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MINIREVIEWS

Colorectal endoscopic submucosal dissection in special locations

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Abstract

Colorectal endoscopic submucosal dissection (ESD) is considered one of the most challenging endoscopic procedures for novice endoscopists. When compared with the stomach, the colon and rectum have a narrower tubular lumen, greater angulation at the flexures, and a thinner muscle layer. These factors make endoscopic control and maneuverability difficult. ESD of the colorectum was considered more difficult than gastric and esophageal ESD. However, with learning from the experts, practicing, and selecting an appropriate technique, most of colorectal ESD could be performed successfully. Nevertheless, some colorectal locations are extremely specialized either from unique anatomy or given unstable scope position. Accordingly, the objective of this review was to provide endoscopists with an overview of the techniques and outcomes associated with ESD at these special colorectal locations. ESD at the discussed special locations of the ileo-colo-rectum was found to be feasible, and outcomes were comparable to those of ESD performed in non-special locations of the ileo-colo-rectum. Practice for skill improvement and awareness of the unique characteristics of each special location is the key to performing successful ESD.

Key words: Colorectal endoscopic submucosal dissection; Endoscopic submucosal dissection; Special locations

Core tip: Colorectal endoscopic submucosal dissection (ESD) involving ileocecal valve, appendiceal orifice or anal canal is considered to be extremely challenging for novice ESD endoscopist. With well-prepared strategies and appropriate assisting devices, the

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successful procedures with less complications can be achieved. We made great efforts to review and summarize the currently proposed techniques to overcome these difficulties.

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INTRODUCTION

Colorectal endoscopic submucosal dissection (ESD) is considered one of the most challenging endoscopic procedures for novice endoscopists. When compared with the stomach, the colon and rectum have a narrower tubular lumen, greater angulation at the flexures, and a thinner muscle layer. These factors make endoscopic control and maneuverability difficult. However, with expert instruction, practice, and awareness of the potential pitfalls at each special colorectal location, most colorectal lesions can be managed by conventional ESD[1]. The rectum is regarded as being the easiest location for beginner endoscopists, while the right-sided colon and lesions on the flexures are considered to be the most problematic locations[2]. Moreover, some locations require special consideration given their unique anatomy. These "special" locations locate at both extreme portions of the colorectal part of the gastrointestinal system. Specifically, these areas include the ileocecal area (including the appendix) and the anorectal area (including the anal canal). Before ESD era, superficial tumors in these special locations required surgical treatment. Currently, most ESD centers are able to successfully manage lesions at these difficult to manage locations. The objectives of this review were to provide endoscopists with an overview of the techniques and outcomes associated with ESD at these special colorectal locations.

ESD AT THE ILEOCECAL VALVE AND TERMINAL ILEUM

Endoscopic treatment of lesions involving the ileocecal valve (ICV) is technically difficult due to poor endoscope maneuverability, abundant fatty tissue, and distinctive anatomic features[3]. Endoscopic mucosal resection (EMR) is a basic technique that can be used to manage lesions at the ICV and terminal ileum. A prospective single-center study by Nanda *et al*[4] reported that EMR for tumors involving the ICV achieved 94% clinical success for complete adenoma clearance. However, *en bloc* resection was achieved in 8.5% of cases, and tumor recurrence was observed in 17.5% of cases in that study. Previously, a surgical operation would be performed when EMR was not considered to be feasible. However, patients are at risk of decreased quality of life after ICV resection as the ICV plays important in bile acid absorption[5,6]. The ICV also functions to prevent regurgitation of material from the cecum backward into the ileum, and it delays passage of ileal contents from the terminal ileum into the cecum. The development and implementation of ESD diminished the role of EMR and surgical resection of ileocecal lesions. The first case series of ESD for colorectal neoplasia involving ileocecal lesions included eight patients, and the *en bloc* resection rate was 75%[7]. A single-center study that compared 38 lesions with ICV involvement to 132 cecal lesions found the *en bloc* resection rate to be similar to that of non-ICV lesions, but the procedure time was 37 min longer[8]. The complication of most concern relative to ESD in the ICV area is post-ESD stricture. The Yoshizaki *et al*[8] study did not describe any incidence of this complication; however, that study did not have any lesions with whole circumferential ICV involvement. Colorectal ESD involving the ICV for a submucosal tumor was also reported in one case[9]. In that case, a 40-mm pedunculated lipoma was resected *en bloc* from the ileocecal area without complication. In short, ESD of lesions involving the ICV is feasible and safe, but it should be emphasized that the aforementioned procedures were all performed by experienced endoscopists. Generally, there was no consensus on the definition of experienced ESD endoscopists. However, the feasibility study on training colorectal ESD revealed that colorectal ESD could be performed safely and effectively when more than 100 colorectal ESD procedures have been reached[10].

TECHNICAL ASPECTS SPECIFIC TO ESD AT THE ICV AND TERMINAL ILEUM

It is essential to examine the ICV circumferentially in both the forward and retroflexed views (Figure 1), particularly when the inferior lip is involved. An endoscope with a smaller retroflexion radius is preferred. When necessary, the tip of the endoscope should be fitted with a transparent plastic cap to deflect mucosal folds and polyp tissue. The distal attachment also helps to increase endoscope stability, facilitate access, and visualization of the very distal ileum and the lips of the ICV. The procedure includes blocking the tumor from moving into the terminal ileum by injecting undiluted sodium hyaluronate (MucoUp®; Boston Scientific Corporation, Marlborough, MA, United States) into the submucosa in the terminal ileum. Starting from the ICV side is a more favorable approach. When fatty tissue is experienced during submucosal dissection (Figure 2), the electrocautery setting may need to be increased. Switching from FORCED COAG mode to ENDO-CUT I or SWIFT COAG mode will enhance cutting ability. Table 1 illustrates suggested settings for submucosal dissection on fatty tissue based on the authors' experience using ERBE VIO 200/300 series (Erbe, Tuebingen, Germany). Nevertheless, be noted that the electrocautery setting depends on endoscopists' preference. In proximal colon tumors with unstable scope position and that are difficult to reach with a conventional colonoscope, balloon-assisted ESD is an option that can help to maintain scope stability and improve maneuverability. Balloon-assisted ESD enhanced the *en bloc* resection and curative resection rates in proximal colon tumors[11].

A recent review collected and evaluated 17 cases of early ileal adenocarcinoma that were reported in the literature. Most of the tumors located < 10 cm from the IC valve, which suggested that they could be reached by a conventional colonoscope[12]. ESD at the terminal ileum can be performed in a manner similar to that employed for colorectal ESD (Figure 3). However, very few cases of ESD performed at the terminal ileum have been reported[12,13], which makes it difficult to arrive at a conclusion regarding the outcome of ESD at this location. In the two immediately aforecited cases, the procedure was successfully accomplished without complications, and no luminal stricture or tumor recurrence was observed during the follow-up.

ESD AT THE APPENDICEAL ORIFICE

Colorectal tumors that involve the appendix were previously surgical candidates. Laparoscopic surgery is the mainstay of treatment after unsuccessful EMR and in cases where it is thought that EMR is unlikely to achieve successful *en bloc* resection. The cost of laparoscopic surgery is higher than the cost of endoscopic resection[14]. In addition, Hon *et al*[15] reported that the burden on patients, in terms of treatment time, time to normalize bowel function, and length of hospital stay, was significantly lower for ESD than for laparoscopic surgery. A retrospective single-center study comparing laterally spreading tumors (LSTs) proximal to the appendiceal orifice to those away from the appendiceal orifice showed similar ESD outcomes relative to *en bloc* resection rate, procedure time, and complications[16]. Another larger retrospective study that included 76 lesions reported a 95% *en bloc* resection rate, with a 2.6% incidence of post-operative appendicitis[17].

TECHNICAL ASPECTS SPECIFIC TO ESD AT THE APPENDICEAL ORIFICE

Lesions located in the cecum that involve the appendiceal orifice can be challenging to treat by ESD (Figure 4) since they are frequently associated with submucosal fibrosis caused by excessive intestinal peristalsis and/or previous appendicitis. In addition, *en bloc* resection is often difficult given the narrow working space. These lesions tend to be visualized en face ahead of the endoscope. The tip of the operating knife is, therefore, often perpendicular to the dissection plane, which results in an inevitable risk of perforation[18]. Moreover, the maneuverability of the endoscope is often hampered by paradoxical movements. Taken together, the procedures associated with and required for ESD of tumors involving the appendiceal orifice are extremely difficult.

Tashima *et al*[16] proposed the following steps to achieve *en bloc* resection. Firstly, a thorough mucosal incision, including cutting of the muscularis mucosae, needs to be performed. This initial step broadens the narrow operating space and facilitates the

Table 1 Electrocautery setting for submucosal dissection in fatty tissue

Mode	Effect	Output (Watts)	Duration	Interval	Effect	Output (Watts)	Duration	Interval
	General	Fatty tissue	General	Fatty tissue	General	Fatty tissue	General	Fatty tissue
Dry cut	2	3-4	30	30-50				
Endo cut i	2	3-4	None	None	3	3	3	3
Forced coag	2	3-4	30-40	30-50				
Swift coag	2	3-4	40-50	50				

resection of the lesion. Secondly, since the lesion could otherwise drop into the appendiceal cavity, an entire circumferential incision should be avoided prior to completion of the submucosal dissection. A small-caliber-tip transparent hood should be used to facilitate the submucosal insertion (Figure 5).

ESD AT THE ANAL CANAL

The rectum is divided into the upper rectum (Ra) and the lower rectum (Rb) by the peritoneal reflection. The lower rectum, given its proximity to the anal canal, has unique anatomical characteristics compared to the upper rectum[19-21]. In this area, blood vessels from the rectal venous plexus are abundant and directly drain into the systemic circulation which bring about to a considerable risk of systemic bacteremia following endoscopic procedures[22,23]. In addition, internal and external hemorrhoids, which are very common in general population, often exist in this area[24]. So there is a higher risk of bleeding after endoscopic procedures[25]. Moreover, the squamous epithelium below the dentate line is rich in sensory nerves, which increases the likelihood of pain during endoscopic procedures[20,23]. Lastly, the narrow lumen proximal to the anal sphincter makes it difficult to maintain good visualization and obtain good scope operability (Figure 6). Accordingly, lesions in the lower rectum must be managed while keep these additional considerations in mind.

In the past, treatment for anorectal tumors located close to the dentate line was mainly transanal surgical resection, which was reported to be safe and effective[26]. The advantage of transanal excision, including transanal endoscopic microsurgery (TEM), is the ability to achieve full-thickness resection, which serves as definitive treatment for invasive carcinomas. However, local recurrence rates ranging from 23% to 31% have been reported[26-28], and complications, such as temporary ileostomy, were necessary in some cases[29-31]. Even though ESD is limited to submucosal and mucosal resection, it is a sufficient treatment method when lesions can be resected *via* the vertical margin according to the preoperative diagnosis. ESD has the additional advantages of minimal invasiveness and minimal use of anesthesia compared to TEM. Whether TEM or ESD is better for removing anorectal tumors remains a topic of debate. Several endoscopic centers recently reported success using ESD to manage lesions located close to the dentate line[25,32,33] and lesions at the anal canal[34-37]. Those findings revealed *en bloc* resection rates comparable to those observed in upper rectal tumors[32,33]. However, lower curative resection rates and longer procedural times were observed in rectal tumors located closes to the dentate line[32]. The main factor that contributes to non-curative resection in anorectal tumors is the presence of burning artifacts in the anal side that are caused by thermal damage.

TECHNICAL ASPECTS SPECIFIC TO ESD AT THE ANAL CANAL

Special measures for ESD of lesions located close to the dentate line have been proposed[32]. A resection line at the anal side is determined under direct visualization of the tumor margin. To maintain a good visual field, a transparent hood is attached to the tip of the endoscope. It is necessary to approach the lesion with the ESD knives in a horizontal direction in order to minimize thermal injury to the muscle layer. This approach is proficient by positioning the lesion in line with the endoscope device port. To relieve pain during the procedure, 1% lidocaine (100 mg/10 mL) is added to the injection solution or is locally injected on the anal side of the lesion before submucosal injection with mixing solution. At the anal canal area, the submucosal layer is united tightly with mucosal epithelium by submucosal muscle strands

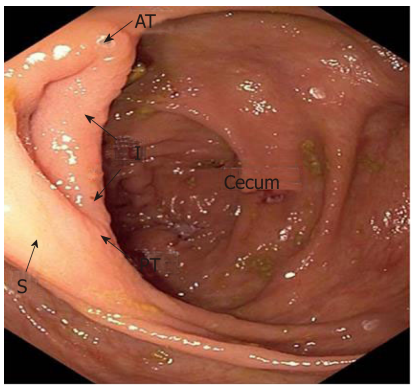

Figure 1 The ileocecal valve was divided into four sections: anterior angle, posterior angle, inferior lip, and superior lip. A: Anterior angle; P: Posterior angle; I: Inferior lip; S: Superior lip.

(musculus submucosa ani), which are derived from longitudinal muscle of the rectum. Complete disunion of these submucosal muscle strands, and achieving access just superior to the muscularis propria layer is of utmost importance. Additionally, hemorrhoidal vessels vertically penetrate the muscle layer, and hemorrhoids develop in the middle of the submucosal layer. Submucosal dissection performed at the level just above the muscularis propria layer leads to shutting off the source of the blood supply into the hemorrhoids. When congested hemorrhoidal columns are observed, preventive hemostasis should be performed. If the dissecting level is too shallow or is contained to the middle submucosal layer, many hemorrhoidal vessels would be encountered and a substantial amount of time would be required to process them. Severe fibrosis is also more often observed with anorectal tumors[33,38]. Scissor-type knives are beneficial for contending with the profuse fibrovascular submucosa at the anal canal. These scissor-type knives perform efficiently in severely fibrotic areas as well as they are effective to control bleeding (Figure 7). Last but not least, Carbon dioxide insufflation is necessities to prevent pneumoretroeritoneal and pneumomediastinum for rectal ESD[39].

Postoperative anal pain can be observed in 16%-18% of patients[33]. Most patients can be managed conservatively by oral non-steroidal anti-inflammatory drugs or steroid suppositories. Pain usually subsiding within a few days. High-grade fever was observed in about 22% of patients in a retrospective study[32]. This study also found that administration of prophylactic antibiotics could decrease the incidence of high-grade fever; however, the difference between groups did not achieve statistical significance[32]. Experience from our institute regarding infectious complication of ESD involving the anal canal was correspondent to the above mentioned study. For postoperative bleeding, the risk was similar to that found in overall rectal ESD, and the presence of hemorrhoid was not associated with perioperative bleeding[32]. Thus, careful prophylactic treatment of blood vessels with hemostatic forceps is the most effective strategy. A few cases of postoperative anal stenosis have been reported, and most of those were successfully and conservatively treated with bougie or balloon dilation[33]. No anal sphincter dysfunction was observed after anorectal ESD[40].

CONCLUSIONS

ESD at the discussed special locations of the ileo-colo-rectum was found to be feasible, and outcomes were comparable to those of ESD performed in non-special locations of the ileo-colo-rectum. Practice for skill improvement and awareness of the unique characteristics of each special location is the key to performing successful ESD.

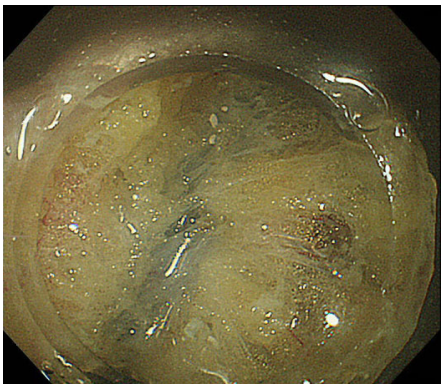

Figure 2 Submucosal fatty tissue around the ileocecal valve.

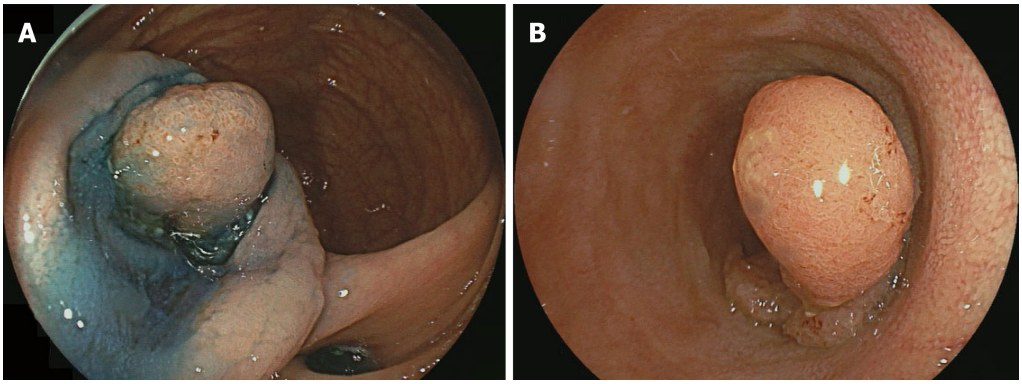

Figure 3 Endoscopic submucosal dissection in terminal ileal tumors. A: Terminal ileal tumor; B: Mucosal incision.

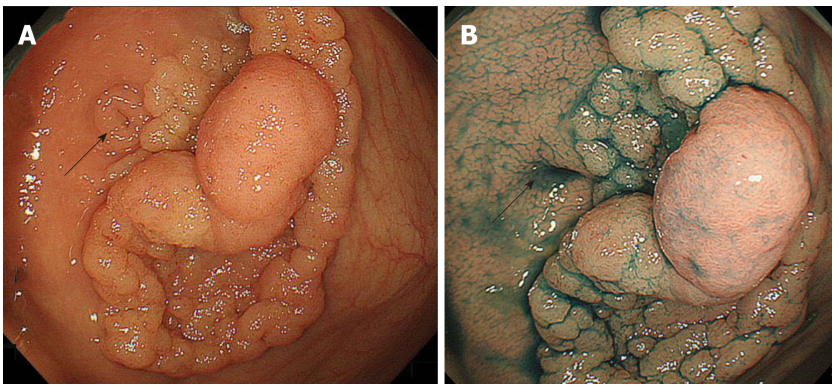

Figure 4 Laterally spreading tumor granular-nodular mix type involvement in the appendiceal orifice (arrow). A: Conventional white light image; B: Chromoendoscopy with indigo carmine.

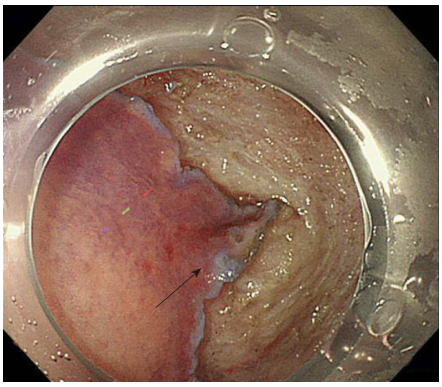

Figure 5 A transparent hood facilitates the endoscopic submucosal dissection of a lesion in close proximity to the appendix (arrow).

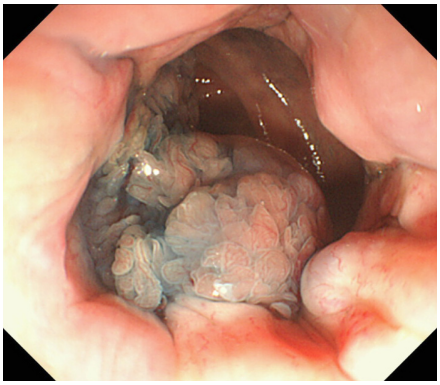

Figure 6 Rectal tumor involvement in the anal canal.

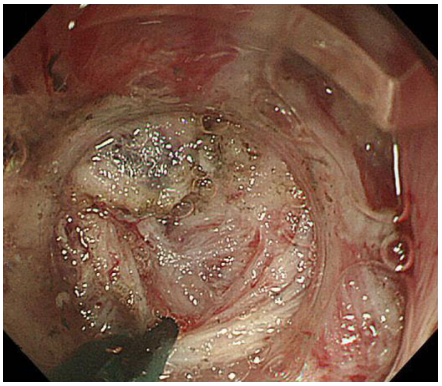

Figure 7 Severe submucosal fibrosis in the anal canal being managed with a scissor-type knife.

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META-ANALYSIS

Efficacy and safety of standard and anti-reflux self-expanding metal stent: A systematic review and meta-analysis of randomized controlled trials

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Abstract

BACKGROUND

Self-expanding metal stents are the main palliative treatment modality for unresectable esophageal cancer. Gastroesophageal reflux is a common adverse outcome after placement of esophageal stent for cancer involving the gastroesophageal junction and the gastric cardia. Anti-reflux stents with valve have been designed to prevent the acid reflux. The superiority of anti-reflux stent over standard stent in preventing gastroesophageal reflux has not been established well. This study compares the anti-reflux stent and the standard stent in terms of their efficacy to prevent acid reflux.

