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REVIEW

Endoscopic luminal stenting: Current applications and future perspectives

Miltiadis Moutzoukis, Konstantinos Argyriou, Andreas Kapsoritakis, Dimitrios Christodoulou

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Abstract

Endoscopic luminal stenting (ELS) represents a minimally invasive option for the management of malignant obstruction along the gastrointestinal tract. Previous studies have shown that ELS can provide rapid relief of symptoms related to esophageal, gastric, small intestinal, colorectal, biliary, and pancreatic neoplastic strictures without compromising cancer patients' overall safety. As a result, in both palliative and neoadjuvant settings, ELS has largely surpassed radiotherapy and surgery as a first-line treatment modality. Following the abovementioned success, the indications for ELS have gradually expanded. To date, ELS is widely used in clinical practice by well-trained endoscopists in managing a wide variety of diseases and complications, such as relieving non-neoplastic obstructions, sealing iatrogenic and non-iatrogenic perforations, closing fistulae and treating post-sphincterotomy bleeding. The abovementioned development would not have been achieved without corresponding advances and innovations in stent technology. However, the technological landscape changes rapidly, making clinicians' adaptation to new technologies a real challenge. In our mini-review article, by systematically reviewing the relevant literature, we discuss current developments in ELS with regard to stent design, accessories, techniques, and applications, expanding the research basis that was set by previous studies and highlighting areas that need to be further investigated.

Key Words: Endoscopic luminal stenting; Obstruction; Stricture; Stenting; Leak; Cancer; Inflammatory bowel disease; Bariatric surgery

Core Tip: Endoscopic luminal stenting (ELS) represents a well-established minimally invasive option for the management of malignant obstruction in the gastrointestinal tract. Following this successful application, recent advances in stent technology have gradually expanded the use of luminal stents in the management of various other disorders and complications. In this rapidly evolving field, clinicians are urgently required to learn new skills in order to advance their current practice. In an effort to facilitate this process, this article summarizes the current knowledge on ELS and highlights areas that need to be investigated in future studies.

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INTRODUCTION

Gastrointestinal intraluminal stents (GISs) are short metal or plastic artificial tubes of different shapes that are endoscopically placed into the lumen of an anatomical channel to restore and maintain its patency. The medical procedure that leads to the endoscopic placement of GISs into the lumen of a hollow viscus of the gastrointestinal tract (esophagus, stomach, duodenum, intestinal, colorectal) is named endoscopic luminal stenting (ELS) whereas the inserted GISs are named endoprostheses[1].

Historically, the first use of GISs dates back to 1885 when Sir Charters Symonds, a British-Canadian surgeon, was the first to successfully place a boxwood endoprosthesis developed for blind oral insertion in a patient with esophageal cancer[2]. Thereafter, the technology of GISs was improved to improve stent elasticity and facilitate insertion, with different designs and materials, such as latex, silicone, and polyvinyl becoming popular in the mid-1970s. However, all these modifications were including semi-rigid tubes of a fixed diameter that required dilatation to be performed prior to their placement, compromising the safety of stenting. To overcome this drawback, a new type of GISs named self-expandable metal stents (SEMS) entered the global market in the early 1990s. This kind of softer GIS rapidly evolved into the gold-standard therapeutic option for the management of malignant esophageal obstruction, irreversibly displacing their more rigid predecessors[1,2]. Nowadays, growing experience and technical advancements progressively widened the indications and increased the use of GISs in the management of a variety of other diseases, making clinicians' adaptation to new technologies a real challenge.

In this mini-review article, we provide a concise overview of the current knowledge on GI stenting, aiming to aid clinicians to advance their current practice and to highlight gaps that need investigation in future studies.

SEARCH STRATEGY

PubMed, Cochrane Library, Medline Scopus-clinical trial register, and Web of Science databases were initially searched by two of the authors (Moutzoukis MK and Kapsoritakis A) to retrieve studies reporting data on GIS from inception up to September 2022. The following Medical Subject Heading terms alone or matched by the logical operators "OR" or "AND" were used: 'GI stents,' 'stents,' 'endoscopic retrograde cholangiopancreatography (ERCP),' 'ERCP', GI malignancy,' 'Crohn Disease (CD),' 'CD,' 'inflammatory bowel disease (IBD),' 'IBD,' 'bariatric surgery.' A manual search of the article reference lists and abstracts from Digestive Disease Week, United European Gastroenterology Week, and European Crohn's Colitis Organization congresses were also conducted up to September 2022. A total of 3,988 references were retrieved. Old, repetitive, and non-English studies were excluded. After an initial title screen, each relevant article was subsequently reviewed and 161 representative scientific papers were finally quoted.

TYPES OF STENTS

By systematically reviewing the relevant literature, it became evident that currently, there is a wide variety of stent types available, corresponding with the wide variety of tissue shapes and mechanical characteristics of the GI tract. With regards to the material used in the creation of a stent, GISs are grouped into three main categories: Metal, plastic, and biodegradable stents. Different stents serve different purposes according to their individual sets of physical characteristics, with the main

advantages and disadvantages of the different available types of stents being shown in Table 1.

Metal stents

Among the different types of GISs, the most common stents used in gastroenterology are SEMSs. SEMSs are made of stainless steel or nitinol and are cylindrical in shape with a funnel-like flange at one or both ends. These metal alloy compounds make the stent cylinder flexible, with nitinol, a nickel-titanium alloy, having shape memory and more hyper-elastic characteristics compared to its counterpart. These characteristics have given nitinol an advantage compared to stainless steel and allowed the development of different designs such as braided or knitted stents that increased the utility of metal stents[3].

Contemporary SEMSs are woven, knitted, or laser-cut nitinol mesh cylinders packed in a compressed form and constrained around a delivery device[4,5]. These cylinders gradually decompress over deployment, allowing the stents to self-expand to their maximum fixed diameter. Compared to the laser-cut, the braided or knitted SEMSs have a lower kinking effect when deployed and allow the placement of another stent across their mesh[6,7]. However, contrary to laser-cut SEMSs, they have a lower radial and axial force and a higher foreshortening property that make these stents less predictable after deployment and hence, less suitable for placement into channels that are straight, narrow, and tight such as those in the biliary tree[6,7]. Despite these advantages, some laser-cut stents have pointed struts at their distal end incurring tissue reaction from the direct piercing which can complicate their removal, limiting their use[6,7].

Early SEMSs were uncovered and carried a significant risk of obstruction secondary to tumor ingrowth[8]. This drawback reduced the popularity of uncovered SEMSs as epithelialization was found to occur from 3 to 6 wk after their placement in 13% of patients[9]. To overcome this drawback, partially covered SEMS (PCSEMSs) were developed[8,10]. PCSEMSs had a synthetic material cover around their body that was acting as a barrier to tissue ingrowth into the lumen of the stent; however, their ends remained uncovered, allowing the development of hypertrophic granulation at the exposed sites making difficult their reposition or removal. This drawback confined the use of PCSEMSs to patients with inoperable malignancy[11-13]. Fully covered SEMSs (FCSEMSs) were then designed to overcome the drawbacks of all other metal stents. Although FCSEMS successfully dealt with tumor ingrowth or overgrowth, they were predisposed to migration, because their outer cover prevented stents from being embedded into the tissue[14]. This led to the development of the covered Gianturco Z stent (Wilson Cook Medical, Letchworth, England), a polyethylene-coated stainless-steel stent, that was specifically designed to prevent migration. This stent had wide distal and proximal ends and strong hooks in the middle, allowing the stent to be held inside the tumor. Compared to FCSEMSs, the Gianturco Z stent was associated with lower migration rates but migration remained a significant problem for approximately 10% of cases. Subsequent developments led to other kinds of antimigratory stents characterized by the presence of a partial cover, flared ends, or a double stent design that managed to further reduce the migration rate of SEMSs to an average of 5%[15-17].

Plastic stents

Plastic stents (PSs) represent the second broad category of GISs. GISs were initially used for the management of inoperable malignant GI obstruction. The first PSs were semi-rigid tubes that were composed of polyvinyl plastic. These stents were effective in more than 80% of cancer patients; however, they were associated with significant complications such as migration, food impaction, and perforation in up to 10% of them[18]. Conversely to the first PSs, contemporary PSs are made of polyethylene, which is a softer plastic with superior molding capabilities. Nowadays, PSs are exclusively used in the management of various pancreatic-biliary disorders and complications, such as strictures and fistulae, as first-line and cost-effective therapeutic options[19].

Self-expanding PSs (SEPSs) represent another category of PSs designed to increase their utility. SEPSs are devices with monofilament braid composed of polyester, with their mesh being fully coated by silicone. This coating is an inherent advantage of this kind of stents as it prevents impaction. However, it facilitates migration to a significant extent (6.7%-52.4%) which limits their popularity.

Biodegradable stents

To overcome the drawbacks of metal and plastic stents, a novel type of stents named biodegradable stents (BDSs) were developed. BDSs are composed of biodegradable materials (*i.e.* polyesters, polycarbonates, bacterial-derived polymers, and corrodible metals) and after deployment exert a continuous radial tension for a defined period of time that ranges between 6 to 8 wk. After this period, BDSs undergo gradual hydrolysis-mediated self-degradation (8-12 wk), preventing tissue ingrowth and the necessity for second endoscopy for stent removal[20,21]. As yet, two types of BDS have been tested in humans. These stents were made of knitted poly-L-lactic acid monofilaments with the first being produced by Marui Textile Machinery of Osaka in Japan which is not currently available, and the second by ELLA-CS, s.r.o. from the Czech Republic which is still in the market[22-24].

Table 1 Types of stents

Types of stents	Appropriate indications	Pros	Cons
Uncovered SEMS	Poor survival	Low risk of migration	High risk of tumor ingrowth
	High risk of migration		Difficult removal
	Gastroduodenal obstruction		
Partially covered SEMS	Risk of migration		Difficult removal
Fully covered SEMS	Risk of tumor in growth	Safe and easy removal	High risk of migration
	Temporary measure	Low risk of tumor in growth	
SEPS	Temporary measure	Safe and easy removal	Complex and stiff stent introducer
	Esophageal stricture	No tumor in growth	High risk of stent failure

SEMS: Self-expanding metal stents; SEPS: Self-expanding plastic stents.

COMMON APPLICATIONS & COMPLICATIONS OF ELS

Over time, there have been made significant changes in the way GISs are used in the GI tract. GISs were initially used only to treat malignant esophageal obstruction; however, in the past decade, their use was expanded to include various other GI pathologies, improving patients' quality of life. The current list of the indications for ELS has expanded to include a variety of malignant strictures, obstructions, external compressions of the GI tract, malignant GI perforations and fistulae, and selected cases of benign strictures that are resistant to repeated balloon dilation or surgical bougienage that are not confined to the esophagus. However, the different applications of ELS are associated with different complications. In this section, we describe the most common applications of stenting and their associated complications per area of interest in the GI tract.

Applications in the esophagus

Malignant strictures: ELS plays a crucial role in the management of strictures associated with esophageal cancer as cancer patients are candidates for surgical resection in less than 50% of the cases due to advanced or disseminated disease. In these patients, obstructing cancer causes significant problems, with dysphagia being their major complaint. Several therapeutic modalities are used alone or in combination for the management of malignant dysphagia, including laser ablation, photodynamic therapy, argon plasma coagulation, intraluminal brachytherapy, external beam radiation therapy, chemotherapy, and stenting. Among the different available options, SEMSs are currently indicated for all cancer patients who are expected to live less than 3 mo and have poor performance status as they provide rapid relief from dysphagia within 1-2 d after their insertion[25]. Instead, for those patients expected to live longer, brachytherapy alone or in combination with SEMSs is indicated because brachytherapy has been found to be associated with better quality of life, better symptom control, and increased survival[25].

Among the different available types of SEMSs, no significant differences were found between FCSEMSs and PCSEMSs. However, special attention is required for cancer patients that develop dysphagia after radiotherapy because in these patients radiation-induced changes can increase the risk of stent-related adverse events. In this difficult patient population, the placement of SEMS cannot be excluded because the available evidence regarding the relationship between previous treatment and stent-related adverse events is controversial[25-27].

With regards to PSs, semi-rigid PSs and SEPSs are inferior to SEMSs in the management of dysphagia, because they are associated with more adverse outcomes such as perforation, bleeding, pain, migration, and fistulation. Therefore, plastic stents are currently excluded from the management of cancer-related dysphagia[25-27].

Conversely to the other stent types, the role of BDSs in the management of malignant dysphagia is not fully elucidated. Preliminary experience shows that BDSs can relieve dysphagia by restoring the patency of the lumen, with their short life span preventing patients from undergoing repeat endoscopy for stent removal. However, their use is associated with high-risk complications in up to 50% of the cases, such as severe retrosternal pain with or without vomiting, hematemesis, and dysphagia recurrence. In light of these findings, the use of BDS is not advised[28-30].

Extrinsic compression: Other than dysphagia associated with esophageal cancer, extrinsic esophageal compression can also cause dysphagia in patients with extraesophageal malignancies. The use of SEMSs in the management of this type of dysphagia shows encouraging results; however, their placement is associated with a lower success rate compared to their application for intraluminal pathologies[31].

Tracheo/broncho-esophageal fistula: Tracheo/broncho-esophageal fistula is a rare complication of esophageal cancer. It results from the infiltration of esophageal cancer to the respective neighboring anatomical structures[32]. This complication is associated with increased morbidity and mortality, with the main goal of treatment being to improve patients' quality of life. Several modalities are used to treat this complication, including the use of feeding gastrostomy/jejunostomy tubes and SEMSs. Although all modalities are effective in the management of malignant fistulas, SEMSs are associated with better quality of life as they preserve oral nutrition. Taking this into account, together with the fact that SEMSs are placed with high clinical and technical success (up to 100%) in some series, the European Society of Gastrointestinal Endoscopy (ESGE) currently recommends SEMSs' placement for the management of malignant fistulas. Based on available evidence, no recommendation can be made as *per* a specific category of SEMSs. However, FCSEMSs may be preferable as their migration rate is lower and their removal is easier compared to PCSEMSs[33].

Bridge to surgery: For operable esophageal cancer, the preoperative nutritional status interferes with the surgical outcomes and hence, patients' prognosis. In an effort to prevent malnutrition and improve survival, the use of preoperative ELS is an interesting new concept. So far, among the different available stent types, only SEMSs were studied, with gathered evidence showing no significant benefit. Therefore, ESGE does not currently recommend SEMS placement as a bridge to surgery in patients with esophageal cancer[34].

Benign strictures: Following the high success rate of ELS in the management of malignant obstruction, the use of stents is expanded in the management of benign strictures. Benign strictures are relatively common in clinical practice and are commonly encountered after caustic substance intake, esophageal surgery, radiation, or advanced polypectomy techniques[35-38]. The current standard of therapy for benign strictures includes endoscopic dilation. However, all types of benign strictures are not amenable to dilation. Benign strictures that have lengths > 2 cm or diameters > 11 mm have irregular edges or are angulated represent a special kind of strictures that is called "complex" and do not respond to endoscopic dilation. For this kind of strictures as well as for strictures that do not respond to biweekly dilatations to reach a target diameter of 14 mm after 5 wk of treatment or to maintain the target diameter over a 4-wk period after the last dilation, ELS can offer an alternative solution to surgery. However, prior to stenting, it is essential to ensure that the stenosis is not malignant and to quantify the severity of dysphagia so that clinicians become able to assess the efficacy of their subsequent intervention[39,40].

Among the different available stent types, SEPSs, PCSEMSs, FCSEMSs, and BDSs have all been studied for the management of benign strictures that do not respond or recur after dilation. Available evidence on clinical success did not point out significant differences[36-40]. Therefore, the clinical decision of selecting a specific type of stents over the others is driven by weighing up the data on their safety. To date, enough evidence exists only for SEPSs and SEMSs, giving an advantage to FCSEMSs whereas for BDSs are scarce. Hence, it is of no surprise that ESGE currently recommends only the use of FCSEMSs in the treatment of refractory benign esophageal strictures[34].

Throughout the literature, the optimal duration for leaving a stent *in situ* remains elusive. Therefore, it is currently suggested that stents should remain positioned for at least 6 wk and for no more than 12 wk because this is the time period that is required for stricture remodeling and for avoiding stent embedment[41-43].

Anastomotic leaks: Esophagectomy plays a key role in the management of various malignant and benign conditions such as cancer, neuromotor dysfunction, scleroderma, acute perforations, and acute caustic injury. Esophagectomy is a high-risk procedure that is associated with increased morbidity and mortality; however, recent advances in surgical techniques and perioperative management improved patients' outcomes. Despite advances, esophagectomy remains a complex procedure. Anastomotic leaks are rare but serious complications that implicate approximately 8.3% of esophagectomy cases even in specialized centers[44]. Anastomotic leaks lead to septic complications, such as abscesses, and fistulas that can be fatal in 30% to 40% of the patients postoperatively[27]. Their management requires immediate treatment in the intensive care unit with intravenous fluid administration, perianastomotic drainage, parenteral feeding, nasogastric decompression, and intravenous antibiotics[45].

For the management of patients with anastomotic leaks, ELS plays a crucial role and should be performed immediately to prevent mediastinal contamination and facilitate the transition from parenteral to enteral nutrition[46]. However, if this is not possible, delayed insertion should be also attempted as it contributes to the healing of the anastomosis. In general, for esophageal leaks, uncovered SEMS have no role in the management of anastomotic leaks. Instead, covered SEMSs and SEPSs achieve great outcomes, with success rates for leaks' closure ranging from 60% to 100% and are preferred[46-49]. However, following successful deployment, a contrast agent should be injected to confirm that the leak is closed. Thereafter, the endoprosthesis should be left in situ for a period that ranges from 14 to 28 d, with removal being decided after radiologic confirmation of the complete leak healing and the absence of septic complications[50-52].

Common complications of esophageal stenting: Esophageal stenting is not a risk-free procedure with complications being divided into early and late complications. The early complication rate of esophageal stenting, defined as the rate of complications that occur within the 1st wk after successful deployment, is about 20% which can be subdivided into 14.6% for clinical complications (pain 12%, perforation 0.6%, bleeding 0.6%, and mortality 1.4%) and 5.3% for technical failures (misplacement 0.3%, expansion/deployment failure in 3.9/0.8%, and stent migration in 0.3%). Late complications include technical failures (stent migration in 7% of cases), lump complications (tissue ingrowth in 11.3% of cases), and clinical complications (gastroesophageal reflux in 3.7% of cases, recurrent dysphagia in 8.2%, esophageal fistula in 2.8% of cases, hemorrhage in 3.9% of cases, esophageal perforation in 0.8% of cases)[53-55]. However, the complication rate is not the same for all stent types and for all cases. For example, PSs have lower rates of migration and can also be removed easier whereas metal stents can cause dysphagia as the tumor progress. Likewise, stents that are placed near the gastroesophageal junction migrate more easily, whereas those extending to or above the level of the aortic arch are more likely to cause bleeding with the reason for this adverse event being debatable and pressure-induced necrosis of the tumor and the esophageal wall being the one plausible explanation[56,57]. An overview of the most common complications that complicate esophageal stenting is given in Table 2.

