80.2% of patients preferred EUS-BD. EUS-BD preference declined as AE increased. The authors concluded that technical innovation and improved proficiency to reduce complications of EUS-BD would increase patient acceptability.

In summary EUS-BD must replace PTBD as the standard procedure of choice in failed ERCP in high volume centers with skilled pancreaticobiliary endoscopists.

COMPARISON OF EUS-BD AND ERCP IN DISTAL MBO

Only 6 very recent studies have compared EUS-BD to ERCP[25-30]. These studies were performed in patients with distal MBO and used PC or FC-SEMS for EUS-BD. All 6 trials included patients treated by EUS-CDS, and of this one trial also used EUS-AGS and another EUS-HGS. We hereby discuss the available data, also summarized in Table 1.

Three trials compared a group of patients with EUS-CDS +/- EUS-AGS to a retrospective ERCP control group:

A single-center retrospective study by Kawakubo *et al*[25] (n = 82) comparing the clinical efficacy and safety of EUS-CDS (PCSEMS) *vs* ERCP (PC or FCSEMS) showed that clinical success rates were equivalent between the groups (EUS-CDS 96.2%, ERCP 98.2%; P = 0.54). Mean procedure time was significantly shorter with EUS-CDS than ERCP (19.7 *vs* 30.2 min; P < 0.01). Overall AE were not significantly different between the groups (EUS-CDS 26.9%, ERCP 35.7%; P = 0.46). Post-procedure pancreatitis was only seen with ERCP (0% *vs* 16.1%; P = 0.03). Re-intervention rate at 1 year was not significantly different (16.6% *vs* 13.6%, P = 0.5).

A multicenter, retrospective analysis by Dhir *et al*[26] (n = 208) compared the outcomes of EUS-BD *vs* ERCP. Patients in the EUS-BD group underwent EUS-CDS or EUS-AGS with FCSEMS or UCSEMS respectively after 1 or more failed ERCP attempts. Patients in the ERCP group underwent retrograde SEMS placement. In the ERCP and EUS-BD groups respectively; technical success was 94.23% *vs* 93.26%, P = 1; AE were 4.8% *vs* 0%, P = 0.06; and mean procedure time was 30.1 *vs* 35.95 min, P = 0.05.

Nakai *et al*[27] performed a multicenter prospective study (n = 34) evaluating EUS-CDS (PC or FC-SEMS) *vs* ERCP (PC or FC-SEMS). For EUS-CDS, technical success rate was 97% and functional success rate 100%, with median procedure time of 25 min. Overall AE were 15% (5/34); 2 with mild abdominal pain and 3 with moderate cholecystitis. Rate of recurrent biliary obstruction (RBO) was 29% (10/34) and non-tumor related. Migration occurred in 6, sludge or food impaction in 3, and stent impaction in duodenal wall in 1. Median time to RBO was 11.3 months. In comparison to the ERCP control group, the rate of RBO and cumulative time to RBO of EUS-CDS was comparable to ERCP, which were 36% and 9.1 months respectively. ERCP procedure time was significantly longer (median of 52 min, P < 0.01), and AE rate were comparable.

Three randomized trials compared EUS-CDS +/- HGS to ERCP.

Park *et al*[28] performed a prospective randomized controlled study comparing efficacy and safety of EUS-CDS (n = 15) *vs* ERCP (n = 15). Both arms used the same PCSEMS. 27 had unresectable pancreatic ductal adenocarcinoma, 1 had distal biliary cancer, and 2 patients had metastatic malignant lymphadenopathy. There were no significant differences for both arms in terms of technical, and clinical success rates (100% *vs* 93%, P = 1.00 and 93% *vs* 100%, P = 1.00 respectively). 4 patients (31%) had tumor ingrowth causing stent dysfunction in the ERCP group. 2 patients had food impaction and 2 patients had stent migration in the EUS-CDS group. There were no significant procedure-related AE in either group. The authors concluded that EUS-CDS and ERCP had similar safety and that EUS-CDS was not superior to ERCP in terms of relieving MBO. EUS-CDS had fewer cases of tumor ingrowth but more cases of food impaction and stent migration.

Bang *et al*[29] performed a single center, single-blind, randomized trial to compare EUS-CDS (n = 33) *vs* ERCP (n = 34) as primary treatment for distal biliary obstruction from pancreatic cancer. Both arms used the same FCSEMS. The primary endpoint was the rate of AE for EUS-CDS compared to ERCP, which was not significantly different (21.2% *vs* 14.7% respectively, risk ratio 0.69, 95%CI: 0.24-1.07, P = 0.49). Moderate AE in both groups were around 6%, with no severe AE or procedure-related deaths. For secondary endpoints there were no significant differences between EUS-CDS and ERCP in the rates of technical success (90.9% *vs* 94.1%, P = 0.67), treatment success (97% *vs* 91.2%, P = 0.61), or re-interventions (3.0% *vs* 2.9%, P = 0.99). EUS-CDS did not impede subsequent pancreaticoduodenectomy that was performed in 5/33 (15.2%) of these patients and in 5/34 (14.7%) in the ERCP group (P = 0.99). Median procedure time was similar for EUS-CDS and ERCP (25 min *vs* 21 min respectively, P = 0.178).

In a larger multicenter randomized non-inferiority study by Paik *et al*[30] (n = 125) EUS-BD (EUS-CDS, and EUS-HGS) was compared to ERCP in palliative drainage of distal MBO. In the EUS-BD group a dedicated hybrid PCSEMS pre-mounted on a one-step delivery device was used, whereas in the ERCP group either a PC or FCSEMS was used. Technical success rates were 93.8% *vs* 90.2% (P = 0.003), and clinical success rates 90% *vs* 94.5% (P = 0.49) for EUS-BD and ERCP respectively. EUS-BD had lower rates of overall AE (6.3% *vs* 19.7% P = 0.03) including post-procedure pancreatitis (0 *vs* 14.8%), and re-intervention (15.6% *vs* 42.6%). EUS-BD had higher rates of stent

Table 1 Summary of trials comparing Endoscopic ultrasound-guided biliary drainage to endoscopic retrograde cholangiopancreatography in distal malignant biliary obstruction

Authors	Yr	Study type patients (*n*)	Type of EUS-BD/ stent used	Technical success (%) EUS-BD/ERCP (*P*-value)	Functional or clinical success (%) EUS-BD/ERCP (*P*-value)	Procedure time (min) BD/ERCP (*P*-value)	AE (%) BD/ERCP (*P*-value); PPP (%) EUS-BD/ERCP (*P*-value)	Stent dysfunction (%)EUS-BD/ERCP (*P*-value)	Re-intervention (%) EUS-BD/ERCP (*P*-value)
Kawakubo *et al*[25]	2016	Single center, retrospective cohort study (82)	EUS-CDS/ PCSEMS	-	96.2/98.2 (0.54)	Mean 19.7/30.2 (0.01)	26.9/35.7 (0.46); 0/16.1 (0.50)	-	20/12.7 (0.50)
Dhir *et al*[26]	2015	Multicenter, retrospective (208)	EUS-CDS + EUS-HGS/ FC +UCSEMS	93.26/94.23 (1.00)	89.42/91.34 (0.814)	Median 35.95/30.1 (0.05)	8.65/8.65 (1.00); 0/4.8 (0.59)	-	-
Nakai *et al*[27]	2018	Multicenter, prospective (34)	EUS-CDS/ PC + FCSEMS	97	100	Median 25/52 (0.01)	15/24	29/36 (0.78)	-
Park *et al*[28]	2018	Single center, prospective, RCT (30)	EUS-CDS/ PCSEMS	92.8/100 (1.00)	92.8/100 (1.00)	Median 43/31 (0.2)	0/0 (1.00)	15.4/30.8 (0.65)	-
Bang *et al*[29]	2018	Single center, prospective, RCT (67)	EUS-CDS/ FCSEMS	90.9/94.1 (0.67)	97/91.2 (0.61)	Median 25/21 (0.173)	21.2/14.7 (0.49)	1/1 (0.97)	3/2.9 (0.99)
Paik *et al*[30]	2018	Multicenter, prospective RCT (125)	Distal MBO/ EUS-CDS, EUS-HGS/hybrid PCSEMS	93.8/90.2 (0.003 for non-inferiority margin 10%)	90/94.5 (0.49)	Median 5/11 (0.01)	Early AE 6.3/19.7 (0.03); 0/14.8 (0.001)	-	15.6/42.6 (0.001) (stent patency 85.1 *vs* 48.9, *P* = 0.001)

EUS-BD: Endoscopic ultrasound-guided biliary drainage; EUS-CDS: EUS-guided choledocoduodenostomy; EUS-HGS: EUS-guided hepaticogastrostomy; AE: Adverse events; PPP: Post procedural pancreatitis; SEMS: Self-expandable metal stents; FCSEMS: Fully-covered SEMS; PCSEMS: Partially-covered SEMS; UCSEMS: Uncovered SEMS; ERCP: endoscopic retrograde cholangiopancreatography.

patency (85.1% *vs* 48.9%). There was no difference in patency between EUS-CDS and EUS-HGS. Median procedure time was significantly shorter in EUS-BD 5 min (IQR 3-12) *vs* ERCP 11 min (IQR 7-18), $P < 0.001$. EUS-BD was associated with higher quality of life (QOL) compared to ERCP at 12 wk post procedure. This study had a notably higher rate of post ERCP pancreatitis and a lower rate of EUS-BD complications compared to other studies. The authors explained these discrepancies by the high number of complex papillary access, and the specific EUS-BD delivery devices used.

In summary, recent randomized studies suggest that EUS-CDS is an effective and safe alternative to ERCP that could reduce the re-intervention rate, and risk of pancreatitis without impeding potential curative surgery. Thus EUS-CDS is a practical route of drainage that should be considered in preoperative drainage.

COMPARISON OF EUS-HGS WITH ERCP IN PROXIMAL MBO

ERCP in non-operable hilar stenosis is more challenging than for distal MBO. Bilateral biliary drainage with placement of multiple metallic stent is often required in order to drain ≥ 50% of the liver volume[2,3,31]. The failure rate can reach 27%, with lower clinical response despite successful stent placement. EUS-HGS enables trans-luminal stenting of the left biliary tree without traversing the stricture. It can be combined with ERCP to drain both left and right hepatic ducts. When feasible, the right biliary ducts can also be accessed via EUS-HGS with bridge trans-hilar stenting[31].

Data on EUS-HGS for proximal MBO are limited[7,31], and there is no data comparing EUS-HGS to ERCP in this situation. Furthermore, except for a single-step delivery device only commercially available in Korea, most EUS-HGS specific stents still require a multi-step procedure for adequate positioning.

In summary, the development of new EUS-HGS specific tools, comparative studies between EUS-HGS and ERCP/PTBD, as well as standardization of procedures should be a future goal.

COMPARISON OF EUS-BD AND ERCP IN CASE OF PRIOR DUODENAL STENTING

Gastro-duodenal and biliary obstruction may occur in advanced pancreatic cancer, and double stenting may be required. ERCP is challenging in the presence of prior duodenal stent placement. Yamao *et al*[32] performed a multicenter retrospective study (n = 39) to evaluate the outcome of EUS-BD in pancreatic patients with an indwelling gastro-duodenal stent (GDS). This study showed that when a GDS overlay the papilla, EUS-BD technical and clinical success were higher than ERCP (95.2% *vs* 56 % $P < 0.01$, and 90.5% *vs* 52% $P = 0.01$ respectively). There was no significant difference in the incidence of AE. The authors concluded that EUS-BD could be a first-line technique for biliary drainage in patients who had a GDS overlying the papilla. In a case series by Anderloni *et al*[33], single session EUS-CDS with LAMS and duodenal stenting was performed. Results showed 100% technical success with no early or late complications. The short length and design of LAMS did not to interfere with duodenal stenting.

EUS-BD: A PARADIGM SHIFT?

Until recently, EUS-BD was reserved for cases of failed ERCP.

Current data suggests that in multi-disciplinary centers with endoscopic pancreatobiliary expertise EUS-BD is a viable alternative to ERCP and should be favored in cases of prior duodenal stenting. EUS-CDS appears to be a simpler and safer procedure than EUS-HGS, and should be favored when both techniques are possible.

Although recent randomized studies have shown that EUS-CDS is as effective as ERCP with longer stent patency, similar AE profile and reduced risk of pancreatitis precluding early surgery, they also show a higher than expected rate complications and failure of ERCP. In contrast, other studies show a meager failure rate of ERCP in expert hands. A prospective study by Holt *et al*[34] (n = 52) showed that ERCP had a high success rate, in particular when advanced techniques of cannulation were available; hence only 0.6% of native papilla having failed ERCP required EUS-BD. Another retrospective study by Ardengh *et al*[35] (n = 3538), also showed that the failure rate for ERCP was low, 0.68%. In light of the long experience and excellent results with ERCP, this technique should be difficult to replace despite the advantages of EUS-BD.

Nevertheless, the development of ECE-LAMS is a significant milestone in EUS-CDS. Growing data suggests it is an efficient and safe tool that reduces procedure time and AE. By virtue of its simple, all-in-one application, ECE-LAMS may reduce the risk of procedural complications such as biliary leakage. Selecting patients with a common bile duct dilation of at least 15 mm diameter, and distal MBO below mid common bile duct appear to be effective measures to reduce procedure-related complications[11,12]. Prospective multicenter, randomized studies are required to compare ECE-LAMS to ERCP in distal MBO. Based on current data it can be hypothesized that such studies would show a comparable efficiency of the two techniques, with reduced pancreatitis and prolonged stent patency in the ECE-LAMS group. Nonetheless, the requirement of EUS and ERCP training to perform EUS-CDS with ECE-LAMS should likely limit the applicability of this technique in a widespread manner. Data are lacking with regards to the learning curve for EUS-BD. A prospective study by Oh *et al*[36] (n = 129) showed that 33 procedures were required to reach a stabilization level in terms of AE and to reduce procedure time. Concerning ECE-LAMS a second follow-up study by Jacques and col[12] (n = 61) re-examined the efficacy of ECE-LAMS in distal MBO after a year of further experience. This study under abstract form showed 98.4% technical and clinical success, 1.6% procedure-related complication (1 bleed during fistulotomy which was self-limited with the expansion of the stent), 0% early complications. Thus, when experience with ECE-LAMS was acquired for EUS-CDS, this technique was effective and safe for biliary drainage.

Finally, concerning EUS-HGS as an alternative to ERCP, the development of effective all-in-one dedicated devices would reduce AE rates and make it an attractive means of drainage in particular for proximal MBO. Due to the complex nature or proximal MBO, it is likely that ERCP, and EUS-HGS will remain complementary in the future.

CONCLUSION

EUS-BD has enormous potential and has already replaced PTBD in salvage of failed ERCP in expert centers. Several challenges remain before it can fully represent a paradigm shift and replace standard biliary drainage techniques in a widespread manner. The advent of novel EUS-BD specific tools enabling simpler and safer techniques, as well as the growing experience and training of endosonographers, will undoubtedly push the frontiers of its application forward.

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World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2019 May 16; 11(5): 354-364

DOI: 10.4253/wjge.v11.i5.354

ISSN 1948-5190 (online)

MINIREVIEWS

Comprehensive review on EUS-guided biliary drainage

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Author contributions: All authors contributed equally to this manuscript.

Conflict-of-interest statement: All authors have no conflicts of interest to report.

Manuscript source: Invited manuscript

Received: March 15, 2019
Peer-review started: March 15, 2019
First decision: April 11, 2019
Revised: April 21, 2019
Accepted: May 1, 2019
Article in press: May 1, 2019
Published online: May 16, 2019

P-Reviewer: Kamimura K, Yeh HZ
S-Editor: Ji FF
L-Editor: Filipodia

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Abstract

Feasibility of endoscopic retrograde cholangiopancreatography (ERCP) for biliary drainage is not always applicable due to anatomical alterations or to inability to access the papilla. Percutaneous transhepatic biliary drainage has always been considered the only alternative for this indication. However, endoscopic ultrasonography-guided biliary drainage represents a valid option to replace percutaneous transhepatic biliary drainage when ERCP fails. According to the access site to the biliary tree, two kinds of approaches may be described: the intrahepatic and the extrahepatic. Endoscopic ultrasonography-guided rendezvous transpapillary drainage is performed where the second portion of the duodenum is easily reached but conventional ERCP fails. The recent introduction of self-expandable metal stents and lumen-apposing metal stents has improved this field. However, the role of the latter is still controversial. Echoendoscopic transmural biliary drainage can be challenging with potential severe adverse events. Therefore, trained endoscopists, in both ERCP and endoscopic ultrasonography are needed with surgical and radiological backup.