AIM

To compare the standard and the anti-reflux stents in terms of their efficacy, safety, and complications.

METHODS

The meta-analysis included 8 randomized clinical trials (RCTs) to compare pooled outcomes of total 395 patients. Primary outcomes include improvement in reflux symptoms and dysphagia score. Secondary outcomes include complications of stent migration, occlusion, and bleeding.

RESULTS

A total of eight RCTs were included in the meta-analysis. Compared to the standard stent, the anti-reflux stent showed a trend towards reduction in the dysphagia score without reaching a statistical significance [Standardized mean

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difference (SMD): -0.33 (-0.71, 0.05); P = 0.09, I^2: 37%]. There was no statistical difference in the gastrointestinal reflux (GER) scores between the two types of stents [SMD: -0.17 (-0.78, 0.45); P = 0.008, I^2: 74%]. Compared to standard stent, anti-reflux stent showed no difference in the risk of stent migration [OR: 1.37 (0.66, 2.83); P = 0.40, I^2: 0 %], bleeding [OR: 1.43 (0.40, 5.13); P = 0.59, I^2: 0 %], and obstruction [OR: 1.66 (0.60, 4.60); P = 0.33, I^2: 0 %].

CONCLUSION
Traditional self-expanding standard esophageal stent and anti-reflux stent with valve are similar in terms of outcomes and complications.

Key words: Self expanding metal stent; Anti-reflux stent; Randomized controlled trial; Esophageal stent; Meta-analysis

Core tip: In this meta-analysis, we studied and compared the traditional standard self-expanding metal stent and anti-reflux stent in terms of their efficacy and safety. We included 8 randomized controlled trials in our meta-analysis from 3 different databases. We expected anti-reflux stent with valves, as its name suggests, to show improvement in reflux symptom score, however, this was not observed in our study. This review study shows that there is no difference between standard stent and anti-reflux stent in terms of improving reflux symptom and dysphagia score. This study also confirms that there is no difference in terms of complications including stent migration, bleeding, and obstruction between standard stent and anti-reflux stent.

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INTRODUCTION

The incidence of esophageal cancer, adenocarcinoma in particular, is rising rapidly in the western countries including the United States[1]. Involvement of the esophagogastric junction (EGJ) and gastric cardia is common for esophageal adenocarcinoma[2]. In 2015, a total of 17281 new cases of esophageal cancer were reported in the United States with 15211 deaths due to cancer[3]. About 50 to 80 percent of esophageal cancer patients present with metastasis and/or locally invasive disease which is surgically unresectable[4]. Palliative chemotherapy, radiation therapy, brachytherapy, and endoscopic management are the available treatment modalities for patients with surgically unresectable cancer[5].

Dysphagia and food bolus impaction are the two most common presentations of esophageal cancer. Placing a stent across the tumor is one of the palliative options to relieve dysphagia, and to improve the quality of life. Nonetheless, placement of esophageal stent is associated with various complications such as stent migration, bleeding, perforation, and stent occlusion. Severe acid reflux is one of the most common symptomatic complaints in patients who undergo standard metal stent placement at tumors involving EGJ or cardia, as the lower esophageal sphincter remains wide open after stent placement[6]. Recently, a study by Włodarczyk *et al*[7] showed that among patients who undergo esophageal stent placement for dysphagia from unresectable esophageal cancer, 45 percent complain of severe acid reflux. To reduce these post stent placement sequels, various modification of traditional standard stent (SS) are in progress, one of them is the development of anti-reflux esophageal stent (ARS).

Many randomized and prospective studies have been reported in literature comparing the efficacy and safety of SS and ARS. Intuitively, ARS with valve is supposed to decrease the gastroesophageal reflux (GER), but multiple studies have shown mixed results. We performed a systematic review and meta-analysis of these studies to ascertain the efficacy and safety of SS and ARS.

MATERIALS AND METHODS

We conducted this systematic review and meta-analysis according to the guidelines provided by the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0[8] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement was adopted in the preparation of this manuscript.

Literature search

All randomized controlled trials (RCTs) including anti reflux stents were identified. A literature search of PubMed, CINAHL, and Cochrane Library for RCTs was performed from inception to 2018. Search terms included self-expanding metal stent, anti-reflux esophageal stent, and RCTs. Additional articles were manually searched from bibliographies of selected articles and pertinent review articles. The title, abstracts, and full text of the articles were reviewed by two independent reviewers (S.P. and H.S.). Abstracts from national and international meetings were also included.

Our inclusion criteria were: (1) RCTs; (2) Age > 18 years old; (3) Esophageal cancer with stent crossing the EGJ and cardia; (4) Comparison between SS and ARS; and (5) Reported improvement in clinical outcome and complications. Exclusion criteria were: (1) Foreign language without English version; (2) Study that included stents for benign esophageal stricture; (3) Stents placed by radiologists; and (4) Prior history of stent placement.

If multiple publications for the same study population were identified, the most recent publication was used. All disagreements were resolved by joint decision between the two authors (S.P. and H.S.), and a senior author (J.M.).

Data extraction and quality assessment

Two authors (S.P. and H.S.) independently extracted data from each study including characteristics of study, characteristics of study population, and results of study. Characteristics of study included first author, year, study design, country, type of stents used, number of patients in each arm, preemptive dilation of stents, and types of procedural sedation. Characteristics of study population included mean age, gender, indications for stent placement, and types of histopathology. Results of study included standard mean difference for GER symptoms, and dysphagia score. Odds ratio (OR) was calculated for comparison of complications which included risk of bleeding, stent migration, and stent occlusion.

Quality assessment was independently performed according to QUADAS-2 by 2 authors (S.P. and H.S.)[9]. The discrepancies between the two authors were resolved by joint decision between the two authors and the senior author (J.M.).

Statistical analysis

Randomized effects model was used to perform meta-analysis according to the heterogeneity. Pooled estimate of major outcomes studied were the improvement in dysphagia, GER scores, which were reported as standardized mean difference (SMD) with 95%CI. The risk of stent migration, bleeding, and obstruction were reported as OR with 95%CI.

Revman review manager version 5.3 was used for data analysis. Results were considered significant if $P < 0.05$.

RESULTS

Characteristics of studies and study population

After initial search using key words (esophageal stent, anti-reflux esophageal stent, self-expanding metal stent) fifty-three potential studies were identified. After excluding duplicate studies, twenty-two studies were screened for title and abstracts. After excluding non-RCTs, only eight studies were included for detailed review for this meta-analysis[6,10-16] (Figure 1).

A total of 395 patients were included in the study, ARS (192 patients) and SS (203 patients), comparing their efficacy and outcome (Table 1). Among them 249 were men with mean age of 70.1 years. The studies were published between 2004 and 2016, and all the studies were conducted in the developed countries in the resource rich settings. Out of the eight studies, three studies were multicenter and five were single center studies. The indication for stent was dysphagia secondary to distal esophageal cancer and gastric cardia cancer. Histologically, 189 patients had adenocarcinoma of esophagus, 90 patients had squamous cell carcinoma of esophagus, and 14 had undifferentiated type (Table 2).

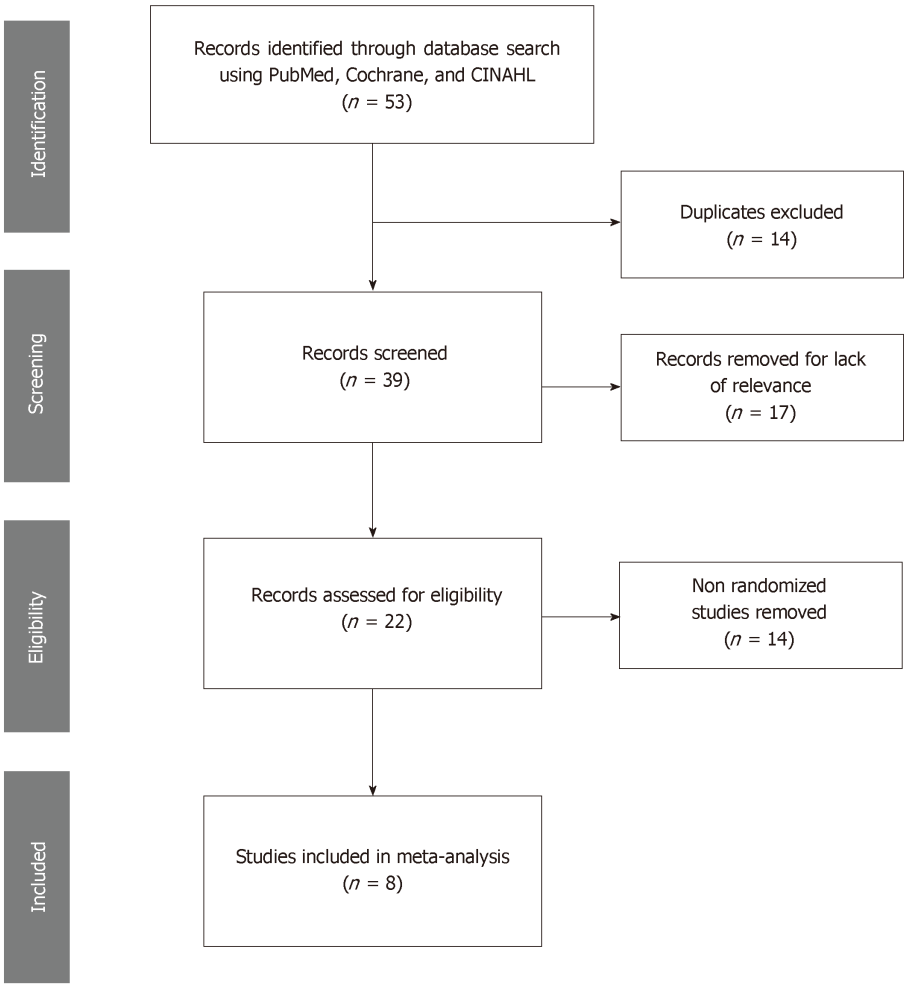

Figure 1 Flow chart of articles selected for this meta-analysis study.

Primary outcomes

Eight studies were included in the meta-analysis, however, only four studies reported primary outcome as GER and dysphagia, before and after stent placement. Among other four studies, Coron *et al*[10], Sabharwal *et al*[13], and Homs *et al*[6] did not report adequate information to calculate SMD. Three studies fail to report necessary statistical information to calculate SMD, and one study provided partial statistical value that could not be used in the study[14]. Compared to the SS, the ARS showed a trend towards reduction in the dysphagia score but it did not reach a statistical significance [SMD: -0.33 (-0.71, 0.05); P = 0.09, I^2: 37%]. And, there was no statistical difference in the GER scores between the two types of stents [SMD: -0.17 (-0.78, 0.45); P = 0.008, I^2: 74%] (Figure 2).

Secondary outcomes

Five studies reported data on stent migration and bleeding related to stent insertion (Figure 3). Out of five studies which reported stent migration, three studies showed stent migration is more likely with SS. However, pooled results showed there was no significant statistical difference between SS and ARS in terms of risk of stent migration (OR = 1.37, 95%CI: 0.66-2.83) (Figure 3).

Five studies reported stent related bleeding but one of them did not provide adequate statistical data to calculate OR. Pooled results from four studies showed no statistical difference in bleeding risk using either SS or ARS (OR = 1.43, 95%CI: 0.40-5.13) (Figure 2).

Four studies reported data on stent occlusion. SS had more cases of stent occlusion; however, pooled data suggested no statistical difference between SS and ARS (OR = 1.66, 95%CI: 0.60-4.60) (Figure 3).

Quality assessment and publication bias

Quality assessment of each study according to the guideline by QUADAS-2 is shown in supplementary Figure 1. Concern for biases regarding patient selection,

Table 1 Patient characteristics

	Anti-reflux stent	Standard stent
Patients, total (*n*)	192	203
Female (*n*)	47	49
Male (*n*)	118	131
mean age (yr)	70	70.24
Histology (*n*)	SCC = 39; Adenocarcinoma = 76; Undifferentiated = 1	SCC = 51; Adenocarcinoma = 113; Undifferentiated = 13

SCC: Squamous cell carcinoma.

randomization, index test, reference standard was overall low except for flow of patients through the study and timing of index tests, and reference standard. By utilizing Revman Manager funnel, plots were created for outcome gastroesophageal reflux disease (Figure 4A) and outcome dysphagia (Figure 4B). No significant publication bias was found among studies evaluated.

DISCUSSION

In this systematic meta-analysis, we compared conventional standard stent with anti-reflux stents in terms of their efficacy and safety. Both types of stents were used as palliative modality to treat dysphagia in unresectable malignant esophageal and gastroesophageal junction cancer. We showed that both types of stents were equivalent in terms of primary outcome including improving GER symptoms, and reducing dysphagia score. The results are similar to the review done by Sgourakis *et al*[17] in 2010. Sgourakis's study compared multiple different types of SEMS with locoregional therapy whereas our study compared SS and ARS only.

Our study showed that there was no difference between the SS and ARS considering secondary endpoints that included stent migration, bleeding related to stent placement, and occlusion of stent from tumor in growth. In a meta-analysis done by Yang *et al*[18] comparing bare metal esophageal stents with fully covered self-expanding metal stents, stent occlusion occurred more in bare metal stents, whereas, stent migration occurred more in the covered stents. In our study, all stents were covered stents, and there was no difference in stent migration or stent occlusion. Two previous studies have shown that stainless steel stents tend to migrate more than nitinol stents[19,20]. In our study, four studies used nitinol stent[6,13,14,16] and one study by Wenger *et al*[15] used combination of nitinol and stainless-steel stents. We found no difference in stent migration with regards to the stent material used. Although more studies showed increased risk of bleeding, stent occlusion, and stent migration with SS; pooled data did not reach statistical significance[6,10,12,13,15].

We anticipated anti-reflux stent to have favorable outcome in improving GER symptom, as it is marketed now, but this was not seen in this study. Even though a favorable trend was seen towards ARS[11,12,15] in improving gastroesophageal reflux and dysphagia score, pooled statistical analysis did not show significant difference between those two stents. Three out of four studies that were included to calculate SMD for improvement of GER symptoms favored ARS, which could be attributed to the variation in the length of stents. Improvement in GER symptoms was seen with 140 mm stent compared to 70 mm stent[11,12,15]. A study by Coron *et al*[10] showed improvement in GER symptoms in ARS group, which included 20 patients, when proton pump inhibitors was used after the stent placement, however due to lack of sufficient data, this study was not included in the primary outcome.

Treatment related deaths are not included in this study, however, one previous network meta-analysis showed that treatment related deaths were reported more in the open stent group compared toanti-reflux stent group[21]. In this network meta-analysis, open stent and ultraflex stent omeprazole was compared with anti-reflux stent. The relative risk (RR) for treatment related deaths were higher in open stent and ultraflex plus omeprazole (RR = 3.00, 95%CI: 0.13-70.23) and (RR = 2.55, 95%CI: 0.11-59.49), respectively[21].

The major limitation of this meta-analysis is, it's underpowered. We included studies with reproducible data and studies which explained our research question. The power could have been improved by including the foreign language studies. Additionally, not all studies provided data on each primary or secondary outcome. Therefore, all eight studies could not be included for both primary and secondary

Table 2 Study characteristics

Study	Country	Design	Brand of stents	*n* (ARS, SS)	Age (ARS, SS)	Male / Female; ARS / SS	Pre-Dysphagia score (ARS / SS)	Follow-up (mo)	Use of PPI (ARS / SS)	Preemptive dilation of stent (ARS/ SS)
Coron *et al*[10], 2016	France	RCT, multicenter	Dostent	20	68.9	16/4	2.75 (0-4)	6	NO	YES
			Choostent	18	74	15/3	2.65 (0-4)	6	YES	YES
Kaduthodil *et al*[11], 2011	United Kingdom	RCT, single center	NR	27	NR	NR	NR	NR	NR	NR
			NR	23	NR	NR	NR	NR		
Blomberg *et al*[12], 2010	Sweden	RCT, multicenter	Z stent-Dua- valve	28	74	21/7	62 (0-100)	3	NR	YES
			Z-stent	37	74	23/14	61 (0-100)	3	NR	YES
Sabharwal *et al*[13], 2008	United Kingdom	RCT, single center	FerX- Ella – valve /	24	71.3	15/7	2.73 (0-5)	3	NO	NR
			Ultraflex	26	66.3	21/5	2.54 (0-5)	3	YES	NR
Power *et al*[14], 2007	Ireland	RCT, single center	Hanaro stent- valve	24	68.4	14/10	NR	2	NR	NR
			Ultraflex	25	73.9	17/8	NR	2	NR	NR
Wenger *et al*[15], 2006	Sweden	RCT, multicenter	Z stent-Dua	19	75	13/6	63 ± 28	6	NR	NR
			Z-stent	25	73	13/9	56 ± 31	6	NR	NR
Shim *et al*[16], 2005	South Korea	RCT, single center	Dostent	12	65.3	12/0	2.83 ± - 0.85	1	NO	YES
			Covered metal	12	62.7	11/1	3.25 ± 0.4	1	NO	YES
Homs *et al*[6], 2004	the Netherland	RCT, single center	FerX-Ella –valve /	15	69	12/3	3 (0-5)	6	NR	NR
			Fer x -Ella	15	69	12/3	3 (0-5)		NR	NR

RCT: Randomized controlled trials; SS: Standard stent; ARS: Anti-reflux esophageal stent; PPT: Proton pump inhibitors.

outcome. Hence, there is a need for larger randomized controlled studies. Although there was significant heterogeneity in reporting primary and secondary end points across studies, all studies passed the heterogeneity test.

In conclusion, both traditional standard open stent and anti-reflux stent with valve are comparable in terms of their efficacy and safety for the palliative treatment of obstructive esophageal and gastroesophageal junction malignancies. Authors believe both SS and ARS could be used in clinical practice as per the availability of clinical expertise, cost, and patient preference with informed decision.

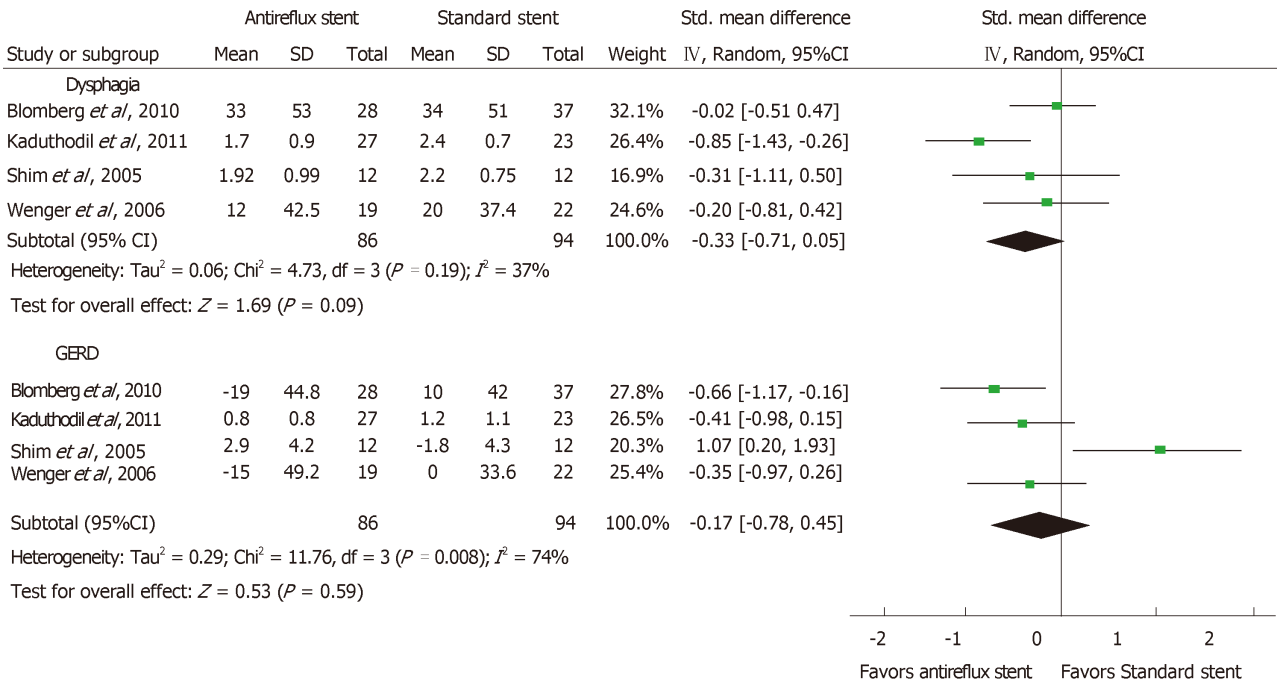

Figure 2 Forest plot comparing standardized mean difference in dysphagia and gastroesophageal reflux disease between anti-reflux stent and standard stent. GERD: Gastroesophageal reflux disease.