Applications in the gastroduodenal tract

Similarly to the esophagus, in the gastroduodenal tract, advanced, metastatic, or inoperable cancer that causes obstruction, most of the time is treated with SEMSs, as curative resection is not possible in 40% of cases of gastric and 20% of cases of pancreatic cancer[58-61]. The same applies to cases where the obstruction is due to extrinsic compression from neighboring inoperable tumors[61,62]. In these cancer cases, stenting can offer an alternative therapeutic option to palliative surgery providing symptom relief in patients with short life expectancy, but with lower morbidity and cost compared to palliative surgery [63,64]. The superiority of stenting over palliative surgery was shown in a prospective randomized trial performed by Jeurnink *et al*[63]. In this trial, the authors found that duodenal stenting was better than surgical gastrojejunostomy for the treatment of malignant gastric outflow obstruction in terms of morbidity, surgical pain, hospital stay, and 30-day quality of life[63,65]. The results of this trial were later confirmed in two subsequent analyses performed by Rodríguez *et al*[66] and Ly *et al*[67], who reported the same mortality and morbidity rates for duodenal stents over palliative surgery. With technical success rates of 89% to 100% and clinical success rates ranging from 72% to 88%, the American Gastroenterology Association currently suggests SEMSs for patients with malignant obstruction who are poor surgical candidates whereas for patients who are fit for surgery with greater life expectancy than 2 mo suggests laparoscopic gastrojejunostomy[68]. However, the presence of multiple strictures that cannot be reached by endoscopists in situations like peritoneal carcinomatosis or in patients that had previous operations are contraindications to duodenal stenting.

With regards to other pathologies, in case of perforation or bleeding, duodenal stenting can rarely be of help, whereas it can be considered for cases of benign strictures that are resistant or refractory to endoscopic dilation in patients who are poor surgical candidates[67]. However, in these cases, BDSs and extractable stents are preferred.

Common complications of gastroduodenal stenting: Table 3 shows the most common complications associated with gastroduodenal stenting. These complications are classified as either early or delayed and require immediate intervention[68,69]. Early complications develop within 1 wk of stenting and mainly include stent migration, obstruction, cholangitis, pain, perforation, bleeding, and misplacement whereas late complications develop after this period of time and mainly include stent migration, obstruction, perforation, fistula formation, and stent fracture[70,71]. Overall, the complication rate of duodenal stenting ranges between 12% and 44%. More specifically, stent occlusion due to tumor ingrowth or overgrowth occurs in 9% to 26% of patients with time to stent occlusion being estimated at 1.6 mo for patients with pancreatic cancer and 4.3 mo for those with other malignancies. Likewise, cholangitis secondary to papilla compression from stenting complicates the procedure in 2% to 6% of patients with non-pancreatic cancer and in 59% of those with pancreatic cancer, whereas perforation due to the strong axial force exerted by metal stents in up to 14% of patients, with concurrent dilations, attempts to pass the stenosis with the endoscope and concurrent use of corticosteroid medication, chemotherapy, and radiation being the major predisposing risk factors. As for the other complications, stent migration complicates stenting in 2% to 10% of patients, pain in 2% to 8%, and bleeding in up to 6% of patients whereas fistula formation is a rare adverse outcome[72].

Applications in the large intestine

Regarding the applications of stenting in the large intestine, following the advances in stent technology, the indications for intraluminal stenting have increased over the last two decades. First, colonic stenting (CS) is used for palliation in all patients who are poor surgical candidates or have inoperable cancer, metastatic or fistulizing disease, with patients treated or who are to be treated with antiangiogenic drugs being excluded as these drugs carry a threefold increased risk of causing perforation. In cancer patients with short life expectancy, CS aims to improve quality of life by offering an alternative less

Table 2 Common complications of esophageal stents

Early complications	Long-term complications
Pain	Occlusion
Migration	Gastroesophageal reflux
Expansion/deployment failure	Dysphagia
Mispositioning	Fistula formation
Bleeding	Bleeding

Table 3 Complications of gastroduodenal stents

Early complications	Long-term complications
Migration	Migration
Obstruction	Perforation
Biliary obstruction	Obstruction
Perforation	Fistula formation
Bleeding	Stent fracture
Mispositioning	None

morbid option to palliative surgery, whereas in those with longer life expectancy, aims to prolong survival by accelerating access to chemotherapy and by preventing the morbidity that is associated with surgery. Among the different available types of stents, SEMSs are currently the best option for palliation as they achieve sustained symptomatic relief in more than 70% of patients for a time period that ranges from 6 to 12 mo[73,74].

Except for palliation, this kind of stents is also used by clinicians as a temporary measure to relieve malignant obstruction in operable cancer patients, eliminating the need for an emergent operation which is associated with high morbidity (40%-60%) and mortality (8%-20%). The use of SEMSs as a bridge to surgery is a highly effective approach, with technical success, defined as the appropriate insertion of SEMSs across the stenosis, being achieved in 90%, and clinical success, defined as the resolution of malignant obstruction with symptomatic relief, in 70% of the cases. With this approach, clinicians do not only avoid emergent surgeries, but also acquire the time they need to accurately stage the disease, optimize patients' condition, avoid emergent multiple-stage surgery with the creation of a temporary or permanent ostomy, give neoadjuvant therapy, and generally prepare their patients for elective surgery. The elective surgery is less morbid and is performed as a one-step procedure 8 to 10 d after the placement of SEMSs, with the presence of SEMSs not being a problem to surgeons since they can be removed together with obstructing cancer. This approach is useful for patients with curable left-sided colonic cancer who have an increased risk for postoperative mortality; however, it cannot be applied to those with rectal tumors because, in the rectum, the placement of SEMSs causes debilitating symptoms such as discomfort, pain, tenesmus, and incontinence[75,76].

Following the successful use of SEMSs in the management of malignant obstruction, their use expanded to the management of the obstruction caused by compression of the bowel from extraintestinal malignancies such as pelvic tumors and peritoneal carcinomatosis. In these cases, current literature shows that SEMSs could be used as alternative therapeutic options to surgery; however, their use is characterized by lower technical and clinical success rates compared to those achieved for colonic cancer[77].

Another application of CS is in the management of obstruction caused by various benign conditions including diverticular disease, Crohn's disease, radiation therapy, and anastomotic strictures. In these cases, the placement of SEMSs is associated with an increased risk of complications and is not recommended. However, it can be useful in patients who are poor surgical candidates or who have strictures that are not amenable to other therapeutic modalities. No advice can be given with regard to other stent types[78-80].

A final indication for stenting in the large bowel is in the management of anastomotic leakage, which is a worrisome complication after colorectal surgery, especially in low colorectal or coloanal anastomosis. In the management of anastomotic leakage, SEMSs and BDSs are used. Both stent types are placed for 2 mo and are used in conjunction with percutaneous drainage of abscesses to promote the healing of the anastomosis. With this approach, it is obviated the need for surgical reintervention that is associated with prolonged hospitalization, increased morbidity, and death. The technical success of stenting reaches 100%, with a clinical success of 80%-100%. However, its application is restricted to

anastomoses that are less than 5 cm above the anal verge because it is associated with an increased risk for migration. In these cases, alternative therapeutic options such as injection of fibrin sealant and clips should be considered[41,79-81]. All common applications of CS are listed in Table 4.

Common complications of large intestinal stenting: CS is regarded as a low-risk procedure, with an associated morbidity of 20%, low mortality, and infrequent need for surgery and stoma[42,82]. However, the complication rate of CS increases in the presence of several predisposing factors such as SEMS caliber ≤ 22 mm, the presence of complete luminal obstruction, right colon malignancy, extraintestinal lesion, and positive history of radio-chemotherapy[83,84]. The most common complications associated with CS are classified as either early or late depending on the time period they present following the successful insertion of stents (Table 5). The early complications usually develop within the 1st wk after stenting and include perforation, bleeding, and stent malpositioning, whereas the late complications develop later and include pain, stent migration, obstruction recurrence, perforation, and fistula formation[85-87]. Every time clinicians have a suspicion of a stent-related complication, the most common modality that can be used to investigate patients is computed tomography (CT). Among the different complications, pelvic or rectal pain is a common complaint of patients with metal stents and is a complication that does not need CT imaging for establishing the diagnosis. For nearly all the other complications, CT imaging is particularly valued[83].

Immediately after CS, patients with obstruction are expected to show clinical improvement. If this improvement does not occur and is associated with persistent pre-stenotic dilatation in radiological imaging, malpositioning or incomplete expansion of the stent should be suspected. Stent malpositioning occurs whenever a stent is deployed more distally and does not cover the full extent of the stricture and requires immediate treatment. This complication can be recognized both on a radiograph or CT by observing the discrepancy between the position of the stent and the site of the obstructing tumor. The differential diagnosis between malpositioning and incomplete expansion is relatively easy to be made since in the case of incomplete expansion the stent maintains its hourglass shape on CT[19,43,83,85,87]. Bleeding is a minor complication of CS that occurs in 5% of cases. Most of the time, it is of low severity and ceases spontaneously. CT imaging is not required for making the diagnosis but in cases where CT is requested for other reasons, the diagnostic hallmark is the presence of hyperdense content within the intestinal lumen[19,43,83,85,87]. Conversely to bleeding, perforation is a dreaded complication of CS because it is associated with an estimated mortality of 10%. It occurs in 5% of the procedures with previous irradiation, concurrent dilatation, and excessive manipulation of guidewires during endoscopy increasing the risk for this complication in the early postinterventional period. However, perforations can occur any time after stenting with some cases being reported even after 6 mo from stenting. Contrary to early perforations, those occurring late are caused by different factors such as systemic chemotherapy. CT imaging is of particular value in making the accurate diagnosis in all but especially in clinically silent cases[19,43,83,85,87]. Among the different complications of CS, migration is the most frequent. It occurs in up to 50% of the patients undergoing this procedure. Small and/or short and/or covered stents as well as concurrent chemotherapy, partial luminal obstruction, extraintestinal lesions, and rectal tumors are all significant factors that predispose to migration. Migration can be asymptomatic or lead to other complications such as obstruction and perforation. Endoscopic repositioning, removal, or replacement may be necessary for symptomatic patients[19,43,83,85,87]. Less frequently than migration, colonic stents can be occluded, leading to symptomatic recurrence. Stent occlusion is caused by tumor ingrowth or overgrowth or the impaction of fecal material. Depending on the etiology, the endoscopic or medical relief of the occlusion should be considered[83,85,87].

Applications in the biliary system and pancreas

In the biliary system and pancreas, the placement of stents allows minimally invasive management of obstruction from benign to malignant causes with high technical and clinical success rates[19,88]. Initially, it was promoted the use of stents with a double-pigtail design to prevent upward migration, but over time, the use of straight stents with side flaps prevailed[89]. Nowadays, various plastic and metal stents with various shapes, diameters, and lengths are available for use in the biliopancreatic system. However, PSs are generally preferred for most of the benign indications that are outlined in the following paragraphs and metal stents for palliative treatment.

Applications in the biliary system

Benign biliary strictures: One common indication for stenting in the biliary system is the management of benign biliary strictures (BBSs). These strictures can be caused by post-operative injury (particularly after cholecystectomy), anastomotic injury following orthotopic liver transplantation (OLT), primary sclerosing cholangitis (PSC), post-endoscopic sphincterotomy (ES) and other less frequent conditions, such as radiation therapy, IgG4-related disease, and portal biliopathy[90,91].

Irrespective of the etiology, BBSs require immediate treatment with stenting playing a central role in their management. The choice of the type and number of stents that are to be used mainly depends on the etiology of BBSs. For a dominant bile duct stricture in PSC patients, defined as stenosis of the common bile duct with a diameter of ≤ 1.5 mm and/or stenosis of the hepatic duct with a diameter of ≤ 1.0 mm, a single plastic stent may be adequate, although, for the majority of other strictures, progressive

Table 4 Common applications of stent placement in the large intestine

Common applications
Colorectal carcinoma and bowel obstruction
In non-operative candidates
Bowel obstruction
In non-operative candidates
Local postoperative neoplastic recurrence
Preoperative decompression in obstructing resectable colorectal carcinoma (bridge-to-surgery)
Relief of large bowel obstruction from extracolonic malignancy, pelvic mass or peritoneal carcinomatosis
Malignant colorectal fistula, *e.g.*, to the urinary bladder or vagina
Postoperative anastomotic leakage
Fistula formation

Table 5 Complications of colon stents

Early complications	Long-term complications
Technical failure (malpositioning or incomplete expansion)	Stent migration
Stent misplacement/failed relief of obstruction	Obstruction recurrence
Bleeding	Chemotherapy-related perforation
Stent migration	Fistula formation
Pelvic or rectal pain	Bleeding
	Ischemia

dilation with the insertion of two or more plastic stents is the common practice[92,93]. Several clinical trials pointed out the high clinical success of the placement of PSs after progressive dilatations for relieving the obstruction in patients with either anastomotic or non-anastomotic post-OLT, or post-ES strictures[94-96]. However, a significant drawback of this approach is the requirement of repetitive endoscopic procedures over a short period of time, which compromises patients' quality of life and concurrently increase healthcare costs. SEMSs overcome this drawback. This is because they can be positioned without dilation and permit the resolution of a benign stricture without the need for progressive stent switching[96]. However, among the different available SEMSs, uncovered SEMSs and PCSEMSs are not advised for the treatment of BBSs. This is because they allow tissue ingrowth and overgrowth that lead to the development of new strictures and/or to the premature occlusion and embedment of these stents into the biliary system. Instead, FCSEMs do not have these limitations. However, due to their full cover, they have increased risk for migration with reported rates approaching 45% in some series[97-100]. This led to the development of a novel type of FCSEMSs, named antimigratory stents that prevent this complication[19,101,102].

Biliary stones: ELS can be also used in cases where complete clearance of common bile duct (CBD) from stones is not achieved, and the placement of stents is required to maintain uninterrupted bile flow into the duodenum[103,104]. This approach entails the use of straight and double pigtail PSs that range in diameter from 2.3 to 3.3 mm (corresponding to 7 and 10 Fr respectively) and does not provide a definite therapeutic option. However, it serves as a temporary measure until complete clearance of CBD is achieved. In most cases, the use of ELS in the management of biliary stones reduces the size of the stones and increases their debris, facilitating complete clearance[105]. However, it is not a risk-free procedure and it is associated with several complications including occlusion, migration, and episodes of cholangitis. Conversely to plastic stents, metal stents have no role in the management of biliary stones.

Biliary leaks: Another common application for ELS is in the management of biliary leaks (BLs). BLs are often a consequence of surgery, such as open or laparoscopic cholecystectomy or hepatic resection, but they can be also caused due to trauma, or invasive procedures, such as liver biopsy and percutaneous transhepatic cholangiography[30].

Biliary stents are used to preserve the bile flow into the duodenum and concurrently cease its outflow from the leaking site. Several studies suggest the use of ES alone for the management of minor leaks and the insertion of PSs for major leaks[106]. However, in the clinical setting, the most common approach entails the placement of a plastic stent that has 2.3 or 3.3 mm in diameter with or without ES for a period of 4 to 6 wk[107].

PSs can be placed with or without ES with a high success rate (90%) for treating leaks at the peripheral duct but their success rate drops to approximately 60% when it comes to leaks at the hilar or the common bile duct. Metal stents are not regularly used for the management of BLs despite the fact that FCSEMSs were shown to lead to the resolution of the leak in approximately 70% of patients in some series. This is because their use was associated with the development of strictures after removal and with higher migration rates compared to PSs. In cases where endotherapy fails, surgery is the sole definite treatment but it is not preferred for high-risk patients with major co-morbidities[108].

Cholecystitis: Transpapillary gallbladder stenting (TGS) is useful for cases of acute calculous or acalculous cholecystitis when conventional therapies fail or cannot be performed. TGS is indicated for patients that are severely ill, with serious comorbidities that prohibit surgical cholecystectomy, and/or have contraindications to undergo percutaneous cholecystostomy (such as severe coagulopathy, ascites, or a bowel loop interference between the diaphragm and the liver preventing percutaneous access). TGS entails the selective cannulation of the cystic duct during ERCP and the placement of small-diameter stents. However, it cannot be performed in patients who cannot undergo ERCP for various reasons such as pregnancy[109,110]. Endoscopic ultrasound-guided gallbladder stenting allowed clinicians to overcome this problem, extending the use of gallbladder stenting. Gallbladder stents are placed with a technical success rate that ranges from 75% to 100%, and an adverse event rate of 0%-20%[37-40]. PSs are exclusively used to ensure continued gallbladder drainage. However, metal stents with large flares at their ends or with a "saddle" form and distal anchor flanges can be alternatively used[110-112].

Post-sphincterotomy /post-dilation bleeding and perforation: Epinephrine injection, thermal therapy, balloon tamponade, clips, and placement of large bore PSs have been used in order to control post-ERCP bleeding. PSs and currently FCSEMSs are effectively used to treat these complications as they exert direct pressure on the bleeding area[113]. Conversely to the management of bleeding, little is known regarding the efficacy of ELS in the management of post-ERCP perforations. This is because on the one hand, the incidence of this complication is very low and on the other hand, its clinical consequences are tremendous leading patients to emergent surgery. A few reports show PSs can be used for the management of post-ERCP perforations, but their small diameter may fail to fully seal the defect. FCSEMs can overcome this problem because they have a larger caliber but more research is currently required to make suggestions.

Malignant biliary diseases: Another common indication for ELS is in the palliative management of obstructive jaundice caused by biliopancreatic cancers that extrinsically compress or intraluminally obstruct the biliary tract such as cholangiocarcinoma, pancreatic cancer, tumors of the papilla of Vater or hilar lymph node compression. Among the different available stent types, PSs are preferred for cancer patients with short life expectancy. The PSs that are commonly selected for these patients have a large diameter that ranges from 2.8 to 3.3 mm and are left in place approximately for 3 mo with high efficiency. Instead, for patients with longer life expectancy, the use of metal stents is preferred because SEMSs are larger, they can be left in place for longer periods of time and their placement is easier. To date, uncovered, partially covered, and fully covered SEMS have been all successfully used for palliation in patients with inoperable cancer. However, the use of uncovered SEMSs was associated with an increased rate of stent occlusion whereas the covered ones with stent migration[91,114,115].

Applications in the pancreatic duct: In the pancreatic duct, the most common application of ELS is in the prevention of post-ERCP pancreatitis (PEP). PEP is a relatively common complication that occurs in up to 10% of patients undergoing ERCP. Multiple factors have been shown to affect the incidence of PEP such as patients' comorbidities, operators' experience, and the indication for ERCP with pancreatic stenting (PS) being found to reduce not only the frequency but also the severity of PEP. Nowadays, PS are used in various situations to prevent PEP. The common indications for placing PS include pancreatic sphincterotomy for sphincter of Oddi dysfunction, acute or recurrent pancreatitis, and ampullectomy. In addition, PS is highly recommended in cases of difficult biliary cannulation, instrumentation or injection of the pancreas, aggressive manipulation of the pancreatic duct (brush cytology, biopsies), balloon dilatation of an intact biliary sphincter (balloon sphincteroplasty), previous PEP and precut sphincterotomy starting at the papillary orifice[116-120].

Except for the prevention of PEP, PS is effectively used in the management of symptomatic main pancreatic duct strictures and after pancreatic sphincterotomy and fragmentation of pancreatic stones [121-124].

Common complications of biliary and PS: Biliary stenting is a relatively safe procedure with complication rates ranging between 8% and 10% and mortality of less than 1%. Migration is the most common complication associated with biliary stenting. It occurs in up to 10% of cases and is classified

into proximal and distal. Distal stent migration into the bowel leads to spontaneous passage of the stent in more than 70% of the cases with the rest being easily retrieved endoscopically. Among the different available stents, SEMS migrate rarely compared to their plastic counterparts. Different stent designs have been used to prevent migration such as double pigtail stents, side flaps, and barbs. However, migration remains a problem with multiple factors being associated with increased migration rates including short or long stents, papillary stenosis, omission of sphincterotomy, and benign strictures. In rare cases where the migrated stents do not pass spontaneously, migration can lead to life-threatening complications including bowel obstruction, perforation, intra-abdominal sepsis, fistula formation, and necrotizing fasciitis[18].