Key words: Endoscopic ultrasonography-guided biliary drainage; EUS; Percutaneous transhepatic biliary drainage; Endoscopic ultrasonography-guided hepatogastric anastomosis; Endoscopic ultrasonography-guided antegrade stent placement; Endoscopic ultrasonography-guided choledochoduodenostomy; Endoscopic ultrasonography-guided transgallbladder; Endoscopic ultrasonography-guided rendezvous

Core tip: Feasibility of endoscopic retrograde cholangiopancreatography for biliary

E-Editor: Xing YX

drainage is not always applicable due to anatomical alterations or to inability to access the papilla. Percutaneous transhepatic biliary drainage has always been considered the only alternative for this indication. Endoscopic ultrasonography-guided biliary drainage represents a valid option to replace the other two methods.

Citation: Salerno R, Davies SEC, Mezzina N, Ardizzone S. Comprehensive review on EUS-guided biliary drainage. *World J Gastrointest Endosc* 2019; 11(5): 354-364
URL: https://www.wjgnet.com/1948-5190/full/v11/i5/354.htm
DOI: https://dx.doi.org/10.4253/wjge.v11.i5.354

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) with stent placement represents standard treatment for the management of benign and malignant biliary obstructions. Approximately 500000 ERCPs are performed annually in the United States alone with a failure rate that varies between 5% and 7%[1]. ERCP-guided biliary drainage is performed by direct cannulation of the papilla under endoscopic vision *via* the duodenoscope with the assistance of radiological cholangiography. Once the biliary tract has been reached, the biliary drainage can be obtained with different devices and technique (with stent positioning) depending on the underlying disease. In light of this, the papilla must necessarily be endoscopically reachable. Therefore, reasons for failure depend mainly on whether the papilla is endoscopically accessible or not. In the first case, ampullary pathology, periampullary diverticulum, and ampullary neoplastic infiltration can cause failure. In the second case, benign (peptic stenosis) and malignant duodenal stenosis or postsurgical anatomy such as a gastrointestinal bariatric bypass, a Roux-en Y gastric bypass or a Billroth II gastroenterostomy may prevent the access to the papilla causing unsuccessful procedures (Table 1).

Until a few years ago, percutaneous transhepatic biliary drainage (PTBD) has been the only possible procedure in case of ERCP failure. PTBD involves the direct transhepatic puncture of the biliary system with consequent cholangiography and positioning of a drainage catheter. According to the literature, this procedure is associated with a morbidity rate up to 33%, including catheter dislocation, infection, bleeding, biliary leakages, acute cholangitis, and pneumothorax[2,3]. An alternative to PTBD is endoscopic ultrasonography-guided biliary drainage (EUS-BD). EUS-BD has several advantages such as internal drainage and a single procedure performed by the same operator without the discomfort of an external catheter. The feasibility of cholangiogram under endoscopic ultrasonography guidance was first reported in 1996 by Wiersema *et al*[4].

EUS-guided bilio-digestive anastomosis, first published by Giovanni *et al*[5] in 2001, is performed worldwide with reported cumulative technical success and post-procedure adverse events of 90% and 17%, respectively[6]. A recent systematic review and meta-analysis[7-15] by Sharaiha *et al*[12] included nine studies comparing the efficacy and safety of EUS-BD and PTBD[16]: three RCTs[7,11,15] and six retrospective studies[8-10,12-14]. All studies included patients undergoing EUS-BD in tertiary centers. One study[11] included both benign and malignant etiologies of biliary obstruction, whereas the remaining studies only included patients with malignant etiologies.

EUS-BD and PTBD showed equivalent technical success (OR: 1.78; 95%CI: 69-4.59; I^2 = 22%). However EUS-BD was associated with a better clinical success (OR: 0.45; 95%CI: 0.23-0.89; I^2 = 0%), less post-procedure adverse events (OR: 0.23; 95%CI: 0.12-047; I^2 = 57%), and lower reintervention rates (OR: 0.13; 95%CI: 0.07-0.24; I^2 = 0%). No significant differences were observed for the duration of hospital stay between EUS-BD and PTBD, but EUS-BD was more cost-effective.

TECHNIQUES

EUS-BD should be performed by experienced endoscopists who have performed at least 20 procedures under tutor supervision[17], and who are trained in both EUS and ERCP. Skilled staff is needed for guidewire manipulation, and carbon dioxide insufflation is compulsory to reduce the risk of pneumoperitoneum.

According to the access to the biliary tree, two approaches can be applied: the

Table 1 Current indications for endoscopic ultrasonography-guided biliary drainage after failure of endoscopic retrograde cholangiopancreatography in referral centers

Accessible papilla
Ampullary pathology
Periampullary diverticulum
Ampullary neoplastic infiltration
Non-accessible papilla
Peptic GI stenosis
Malignant GI strictures
Gastrointestinal bariatric bypass
Roux-en Y gastric by-pass
Billroth II gastroenterostomy

GI: Gastrointestinal.

intrahepatic approach [hepatogastric anastomosis (EUS-HGA) or antegrade stent placement] or the extrahepatic approach [choledochoduodenostomy (EUS-CDS) or transgallbladder (EUS-GBD)] (Figure 1).

EUS-guided rendezvous (EUS-RV) transpapillary drainage is performed where the second portion of the duodenum is easily accessible but conventional ERCP failed. In EUS-RV, the biliary duct is punctured by using a fine needle aspiration needle from the upper gastrointestinal tract under EUS guidance followed by guidewire placement into the duodenum through the needle. After exchanging the endoscope with the ERCP duodenoscope, biliary cannulation is then reattempted by using the EUS-placed guidewire.

The intrahepatic approach

Such approach is typically preferred in cases where the papilla is not endoscopically accessible due to gastric outlet obstruction, to an obstructing proximal duodenal tumor, or in patients with surgically altered anatomy. Dilatation of intrahepatic ducts is compulsory to perform this approach. Cancer infiltration of the gastric wall within the planned path of approach to the biliary ducts or massive ascites and coagulopathy are contraindications to this type of approach.

With the tip of the echoendoscope positioned along the lesser curvature of the stomach, the dilated left hepatic duct (segment III) can be correctly visualized. Transgastric needle (19-22 G) insertion into the left hepatic duct and contrast injection clearly show the biliary tree under fluoroscopy. The next step is to exchange the needle over a guidewire for a 6.5-Fr cystotome used to create the fistula between the stomach and the left hepatic duct with a cutting current. Either plastic stents or self-expandable metal stents (SEMS) are then positioned over the guidewire (hepatic-gastric stent) or advancing the guidewire across the stricture and the papilla to complete an antegrade stent placement.

This kind of technique is not actually standardized, and no pooled data is available comparing the efficacy of different devices. The choice of the needle is still in debate because some operators suggest the 19 G needle because the large diameter reduced the risk of shearing the guidewire coating during manipulation although the 19 G needle can be stiffer and more difficult to handle compared to a 22 G needle. Usually a hydrophilic guidewire is preferred because strictures can be crossed more easily. The 0.025-inch guidewire, which fits a 22 G needle, can help during manipulation maneuvers due to its flexibility. However, it can make the stent insertion challenging due to the lack of stiffness and the less stable scope position.

The optimal biliary access points and learning curves for technically successful EUS-HGA have been evaluated by Oh *et al*[18] in 129 consecutive patients who underwent EUS-HGA. For each EUS-HGA session the following measurements were taken: intrahepatic bile duct diameter at the point of puncture, the hepatic portion length and bile duct segment for each needle puncture attempt, and procedure times (from initial bile duct puncture to final transmural stenting).

In the logistic regression model, low technical success rates were related with intrahepatic bile duct diameter of puncture site ≤ 5 mm (OR: 3.7; 95%CI: 1.71–8.1; P < 0.01) and hepatic portion length > 3 cm (OR: 5.7; 95%CI: 2.7–12; P < 0.01). The learning curve for technical success was evaluated by measuring procedure time and adverse events by using the moving average method and cumulative sum analysis, respectively. Procedure times and adverse events were shorter after 24 cases had been

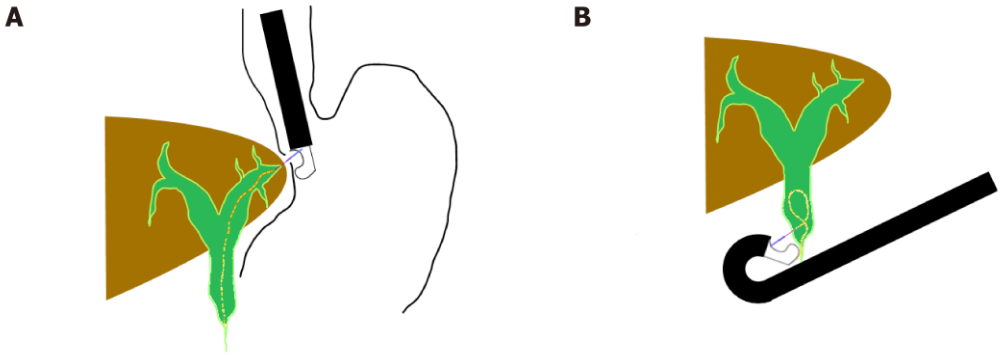

Figure 1 The access points of different endoscopic ultrasonography-guided biliary drainage procedures. A: The intrahepatic approach; B: The extrahepatic approach.

performed by the same operator and became stable at 33 cases of EUS-HGA.

These data suggest that a bile duct diameter > 5 mm and hepatic portion length 1 cm to ≤ 3 cm on EUS may guide the choice for the optimal site of puncture for successful EUS-HGA and that 33 cases of EUS-HGA are needed to achieve technical proficiency.

A crucial step for technical success is the creation of a fistula, which can potentially have an impact on complications such as biliary leakage, bilioperitoneum, or perforation. In order to insert the stent, the dilatation of the fistula is compulsory and can be performed by using balloon dilatators, stiff gradual catheters, needle knives, and cystotomes with cutting current. Advancing of stiff catheter may create tissue resistance forming a gap between the stomach and the liver with post-procedural biliary leak. Balloon dilatation also generates radial force, which is why some endoscopists prefer 6.5-Fr cystotomes. In a recent meta-analysis of EUS-BD technique, Wang *et al*[19] reported adverse event rates of 19.68% (49/249) with needle knife, 20.37% (44/216) with balloon catheter, and 38.46% (10/26) with cystotome.

The choice of the stent depends on the indication (benign *vs* malignant), the degree of ductal dilatation, whether the wire could cross the anastomosis, the length of fistula tract, and surgical indication for the patient[20]. In the first reported cases of HGA, plastic stents involved significant post-procedural biliary leakage. The use of fully covered self-expandable metal stents may cause side biliary duct obstruction, cholangitis, and significant stent migration. To prevent these complications, Giovannini *et al*[11] used the "stent-in-stent technique" with insertion of two metal stents: firstly, an uncovered metal 8-10 cm stent is placed to prevent migration and to occlude side biliary branch; secondly, a fully covered 6 cm stent is placed in the uncovered stent to prevent the biliary leakage. Recently, Song *et al*[21] reported no proximal or distal stent migration in any of the 27 patients who had undergone EUS-BD using a hybrid metal stent (Standard Sci Tech Inc, Seoul, South Korea) partially covered by SEMS (uncovered in the intrahepatic portion and covered in the transmural distal). SEMS are considered an interesting option compared to plastic stents due to a bigger caliber and longer patency especially when reintervention for stent substitution is not required.

The extrahepatic approach

The extrahepatic approach, including EUS-CDS and, when feasible, choledochoantrostomy, is usually performed in case of failure of selective cannulation of the common biliary duct because of ampullary neoplasm, neoplastic infiltration from pancreatic cancer, or when the access to the papilla is prevented by benign (peptic stenosis) or malignant duodenal stenosis. In all these cases, there is no consensus about the choice between the intrahepatic or the extrahepatic approach depending on the endoscopist's discretion and expertise. More recently some authors have described gallbladder drainage for biliary drainage in patients with distal biliary obstruction and patent cystic duct[22,23] meaning that this technique can be literally considered an extrahepatic approach.

The tip of the echoendoscope is advanced to the duodenal bulb or, when feasible, to the antrum wall where the dilated common biliary duct is closer to the wall. Likewise, in the extrahepatic approach technique, the access to the bile duct is achieved with a 19-gauge EUS needle with subsequent bile aspiration, 0.035-inch guidewire manipulation into the intrahepatic tree, dilatation of the fistula, and stent insertion. Because stent migration is the main post procedural complication, similarly to HGA,

some endoscopists prefer 4 cm or more, fully covered biliary metal stents. However, the use of these stents can make reintervention more difficult, and duodenal trauma and even perforation can be caused by the distal portion of the stent.

Clinical efficacy and safety of EUS-CDS *versus* endoscopic transpapillary stenting (ETS) as first-line treatment were tested by Kawakubo *et al*[24] in 82 patients with distal malignant biliary obstruction. The found equivalent clinical success rates (EUS-CDS 96.2%, ETS 98.2%; $P = 0.54$) and overall adverse event rates (EUS-CDS 26.9%, ETS 35.7%; $P = 0.46$). However, a shorter mean procedural time was found with EUS-CDS rather than with ETS (19.7 min *vs* 30.2 min; $P < 0.01$)[24]. These data were confirmed by Nakai *et al*[25] in a prospective multicenter study.

Lumen-apposing metal stents (LAMS) were first introduced to drain peripancreatic fluid collections, but recently they have been used for EUS-BD. The stent includes a full silicone covered, wider lumen and bigger flanges to prevent tissue ingrowth, provide fast drainage, reduce the risk of migration with biliary leakage, and allow removability. New cautery-enhanced delivery systems (Hot AXIOS device, Boston Scientific) are available allowing EUS-BD in one step with no need for prior needle puncture, guidewire insertion, or fluoroscopy. Biliary duct dilatation and a distance of no more than 10 mm are required to avoid stent migration, leakage, and pressure necrosis.

EUS-CDS using a LAMS was proposed as an alternative approach for patients with malignant obstructive jaundice and ERCP failure. Tsuchiya *et al*[26] evaluated prospectively the long-term outcome (median: 184 d; range: 12-819) in 19 patients undergoing EUS-CDS using a fully covered LAMS with a cautery-enhanced delivery system. Technical success was achieved in all patients and jaundice improvement in 95% of patients (18/19).

No intraprocedural adverse events were recorded, but the post procedure related adverse events ratio was 15.8% [3/19; acute cholangitis ($n = 2$) and fever ($n = 1$)]. Five patients had secondary stent obstruction because of food residue ($n = 2$), kinking ($n = 1$), suspected tumor ingrowth ($n = 1$), and spontaneous dislodgement ($n = 1$) with reintervention in four of these five patients. The authors suggested that food impaction and bile duct kinking were consequences of the small diameter of the LAMS (6-8 mm diameter could have shorter patency compared to 10 mm diameter) and of the absence of the spontaneous outflow of the bile after decompression. The efficacy of EUS-CDS using the LAMS was recently confirmed by Anderloni *et al*[27] in a retrospective analysis in 46 patients. They reported technical and clinical success rates of 93.5% and 97.7%, respectively. However, adverse events were found in five patients (11.6%) with one fatal bleeding 17 d after stent placement, three episodes of stent occlusion (food impaction), and one of spontaneous migration (all four required reintervention). Despite these encouraging results, the authors suggested a careful evaluation before using the stent in this clinical setting due to serious adverse events.

Recently, EUS-GBD was reported to be useful for acute cholecystitis in patients unfit for surgery. Jang *et al*[28] found that EUS-GBD was comparable to percutaneous transhepatic gallbladder drainage in terms of technical feasibility, efficacy, and safety of the procedures. In a pooled analysis on the efficacy and safety of EUS-GBD with LAMS in nonoperative candidates with acute cholecystitis, Kalva *et al*[29] showed that technical success represented 93.86% (95%CI: 90.56-96.49) while clinical success was obtained in 92.48% (95%CI: 88.9-95.42). The overall complication rate was 18.31% (95%CI: 13.49-23.68), and the stent related complication rate in the pooled percentage of patients was 8.16% (95%CI: 4.03-14.96).

Some authors reported encouraging results with EUS-GBD in case of failure to treat malignant distal biliary obstruction and cystic duct patent. Imai *et al*[22] reported technical success rates and functional success rate of 100% and 91.7%, respectively with 16.7% of adverse events in a series of 12 patients with obstructive jaundice due to unresectable malignant distal biliary stricture who underwent EUS-GBD after ERCP failure.

The rendez-vous technique

EUS-RV is considered a second-line approach in case of ERCP failure due to juxtapapillary diverticulum or ampullary cancer. Once the dilated intrahepatic or extrahepatic duct is identified and punctured with the 19-gauge EUS aspiration needle, a long (450 cm) 0.035-inch or 0.025-inch guidewire is inserted downstream through the stenosis and into the duodenum.