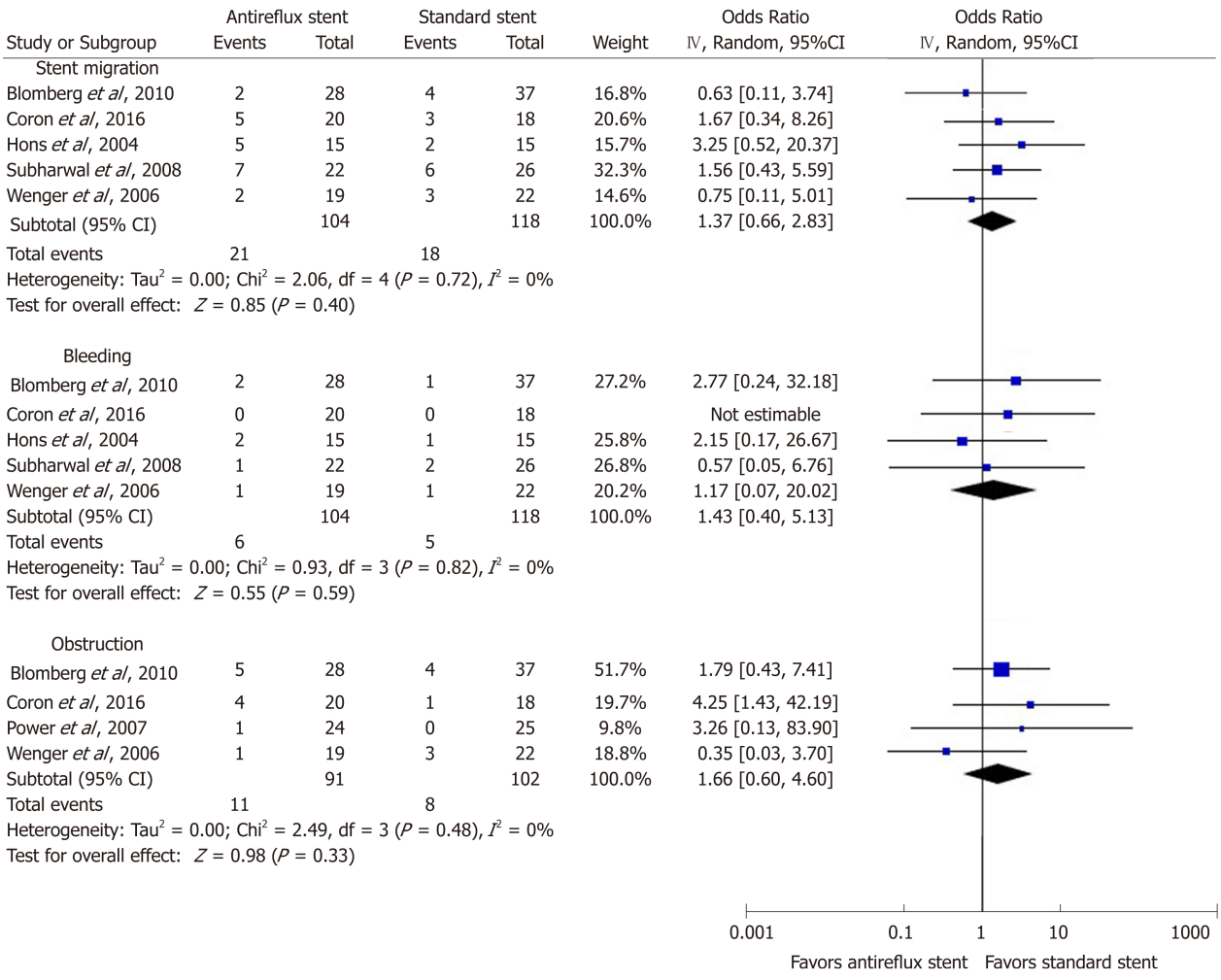

Figure 3 Forest plot comparing complications of stent migration, bleeding and obstruction between anti-reflux and standard stent.

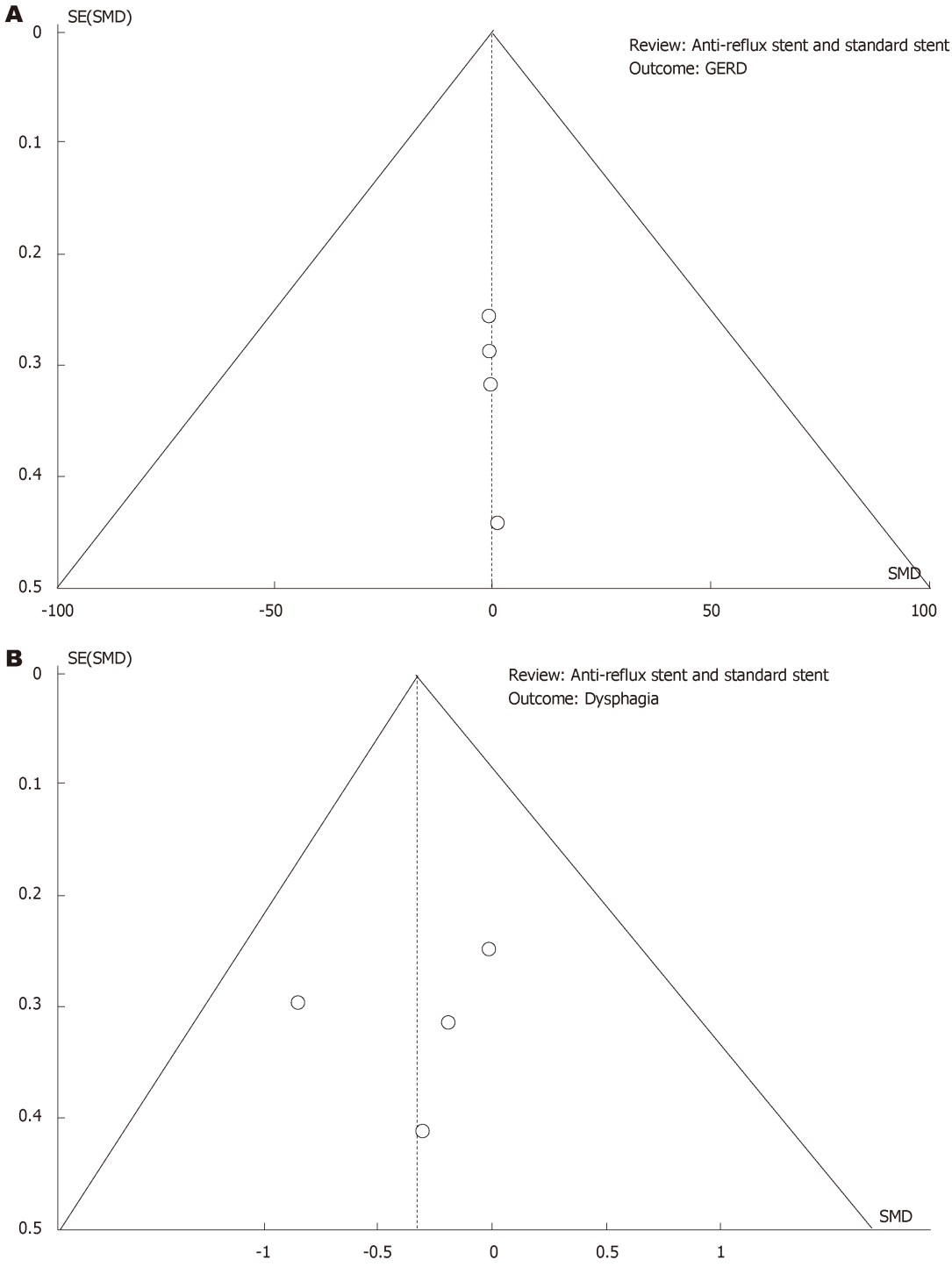

Figure 4 Funnel plot for publication bias. A: Outcome gastroesophageal reflux disease; B: Outcome dysphagia. SMD: Standard mean difference; GERD: Gastroesophageal reflux disease.

ARTICLE HIGHLIGHTS

Research background

Self-expanding metal stents are one of the palliative treatment modalities to relieve dysphagia and to improve quality of life in patients with unresectable esophageal cancer involving the gastroesophageal junction and gastric cardia. Although the quality of life improves after stent placement, it is severely limited by gastroesophageal reflux disease (GERD) especially when stent is placed across the gastroesophageal junction. To improve GERD, anti-reflux stents with valve have been designed and studied in many randomized controlled trials. However, the results from these studies are mixed. The main purpose of this study is to identify how effective is anti-reflux stent in improving gastroesophageal reflux and dysphagia when compared to standard stent.

Research motivation
Gastroesophageal reflux is one of the most common adverse outcomes after placement of esophageal stent in esophageal cancer involving the gastroesophageal junction and gastric cardia. Effective anti-reflux stents needs to be designed to overcome the problem of gastroesophageal reflux.

Research objectives
The main objective of this meta-analysis was to assess the efficacy of anti-reflux stents in improving GERD. During data gathering and analysis, authors realized that many randomized controlled trials which compared anti reflux stent and standard stents were under powered. So, more randomized controlled trials with larger number of patients are needed.

Research methods
Literature search was done using electronic database to gather data for this meta-analysis where we analyzed the efficacy and safety of anti-reflux stent and standard stent. We collected data focusing on the indication for stents, material and type of stent used, demographics of patient, endoscopic technique, type of sedation used. Gastroesophageal reflux and dysphagia improvement score were our primary outcomes. Bleeding risk, stent migration risk, and stent occlusion were our secondary outcome.

Research results
There was no difference in terms of GERD score and dysphagia score between anti reflux stent and standard stent. The complications such as bleeding, stent migration, and stent occlusion were also similar between anti reflux and standard stent. Our study showed a favorable trend for anti-reflux stent to improve GERD score, though it was not statistically significant. We believe that further randomized controlled trials with larger number of patients might be helpful to ascertain if anti reflux stent indeed improves GERD score compared to standard stent.

Research conclusions
Anti-reflux stent is not superior to standard stent in preventing GERD related to stent placement. The risk of adverse outcomes of bleeding related to stent, stent migration and stent occlusion was also comparable between anti reflux and standard stent. Both anti reflux stent and standard stent are similar in efficacy and safety. Either stent could be selected as a palliative treatment modality to relieve dysphagia in unresectable esophageal cancer. There is no difference between anti reflux stent and standard stent to prevent GERD due to stent placement across the gastroesophageal junction. Few randomized controlled trials at present suggest that anti reflux stent improve GERD related to stent placement across the gastroesophageal junction. The result from this meta-analysis did not show significant statistical difference between anti reflux stent and standard stent in terms of improving GERD score. Clinicians can choose either stent sto treat dysphagia related to esophageal cancer.

Research perspectives
This meta-analysis showed that there are no difference in terms of safety and efficacy between anti reflux stent and standard stent. We should focus towards betterment of safety and efficacy of newer esophageal stents. More randomized clinical trials comparing the standard and anti-reflux stents are needed to further characterize their safety and efficacy.

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META-ANALYSIS

Endoscopic ultrasound-guided *vs* endoscopic retrograde cholangiopancreatography biliary drainage for obstructed distal malignant biliary strictures: A systematic review and meta-analysis

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Abstract

BACKGROUND

For palliation of malignant biliary obstruction (MBO), the gold-standard method of biliary drainage is endoscopic retrograde cholangiopancreatography (ERCP) with the placement of metallic stents. Endoscopic ultrasound (EUS)-guided drainage is an alternative that is typically reserved for cases of ERCP failure. Recently, however, there have been robust randomized clinical trials (RCTs) comparing EUS-guided drainage and ERCP as primary approaches to MBO.

AIM

To compare EUS guidance and ERCP in terms of their effectiveness and safety in palliative biliary drainage for MBO.

METHODS

This was a systematic review and meta-analysis, in which we searched the MEDLINE, *Excerpta Medica*, and Cochrane Central Register of Controlled Trials databases. Only RCTs comparing EUS and ERCP for primary drainage of MBO were eligible. All of the studies selected provided data regarding the rates of technical and clinical success, as well as the duration of the procedure, adverse

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events, and stent patency. We assessed the risk of biases using the Jadad score and the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation criteria.

RESULTS

The database searches yielded 5920 records, from which we selected 3 RCTs involving a total of 222 patients (112 submitted to EUS and 110 submitted to ERCP). In the EUS and ERCP groups, the rate of technical success was 91.96% and 91.81%, respectively, with a risk difference (RD) of 0.00% (95%CI: -0.07, 0.07; $P = 0.97$; $I^2 = 0\%$). The clinical success was 84.81% and 85.53% in the EUS and ERCP groups, respectively, with an RD of −0.01% (95%CI: -0.12, 0.10; $P = 0.90$; $I^2 = 0\%$). The mean difference (MD) for the duration of the procedure was -0.12% (95%CI: -8.20, 7.97; $P = 0.98$; $I^2 = 84\%$). In the EUS and ERCP groups, there were 14 and 25 adverse events, respectively, with an RD of -0.06% (95%CI: -0.23, 0.12; $P = 0.54$; $I^2 = 77\%$). The MD for stent patency was 9.32% (95%CI: -4.53, 23.18; $P = 0.19$; $I^2 = 44\%$). The stent dysfunction rate was significantly lower in the EUS group (MD = -0.22%; 95CI:-0.35, -0.08; $P = 0.001$; $I^2 = 0\%$).

CONCLUSION

EUS represents an interesting alternative to ERCP for MBO drainage, demonstrating lower stent dysfunction rates compared with ERCP. Technical and clinical success, duration, adverse events and patency rates were similar.

Key words: : Common bile duct neoplasms; Endoscopic retrograde cholangiopancreatography; Endosonography; Ultrasonography; Interventional/methods; Endoscopic ultrasound; Systematic review; Meta-analysis

Core tip: No consensus is available in the literature regarding whether endoscopic retrograde cholangiopancreatography or endoscopic ultrasound-guided biliary drainage is more beneficial to the patient. This is the first systematic review and meta-analysis comparing the two methods. We investigated these two techniques in terms of technical and clinical success, as well as duration of the procedure, adverse events, stent dysfunction and stent patency.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is currently the gold-standard method to address malignant biliary obstruction (MBO) of the distal common bile duct[1,2], the procedure consists in endoscopic guidewire access to the duodenal papilla, with further injection of contrast on the bile ducts and placement of an endoscopic stent in order to treat MBO, and there are data favoring the use of self-expanding metal stents over that of plastic stents[3]. However, ERCP is not free of complications, the most common being post-ERCP pancreatitis and cholangitis[4]. In addition, there is a non-negligible risk of failed biliary cannulation in ERCP due to dysfunctional biliary sphincter or anatomical alterations[5].

Percutaneous transhepatic biliary drainage (PTBD) and surgical bilioenteric anastomosis are traditional alternatives to ERCP, although both have their particular drawbacks. PTBD requires multiple interventions and carries an increased risk of cholangitis, bacteremia, and hemobilia[6], whereas bilioenteric anastomosis is associated with high morbidity and mortality[7].

Endoscopic ultrasound (EUS) has long been of paramount importance for the

workup of patients with biliary obstruction[8-10]. Some recent reports have described EUS-guided drainage as an alternative in cases of ERCP failure[11-13]. The efficacy and safety profile of EUS-guided drainage have improved over time, as has the availability of specific accessories, allowing some authors to test EUS-guided biliary drainage, in comparison with ERCP, as a primary approach to biliary obstruction.

Transluminal EUS-guided biliary drainage consists of needle access to the biliary ducts by hepatogastric or choledocoduodenal puncture under EUS guidance. Then, a guidewire is inserted through the needle, followed by dilation of the fistula and stent placement.

Although there have been a number of randomized clinical trials (RCTs) comparing EUS-guided biliary drainage and ERCP[14-16], there have yet to be any systematic reviews or meta-analyses regarding the topic. Therefore, the aim of the present study was to summarize all available data comparing EUS and ERCP in terms of their effectiveness and safety in the primary drainage of MBO. To that end, we conducted a systematic review and meta-analysis, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology, of RCTs comparing EUS and ERCP in the primary drainage of distal MBO, assessing technical success, clinical success, cost-effectiveness, duration of the procedure, adverse events, mortality, stent patency, and stent dysfunction.

MATERIALS AND METHODS

Protocol and registration

This study followed the PRISMA guidelines[17] and was registered in the International Prospective Register of Systematic Reviews database[18] (CRD42018108712). The study was approved by the local institutional review board.

Study criteria

Only RCTs were considered eligible, without barriers as to the language or year of publication. We included RCTs that had evaluated patients diagnosed with distal MBO and undergoing primary drainage of the biliary tract under EUS guidance or by ERCP. Studies evaluating patients with benign biliary obstruction were excluded, as were those evaluating EUS-guided biliary drainage after failure of another method and those including only patients undergoing primary EUS-guided drainage due to an anatomical alteration that precluded ERCP.

Search strategy and study selection

We searched the MEDLINE, Excerpta Medica, Cochrane Central Register of Controlled Trials, Latin-American and Caribbean Health Sciences Literature databases, as well as the gray literature, for RCTs published up to and including November 2018. We employed descriptors available from the United States National Library of Medicine Medical Subject Headings and, to a lesser degree, other related terms aiming at a more sensitive strategy. For Medline, our search strategy was as follows: [(ERCP OR Endoscopic Retrograde Cholangiopancreatograph*) OR (EUS OR endosonography OR Endoscopic Ultrasonograph* OR Echo Endoscop*)] AND (decompression OR drain*). For the other databases, the following search strategy was applied: (EUS OR Endoscopic Ultrasonography) AND (decompression OR drainage).

Two independent researchers assessed titles and abstracts for eligibility. Any disagreement was resolved by consensus with a third experienced researcher. The articles were included after an evaluation of the full-text based on the study criteria.

Data extraction and evaluation

Data related to EUS-guided and ERCP biliary drainage were collected using a preformatted Excel workbook. The data collected included technical and clinical success rates, as well as the duration of the procedure, adverse events, stent patency, and stent dysfunction.

In our quantitative analysis, we used the absolute values, means, and standard deviations. If a study expressed outcomes using median and interquartile range, mathematical formulas were used for data conversion[19]. In case of the study fails to present means and standard deviations or median and interquartile range of the continuous variables of specific outcomes, rendering impossible to include the data for meta-analysis evaluation, the study in question was excluded from the outcome appraisal.

Evaluation of biases and quality of studies

The biases of the RCTs were assessed with the Jadad scale[20], which allows critical appraisal regarding blinding, randomization, and information on losses to follow-up.

Jadad score is applied to evaluate the methodological quality of RCTs, rating the study from zero (poor quality) to five points (rigorous). The evaluation criteria are "description of the study as randomized", "employment of appropriated randomization method", "description of the method of blinding", "employment of appropriated blinding method" and "description of losses to follow-up" whereupon each present criteria grants one point.

The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria with the GRADEpro Guideline Development Tool software (McMaster University, 2015; Evidence Prime, Inc., Ontario, Canada)[21]. GRADE is an approach to rate the quality of evidence based on criteria guideline developed by the GRADE working group and involves the appraisal of risk of bias, inconsistency, indirectness, imprecision and publication bias. Evaluation of biases and quality of studies was performed under supervision of our statistic team.

Data analysis

For the dichotomous variables, we calculated the risk difference (RD) values, using the Mantel-Haenszel test, together with the corresponding 95% confidence intervals. For continuous variables, we calculated the mean difference values, also with the corresponding 95% confidence intervals, using the inverse variance test. The results were displayed with forest plots.

We assessed the heterogeneity among studies using the Higgins test (I^2). If there was an $I^2 < 50\%$, we used a fixed-effect model, whereas we used funnel plot analysis if there was an $I^2 > 50\%$. If we detected an outlier article, we removed it from the analysis and kept the fixed-effect model. If we could not detect an outlier, we switched to the random-effect model analysis to ameliorate the impact of the high heterogeneity. All analyses were carried out with Review Manager software, version 5.3.5 (RevMan 5; Cochrane Collaboration, Oxford, United Kingdom).

RESULTS

Overview

The database searches retrieved a total of 5920 studies, 164 of which were selected for full-text evaluation. Based on the study criteria, three RCTs were included in the qualitative analysis and meta-analysis (Figure 1).