Similar to biliary stenting, PS is not a risk-free procedure. The most common complication associated with PS is the development of morphological changes in the pancreatic duct. Morphologic changes are found in more than 50% of patients and resemble chronic pancreatitis. Although the consequences of this complication are unknown, ductal strictures can develop in a few patients requiring balloon dilatations. Stent occlusion represents another common complication associated with PS. The rate of pancreatic stent occlusion is similar to that of biliary stents with most stents being occluded within 3 mo after insertion. However, in most cases, stent occlusion is not associated with adverse outcomes since pancreatic juices can siphon across the sides of the stent. Other stent-related complications that are commonly reported to be associated with PS include acute pancreatitis, pancreatic infection, pseudocyst formation, duct injury, stone formation, and migration[18].

Applications in IBD

Following the successful application of ELS in the management of a variety of gastrointestinal and biliopancreatic disorders, the use of ELS has expanded to include the management of CD-related strictures. Strictures in CD occur in up to one-third of patients within 11 years of diagnosis secondary to chronic transmural inflammation, and in 50% of those undergoing ileocolic resection. Most strictures are located in the small intestine rather than in the colon (64% *vs* 5%, respectively)[125]. Endoscopic balloon dilation (EBD) is currently the preferred endoscopic therapy for CD strictures[126,127]. However, the use of EBD is confined to the management of primary or anastomotic strictures that do not exceed 5 cm because this is the maximum length of the largest balloon that is available for dilations. Longer strictures are not amenable to EBD. For these strictures, ELS can offer a minimally invasive alternative to surgery[126]. Among the different available stent types, FCSEMSs and PCSEMSs were used for this indication[128,129]. Preliminary experience has shown conflicting results with several studies reporting different clinical success rates that range between 36% to 100%. However, in all cases in that SEMSs were successfully applied, patients remained asymptomatic for a period of 10 to 12 mo of follow-up signifying a positive clinical outcome[129-133] (Figure 1).

Common complications of stenting in IBD: The use of SEMSs for the management of CD strictures can be challenging or impossible depending on the location and degree of the stenosis and is associated with several complications[134]. Migration is a common complication of ELS. It occurs in up to 52% of the cases with 70% of the episodes occurring within the first 3 d. It is classified into proximal or distal migration depending on the direction of the misplacement of the stent. Although migration is not considered a serious condition, it can lead to dreaded complications such as impaction and perforation, that require surgery. In the majority of cases, migrated stents are spontaneously expelled from the body, leaving a small minority for endoscopic retrieval. Except for migration, another common complication of ELS in IBD is stent occlusion. Stent occlusion develops secondary to the development of hyperplastic tissue at the exposed ends of several metal stents and occurs in up to 24% of some patient series. To prevent this complication, depending on the type of SEMSs (FCSEMS or PCSEMS) that was used, it is recommended to remove stents within 4 to 6 wk after their placement[134,135]. With regard to other complications associated with ELS in IBD, there is a theoretical risk for perforation due to mucosal erosion; however, this concern mainly stems from observations in cancer and not from IBD patients[134, 135]. Nevertheless, more research is required in order to fully determine the risks associated with the use of ELS in IBD.

Applications in bariatric surgery

Obesity rates have significantly grown over the last decades constituting a global health problem. Obesity often contributes to the development of various chronic diseases such as type 2 diabetes, hypertension, heart disease, and cancer, adversely affecting patients' quality of life and life expectancy [136-138]. Many treatments for obesity exist but bariatric surgeries are by far the most effective in achieving significant weight loss. Nowadays, the three most common types of performed bariatric surgeries include Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric band (LAGB), and sleeve gastrectomy (SG). However, all these operations are invasive therapeutic options with up to 12% of patients experiencing adverse events in the 1st 5 years after surgery. ELS represents a minimally invasive option that can be employed in the management of several post-bariatric complications including anastomotic strictures, anastomotic leaks, choledocholithiasis, sleeve stenosis, and band erosion[136-140].

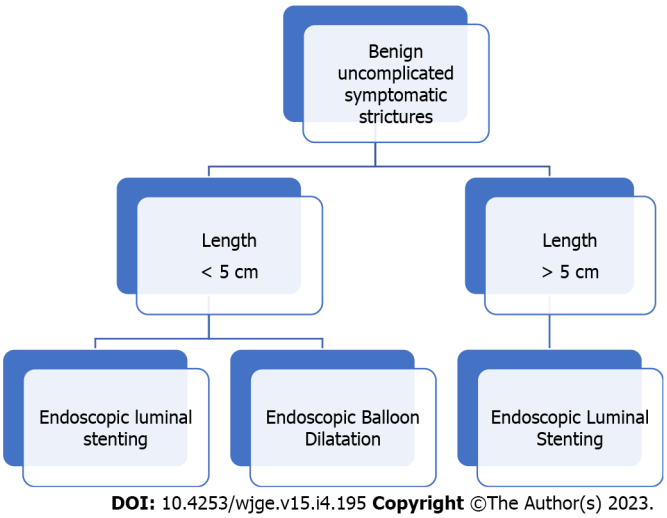

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Figure 1 Simplified algorithm for the endoscopic management of uncomplicated symptomatic Crohn's disease-related strictures.

In particular, in the management of post-bariatric strictures, available evidence suggests that ELS can be effective in up to 40% of the refractory cases presenting after RYGB whereas no suggestion can be made for the use of ELS in the management of strictures that develop after SG. In the management of anastomotic leaks, after RYGB, accumulated evidence suggests that FCSEMSs and PCSEMSs can lead to a high leak resolution rate (87.8%). However, these stents are poorly tolerated necessitating their removal after 6-8 wk. Alternatively to SEMSs, when the leak leads to an abscess cavity and persistent drainage is required until the resolution of the abscess, PSs with a double pigtail design can be a safe and effective solution. Likewise, FCSEMSs and PCSEMSs can be effectively used in the management of leaks associated with SG with a high success rate (72.8%). Regarding the use of PSs for the internal drainage of an abscess, their use after SG is a novel approach with preliminary evidence from retrospective studies showing a high efficacy (72.8% clinical success rate). As for the other bariatric complications, covered metal stents can be placed for a 2-wk period in order to promote migration if an eroded band after LAGB appears to be insufficiently migrated for endoscopic removal, facilitating its extraction whereas no differences exist as *per* the instruments that will be used for the management of RYGB-related choledocholithiasis between operated and non-operated patients[136-140].

Common complications of post-bariatric stenting

Reflux, discomfort, gastric ulcers, nausea/vomiting, and migration are common adverse events associated with ELS when used in the management of post-bariatric complications. Among these complications, the incidence rates of discomfort (6%), ulcer (4%), and nausea/vomiting (11%) are generally low[140]. Stent migration (39%) is the most common adverse event that can complicate ELS. Although in most cases migration is not associated with adverse clinical outcomes, it can have significant consequences when related to RYGB. This is because in RYGB cases, the migrated stent can be displaced outside of the range of a standard endoscope, making its retrieval challenging[138,141,142].

FUTURE PERSPECTIVES

The placement of GISs is a minimally invasive option for treating various benign and malignant conditions with high technical and clinical success rates. Current stent technology has astonishingly progressed allowing the development of various stent types with cutting-edge designs and materials that expanded the indications of ELS and improve patients' quality of life. However, there are still several drawbacks, such as stent occlusion and migration, that are difficult to overcome. Antimigratory, antireflux, shape-modified, irradiating, drug-eluting, and novel biodegradable stents specifically designed for various esophageal, gastroduodenal, biliary, and colonic indications are just a few of the significant advancements in the field of ELS. Current GISs innovations are outlined in the following paragraphs but more research is underway aiming to improve the properties of stents, reinforce their benefits, and lessen their drawbacks.

Antimigratory stents

Migration constitutes a significant problem associated with FCSEMSs that compromise the safety of ELS. This led to the development of several stents with cutting-edge designs aiming to prevent this complication named antimigratory stents. This kind of stents includes anchoring components, such as flared ends, anchoring flaps, or serrated anchoring pins. These anchoring components were found to

have been associated with lower migration rates compared to traditional FCSEMSs, with anchoring flaps being superior to the flared end with regard to stent migration. However, serrated anchoring pins are by far more effective for the prevention of migration but this design makes difficult the removal of the stent[143-145].

Drug-eluting stents

Tumor ingrowth and overgrowth are significant adverse events that complicate the use of GISs. Although PCSEMSs and FCSEMSs are designed to prevent these adverse events, their occlusion is inevitable because their cover is gradually degraded due to hydrolysis, oxidation, and contact with the luminal content GI. In an effort to prevent stent occlusion, a new kind of metal stents, named drug-eluting stents (DESs), was developed[146-150].

DESs are composed of three primary components that include a drug, a polymeric drug-delivery coating/carrier, and a stent platform. To date, various chemotherapeutic drugs such as paclitaxel have been trialed in different experimental models to evaluate the efficacy and safety of their local administration for different purposes. Paclitaxel is a chemotherapeutic agent that inhibits the proliferation of epithelial gallbladder cells, fibroblasts, and pancreatic carcinoma cells in a dose-dependent manner. In vitro trialing of paclitaxel in animal biliary ducts showed that it causes epithelial stripping and metaplasia, thickening of the bile duct, hypersecretion of mucus, and fibrosis, without significant complications. These positive outcomes allowed further testing in humans. However, accumulated evidence from human studies has shown conflicting results regarding the efficacy and safety of paclitaxel-eluting stents signifying a need for further improvement[146-150].

Another chemotherapeutic agent that was trialed for local delivery is gemcitabine. This agent is used in advanced pancreatic and biliary tract cancer. The hydrophilic properties of this agent make difficult its local delivery due to rapid degradation. A gemcitabine-eluting stent was designed to allow prolonged gemcitabine release by increasing the contact surface between the stent and the tumor. In this stent pullulan, a natural polysaccharide was used to increase the loading capacity of gemcitabine when loaded onto polytetrafluoroethylene, allowing a continuous release of the drug for 30 d[146-150].

With regards to other chemotherapeutic agents, Lee *et al*[146] developed a 5-Fluorouracil (5-FU)-eluting esophageal stent. Preliminary experience with this stent showed that the concentration of 5-FU that is achieved in the esophagus is higher than in other areas, with the highest levels being observed at the contact site in the mucosa. However, its use was associated with target and non-target organ dose-dependent toxicity. This adverse outcome led to ongoing research studies that aim to determine the ideal stent design and appropriate drug concentration, with their results being currently awaited[146-150].

Radioactive stents

In esophageal cancer, brachytherapy reduces dysphagia symptoms more slowly than stent implantation but offers longer patency and fewer complications. Patients with inoperable esophageal cancer may benefit from a palliative treatment approach consisting of stent implantation, combined with brachytherapy[151,152]. Radioactive stents that carry the advantages of traditional stents and brachytherapy were designed[30]. This kind of stents is loaded with iodine-125 seeds, with the interior being composed of standard metal, to facilitate insertion. Preliminary evidence suggests that these stents when used in cancer patients improve malignant dysphagia and prolong survival whereas their insertion is easy and safe. However, these results derive from small studies, with larger studies being needed prior to making any recommendation[153-155].

Antireflux stents

The use of SEMSs restores and maintains the patency of the obstructed lumen, relieving the symptoms associated with malignant obstruction in patients with inoperable cancer. Clinically approved SEMSs have a larger diameter than their plastic counterparts with reflux being a significant problem that adversely affect the quality of life of cancer patients[156,157]. In an effort to prevent reflux and improve patients' quality of life, new stents with an attached antireflux valve are being developed. The preliminary experience did not show encouraging results but further improvement in the design of the antireflux valve is currently awaited.

Shape-modified stents

One strategy to improve the efficacy and safety of ELS is to modify the stent's design. Over the last 10 years, the stents' design has undergone several changes aiming to reduce complication rates associated with ELS. One interesting modification refers to winged PSs with small central lumens. These stents were developed to prevent the occlusion associated with the placement of conventional SEMS. Despite expectations, these stents did not show positive results compared to conventional SEMS and hence, are not advised. Another interesting modification in the design of stents is the development of a dumbbell-shaped SEMS for minimizing the risk of migration and bile leakage associated with endoscopic ultrasound-guided gallbladder drainage. Preliminary experience with this stent showed that its use was associated with high clinical and technical success and no major complications, promoting its use[158,

159].

Biodegradable stents

BDSs have shown promising results in the management of benign strictures. Compared to other stent types, BDSs have several advantages such as their ability not to occlude, not to require repetitive endoscopies for removal, and being equipped with antibacterial or antitumor agents. However, BDSs have also disadvantages that can preclude their use such as the exertion of weaker radial forces than conventional metal stents and the need for balloon dilatation for their placement. Ongoing research in this field is awaited to reduce these drawbacks and enhance the use of BDSs in the future[19,160,161].

CONCLUSION

The role of stenting in the management of patients with malignant GI obstruction has expanded in recent years to include a variety of disorders in the esophagus, stomach, biliopancreatic system, small bowel, and colon. Recent advances in technology have improved stent efficacy and reduced stent-related complications, resulting in better clinical outcomes. However, GISs continue to undergo design improvements to address their limitations. Further research is required in order to enhance the use of ELS in the management of various conditions in the gastrointestinal tract.

FOOTNOTES

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REVIEW

Endoscopic ultrasound-guided vascular interventions: An expanding paradigm

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Abstract

Endoscopic ultrasound (EUS) has expanded its arena from a mere diagnostic modality to an essential therapeutic tool in managing gastrointestinal (GI) diseases. The proximity of the GI tract to the vascular structures in the mediastinum and the abdomen has facilitated the growth of EUS in the field of vascular interventions. EUS provides important clinical and anatomical information related to the vessels' size, appearance and location. Its excellent spatial resolution, use of colour doppler with or without contrast enhancement and ability to provide images "real-time" helps in precision while intervening vascular structures. Additionally, structures such as venous collaterals or varices can be dealt with optimally using EUS. EUS-guided vascular therapy with coil and glue combination has revolutionized the management of portal hypertension. It also helps to avoid radiation exposure in addition to being minimally invasive. These advantages have led EUS to become an upcoming modality to complement traditional interventional radiology in the field of vascular interventions. EUS-guided portal vein (PV) access and therapy is a new kid on the block. EUS-guided portal pressure gradient measurement, injecting chemotherapy in PV and intrahepatic portosystemic shunt has expanded the horizons of endo-hepatology. Lastly, EUS has also forayed into cardiac interventions allowing pericardial fluid aspiration and tumour biopsy with experimental data on access to valvular apparatus. Herein, we provide a comprehensive review of the expanding paradigm of EUS-guided vascular interventions in GI bleeding, portal vein access and its related therapeutic interventions, cardiac access, and therapy. A synopsis of all the technical details involving each procedure and the available data has been tabulated, and the future trends in this area have been highlighted.

Key Words: Gastrointestinal bleeding; Vascular intervention; Gastric varices; Pseudoaneurysm; Portal vein; Portal pressure gradient measurement

Core Tip: Therapeutic endoscopic ultrasound (EUS) has rapidly expanded into the field of vascular interventions. Published literature has shown that EUS-guided endovascular therapy is safe and scores over conventional endoscopic techniques achieving high obliteration rates with minimum re-intervention in variceal bleeding. EUS currently acts as a "rescue therapy" in cases of re-bleed or refractory bleeding from non-variceal sources, especially a pseudoaneurysm. In addition, portal vein access, portal pressure gradient measurement, and variceal assessment with liver biopsy have shown that EUS can act as a "one-stop-shop" for "Endo-hepatology". This ever-expanding role of EUS-related vascular interventions has been thoroughly detailed in this comprehensive review.

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INTRODUCTION

Therapeutic endoscopic ultrasound (EUS) procedures have come a long way using curvilinear array echo-endoscopes and various accessories. EUS, with its high spatial and contrast resolution, is constantly evolving and is currently one of the most commonly used minimally invasive techniques for diagnosing and managing various gastrointestinal (GI) disorders. The proximity of the GI tract to various vascular structures in the mediastinum and abdomen has allowed EUS to play a significant role in the field of vascular interventions. The necessity of developing a minimally invasive as well as a radiation-free alternative to interventional radiology (IR) or surgery has further strengthened its growth. The advantage of visualizing vascular structures in "real-time" has enabled access and delivery of targeted therapy[1]. EUS-guided vascular therapy has been found extremely useful in cases of variceal bleeding. EUS-guided injection of sclerosants, cyanoacrylate glue (CYA), thrombin, gelatin sponge and deployment of coils in gastric varices (GV) is safer and more effective over traditional endoscopic glue injection in terms of lower adverse events and reintervention rates.

Furthermore, EUS-guided portal vein (PV) access has opened the doors to experimental and clinical studies on portal pressure gradient (PPG) measurement, injection of chemotherapy, PV thrombus fine needle aspiration (FNA), and intrahepatic portosystemic shunt placement. This gamut of therapeutic options, combining EUS guided PPG (EUS-PPG) with variceal therapy and liver biopsy in a single session, represents an attractive option in the expanding field of "endo-hepatology"[2]. Therefore, this review focuses on elucidating the role of EUS-guided vascular interventions (Figures 1 and 2), a synopsis of the various available techniques, data on their safety and efficacy, and future advancements in this domain.

LITERATURE SEARCH

A detailed strategy, as outlined in Supplementary material, was performed in PubMed and Embase. All studies pertaining to applications of endoscopic ultrasound (EUS) in the field of vascular interventions (for example case series, review articles and clinical studies) were reviewed. Topics concerning GI bleeding (both variceal and non-variceal), PV-related interventions and cardiac access with therapy were looked into. Non-English language literature was excluded. EUS-guided liver biopsy and other aspects of Endo-hepatology are beyond this review's scope and have been excluded.

EUS-GUIDED MANAGEMENT OF VARICEAL BLEED

GI bleeding secondary to gastro-esophageal varices is a well-known but one of the most lethal complications of portal hypertension (PHTN)[3,4]. The annual bleeding rate has been reported to be around 5%-15%, with a 20% 6-wk mortality rate[5]. In half of the cases, bleeding stops spontaneously but has a re-bleeding rate of 30%-40%[3,6]. The standard treatment options for gastro-esophageal varices have been conventional endoscopic band ligation (EBL) or CYA glue injection. For refractory bleed, transjugular intrahepatic portosystemic shunt (TIPS) and balloon-occluded retrograde transvenous obliteration (BRTO) are other options[7]. EUS-guided management of varices has recently become an additional tool

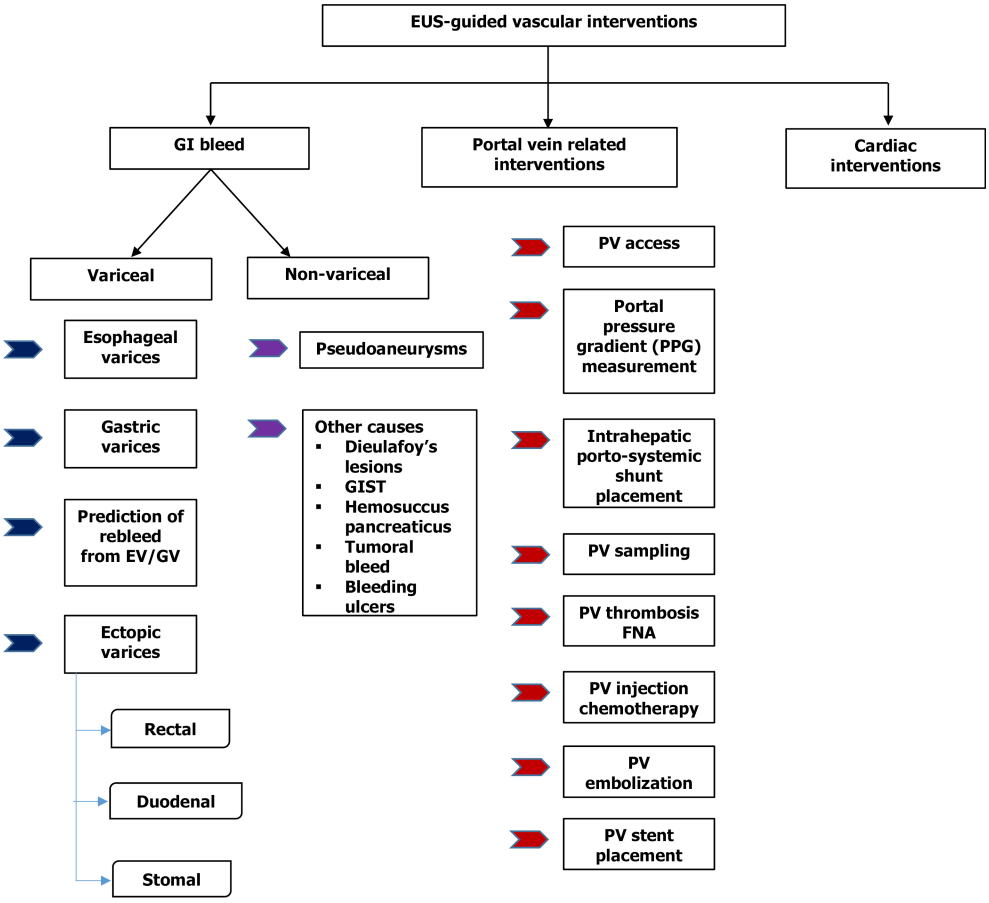

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Figure 1 Flowchart of various endoscopic ultrasound guided vascular interventions. EUS: Endoscopic ultrasound; GI: Gastrointestinal; EV: Esophageal varices; GV: Gastric varices; GIST: Gastrointestina stromal tumour; PV: Portal vein; FNA: Fine needle aspiration.

in the armamentarium. EUS offers theoretical as well as practical advantages over the conventional techniques such as: (1) It helps to identify the actual size as well as the number of varices for precise vascular therapy; (2) It can locate feeders, perforators or shunts; (3) Enables real-time puncture of the varices under vision; (4) One need not have to "see" the endoscopic image while delivering targeted therapy. This is especially useful in cases of active bleed or when there are contents in the fundus, and (5) Objective obliteration of the varices can be confirmed by lack of flow in "real-time".