The echoendoscope is withdrawn leaving the wire in place, and a duodenoscope is inserted to grasp the wire into the scope channel with forceps or a snare. The traditional cannulation over the wire is then performed to access the biliary duct. Crossing the stenosis and the papilla with the guidewire can be difficult and the need to exchange endoscopes may prolong procedural time. This kind of approach is generally preferred for benign indications because there is no anatomical alteration of

the biliary duct as when the fistula is created with subsequent stent placement in EUS-HGA or EUS-CDS. The site of the puncture (duodenal bulb, second portion, and stomach) has been examined by Iwashita *et al*[30] in 20 patients after failed cannulation. The guidewire was successfully manipulated in 100% (10/10) with the second portion (D2) approach, and 66.7% (6/9) with other approaches, thus suggesting that the extrahepatic approach from D2 may improve the success rate of EUS-RV.

EUS-RV seems to be the safest of all three approaches[31] and has been supported by several studies. Safety and efficacy of EUS–RV have been evaluated by Iwashita *et al*[32] in 40 patients who underwent salvage EUS–RV immediately after failed biliary cannulation. Successful manipulation of the guidewire into the small intestine was achieved in 29 of 40 patients. Five patients (13%) had complications including pancreatitis, abdominal pain, pneumoperitoneum, and sepsis/death, which were believed to be unrelated to the procedure.

The algorithm for EUS-BD guidance

The choice of approach is still under debate and is mainly based on anatomical factors, indication of the procedure, and the endoscopist's experience. Ascites or non-dilated intrahepatic left biliary ducts are conditions for an extrahepatic approach, while for benign indications (*e.g.*, biliary duct stone removal) a mini-invasive approach like the rendez-vous technique is recommended.

Artifon *et al*[33] compared the outcomes of EUS-HGA and EUS-CDS in a prospective randomized trial of 49 patients with distal malignant biliary obstruction. The technical success rate was 96% *versus* 91% with a clinical success rate of 91% *versus* 77% and similar procedural time. The overall adverse event rates were 16.3% (20% for the HGA group and 12.5% for the CDS group). These data show no significant differences between the two techniques.

These data have been confirmed by Khashab *et al*[34] in an international multicenter comparative trial with 121 patients who underwent EUS-BD (CDS: 60, HGA: 61). However, CDS was found to be associated with shorter hospital stay, improved stent patency, and fewer procedural and stent-related complications[34].

The anatomical site of transmural biliary drainage was also evaluated in a review by Wang *et al*[19], which included 42 studies with 1192 patients. The cumulative technical success rate, the functional success rate, the adverse event rate of EUS-BD, and the pooled odds ratio of technical success rate, functional success rate, and adverse event rates of the transduodenal approach *versus* transgastric approach were calculated. No significant difference was found.

Some authors have suggested different algorithms to guide the choice of approach (Table 2). Park *et al*[35] evaluated an algorithm based on enhanced guidewire manipulation for EUS-BD after ERCP failure in 45 patients achieving overall technical and functional success rates of 91% (intention to treat, 41/45) and 95% (per protocol, 39/41), respectively. More recently other authors have suggested an algorithm for biliary drainage based on patient anatomy[20].

Patients with a dilated intrahepatic biliary tree on cross-sectional imaging received an intrahepatic approach, while patients with a nondilated intrahepatic biliary tree on cross-sectional imaging underwent an extrahepatic approach. In case of failure of intrahepatic drainage, conversion to an extrahepatic approach was proposed. Following this algorithm, technical success in 50/52 patients (96%) was reported with adverse events in five patients (10%).

A recent worldwide multi-institutional survey[36] consisting of ten questions related to the practice of EUS-BD among regional experts revealed the general feeling that EUS-BD could replace PTBD after ERCP failure and that the rendez-vous stenting technique should be first choice. Most endoscopists recommended the use of SEMS for EUS-BD while there was no agreement about the superiority of partially-covered SEMS over fully covered SEMS for EUS-HGA. Regarding the length of the stent, 8-10 cm SEMS were recommended for EUS-HGA while 6 cm SEMS for EUS-CDS. There was general agreement about the use of 6-Fr cystotomes for fistula creation.

There are no prospective studies evaluating the role of EUS-BD as a primary drainage technique in comparison to ERCP. The ERCP related complications like pancreatitis in difficult cannulation might suggest the role of EUS-BD as a good primary alternative in these setting or in patients with altered anatomy or malignant obstruction. However, the use of advanced ERCP techniques in a tertiary-care center usually provides high technical success rate so that EUS-BD is required in a very limited number of cases (only 0.6% of native papilla ERCPs according to the authors)[37].

CONCLUSION

Table 2 Algorithms for guidance endoscopic ultrasonography-guided biliary drainage

Ref.	Design	Proposed algorithm	No. of patients	Technical success rate	Complication rate
Park *et al*[35]	PS	"Enhanced guidewire manipulation protocol" EUS-RV/EUS-AS with guidewire manipulation protocol as a first-line In case of failure or duodenal invasion, transmural EUS-BD	45	91%	11%
Tyberg *et al*[20]	PS	"Patient anatomy" Dilated IHBT on cross-sectional imaging, received IHa Nondilated IHBT on cross-sectional imaging, received EHa In case of failure of IHa, conversion to an EHa	52	96%	10%

PS: Prospective study; EUS-RV: Endoscopic ultrasonography-guided rendez; EUS-AS: Endoscopic ultrasonography-guided antegrade stent placement; EUS-BD: Endoscopic ultrasonography-guided biliary drainage; IHBT: Intrahepatic biliary tree; IHa: Intrahepatic approach; EHa: Extrahepatic approach.

PTBD represents a rescue procedure for ERCP failure. The technical success rate of PTBD is over 95% with a 33% or higher overall adverse event rate including bleeding, infection, dislodgement, biliary leak, and tract seeding[2]. Moreover, this technique can be uncomfortable for the patient due to an external drainage catheter and is contraindicated with ascites or multiple liver metastasis. EUS-BD has become an evolving alternative to PTBD with a better clinical success rate (OR: 0.45), fewer adverse events (OR: 0.23), and fewer reinterventions (OR: 0.13)[16] (Tables 3 and 4). EUS biliary drainage can be achieved by puncturing the intrahepatic duct in the III segment (intrahepatic approach) and inserting an HGA stent, advancing a guidewire across the stricture and the papilla to complete an antegrade stent placement, or by puncturing the common bile duct, or the gallbladder (extrahepatic approach) with CDS or GBD (Figure 2). When the papilla is accessible, puncturing the biliary tree (intrahepatic or extrahepatic) and inserting the guidewire into the small intestine to cannulate with the rendez-vous technique (EUS-RV) represents the most appropriate and safe route.

There is general agreement that EUS-BD may replace PTBD as a drainage method after failure of ERCP[36]. There is no formal consensus on how to choose between the intrahepatic or the extrahepatic approach or rendezvous technique. Algorithms for biliary drainage based on patient anatomy[20] or guidewire manipulation[35] have been developed with encouraging results, but probably the appropriate approach should be decided on a case-to-case basis according to the patient's anatomy and condition. The most crucial step for both approaches is represented by the dilatation of the fistula that potentially can impact the technical success or failure of the drainage procedure. For this reason, most operators prefer transpapillary (rendezvous) EUS-BD or the antegrade technique because the post-procedure biliary leak risk is inferior. The recent introduction of LAMS has improved this field by reducing leakage and the mean procedural time, however potential severe adverse events can occur and need to be carefully evaluated[27].

In 2011, a consortium involving 40 international experts decided upon a standardized terminology, nomenclature, and indications for EUS-BD concluding that due to the potential serious adverse events associated with the procedure, EUS-BD should only be performed by endoscopists trained in both EUS and ERCP, performing pancreatic-biliary EUS and fine needle aspiration with large ERCP and EUS experience of at least 4-5 years (at least 200-300 EUS and ERCP each year) with a 95% to 98% success rate for standard ERCP, with a surgical and interventional radiology backup[38]. Therefore, the endoscopist must have mastery of multiple techniques to be able to fully perform EUS-BD.

Table 3 Comparative studies among different techniques of biliary drainage

Ref.	Design	Technique	No. of patients	Technical success rate	Complication rate
Artifon *et al*[33]	PS	EUS-HGA *vs* EUS-CDS	49	96% *vs* 91%	20% *vs* 12.5%
Khashab *et al*[34]	PS	EUS-HGA *vs* EUS-CDS	121	91.8 *vs* 93.3%	19.6% *vs* 13.3%
Sharaiha *et al*[16]	RS rev	PTBD *vs* EUS-BD	60	84.6% *vs* 91.4%	25% *vs* 13%
Artifon *et al*[7]	PS	PTBD *vs* EUS-CDS	25	100% *vs* 100%	25% *vs* 15.3%
Bapaye *et al*[8]	RS	PTBD *vs* EUS-BD	50	100% *vs* 92%	46% *vs* 20%
Bill *et al*[10]	RS	PTBD *vs* EUS-RV	50	100% *vs* 76%	17% *vs* 28%
Jang *et al*[28]	PS	PTGD *vs* EUS-GBD	29	97% *vs* 97%	3% *vs* 7%
Khashab *et al*[9]	PS	PTBD *vs* EUS-BD	73	100% *vs* 86.4%	39.2% *vs* 18.2%

PS: Prospective study; RS: Retrospective study; Rev: Review; EUS-BD: Endoscopic ultrasonography-guided biliary drainage; EUS-HGA: Endoscopic ultrasonography-guided hepatogastric anastomosis; EUS-CDS: Endoscopic ultrasonography-guided choledochoduodenostomy; EUS-RV: Endoscopic ultrasonography-guided rendezvous; EUS-GBD: Echoendoscopic transgallbladder drainage.

Table 4 Advantages and disadvantages of the different techniques

	Advantages	Disadvantages
ERCP	Widely available Relative low complication rate (compared to PTBD and EUS-BD)	Not feasible in case of inaccessible papilla
PTBD	Available rescue therapy for ERCP failure	High complication rate (bleeding-infection) External catheter Contraindicated if ascites
EUS	Different possible approaches (HGA, CDS, GBD, RV) Internal drainage Same session of failed ERCP Fewer re-interventions	Not widely available High endoscopic ERCP/EUS expertise required Not yet standardized algorithm

ERCP: Endoscopic retrograde cholangiopancreatography; PTBD: Percutaneous transhepatic biliary drainage; EUS: Endoscopic ultrasonography; EUS-BD: Endoscopic ultrasonography-guided biliary drainage; HGA: Hepatogastric anastomosis; CDS: Choledochoduodenostomy; RV: Rendezvous; GBD: Transgallbladder drainage.

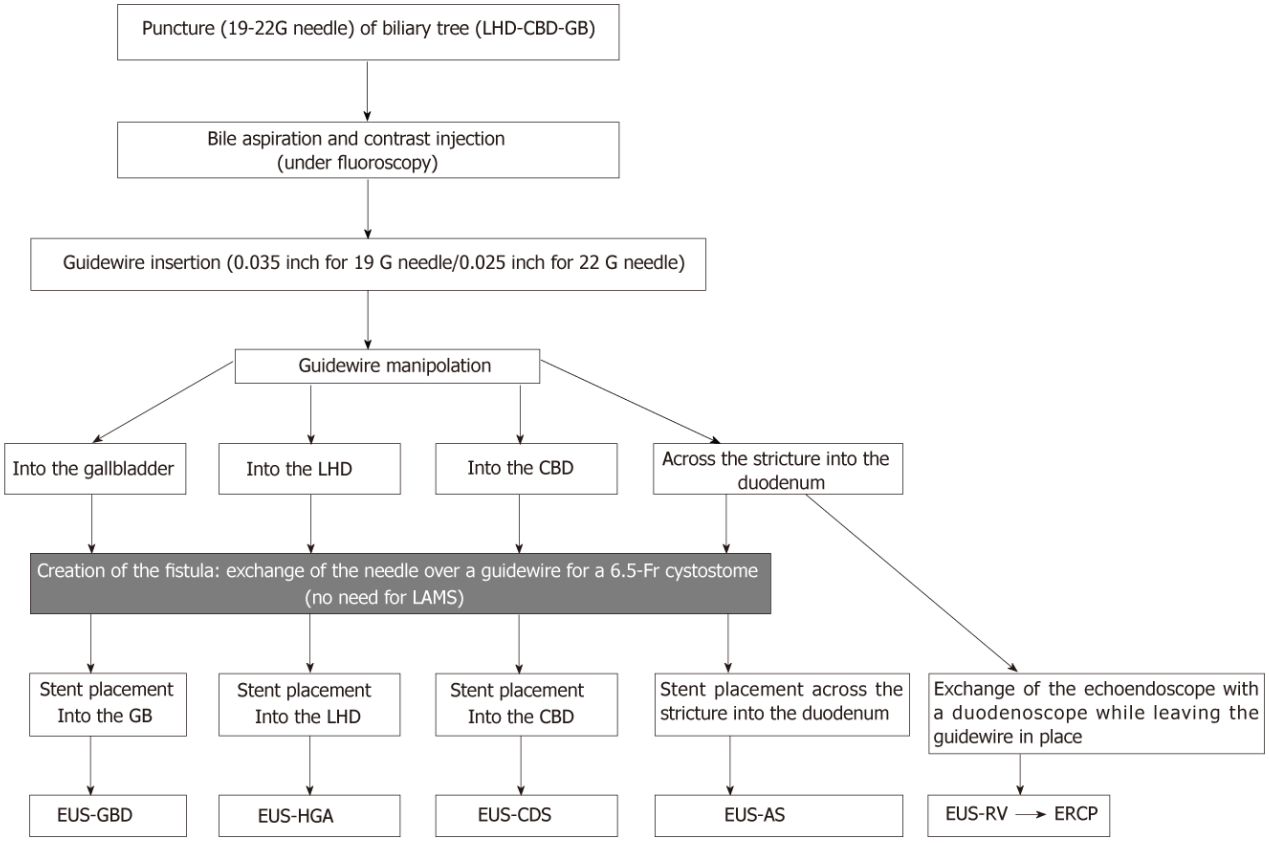

Figure 2 Steps for endoscopic ultrasonography-guided biliary drainage: The crucial step for complication is enhanced in red. LHD: Left hepatic duct; CBD: Common bile duct; GB: Gallbladder; LAMS: Lumen apposing metal stent; EUS-BD: Endoscopic ultrasonography-guided biliary drainage; EUS-HGA: Endoscopic ultrasonography-guided hepatogastric anastomosis; EUS-CDS: Endoscopic ultrasonography-guided choledochoduodenostomy; EUS-RV: Endoscopic ultrasonography-guided rendez-vous.

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World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2019 May 16; 11(5): 365-372

DOI: 10.4253/wjge.v11.i5.365

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Study

Should a fully covered self-expandable biliary metal stent be anchored with a double-pigtail plastic stent? A retrospective study

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Author contributions: Saad Emhmed Ali, Mardini H, Frandah WM and Cory Fielding C made the study design, data collection, and script preparation. Su L and Mardini H made the data analysis. Emhmed Ali SM, Frandah WM and Mardini H wrote the manuscript. Mardini H and Frandah WM was the reviewers of the paper.

Institutional review board statement: This study was approved by the Ethics Committee of the University of Kentucky Medical Center, No: 17-0287-X6B.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Data sharing statement: No additional data are available.

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Abstract

BACKGROUND

The migration rate of fully covered self-expandable metal stents (FCSEMSs) has been reported to be between 14% to 37%. Anchoring of FCSEMSs using a double-pigtail plastic stent (DPS) may decrease migration.

AIM

To compare stent migration rates between patients who received FCSEMS alone and those who received both an FCSEMS and anchoring DPS.

METHODS

We conducted a retrospective analysis of endoscopy reporting system and medical records of 1366 patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) with FCSEMS placement at the University of Kentucky health care. Between July 2015 and April 2017, 203 patients with FCSEMS insertion for the treatment of malignant biliary stricture, benign biliary stricture, post-sphincterotomy bleeding, bile leak, and cholangitis drainage were identified. The review and analysis were conducted through our endoscopy reporting system (ProVation® MD) and medical records. Categorical data were analyzed using Chi-Square and Fischer exact test and continuous data using non-parametric tests. A regression analysis was performed to identify factors independently associated with increased risk of stent migration. We determined

Manuscript source: Unsolicited manuscript

Received: March 6, 2019
Peer-review started: March 8, 2019
First decision: April 13, 2019
Revised: April 30, 2019
Accepted: May 10, 2019
Article in press: May 11, 2019
Published online: May 16, 2019

P-Reviewer: Gurkan A, Fiori E, Goral V, Osawa S, Fogli L
S-Editor: Dou Y
L-Editor: A
E-Editor: Xing YX

an FCSEMS migration endoscopically if the stent was no longer visible in the major papilla.