The collective sample comprised 222 patients: 112 in the EUS group and 110 in the ERCP group. The mean age was similar between the two groups and among the samples of the RCTs included. The etiology of MBO in the studies selected is outlined in Table 1.

On the Jadad scale (Table 2), all of the RCTs evaluated had a score of 3, which is the highest possible score for unblinded studies. According to the GRADE criteria for the quality of evidence, the evidence for technical success generated moderate certainty, the evidence for stent dysfunction generated low certainty, and the evidence for the remaining outcomes generated very low certainty (Table 3).

Technical success

All three RCTs[14-16] reported technical success rates. The mean rate of technical success was 91.96% and 91.81% in the EUS and ERCP groups, respectively, with an RD of 0.00% (95%CI: −0.07, 0.07; $P = 0.97$), demonstrating no statistical difference between the two techniques (Figure 2).

Clinical success

All three RCTs included data on clinical success[14-16]. However, Bang *et al*[16] included cross-over procedures in their final results, precluding the intention-to-treat analysis and thus excluding 67 patients. Therefore, the final collective sample in our analysis of clinical success comprised 155 patients: 79 in the EUS group and 76 in the ERCP group. The mean clinical success rate was 84.81% and 85.53% in the EUS and ERCP groups, respectively, with an RD of −0.01% (95%CI: −0.12, 0.10; $P = 0.90$), as shown in Figure 3.

Duration of the procedure

All three studies[14-16] reported the duration of the procedure in minutes. The mean time difference between EUS-guided and ERCP drainage was -0.12% (95%CI: -8.20, 7.97; $P = 0.98$), showing no statistical difference between the two groups (Figure 4). We found high heterogeneity among the studies ($I^2 = 84\%$). Because there were no outliers, we employed the random-effect model in our analysis.

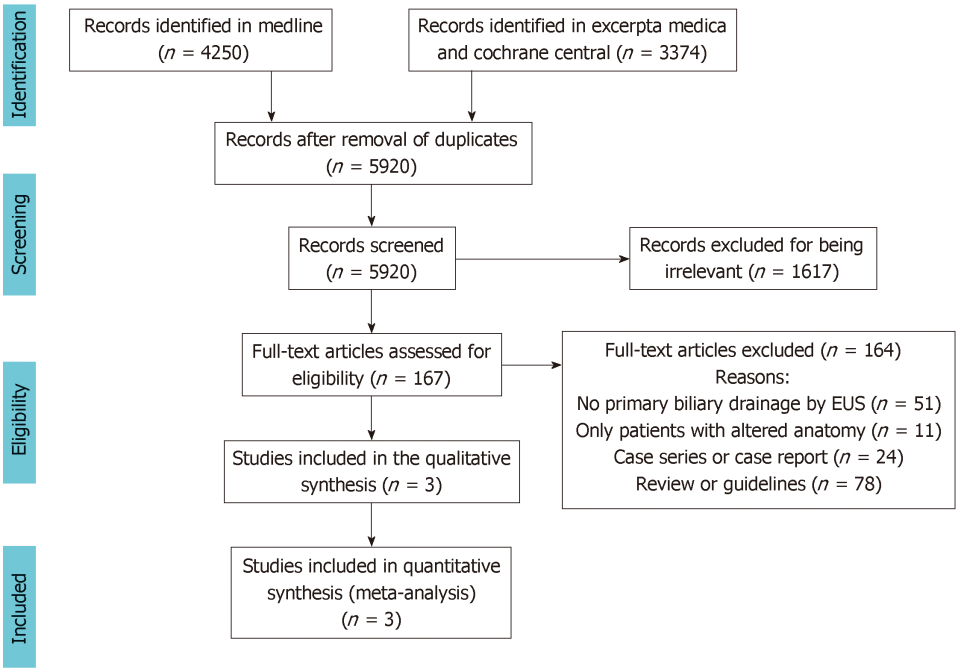

Figure 1 Flow chart of study selection. Cochrane CENTRAL: Cochrane Central Register of Controlled Trials; EUS: Endoscopic ultrasound.

Adverse events

All three RCTs[14-16] described the adverse events reported. In the EUS group, 14 adverse events were reported: abdominal pain (n = 5); cholangitis (n = 4); pneumoperitoneum (n = 2); biliary peritonitis (n = 2); and cholecystitis (n = 1). In the ERCP group, there were 25 adverse events: pancreatitis (n = 10); cholangitis (n = 7); cholecystitis (n = 5); and abdominal pain (n = 3). No procedure-related mortality was reported in any of the studies.

Although we identified high heterogeneity (I^2 = 77%), there were no outlier studies, and the random-effect model was therefore employed. The mean difference between the two techniques was −0.06% (95%CI: −0.23, 0.12; P = 0.54), indicating that there was no statistical difference (Figure 5).

Stent patency

Although all three RCTs reported data on stent patency, Paik *et al*[15] did not detail standard deviation values, precluding the inclusion of that study in the analysis and thus excluding 125 patients. Therefore, the final collective sample in our analysis of stent patency comprised 97 patients: 48 in the EUS group and 49 in the ERCP group. The mean difference was 9.32% (95%CI: −4.53, 23.18; P = 0.19), demonstrating no significant difference between the two methods in terms of stent patency (Figure 6)

Stent dysfunction

All three studies[14-16] provided data on stent dysfunction. We found high heterogeneity (I^2 = 86%) among the studies, and the funnel plot analysis identified the Bang *et al*[16] study as an outlier. When we excluded that study from the analysis, the I^2 value was 0%. Between the two remaining studies, there were 12 cases of stent dysfunction requiring intervention in the EUS group and 28 such cases in the ERCP group. The RD between the groups was −0.22% (95%CI: −0.35, −0.08; P = 0.001), thus favoring EUS-guidance over ERCP (Figure 7).

DISCUSSION

Summary of evidence

To our knowledge, this is the first systematic review and meta-analysis including only RCTs that compared EUS-guidance and ERCP as the primary approach to biliary drainage in cases of MBO. Our strict methodology, which included critical appraisal of biases, quality of evidence assessment, and a report prepared in accordance with the PRISMA guidelines[17], underscores the strength of our findings.

EUS-guided biliary drainage was first introduced as an alternative to be employed

Table 1 Characteristics of the patient samples and etiology of malignant biliary obstruction in the studies selected

Variable	Study					
	Bang *et al*[16]		Paik *et al*[15]		Park *et al*[14]	
	EUS	ERCP	EUS	ERCP	EUS	ERCP
n	33	34	64	61	15	15
Age (yr), mean (SD)	69.4 (12.6)	69.2 (11.6)	64.8 (12.5)	68.4 (10.5)	66.8 (8)	65.4 (9.3)
Etiology of MBO	Pancreas (*n* = 33)	Pancreas (*n* = 31); pancreatic metastasis (*n* = 3)	Pancreas (*n* = 38); cholangiocarcinoma (*n* = 3); gallbladder (*n* = 4); papilla (*n* = 5); gastric (*n* = 4); duodenal (*n* = 2); other (*n* = 8)	Pancreas (*n* = 40); cholangiocarcinoma (*n* = 8); gallbladder (*n* = 4); papilla (*n* = 3); gastric (*n* = 2); duodenal (*n* = 1); hepatocellular carcinoma (*n* = 1); other (*n* = 2)	Pancreas (*n* = 14); cholangiocarcinoma (*n* = 1)	Pancreas (*n* = 13); metastatic lymph node (*n* = 2)

EUS: Endoscopic ultrasound; ERCP: Endoscopic retrograde cholangiopancreatography; MBO: Malignant biliary obstruction.

after ERCP failure[11-13]. Moole *et al*[22] recently published a systematic review and meta-analysis comparing PTBD and EUS-guided drainage as alternatives to be employed after failed ERCP, demonstrating that the latter was superior, as has been corroborated by other authors[23].

Because of improvements in the technique and accessories over time, some authors have reported EUS-guided biliary drainage as a first-line modality in patients presenting with factors predictive of difficult biliary access by ERCP (*e.g.*, altered anatomy, duodenal obstruction, and previous duodenal stent)[24-28]. Okuno *et al*[27] published a prospective study of 20 patients undergoing EUS-guided hepaticogastrostomy with a 6-mm self-expanding metallic stent. The rates of technical success, clinical success, and adverse events were 100%, 95%, and 15%, respectively. In a recent multicenter cohort study[28], EUS-guided biliary drainage was compared with ERCP in patients with an indwelling duodenal stent. The authors identified a trend toward higher technical and clinical success rates in the EUS group and found no difference regarding adverse events. Finally, Nakai *et al*[29] published a retrospective study comparing primary and rescue EUS-guided biliary drainage in terms of the rates of technical success and adverse events, both of which the authors found to be similar between the two approaches.

In a recent retrospective study of patients with distal biliary obstruction, Kawabuto *et al*[30] demonstrated that EUS-guided choledochoduodenostomy was similar to transpapillary stenting in terms of the rates of clinical success and adverse events, although the duration of the procedure was shorter and there were no cases of pancreatitis among the patients submitted to the former. Therefore, the EUS-guided procedure was considered a plausible first-line method to address MBO. Subsequent RCTs comparing those techniques have shed light on the matter[14-16].

The availability of three high-quality RCTs allowed us to perform a consistent meta-analysis that will likely contribute to making daily practice more evidence based. Our analysis of technical success is extremely reliable because of the similar definitions employed and homogenous results among the three studies. However, the clinical success analysis lacked consistency because of indirectness due to different outcome definitions. In addition, Bang *et al*[16] included cross-over procedures in the data report, which impeded the intention-to-treat analysis. Therefore, caution should be taken in drawing conclusions based on the results of this analysis.

During our evaluation of the duration of procedures, we found high heterogeneity among the studies. Such true heterogeneity is likely attributable to the participation of endoscopists with different levels of expertise. In addition, various stents have been used in biliary drainage. Paik *et al*[15] employed insulated delivery systems to perform EUS-guided drainage, which probably shortened the duration of the procedure in their EUS group and promoted heterogeneity. Our analysis showed equivalence between the two methods regarding the duration of the procedure. It should be borne in mind that, whereas ERCP is a well-established technique, EUS-guided drainage is still in development, and its duration could therefore become shorter in the near future.

As to the safety of the procedure, our analysis showed similar rates of adverse events after EUS and ERCP. Although there was no difference between the two

Table 2 Jadad scale scores for the studies selected

Study	Jadad scale scoring					
	Randomization	Appropriate randomization	Blinding	Appropriate blinding	Losses described	Total
Bang *et al*[16]	Yes	Yes	No	No	Yes	3
Paik *et al*[15]	Yes	Yes	No	No	Yes	3
Park *et al*[14]	Yes	Yes	No	No	Yes	3

approaches regarding the overall rates, there was a substantial difference regarding the types of adverse events observed. In the ERCP group, the most common complication was pancreatitis, which was not reported in the EUS group. Conversely, pneumoperitoneum and biliary peritonitis were reported only in the EUS group, although none of patients required surgical intervention. Cholangitis was reported in both groups: 7 cases in the ERCP group and 4 in the EUS group.

The stent patency was equivalent for both methods, although the largest study[15] did not provide standard deviation values and was therefore excluded. That significantly reduced the size of the sample evaluated in the stent patency analysis.

Finally, the results of our analysis of the stent dysfunction rate favored EUS-guided drainage. That might be explained by the fact that this method allows a puncture far from the tumor rather than through it, thus avoiding tumor ingrowth or overgrowth. Although EUS-guided drainage can promote stent dysfunction due to food bolus impaction, that risk does not seem to outweigh its advantages. It should also be borne in mind that the employment of diverse stents for biliary drainage could be a confounding factor in the analysis of stent patency and dysfunction.

None of the RCTs evaluated in our systematic review described a cost-effectiveness analysis. Because the differences between ERCP and EUS-guided drainage are still slight, such information might create a tipping point to recommend one approach over the other. Future trials should address this knowledge gap.

Limitations

Our study has some limitations. First, a lack of standard deviation data precluded the inclusion of the largest trial in the stent patency analysis, thus limiting our ability to draw conclusions regarding that aspect. Second, different definitions of clinical success resulted in a very low quality of evidence, also precluding any firm conclusions. Finally, the small number of RCTs included constitutes a major limitation. Future studies might therefore contradict our results. Nevertheless, to our knowledge, this is the first meta-analysis comparing ERCP and EUS-guided biliary drainage in MBO. Our findings could have significant clinical implications for the management of patients with MBO.

Conclusion

In patients with distal MBO, EUS-guided drainage shows rates of technical success, clinical success, adverse events, and stent patency similar to those of ERCP. The rates of stent dysfunction appear to be lower for stents placed under EUS guidance. Cost-effectiveness studies might solidify the role of EUS-guided drainage in the management of MBO.

Table 3 Quality (certainty) of evidence of the studies selected, as determined by the GRADE criteria

Parameter No. of patients (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence
Technical success						
222 (3 RCTs)	Not serious	Not serious	Not serious	Serious[a]	None	Moderate
Clinical success						
155 (2 RCTs)	Serious[b]	Not serious	Serious[c]	Serious[a]	None	Very low
Procedure duration						
222 (3 RCTs)	Not serious	Very serious[d]	Serious[e]	Serious[a]	None	Very low
Adverse events						
222 (3 RCTs)	Not serious	Very serious[d]	Not serious	Serious[a]	None	Very low
Stent patency						
97 (2 RCTs)	Serious[b]	Not serious	Serious[e]	Serious[a]	None	Very low
Stent dysfunction						
155 (2 RCTs)	Not serious	Not serious	Serious[e]	Not serious	Strongly suspected	Low

[a]No significant difference found. [b]Incomplete outcome data in one study. [c]Studies used different criteria for clinical success. [d]I^2 > 75%. [e]Outlier identified. RCTs: Randomized clinical trials.

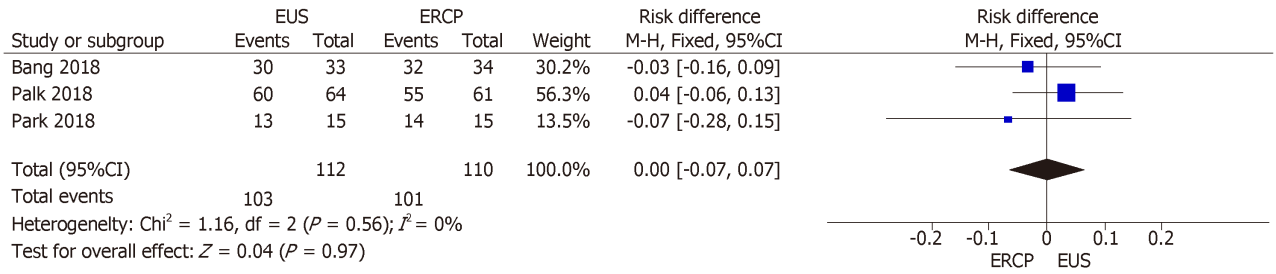

Figure 2 Forest plot of technical success. M-H: Mantel-Haenszel test; EUS: Endoscopic ultrasound; ERCP: Endoscopic retrograde cholangiopancreatography.

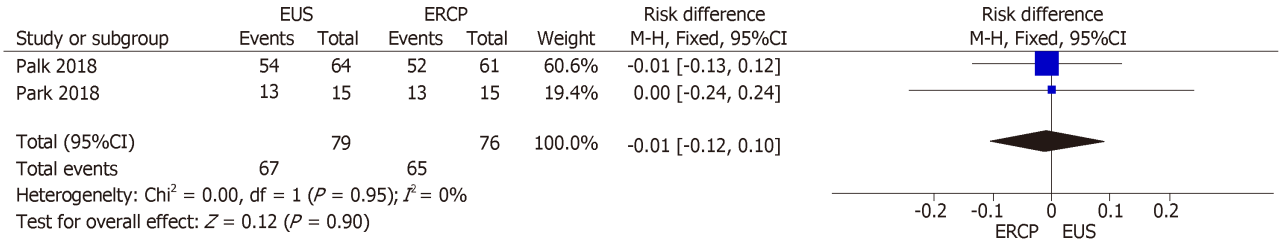

Figure 3 Forest plot of clinical success. M-H: Mantel-Haenszel test; EUS: Endoscopic ultrasound; ERCP: Endoscopic retrograde cholangiopancreatography.

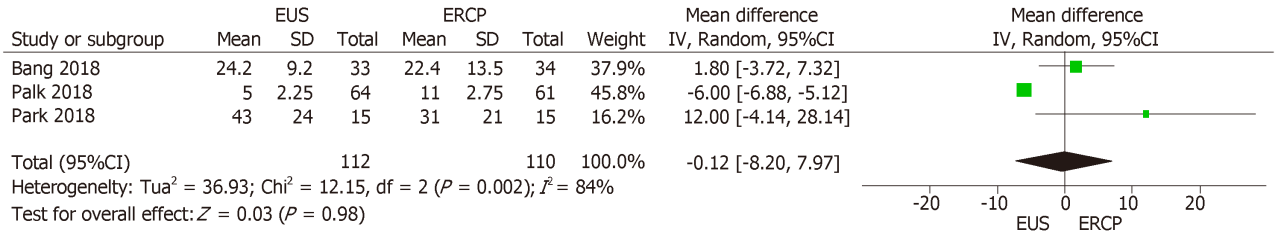

Figure 4 Forest plot of procedure duration in minutes. IV: Inverse variance test; EUS: Endoscopic ultrasound; ERCP: Endoscopic retrograde cholangiopancreatography.

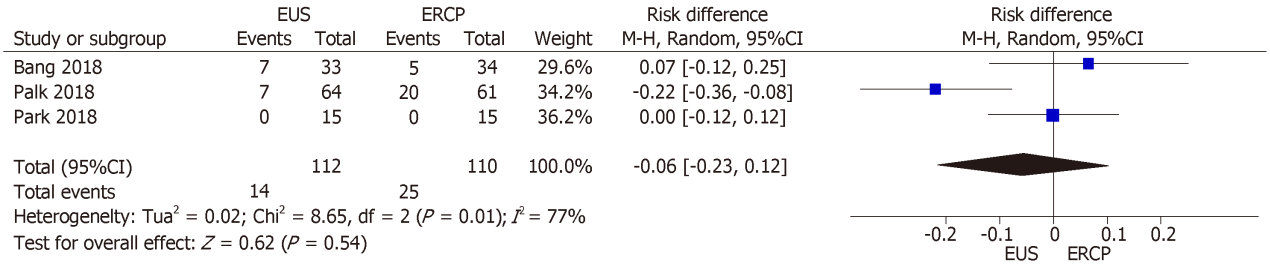

Figure 5 Forest plot of adverse events. M-H: Mantel-Haenszel test; EUS: Endoscopic ultrasound; ERCP: Endoscopic retrograde cholangiopancreatography.

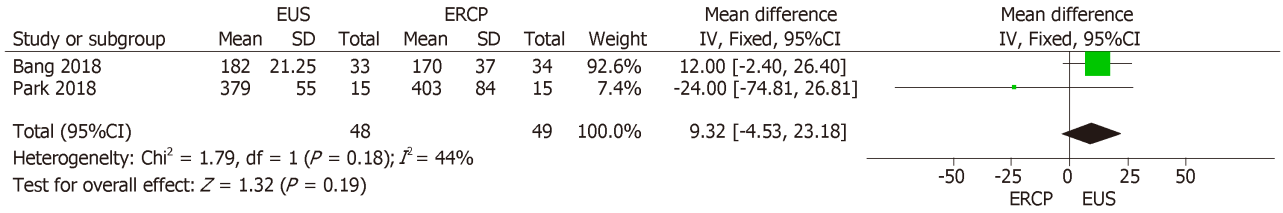

Figure 6 Forest plot of stent patency. IV: Inverse variance test; EUS: Endoscopic ultrasound; ERCP: Endoscopic retrograde cholangiopancreatography.

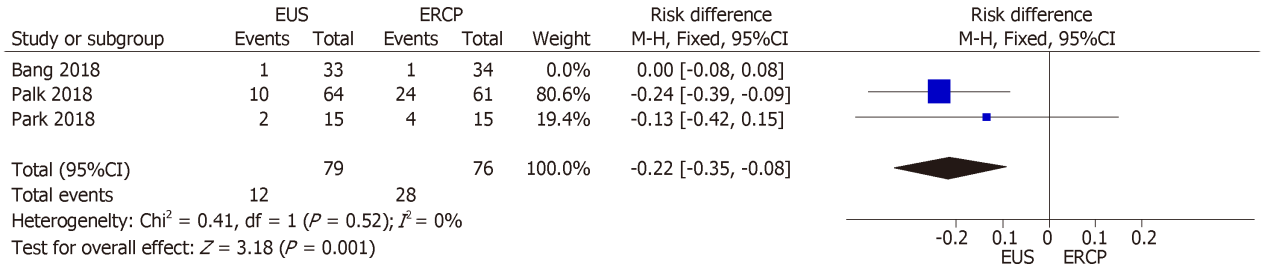

Figure 7 Forest plot of stent dysfunction requiring intervention. M-H: Mantel-Haenszel test; EUS: Endoscopic ultrasound; ERCP: Endoscopic retrograde cholangiopancreatography.