Esophageal varices

EBL has been the first line of management for both primary and secondary prophylaxis of esophageal varices (EV)[4,8]. But high re-bleeding rates have been reported (15%-65%)[9,10], probably as a result of failure to obliterate the perforators or paraesophageal vessels that feed the EV[11,12]. Anecdotal case series exist on the use of EUS for EV management.

Existing literature: Lahoti *et al*[13] first described EUS-guide sclerotherapy for EV obliteration in 5 patients. Sodium morrhuate (sclerosant) was used to inject the perforators and feeder vessels until flow was obliterated using colour doppler, with no re-bleeding on a 15-mo follow-up period. One case had developed esophageal stricture, which was responsive to balloon dilatation. The only randomized controlled trial (RCT) comparing endoscopic *vs* EUS-guided sclerotherapy showed that there was no difference in the mean number of sessions needed for complete obliteration (4.3 *vs* 4.1) and re-bleeding rates (16.7% *vs* 4.2%). However, collaterals noted on EUS post-therapy were lower in the EUS arm (33.3% *vs* 0%)[14].

While EBL is still the preferred option, more data will be needed to define the role of EUS for EV management algorithms in clinical practice.

Future trends: Recently, a "jelly-filling" method has been found superior to the traditional water-filling method for EV visualization using EUS. The image quality score was significantly higher but with a longer procedure time using the former technique[15].

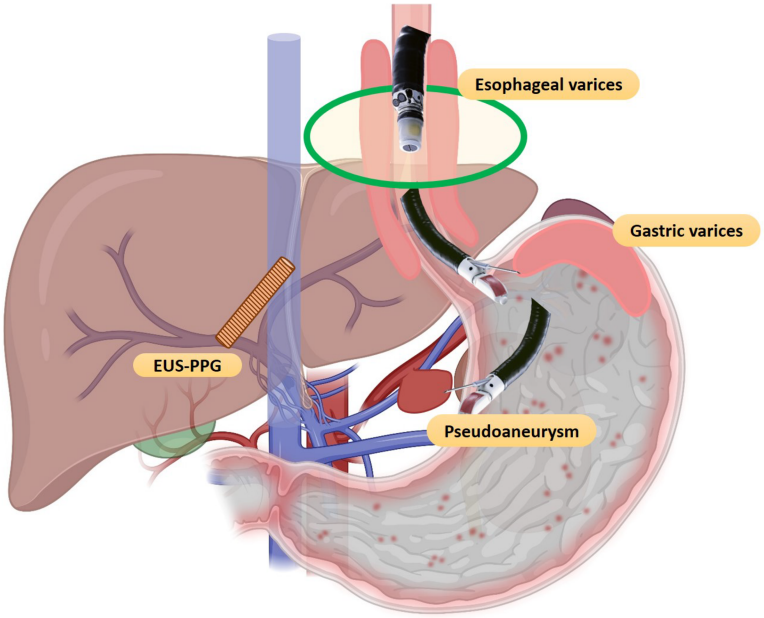

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Figure 2 Spectrum of endoscopic ultrasound-guided vascular interventions. EUS-PPG: Endoscopic ultrasound-portal pressure gradient.

GV

While EV account for a majority of the cases of GI bleeding in cirrhosis, GV can account for 20%-25% of them, with re-bleeding rates amounting to 65% in 2 years. Although GV bleeds less frequently, they are usually associated with an increased risk of uncontrolled bleeding, re-bleeding, more transfusion requirements and higher mortality. Described as per Sarin's classification, varices along cardia (GOV2) or isolated GV in the fundus (IGV1) are the most difficult to treat[3,4,16]. Therefore, both endoscopic sclerotherapy and EBL are discouraged for GV. While the former leads to an unusually high incidence of adverse events (37%-53%) like ulceration, re-bleeding, or perforation, the latter is difficult to execute due to thick musculature of the gastric wall leading to possible catastrophic post-banding bleed[17,18].

Thus, the first line of therapy for managing bleeding GV is the endoscopic injection of acrylate polymers such as CYA under direct vision. First described by Soehendra *et al*[19] in 1986, this technique has success rates of 58%-100% with re-bleeding of 40%-65%. This technique, however, has its own set of complications, including the risk of systemic embolization, bleeding from needle site ulcers, peritonitis, needle impaction, scope damage and even death. On the other hand, EUS-guided management has some advantages over conventional glue injection, *i.e.*, (1) Higher detection rate (6 times) over conventional endoscopy, as GV is located deep in the submucosa and commonly mistaken as thick gastric folds [20,21]; and (2) avoidance of inadvertent para-variceal injection (in up to 60%)[22].

The technique of EUS-guided GV management: The most commonly used method is a combination of coil and CYA glue, as outlined in Table 1[2] and Figure 3.

Existing literature: The options for EUS-guided GV therapy include: CYA glue, coils alone, a coil with glue combination, gelatin sponge and thrombin.

EUS-guided glue injection only: In their pilot study, Romero-Castro *et al*[23] evaluated the efficacy of CYA glue with lipiodol mixture in 5 cases of bleeding GV using a 22-G needle. Complete obliteration was achieved in all with no re-bleeding or complications.

EUS-guided coil injection only: A life-threatening complication of CYA injection is systemic embolization, the most common location being the lungs[24]. Coils can be used as an alternative to glue injection to mitigate this risk. Coils are made of a stainless-steel alloy with radially extending synthetic fibres that induce clot formation and hemostasis. The coils are usually 2-15 mm in length, and the loops are 2-20 mm in diameter. The choice of size would depend on the diameter of the varix.

The first report by Romero-Castro *et al*[25] demonstrated its efficacy in 4 cases. Complete obliteration was achieved in 75% of patients. Furthermore, the same group compared the EUS-guided coil (11 patients) *vs* CYA (19 cases). Though the obliteration rates were similar (91% *vs* 95%), the coil group needed fewer endoscopy sessions and had lower adverse event rates (9.1% *vs* 58%)[26].

EUS-guided coil with glue combination: This combination is based on the concept that use of coil with glue: (1) Achieves higher variceal obliteration rates with better hemostasis control; (2) decreases the amount of CYA needed; and (3) provides a framework or scaffold to hold the CYA glue within the varix, thus mitigating the risk of embolization. The largest data by Bhat *et al*[27] evaluated it in 152 cases of GV. The mean number of coils and glue used was 1.4 and 2 mL, respectively. On follow-up, complete

Table 1 Steps of endoscopic ultrasound-guided management (coil and glue combination) of Gastric varices

EUS-guided management of gastric varices using coil and glue combination
Pre-procedure requirements
All procedures are done under the cover of pre/peri-procedural antibiotics
Patient is usually kept fasting for 4-6 h before the procedure
Adequate resuscitation of the patient, in case of active bleeding is ensured, prior to the procedure
Informed consent prior to the procedure
What is needed prior to the procedure
Linear echoendoscope with at least a 3.7 mm working channel
Needle size: depends on the choice of the endoscopist; for > 10 mm coils, we need 0.035′ coil (19-G needle); can also use 0.018′ coil (22-G needle)
Diameter of the coils: 1.2-1.5 times the largest diameter of varix
Number of coils: depends on size of the varix
Amount of glue: depends on the size of the varix; but usually 2-4 mL is sufficient
Technical aspects
A proper diagnostic EUS is performed
The echoendoscope is usually positioned either in the distal esophagus or the gastric fundus
Saline is filled intra-luminally in the fundus to let the varices "float". This enables a good acoustic coupling for better visualization of the gastric varices
Adequate examination of the fundus, the intramural varices and the feeder vessels is carried out
The approach can be trans-esophageal or trans-gastric, wherein the trans-esophageal route is given preference
Aim is to obliterate the intramucosal part of the varix
EUS-guided coil and glue embolization is usually performed using a 22-G/19-G (gauge) FNA needle
The size of the coil is determined by the short axis of the diameter of the varix
After puncture of the varix, blood is aspirated to confirm the location. This is followed by flushing of the needle with saline
The coils are then deployed into the varix using the stylet as a pusher. Once the coils are deployed, flushing of the needle is done with normal saline
After coil deployment, 1-2 mL of cyanoacrylate glue is injected followed by rapid flushing with saline
Once, the varix is obliterated, visualized by absence of flow on colour Doppler, the sheath of the needle is advanced beyond the endoscope tip for 2-3 cm before withdrawing the scope. This avoids contact of glue with the endoscope tip
Post procedure
The patients are kept under observation for 12 h
Repeat EUS can be done after 2 d to look for residual varices
Follow-up EUS to be performed at 1- and 3-mo intervals

EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; G: Gauge.

obliteration was achieved in 93% of cases. Furthermore, mild post-procedure pain was seen in 3% of cases, with only one case of embolization. This data strongly supports the use of combination therapy for GVs. Recently, Kouanda *et al*[28] demonstrated its effectiveness in primary prophylaxis, with an obliteration rate of 96.7% with 2.5% re-bleed rates. A recent RCT and a meta-analysis have confirmed the superiority of EUS-guided coil with glue as the best modality for tackling GV[29,30].

Comparison of EUS-coil with CYA *vs* endoscopic glue injection: Limited data exist (retrospective and one RCT) comparing EUS combination therapy *vs* conventional endoscopic glue injection[31-34]. Robles-Medranda *et al*[31] compared the cost-effectiveness of the two procedures and found EUS therapy to be better.

The author's experience of the largest multicenter study involving four centers to evaluate the effectiveness of EUS combination therapy (52 cases) *vs* endoscopic therapy (118 patients) showed that the EUS arm required a lower number of sessions for complete obliteration (1 *vs* 2), lower re-bleeding rates (15.4% *vs* 31.3%) and lower post-procedure abdominal pain (0% *vs* 13.9%)[34]. Currently, an RCT is recruiting patients for EUS-guided coil and glue *vs* endoscopic CYA therapy for GV[35].

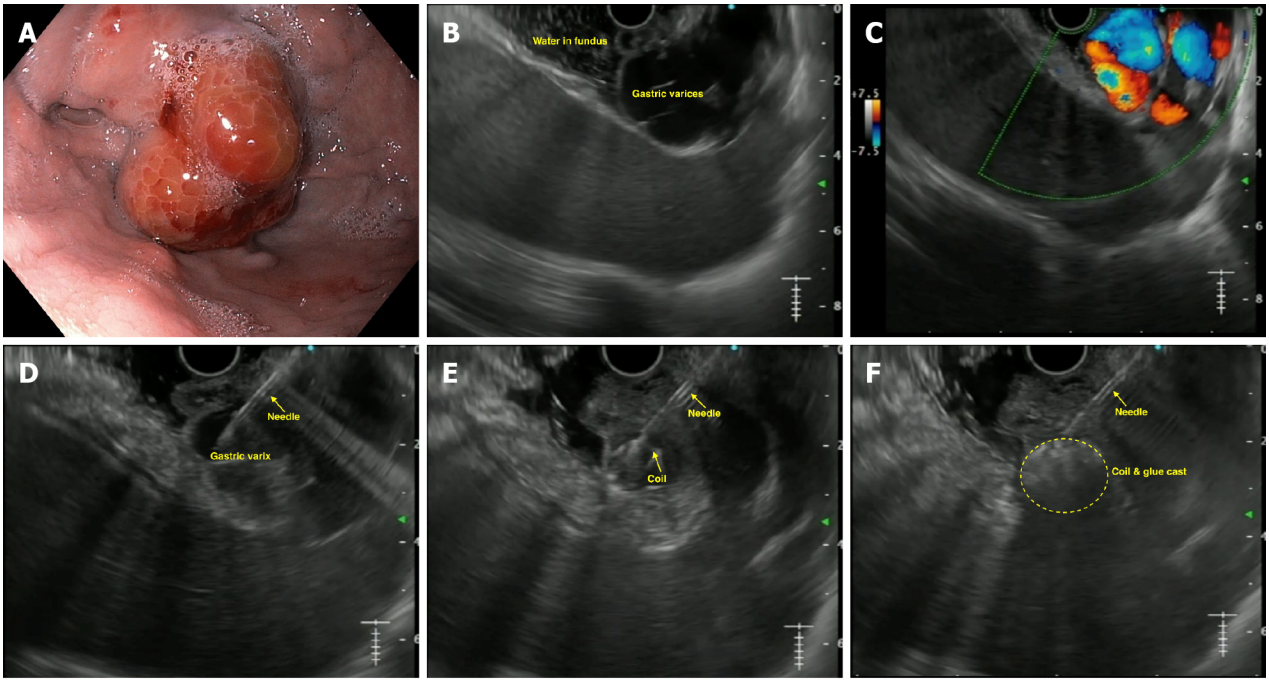

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Figure 3 Endoscopic ultrasound-guided coil and glue injection for gastric varices. A: Endoscopic image of gastric varix; B: Endoscopic ultrasound image of gastric varix; C: Colour Doppler showing flow in the varix; D: Puncture of the varix with 19-G needle; E: Coil being deployed in the varix; F: Glue injected leading to coil-glue cast with varix obliteration.

Newer therapies: Isolated case series exists on the utilization of thrombin, a coil with an absorbable gelatin sponge and ethanolamine oleate, with good results[36-38].

Various studies published on EUS-guided vascular interventions in GV have been tabulated in Table 2[39-47]. Published literature strongly supports using EUS-guided vascular therapy for managing GV for primary and secondary prophylaxis. The combination strategy has definite advantages and may be preferred over conventional CYA therapy in certain situations.

Future trends: Zhang *et al*[48] described a novel technique that can be incorporated into the EUS-hepatology toolbox. They described partial splenic embolization with endoscopic CYA for GV in cases with underlying hypersplenism with excellent results post-procedure.

Prediction of variceal re-bleed using EUS

EUS along with Doppler detects EV and GV with higher sensitivity, as compared to upper GI endoscopy, which helps in assessing the risk of bleeding, pre-procedure evaluation and predicting recurrence.

Predicting the risk of bleeding: The presence of hematocystic spots usually correlate with increased risk of esophageal variceal rupture. They can be identified as "saccular aneurysm" on EUS[49].

Preoperative evaluation: EUS-doppler can diagnose collateral veins, peri and para esophageal veins, and the perforators found adjacent to or outside the esophageal wall in patients with EV. The presence of the former is a strong indicator of a future occurrence of a re-bleed[50,51]. Intravariceal pressure can also be recorded in animal models by Miller *et al*[52] using a non-invasive EUS-based 20-MHz ultrasound transducer in a latex balloon catheter sheath.

Predicting recurrent bleed: The main factor predicting re-bleed for EV is the diameter of the paraesophageal vessels. Paraesophageal diameter before or after EVL is a better recurrence predictor (cut-off of 6.3 mm and 4 mm, respectively, having 60% and 70.6% sensitivity)[53]. Additionally, the velocity of hepatofugal blood flow in the left gastric vein and the branching pattern are associated with variceal recurrence after endoscopic treatments[54]. A cut-off of 0.45 cm^2 on digital image analysis using EUS (which identifies distal esophageal cross-sectional area) has 83% sensitive in predicting the risk of re-bleeding[55]. EUS has also been shown to objectively assess response to propranolol to determine variceal recurrence post-EBL[56].