RESULTS

1366 patients had undergone ERCP by three advanced endoscopists over 21-mo period; among these, 203 patients had FCSEMSs placed. 65 patients had FCSEMSs with DPS, and 138 had FCSEMSs alone. 65 patients had FCSEMSs with DPS, and 138 had FCSEMSs alone. 95 patients had a malignant stricture, 82 patients had a benign stricture, 12 patients had bile leak, 12 patients had cholangitis, and nine patients had post-sphincterotomy bleeding. The migration rate in patients with anchored FCSEMSs with DPS was 6%, and those without anchoring DPS was 10% (P = 0.35). Overall, migration was reported in 18 patients with FCSEMSs placement out of 203 patients with an overall migration rate of 9.7%. There was no significant association between anchoring the FCSEMSs with DPS and the risk of stent migration. Only patients with the previous sphincterotomy and begin biliary stricture were found to have a statistically significant difference in the migration rate between patients who had FCSEMS with DPS and FCSEMS alone (P = 0.01).

CONCLUSION

The risk of migration of biliary FCSEMS was 9.7 %. Anchoring an FCSEMS with DPS does not decrease the risk of stent migration.

Key words: Metal stents; Double-pigtail plastic stent; Endoscopic retrograde cholangiopancreatography; Biliary drainage; Biliary obstruction

Core tip: In this study, we conducted a retrospective analysis to evaluate the efficacy of 7-French (Fr) and 10-Fr double-pigtail plastic stent (DPS) within the fully covered self-expandable metal stent (FCSEMS) as an anti-migration technique. We compared the rate of stent migration between patients who received FCSEMS alone and those who received both an FCSEMS and anchoring DPS in a large patient population with both benign and malignant strictures as well as non-stricture etiologies. Our findings suggest that anchoring of FCSEMS with a 7-Fr or 10-Fr DPS does not decrease the risk of stent migration. Only benign biliary stricture and previous sphincterotomy were to have a significant association with stent migrations (P = 0.01). We did not find evidence to support the routine placement of anchoring DPS.

Citation: Emhmed Ali S, Frandah WM, Su L, Fielding C, Mardini H. Should a fully covered self-expandable biliary metal stent be anchored with a double-pigtail plastic stent? A retrospective study. *World J Gastrointest Endosc* 2019; 11(5): 365-372
URL: https://www.wjgnet.com/1948-5190/full/v11/i5/365.htm
DOI: https://dx.doi.org/10.4253/wjge.v11.i5.365

INTRODUCTION

Fully covered self-expandable metal stents (FCSEMSs) have been widely used as an effective biliary endoprosthesis in the setting of pancreaticobiliary conditions such as benign and malignant strictures, post-sphincterotomy bleeding, and occasionally bile leaks[1]. The primary advantages of covered stents are a lower rate of tumor ingrowth, longer patency, and their potential removability compared to uncovered stents. However, one concern about FCSEMSs is a higher migration rate than uncovered stents[2]. The migration rate of FCSEMSs in prospective studies for benign biliary strictures is 5%-37%[1]. In this study, we conducted a retrospective analysis to evaluate the efficacy of 7-French (Fr) and 10-Fr double-pigtail plastic stent (DPS) within the FCSEMS as an anti-migration technique. We compared the rate of stent migration between patients who received FCSEMS alone and those who received both an FCSEMS and anchoring DPS in a large patient population with both benign and malignant strictures as well as non-stricture etiologies.

MATERIALS AND METHODS

Between July 2015 and April 2017, 1366 patients had undergone endoscopic retrograde cholangiopancreatography (ERCP) at our institution. Among these, 203 patients with FCSEMS placement with or without DPS were identified. The review and analysis were conducted through our endoscopy reporting system (ProVation® MD) and medical records. Patients included in the study had FCSEMS insertion for the treatment of malignant biliary stricture, benign biliary stricture, and non-stricture etiology such as post-sphincterotomy bleeding and bile leak.

After the Institutional Review Board and the Ethics Committee of our hospital approved the study protocol, data was extracted by reviewing patient charts, ERCP reports, and fluoroscopic images. Patients who only had uncovered stents or plastic stents placed were excluded. All endoscopic procedures were performed by three advanced endoscopists. Comprehensive data were collected through Microsoft Excel spreadsheet and included the following: stent type [WallflexTM (Boston Scientific) *vs* Viabil® (Gore Medical)], the diameter of double-pigtail PS (7-Fr *vs* 10-Fr), indications for FCSEMS placement including stricture type (malignant *vs* benign), and non-stricture etiologies such as post-sphincterotomy bleeding and bile leak.

Baseline patient characteristics were identified, such as previous cholecystectomy, biliary sphincterotomy, history of stent migration, choledocholithiasis, and diameter of the common bile duct (CBD). After stent placement and during the follow-up period, patients' records were reviewed to verify the stent position. We defined FCSEMS migration endoscopically if the stent was no longer visible through the major papilla. It either migrates proximally (into the bile duct) or distally (out of the bile of duct). The anti-migration properties of FCSEMSs include higher radial force, anchoring flap, anchoring fins and flared ends have been designed to prevent the migration. Categorical data were analyzed using the Chi-Square test and Fisher Exact test and continuous data using non-parametric tests. A regression analysis was performed to identify factors independently associated with increased risk of stent migration. All analyses were completed in SAS 9.4 (SAS Institute Inc., Cary, NC, United States).

The primary endpoint of the study was to compare stent migration rates between patients who received FCSEMSs alone and those who received both an FCSEMS with an anchoring DPS. A secondary endpoint was the presence of complications related to stent migration.

RESULTS

1366 patients had undergone ERCP by three advanced endoscopists over 21-mo period; among these, 203 patients had FCSEMS placed with or without DPS (88 females and 115 males). 65 patients had FCSEMSs with DPS, and 138 had FCSEMSs alone (Table 1 and Table 2). 95 patients had a malignant stricture, 82 patients had a benign stricture, 12 patients had bile leak, 12 patients had cholangitis, and nine patients had post-sphincterotomy bleeding (Figure 1). For the patients with stent migration, 12 (66.7%) had a benign biliary stricture, and 6 (33.3%) did not have, while for the patients without stent migration, 70 (37.8%) had a benign biliary stricture and 115 (62.2%) did not have (P = 0.01). Also. For patients with stent migration, 12 (66.7%) had the previous sphincterotomy, and 6 (33.3%) did not have, while for the patients without stent migration, 71 (38.4%) had the previous sphincterotomy and 114 (61.6%) did not have (P = 0.01). The migration rate in patients with benign biliary stricture was 14.6% and for those with non-benign biliary stricture was 5%. Migration rate in patients with the previous sphincterotomy was 14.5%, and those without previous sphincterotomy was 5%. Therefore, the distribution of patients that had a benign biliary stricture and previous sphincterotomy were significantly different between patients with stent migration and patients with no stent migration. There was no significant association between any of the other tested variables including anchoring the FCSEMSs with DPS and the risk of stent migration. The migration rate in patients with anchored FCSEMSs with DPS was 6%, and those without anchoring DPS was 10% (P = 0.35). Overall, migration was reported in 18 patients with FCSEMS placement out of 203 patients with an overall migration rate of 9.7%.

DISCUSSION

FCSEMS has been associated with longer patency than uncovered stents in some studies even though they may have higher rates of migration[3-5]. To minimize the risk

Table 1 Clinical characteristics of patients who underwent fully covered self-expanding metal stent placement with or without double-pigtail plastic stent

Characteristic	Determinant	Frequency count	Percent of total frequency
Gender	Female	88	43.34
	Male	115	56.65
Race	Black	9	4.43
	White	194	95.56
Age	Mean (62.97); Range (23.00-91.00)		
Brand of FCSEMS	Viabil fully covered	90	44.33
	Viabil fully covered with proximal fenestration	63	31.03
	WallFlex	50	24.63
Cholangitis drainage	No	191	94.08
	Yes	12	5.91
Choledocholithiasis at time of stent placement	No	188	92.61
	Yes	15	7.38
History of cholecystectomy	No	92	45.32
	Yes	111	54.67
History of stent migration	No	196	96.55
	Yes	7	3.44
Length of FCSEMS (cm)	4	30	14.77
	6	106	52.21
	8	47	23.15
	10	20	9.85
Length of Stricture (mm)	Mean (19.21); Range (0.00-90.00)		
CBD diameter (mm)	Mean (11.19); Range (3.00-35.00)		
Malignant stricture	No	108	53.20
	Yes	95	46.79
Migration	No	185	91.13
	Yes	18	8.86
Post sphincterotomy bleed	No	194	95.56
	Yes	9	4.43
Previous sphincterotomy	No	120	59.11
	Yes	83	40.88
Sphincterotomy at time of stent deployment	No	82	40.39
	Yes	121	59.60

FCSEMS: Fully covered self-expanding metal stent; DPS: Double-pigtail plastic stent.

of migration, FCSEMSs have been designed with anti-migration mechanical properties, such as higher radial force, an anchoring flap, and specific stent flare structures[6-8]. Nevertheless, other modifications such as anchoring fins and flared ends have been designed to prevent the migration of FCSEMSs, even though; there are no randomized studies to evaluate their effectiveness[7,9].

In our study, the risk of migration of biliary FCSEMS seemed to be lower than previous studies at 9.7%. In contrast, migration rates have been reported to be up to 37.5% in the previous study[1]. To our knowledge, there are only two studies that have evaluated the efficacy of anchoring DPS to prevent migration of FCSEMS.

In a randomized controlled study, Park *et al*[10] described their experience of placing a 5-Fr DPS into FCSEMS in 17 patients out of 33 patients who received FCSEMS for benign biliary strictures. During the follow-up, the migration rate was significantly lower in the anchored group (FCSEMS + anchoring DPS) compared with a non-anchored group (FCSEMS alone): 1/16 (6.3%) *vs* 7/17 (41.2%) respectively, $P = 0.024$. However, in the study by Park *et al*[10], their sample size was underpowered to identify any significant clinical difference between the two groups and the study was terminated before the planned sample size was reached.

Recently, Katsinelos *et al*[11] investigated the efficacy of using a 10-Fr DPS to prevent migration in 10 patients with malignant biliary strictures and one patient with a suprapapillary benign biliary stenosis. These patients were prospectively enrolled.

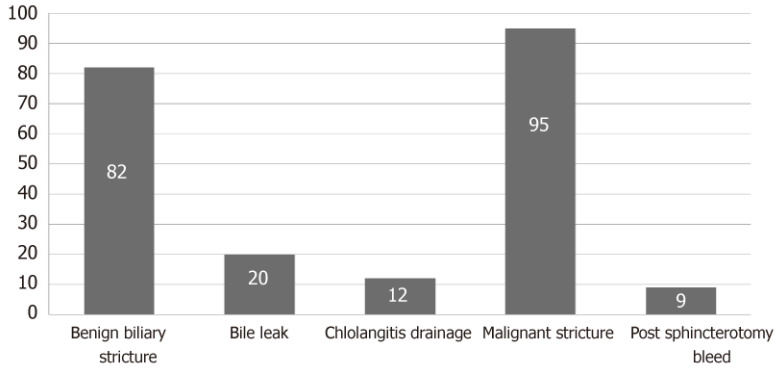

Figure 1 Indication for fully covered self-expandable metal stent with or without double-pigtail plastic stent placement.

The median follow-up period was eight months, and no migration of FCSEMS was reported. Even though it was the first study to assess the use of anchoring a 10-Fr DPS inside an FCSEMS as anti-migration technique, it was limited by small sample size and lack of randomization.

Our study contains a much larger sample size than the studies described above. Also, we included patients with a variety of indications for FCSEMS placement, such as benign and malignant biliary stricture, post sphincterotomy bleed, cholangitis drainage, and bile leak. Our study was different from the above studies because 90% of DPS were 7-Fr and 10% were 10-Fr.

The complication rate from stent migration was very low in our study. Five patients developed obstructive jaundice due to stent migration, and only one patient developed stent-induced cholecystitis secondary to the occlusion of the cystic orifice by a proximally migrated stent in a patient with pancreatic cancer. Acute cholecystitis after placement of a biliary metallic stent has been reported in up to 13% and is likely associated with tumor involvement at the orifice of the cystic duct[12-14].

This study was limited by being retrospective and not being randomized. However, this is the first study to investigate the efficacy of a 7-Fr DPS inside an FCSEMS as an anti-migration technique and the first study to assess the migration rate of FCSEMS with or without anchoring DPS among those with non-stricture etiologies such post-sphincterotomy bleeding and bile leak.

In conclusion, our findings suggest that anchoring of FCSEMS with a 7-Fr or 10-Fr DPS does not decrease the risk of stent migration. Only benign biliary stricture and previous Sphincterotomy were to have a significant association with stent migrations (P = 0.01). We did not find evidence to support the routine placement of anchoring DPS. However, prospective randomized controlled studies are needed to evaluate the efficacy of an anchoring DPS within an FCSEMS as an anti-migration technique.

Table 2 Comparison between patients who had migration of fully covered self-expanding metal stent placement (FCSEMS) and patient who had no migration of FCSEMS

Characteristic	Determinant	Migration (*n* = 18)	No migration (*n* = 185)	*P*-value
Gender	Female	5 (27.8%)	83 (44.9%)	0.1626
	Male	13 (72.2%)	102 (55.1%)	-
Age	mean ± SD (range)	59.83 (12.38) - (34.00, 91.00)	63.28 (15.23) - (23.00, 91.00)	0.3539
Race	Black	2 (11.1%)	7 (3.8%)	0.1494
	White	16 (88.9%)	178 (96.2%)	-
Post sphincterotomy bleed	No	17 (94.4%)	177 (95.7%)	0.8086
	Yes	1 (5.6%)	8 (4.3%)	-
Bile leak	No	18 (100.0%)	165 (89.2%)	0.1418
	Yes	0 (0.0%)	20 (10.8%)	-
Benign biliary stricture	No	6 (33.3%)	115 (62.2%)	0.0173
	Yes	12 (66.7%)	70 (37.8%)	-
Cholangitis drainage	No	18 (100.0%)	173 (93.5%)	0.2653
	Yes	0 (0.0%)	12 (6.5%)	-
Malignant stricture	No	13 (72.2%)	95 (51.4%)	0.0902
	Yes	5 (27.8%)	90 (48.6%)	-
Brand of FCSEMS	Viabil fully covered	8 (44.4%)	82 (44.3%)	0.2294
	Viabil fully covered with proximal fenestration	3 (16.7%)	60 (32.4%)	-
	WallFlex	7 (38.9%)	43 (23.2%)	-
Length of FCSEMS (cm)	4	2 (11.1%)	28 (15.1%)	0.9376
	6	9 (50.0%)	97 (52.4%)	-
	8	5 (27.8%)	42 (22.7%)	-
	10	2 (11.1%)	18 (9.7%)	-
Anchored FCSEMSs with DPS	No	14 (77.8%)	124 (67.0%)	0.3507
	Yes	4 (22.2%)	61 (33.0%)	-
Length of stricture (mm)	mean ± SD (range)	14.67 (10.72) - (0.00, 40.00)	19.65 (19.32) - (0.00, 90.00)	0.0958
CBD diameter (mm)	mean ± SD (range)	11.61 (4.50) - (5.00,22.00)	11.15 (4.70) - (3.00,35.00)	0.6878
History of cholecystectomy	No	5 (27.8%)	87 (47.0%)	0.1173
	Yes	13 (72.2%)	98 (53.0%)	-
Previous sphincterotomy	No	6 (33.3%)	114 (61.6%)	0.0198
	Yes	12 (66.7%)	71 (38.4%)	-
Sphincterotomy at time of stent deployment	No	9 (50.0%)	73 (39.5%)	0.3843
	Yes	9 (50.0%)	112 (60.5%)	-
History of stent migration	No	17 (94.4%)	179 (96.8%)	0.6078
	Yes	1 (5.6%)	6 (3.2%)	-
Choledocholithiasis at time of stent placement	No	16 (88.9%)	172 (93.0%)	0.5272
	Yes	2 (11.1%)	13 (7.0%)	-

FCSEMS: Fully covered self-expanding metal stent; DPS: Double-pigtail plastic stent.

ARTICLE HIGHLIGHTS

Research background

Fully covered self-expandable metal stents (FCSEMSs) have been widely used as an effective biliary endoprosthesis in the setting of pancreaticobiliary conditions such as benign and malignant strictures, post-sphincterotomy bleeding, and occasionally bile leaks. The primary advantages of covered stents are a lower rate of tumor ingrowth, longer patency, and their potential removability compared to uncovered stents. However, one concern about FCSEMSs is a higher migration rate than uncovered stents. In this study, we conducted a retrospective analysis to evaluate the efficacy of 7-French (Fr) and 10-Fr double-pigtail plastic stent (DPS) within the FCSEMS as an anti-migration technique. We compared the rate of stent migration between patients who received FCSEMS alone and those who received both an FCSEMS and anchoring DPS in a large patient population with both benign and malignant strictures as well as non-stricture etiologies. We did not find evidence to support the routine placement of anchoring DPS.