ARTICLE HIGHLIGHTS

Research background

Endoscopic retrograde cholangiopancreatography (ERCP) is currently the gold standard palliation approach for distal malignant biliary obstruction (MBO) but as endoscopic ultrasound (EUS)-guided techniques develop and became more commonly available question arises whether EUS-guided biliary drainage cloud be a first line method for treatment of distal MBO.

Research motivation

EUS-guided biliary drainage and ERCP are recognized endoscopic approaches for palliation of MBO. Our initial motivation was to compare EUS and ERCP techniques for primary drainage of distal MBO. By performing a systematic review and meta-analysis following a rigorous methodological approach we aimed to increase the available knowledge regarding endoscopic palliation of MBO.

Research objectives

To perform a systematic review and meta-analysis comparing EUS and ERCP as primary methods of biliary drainage in distal MBO regarding technical success, clinical success, duration of the procedure, adverse events, stent patency and stent dysfunction.

Research methods

We conducted a systematic review and meta-analysis based on the PRISMA Statement and registered on PROSPERO international database. We searched the Medline, *Excerpta Medica*, and Cochrane Central Register of Controlled Trials databases. Only randomized clinical trials (RCTs) comparing EUS and ERCP for primary drainage of MBO were eligible. We assessed the risk of biases using the Jadad score and the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation criteria.

Research results

Three RCTs were included in the final analysis comprising a total of 222 patients (112 submitted to EUS and 110 submitted to ERCP). The stent dysfunction rate was significantly lower in the EUS group (MD = −0.22%; 95%CI: −0.35, −0.08; P = 0.001; I^2 = 0%). There were no statistically significant difference regarding technical success, clinical success, duration of the procedure, adverse events and stent patency among the compared techniques.

Research conclusions

In palliative drainage of distal MBO, EUS-guided and ERCP drainage presents similar rates of technical success, clinical success, adverse events, and stent patency. The rates of stent dysfunction appear to be lower for stents placed under EUS guidance.

Research perspectives

We considered meaningful to stablish a present evaluation of both techniques and as the procedures continue to develop, further widespread and new technologies emerge, we encourage that additional RCT's and meta-analisys are performed.Cost-effectiveness studies might solidify the role of EUS-guided drainage in the management of MBO.

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CASE REPORT

Rare cause of dysphagia after esophageal variceal banding: A case report

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Author contributions: Sobotka LA, Ramsey ML, Wellner M and Kelly SG contributed equally to this work; all authors participated in collection of information, drafting of the case series, critical review and approve of the final draft.

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Conflict-of-interest statement: The authors that they have no conflict of interest.

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Abstract

BACKGROUND

Esophageal varices are a result of progressive liver disease and portal hypertension. Treatment can be performed with band ligation versus non-selective beta blockers depending on the size of varices, ability to tolerate medications and history of variceal bleeding. Band ligation is an effective intervention with rare but serious complications including bleeding, ulcers and rarely obstruction. Few cases of esophageal obstruction and necrosis caused by banding have been reported, each with varied management from conservative treatment to band removal.

CASE SUMMARY

An 89 years old woman with a past medical history of nonalcoholic steatohepatitis cirrhosis presented to the hospital with an inability to swallow one day after screening esophagogastroduodenoscopy where band ligation of esophageal varices was performed for primary prophylaxis. The patient was not able to tolerate her oral secretions. Initial blood work revealed a Model of End Organ Liver Disease score of 7. She was treated with sublingual nitroglycerin for esophageal spasm, a known complication after esophageal banding. When she failed to improve, esophagogastroduodenoscopy was performed and revealed the mucosa surrounding the banded varix was necrosed and blocking the lumen of the esophagus. The band was purposefully dislodged, revealing distal ulceration and stricturing. Within 72 h after band removal, she was tolerating an oral diet. Endoscopy performed 2 wk later revealed an intrinsic stenosis, measuring 8 mm in diameter by 1 cm in length, which was dilated.

CONCLUSION

Esophageal obstruction is a complication of variceal banding that should be considered in patients with inability to tolerate oral diet after banding.

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Key words: Case report; Esophageal varices; Band ligation; Esophageal necrosis; Esophageal obstruction

Core tip: Complete esophageal obstruction and necrosis is a rare complication of esophageal variceal banding. Patients typically present with dysphagia and inability to tolerate secretions shortly after banding. Diagnosis is made with a barium esophagram or upper endoscopy. Treatment consists of supportive care and total parental nutrition until recovery or removing the band endoscopically. Most patients recover but may require esophageal dilation afterwards.

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INTRODUCTION

Esophageal and gastric varices are a result of progressive liver disease and portal hypertension. Screening and management of varices is a crucial part of the management in patient with end stage liver disease. Treatment can be performed with band ligation versus non-selective beta blockers depending on the size of varices, ability to tolerate medications and history of esophageal variceal bleeding. Variceal band ligation is a safe and effective intervention for varices with rare but serious complications including bleeding, ulcers and rarely obstruction[1-4].

We present a case of complete esophageal obstruction and necrosis as a result of esophageal variceal banding. The case report explores the differential diagnosis of dysphagia after band ligation, diagnosis of obstruction and reviews potential treatment options.

CASE PRESENTATION

Chief complaint

An 89 years old woman presented with an inability to swallow one day after band ligation of esophageal varices.

History of present illness

The patient experienced almost immediate regurgitation after any oral intake on the way home from endoscopy. Her initial esophagogastroduodenoscopy (EGD) was performed for surveillance of varices. She was found to have large, non-bleeding esophageal varices and type 1 gastroesophageal varices. Two bands were placed on the esophageal varices in the lower esophagus in an upward spiral motion for primary prophylaxis and varices were completely eradicated. She reported feeling well in recovery after the procedure and was discharged.

History of past illness

She has a past medical history of nonalcoholic steatohepatitis cirrhosis.

Physical examination

Upon arrival to the hospital the day after endoscopy, her vital signs were stable. The patient appeared uncomfortable and was not able to tolerate her oral secretions. Her physical exam was otherwise unremarkable with pertinent negatives including ascites, hepatic encephalopathy, hepatosplenomegaly, lower extremity edema or crepitus.

Laboratory abnormalities

Initial blood work revealed a Model of End Organ Liver Disease score of 7. The rest of her blood work was unremarkable including a complete blood count, chemistry and liver function tests. She underwent a chest X-ray, which did not reveal any acute

abnormalities.

Further diagnostic workup and interventions

She was treated symptomatically with sublingual nitroglycerin for esophageal spasm, which is a known complication after esophageal banding and was the presumed issue here. She failed to improve with intravenous fluids and conservative management for several days and, therefore, underwent an EGD for further evaluation. Images from endoscopy five days after initial band placement are shown in Figure 1. Endoscopy revealed the mucosa surrounding the banded varix was now necrosed and blocking the lumen of the esophagus.

FINAL DIAGNOSIS

Complete esophageal obstruction and necrosis due to esophageal variceal band ligation.

TREATMENT

The band was purposefully dislodged, revealing distal ulceration and stricturing which could not be transversed with an endoscope. She underwent a computed topography of the chest which did not reveal perforation. Surgery evaluated the patient and did not feel that an operation was warranted. Subsequent gastrografin swallow study revealed passage of contrast into the stomach without extravasation (Figure 2). Within 72 h after the procedure, she was tolerating an oral diet and was discharged home.

OUTCOME AND FOLLOW-UP

She returned as an outpatient for an EGD two weeks after discharge. Endoscopy revealed intrinsic moderate stenosis 34 cm from the incisors. The stenosis was 8 mm in diameter by 1 cm in length and dilated with a through-the-scope balloon (Figures 3 and 4).

DISCUSSION

Band ligation is one of the most effective interventions for the prevention and treatment of esophageal variceal hemorrhage. When esophageal varices are banded, local venous occlusion and thrombosis leads to tissue necrosis at the site of the band. The band subsequently sloughs off within about 72 h of placement and a small ulceration is left at the place of the band[2]. Varices subsequently become smaller in diameter, reducing risk of life-threatening bleeding. Patient typically require multiple treatments in order to completely eradicate varices[5].

Variceal banding is an effective and well tolerated procedure; however, side effects including dysphagia, ulcer bleeding, pneumonia, and strictures have been reported[6,7]. The prevalence of these side effects, including dysphagia, have been reported in the literature; however rates have varied significantly from 0 to 75% of affected patients[8]. Dysphagia after variceal banding is more commonly due to dysmotility and esophageal spasms after banding. These symptoms tend to be transient and typically last about 24 to 48 h and most patients can successfully advance their diet[9]. Rarely dysphagia is a result of complete esophageal obstruction and necrosis. To our knowledge, there has only been 8 cases reports in the literature highlighting the diagnosis and management of this complication[10-18]. While the exact cause of obstruction and factors that predispose patients to developing this are unknown, some authors postulate that obstruction after banding may occur if a band is placed too close to mucosa that is already edematous or necrotic, which can be seen after previous banding[3].

Given the rarity of this complication, management has been based upon previous case reports in the literature and therefore has varied. Many patients were treated conservatively with no oral intake and received total parental nutrition until symptoms resolved. According to previous case reports, this has been a successful intervention and most patients began to show signs of improvement within a week[2,10-12]. Other case reports have highlighted removing the band endoscopically with mixed outcomes. Endoscopists have attempted band removal with biopsy

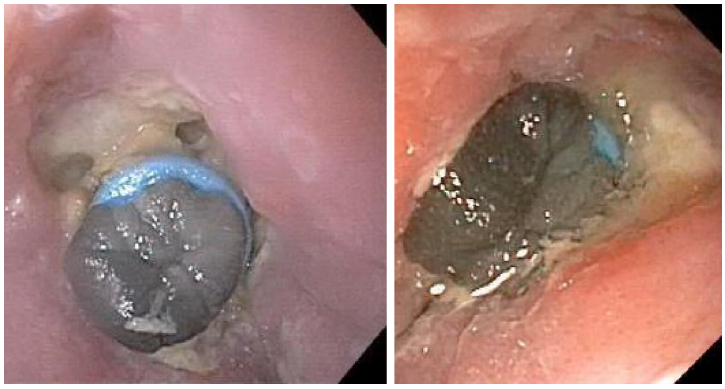

Figure 1 Necrosed esophageal varix causing complete esophageal obstruction.

forceps and rat tooth forceps. While many patients tolerated removal, were able to advance their diet and be discharged from the hospital faster, one patient suffered an intramural esophageal dissection and bleeding[16]. We opted to remove the band with biopsy forceps and this intervention was successful with no complications. Patient was able to safely advance her diet within 24 h. Our patient improved quickly once the band was removed from the obstructing varix, suggesting this could be an ideal intervention if the endoscopist is able to safely perform this maneuver.

CONCLUSION

In conclusion, complete esophageal obstruction and localized necrosis is an extremely rare complication of variceal banding. This should be considered in any patient that presents with an inability to tolerate an oral diet after band ligation of esophageal varices. Diagnosis of this complication is typically with a barium esophagram or repeat upper endoscopy. Treatment may consist of supportive care and nothing by mouth until symptoms resolve or with removing the band endoscopically.

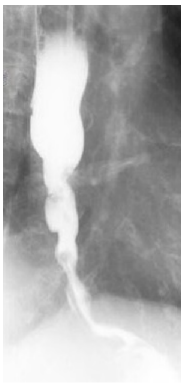

Figure 2 Barium esophagram after band removal.

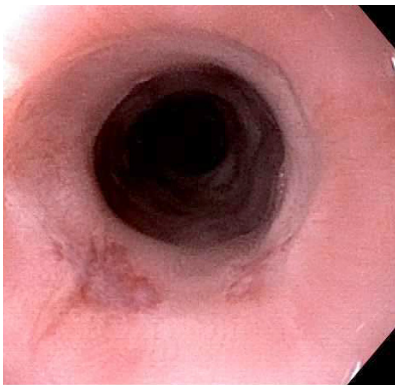

Figure 3 Esophageal stenosis after band removal.

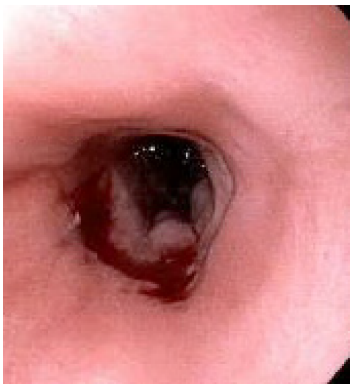

Figure 4 Balloon dilation of esophageal stenosis.

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CASE REPORT

Percutaneous transhepatic cholangioscopy and lithotripsy in treating difficult biliary ductal stones: Two case reports

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Abstract

BACKGROUND

Endoscopic retrograde cholangiopancreatography (ERCP) is preferred for managing biliary obstruction in patients with bilio-enteric anastomotic strictures (BEAS) and calculi. In patients whose duodenal anatomy is altered following upper gastrointestinal (UGI) tract surgery, ERCP is technically challenging because the biliary tree becomes difficult to access by per-oral endoscopy. Advanced endoscopic therapies like balloon-enteroscopy or rendevous-ERCP may be considered but are not always feasible. Biliary sepsis and comorbidities may also make these patients poor candidates for surgical management of their biliary obstruction.

CASE SUMMARY

We present two 70-year-old caucasian patients admitted as emergencies with obstructive cholangitis. Both patients had BEAS associated with calculi that were predominantly extrahepatic in Patient 1 and intrahepatic in Patient 2. Both patients were unsuitable for conventional ERCP due to surgically-altered UGI anatomy. Emergency biliary drainage was by percutaneous transhepatic cholangiography (PTC) in both cases and after 6-weeks' maturation, PTC tracts were dilated to perform percutaneous transhepatic cholangioscopy and lithotripsy (PTCSL) for duct clearance. BEAS were firstly dilated fluoroscopically, and then biliary stones were flushed into the small bowel or basket-retrieved under visualization provided by the percutaneously-inserted video cholangioscope. Lithotripsy was used to fragment impacted calculi, also under visualization by video cholangioscopy. Satisfactory duct clearance was achieved in Patient 1 after one PTCSL procedure, but Patient 2 required a further procedure to clear persisting intrahepatic calculi. Ultimately both patients had

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successful stone clearance confirmed by check cholangiograms.

CONCLUSION
PTCSL offers a pragmatic, feasible and safe method for biliary tract clearance when neither ERCP nor surgical exploration is suitable.

Key words: Percutaneous transhepatic cholangiography; Video cholangioscopy; Lithotripsy; Biliary calculi; Endoscopic retrograde cholangiopancreatography; Case report; Bilio-enteric anastomotic strictures

Core tip: The purpose of this case report is to highlight the feasibility of percutaneous transhepatic cholangioscopy and lithotripsy (PTCSL) as therapy for biliary obstruction in patients with surgically altered anatomy which makes them unsuitable for conventional endoscopic retrograde cholangiopancreatography. Percutaneous transhepatic cholangiography used for emergency biliary drainage provides the access required for PTCSL, so it is reasonable to consider PTCSL in such patients. PTCSL attractively combines radiological and endoscopic techniques already established in most Hepato-Pancreato-Biliary units. Advanced endoscopic options are not widely available, and surgical options are limited as such patients are poor surgical candidates. We review the literature to compare our cases to previously reported cases of PTCSL.

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INTRODUCTION

Per-oral endoscopic access to the biliary tree is difficult after surgical procedures which alter the upper gastrointestinal (UGI) anatomy. These procedures include Billroth II distal gastrectomy, total gastrectomy, Roux-en-Y reconstruction gastric bypass, and, those involving bilio-enteric anastomotic strictures (BEAS) such as pancreaticoduodenectomy and hepaticojejunostomy. BEAS could be particularly problematic as they promote cholestasis and their sutures generate foreign body reaction, thus forming calculi that cause further biliary strictures[1-4].

Biliary tree calculi in these patients with altered upper GI anatomy can be managed by advanced endoscopic procedures such as balloon-assisted endoscopic retrograde cholangiopancreatography (ERCP)[5], or, rendezvous ERCP facilitated by Endoscopic Ultrasound (EUS)-guided or percutaneous biliary tree puncture[6]. Enteroscopes used for balloon-assisted ERCP have smaller working channels than those used for conventional ERCP and so may not permit use of adjuncts such as lithotripsy[5]. EUS-guided procedures are technically challenging and not widely available.

Another option is surgical bile duct exploration but patients presenting with cholangitis on a background of BEAS and calculi are usually poor surgical candidates due to their comorbidities. Re-operation can also be difficult due to adhesions from previous surgery. Surgical treatment options are thus limited by the potential for increased morbidity and mortality.

Current guidance recommends percutaneous radiological stone extraction for the small number of patients in whom endoscopic techniques are unsuccessful or impossible[7]. Biliary access is usually achieved by inserting a percutaneous transhepatic cholangiography (PTC) drain *via* which catheter interventions are performed under fluoroscopic guidance. In this context, a less commonly reported procedure is percutaneous transhepatic cholangioscopy and lithotripsy (PTCSL) which uses PTC biliary access for duct clearance under video cholangioscopy guidance with lithotripsy as an adjunct for stone fragmentation[7]. PTCSL is more established in East Asia where primary choledocholithiasis and hepatolithiasis are more prevalent, and PTCSL is used in their management. There are very few reports of PTCSL from other parts of the world; mostly case reports[8-10] and one single-centre

case series[11]. In this first report of PTCSL from a UK centre, we describe our first 2 cases of PTCSL in patients with symptomatic BEAS associated with ductal stones.

CASE PRESENTATION

Patient 1

Chief complaint: Patient 1 is a 70-year-old man who was admitted with acute cholangitis. He previously underwent curative total gastrectomy for gastro-oesophageal cancer 3-years prior, with reconstruction by Roux-en-Y oesophagojejunostomy. He underwent open repair of an incarcerated hiatus hernia two years later at which time symptomatic choledocholithiasis was treated by surgical common bile duct (CBD) exploration and side-to-side choledochoduodenostomy. His other co-morbidities were atrial fibrillation for which he was anticoagulated with warfarin, previous myocardial infarction, and limited mobility due to Paget's disease affecting both of his hips. He was malnourished and significantly underweight as a result of his previous surgeries.

Diagnostic evaluation: Physical examination of Patient 1 revealed a tachycardia of 120 bpm, and pyrexia of 38.5 °C. Abdominal exam demonstrated multiple previous surgical scars but a soft and non-distended abdomen. Laboratory work-up showed raised circulating white blood cell count of 19.6 × 10^9/L and raised bilirubin of 204 μmol/L.

Computerised tomography (CT) scanning in Patient 1, after broad-spectrum antibiotics and intravenous fluid resuscitation, showed dilated left intrahepatic ducts Figure 1. USS-guided PTC (PTC) showed a large extrahepatic calculus and choledochoduodenostomy stricture Figure 2.

Patient 2

Chief complaint: Patient 2 is a 70-year-old female who was admitted as an emergency with acute cholangitis. She underwent curative subtotal-gastrectomy, en bloc right hemihepatectomy, and reconstruction by roux-en-y hepaticojejunostomy 4-years prior for metastatic gastric GIST down-staged with Imatinib. She also previously had left breast cancer treated with curative wide local excision and axillary node clearance 1-year prior. Her regular medications were Imatinib and Letrozole.

Diagnostic evaluation: Physical examination of Patient 2 revealed tachycardia of 115 bpm, pyrexia of 38.7 °C, soft non-distended abdomen and previous abdominal surgical scars. Her circulating white blood cell count and bilirubin were raised at 17.8 × 10^9/L and 163 μmol/L respectively.

Patient 2 received broad-spectrum antibiotics and intravenous fluid resuscitation, then CT scanning showed dilated left intrahepatic ducts Figure 3. USS-guided PTC in Patient 2 showed multiple calculi in the dilated left intrahepatic ducts Figure 4 and a hepaticojejunostomy stricture.

FINAL DIAGNOSIS

Patient 1

Patient 1 had a BEAS of his choledochoduodenostomy and biliary calculi causing symptomatic biliary obstruction.

Patient 2

Patient 2 had a symptomatic hepaticojejunostomy stricture and biliary calculi.