Ectopic varices

Ectopic varices account for 1%-5% of cases of variceal bleeding. However, the management of ectopic

Table 2 Existing literature on endoscopic ultrasound-guided vascular interventions for gastric varices

Ref.	Cases	Treatment used in EUS	EUS needle size	Number of coils (EUS only)	Use of Glue/others (mL) (EUS/endoscopic therapy)	Number of sessions (EUS/endoscopic)	Technical success (%)	Clinical success (%)	Adverse events (overall) (%)	Reintervention rates (%)	Rebleeding rates (%)	All-cause mortality (%)
Studies on only EUS-guided Glue injection												
Lee *et al*[39], 2000	54	CYA (0.5 mL) with lipiodol (0.7 mL)	-	-	3 (1-8)	2.2 ± 1.7	52/54 (96.3%)	43/54 (79.6%)	22/54 (40.7%)	-	19/54 (35.2%)	28/54 (51.9%)
Romero-Castro *et al*[23], 2007	5	CYA-lipiodol (1 mL; 1:1)	22-G	-	1.6 (1-2)	2 cases: 1 each; 3 cases: 2 each	100%	100%	None	-	None	20%
Gubler and Bauerfeind[40], 2014	40	CYA-lipiodol (1 mL; 1:1)	22-G	-	1.9 (1-10)	1.4 (1-7)	40/40 (100%)	36/36 (100%)	2/40 (5%)	6/40 (15%)	-	6/40 (15%)
Studies on only EUS-guided coil injection												
Romero-Castro *et al*[25], 2010	4	Coils	19-G	Each case: 22; 7; 3; 2	-	-	100%	3/4 (75%)	None	-	None	25%
Khoury *et al*[41], 2018	10	Coils	19-G	4.5 (mean)	-	2.8 (mean)	100%	complete (20%); near-complete (50%)	5 cases (minimal self-limited bleeding); 1 case needing blood transfusion	30% (3/10)	1 case (10%)	None
Studies on only EUS-guided coil + glue injection												
Binmoeller *et al*[42], 2011	30	Coil + 1 mL CYA	19-G	-	1.4 (1-4)	1	30/30 (100%)	23/24 (95.8%)	None	1/30 (3.3%)	4/24 (16/6%)	1/30 (3.3%)
Bhat *et al*[27], 2015	152	Coil + 1 mL CYA	19/22-G	1.4 (1-4)	2 (0.5-6)	-	151/152 (99.3%)	93/100 (93%)	9/124 (7%)	7/125 (5.6%)	20/125 (16%)	3/151 (1.98%)
Kozieł *et al*[43], 2019	16	Coil + CYA (1:1 with lipiodol)	19-G	Total 21; mean 1.7 (1-3)	2 (1-9)	-	15/16 (94%)	Overall, 12/15 (75%) {coil+CYA (11/12 [92%]; only CYA [0%]}	6/16 (37.5%)	5/16 (31.3%)	1/16 (6.25%)	None
Robles-Medranda *et al*[44], 2019	30	Coil + CYA	19-G	2 (1-3)	1.8 (1.2-2.4 mL)	Mean 1.1	100%	96.6%	2 cases (6.7%)	3/27 (11.1%)	5 (16.7%)	4/30 (13.3%)
Kouanda *et al*[28], 2021	80	Coil + CYA	-	1.5 (1-3)	2 (0.5-5) mL	Mean 1.4	100%	60/62 (96.7%)	4 (4.9%)		6 (7.5%)	17 (21.3%)

Comparison of different treatment modalities for GV management												
Romero-Castro *et al* [26], 2013	30	EUS-Coil (11) *vs* EUS-CYA (19)	19/22-G	5.8 (2-13) (overall 64 coils)	1.5 (1-3) (overall 29 mL)	Overall, 1.4 ± 0.1 (14 *vs* 29)	Overall, 27/30 (90%): 10/11 (90.9%) *vs* 17/19 (89.5%)	Overall, 29/30 (96.7%): 10/11 (90.9%) *vs* 19/19 (100%)	Overall, 12/30 (40%): 1/11 (9.1%) *vs* 11/19 (57.9%)	2/11 (18.1%) *vs* 9/19 (47.3%)	None (0 *vs* 0)	Overall, 6/30 (20%)
Bick *et al*[45], 2018	104	EUS-CYA (64) *vs* endoscopic CYA (40)	19/22-G	-	2 (0.8) *vs* 3.3 (1.3) mL	1 session (79% *vs* 75%); 2 sessions (21% *vs* 17.5%); 3 sessions (0% *vs* 7.5%)	100% *vs* 100%	49/64 (79%) *vs* 30/40 (75%)	13/64 (20.3%) *vs* 7/40 (17.5%)	-	5/57 (8.8%) *vs* 9/38 (23.7%)	-
Mukkada *et al* [32], 2018	81	EUS-coil +/- CYA (30) *vs* endoscopic CYA (51)	19-G	2.36 (mean) (total 71)	2 (1-10 mL) in 15 cases *vs* 3 ± 1.5 ml	Overall [42 *vs* 77]	100% *vs* 100%	8/20 (40%) *vs* (NA)	0% *vs* 0%	12/30 (40%) *vs* 26/51 (51%)	6/30 (20%) *vs* 26/51 (51%)	3/30 (10%) *vs* 2/51 (4%)
Robles-Medranda *et al*[29], 2019	60	EUS-coil + CYA (30) *vs* EUS-coil (30)	19-G	2 (1-3) *vs* 3 (1-7)	1.8 (1.2-2.4) *vs* -	-	100% *vs* 100%	30/30 (100%) *vs* 27/30 (90%)	2 (6.7%) *vs* 1 (3.3%)	5 (16.7%) *vs* 12 (40%)	1 (3.3%) *vs* 6 (20%)	9/30 (30%) *vs* 8/30 (26.7%)
Lôbo MRA *et al*[33], 2019	32	EUS-coil + CYA (16) *vs* endoscopic CYA (16)	19-G	Total 21	1.4 ± 0.74 *vs* 3.07 ± 1.94	Overall, 20 *vs* 18	100% *vs* 100%	11 (73.3%) *vs* 12 (75%)	8 (50%) *vs* 10 (62.5%)	4/15 (26.7%) *vs* 4/16 (25%)	2 (12.5%) *vs* 2 (12.5%)	0 (0%) *vs* 2 (12.5%)
Bazarbashi *et al*[46], 2020	40	EUS-coil + AGS (10) *vs* EUS/endoscopic CYA/histocryl (30)	19/22-G	8 ± 2.9	1.7 ± 2.9	-	10/10 (100%) *vs* 29/30 (96.7%)	100% *vs* 87%	1/10 (10%) *vs* 5/30 (20%)	1/10 (10%) *vs* 17/20 (56%)	0% *vs* 38%	1/10 (10%) *vs* 5/30 (16.6%)
Robles-Medranda *et al*[31], 2021	36	EUS-coil + CYA (17) *vs* endoscopic CYA (19)	19-G	0 *vs* 2 (1-3)	1.8 (1.2-2.4) *vs* 1.8 (0.6-6.6)	1 *vs* 1 (1-4)	17/17 (100%) *vs* 16/19 (84.2%)	-	2/17 (11.8%) *vs* 3/19 (15.8%)	-	0 *vs* 3/19 (15.8%)	-
Seven *et al* [47], 2022	28	EUS-coil (19) *vs* EUS-coil + CYA (9)	19-G	5 (3-9) *vs* 5 (3-9)	-	1 *vs* 1	19/19 (100%) *vs* 9/9 (100%)	19/19 (100%) *vs* 8/9 (88.9%)	1/19 (5.3%) *vs* 1/9 (11.1%)	1/19 (5.3%) *vs* 0/9 (0%)	1/19 (5.3%) *vs* 22.2%)	6/28 (21.42%)
Samanta *et al* [34], 2022 (Author's centre)	170	EUS-coil+CYA (52) *vs* endoscopic CYA (118)	19-G	Median 2	2 (1) *vs* 2 (1) mL	1 (0) *vs* 2 (2)	52 (100%) *vs* 117 (99.2%)	-	0% *vs* 13.9%	7 (13.5%) *vs* 58 (49.6%)	8 (15.4%) *vs* 36 (31.3%)	-
Studies on EUS-guided treatment of GV using agents other than glue												
Frost and Hebbar[36], 2017	8	Thrombin (1000 IU/5 mL; 2500 IU/5 mL)	22-G	-	For active bleeder: mean 7250 IU; for elective: mean 2520 IU	1 for each case	100% overall	Overall, 75% (active bleeder: 67%; elective cases: 80%)	None	None	None	1 case
Bazarbashi *et al*[37], 2019	10	Coil + AGS	19/22-G	8 ± 2.9	AGS: 2.5 ± 0.7	1 each	100%	9/9 (100%)	None	None	1/10 (10%)	None
Irisawa *et al* [38], 2020	8	Coil + sclerosant [EO]	19-G	5.6 ± 2.9	EO: 7.8 ± 6.7 mL	1.9 ± 1	100%	7/8 (87.5%)	None	-	-	-

EUS: Endoscopic ultrasound; G: Gauge; CYA: Cyanoacrylate; AGS: Absorbable gelatin sponge; EO: Ethanolamine oleate; IU: International units.

varices holds a diagnostic challenge because of the diverse clinical presentation and lack of defined gui

Duodenal varices: Duodenal varices (DV) is extremely rare (0.4% cases). They are isolated in the submucosa and are easily missed on routine EGD. EUS plays an important role in determining the exact site, size, and location necessitating targeted therapy. Unfortunately, few case reports exist on using EUS-guided vascular therapy for DV[59-61] (Figure 4).

Rectal varices: Rectal varices (RV) has been reported in up to 44%-89% of cases of cirrhosis[62,63]. Due to their 'deep submucosal' nature, EUS has a higher sensitivity in identifying them over endoscopy (75% *vs* 43.3%), including perirectal collateral veins and perforators[64,65]. Multiple case reports have been published using EUS for RV management[66,67].

Parastomal varices: Bleeding stomal varices account for only 5% of bleeding ectopic varices (1%-5% of all cases)[57]. EUS-guided angiotherapy can be used as an alternative in managing such cases[68,69]. The author's center has experience performing EUS-coil with glue injection for parastomal varices in a cirrhotic patient ineligible for TIPS[70] (Figure 5).

Choledochal varices: The first case of ectopic variceal bleeding was reported in a case of anastomotic choledocho-jejunal varices[71]. They are rare, and EUS may help diagnose such cases. EUS mini probe can identify pericholedochal varices in patients with extrahepatic venous obstruction and help differentiate from biliary stones or sludge (Figure 6).

Table 3 summarizes published literature on EUS-guided angiotherapy for ectopic variceal bleeding [72-79].

EUS-guided angiotherapy has theoretical benefits for variceal bleeding over the standard of care, primarily for GV. EUS offers additional benefits as a "rescue" modality for refractory/unsuccessfully treated cases. This management modality may be considered in the management algorithm of variceal bleed, albeit only in expert centers with adequate backup.

EUS-GUIDED MANAGEMENT OF NON-VARICEAL GI BLEED

Treatment of non-variceal bleed (NVB) entails the standard use of well-established therapies categorized into injection (epinephrine), mechanical (clip/EBL) or thermal (argon plasma coagulation) or hemostatic agents[80-82]. Despite this, 10%-24% of cases re-bleed or are refractory to the standard treatment modalities. In these cases, EUS-guided angiotherapy can be beneficial by helping in directly visualizing the bleeding vessel, its feeders or perforators and help in targeted therapy. Currently, the role of EUS for the management of NVB is more of a rescue therapy. However, a recent systematic review reported a favourable outcome of EUS-guided therapy in 91.4% of cases[83]. In addition, EUS-angiotherapy is feasible and safe for managing Dieulafoy's lesion, bleeding ulcer or tumour, GI stromal tumour (GIST) and sometimes, visceral artery pseudoaneurysms (PsA).

Visceral artery pseudoaneurysms

PsA is a rare vascular complication noted in various conditions, more commonly in acute or chronic pancreatitis, with an incidence of 0.05% and 0.03%, respectively. The splenic artery is the most common vessel involved (37.7%). The most frequent line of management is IR-guided endovascular therapy[84, 85]. However, EUS-guided angiotherapy can be an exciting alternative to manage such cases. The proximity of PsA of splenic vessels or gastroduodenal artery to the GI wall enables them to be targeted and obliterated. Various agents like coil, CYA glue, a coil with glue combination and thrombin have been used.

The technique of performing EUS-guided angiotherapy in PsA: The technical details have been highlighted in Table 4.

Existing literature: Case reports: The use of thrombin in PsA was first described by Roach *et al*[86], wherein thrombin (500 IU, 1 mL) was injected in a PsA arising from a superior mesenteric artery under EUS guidance with no re-bleeding at 42 wk of follow-up. The use of CYA glue with lipiodol was described by Gonzalez *et al*[87], wherein a splenic artery PsA was tackled, and there was no re-bleed on a 2-mo follow-up. Similarly, the first use of coil was described by Robb *et al*[88] in superior mesenteric artery PsA using multiple Nester coils, achieving complete obliteration in one session. Rai *et al*[89] used coil with CYA glue combination in a 3 cm splenic artery PsA in a single sitting with no re-bleed in 1 mo. Giant PsA (> 5 cm) have also been reported to have been managed with EUS-angiotherapy. The author's center reported a 6.5 cm splenic artery PsA using a coil and glue combination in 2 sessions achieving complete obliteration[90]. The case reports have been outlined in Supplementary Table 1.

Case series: Only 5 case series (> 3 cases) have been reported, mainly from the Indian subcontinent and have been tabulated in Table 5. Three of them have utilized thrombin, while two have used coil with glue[91-95]. The author's centre has reported the largest series of 16 cases of visceral artery PsA in 15 patients. The median size of the PSA was 2.8 cm (0.9-9.7 cm). A median of 2 coils (1-8) and 2 mL of CYA (1-5 mL) was used. Complete obliteration in the first session was achieved in 15 PSA (93.8 %)[95]

Table 3 Published literature on the use of endoscopic ultrasound-guided vascular interventions in ectopic varices

Ref.	Cases	Underlying diagnosis	Age/sex	Size of varix	Any prior therapy given	EUS therapy (agent used)	EUS needle used	Coils	Glue	Post procedure EUS findings	Follow-up duration	Comments
Duodenal varices												
So *et al*[60], 2016	1	PC/EHPVO	65/F	2 cm	-	Coil	19-G FNA	3	-	Color Doppler: cessation of blood flow	10 mo	No bleeding on F/U
Kimura *et al* [61], 2017	1	PC	76/F	-	-	CYA glue	22-G FNA	-	0.5 mL (3 sessions)	- (f/u CT: shows extinction of contrast enhancement in DV)	6 mo	No bleeding on F/U
Kinzel *et al* [72], 2014	1	Cirrhosis (Child C)	31/M	10 mm	Endoscopic ethanolamine oleate	Coil + CYA glue	19-G (for coil) + 22-G (for glue) FNA	1	2 mL	Near complete thrombosis of varix	3 mo	No bleeding on F/U
Fujii-Lau *et al* [73], 2016	3	PVT; SMV-T; SMV-T	57/M; 46/F; 62/F	-; -; -	Glue; -; Clip + coil (IR)	Coil; Coil; Coil + CYA glue	22-G FNA (for all)	4; 4; 8	-; -; 2 mL	dec. flow; dec. flow; no flow	30 mo; 12 mo; 6 mo	No bleeding on F/U (all cases)
Bahdi *et al* [74], 2020	1	Cirrhosis	41/M	-	None	Coil + CYA glue	22-G FNA	8	2 mL	-	-	-
Rectal varices												
Messallam *et al*[66], 2014	1	Cryptogenic cirrhosis	78/M	45 × 12 mm	None	Coil + CYA glue	19-G FNA	2	4 mL	No flow	12 wk	No bleeding on F/U
Sharma *et al* [67], 2010	1	PHTN	68/M	2.2 mm	None	Histocryl glue	-	-	1 mL	Decreased flow	6 mo	No bleeding on F/U
Mukkada *et al* [75], 2017	1	PHTN	65/M	5.9 mm	Endoscopic sclerotherapy (tetradecyl sulphate 16 ml; CYA glue)	Coil	19-G FNA	2	-	No flow	-	-
Bazarbashi *et al*[76], 2020	1	Cirrhosis	71/M	4 mm	None	Coil	19-G FNA	1	-	No flow	6 mo	No bleeding on F/U
Philips *et al* [77], 2017	1	Cirrhosis	48/M	-	None	Coil + CYA glue	22-G FNA	1	1 mL	No flow	1 mo	No bleeding on F/U
Weilert *et al* [78], 2012	1	Cirrhosis	60/F	> 3 cm	None	Coil + CYA glue	19-G FNA	5	4 mL	No flow	12 mo	No bleeding on F/U
Jana *et al*[79], 2017	1	Hepatitis C/PHTN	54/M	-	None	Coil + CYA glue	22-G FNA	3	0.8 mL	No flow	1 mo	No bleeding on F/U
Stomal varices												

Tabibian *et al* [68], 2016	1	Cirrhosis PSC/post colectomy for UC	70/F	5 mm	Somatostatin/topical silver nitrate	Coil	22-G FNA	6	-	No flow	9 mo	No bleeding on F/U
Tsynman *et al* [69], 2014	1	UC/post colectomy/cirrhosis	74/F	-	TIPS	CYA glue with lipiodol	22-G FNA	-	0.5 mL	No flow	8 mo	No bleeding on F/U
Samanta *et al* [70], 2022	1	Alcohol cirrhosis/tubercular cocoon/ileostomy	52/M	-	Endoscopic glue injection	Coil + CYA glue	19-G FNA	2	4 mL	No flow	6 mo	No bleeding on F/U
Choledochal varices												
Levy *et al*[71], 2008	1	CP/post total pancreatectomy	50/F	14 mm	-	Coil	22-G FNA	5	-	No flow	1 mo	No bleeding on F/u
Fujii-Lau *et al* [73], 2016	5	Cirrhosis; SMV-T; PVT; PHTN; PVT	61/M; 56/M; 27/M; 71/M; 50/F	-; -; -; -; -	None; None; None; None; None	Coil; Coil; Coil; Coil; Coil	22-G FNA (for all)	7; 9; 4; 5; 5	-; -; -; -; -	dec. flow; dec. flow; dec. flow; dec. flow; dec. flow	24 mo; 37 mo; 26 mo; 1 mo; 87 mo	Recurrent bleed in 3 cases; one case died due to underlying disease

EUS: Endoscopic ultrasound; PC: Pancreatic cancer; EHPVO: Extrahepatic portal vein obstruction; F: Female; M: Male; G: Gauge; FNA: Fine needle aspiration; F/U: Follow-up; CT: Computed tomography; DV: Duodenal varices; CYA: Cyanoacrylate; PVT: Portal vein thrombosis; SMV-T: Superior mesenteric vein thrombosis; IR: Interventional radiology; Dec.: Decreased; PHTN: Portal hypertension; PSC: Primary sclerosing cholangitis; UC: Ulcerative colitis; TIPS: Transjugular intrahepatic portosystemic shunt; CP: Chronic pancreatitis

(Figure 7).

Other causes of NVB (Dieulafoy's/bleeding tumors)

Anecdotal reports have been published on using EUS-guided angiotherapy to manage NVB (Supplementary Table 2). In 1996, the first report used EUS-guided epinephrine/polidocanol injection for managing bleeding dieulafoy's lesion[96] (Figure 8). Levy *et al*[97] reported a series of 5 refractory NVBs, including dieulafoy's lesion, hemosuccus pancreaticus, duodenal ulcer and GIST. The largest data of EUS-guided therapy reported to date involves a cohort of 17 cases using various agents. On a median 12-mo follow-up, 15/17 (88%) patients had no re-bleed[98].

The data on EUS-guided vascular interventions for NVB is limited and comparative studies are needed to establish its role in therapeutic algorithms. However, EUS-guided angiotherapy may be considered a second-line "rescue" treatment, especially in refractory/re-bleeding cases. The feasibility and safety data are encouraging, though larger multicentre data is required to define its role further.

EUS-GUIDED PV-RELATED INTERVENTIONS

PV dynamics are crucial for decision-making in chronic liver disease and PHTN cases. EUS-guided PV access is a viable option with a probable advantage over the percutaneous route owing to the relative difficulty experienced in the latter in patients with obesity, ascites, and overlying distended bowel[99]. In addition, there are various potential clinical applications of EUS-guided PV access that include angiography, measurement of the PPG, EUS-guided TIPS, and PV sampling for evaluation in GI cancer

Table 4 Steps for endoscopic ultrasound-guided management of visceral artery pseudoaneurysm

EUS-guided angioembolization of visceral artery pseudoaneurysm
Pre-procedure requirements
All procedures are done under the cover of pre/peri-procedural antibiotics
Patient is usually kept fasting for 4-6 h before the procedure
Adequate resuscitation of the patient, in case of active bleeding is ensured, prior to the procedure
Informed consent prior to the procedure
What is needed prior to the procedure
Linear echoendoscope with at least a 3.7 mm working channel
Needle size: depends on the choice of the endoscopist; usually a 19-G needle is used with 0.035'coil. However, a 22-G needle with 0.018' coils may be used
Diameter of the coils: Smaller than the shortest diameter of the PsA
Number of coils: depends on size of the PsA
Amount of glue: depends on the size of the PsA
Technical aspects
A proper diagnostic EUS is performed
The echoendoscope is positioned optimally for a stable PsA access
Optimum examination of the PsA, the feeding vessel and the anatomy is delineated
The approach should always be through parenchyma, either pancreatic or hepatic. Bare puncture of the PsA without supporting parenchyma should not be performed
EUS-guided coil and glue embolization is usually performed using a 22-G/19-G (gauge) FNA needle
The size of the coil is determined by the short axis of the diameter of the PsA
After puncture of the varix, blood is aspirated to confirm the location. This is followed by flushing of the needle with saline. The pressure is high in the aneurysm, hence care should be taken to avoid creeping of blood along the hollow of the needle and causing needle block
The coils are then deployed into the varix using the stylet as a pusher. Packing with coils slows the flow inside the PsA, which can be visualized and further requirement of coils is assessed. Once the coils are deployed, flushing of the needle is done with normal saline
After coil deployment, cyanoacrylate glue is injected using the coils as scaffold
Once, the PsA is obliterated, visualized by absence of flow on colour Doppler, the sheath of the needle is advanced beyond the endoscope tip for 2-3 cm before withdrawing the scope. This avoids contact of glue with the endoscope tip
Post procedure
The patients are kept under observation for 12 h
Post embolization X-ray would help visualize the coils and also look for complications
Repeat EUS can be done after 48 hrs. to look for residual flow
Cross-sectional imaging is usually done after 72 h. to document success of therapy
Follow-up EUS may be performed at 1-mo

G: Gauge; PsA: Pseudoaneurysm; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration.