We found that anchoring of FCSEMS with a 7-Fr or 10-Fr DPS does not decrease the risk of stent migration.

Research motivation

FCSEMSs have been commonly used as an effective biliary endoprosthesis in the setting of pancreaticobiliary conditions such as benign and malignant strictures. To minimize the risk of migration, FCSEMSs have been designed with different anti-migration mechanical properties. The use of DPS is still unclear as an anti-migration method. Prospective randomized controlled studies are needed to evaluate the efficacy of an anchoring DPS within an FCSEMS as an anti-migration technique.

Research objectives

The main objective of the study was to assess to the rate of stent migration between patients who received FCSEMS alone and those who received both an FCSEMS and anchoring DPS in both benign and malignant strictures as well as non-stricture etiologies. To our knowledge, there are only two small retrospective studies that have evaluated the efficacy of anchoring DPS to prevent migration of FCSEMS. So, more randomized controlled trials with a larger number of patients are needed.

Research methods

A retrospective analysis of endoscopy reporting system and medical records of patients who underwent ERCP with FCSEMS placement was conducted. The review and analysis were conducted through our endoscopy reporting system (ProVation® MD) and medical records. Patients included in the study had FCSEMS insertion for the treatment of malignant biliary stricture, benign biliary stricture, and non-stricture etiology such as post-sphincterotomy bleeding and bile leak. Data included stent type [WallflexTM (Boston Scientific) *vs* Viabil® (Gore Medical)], the diameter of double-pigtail PS (7-Fr *vs* 10-Fr), and indications for FCSEMS placement. We defined FCSEMS migration endoscopically if the stent was no longer visible through the major papilla. It either migrates proximally (into the bile duct) or distally (out of the bile of duct).

Research results

There was no significant association between any of the other tested variables including anchoring the FCSEMSs with DPS and the risk of stent migration. The migration rate in patients with anchored FCSEMSs with DPS was 6%, and those without anchoring DPS was 10% (P = 0.35). Overall, migration was reported in 18 patients with FCSEMS placement out of 203 patients with an overall migration rate of 9.7%. The distribution of patients that had a benign biliary stricture and previous sphincterotomy were significantly different between patients with stent migration and patients with no stent migration.

Research conclusions

In our study, the risk of migration of biliary FCSEMS was 9.7 %. Anchoring an FCSEMS with a 7-Fr or 10-Fr DPS does not decrease the risk of stent migration. Routine placement of anchoring stents is unnecessary. We believe that further randomized controlled trials with a larger number of patients might be helpful to ascertain if anchoring an FCSEMS with DPS is useful as an anti-migration technique.

Research perspectives

Anchoring of FCSEMS with a 7-Fr or 10-Fr DPS does not decrease the risk of stent migration. Only benign biliary stricture and previous Sphincterotomy were to have a significant association with stent migrations. Needs more prospective large studies. More randomized controlled trials with a larger number of patients are needed.

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World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2019 May 16; 11(5): 373-382

DOI: 10.4253/wjge.v11.i5.373

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Study

Endoscopic characteristics of small intestinal malignant tumors observed by balloon-assisted enteroscopy

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Abstract

BACKGROUND

Capsule endoscopy and balloon-assisted enteroscopy (BAE) enable visualization of rare small bowel conditions such as small intestinal malignant tumors. However, details of the endoscopic characteristics of small intestinal malignant tumors are still unknown.

AIM

To elucidate the endoscopic characteristics of small intestinal malignant tumors.

METHODS

From March 2005 to February 2017, 1329 BAE procedures were performed at Keio University Hospital. Of these procedures, malignant tumors were classified into three groups, Group 1: epithelial tumors including primary small intestinal cancer, metastatic small intestinal cancer, and direct small intestinal invasion by an adjacent organ cancer; Group 2: small intestinal malignant lymphoma; and Group 3, small intestinal gastrointestinal stromal tumors. We systematically collected clinical and endoscopic data from patients' medical records to determine the endoscopic characteristics for each group.

statement: This study was reviewed and approved by the Ethics Committee of the Keio University Hospital (approval number, 20160431).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

Received: March 23, 2019
Peer-review started: March 25, 2019
First decision: April 11, 2019
Revised: May 11, 2019
Accepted: May 13, 2019
Article in press: May 14, 2019
Published online: May 16, 2019

P-Reviewer: Chiu CT, Wadhwa V
S-Editor: Wang JL
L-Editor: A
E-Editor: Xing YX

RESULTS

The number of patients in each group was 16 (Group 1), 23 (Group 2), and 6 (Group 3), and the percentage of solitary tumors was 100%, 43.5%, and 100%, respectively ($P < 0.001$). Patients' clinical background parameters including age, symptoms, and laboratory data were not significantly different between the groups. Seventy-five percent of epithelial tumors (Group 1) were located in the upper small intestine (duodenum and ileum), and approximately 70% of gastrointestinal stromal tumors (Group 3) were located in the jejunum. Solitary protruding or mass-type tumors were not seen in malignant lymphoma (Group 2) ($P < 0.001$). Stenosis was seen more often in Group 1, (68.8%, 27.3%, and 0%; Group 1, 2, and 3, respectively; $P = 0.004$). Enlarged white villi inside and/or surrounding the tumor were seen in 12.5%, 54.5%, and 0% in Group 1, 2, and 3, respectively ($P = 0.001$).

CONCLUSION

The differential diagnosis of small intestinal malignant tumors could be tentatively made based on BAE findings.

Key words: Small intestine; Malignant; Tumor; Double balloon enteroscopy; Balloon enteroscopy; Video capsule endoscopy; Endoscopy

Core Tip: The aim of this study was to elucidate the endoscopic characteristics of small intestinal malignant tumors. Balloon-assisted enteroscopy procedures at our institution were enrolled in the analysis. Malignant tumors were classified into three groups, Group 1: epithelial tumors; Group 2: small intestinal malignant lymphoma; and Group 3, small intestinal gastrointestinal stromal tumors. We collected data from patients' medical records to determine the endoscopic characteristics for each group. Group 1 and Group 2 were observed as solitary tumors. Enlarged white villi inside and/or surrounding the tumor were seen in 12.5%, 54.5%, and 0% in Group 1, 2, and 3, respectively (P <0.001).

Citation: Horie T, Hosoe N, Takabayashi K, Hayashi Y, Kamiya KJL, Miyanaga R, Mizuno S, Fukuhara K, Fukuhara S, Naganuma M, Shimoda M, Ogata H, Kanai T. Endoscopic characteristics of small intestinal malignant tumors observed by balloon-assisted enteroscopy. *World J Gastrointest Endosc* 2019; 11(5): 373-382
URL: https://www.wjgnet.com/1948-5190/full/v11/i5/373.htm
DOI: https://dx.doi.org/10.4253/wjge.v11.i5.373

INTRODUCTION

The small intestine is a long luminal organ that constitutes 75% of the length of gastrointestinal tract and 90% of its mucosal surface area. Small intestinal cancer is relatively rare, accounting for less than 5% of gastrointestinal cancers[1] and with an incidence of 6.8 cases per million[2]. The gastrointestinal tract is a major organ affected by extranodal malignant lymphoma, accounting for 30%–40% of all extranodal lymphomas and 5%–20% of all non-Hodgkin lymphomas[3]. The most frequent primary gastrointestinal site of malignant lymphoma is the stomach (60%–70%), followed by the small intestine (20%–30%)[4]. Until the development of balloon-assisted enteroscopy (BAE) and video capsule endoscopy, small intestinal malignant tumors could not be observed endoscopically. Moreover, BAE enables direct observation of these small intestinal lesions, and also permits biopsy and endoscopic therapy, such as stent placement and endoscopic tattooing for subsequent surgical therapy[5,6]. A previous study reported the incidence of small intestinal tumors detected by BAE[6,7]; however, the endoscopic characteristics of small intestinal tumors have been reported only in a limited number of case reports[8-10], and the details of these characteristics are still unknown.

The aim of this study was to investigate the endoscopic characteristics of small intestinal malignant tumors observed by BAE.

MATERIALS AND METHODS

This study was a retrospective medical record analysis and was approved by the ethics committee of Keio University Hospital (approval number, 20160431). Data was collected from patients' medical records, and the endoscopy findings were collected using an endoscopy reporting system (Solemio ENDO®, Olympus, Tokyo, Japan). Patients who underwent BAE (EN450/T5 or EN450/P5; Fujifilm, Tokyo, Japan or SIF-Q260; Olympus, Tokyo, Japan) between March 2005 and February 2017 in Keio University Hospital were screened. Of the 1329 procedures, 44 small intestinal malignant tumors were seen endoscopically, and data for these tumors were included in the analysis. Benign small intestinal polyp and polyposis syndrome such as Peutz–Jeghers syndrome and familial adenomatous were excluded from the analysis. The included small intestinal malignant tumors were classified into three groups: Group 1: epithelial tumors including primary small intestinal cancer (ade-no-carcinoma), metastatic small intestinal cancer (adenocarcinoma), and direct small intestinal invasion by adjacent organ cancer (adenocarcinoma); Group 2: small intestinal malignant lymphoma; and Group 3: small intestinal gastrointestinal stromal tumors (GIST). Patients' clinical background parameters included age, symptom, and laboratory data. To define the endoscopic characteristics for each group, endoscopic data such as tumor location, solitary or multiple lesions, type or form, presence of stenosis, presence of bleeding, and presence of white villi were systematically collected from patients' medical charts and the endoscopy reporting system. Solitary and multiple lesions were confirmed by computed tomography and/or barium swallow. Stricture was defined as a stenosis through which we could not pass an enteroscope (EN450/T5 or SIF-Q260). Bleeding was defined as spontaneous bleeding before passing the enteroscope. We also focused on the endoscopic findings of white villi in malignant lymphoma. To determine the morphological and pathological characteristics of white villi in malignant lymphoma, we compared the pathological findings and endoscopic findings from each biopsy site.

Statistical analysis

Statistical analyses were performed using the Fisher's exact test for percentages and one way ANOVA to assess differences in parameters showing a normal distribution. Non- normally distributed data were analyzed using the Kruskal–Wallis test. *P*-values < 0.05 were considered significant, and SPSS version 22 software (SPSS Inc., Tokyo, Japan) was used for all statistical analyses.

RESULTS

A flow diagram of patient enrollment is shown in Figure 1. In total, 1328 BAE procedures were performed from March 2005 to February 2017. Of these 1328 procedures, the number of patients in each group was 16 (Group 1), 22 (Group 2), and 6 (Group 3) (Figure 1). Table 1 shows the patients' characteristics. We found no statistically-significant difference in age, symptoms (epigastric pain, melena, weight loss), and blood test results (white blood cell count, hemoglobin, lactate dehydrogenase) between the groups. The endoscopic characteristics of the small intestinal malignant tumors are shown in Table 2 and Figure 2. Seventy-five percent of epithelial tumors (Group 1) were located in the upper small intestine (duodenum and jejunum), and approximately 70% of GISTs were located in the jejunum. The percentage of solitary tumors was 100%, 45.5%, and 100% in Group 1, 2, and 3, respectively ($P < 0.001$). Solitary protruding or mass-type tumors were not seen in malignant lymphoma (Group 2) ($P < 0.001$). Solitary infiltrative ulcerated type tumors were seen only in Group1 ($P = 0.007$) (Figure 2A). Multiple lesions with ulcerated surfaces or polyposis were seen only in Group 2, and stenosis was seen more frequently in Group 1, (68.8%, 27.3%, and 0%; Group 1, 2, and 3, respectively; $P = 0.004$). Although the difference was not statistically significant, Group1 tended to have more bleeding compared with Group 2 and 3. Enlarged white villi inside and/or surrounding the tumor were seen in 12.5%, 54.5%, and 0% in Group 1, 2 and 3, respectively ($P < 0.001$) (Figure 2B and C). We further investigated the pathological and morphological features of white villi in Group 2. Adequate biopsy samples were not obtained from four patients; therefore, we excluded data for these patients from the analysis (Table 3). Of the 22 Group 2 patients, enlarged white villi were seen in 12 patients. At the biopsy sites where most of the white villi were seen, lymphoma cells infiltrated into the villi with an intact epithelium; villi were filled with lymphoma cells (Table 3 and Figure 3). When the intact epithelium was ulcerated or lymphoma cells were present in the deep mucosa, white villi could not be seen (Table 3 and Figure 4).

Table 1 Patients' characteristics

	Group 1 (epithelial)	Group 2 (malignant lymphoma)	Group 3 (GIST)	*P*-value
Age (mean ± SD)	62.9 ± 13.7	67.7 ± 7.1	67.0 ± 11.9	0.47
Symptom (%)				
Epigastric pain	25.0 (4/16)	27.3 (6/22)	0 (0/6)	0.36
Melena	25.0 (4/16)	13.6 (3/22)	16.7 (1/6)	0.67
Weight loss	6.3 (1/16)	4.5 (1/22)	0 (0/16)	0.82
Other	43.8 (7/16)	54.5 (12/22)	83.3 (5/6)	N/A
Blood test results (mean ± SD)				
WBC (/μL)	7712.5 ± 3428.1	6536.4 ± 2858.5	4950.0 ± 1312.6	0.25
Hb (g/dL)	10.7 ± 2.7	11.6 ± 2.1	12.2 ± 2.4	0.63
LDH (IU/L)	201.0 ± 52.1	189.9 ± 49.1	175.0 ± 35.8	0.35

N/A: Not applicable: GIST: Gastrointestinal stromal tumor; WBC: White blood cell count; Hb: Hemoglobin; LDH: Lactate dehydrogenase.

DISCUSSION

In the current study, we described the endoscopic characteristics of tumor location and morphology of small intestinal malignant tumors. Small intestinal malignant tumors were classified into three groups, and statistical analyses were performed between the groups. Patients' clinical background parameters including age, symptoms, and laboratory data were not significantly different between the groups. First, we evaluated the endoscopic characteristics of tumor location and the number of tumors. Approximately three quarters of epithelial tumors were found in the duodenum or jejunum, and all were observed as solitary lesions (Table 2). Previous studies using BAE reported that primary small intestinal adenocarcinoma was located mainly in the duodenum or jejunum with a range of 77.8%–100.0%[6,7,11-14]. Primary small intestinal adenocarcinoma was reported as a solitary lesion in several studies[6,7,12-14], which was consistent with our results, whereas metastatic tumors were sometimes observed as multiple lesions[11,15]. In our classification, primary and metastatic tumors were classified into the same groups; however, it might be better to distinguish between metastatic and primary tumors. In the current study, malignant lymphoma lesions were located mainly in the jejunum and ileum, and approximately 60% were multiple lesions (Table 2), consistent with previous reports[11-14,16]. GISTs are reported mainly as solitary jejunal tumors[11-13,17,18]. Nakano *et al*[19] reported that 76% of patients with GIST had jejunal lesions, and that 3/25 patients had tumors in multiple sites (stomach and jejunum: 1; duodenum and jejunum: 1; and stomach, duodenum, and jejunum: 1). A particular type of GIST that is associated with neurofibromatosis type1 appears as multiple tumors[20-22]. However, as our results, most GISTs appeared as a solitary jejunal tumor, except for neurofibromatosis type1 associated type[20-22].

The endoscopic morphology of small intestinal tumors has not been systemically evaluated. In the current study, we evaluated the endoscopic morphology of small intestinal tumors. Epithelial tumors appeared as protruded or mass type, ulcerated type, or infiltrative ulcerated type, and 68.8% (11/16) were associated with stenosis. The infiltrative ulcerated type was typically recognized in epithelial tumors (Figure 2A). Malignant lymphoma appeared mainly as multiple lesions such as multiple ulcers or multiple lymphomatous polyposis (MLP), and stenosis was detected in 6/22 patients (27.3%). GIST was observed as the protruded or mass type [66.7% (4/6)], or the ulcerated type [33.3 % (2/6)] without stenosis. Chung *et al*[7] and Imaoka *et al*[12] reported that most small bowel adenocarcinomas appeared as the ulcerative form. Imaoka *et al*[12] and Almeida *et al*[23] reported that most epithelial small bowel tumors were associated with stenosis [70% (7/10) and 100% (3/3), respectively], similar to our findings. Previous reports[12,23,24] showed that malignant lymphoma occurred mainly as multiple lesions, such as multiple ulcers or MLP. MLP as multiple white nodules was observed in follicular lymphoma in previous studies[3,24-27]. Nakano *et al*[19] reported that the morphology of GISTs was classified into three groups: intraductal, extraductal, and mixed type. Lesions in 21 patients occurred as submucosal tumors and two occurred as diverticular transformation, in the 18 patients with ulceration. We saw no diverticular transformation in our study.