TREATMENT

Patient 1

Emergency biliary drainage was achieved with an 8Fr locking pigtail external biliary drain inserted into the left hepatic ducts at diagnostic PTC in Patient 1 Figure 2. When the patient was clinically improved, the drain was internalised 6 d later Figure 5 with the internal component crossing the choledochoduodenostomy stricture. Jaundice resolved and cytology from PTC brushings did not show malignancy. Patient 1 was unsuitable for ERCP due to surgically altered anatomy and was a poor surgical candidate, so he was treated by PTCSL (procedure described in section titled "Treatment: PTCSL procedure").

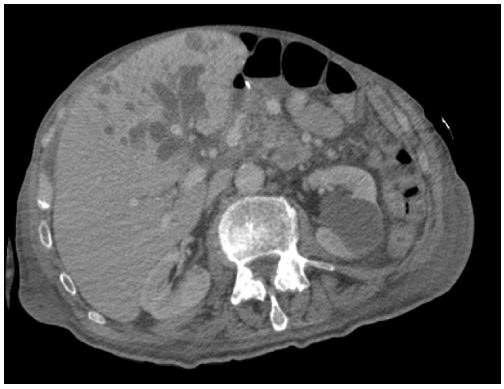

Figure 1 Computerised tomography scan image in Patient 1 showing dilated segment 4, 2 and 3 ducts.

PTCSL procedure

PTC tracts were allowed to mature for 6-wk; then PTCSL procedure performed aseptically under general anaesthesia administering prophylactic Co-Amoxiclav targeting Enterococci and gram-negative bacilli. Normal blood clotting was also ensured and the PTCSL procedure performed as follows: (1) PTC drains were exchanged over stiff wires (Terumo, Tokyo) for 23 cm 8F vascular sheaths (Cordis Milpitas, California) that were cannulated through the BEAS to serve as PTCSL access; (2) The vascular sheaths were exchanged for stiff Amplatz (Boston Scientific, Washington, United States) and standard J tipped (Kimal, Droitwich, United Kingdom) wires over which the tracts were dilated for insertion of 20F vascular sheaths. The sheaths were attached to skin with heavy silk sutures and trimmed to leave 20 French conduits for access into the left hepatic duct; (3) BEAS were dilated with 10mm Mustang angioplasty balloons (Boston Scientific, Washington) and some stones pushed into the small bowel; (4) Under direct visualisation with a 16F Choledochoscope (Karl Storz, Tuttlingen, Germany), stones were basket-retrieved Figure 6. Impacted stones were first fragmented using a Wolf 2280 Riwolith electrohydraulic lithotriptor (Richard Wolf, Knittliger, Germany) with a 5F flexible probe Figures 7 and 8; (5) At the end of the PTCSL procedure, the 20F sheaths were exchanged for 14F Flexima locking pigtail drains (Boston Scientific, Washington) over stiff Amplatz wires. Additional side holes were cut in the intra-biliary segment of the pigtail drains to create internal-external drains; the distal loops locked in the small bowel; (6) Drain position was confirmed fluoroscopically before securing with skin-suture and RevolutionTM catheter securement device (Merit Medical, Utah, United States); and (7) PTC drains were clamped after 24 h free-drainage and check cholangiogram performed 1-2 wk later.

Patient 2

Emergency biliary drainage was achieved with an 8Fr internal-external biliary drain inserted into the left hepatic ducts at diagnostic PTC in Patient 2 Figure 9. Jaundice resolved and cytology from PTC brushings did not show malignancy. Surgically altered anatomy made ERCP unfeasible and she was high-risk for surgery, so had PTCSL (procedure described in section titled "Treament: PTCSL procedure").

OUTCOME AND FOLLOW-UP

Patient 1

Patient 1 made a good recovery with ward-based care following PTCSL. He had nasojejunal (NJ) feeding nutritional support. Check cholangiogram Figure 10 showed four small non-obstructing calculi in peripheral ducts of Segment 6 but good flow of contrast into the duodenum. The internal-external drain was removed, and the tract sealed with Avitene™ microfibrillar collagen haemostat (Bard, Rhode Island, United States), and he was discharged from hospital to continue NJ feeding at home. Patient 1 was clinically well and reported no further episodes of symptomatic biliary obstruction at 6-mo follow-up.

Patient 2

Patient 2's check cholangiogram showed remnant stones in segment 2 but contrast flowing freely into jejunum Figure 11. She was discharged home with the PTC drain clamped. She was readmitted 4 wk later for flushing of PTC drain to remove remnant

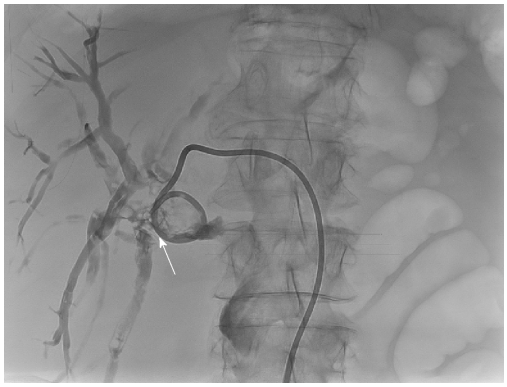

Figure 2 Percutaneous transhepatic cholangiography *via* segment 3 duct in Patient 1 showing filling defect consistent with an obstructing extrahepatic calculus (white arrow) at origin of the left hepatic ducts and located just proximal to the choledochoduodenostomy anastomosis. An external biliary drain is inserted.

stones. Subsequent cholangiogram showed fewer intrahepatic biliary duct stones Figure 12. Her PTC drain was removed the day after, and the track sealed by Avitene™. She was discharged home without complications and remained well with no further episodes of symptomatic biliary obstruction at 6-mo follow-up.

DISCUSSION

The attractiveness of this PTCSL is that it combines two techniques that are routinely used in most Hepato-Pancreato-Biliary (HPB) Centres, namely: PTC and endoscopic biliary cholangioscopy. This makes it more feasible to establish PTCSL as a treatment for difficult ductal calculi in most HPB Centres. Patients with acute cholangitis may require emergency biliary drainage which when not possible by ERCP, is done by PTC drain insertion. As in both of our cases, emergency biliary decompression in patients with surgically-altered UGI anatomy is usually be done by PTC which makes it pragmatic to subsequently adopt PTCSL for definitive biliary clearance. We uniquely describe the first report of PTCSL from a UK Centre.

Although percutaneous access for PTCSL is usually transhepatic, it is also possible to gain access *via* a small bowel access loop; a T-tube sinus tract; or trans-cholecystically. However, none of these alternative access routes were available in our cases. It is preferable to perform PTCSL under general anaesthesia as the procedure is painful due to its working sheath which traverses skin, intercostal muscles, and the liver capsule. The absence of enhanced sedation or general anaesthesia has been correlated with lack of therapeutic success in long and complex endoscopic procedures to manage difficult ductal calculi[12].

Complications occur in approximately 7% of patients treated with PTCSL, mainly biliary sepsis, haemobilia and bile duct injuries[13,14]. In order to reduce complication risk, PTC tracts must be allowed to mature and gradually dilated before use in PTCSL[3]. Tract maturation time vary depending on size of the final working sheath for PTCSL. Reported tract maturation times have been as short as ≤ 4 d for 8-10F access sheaths which are used for fluoroscopic mechanical lithotripsy without any video cholangioscopy[13,14]. Longer tract maturation times of up to 6 wk have been described for 16-18F working sheaths used for video cholangioscopy-guided interventions[15,16]. An average of 2 PTCSL treatments are required to clear CBD calculi[14,17] while 5 are needed for intrahepatic calculi[15,18]. Our case with mainly intrahepatic calculi required 2 treatment sessions with PTCSL while the case extrahepatic calculi required only 1 session. Comparative studies show clearance rates for calculi are better for extrahepatic than for intrahepatic stones[3,13].

Lithotripsy is a therapeutic adjunct that improves success rates in patients undergoing video cholangioscopy-guided clearance of biliary calculi[19]. The most commonly used modality is electrohydraulic lithotripsy (EHL) which fragments stones by generating shock waves from rapid expansion of surrounding fluid in response to short pulses of high-voltage electric sparks. Laser lithotripsy fragments stones by producing strong shockwaves using infrared light energy generated by the applied laser. Laser lithotripsy is more expensive and although randomized studies are lacking, systematic review shows it is more successful than EHL in treating impacted biliary tract calculi[20].

The recurrence rate for intrahepatic calculi post-PTCSL varies from 21%-40% after

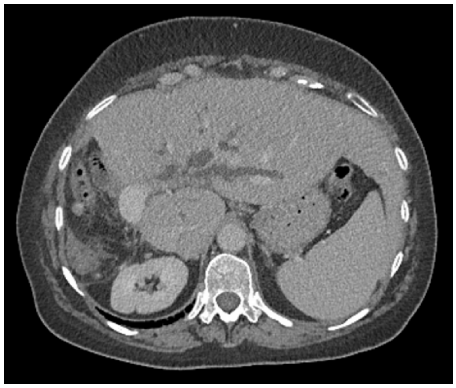

Figure 3 Computerised tomography scan image in Patient 2 showing previous right hemihepatectomy and dilated left intrahepatic ducts.

10-years follow-up[15,18,21], bile duct strictures being the main risk factor[18]. The recurrence rate for CBD calculi post-PTCSL is 45% after 7-years follow-up[17]. The only 3 deaths reported due to PTCSL have been caused by biliary sepsis[14,15].

CONCLUSION

Our experience is that PTCSL is feasible and safe for biliary clearance when neither ERCP nor surgical exploration are suitable. PTCSL attractively combines PTC and video cholangioscopy which are techniques that are readily available in most HPB Centres, thus making it a pragmatic option for bile duct clearance when endoscopy is not feasible, and surgery is high-risk. Our report is limited by lack of long-term follow-up data.

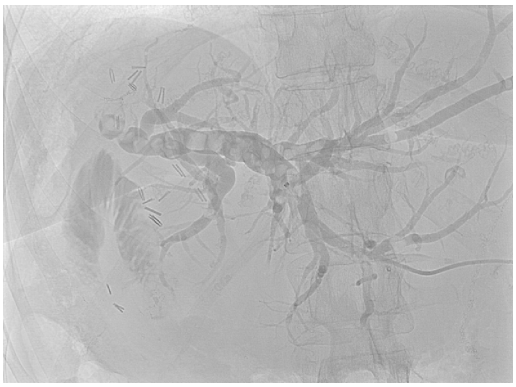

Figure 4 Percutaneous transhepatic cholangiography shows dilated left intrahepatic in addition to peripheral segment 3 ducts containing multiple calculi.

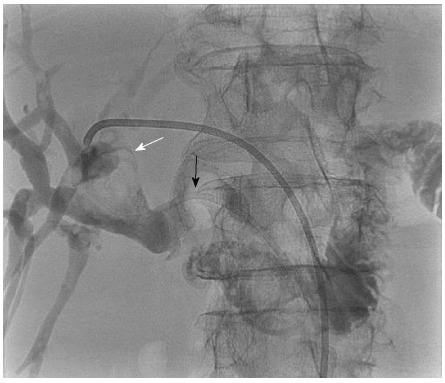

Figure 5 The external percutaneous transhepatic cholangiography drain was converted to an internal-external drain (black arrow) 6 d following the original percutaneous transhepatic cholangiography. The obstructing stone (white arrow) is again seen in the same position as in **Figure 2**. The distal locking loop of the drain is left in the duodenum and thus permits entry of contrast into the small bowel.

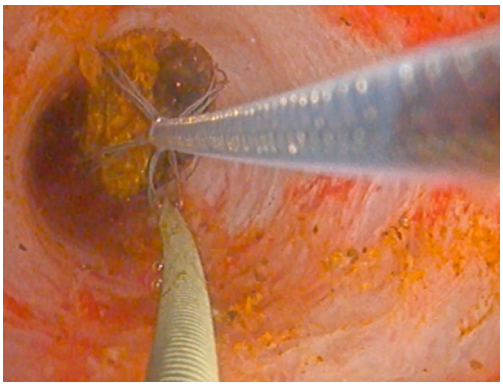

Figure 6 Video cholangioscopy image showing a guide wire (on left side of image) in the bile duct and a mobile stone being basket-retrieved from bile duct using an introduced Dorma basket (on right side of image).

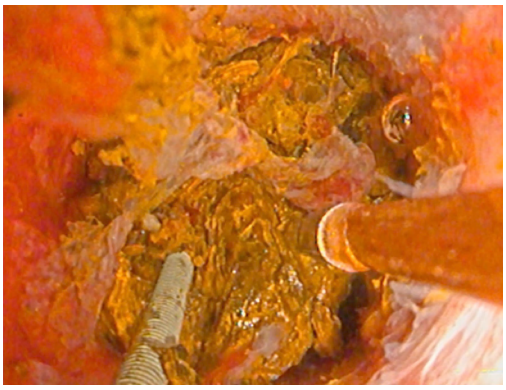

Figure 7 Video cholangioscopy image showing guide wire (on left side of image) in bile duct lumen alongside impacted stone cluster with lithotripsy probe introduced (on right side of image) for electrohydraulic stone fragmentation.

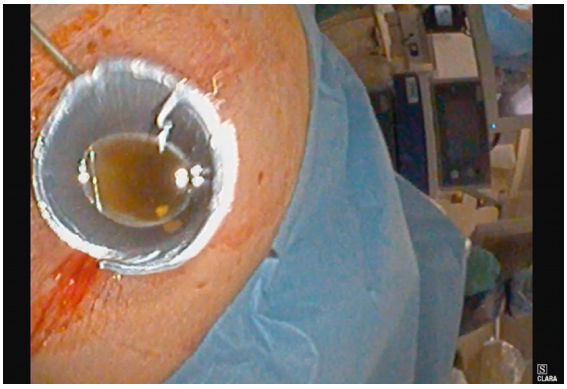

Figure 8 Percutaneous transhepatic cholangioscopy and lithotripsy for ductal calculi.

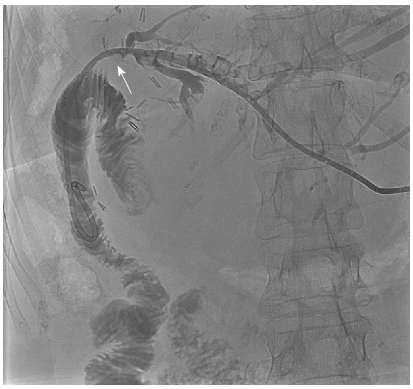

Figure 9 Percutaneous transhepatic cholangiography image for Patient 2 demonstrating the internal-external biliary drain (arrowed) traversing the hepaticojejunostomy stricture so contrast is now seen in the jejunum.

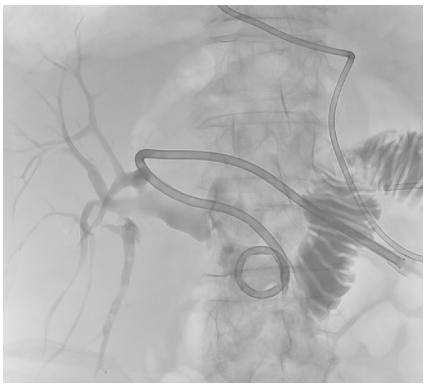

Figure 10 Post-percutaneous transhepatic cholangioscopy and lithotripsy cholangiogram in Patient 1 showing unobstructed bile ducts but few small calculi in Segment 6. Internalised percutaneous transhepatic cholangiography drain is seen with distal locked end in the duodenum.

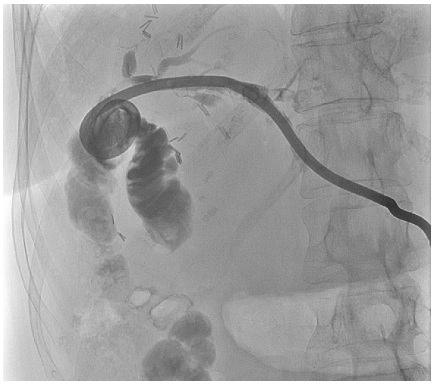

Figure 11 Post-percutaneous transhepatic cholangioscopy and lithotripsy check cholangiogram after in Patient 2 showed stones in segment 2.

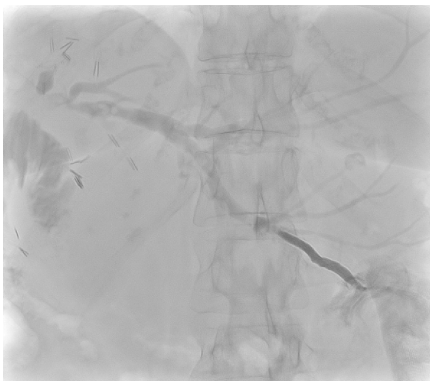

Figure 12 Cholangiogram performed after repeat procedure in Patient 2 to flush remnant stones showed smaller and fewer remnant intrahepatic biliary duct stones.

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CASE REPORT

Gastrointestinal bleeding as initial presentation of extramedullary plasma cell neoplasms: A case report and review of the literature

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Author contributions: Iosif E, Shamali A, Kyriakides C and Lauro R designed the study; Iosif E, Rees C, Beeslar S contributed to data acquisition and interpretation; Iosif E, Rees C and Kyriakides C wrote the manuscript. The final manuscript was approved by all authors. Rees C and Kyriakides C were the supervising consultants.

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Abstract

BACKGROUND

Plasma-cell neoplasms rarely involve the gastrointestinal tract and manifest as gastrointestinal bleeding. Plasmablastic myeloma is an aggressive plasma cell neoplasm associated with poor outcomes. A small number of cases with gastrointestinal involvement is reported in the literature and therefore high index of suspicion is essential for avoiding delays in diagnosis and treatment.

CASE SUMMARY

Our aim is to present our experience of a 70-year-old patient with a secondary presentation of plasmablastic myeloma manifesting as unstable upper gastrointestinal bleeding and to review the literature with the view to consolidate and discuss information about diagnosis and management of this rare entity. In addition to our case, a literature search (PubMed database) of case reports of extramedullary plasma cell neoplasms manifesting as upper gastrointestinal bleeding was performed. Twenty-seven cases of extramedullary plasmacytoma (EMP) involving the stomach and small bowel presenting with upper gastrointestinal bleeding were retrieved. The majority of patients were males (67%). The average age on diagnosis was 62.7 years. The most common site of presentation was the stomach (41%), followed by the duodenum (15%). The most common presenting complaint was melena (44%). In the majority of cases, the EMPs were a secondary manifestation (63%) at the background of multiple myeloma (26%), plasmablastic myeloma (7%) or high-grade plasma cell myeloma (4%). Oesophagogastroscopy was the main diagnostic modality and chemotherapy the preferred treatment option for secondary EMPs.

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CONCLUSION
Despite their rare presentation, upper gastrointestinal EMPs should be considered in the differential diagnosis of patients with gastrointestinal bleeding especially in the presence of systemic haematological malignancy.

Key words: Gastrointestinal bleeding; Extramedullary plasma cell neoplasm; Plasmablastic myeloma; Multiple myeloma; Extramedullary plasmacytoma; Case report

Core tip: The involvement of gastrointestinal tract by plasma cell neoplasms and the manifestation as gastrointestinal bleeding is very rare. However, patients can be profoundly unstable on presentation requiring immediate diagnosis and intervention. As the existing literature is very scattered and it mainly consists of case reports, we are aiming with our present work not only to describe our experience but also to review, consolidate and discuss information about diagnosis and management of this rare cause of gastrointestinal bleeding. The management these patients requires a multidisciplinary team approach and should involve not only the gastroenterology and surgical teams but also haematology and oncology teams for achievement of the best possible outcomes.

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INTRODUCTION

Plasmablastic myeloma is a rare variant of multiple myeloma and is categorised amongst the plasma cell neoplasms. It is characterised by the neoplastic proliferation of a single clone of plasma cells which produces a monoclonal immunoglobulin. The malignant plasmablastic clones reside in the bone marrow but in rare occasions can migrate into extramedullary tissues like the upper respiratory tract, lymph nodes, central nervous system and gastrointestinal tract and present with symptoms or complications from the organs involved. Gastrointestinal involvement includes lesions in the stomach, liver and large bowel, with involvement of the small bowel being a rare presentation.

The most frequent manifestation of gastrointestinal tract extramedullary plasma cell neoplasm is abdominal pain which can be associated with symptoms of small bowel obstruction. Gastrointestinal bleeding can also occur, more often in gastric and jejunal lesions compared to ileal. It can present as haematemesis, melena or anaemia due to chronic blood loss due to vascular or ulcerated bleeding lesions[1,2]. The pathogenesis of gastrointestinal bleeding in plasma cell myelomas is multifactorial. Direct plasma cell infiltrates in the form of extramedullary plasmacytomas (EMPs)[2,3], coagulation abnormalities as a result of paraproteinaemia[4,5], peptic ulcers secondary to corticosteroid and anti-inflammatory therapeutic regimes and[2] finally amyloid infiltrates of the bowel wall[6]. Patients presenting with GI bleeding could be challenging in diagnosis and treatment, as they might be clinically unstable requiring an immediate intervention.