[1,99].

EUS-guided portal vein access

Access to the PV can be achieved on EUS *via* both, trans-gastric or trans-duodenal route. However, the most frequently targeted site is the intrahepatic PV through the hepatic parenchyma[1,2,99].

The technique: PV puncture is done using the standard EUS-FNA needle after confirming with colour doppler and pulse-wave verification. Some important points for consideration are: (1) 25-G needle is the least traumatic; (2) trans-gastric, trans-hepatic route on EUS is safer than accessing from duodenum; and (3) use of CO_2 as a contrast agent is better than iodine, as it allows better visualization of needle as-well-as easier administration using small-caliber FNA needle. Following the puncture of PV, the needle is slightly withdrawn and the tract is monitored using colour-Doppler for any bleeding episodes. If positive signal is reported, the needle is kept in place until the bleeding has stopped[100].

Table 5 Published case series on endoscopic ultrasound-guided angiotherapy for arterial pseudoaneurysm

S.No.	Ref.	Cases	Age/sex	Chief complaints	Artery involved	PSA size (mm)	EUS needle used	Embolization agent used	EUS sessions needed	Technical/clinical success	Complications	Follow up and comments
1	Gamanagatti *et al*[91], 2015	3	56/M; 45/M; 30/M	Upper GI bleed (all 3)	GDA; Splenic; Splenic	-	22-G	Thrombin (500 IU, 300 IU, 400 IU)	1 each	Yes/yes	None	Imaging F/U: complete obliteration; no bleeding at 1 mo F/U
2	Jhajharia *et al* [92], 2018	3	43/M; 25/M; 55/M	Pain abdomen; hematemesis; Malena (respectively)	GDA; Right hepatic; splenic	40 × 50; 30 × 22 × 27; 15 × 13	22-G	Thrombin (1000 IU; 1000 IU; 500 IU)	1 each	Yes/yes	None	F/U at 1.5 years, 1 year and 3 mo: no bleeding (respectively)
3	Rai *et al*[93], 2018	6	Median 36.7 years (19-60); 5 men	3 asymptomatic; 3 upper GI bleed	All Splenic artery PSA	25-65 (range)	19-G	Coils (size 8, 14, 16; number 1-5) and glue (1-2 mL)	3 cases needed 2 EUS sessions (size > 4 cm)	Yes/yes (all cases)	None	EUS (4 wk) and CT (3 mo): complete obliteration
4	Maharshi *et al* [94], 2020	8	Median 34 years (27-58); all males	Malena (100%); hematemesis (75%)	Splenic (5); left hepatic (2); GDA (1)	Median 29 × 26 (range 18 × 19 – 40 × 50)	22-G	Thrombin (200-500 IU)	1	Yes/87.5% clinical success (7/8 cases)	2 cases post procedural pain	EUS (1 and 3 mo) and CT (1 mo): complete obliteration; only 1 case with PSA > 5 cm needed second EUS session after 6 wk
5	Samanta *et al* [95], 2022	16 PsA (in 15 patients)	Median 44 (17-56); males 14 (93.3%)	Malena/ incidental/ PCD bleed	Splenic (12); GDA (4)	Median 2.8 (0.9-9.7 cm)	19-G	Coils (median 1[1-8]) with CYA glue (median 2 [1-5 mL])	1 session in 15 (93.8%)	Yes/yes	One case had splenic infarct (managed conservatively)	Follow-up at 6 mo: no rebleed; one case developed recurrent PsA at a site separate from first PsA (managed again with EUS)

PsA: Pseuoaneurysm; EUS: Endoscopic ultrasound; F/U: Follow-up; IU: International units; GDA: Gastroduodenal artery; PCD: Percutaneous catheter drainage; CYA: Cyanoacrylate glue; GI: Gastrointestinal; CT: Computed tomography.

Existing literature in animal models: Lai *et al*[101] proved the technical feasibility of the procedure by reporting the first case of PV access in 2004 using EUS guidance wherein extrahepatic PV was accessed using 22-G FNA needle, *via* duodenum, in 21 swine models. Subsequently, Magno *et al*[102] performed PV angiography in 2007 in 5 pigs, demonstrating that the 25-G needle showed no signs of injury. Subsequently, Giday *et al*[100,103] performed trans-hepatic PV access using a 25-G FNA needle under CO_2 insufflation. Portal pressure measurements were also taken, indicating it to be technically feasible (Supplementary Table 3).

Once it is established that EUS-guided PV access is feasible, it paves the path for further interventions such as PPG measurement, PV sampling and even EUS-guided intrahepatic portosystemic shunt.

EUS-PPG measurement

PPG measurement has been shown to correlate with the prognosis and complications of cirrhosis. In addition, PPG ≥ 10 mmHg and ≥ 12 mmHg are associated with the development of EV and bleeding,

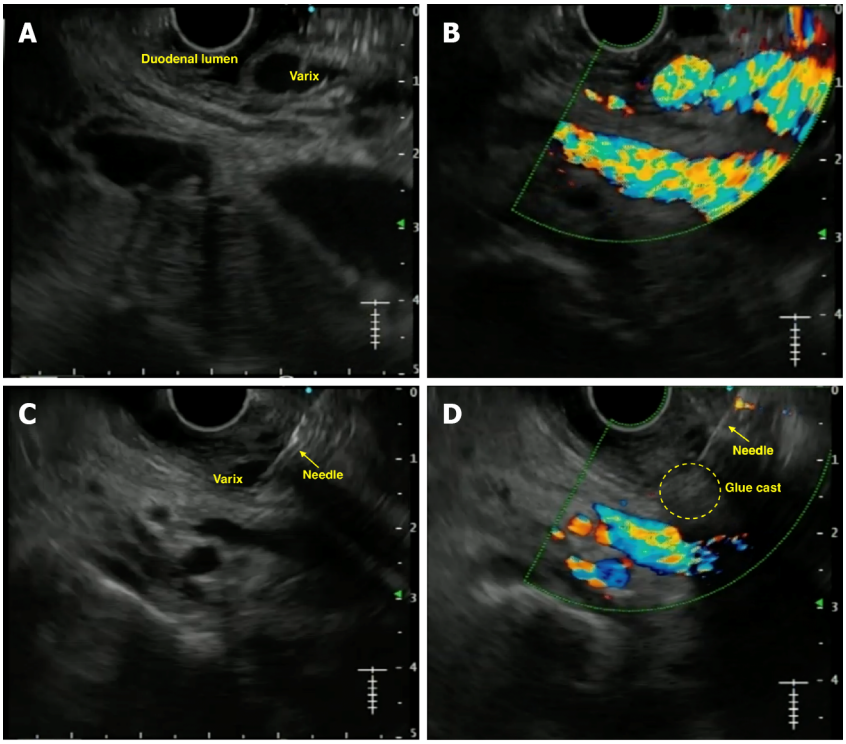

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Figure 4 Endoscopic ultrasound-guided vascular therapy for duodenal varix. A: Endoscopic ultrasound image of duodenal varix; B: Colour Doppler showing flow in the varix; C: Puncture of the varix with 19-G needle; D: Obliteration of the varix noted on Doppler flow.

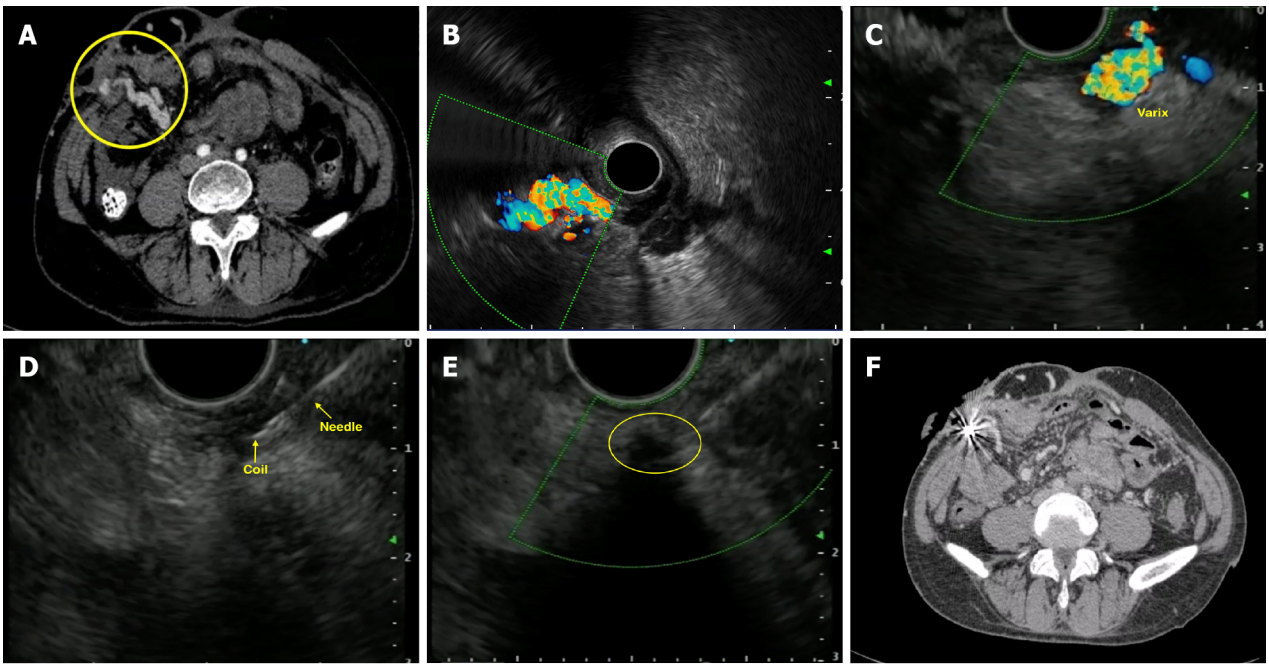

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Figure 5 Endoscopic ultrasound-guided vascular therapy for parastomal varices. A: Contrast enhanced computed tomography (CT) showing parastomal varices; B: Radial endoscopic ultrasound (EUS) image demonstrating the parastomal varices; C: Linear EUS image of the varices; D: Puncture of the varix with coil deployment; E: Obliteration of the varix with coil-glue cast; F: Post-intervention CT showing coil artifacts with obliteration of varices.

respectively. Currently, the standard practice is to measure hepatic venous pressure gradient (HVPG) *via* the percutaneous route. But, both direct PV access and HVPG measurement have high complication rates[104]. Moreover, HVPG correlated poorly with presinusoidal PHTN. Hence, the concept of EUS-PPG arose to overcome these difficulties, with the added benefit of assessment of varices and liver biopsy in the same setting, if required.

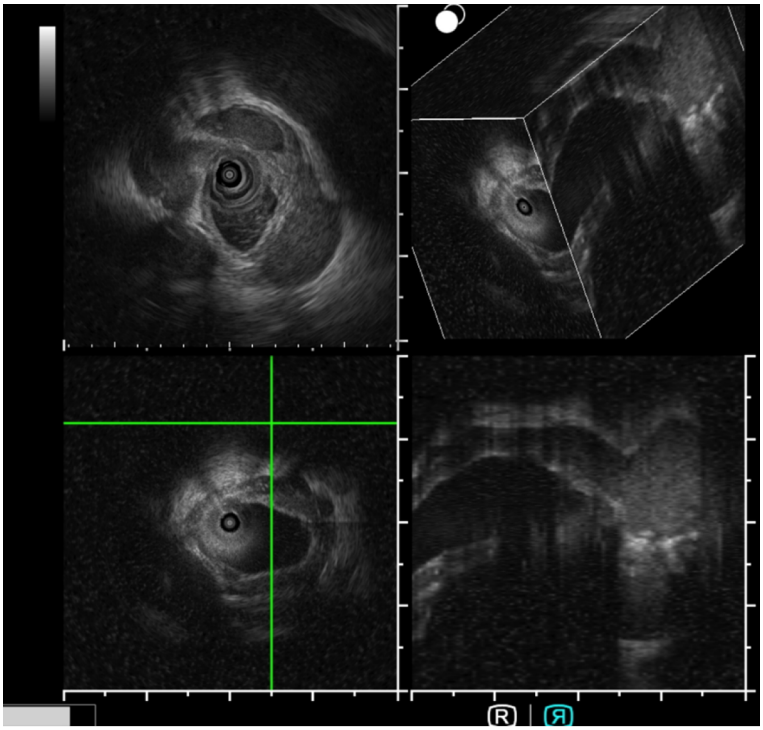

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Figure 6 Intraductal ultrasound for pericholedochal varices. Intraductal ultrasound using endoscopic ultrasound miniprobe (UM-DG20-31R IDUS probe, Olympus, Japan) for imaging in a case of portal cavernoma cholangiopathy with 3D reconstruction.

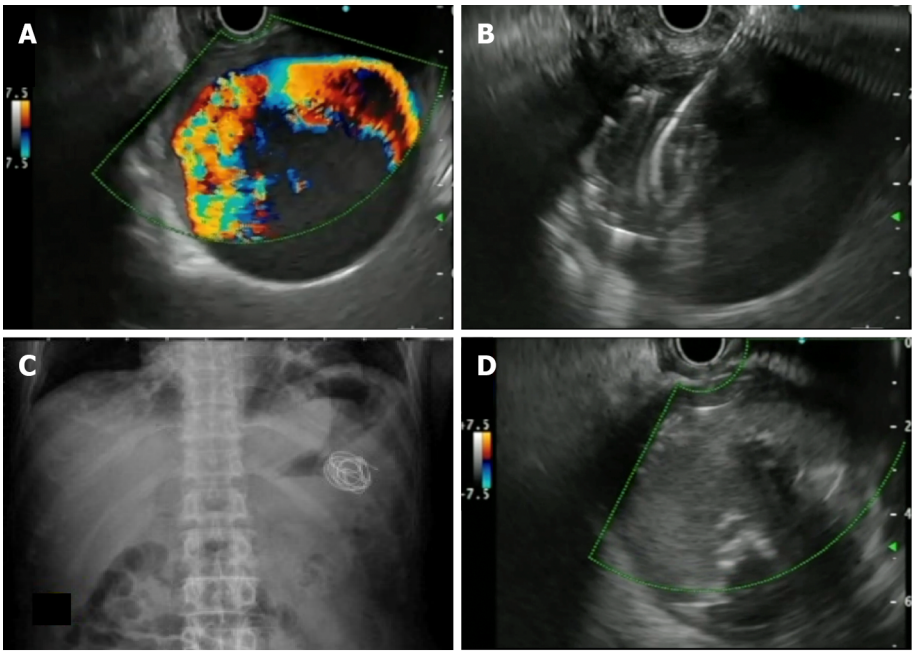

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Figure 7 Endoscopic ultrasound-guided vascular therapy for pseudoaneurysm: A: Giant splenic artery pesudoaneursym with Doppler flow; B: Puncture of the pseudoaneurysm with 19-G needle and deployment of coils; C: Abdominal X-ray showing deployed coils; D: Endoscopic ultrasound image of obliterated pseudoaneurysm after coil and glue injection.

The technique of the procedure: This has been highlighted in Table 6[105].

Existing literature and future trends: The first clinical report of the use of EUS-PPG was given by Fujii-Lau *et al*[106], wherein a 27-year-old man with recurrent GI bleed (post EUS-coil insertion in duodenal vessels) underwent this procedure. The first large-scale study in 28 cases was done by Huang *et al*[105],

Table 6 Technique for assessing endoscopic ultrasound-guided portal pressure gradient

Procedural steps for measuring EUS-PPG
The measurement of PPG *via* EUS requires 4 components: 25-G FNA needle, non-compressible tubing, a compact digital manometer, and heparinized saline. The tubing is connected by a luer lock to the distal port and heparinized saline is connected the proximal port of the manometer
With the patient supine, the manometer is placed at the patient's midaxillary line
The HV measurement is conducted first, in which middle HV is targeted most often (larger calibre and better alignment with the needle trajectory). Then PV measurement is taken (umbilical portion of left PV is the target)
Doppler flow is used to confirm the typical multiphasic waveform of hepatic venous flow and typical venous hum of the portal venous flow
Trans-gastric trans-hepatic route is taken for HV and PV puncture
Needle is flushed with heparinized saline (1 mL). The steadiest reading at equilibrium is recorded. Three measurements are taken and their mean is calculated (both HV and PV pressures)
The FNA needle is slowly withdrawn from the vein into the liver parenchyma and then back into the needle sheath with Doppler flow on to ensure there is no flow within the needle tract

EUS: Endoscopic ultrasound; PPG: Portal pressure gradient; G: Gauge; FNA: Fine needle aspiration; PV: Portal vein; HV: Hepatic vein.

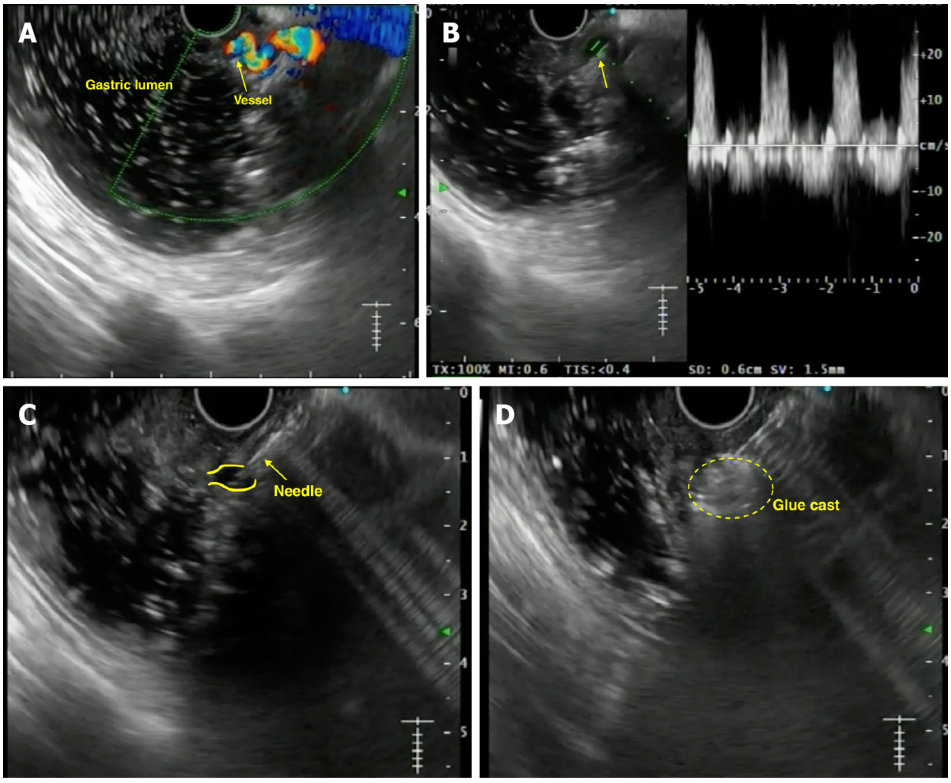

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Figure 8 Endoscopic ultrasound-guided vascular therapy for dieulafoy's lesion. A: Endoscopic ultrasound image showing the culprit tortuous vessel coursing up to the mucosa; B: Power Doppler showing the flow pattern; C: Puncture of the vessel with a 22-G needle; D: Obliteration of the flow with formation of glue cast.

using a 25-G FNA needle with 100% technical success and no adverse events. PPG correlated with varices, thrombocytopenia, and notable clinical evidence of cirrhosis. Zhang *et al*[107] demonstrated its use in patients with acute or subacute PHTN, with an excellent correlation between EUS-PPG and HVPG (r = 0.923). Acting as a "one-stop-shop", performing EUS-PPG with EUS-liver biopsy in the same sitting has shown to be technically feasible in a study of 24 cases, with good correlation with the non-invasive markers of fibrosis[108]. Table 7 highlights the published literature on the use of EUS-PPG[105-111].