Of 22 patients with malignant lymphoma, enlarged white villi were seen in 12 patients (Table 2, Figure 3). The pathological and morphological features of the white villi biopsy sites showed that the lymphoma cells had infiltrated into the villi with an

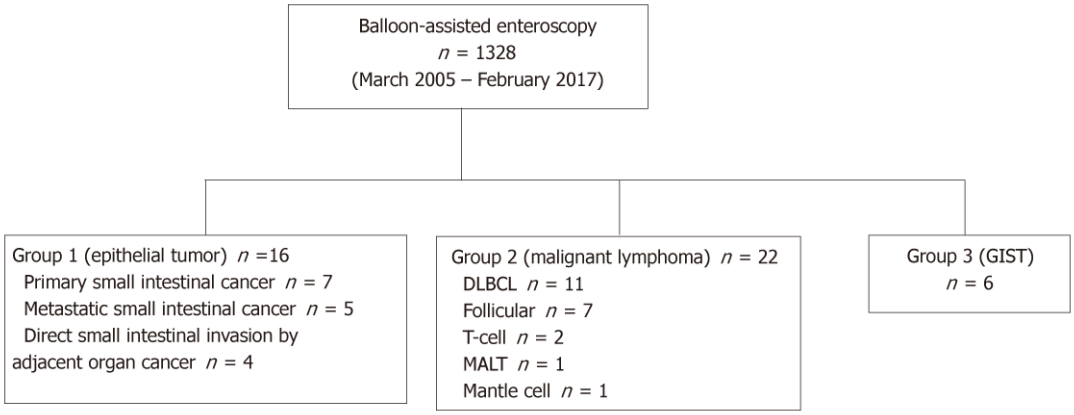

Figure 1 Flow diagram of the patient enrollment. DLBCL: Diffuse large B-cell lymphoma; GIST: Gastrointestinal stromal tumor; MALT: Mucosa-associated lymphoid tissue.

intact epithelium (Table 3 and Figure 3). In the current study, there were two types of malignant lymphoma that did not exhibit white villi. The first type showed the lymphoma cells sparsely infiltrated the villi, some lymphoma cells presented in the deep mucosa (Figure 4A and B). The second type showed the lymphoma cells infiltrated the mucosa without an intact epithelium (Figure 4C and D). Endoscopic findings of follicular lymphoma were described as "multiple polypoid lesions" and "multiple whitish small polyps" in a previous study[24]. These whitish polypoid lesions were seen as enlarged white villi using magnifying endoscopy[28-30]. Yamamoto *et al*[24] reported that each white enlarged villus was an enlarged neoplastic follicle consisting of lymphoma cells in the lamina propria, which was confirmed histologically. Another report showed that enlarged white duodenal villi were caused by infiltration of lymphoma cells into the villi, which formed lymphoid follicles[29]. From the pathological findings of our study, jejunal and/or ileal white villi in malignant lymphoma, even in other than the follicular type, are considered to consist of lymphoma cells in the lamina propria as with duodenal follicular lymphoma. Previous reports describe white villi of duodenal follicular lymphoma using esophagogastroduodenoscopy[24,28-30]. To our knowledge, ours is the first report of white villi in jejunal and ileal malignant lymphoma observed by BAE.

The endoscopic characteristics of the small intestinal tumors in our study are summarized in Table 4. Generally, epithelial small intestinal tumors appeared as solitary tumors with stenosis, small intestinal malignant lymphoma tumors as multiple tumors with white villi, and GISTs as solitary protruded lesions.

Several limitations of this study should be addressed. First, this was a retrospective study; thus, many confounding factors could affect the results. Second, small intestinal tumors are very rare, and our sample size was relatively small. Future studies require higher numbers of patients to analyze larger datasets. However, there have been few studies to show the differences of endoscopic features among group1, 2 and 3. Furthermore, the importance of "white villi" could be emphasized in our study.

In conclusion, based on endoscopic findings during BAE, we were able to make tentative differential diagnoses of small intestinal malignant tumors.

Table 2 Endoscopic characteristics of the small intestinal malignant tumors

	Group 1 (Epithelial) (%)	Group 2 (Malignant lymphoma) (%)	Group 3 (GIST) (%)	*P*-value
Tumor location				
Duodenum	43.8 (7/16)	18.2 (4/22)	16.7 (1/6)	0.18
Jejunum	31.3 (5/16)	50.0 (11/22)	66.7 (4/6)	0.28
Ileum	25.0 (4/16)	45.5 (10/22)	16.7 (1/6)	0.26
Solitary lesion	100.0 (16/16)	45.5 (10/22)	100.0 (6/6)	< 0.001
Type or form				
Solitary				
Protruded or mass type	31.3 (5/16)	0 (0/22)	66.7 (4/6)	< 0.001
Ulcerated type (with raised margins)	37.5 (6/16)	40.9 (9/22)	33.3 (2/6)	0.94
Infiltrative ulcerated type	31.3 (5/16)	0 (0/22)	0 (0/6)	0.007
Multiple				
Multiple ulcers	0 (0/16)	22.7 (5/22)	0 (0/6)	0.06
MLP	0 (0/16)	13.6 (3/22)	0 (0/6)	0.20
Others	0 (0/16)	22.7 (5/22)	0 (0/6)	N/A
Presence of stenosis	68.8 (11/16)	27.3 (6/22)	0 (0/6)	0.004
Presence of bleeding	43.8 (7/16)	22.7 (5/22)	16.7 (1/6)	0.178
White villi	12.5 (2/16)	54.5 (12/22)	0 (0/6)	< 0.001

GIST: Gastrointestinal stromal tumor; MLP: Multiple lymphomatous polyposis.

Table 3 Pathological features of the biopsy sites with or without white villi in malignant lymphoma

	White villi		*P*-value
	Presence	Absence	
Lymphoma cells infiltrating the villi with an intact epithelium	91.7% (11/12)	0 % (0/10)	< 0.001
Lymphoma cells infiltrating the villi without an intact epithelium	0% (0/12)	50.0% (5/10)	0.293
Lymphoma cells present in the deep mucosa	0% (0/12)	20.0% (2/10)	0.195
Not assessed	8.3% (1/12)	30% (3/10)	N/A

N/A: Not applicable.

Table 4 Summary of the endoscopic characteristics of the small intestinal tumors

	Group 1 (Epithelial)	Group 2 (Malignant lymphoma)	Group 3 (GIST)
Solitary tumor	1	2	1
Protruded or mass type	2	3	1
Infiltrative ulcerated type	2	3	3
Presence of stenosis	1	2	3
White villi	3	2	3

1: More likely; 2: Intermediate; 3: Less likely; GIST: Gastrointestinal stromal tumor.

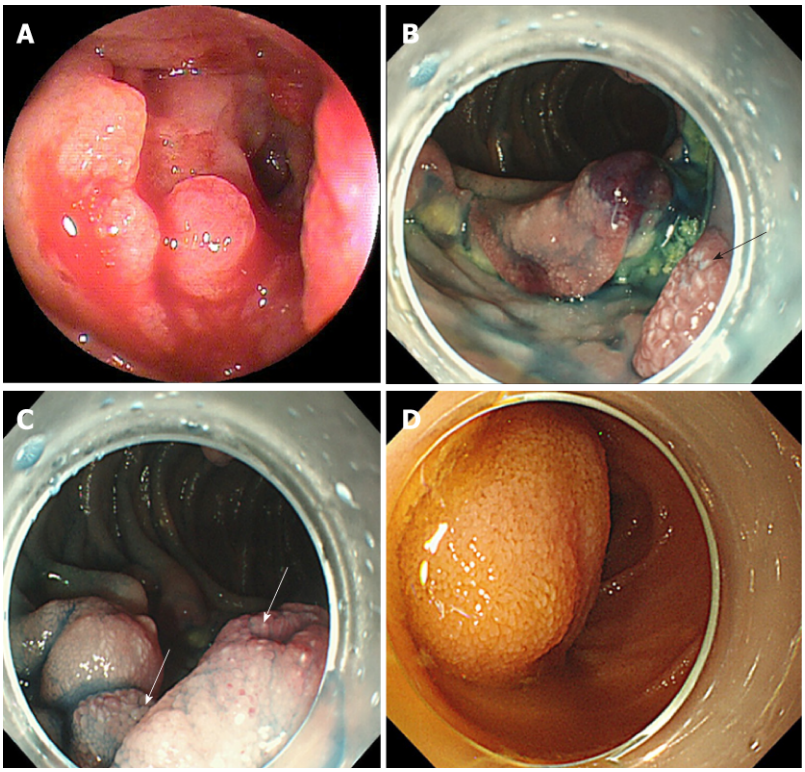

Figure 2 Endoscopic findings for each small intestinal tumor. A: Representative image of an epithelial tumor (Group 1: primary small intestinal cancer). This tumor was solitary and located in the jejunum. The type was infiltrative ulcerated type. This tumor was also associated with stenosis and bleeding; B and C: Representative images of malignant lymphoma (Group 2: diffuse large B-cell lymphoma). These tumors were multiple and located in the jejunum and ileum and appeared as ulcerated masses with raised margins. These tumors also had white villi (arrows) and were not associated with stenosis or bleeding; D: Representative image of a gastrointestinal stromal tumor (Group 3). This tumor was solitary and located in the jejunum and appeared as a protruded mass. This tumor was not associated with stenosis or bleeding.

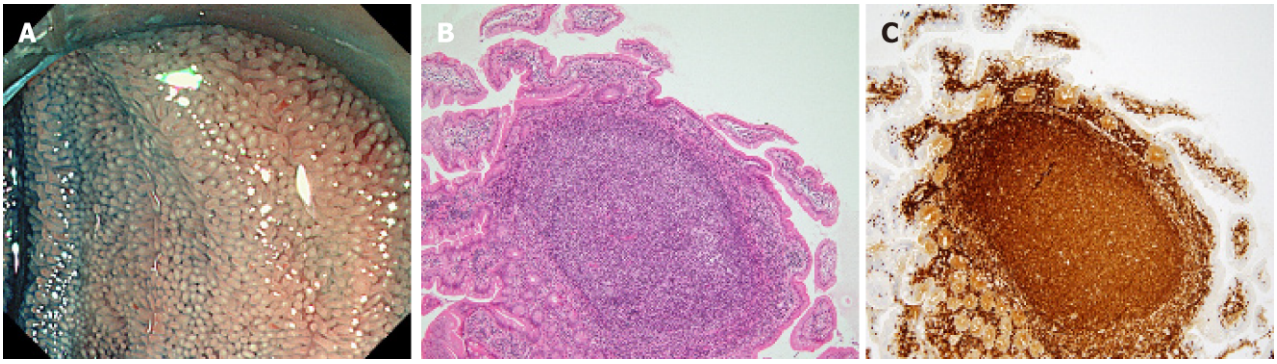

Figure 3 Endoscopic and pathological findings of the white villi. Representative endoscopic and pathological images of the white villi (Follicular lymphoma). A: White light image with indigo carmine staining shows diffuse white villi in the ileum; B, C: Pathological images are showing the lymphoma cells infiltrating the villi with an intact epithelium. Most of the villi are filled with lymphoma cells, which formed lymphoid follicles (B: Hematoxylin and eosin staining, × 10; C: Immunohistochemical staining for bcl-2 was positive, ×10).

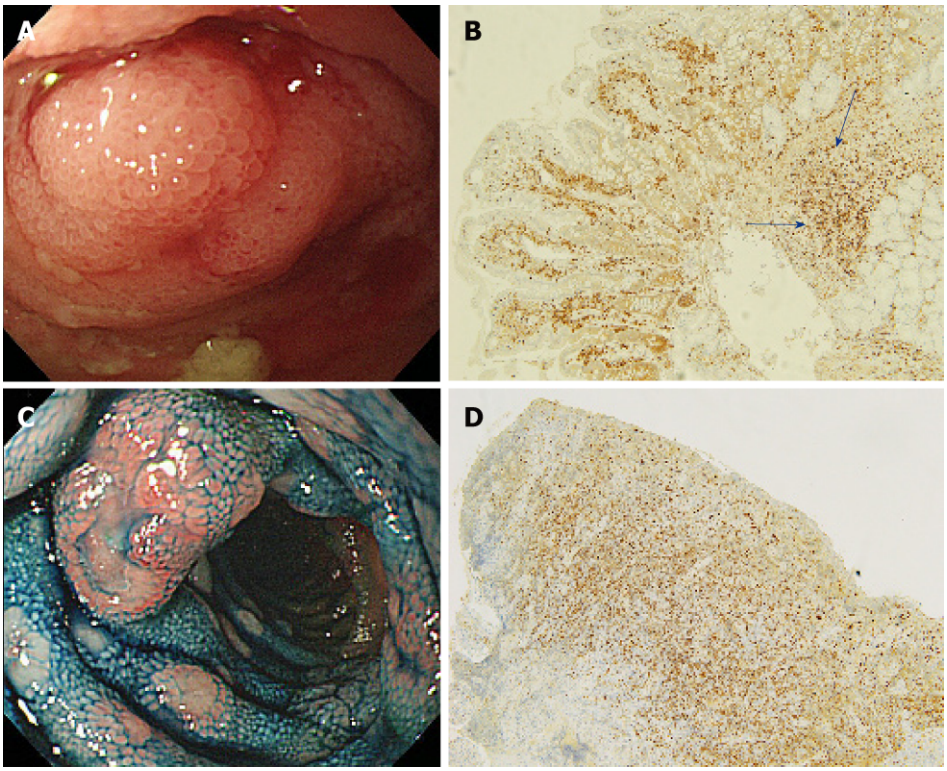

Figure 4 Endoscopic and pathological images of malignant lymphoma without white villi appearance. A, B: Representative endoscopic and pathological images of malignant lymphoma without white villi appearance (Follicular lymphoma) [A: White light image shows enlarged villi with stenosis, without white villi appearance in the ileum (with stenosis); B: Pathological image is showing the lymphoma cells sparsely infiltrating the villi, some lymphoma cells present in the deep mucosa (blue arrow), immunohistochemical staining for bcl-2, ×10]; C, D: Representative endoscopic and pathological images of malignant lymphoma without white villi appearance (Mantle cell lymphoma) (C: White light image with indigo carmine staining shows multiple polyposis with ulceration, without white villi appearance in the ileum; D: Pathological image is showing the lymphoma cells infiltrating the mucosa without an intact epithelium, immunohistochemical staining for cyclin D1, ×10).

ARTICLE HIGHLIGHTS

Research background

Capsule endoscopy and balloon-assisted enteroscopy (BAE) enable visualization of rare small bowel conditions such as small intestinal malignant tumors.

Research motivation

The details of the endoscopic characteristics of small intestinal malignant tumors are still unknown.

Research objectives

The aim of this retrospective study was to elucidate the endoscopic characteristics of small intestinal malignant tumors.

Research methods

This study was a retrospective medical record analysis. From March 2005 to February 2017, 1329 BAE procedures were performed at Keio University Hospital. Of these procedures, malignant tumors were classified into three groups, Group 1: epithelial tumors including primary small intestinal cancer, metastatic small intestinal cancer, and direct small intestinal invasion by an adjacent organ cancer; Group 2: small intestinal malignant lymphoma; and Group 3, small intestinal gastrointestinal stromal tumors. We systematically collected clinical and endoscopic data from patients' medical records to determine the endoscopic characteristics for each group.

Research results

The number of patients in each group was 16 (Group 1), 23 (Group 2), and 6 (Group 3), and the percentage of solitary tumors was 100%, 43.5%, and 100%, respectively ($P < 0.001$). Solitary protruding or mass-type tumors were not seen in malignant lymphoma (Group 2) ($P < 0.001$). Stenosis was seen more often in Group 1, (68.8%, 27.3%, and 0%; Group 1, 2, and 3, respectively; $P = 0.004$). Enlarged white villi inside and/or surrounding the tumor were seen in 12.5%, 54.5%, and 0% in Group 1, 2, and 3, respectively ($P = 0.001$).

Research conclusions

The differential diagnosis of small intestinal malignant tumors could be tentatively made based on BAE findings.

Research perspectives

Future studies require higher numbers of patients to analyze larger datasets.

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World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2019 May 16; 11(5): 383-388

DOI: 10.4253/wjge.v11.i5.383

ISSN 1948-5190 (online)

CASE REPORT

Role of colonoscopy in diagnosis of capecitabine associated ileitis: Two case reports

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Author contributions: Dao AE contributed to study design, data collection, manuscript writing and editing; Hsu A contributed to data collection, manuscript writing and editing; Nakshabandi A contributed to data collection and manuscript writing; Mandaliya R, Nadella S, Sivaraman A and Mattar M contributed to data collection and editing; Charabaty A contributed to study design, data collection and editing.