The literature is scattered with case reports of patients who have been affected with extramedullary plasma cell neoplasms with gastrointestinal tract involvement, especially with GI bleeding. We are aiming not only to describe our experience of one case of upper gastrointestinal bleeding due to secondary extramedullary plasma cell neoplasm but also to provide a comprehensive review of all published cases of stomach and small bowel EMPs to date with similar presentation.

CASE PRESENTATION

Chief complaints

This is a case of a 70-year-old male patient who initially presented to his oncologist at

another hospital with right shoulder and neck pain associated with paraesthesia affecting the C8-T1 dermatome area. The patient was then admitted to our hospital under the gastroenterology team with fresh bleeding per rectum and melena.

History of present illness
Two-day history of melena and fresh PR bleeding without any abdominal pain.

History of past illness
His past medical history included essential hypertension, paroxysmal atrial fibrillation on beta blockers but not on anticoagulation, a prostatectomy (TURP) for cancer and still on hormone therapy for non- metastatic prostate cancer. To investigate his shoulder pain and paraesthesia he underwent (at his local hospital under oncology team) a magnetic resonance imaging (MRI) of his spine which revealed multiple bony lesions and a soft tissue lesion at the level of T8-T9 vertebrae. A staging computer tomography (CT) of chest, abdomen and pelvis did not reveal any additional pathology. To reduce the risk of cord compression urgent radiotherapy (five sessions) at T7-T10 level was given.

Personal and family history
His family history was clear and didn't include any haematological or gastrointestinal malignancies.

Physical examination upon admission
On examination patient was pale, clammy and sweaty, hypotensive but not markedly tachycardic (on beta blockers). His abdomen was soft, mildly tender in the centre but with no signs of peritonism. Digital rectal examination revealed the presence of fresh blood and melena in the rectum.

Laboratory examinations
The patient's haemoglobin on presentation was 58 g/L, MCV 92.3 fL, MCH 29 pg, MCHC 315 g/L consistent with normochromic normocytic anaemia and acute severe blood loss. His urea was raised 9.9 mmol/L sign of blood digestion in the upper gastrointestinal tract.

Imaging examinations
When the patient presented in our Centre, due to haemodynamic instability, after initial resuscitation and blood transfusion he had an oesophagogastroscopy which apart from mild gastritis showed no cause for his symptoms. A CT angiogram did not show any signs of active bleeding but mild prominence of the colonic hepatic flexure and the rectum was reported. A subsequent colonoscopy to the terminal 30cm of ileum reported large clots in the large and small bowel but no obvious bleeding point was demonstrated. Following this, he underwent a small bowel capsule endoscopy (Figure 1) which showed mid-small bowel bleeding from a likely submucosal lesion which was associated with intestinal lymphangiectasia. As he continued to bleed a further CT angiogram was performed. This last showed a potential small bowel mass with a contrast blush suggestive of slow haemorrhage, therefore the patient was taken to theatre for an emergency laparotomy and resection of the small bowel lesion.

Intra-operative findings and post-operative course
The lesion was located at the proximal ileum (150 cm from DJ flexure), was resected and sent for histology and a primary side-to-side small bowel anastomosis was performed. There was no macroscopic evidence of lymphadenopathy, peritoneal or disseminated malignant disease intraoperatively. A segment of proximal ileum 95 mm in length was resected, which on opening, revealed a centrally ulcerated fungoid lesion which was 32 mm in maximum diameter and 40 mm from the nearest end resection margin. The lesion had a solid white appearance and involved the entire thickness of the bowel wall.

The patient had a smooth and uncomplicated post-operative recovery and was discharged from the hospital a week following his laparotomy.

FINAL DIAGNOSIS

Histopathology revealed sheets of pleomorphic cells which had a plasmacytoid appearance with highly atypical nuclei containing prominent nucleoli (Figure 2). On immunohistochemical staining the cells were positive for CD38 (Figure 3A), CD138 (Figure 3B), MUM-1 (Figure 3C), Ki 67 (MIB-1) (Figure 3D) with lambda light chain restriction (Figure 4). There was also weak nuclear expression for cyclin D1 in some of

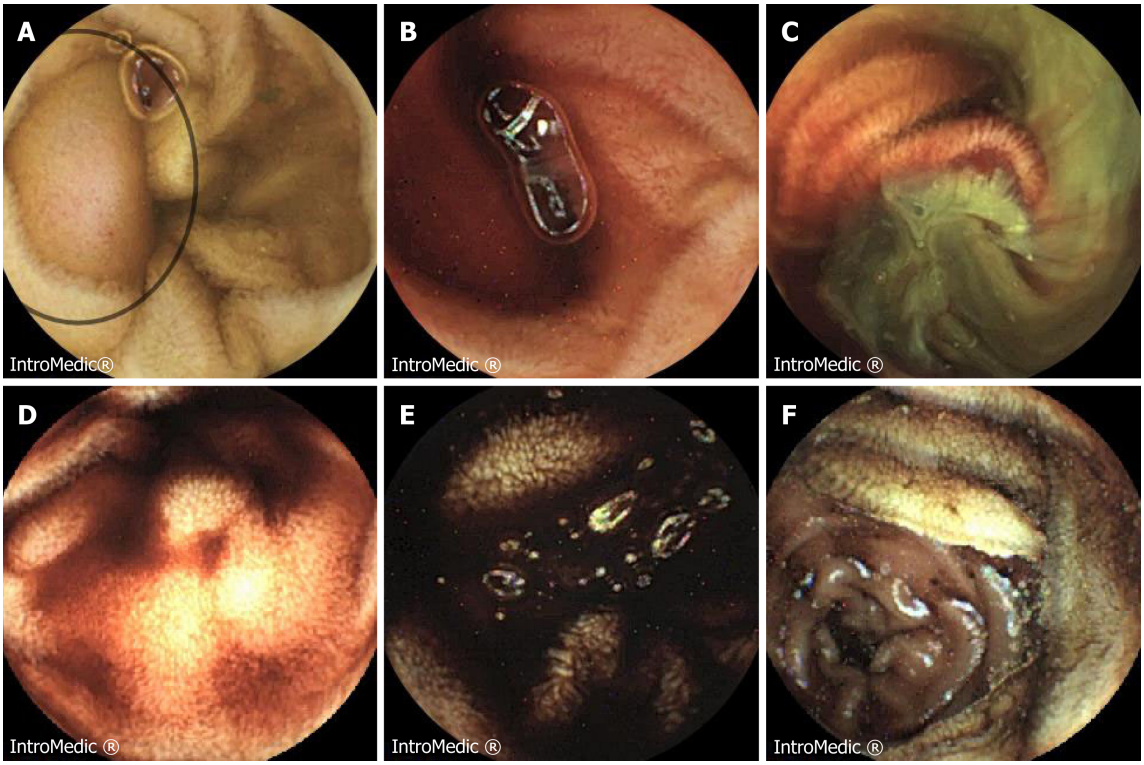

Figure 1 Images from small bowel capsule endoscopy. A: Images from small bowel capsule endoscopy demonstrates a submucosal lesion in the mid-small bowel; B-D: It demonstrates in close proximity to active bleeding, which was likely to be the cause of the patient's presenting complain; E, F: Progressively darker bleeding towards the rest of the ileum turning to melena.

the cells. The morphological and immunophenotypical features were those of a high-grade plasma cell neoplasm.

Considering the presence of bony lytic lesions and IgG lambda paraproteinaemia (17 g/L, lambda light chains 84.1 mg/L) a diagnosis of plasma cell myeloma was given. A bone marrow biopsy confirmed the diagnosis of myeloma. This showed several markedly pleomorphic small nodular foci of tumour comprising plasmablastic cells with prominent nucleoli. Those cells, which represented 10%-15% of the marrow cellularity, were identical to the cells seen in the small bowel resection, confirming bone marrow involvement with an aggressive plasmablastic neoplasm. Bone marrow cytogenetic studies showed gain of 1q21.3, consistent with aggressive tumour behaviour.

TREATMENT

After discussion in the local network haematology multidisciplinary team meeting a trial of VCD (Velcade/ Cyclophosphamide/ Dexamethasone) chemotherapeutic regimen was given, with a view to consolidative autologous stem cell transplantation in the event of a good response. Thalidomide was avoided initially in view of perceived thrombotic risk post-surgery. Despite reduction in his paraprotein to 7 g/L, clinical examination after 2 cycles of treatment showed clear progression of a soft tissue lesion arising from the right first rib and progression was confirmed on MRI and PET-CT imaging. He wished to continue active treatment and was commenced on second-line treatment with Bendamustine/Thalidomide/Dexamethasone, with a view to switching to Lenalidomide/Ixazomib/Dexamethasone therapy in the event of disease progression.

OUTCOME AND FOLLOW-UP

Due to disease progression, and no further response to active treatment, the patient was fast tracked with the palliative care team involvement to Hospice where he died six months after his diagnosis.

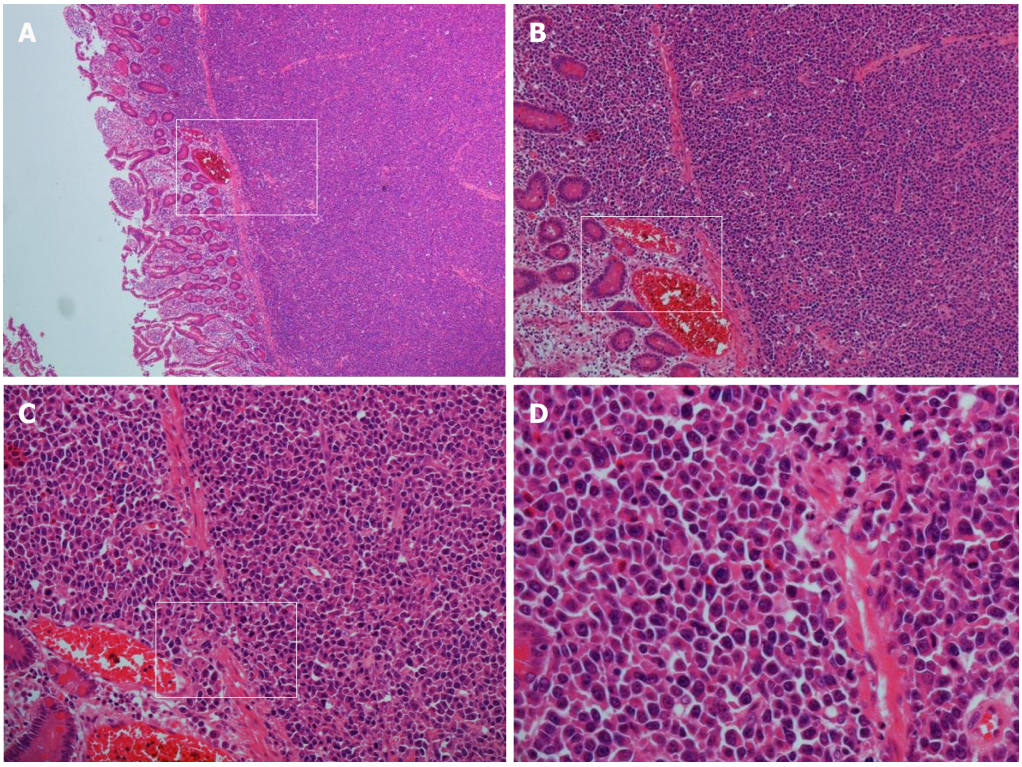

Figure 2 Haematoxylin and eosin staining. Infiltration with sheets of neoplastic pleomorphic cells with plasmacytoid appearance involving the full thickness of the bowel wall. Plasmablasts have highly atypical nuclei with prominent nucleoli. Magnifications: A: ×4; B: ×10; C: ×20; D: ×40.

DISCUSSION

Literature review methods

In addition to presenting and discussing our case, a literature search (PubMed database) was performed using the following searching terms: "extramedullary plasmacytoma", "gastrointestinal plasmacytoma", "gastrointestinal bleeding", "small bowel extramedullary plasmacytoma", "plasmablastic myeloma". The search was limited to articles published in the English language. All published case reports presenting cases of EMP manifesting as upper gastrointestinal bleeding have been analysed. The following variables have been extracted, when available: patient's age, gender, location of EMP in the gastrointestinal tract, presenting complaint, associated symptoms, primary or secondary nature of EMP, diagnostic modalities, treatment choices and outcomes. Cases involving colonic EMP and therefore not presented as upper gastrointestinal bleeding were excluded from the analysis. GraphPad Prism 6 (GraphPad Software, San Diego, CA, United States) and Microsoft Excel (Version 16.15) were used to design the graphs extracted from our results.

Literature review results

Sixty-eight cases of EMP involving the upper gastrointestinal tract have been reported in the literature[1]. Twenty-seven cases, including our case of EMP involving the stomach and small bowel presenting with upper gastrointestinal bleeding were retrieved and have been included in our analysis. Patients' characteristics (age, gender), presenting symptoms, tumour characteristics (location, primary or secondary nature), details about diagnostic and treatment modalities and all the available information about follow up and survival are shown on (Table 1). The majority of patients were males (67% *vs* 18% females) and details about gender were not available in four cases (15%). The average age on diagnosis was 62.7 years. In regards to the location of the EMPs, the most common site of presentation was the stomach (41%)[7-17], followed by the duodenum (15%)[18-21], but noticeable is the presence of concurrent lesions in stomach and duodenum (22%)[2,3,22-25]. Jejunal EMPs were less common (11%)[26-28], whereas ileal presentation was the rarest and was mentioned only in one more case report apart from our case (7%)[29]. A very rare presentation with concurrent lesions in the duodenum, jejunum and ileum was also mentioned[30] (Figure 5). A total of 18% of cases had localisation distal to the Treitz ligament and therefore diagnosis was difficult using oesophagogastroscopy.

Gastrointestinal bleeding in these cases had different presentations. The most

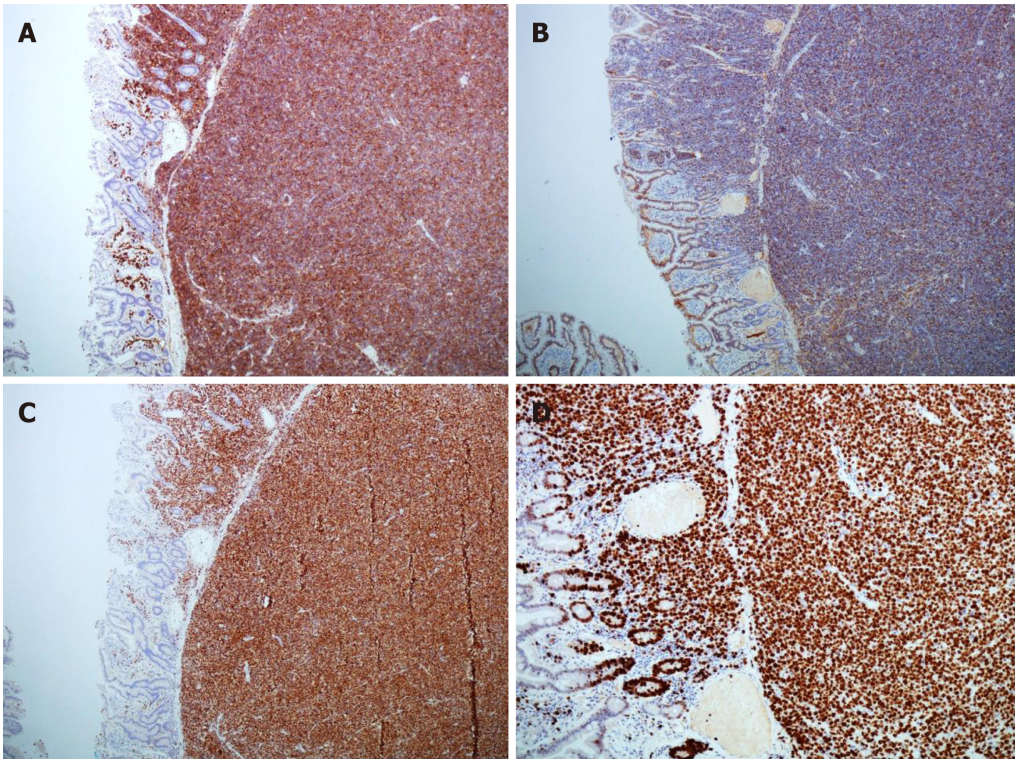

Figure 3 Small bowel plasmablastic myeloma staining. A: Small bowel plasmablastic myeloma positive CD38 staining. CD38 is routinely used for identification of plasma cell neoplasms and stains primarily the membrane due to expression of the transmembrane protein cyclic ADP ribose hydrolase; B: Same specimen positive for CD 138 staining. CD138 is a transmembrane heparan sulphate proteoglycan (syndecan-1). CD138 staining is positive in normal B-cell precursors and plasma cells, along as plasmablastic lymphomas and myelomas; C: Same specimen positive for MUM-1 (Multiple Myeloma-1) nuclear stain. MUM-1 is a nuclear transcriptional factor that is expressed in late plasma cell directed stages of B cell differentiation and also in activated T cells; D: Small bowel plasmablastic myeloma staining positive for Ki 67 (MIB-1). MIB-1 is the IgG1 antibody against Ki 67 which can be detected in the cellular nucleus and is a marker of cell proliferation. Strong expression of the nuclear marker Ki 67 with MIB-1 staining indicates high proliferation rate and is a sign of clinical aggressiveness.

common presenting complaint was melena (44%)[7,9,10,13-16,18,19,23,24,29] and four patients (15%) had melena associated with anaemia[21,27,28]. In five cases (19%), the gastrointestinal bleeding was reported as Upper gastrointestinal bleeding with no further clarification[11,12,20,22,30]. Haematemesis was the presenting complaint in 7% of cases[3,26] and concurrent melena and haematemesis in 7%[8,17]. One patient presented with haematochezia (4%)[2], and one patient was found to have secondary gastroduodenal EMP as part of his investigations for anaemia[25] (Figure 6).

In the majority of the cases analysed the EMPs were a secondary manifestation (63%) at the background of either multiple myeloma (26%)[3,8,14,16,18,25] or more rarely plasmablastic myeloma (7%)[28] or high-grade plasma cell myeloma (4%)[21]. However, there were ten cases (37%)[9-12,19,20,23,26,27,29] of primary EMPs not associated with systemic disease (Figure 7).

Apart from the gastrointestinal bleed, other frequent clinical manifestations are demonstrated in (Figure 8) and they include abdominal pain, diarrhoea, symptoms of bowel obstruction and other gastrointestinal symptoms (jaundice, dyspepsia and anorexia). Bone pain due to bony lesions, weight loss and skin lesions were also present in cases of secondary EMP.

Oesophagogastroscopy was the main initial diagnostic modality used in 26 out of the 27 cases analysed. For lesions located in jejunum and ileum, where Oesophagogastroscopy was not diagnostic further investigations (small bowel capsule endoscopy, CT angiogram, laparotomy) were used.

Unfortunately, we were unable to retrieve any data about the treatment eleven of the cases had because there was no information on the reports. For the remaining sixteen case reports there were ten cases of secondary EMP, eight of which received chemotherapy[2,15,17,21,25,28,30], only one radiotherapy due to patient's co-morbid status[18] and three had surgical treatment[7,18]. The treatment modality selected for the remaining six cases of primary EMP varied between surgery in three cases[26,27,29], chemotherapy in one case[12], radiotherapy in one case[23] and embolization of gastroduodenal artery in one case[19]. Data about patients' follow up and outcome were very scattered and incomplete and therefore no significant results and associations could be made.

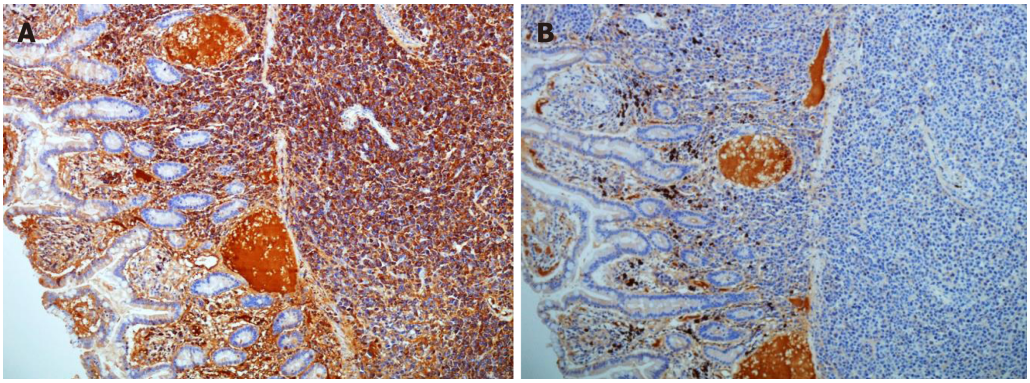

Figure 4 Small bowel plasmablastic myeloma specimen. A: Small bowel plasmablastic myeloma specimen demonstrating strong staining with lambda in keeping with lambda light chain restriction; B: Same specimen showing very weak staining with kappa.