EUS-guided trans-jugular intrahepatic portosystemic shunt

The benefits of trans-jugular intrahepatic portosystemic shunt (TIPS), as a pre-emptive or rescue

Table 7 Published literature (human studies) on the use of endoscopic ultrasound-guided portal pressure measurement

Ref.	Year	Number of cases	Approach	EUS-FNA needle	Technical success	Complications	Correlation between EUS and trans-hepatic PVP measurement
Fujii-Lau *et al* [106]	2014	1	Trans-gastric	22-G	1	None	PPG 1 mmHg (excellent correlation with HVPG)
Huang *et al* [105]	2017	28	-	25-G	25/25 cases	None	Excellent correlation with varices (P = 0.0002), PHG (P = 0.007), and thrombocyt-openia (P = 0.036); few of them also underwent liver biopsy in same setting
Zhang *et al* [107]	2020	12	-	22-G	11/12 cases (91.7%)	None	R = 0.923
Shah *et al*[109]	2021	1	Trans-gastric	25-G	1	None	NA (same session EUS-liver biopsy was done)
Hajifathalian *et al*[108]	2021	24	Trans-gastric	25-G	23/24 (96%) patients also underwent EUS-liver biopsy (TS: 24/24 [100%])	One case of mild abdominal pain (resolved with analgesics)	NA; excellent correlation with fibrosis-4 score (P = 0.026) and transient elastography (P = 0.011)
Choi *et al*[110]	2022	83	Trans-gastric	25-G	100%; 71 cases underwent EUS-liver biopsy	No major events; minor abdominal pain (8 [9.6%] cases)	Correlation with clinical features of cirrhosis (9.46 *vs* 3.61 mmHg, P < 0.0001), EV/GV (13.88 *vs* 4.34 mmHg, P < 0.0001), and thrombocytopenia (9.25 *vs* 4.71 mmHg, P = 0.0022)
Choi *et al*[111]	2022	64	Trans-gastric	25-G	100% (concurrent EUS-LB in 43/64 [67.2%])	1 case (EUS-PPG alone); 5 cases (EUS-PPG + EUS-LB both)	EUS-PPG > 5 mmHg correlated with EUS-liver biopsy fibrosis stage ≥ 3 [LR 27] (P = 0.004)

EUS: Endoscopic ultrasound; PPG: Portal pressure gradient; FNA: Fine needle aspiration; PVP: Portal venous pressure; G: Gauge; LB: Liver biopsy; EV: Esophageal varices; GV: Gastric varices; LR: Likelihood ratio; NA: Not available; PH: Portal hypertensive gastropathy.

procedure in cases of variceal bleeding or refractory ascites has been well established. Buscaglia *et al* [112] described the first case of EUS-TIPS in a live porcine model in 2009, wherein after sequential puncture of HV and PV, a metal stent was inserted with the distal end in PV and proximal end in HV with no complications on follow-up in 2 wk. Similarly, Binmoeller *et al*[113] and Schulman *et al*[114] have reported similar results in porcine models using lumen-apposing metal stent (LAMS). Poincloux *et al*[115] reported the largest series of 21 porcine models showing a technical success of 91% with 14.2% morbidity. EUS-guided TIPS is still in the pre-clinical stages, and many technical issues must be resolved before embarking on human trials.

EUS-guided PV sampling

"Liquid biopsy" for hepatobiliary malignancies is gaining popularity. The PV has been shown to harbour circulating tumour cells (CTCs) for the primary tumour, forerunners of future metastasis of solid organ cancers. This signifies tumor signature and can help in prognostication and also can be used for organoid formation for future studies. The first human study was reported by Catenacci *et al*[116] wherein CTCs were detected in 100% of cases of PV and 4/18 (22.2%) cases from peripheral blood. Zhang *et al*[117] reported that CTCs are more in PV than peripheral blood (97% *vs* 87%; 10 *vs* 6 cells per 5 mL). Further studies are needed to standardize this technique.

EUS-guided FNA of portal vein thrombosis

The presence of malignant PV thrombosis (PVT) is a poor prognostic sign and precludes curative resection. Usually, imaging (ultrasound/computed tomography) can help differentiate bland and malignant PVT, but definitive confirmation would require sampling. Performing the latter *via* the percutaneous route is difficult and may lead to serious vascular and biliary injury. This can be overcome by EUS-guided PV access. Trans-duodenal approach to extrahepatic PV using a 25-G FNA needle yields excellent results. Various case reports have been published on using EUS-FNA of PVT, especially in cases of hepatocellular carcinoma[118-122]. Rustagi *et al*[118] showed that in 17 patients, EUS-FNA of remote malignant thrombi upstaged the diagnosis by 37.5% and converted 25% to an unresectable stage. This underlines using EUS-FNA of PV thrombus as a cancer staging modality.

EUS-guided PV injection of chemotherapy

Systemic palliative or trans-arterial chemotherapy for diffuse liver metastasis is fraught with problems like suboptimal hepatic tissue levels and the possibility of secondary sclerosing cholangitis. However,

Faigel *et al*[123,124] first reported the technical feasibility of EUS-guided PV injection of chemotherapy (EPIC) using drug-eluting microbeads and nanoparticle in 24 swine models. Although further studies are warranted, this study proved the feasibility of EPIC in an animal model.

EUS-guided PV embolization

Preoperative PV embolization (PVE) before liver resection has been practiced *via* IR[125]. In addition, preliminary studies in an animal model by Matthes *et al*[126] using EUS-guided ethylene-vinyl alcohol copolymer leading to PVE have been reported. Recently, Park *et al*[127] reported technical success of 88.9% and 87.5%, respectively, with coil and CYA glue embolization in 9 swine models with no evidence of organ damage. Although further studies are needed, this technique does show promise for future application.

EUS-guided PV stent placement

The PV-stenting (for occlusion/thrombosis) is usually carried out by the percutaneous route (USG-guided catheter-directed thrombolysis). The use of EUS has opened up avenues of PV access and subsequent stent placement. This was first reported by Park *et al*[128] in 6 swine models, using uncovered stents, with 100% technical success.

EUS-GUIDED CARDIAC INTERVENTIONS

The proximity of the posterior mediastinum to the esophagus has allowed EUS easy access to the heart and associated vascular structures. Like trans-esophageal echocardiography, EUS is technically feasible in animal models to sample the coronaries, atria, ventricles, and valvular apparatus. Fritscher-Ravens *et al*[129] demonstrated radiofrequency ablation of the aortic valve, pericardial fluid aspiration, and atrial mass biopsy in swine models with no major adverse events. Most isolated case reports exist on EUS-biopsy of intracardiac/pericardial tumours[130-132]. EUS-aspiration of pericardial fluid has been performed with no reported arrhythmias[133]. Even EUS-guided thrombolysis of pulmonary artery and mesenteric thrombi has been reported. Under EUS guidance, Tenecteplase was injected into the thrombus using a 25-G needle[134].

While the reports are exciting, these are anecdotal cases, and more data is warranted in the future to establish the safety and efficacy of such interventions.

CONCLUSION

EUS-guided vascular intervention is gradually becoming a promising new technique for managing vascular complications around the GI tract as a salvage and/or primary modality. While comprehensive data has established its safety and efficacy in managing conditions such as GV and measurement of PPG, its role for other applications such as management of visceral artery pseudoaneurysms and PV access for various therapies needs further validation. Nevertheless, proper selection of cases, adequate precautions and optimum backup can make EUS-guided angiotherapy an essential tool in the endoscopist's armamentarium.

FOOTNOTES

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MINIREVIEWS

Update on diagnosis and treatment of early signet-ring cell gastric carcinoma: A literature review

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Abstract

Gastric signet-ring cell gastric carcinoma (GSRC) is an unfavorable subtype of gastric cancer (GC) that presents with greater invasiveness and poorer prognosis in advanced stage than other types of GC. However, GSRC in early stage is often considered an indicator of less lymph node metastasis and more satisfying clinical outcome compared to poorly differentiated GC. Therefore, the detection and diagnosis of GSRC at early stage undoubtedly play a crucial role in the management of GSRC patients. In recent years, technological advancement in endoscopy including narrow-band imaging and magnifying endoscopy has significantly improved the accuracy and sensitivity of the diagnosis under endoscopy for GSRC patients. Researches have confirmed that early stage GSRC that meets the expanded criteria of endoscopic resection showed comparable outcomes to surgery after receiving endoscopic submucosal dissection (ESD), indicating that ESD could be considered standard treatment for GSRC after thorough selection and evaluation. This article summarizes the current knowledge and updates pertaining to the endoscopic diagnosis and treatment of early stage signet-ring cell gastric carcinoma.

Key Words: Gastric signet-ring cell gastric carcinoma; Narrow-band imaging; Magnified endoscopy; Endoscopic submucosal dissection

Core Tip: Gastric signet-ring cell gastric carcinoma (GSRC) represents a special subtype of gastric cancers with unique clinical and pathological characteristics. With the advancement of endoscopic technology, the diagnosis and curability of early GSRC have been substantially improved. This overview gives the latest update on the endoscopic diagnosis and treatment of early GSRC.

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INTRODUCTION

Gastric signet ring cell carcinoma (GSRC) is a unique histological type of gastric cancer (GC). GSRC is mainly composed of more than 50% of signet ring cells (SRC) based on the World Health Organization (WHO) classification. The SRC is characterized by crescent-shaped nuclear distributed in the side of the cell and substantial cytoplasm filled with large mucin vacuole[1,2]. GSRC is associated with aggressive invasiveness and abdominal implantation metastasis due to E-cadherin down-regulation[3]. Most GSRC patients were diagnosed at an advanced stage in the past years due to the underdevelopment of screening technology, leading to poorer prognosis and decreased quality of life compared with patients with other types of GC. However, studies have shown that the clinical course of GSRC is significantly different between the early stage and advanced stage, indicating that treatment at an early stage can improve the prognosis of GSRC patients. Therefore, different treatment methods should be applied for early GSRC and advanced GSRC[4]. Conventional endoscopy may miss early GSRC due to its morphological traits. However, the diagnosis rate of GSRC has significantly increased due to the advancement of endoscopic imaging technology, including narrow-band imaging (NBI), magnifying endoscopy (ME), and endoscopic ultrasonography (EUS). The margin and size of the tumor can be determined using NBI, while the invasion depth and lymph node metastasis (LNM) can be detected using EUS[5].

Endoscopic resection (ER) is the current standard treatment for early GC that meets the indication for ER. ER includes endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)[6,7]. Nevertheless, ESD is the current standard treatment for early GC since it allows complete dissection of intramucosal lesions with better flexibility and effectiveness than EMR. Although some early GSRC patients undergoing ER experience local recurrence and LNM, they have better overall survival (OS) than patients with poorly differentiated adenocarcinoma (PDC)[8,9]. This article reviews the progress related to the endoscopic diagnosis and treatment of early GSRC in recent years and offers a different perspective on managing early GSRC patients.

CLINICOPATHOLOGIC CHARACTERISTICS OF EARLY GSRC

GSRC is more common in women and young patients than non-SRCC (NSRC). Early-stage GSRC lacks typical clinical manifestations. Most patients with early GSRC complain of chronic gastritis-like symptoms, such as abdominal pain and abdominal distension, which can be misdiagnosed as gastritis and peptic ulcer. Although both SRC and PDC are grouped into the "undifferentiated type" (UD) based on Nakamura classification, the two subtypes may have different histological and clinical characteristics [6]. Unlike PDC which tends to infiltrate the submucosa, early GSRC is common in the mucus layer of the stomach, showing a comparably lower risk of LNM[4]. The intramucosal GSRC yields a more agreeable clinical course than PDC, possibly due to its subepithelial spreading pattern[10]. SRC spreads horizontally in the laminapropria without invading the gastric epithelium. As a result, it is difficult to accurately evaluate the size and margin of SRC since endoscopy may not detect the part of SRC hiding beneath the normal gastric epithelium.

Most intramucosal GSRCs have a double-layer structure (DLS)[11]. The upper layer of DLS is mainly composed of abundant mucins in the cytoplasm and an eccentric nucleus, while the lower layer mainly contains a few intracytoplasmic mucins and acidophilic cytoplasm. Proliferative cells disseminate between these two layers. DLS is defined if the lesion satisfies the following criteria in immunohistochemical staining: (1) MUC5AC is positive only in the superficial layer; (2) Ki-67 is positive only in the middle proliferative area; and (3) MUC6 is positive in the deep layer. The existence of DLS suggests that SRCs are in a low proliferative station, while the destruction or the absence of DLS indicates an activated phase of proliferation and invasion, resulting in a higher risk of LNM and submucosal infiltration.

ENDOSCOPIC DIAGNOSIS OF EARLY GSRC

White light imaging

Early GSRC has similar endoscopic features to other types of undifferentiated carcinoma. Early GSRC is characterized by flat or depressed lesions with discoloration under traditional white light imaging

(WLI) (Figure 1A). Most lesions are located in the middle 1/3 of the stomach, without signs of mucosal change, such as ulcers, depressions, or elevation[12,13]. Biopsies and further endoscopic imaging techniques should be actively used when lesions with the above characteristics are encountered under WLI to prevent missed diagnosis.

Early GSRC under magnifying endoscopy combined with narrow-band light imaging

Magnifying endoscopy combined with narrow-band light imaging (ME-NBI) is crucial for diagnosing GC. Endoscopists can capture the microsurface structure (MS) and microvascular architecture (MV) of early GC through NBI without chemical staining[14]. Yao *et al*[14] Invented the "VS classification" based on the MS and MV pattern under ME-NBI and described the surface structure of early gastric cancer (EGC), and set the criteria for EGC that distinguishes it from noncancerous lesions. They found that most carcinomas under ME-NBI have either an irregular microvascular pattern or an irregular microsurface pattern with a demarcation line. Ok *et al*[15] showed that most early GSRC do not have MS, and have a corkscrew MV pattern similar to that of other undifferentiated carcinomas (Figure 1B). Phalanusitthepha *et al*[12] investigated the endoscopic features of SRC using ME-NBI and found that early GSRC has a specific "stretching sign" under NBI. The stretching sign indicates the stretching and dilatation of the irregular gastric glands and microvasculature that cannot be identified in non-SRC lesions (Figure 1C). However, further investigations with a larger sample are required to confirm the accuracy of this result. Meanwhile, ME-NBI can be used in the diagnosis and prediction of GSRC before the histological examination.

Early GSRC under NM-NBI

Although ME-NBI shows a clear demarcation line in most EGC patients that separates the lesion from the surrounding mucosa, studies have confirmed that ME-NBI cannot accurately identify the lateral extent of undifferentiated EGC as in the case of differentiated GC[14,16,17]. Watari *et al*[18] found that non-magnifying NBI (NM-NBI) can also detect early GSRC. GSRCs, including early GSRC have well-defined whitish lesion differentiating them from the surrounding brown mucosa (Figure 1D). Therefore, the NBI combined with magnifying endoscopy may improve the diagnosis of early GSRC and the accurate delineation of such lesions.

EUS FOR EARLY GSRC

EUS is widely used to predict the depth of tumor invasion and LNM in GC patients. However, its efficacy in predicting the invasion depth of EGC is controversial (accuracy 76%-97%)[19,20]. Kuroki *et al*[19] reported that EUS has better sensitivity, specificity, and accuracy in terms of diagnosis of infiltration depth for mucosal tumors than conventional endoscopy. However, they also showed that the accuracy of EUS in diagnosing invasion depth is less comparable for lesions larger than 20 mm, or those with ulcerations[21]. Pei *et al*[20] indicated that the accuracy, sensitivity, and specificity of preoperative EUS in lymph node staging are about 65%-95%, 0.82 and 0.68, respectively. Therefore, further investigations should be conducted to assess the value of EUS in diagnosing invasion depth and LNM in GSRC patients.

ENDOSCOPIC SUBMUCOSAL DISSECTION FOR EARLY GSRC

Early GSRC patients are eligible for ESD

ESD has become the optimal treatment for early GC due to the rapid development of endoscopic diagnosis and treatment. Besides, ESD is less invasive, less costly, and can maintain gastric function in patients[22]. Patients with undifferentiated cancer less than 2 cm, without ulcer, with a negative margin, and negative lymphovascular invasion (LVI) are included as the expanded indication of ESD based on the guidelines for GC treatment of Japanese Gastric Cancer Association (JGCA)[2]. Therefore, the clinicopathological features of the patients should be carefully evaluated before using ESD for the treatment of early GSRC. ESD could be a safe and effective treatment for patients with pure SRC who meet the absolute indications. Besides patients meeting the absolute indications, the LNM risk of intramucosal GSRC lesions between 20 mm and 40 mm is also relatively low[11,23]. The presence of DLS guarantees low LNM risk and prevents submucosal invasion. DLS can only serve as a predictive factor in curability evaluation after ESD since the determination of DLS presence depends on postoperative pathological specimens of ESD. Therefore, future studies should assess whether the presence of DLS can be identified based on preoperative pathology to extend the indication for early GSRC to lesions of 20-40 mm with positive DLS, without ulceration and without lymphovascular invasion. However, surgical gastrectomy and lymphectomy should be performed for early mixed GSRC with poorly differentiated components because of the higher LNM risk. Furthermore, a more strict surveillance strategy should be applied in such patients if they have been treated with ESD to prevent

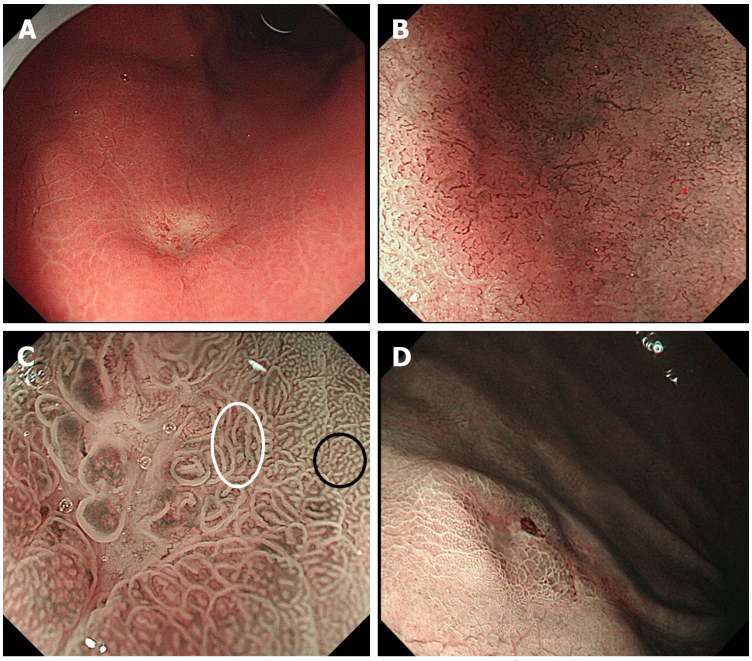

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Figure 1 Endoscopic images of gastric signet ring cell carcinoma. A: Endoscopy with white light imaging revealed a 0-IIc lesion with discoloration at the lesser curvature of the gastric body; B: Magnifying endoscopy combined with narrow-band light imaging revealed the irregular capillaries in a corkscrew pattern of a gastric signet ring cell carcinoma (GSRC) lesion; C: A GSRC demonstrating an elongated or "stretched" gastric gland (white circle) compared to the normal gastric glands (black circle); D: GSRC under Non-magnifying narrow-band imaging showed an isolated, clear area compared to the surrounding mucosa.

local recurrence.