Informed consent statement: All procedures performed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1964 and later versions. Informed consent or a substitute of consent was obtained from all patients prior to inclusion in the study.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

CARE Checklist (2016) statement: The authors have read the CARE

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Abstract

BACKGROUND

Capecitabine is considered a first line agent in adjuvant therapy for breast and colorectal cancer. However, cases of severe diarrhea have been reported with increasing frequency in recent years. When diarrhea is severe and prolonged, capecitabine associated ileitis should be considered as a possible etiology.

CASE SUMMARY

Herein, we present two cases of capecitabine ileitis, specifically involving the terminal ileum and ascending colon. We will demonstrate the disease course and treatment modalities applied to alleviate this condition, as well as discuss the merits of using colonoscopy to aid in diagnosis.

CONCLUSION

Ultimately our cases demonstrate that symptomatic management with traditional anti-diarrheal medications is largely ineffective. Prompt recognition and discontinuation of capecitabine is an imperative step in proper management of this condition and colonoscopy with biopsy can be helpful when the diagnosis is unclear.

Key words: Capecitabine; Xeloda; 5-Fluorouracil; Ileitis; Ileocolitis; Colonoscopy; Case report

Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Manuscript source: Unsolicited manuscript

Received: January 29, 2019
Peer-review started: January 29, 2019
First decision: April 13, 2019
Revised: May 9, 2019
Accepted: May 13, 2019
Article in press: May 14, 2019
Published online: May 16, 2019

P-Reviewer: Guo JT, Lee CL, Smith RC, Wan QQ
S-Editor: Ji FF
L-Editor: A
E-Editor: Xing YX

Core tip: There have been nine published cases describing capecitabine associated ileitis, and only four of these cases document use of colonoscopy. We are presenting the fifth and sixth case reports of colonoscopy-assisted diagnosis of this condition. Combining analysis of these six colonoscopy reports, we determined patterns in the presentation of this condition. Given that the differential etiologies of diarrhea are so broad, we believe that our findings collectively can improve the diagnostic accuracy and optimize treatment. Additionally, we believe that colonoscopy with biopsy should be indicated as a standardized diagnostic measure in patients on capecitabine with refractory diarrhea.

Citation: Dao AE, Hsu A, Nakshabandi A, Mandaliya R, Nadella S, Sivaraman A, Mattar M, Charabaty A. Role of colonoscopy in diagnosis of capecitabine associated ileitis: Two case reports. *World J Gastrointest Endosc* 2019; 11(5): 383-388
URL: https://www.wjgnet.com/1948-5190/full/v11/i5/383.htm
DOI: https://dx.doi.org/10.4253/wjge.v11.i5.383

INTRODUCTION

Capecitabine (Xeloda) is an oral 5-fluorouracil (FU) prodrug used as adjuvant and/or palliative chemotherapy in the treatment of colorectal and breast cancer. According to monotherapy trials, up to 53% of patients develop diarrhea as an adverse effect. This diarrhea is usually self-limited, allowing patients to continue capecitabine with dose limitation[1]; however, in rare cases capecitabine associated ileitis can occur, causing a severe persistent diarrhea characterized on endoscopy by mucosal inflammation in the ileum despite discontinuation of the drug. This complication has the potential to result in severe pain, electrolyte imbalances, nutritional deficiencies, and life-threatening hemodynamic instability. Our two cases characterize the disease course of capecitabine associated ileitis with a focus on imaging, colonoscopy findings, and treatment options for this uncommon condition.

CASE PRESENTATION

Chief complaints

(1) Case 1: A 72-year-old Caucasian female presented to the hospital with severe watery diarrhea; and (2) Case 2: A 42-year-old African American female presented to the hospital with severe voluminous bloody diarrhea.

History of present illness

(1) Case 1: She denied bloody stools, abdominal pain, fevers, or chills; and (2) Case 2: She was having six to ten bowel movements per day (some of which were bloody) with associated abdominal pain and fever.

History of past illness

(1) Case 1: The patient had a past medical history of with stage IIIC ascending colon adenocarcinoma and previously underwent laparoscopic right hemicolectomy and was started on adjuvant chemotherapy with capecitabine. She additionally had a history significant for diabetes, hypertension, ischemic cardiomyopathy with a biventricular pacemaker, as well as coronary artery disease status post stent placement; and (2) Case 2: The patient had a past medical history of stage IIIC recurrent right breast cancer as well as deep vein thrombosis with pulmonary embolus on lovenox.

Personal and family history

(1) Case 1: The patient was a nonsmoker and social drinker, with no relevant family history; and (2) Case 2: The patient was a nonsmoker and denied alcohol use. Family history was negative for cancer and otherwise noncontributory.

Physical examination

(1) Case 1: On admission, physical examination was notable for multiple oral ulcers, however she had a nontender abdominal exam and was otherwise unremarkable; and (2) Case 2: Physical exam was notable for mild tenderness to palpation of the epigastrium and right lower quadrant of the abdomen. Initial labs were notable for

hypokalemia (K 2.9) and mild anemia (Hb 10.2), however there was no leukocytosis (WBC 4.4) or kidney injury (Cr 0.8).

Laboratory examination

(1) Case 1: Initial labs were concerning for severe malnutrition (albumin 1.7), leukopenia (WBC 1.5 K/mm^3 with ANC 900) and acute kidney injury (Cr 1.32, baseline 1). Laboratory examination also included infectious workup with Clostridium difficile, stool cultures, ova and parasites, and rotavirus, all of which resulted as negative. Given her cardiac risk factors, there was concern for ischemic colitis, however lactate was normal and she denied any history of abdominal pain, melena, or hematochezia; and (2) Case 2: Laboratory examination included negative infectious workup with Clostridium difficile, Giardia, Ova and Parasites, stool culture, and rotavirus all resulting as negative.

Imaging examination

(1) Case 1: Initial computed tomography (CT) abdomen and pelvis showed mildly dilated fluid-filled loops of small bowel with adjacent engorgement of vasa recta and mesenteric edema consistent with enteritis (Figure 1); and (2) Case 2: Initial CT Abdomen and Pelvis with contrast revealed marked thickening of the small bowel with fluid filled bowel loops.

Colonoscopy and histology

(1) Case 1: This prompted subsequent colonoscopy and ileoscopy, which demonstrated granular erythematous mucosa with ulceration both above and below the ileocolonic anastomosis (Figure 2). Ileal biopsy showed mucosal erosion with acute inflammation and occasional atypical glands most likely representing reactive changes without evidence of Cytomegalovirus or herpes simplex viruses on immunohistochemical stains; and (2) Case 2: On colonoscopy, the terminal ileum was found to have diffuse pseudomembranes with severe inflammatory exudates and spontaneous bleeding (Figure 3). The right colon demonstrated erythema and mucosal thickening suggestive of mild colitis. Biopsy from the ileum and colon showed necrotic and inflammatory debris, but was negative for granulomas or viral inclusions.

FINAL DIAGNOSIS

(1) Case 1: The final diagnosis was refractory diarrhea due to capecitabine associated ileitis; and (2) Case 2: The final diagnosis was bloody diarrhea due to capecitabine associated ileitis.

TREATMENT

Case 1

On admission, the patient's capecitabine was held. In addition to fluid and electrolyte resuscitation, diarrhea was addressed with loperamide, lomotil, and octreotide - however symptoms did not improve. Cholestyramine (4 mg daily) was trialed to counter any biliary diarrhea that may have contributed due to her prior right hemicolectomy. Additionally oral budesonide was trialed for three days in case of chemotherapy induced mucositis given the development of oral sores. She eventually required a three week course of total parenteral nutrition to address her severe protein deficiency.

Case 2

Capecitabine was held on admission due to concern that this was a potential etiology of the diarrhea. She underwent a short course of antibiotics that was then discontinued when infectious etiology was adequately ruled out. Despite stopping chemotherapy, diarrhea persisted and workup with a colonoscopy including ileoscopy was performed. As in the case above, the patient was initially fluid and electrolyte resuscitated and once infection was no longer a concern she was trialed on various anti-diarrheal medications that were ultimately unsuccessful including lomotil, loperamide, cholestyramine, and octreotide. Additionally, she was trialed on oral budesonide which improved abdominal pain however did not resolve the diarrhea. There was a discussion regarding initiation of parenteral nutrition however it was ultimately decided against as symptoms appeared to be improving by this time. Instead, she was trialed on a low lactose, low fat, high protein diet which seemed to

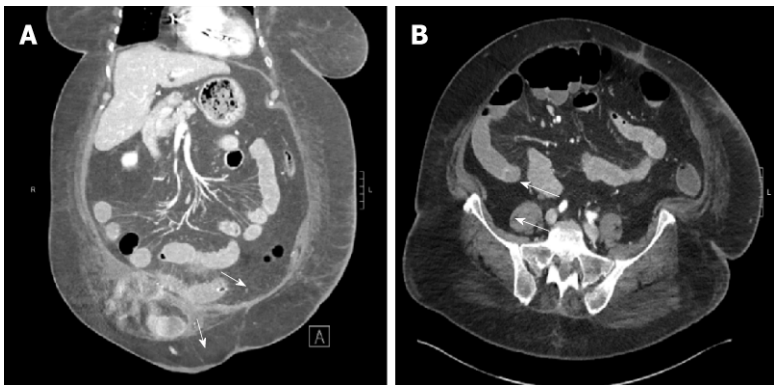

Figure 1 Abdominal computed tomography findings of enteritis. A: Axial computed tomography (CT) of the abdomen demonstration vasa recta engorgement and mesenteric edema (arrows); B: Coronal CT of the abdomen with "comb sign" demonstrating vasa recta engorgement and mesenteric edema (arrows).

contribute to the improvement of diarrheal symptoms by the end of her course.

OUTCOME AND FOLLOW-UP

(1) Case 1: Despite these interventions, the patient still had voluminous diarrhea for a total of four weeks after cessation of capecitabine. To date, she has not been restarted on capecitabine at any dose given the severity of her symptoms; and (2) Case 2: By four weeks after discontinuation of capecitabine, diarrhea had resolved and stools were improving in frequency and consistency. As in case 1, this patient was never restarted on capecitabine due to the severity of her diarrhea.

DISCUSSION

Capecitabine is an oral precursor of the antineoplastic agent FU. FU is a pyrimidine analog that inhibits the synthesis of the nucleoside thymidine, therefore interfering with normal DNA replication. Administration of FU is intravenous and nonspecific, resulting in harsh widespread toxicities including neutropenia, stomatitis, and diarrhea[2]. Capecitabine was developed as a preferred agent to FU due to its oral route of administration and its multi-step metabolism conferring a more targeted distribution of active metabolite. It is considered a first line therapy for metastatic colorectal cancer when single agent fluoropyrimidines are indicated. The most clinically significant adverse effects of capecitabine include hand-foot syndrome and diarrhea, both of which can be so severe that treatment must be redirected.

Capecitabine induced ileitis is a rare yet severe adverse effect that has only been documented in few cases in the recent past. Roche Drug Safety identifies the incidence of suspected ileitis to be less than 0.01% of their patient population[3]. It was first recognized as a complication of capecitabine in 2012 by Radwan *et al*[3], however its exact pathophysiology is still unknown. It has been proposed that decreased blood flow to intestinal mucosa and pro-inflammatory cytokines may contribute to mucosal injury[4]. In a report by Lee *et al*[5], the authors describe two cases of capecitabine induced ileitis based on radiological evidence. Key management principles include early recognition of the adverse reaction, immediate cessation of capecitabine, and supportive therapy with total parenteral nutrition. In one of these cases, the diarrhea subsided 29 d post cessation of capecitabine[5]. This was the same amount of time required to resolve the diarrhea after stopping the chemotherapy as reported in our two cases. These findings suggest that capecitabine induced ileitis can last multiple weeks and is not likely to respond to more conservative methods such as antimotility agents (*i.e.*, lomotil, loperamide) or antisecretory agents (*i.e.*, octreotide).

To date, there have been only nine published cases describing capecitabine associated ileitis, and only four of these cases document use of colonoscopy in diagnosis[6-9]. We are presenting the fifth and sixth case reports of colonoscopy-assisted diagnosis of this condition. Combining our analysis of these six colonoscopy reports (Table 1), we have determined some patterns in the presentation of this condition. Firstly, capecitabine associated ileitis tends to localize in the terminal ileum. Secondly, a granular erythematous appearance of mucosa with ulcerations is

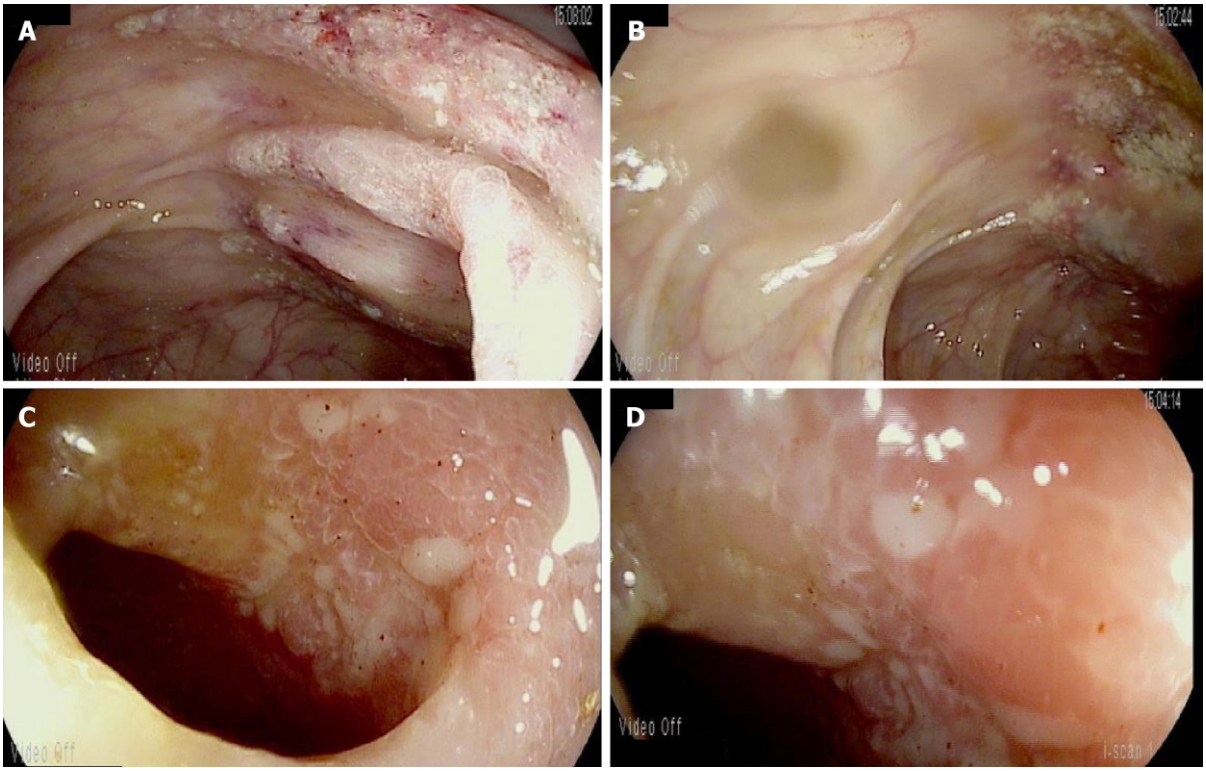

Figure 2 Colonoscopy and ileoscopy findings for case 1. A, B: For our first case, colonoscopy shows granular erythematous mucosa of the ascending colon (A and B) distal to the ileocolonic anastomosis; C, D: On ileoscopy, evidence of ulceration can be seen in the distal ileum (C and D).

commonly seen. Two of the six reports disclose a biopsy that is positive for eosinophilic infiltrates, and one report from our institution describes a pseudomembrane with inflammatory exudates. Given that the differential etiologies of diarrhea in a hospitalized patient is so broad (colitis, bacterial vs viral infection, inflammation, medication-induced) we believe that these findings collectively can improve the diagnostic accuracy of this condition and optimize treatment options. Additionally, we believe that colonoscopy with biopsy should be indicated as a standardized diagnostic measure in patients on capecitabine with diarrhea refractory to conservative methods.

In all published cases, approach to management posed a significant challenge. It appears that a combination or trial of cessation of capecitabine, fluid and nutritional resuscitation with TPN, and administration of steroids have shown some benefit[6,7,10].