Discussion

Despite plasma cell neoplasms being a rare cause of gastrointestinal bleeding, patients affected could present clinically unstable requiring an immediate intervention and therefore, by presenting a review of the above mentioned twenty-seven cases, we have created a consolidative reference for further use not only by haematologists and oncologists, who are more familiar with the presentation, diagnosis and management of these rear entities but also for all the clinicians who deal with unstable patients with gastrointestinal tract bleeding on the acute setting.

Basic understanding of the biology of plasma cell neoplasms is fundamental. Plasma cell neoplasms have the mutual characteristic of neoplastic proliferation of a single clone of plasma cells which produces a monoclonal immunoglobulin[31,32]. Monoclonal immunoglobulin's (M-protein) detection in the serum or urine indicates an underlying clonal plasma cell disorder and its level can be used to determine myeloma activity. M-protein's properties are associated with the adverse effects that can be observed in patients with paraproteinaemia. These include its ability to agglutinate red blood cells causing increased blood viscosity and to bind into normal blood clotting factors causing bleeding and clotting abnormalities. In addition, its deposition in tissues can result in organ dysfunction and specifically its ability to bind to nerves can lead to neuropathy[32].

Plasmablastic myeloma is considered a rare variant of multiple myeloma and it is categorised amongst the plasma cell neoplasms. The diagnosis of plasma cell myeloma and subsequently the diagnosis of plasmablastic variant involves: (1) the presence of M-protein in serum or urine (usually > 30 g/L of IgG in serum or > 1g/24 h of urine light chain, but no minimal levels are designated); (2) the presence of monoclonal plasma cells in bone marrow biopsy (usually > 10% of the nucleated BM cells); and (3) evidence of organ or tissue impairment related to M-protein (hypercalcaemia, renal failure, anaemia, bony lytic lesions, hyperviscosity, recurrent infections)[33]. In the cases with extramedullary involvement and gastrointestinal manifestation with gastrointestinal bleeding, attempt for direct visualisation of the bleeding lesion is recommended with diagnostic and simultaneously therapeutic purposes. Oesophagogastroscopy was the main diagnostic modality used in the majority of the cases we have reviewed, during which biopsies are retrieved to provide histopathologic confirmation. However, 18% of cases were located distal to the Treitz ligament and therefore diagnosis was difficult using oesophagogastroscopy and further investigations were required.

Plasma cell neoplasms present distinct histopathological and immunohistochemical characteristics. Specifically, in plasmablastic myeloma, the abnormal plasma cells (plasmablasts) are large with hyperchromatic centrally placed nuclei (> 10 μm in diameter) and often prominent nucleoli. They have high nuclear to cytoplasmic ratio and high mitotic activity[34]. Plasma cell aggregates composed of more than 10 plasma cells with perivascular distribution can be seen in one third of the myeloma bone marrow biopsies[35,36]. Pathological plasma cells express strong CD38, CD138 and light chain restriction. CD38 stains primarily the plasma cell cytoplasmic membrane due to expression of the transmembrane protein cyclic ADP ribose hydrolase and it is routinely used for identification of plasma cell neoplasms. CD138 (syndecan-1) is a transmembrane heparan sulphate proteoglycan which is present on the cytoplasmic membrane of up to 95% of plasma cells[36]. In addition, the low ratio of cytoplasmic κ to λ light chains favours the diagnosis of myeloma versus reactive plasmacytosis[37]. If plasmablasts comprise 2% or more of the nucleated cells in the bone marrow aspirate

Table 1 Case reports from the literature review performed

Ref.	Year	Age	Gender	Location of EMP	Presenting Complaint	Outcome	Other symptoms	Primary or Secondary	Diagnostic tests	Treatment
Line *et al*[7]	1969	46	Male	Gastric	Melena	Dead after 2 yr	Bone pain and swelling, weight loss, indigestion	Secondary	Barium meal, laparotomy	STx
Yasar *et al*[8]	2015	69	Male	Gastric	Melena, Haematemesis	N/A	None	Secondary (BG: MM)	OGD	N/A
Krishnamoorthy *et al*[9]	2010	57	Male	Gastric	Melena	N/A	None	Primary	OGD	N/A
Morinaga *et al*[10]	2010	61	Male	Gastric	Melena	N/A	Abdominal distention	Primary	CT AP OGD	N/A
Ruiz Montes *et al*[11]	1995	N/A	N/A	Gastric	Upper GI Bleeding	N/A	None	Primary	OGD	N/A
Katodritou *et al*[12]	2008	68	Male	Gastric	Upper GI Bleeding	Remission 13 mo post diagnosis	None	Primary	OGD	CTx (Bortezomib + Dexamethasone)
Chim *et al*[13]	2002	N/A	N/A	Gastric	Melena	N/A	N/A	Secondary (new Dx of MM)	OGD	N/A
Sanal *et al*[14]	1996	75	Male	Gastric	Melena	N/A	Obstructive jaundice (pancreatic plasmacytoma), bony lesions, Skin lesions	Secondary (BG: MM)	OGD	N/A
Güngör *et al*[15]	2009	77	Male	Gastric	Melena	N/A	Skin lesions	Secondary (BG: MM)	OGD	CTx
Daram *et al*[3]	2012	53	Female	Gastric Duodenal	Haematemesis	N/A	None	Secondary (BG: MM)	OGD	N/A
Sloyer *et al*[16]	1988	60	Male	Gastric	Melena	N/A	Bone pain (bony lesions)	Secondary (BG: MM)	OGD	N/A
Hamilton *et al*[17]	1999	53	Male	Gastric	Melena/Haematemesis	Dead in < 12 mo	Epigastric pain Previous orbital plasmacytoma	Secondary (new Dx of MM)	OGD	CTx
Maskin *et al*[22]	2008	53	Male	Gastric/Duodenal	UGI Bleeding	N/A	Back pain (bony lesions), Anorexia, Vomiting	Secondary (new Dx of MM)	OGD	N/A
Ammar *et al*[23]	2010	69	Female	Gastric/Duodenal	Melena	Alive (report in 2012)	Fatigue	Primary	OGD	RTx (Patient not fit for ChemoTx/Surg) PTC for subsequent biliary obstruction
Lin *et al*[2]	2012	47	Male	Gastric/Duodenal	Haemato - chezia	Alive for 6-mo follow up	Palpitations	Secondary (new Dx of MM)	OGD, small capsule endoscopy	CTx (Melphalan, prednisone, oral thalidomide) +/- Stem cell transplantation

Wang *et al*[24]	2013	52	Female	Gastric/Duodenal	Melena	Dead after 2 mo	Back pain, weakness (bony lesions), dyspnoea (pleural effusion)	Secondary (new Dx of MM)	OGD	N/A
Esfandyari *et al*[25]	2007	70	Male	Gastric/Duodenal	Anaemia	Dead	Astenia	Secondary (BG: MM)	OGD	CTx
Gradishar *et al*[18]	1988	65	Male	Duodenal	Melena	Alive (reported in 2012)	Abdominal pain, obstruction	Secondary (BG: MM)	OGD	RTx STx
Siddique *et al*[19]	1999	N/A	N/A	Duodenal	Melena	N/A	None	Primary	OGD	Gastroduodenal artery embolization
Fowell *et al*[20]	2007	88	Male	Duodenal	UGI Bleeding	N/A	Abdominal pain, dyspepsia, diarrhoea, fever, weight loss	Primary	OGD	N/A
Licci *et al*[21]	2017	60	Female	Duodenal	Melena Anaemia	N/A	Weight loss	Secondary (High-grade plasma cell myeloma)	OGD	CTx
Prachayakul *et al*[30]	2013	48	Male	Duodenumjejunum, ileum	UGI Bleeding	N/A	Abdominal pain + Diarrhoea Bony lesions	Secondary (new Dx of MM)	OGD	CTx
Ingegno *et al*[26]	1954	51	Female	Jejunum	Haematemesis	Alive after 32 mo	None	Primary	OGD	STx
Michotey *et al*[27]	1970	N/A	N/A	Jejunum	Melena, Anaemia	N/A	Abdominal pain	Primary	OGD	STx
Reddy *et al*[28]	2015	69	Male	Jejunum	Melena, Anaemia	N/A	None	Secondary (BG of plasmablastic myeloma)	OGD, Small bowel endoscopy, double balloon endero-scopy	CTx (cyclophosphamide, bortezomib, dexamethasone) +/- stem cell transplantation
Fisher *et al*[29]	1975	81	Male	Ileum	Melena	N/A	Obstruction, skin lesions, lymphadeno-pathy	Primary	OGD Laparotomy	STx
Monohan *et al*[31]	2018	70	Male	Ileum	Melena, Anaemia	Died 6 mo after diagnosis	Bony lesions	Secondary (BG of plasma-blastic myeloma)	OGD Colono-scopy Small capsule endoscopy CT Angiogram	CTx STx (emergency)

EMP: Extramedullary Plasmacytoma; N/A: N/A; OGD: Oesophagogastroscopy; GI: Gastrointestinal; CTx: Chemotherapy; RTx: Radiotherapy; STx: Surgery; MM: Multiple myeloma; Dx: Diagnosis; CT AP: Computed tomography abdomen and pelvis; UGI: Upper gastrointestinal.

then the plasma cell myeloma can be classified as plasmablastic[34,38]. In general, plasmablastic morphologic features are associated with a poor clinical prognosis.

Plasmablastic myeloma is associated with frequent extramedullary involvement which is one of the features of clinical aggressiveness reflecting independence from the bone marrow stroma derived growth factors. Gastrointestinal involvement includes lesions in the stomach, liver and large bowel, with the involvement of the small bowel being a rare presentation, with 68 cases[1] been reported in literature currently. The most frequent manifestation of small bowel EMP is abdominal pain but gastrointestinal bleeding can also occur, more often in gastric and jejunal lesions compared to ileal. It can present as haematemesis, melena or anaemia due to chronic blood loss due to vascular or ulcerated bleeding lesions[1,2]. The pathogenesis of gastrointestinal bleeding in plasma cell myelomas is multifactorial. In the case of the ileal plasmablastic myeloma we described, gastrointestinal bleeding was attributed to

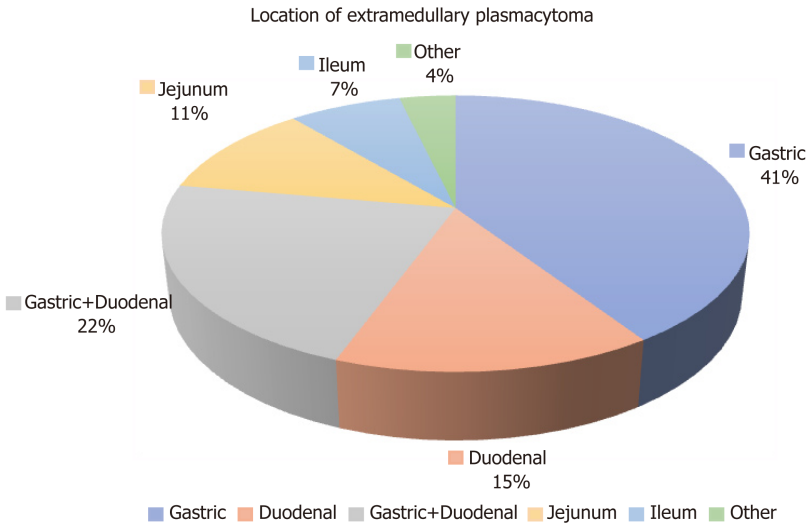

Figure 5 Location in the gastrointestinal tract of the extramedullary plasma cell neoplasms in the case reports reviewed.

the infiltration of the ileal wall with pleomorphic plasma cell infiltrates in the form of EMP and to the potential coagulopathy due to IgG lambda paraproteinaemia (level prior to treatment 17 g/L).

Once the patients are clinically stable and the diagnosis of extramedullary plasma cell neoplasm has been established, it is vital to confirm whether there is bone marrow involvement as this will not only affect the choice of treatment but also the prognosis[1]. The presence of clonal plasma cells in the bone marrow in association with the presence of M-protein in serum or urine and evidence of end organ dysfunction differentiates cases of secondary extramedullary involvement from cases of primary EMPs[28,33,39]. In general, primary EMPs have a more favourable prognosis than extramedullary manifestations of plasma cell myelomas.

The decision for the treatment pathway arises from multidisciplinary team discussions and it is usually in the form of local radiotherapy and surgery for cases of primary extramedullary plasma cell neoplasms and systemic chemotherapy for secondary neoplasms. Systemic therapy is in the form of induction chemotherapy with immunomodulatory agents (*e.g.*, thalidomide), proteasome inhibitors (bortezomib) and corticosteroids (*e.g.*, dexamethasone) which can be reinforced with autologous hematopoietic stem cell transplantation[1,32]. Autologous stem cell transplantation can prolong overall survival[40]. In our case, VCD regimen was attempted initially. Velcade (Bortezomib) is an inhibitor of ubiquitin-mediated proteasome degradation, and its combination with the alkylating agent cyclophosphamide and dexamethasone constitutes first line induction regimen. Due to progression of the disease we escalated to BTD regimen, introducing the thalidomide which it is broadly used in current practice for patients who relapse early after initial chemotherapy[41-43]. Thalidomide is a glutamic acid derivative which inhibits the production of tumour necrosis factor a (TNFa) and angiogenic cytokines inhibiting angiogenesis in plasma cell myelomas[32]. A thalidomide analogue, called lenalidomide can also be used in relapse refractory cases and was indeed used as third line in our case. Lenalidomide is a third-generation immunomodulatory medication with anti-TNF and anti-cancer activity[32,44,45].

The information provided in the cases we have reviewed about the outcome and prognosis of the patients with gastrointestinal bleeding is very scattered. However, we acknowledge the presence of poor prognostic factors for plasma cell neoplasms in literature. Plasmablastic variant tends to have worse prognosis than other plasma cell neoplasms[31]. The International staging system is used as a prognostic tool to estimate median survival based on the albumin and β2 microglobulin levels. Stage I with β2 microglobulin < 3.5 mg/L and albumin > 35g/L is associated with the best prognosis and a median survival of 62 mo. This was not the case with our patient who was categorised as ISS stage III on diagnosis with β2 microglobulin of > 5.5 mg/L and a median survival of 29 mo[32,46,47]. Numerous genetic alterations have also been associated with tumour progression and aggressive behaviour including chromosome 1q21 amplifications, and 1p deletions, *KRAS* and *TP53* mutations and finally translocations of *MYC*[31], supporting the fact that cytogenetic or FISH analyses should

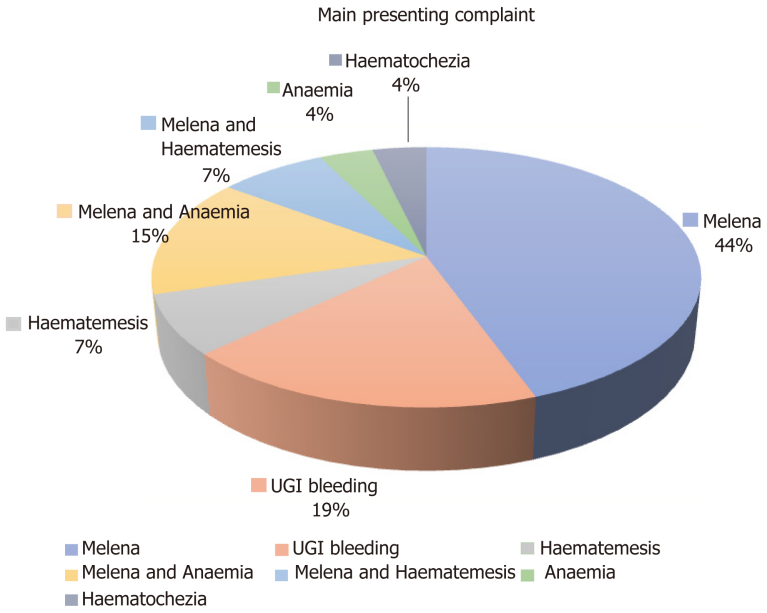

Figure 6 Main presenting complaints described in the case reports reviewed. UGI: Upper gastrointestinal.

be performed in all cases of plasma cell myelomas to define prognosis[33]. Further markers of poor prognosis and tumour aggressiveness that were demonstrated in our case was the nuclear expression of cyclin D1 at the small bowel segment, and the Ki-67 expression[48,49].

CONCLUSION

Although very rare in presentation, upper gastrointestinal extramedullary plasma cell tumours should be considered in the differential diagnosis of patients with gastrointestinal bleeding especially in the presence of a concurrent systemic haematological malignancy. The presence of gastrointestinal involvement and aggressive behaviour of this plasma cell neoplasm are associated with poor prognosis despite aggressive therapy and it is therefore fundamental to establish an accurate diagnosis early in order to avoid any delays in treatment.

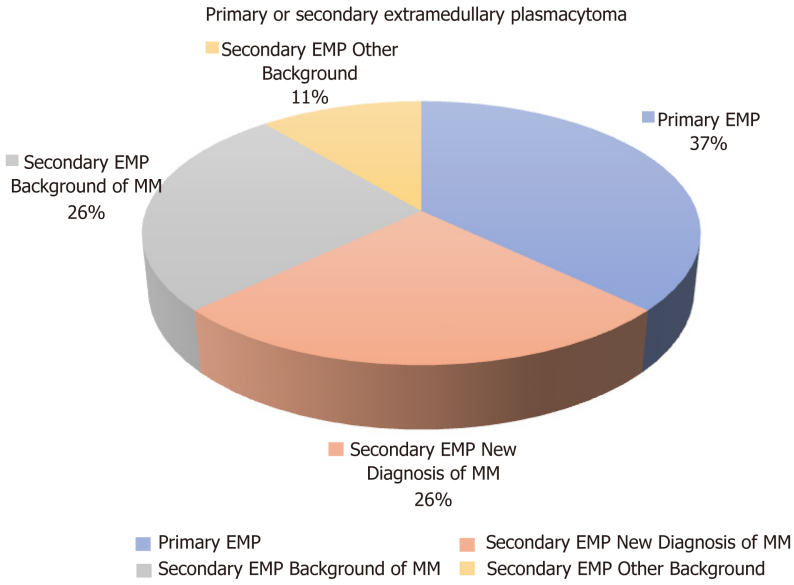

Figure 7 Primary of secondary nature of the extramedullary plasmacytomas described in the case reports reviewed. EMP: Extramedullary plasmacytoma; MM: Multiple myeloma.

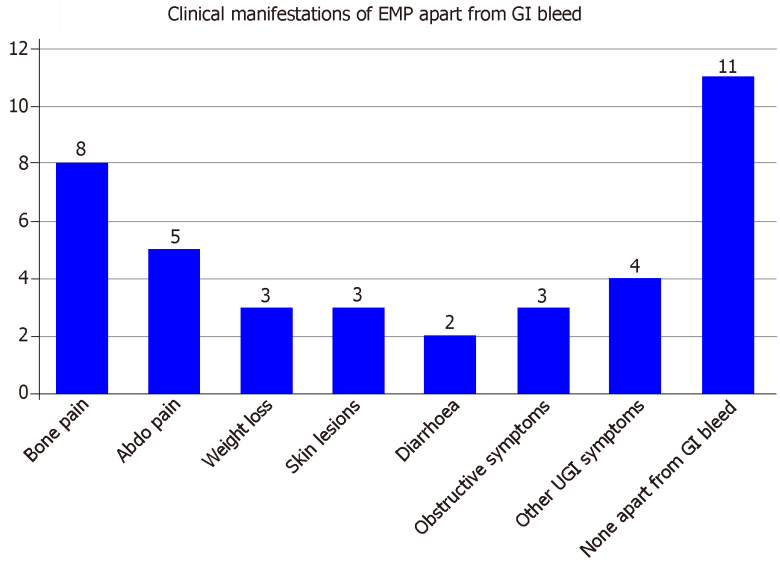

Figure 8 Associated clinical manifestations of extramedullary plasmacytomas apart from gastrointestinal bleeding described in the case reports reviewed. GI: gastrointestinal; EMP: Extramedullary plasmacytoma; UGI: Upper gastrointestinal.

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