CONCLUSION

Ultimately our cases demonstrate that symptomatic management with traditional anti-diarrheal medications is largely ineffective. There may be some role in symptomatic management of abdominal pain with the use of oral steroids, however this prospect requires further study. Overall, capecitabine induced ileitis is a serious adverse effect that is being recognized with increasing frequency in recent years. Supportive management with parenteral nutrition, hydration, and pain management are the cornerstone of treatment while inflamed intestinal mucosa heals. Prompt recognition and discontinuation of capecitabine is an imperative step in proper management of this condition and colonoscopy with biopsy can be helpful when the diagnosis is unclear.

Table 1 Colonoscopy and histology reports from previous case reports of capecitabine associated ileitis

Case report	Findings seen on (1) colonoscopy and (2) histology
Barton[6], 2006	(1) Ulcerative ileitis (2) Eosinophilic infiltrates
Al-Gahmi *et al*[7], 2012	(1) Isolated ulceration in the terminal ileum (2) Inflammatory changes and eosinophilic infiltrate but no evidence of malignancy or granulomas
Mokrim *et al*[8], 2014	(1) Inflammatory changes in the ileal mucosa (2) Absence of intraepithelial lymphocytic infiltrates in favour of a non-atrophic ileitis
Van Hellemond *et al*[9], 2018	Terminal ileitis Extensive inflammation of the small intestine
Case 1	(1) Evidence of granular erythematous mucosa with ulceration both above and below the ileocolonic anastomosis in the terminal ileum and ascending colon(2) Mucosal erosion with acute and chronic inflammation and occasional atypical glands most likely representing reactive changes without evidence of Cytomegalovirus or herpes simplex viruses on immunohistochemical stains
Case 2	(1) On colonoscopy, the terminal ileum was found to have diffuse pseudomembranes with severe inflammatory exudates and spontaneous bleeding.(2) Necrotic and inflammatory debris, but was negative for granulomas or viral inclusions.

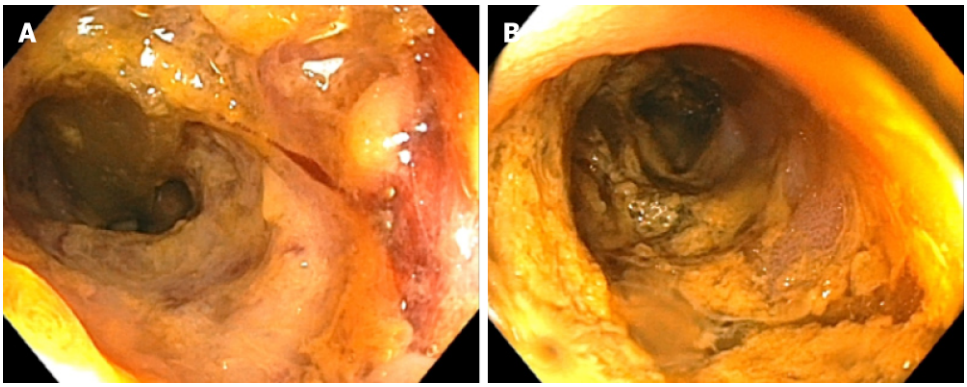

Figure 3 Colonoscopy and ileoscopy findings case 2. For our second case, the ileum was noted to be severely granular and friable, with ulceration seen throughout.

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World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2019 May 16; 11(5): 389-394

DOI: 10.4253/wjge.v11.i5.389

ISSN 1948-5190 (online)

CASE REPORT

Post-oesophagectomy gastric conduit outlet obstruction following caustic ingestion, endoscopic management using a SX-ELLA biodegradable stent: A case report

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Author contributions: Musbahi A compiled case notes and wrote the first draft; Viswanath YKS contributed to editing, redrafted few times and submitted.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment

Conflict-of-interest statement: Nothing to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Manuscript source: Invited

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Abstract

BACKGROUND

Benign oesophageal strictures secondary to caustic ingestion are rare and difficult to manage. They often present with symptoms such as chest pain, dysphagia and vomiting. Surgical resection is often not justified in majority of these cases who later presents with recurrent benign stricture.

CASE SUMMARY

We present a unique case of a patient who presented with post-oesophagectomy gastric conduit outlet obstruction (POGO) secondary to caustic ingestion. Our patient had already undergone two stage oesophagectomy with pyloroplasty for operable oesophageal cancer with curative intent 5 years prior. This is a distinctive case, where a successful deployment of a SX-ELLA biodegradable (BD) stent (019-10A-28/23/28-080) after failed dilatations. We have briefly reviewed literature with regards to the role BD stents in patients with recurrent benign stricture and discussed management dilemma.

CONCLUSION

We recommend the attending gastroenterologist should bear the usefulness of BD stents in the management of refractory POGO after oesophagectomy.

Key words: : Biodegradable; Stent; Oesophagectomy; Case report

Core tip: A 69 years old, who had previous oesophagectomy, presented with weight loss, regurgitation and vomiting. He gave a history of recent caustic ingestion. Subsequent

manuscript

Received: February 28, 2019
Peer-review started: March 1, 2019
First decision: April 5, 2019
Revised: April 23, 2019
Accepted: May 1, 2019
Article in press: May 1, 2019
Published online: May 16, 2019

P-Reviewer: Dinç T, El-Shabrawi MHF, Qi XS, Sterpetti AV
S-Editor: Ji FF
L-Editor: A
E-Editor: Xing YX

assessments revealed, delayed gastric conduit emptying with features indicative of post-oesophagectomy gastric conduit outlet obstruction (POGO). Initial conservative measures followed by 3 attempts at dilatations failed, and later endoscopically managed by deployment of SX Ella biodegradable (BD) stent across the scarred pyloric channel. He has remained symptom free and has put on weight at 8 months follow up. This is a distinctive case of utilization of BD stent in the management of post caustic pyloric stricture after previous two-stage Ivor Lewis oesophagectomy.

Citation: Musbahi A, Viswanath Y. Post-oesophagectomy gastric conduit outlet obstruction following caustic ingestion, endoscopic management using a SX-ELLA biodegradable stent: A case report. *World J Gastrointest Endosc* 2019; 11(5): 389-394
URL: https://www.wjgnet.com/1948-5190/full/v11/i5/389.htm
DOI: https://dx.doi.org/10.4253/wjge.v11.i5.389

INTRODUCTION

Benign upper gastrointestinal and oesophageal strictures secondary to caustic ingestion are rare and management remains challenging. They often present with symptoms such as chest pain, dysphagia and vomiting[1]. Symptomatic strictures often require endoscopic intervention usually via dilatation either using a balloon or bougie[2]. Patients with recurrent strictures are offered endoscopic stent using a biodegradable (BD) stent rather a self-expanding metallic stent. The later are associated with problems secondary to migration, erosions and the need for their removal. Surgical resection is often not justified in majority of these cases who later presents with recurrent benign stricture.

We report a patient with a back-ground history of psychiatric illness and who have undergone Ivor Lewis oesophagectomy with vagotomy for operable cancer 5 years prior. He presents with chest pain vomiting and weight loss with recent history of caustic ingestion. Endoscopy and imaging assessments revealed post-oes-ophagectomy gastric conduit outlet obstruction (POGO) and he failed to respond to initial endoscopy dilatations. Consequently, a decision to manage POGO with a BD stent was taken with a successful outcome.

CASE PRESENTATION

Chief complaints

We present a 69-year-old man with previous curative two stage Ivor Lewis oes-ophagectomy with concomitant pyloroplasty, 5 years prior for operable oes-ophageal adenocarcinoma.

History of past illness

He carried a past history of bipolar psychiatric illness requiring multiple emergency admissions with history of deliberate self-harm.

History of present illness

He presented to emergency room with history of caustic ingestion with symptoms of odynophagia, dysphagia, hematemesis, chest pain and vomiting. Patient was treated conservatively with high dose proton pump inhibitors, tranexamic acid, blood products, antibiotics, total parenteral nutrition initially followed by enteral nutrition. After initial endoscopic assessments, he was discharged on high dose proton pump inhibitors. Three months later, he represents with weight loss, chest pain and vomiting.

FINAL DIAGNOSIS

Subsequent assessments on endoscopy, CT, chest X ray (Figure 1A), contrast swallow (Figure 1B), a diagnosis of caustic stricture with fibrosis at pyloric channel of the gastric conduit was established (POGO, Enteral naso-jejunal feed was used to oversee his nutrition and allowed intake of his routine medication. Treatment with initial two

balloon dilatations and one bougie dilatation (Figure 2) failed with follow-on recurrence of vomiting. All along, at endoscopy he was found to have lot of fluid residue in the gastric conduit alongside negotiable pyloric channel with difficulty. This was due to angulation diaphragmatic hiatus and associated scarring on over one third of its circumference. He was then considered for the possibility of placement of a BD stent with definitive intent rather a removable metallic stent.

TREATMENT

Placement of BD stent; Under sedation, with midazolam (5 mg) and Alfentanyl (150 micrograms), a 24 mm SX-ELLA (019-10A-28/23/28-080) BD stent (Figure 3A) was placed over a guidewire under X-ray guidance. The deployed Ella BD stent had a diameter of 23 mm for the body and 28 mm for proximal and distal flare. A conclusion contrast stentogram confirmed satisfactory position of BD stent, so also on check completion endoscopy (Figure 3B and C). He was kept as an inpatient for 48 h with intravenous antiemetics and was allowed oral fluids and liquid diet for 6 wk.

OUTCOME AND FOLLOW-UP

Follow up at 8 wk and 6 mo revealed complete symptomatic resolution with improved nutritional status and subsequently he was discharged. Follow up X ray confirmed normal looking shadow of the decompressed conduit without a fluid level (Figure 4)

DISCUSSION

In upper gastrointestinal tract, oesophageal strictures of benign etiology can occur commonly secondary to gastro-esophageal reflux disease, post-surgery such as oesophagectomy at the anastomosis, after radiotherapy or secondary to caustic ingestion[1]. However, benign stricture following caustic ingestion causing pyloric channel stricture at the outlet of gastric conduit are rare.

Management of benign upper GI and esophageal strictures remains challenging. Mainly in majority of endoscopy units, the dilation is carried out with either a bougie or a balloon. More than 80% of these patients usually respond and a proportion of them need more than one session. Around 10% develop a refractory or recurrent stricture. These usually require several dilatations raising risks of bleeding and perforation[2].

Oesophageal strictures can be simple or complex. Simple strictures are short (< 2 cm), focal, straight, and passable with an endoscope such oesophageal web or Schatzki's ring. A non-passable or significantly narrowed diameter (< 12 mm) stricture, that is longer than 2 cm and tortuous are deemed complex. These are mainly occur following surgery, radiotherapy or corrosive ingestion and are difficult treat[3]. Management of POGO remains a challenge, endoscopic intervention is technically demanding given the angulation at the level of diaphragm and postsurgical anatomic configuration.

Recurrent and refractory strictures are usually distinguished by; fibrotic stenosis restricting the oesophageal lumen, absence of active inflammation or motility disorder, and failure to achieve a luminal diameter of 14 mm for 4 wk after 5, two weekly dilatations[3].

There are no defined characteristics for refractory POGO published in the literature. In this case, persistent symptoms and failed 3 dilations are taken in to account prior to the placement of a BD stent.

Since 2008, BD stents are accessible for endoscopic intervention; they usually degrade after 11-12 wk. Therefore, BD stents are an attractive substitute to treat dysphagia secondary to benign or malignant strictures[4]. Placement of a BD stent is seen as an alternative to repeated dilatations in a patient with benign refractory stricture, with the objective of reducing dilatations and allowing remodeling at stricture site[5].

The use of stents as a palliative measure in malignant strictures has been well established. A range of benign stenosing disorders of the esophagus and upper gastro-intestinal tract can also be treated safely with a self-expanding or BD plastic stent such as benign oesophageal strictures secondary to peptic disease or caustic injury[5]. In this case, ingested caustic caused initial inflammation with ulceration followed by pyloric channel fibrosis, resulting in POGO. This is a distinctive case

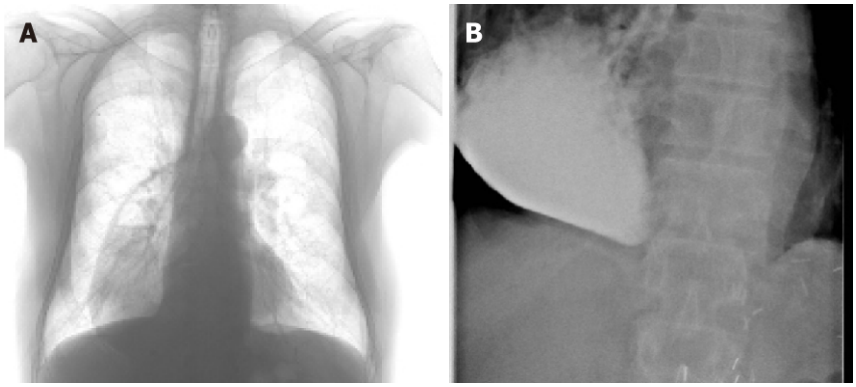

Figure 1 Chest x ray with a dilated gastric conduit with air fluid level and a contrast X ray showing meagre passage of contrast with dilated gastric conduit. A: Chest X ray demonstration a dilated gastric conduit with air fluid level; B: Contrast X ray showing meagre passage of contrast with dilated gastric conduit.

report we know of a BD stent being used in an obstructed gastric conduit in a post-oesophagectomy patient to treat a caustic stricture of the pylorus. We advocate attending gastroenterologist to contemplate using BD stents in selected patients at similar clinical situations.

CONCLUSION

In this article, authors have illustrated the role of a BD stent in the management of caustic pyloric stricture. The treating endoscopic physician should contemplate the usage of a BD stent in these challenging situations even after oesophagectomy. The role of a BD stent in the management caustic Upper GI refractory stricture is not well understood needs further investigation.

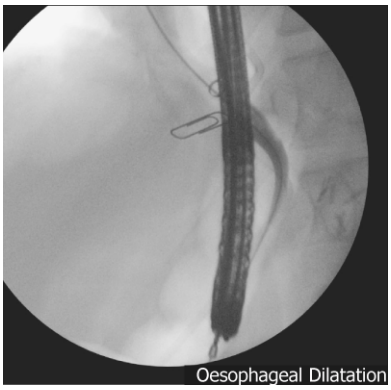

Figure 2 Bougie dilatation with two clip markers at the site of pyloric stricture.

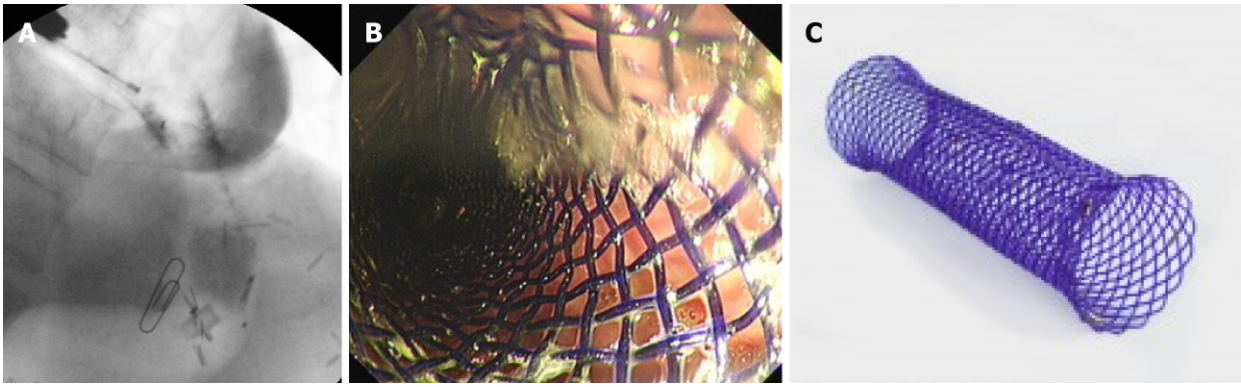

Figure 3 Contract X ray deployed biodegradable stent with endoscope in the gastric conduit together injection catheter, endoscopic and outside view of the biodegradable stent. A: Contrast in the deployed biodegradable (BD) stent with endoscope in the gastric conduit together injection catheter; B: Endoscopic view of the deployed BD stent; C: Sx Ella BD stent.

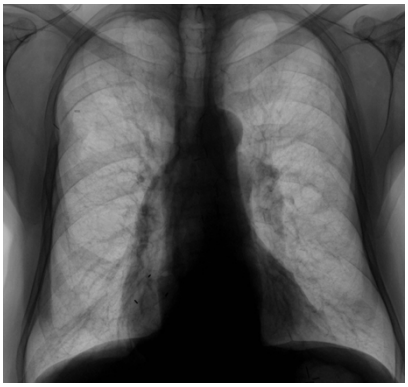

Figure 4 X ray showing well decompressed gastric conduit with proximal radio opaque markers of the biodegradable stent.

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