THE CURABILITY OF EARLY GSRC AND ASSOCIATED RISK FACTORS

ESD curative resection (CR) is defined as the complete removal of the lesion with no evidence of tumor invasion on both horizontal and vertical margins of the resected specimen[24]. Studies have found that early GSRC patients undergoing ESD have an unfavorable CR rate. For example, Kim *et al*[25] reported a CR rate of 70.7% for SRC patients, while Bang *et al*[26] detected a CR rate of only 36.4% for patients receiving CR after ESD. Kim *et al*[27] found that tumor size is a key risk factor for non-curative resection (NCR) in ESD patients. Among patients who received NCR, tumors in PDC patients had a higher tendency to infiltrate into the SM layer, creating a higher possibility of a positive vertical margin. In contrast, tumors in most early GSRC patients receiving NCR were positive at the horizontal margin[26].

This phenomenon could be due to the special growth pattern of GSRC. Tubular cervical dysplasia located in the lamina propria of the mucosa is the precursor of GSRC[28]. GSRC grows horizontally in the lamina propria, and its surface is covered by intact gastric foveolar epithelium. Therefore, the actual size of the tumor might be larger than the size measured by endoscopy, even if the boundary of GSRC can be clearly identified. Lee *et al*[10] evaluated the pathological specimens and background mucosa of 86 GSRC patients and found that 75% had a subepithelial growth pattern, especially in lesions with discoloration. Kim *et al*[13] discovered that subepithelial spreading is common in GSRCs surrounded by atrophic mucosa or intestinal metaplasia (IM). This growth pattern can make the tumor look small, leading to inaccurate delineation of the tumor, thus increasing the likelihood of tumor invasion on the horizontal margin and consequently resulting in NCR.

Kim *et al*[29] compared the endoscopic size and pathological size of GSRC patients after ESD and found no statistical difference. However, the pathological size of the tumor was larger than the endoscopic size by 0.2 mm. The results further confirmed that the tumor size was underestimated in more than 30% of total patients due to the subepithelial growth pattern of GSRC. Furthermore, the maximum difference between endoscopic size and pathological size reached 6 mm. Multivariate analysis showed that tumor size and atrophy of the surrounding mucosa are the risk factors for size underestimation.

Therefore, accurate evaluation of tumor size and determination of the resection margin is crucial for complete resection. Besides, four-quadrant biopsies should be performed, followed by ESD if all the biopsies are negative for tumor involvement. ME-NBI and NM-NBI should be used to decide on the size measurement and delineation of GSRC. The horizontal margin of the tumor should be at least 1 cm from the margin of the tumor to reduce the possibility of tumor involvement and improve the curability of

GSRC, especially for patients with atrophic surrounding mucosa and discolored lesions or IM confirmed *via* endoscopic inspection.

MANAGEMENT OF EARLY GSRC AFTER NON-CURATIVE RESECTION

Although gastrectomy is recommended for GSRC patients receiving NCR after ESD, most studies have shown that only a few patients are exposed to LNM after NCR[30]. The curability evaluation algorithm proposed by JGCA is widely used in decision-making after non-curative resection of ESD[2]. Patients are divided into four grades based on their postoperative pathological results (A/B/C1/C2). The GSRC corresponds to eCura B based on the eCura grade, indicating tumors less than 2 cm, without ulcer, negative on both margins, and with negative LVI, and are not recommended for additional surgery. However, eCura C patients with tumors over 2 cm, without ulcer, negative on both margins, and negative LVI require additional treatment strategy if the presence of DLS has been detected through immunohistochemistry. Furthermore, curative gastrectomy can be avoided in DLS-positive patients. Additional gastrectomy and lymph node dissection should be performed if the patients do not have the above conditions. Although Hatta *et al*[31] showed that the eCura system that was designed for risk stratification after ESD can guide EGC patients in choosing the appropriate treatment strategy after NCR, most patients have differentiated GC. However, a multi-center, prospective study is needed to verify the value of eCura system for UDC, especially early GSRC. Therefore, GSRC patients should make careful decision-making when using eCura system after NCR.

PROGNOSIS OF PATIENTS WITH EARLY GSRC AFTER ESD

Lymph node metastasis and associated factors of early GSRC

The indication of ER for undifferentiated carcinoma (UDC) is limited to tumors less than 2 cm, with ulceration (-), and without lymphovascular invasion due to the higher risk of LNM[2,32]. However, LNM risk varies in different subtypes of UDC. Early GSRC has a relatively lower risk of LNM than PDC. Lee *et al*[33] conducted a retrospective analysis of 1837 surgical resected UDC patients and showed that only 2.2% of SRC patients had LNM. No LNM was detected in GSRC patients with intramucosal tumors smaller than 1 cm. Jin *et al*[9] also found that GSRC patients have LNM similar to that of differentiated adenocarcinoma, but much lower than that of PDC patients. Therefore, the expansion of indication for early GSRC in endoscopic resection should be further discussed. Submucosal infiltration, tumor size, ulcer, and lymphovascular invasion are the common independent risk factors for LNM in GSRC patients[34].

LNM in early mixed GSRC

Mixed GSRC is defined as GSRCs that contain less than 50% of the SRC component of the tumor. Notably, low risk of LNM does not apply to the mixed GSRC. Mixed GSRC is associated with increased invasiveness, increased risk of developing submucosal invasion, and larger tumors. Lee *et al*[33] showed that the LNM risk is higher (6.3%) in mixed-type GC than in both PDC and pure GSRC. Chen *et al*[35] divided mixed GC into four categories based on the predominant component of the tumor: differentiated-predominant type mixed with poorly differentiated component (MD-P), poorly differentiated-predominant type mixed with differentiated component (MP-D), differentiated-predominant type mixed with SRC component (MD-S), and poorly differentiated-predominant type mixed with SRC component (MP-S). The results showed that the LNM risk was higher in MP-S (24.5%) than in pure GSRC (11.3). The increased LNM risk is mainly due to the PD component of the tumor. The SRC component does not increase the LNM risk of mixed-type GC. The estimation of LNM risk and treatment strategies should be determined based on the predominant composition of mixed-type GSRC. The LMN risk is higher in MP-S than in other mixed types even if it is meeting the indication for ER, and thus should be carefully handled when deciding the treatment strategy.

Correlation between double-layer structure and LNM in early GSRC

The double-layer structure (DLS) of GSRC is closely related to LNM of GSRC. Takizawa *et al*[36] found that DLS serves as a protective factor against GSRC, indicating that its absence leads to an increased risk of submucosal invasion. Murai *et al*[11] showed that the absence of DLS, ulcers, tumors greater than 20 mm are independent risk factors for LNM in SRC. Yusuke Horiuchi *et al*. reviewed and analyzed the survival data of 1425 patients with undifferentiated cancer who underwent surgery and found that tumors > 40 mm is an independent risk factor of LNM. Besides, there was no risk of LNM in patients with tumors smaller than 40 mm, negative resected margins, without ulcer, and without LVI[23]. Notably, LNM was not detected in early intramucosal GSRC with DLS, even for tumors larger than 20 mm, indicating that the indications of ESD treatment could be expanded for patients with early GSRC. Besides, future studies should include DLS in the stratification of early GSRC patients before ESD and

evaluation of ESD curability for a more personalized management strategy that improves the overall survival and quality of life.

Survival outcomes for early GSRC after ESD

The confirmative trial JCOG1009/1010 in Japan confirmed that the 5-year OS and RFS of patients with undifferentiated cancer after ESD resection are comparable to those of patients who received curative gastrectomy (98.6%, 98.5%)[36]. Ahn *et al*[37] conducted a retrospective study and showed that OS was not significantly different between 328 patients who underwent ESD and 383 patients who underwent surgery. Furthermore, the early GSRC patients had better OS than PDC patients. A propensity score-matched analysis compared the long-term outcomes between ESD and surgery in UDC patients and showed that OS is not significantly different between early GSRC patients undergoing ESD and those undergoing surgery. JGCA later changed the expanded indications into the absolute indications of ESD due to the satisfying prognostic outcome of patients who received ESD[35]. Therefore, ESD is a reliable and safe treatment for early GSRC patients who meets the expanded indications.

CONCLUSION

Early GSRC is characterized by unique biological behavior and favorable prognosis. It appears as flat or depressed lesions with discoloration under WLI, NM-NBI, and ME-NBI, which could further consolidate the diagnosis and delineation of the tumor. The depth of tumor invasion and LNM can be predicted using EUS. Pure GSRC lesions that meet the expanded indications of ESD are associated with a low risk of submucosal invasion and LNM, thus have desirable prognostic outcomes. As a result, ESD is the optimal treatment for such lesions instead of traditional surgical resection. However, tumor size may be underestimated due to the subepithelial spreading of SRC, thus limiting curative resection. Therefore, the preoperative biopsies in the surrounding mucosa of the lesion should be used to help determine the safe resection margin of the tumor. The eCura grade could serve as a reliable reference for the management of patients with non-curable resection after ESD. Particularly, early mixed GSRC or DLS-negative GSRC should be closely followed-up to prevent LNM and local recurrence. Additionally, ESD should be considered for tumors larger than 20 mm if an effective method can be developed to predict the presence of DLS before ESD.

FOOTNOTES

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MINIREVIEWS

Endoscopic resection of non-ampullary duodenal adenomas: Is cold snaring the promised land?

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Abstract

Due to the high risk of morbidity and mortality associated with surgical resection in this tract, endoscopic resection (ER) has taken the place of surgical resection as the first line treatment for non-ampullary duodenal adenomas. However, due to the anatomical characteristics of this area, which enhance the risk of post-ER problems, ER in the duodenum is particularly difficult. Due to a lack of data, no ER technique for superficial non-ampullary duodenal epithelial tumours (SNADETs) has yet been backed by strong, high-quality evidence; yet, traditional hot snare-based techniques are still regarded as the standard treatment. Despite having a favourable efficiency profile, adverse events during duodenal hot snare polypectomy (HSP) and hot endoscopic mucosal resection, such as delayed bleeding and perforation, have been reported to be frequent. These events are primarily caused by electrocautery-induced damage. Thus, ER techniques with a better safety profile are needed to overcome these shortcomings. Cold snare polypectomy, which has already been shown as a safer, equally effective procedure compared to HSP for treatment of small colorectal polyps, is being increasingly evaluated as a potential therapeutic option for non-ampullary

duodenal adenomas. The aim of this review is to report and discuss the early outcomes of the first experiences with cold snaring for SNADETs.

Key Words: Non-ampullary duodenal adenomas; Endoscopic resection; Cold snare polypectomy; Hot snare polypectomy; Safety; Efficacy

Core Tip: A high risk of adverse events has been associated with endoscopic resection of non-ampullary duodenal adenomas. As cold snare polypectomy demonstrated a better safety profile and a similar efficacy comparing with conventional hot polypectomy in the colon, it has been increasingly considered also in the duodenum over the very last few years. Goal of this review is to summarize efficiency and safety outcomes of cold resection as a treatment for non-ampullary duodenal adenomas.

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INTRODUCTION

With a relatively low incidence, non-ampullary duodenal adenomas make up a small portion of gastrointestinal (GI) tumors[1-3]. In about 40% of instances, they could be spontaneous or related to familial hereditary diseases such Familial Adenomatous Polyposis (FAP)[4,5]. Incidence of superficial non-ampullary duodenal epithelial tumours (SNADETs) has increased[6] recently due to an increase in endoscopies conducted on the general population and a considerable improvement in endoscopic equipment that have facilitated the identification and characterization of such lesions[7,8]. As duodenal adenoma represents the precursor of duodenal carcinoma similarly to the colorectal adenoma-carcinoma sequence, an effective treatment is required[9,10]. However, since surgical options are too invasive and significantly associated with high rates of morbidity and mortality[11-13], endoscopic resection (ER) has become the preferred approach for SNADETs[14]. However, due to the lack of evidence and the unique properties of the duodenum, which is more susceptible to complications than other parts of the GI tract, the optimum resection approach has been controversial at best[15].

Nowadays, hot snare polypectomy (HSP) and conventional endoscopic mucosal resection (EMR) have been shown highly effective and are considered the standard choices for non-ampullary duodenal adenomas[16]. However, a considerable amount of electrocautery-related complications has been reported with major adverse events mainly secondary to thermal injury[15]. Thus, cold snaring, which has been shown equally effective and safer than hot snaring for removal of colorectal lesions[17-20], has been increasingly considered for SNADETs over the last few years. In this review we summarize efficacy and safety outcomes of cold approach for non-ampullary duodenal adenomas.

CURRENT STATUS AND ISSUES OF ER FOR SNADETS

ER is currently regarded as the gold standard treatment of SNADETs as it is a more conservative approach than surgery, preserving patients' anatomy and quality of life[14]. Although a well-established first-line ER technique for SNADETs has not been established by robust high-quality evidence, hot snare techniques are conventionally regarded as the standard of care for these lesions[16].

Nevertheless, more recent retrospective studies reported a delayed bleeding rate of about 4%-17%, while perforations occurred in about 2%-7% of cases[1,15,21-25], being these risk increased with the size of the lesion. Notably, recently Probst *et al*[26] carried out the largest prospective trial on hot EMR for SNADETs enrolling 110 patients and 118 duodenal lesions (mean size 15 mm, range 4–70 mm). Authors reported an excellent complete resection rate (94.1%)[26]. However, complications and major complications had an incidence of 22.9% and 15.3%, respectively, with a procedure-related death rate of 1.7%; off note, the most common adverse events were delayed bleeding (18.6%) and perforation (4.2%)[26].

These consequences are typical of HSP and conventional EMR and are linked to the damage brought on by electrocautery. Additionally, ER in the duodenum is more difficult and potentially risky than in

the other GI tracts due to physical factors. The duodenum is heavily vascularized, and the scope's inadequate capacity to manoeuvre in this tight space hinders a proper approach to the lesion and, consequently, the viability of resection. In addition, the duodenal wall is extremely thin and can be easily perforated. Furthermore, bile acid and pancreatic juice have an impact on the post-ER defect. Compared to hot EMR of lesions in the other GI tracts, duodenal hot EMR is more likely to have post-procedural bleeding and perforation due to these characteristics[27].

Preventive measures to minimize these complications after duodenal EMR have been evaluated. Prophylactic argon plasma coagulation (APC) of the resection bed has been shown to reduce the risk of delayed bleeding in a prospective study enrolling 61 duodenal lesions, although statistical significance was not achieved due to the small sample size (P = 0.31); moreover, as one of the six patients treated with APC suffered from delayed perforation, the safety of this approach is questionable[28]. A retrospective study, including 37 duodenal adenomas treated by hot EMR, reported delayed bleeding rate was significantly lower in patients treated by prophylactic clipping than in the no prophylaxis group (0% *vs* 21.7%, P < 0.05)[29]. Additionally, post-EMR prophylactic clipping was associated with a significant decrease in delayed bleeding rate (from 32% to 7%, P < 0.004) in another retrospective study encompassing 121 duodenal adenomas[14]. Furthermore, in a prospective study the systematic preventive application of hemostatic clips after underwater EMR of 31 duodenal lesions resulted in the absence of major complications[30]. However, despite these encouraging results, evidence is still very limited and controversial. In the retrospective study by Tomizawa and Ginsberg[15] no decrease in delayed bleeding rate after prophylactic clip placement was observed[15]. Similarly, in the large prospective study by Probst *et al*[26], delayed bleeding rate was not reduced by endoscopic prophylaxis [26]. Moreover, the unneglectable perforation risk due to clips application, the costs, the inefficacy of a partial closure and the unfeasibility of a complete closure for mucosal defects larger than 20 mm remarkably hinder the wide implementation of this option in clinical practice.

Thus, to overcome these drawbacks, in the last few years alternative resectional techniques with a better safety and cost-effectiveness profile have been increasingly proposed for ER of duodenal lesions.

COLD SNARE POLYPECTOMY

Tappero *et al*[31] first described cold snare polypectomy (CSP) for excision of colorectal tumors[31]. CSP is an easy and safe endoscopic procedure in which a lesion is captured and resected using only a snare without electrical current. Instead, if a submucosal injection is used to better visualize and capture the polyp, in case of large flat lesions or in presence of unclear margins, the resection technique is named cold EMR.

CSP has proved to be a valuable ER method for colorectal lesions. A prospective multicenter trial by Repici *et al*[17] enrolling 1015 subcentimetric polyps in 823 patients, showed CSP had a very low rate of post-polypectomy bleeding (2.2%), which was easily managed with endoscopic hemostasis in all cases [17]. A multicenter randomized controlled study compared the outcomes of CSP with HSP for removal of 796 sessile adenomatous colorectal polyps that were 4-9 mm in size. CSP and HSP achieved a similar complete resection rate (98.2% and 97.4%, respectively)[18]. Moreover, a systematic review and meta-analysis including 32 trials, reported that the pooled incomplete resection rate of CSP and HSP for colorectal polyps 1 to 10 mm was 17.3% [95% confidence intervals (CI): 14.3–20.3%] and 14.2% (95%CI: 14.3–20.3%), respectively, with no significant difference[32]. Furthermore, Sidhu *et al*[33] carried out a multicenter randomized trial enrolling 660 patients who underwent CSP for small (5-9 mm) colorectal polyps. An excellent incomplete resection rate was revealed (1.5%)[33].

In terms of safety profile, Yamashina *et al*[19] observed in a retrospective cohort of 538 patients with colorectal polyps of 2-11 mm in size a significantly higher delayed bleeding rate after HSP in comparison with CSP (0.02% *vs* 0%, P = 0.04)[19]. Further, a large multicenter randomized controlled trial, recruiting 4270 patients, found that HSP arm had a significantly higher delayed bleeding rate than CSP arm (1.5% *vs* 0.4%, P < 0.001)[34]. Moreover, a prospective randomized study comparing HSP and CSP for polyps up to 10 mm in 70 anticoagulated patients proved a significantly lower delayed bleeding rate in the CSP arm (0% *vs* 14%, P = 0.27)[35].

A systematic review and meta-analysis, encompassing 8 trials, confirmed a comparable complete resection rate between HSP (95%) and CSP (94%), but demonstrated HSP was associated with significantly longer colonoscopy and polypectomy time (mean difference: 7.1 min and 30.9 s, respectively). A higher delayed bleeding rate was reported in HSP group, although statistically significance was not achieved[36].

According to the established excellent efficacy and safety profile, CSP is currently regarded as the standard treatment for the resection of nonpedunculated colorectal polyps of size < 10 mm[37-39]. Additionally, the potential expanded application of cold snare resection for nonpedunculated polyps larger than 10 mm has increasingly raised attention. A recent retrospective study compared outcomes of piecemeal CSP with piecemeal hot EMR for removal of large (≥ 20 mm) sessile serrated lesions assessing 562 lesions in 474 patients[40]. Authors reported comparable technical success and recurrence rates for both techniques; while no adverse event was reported in the CSP group, deep mural injury and delayed

bleeding occurred in 3.4% and 5.1% of lesions treated by hot EMR, respectively[40]. Moreover, a systematic review and meta-analysis by Thoguluva Chandrasekar *et al*[41] evaluating outcomes of endoscopic removal of 1137 sessile serrated lesions that were > 10 mm in size, found cold EMR had similar rates of recurrence, but significantly lower rates of delayed bleeding than conventional hot EMR (0% *vs* 2.3%; $P = 0.03$)[41]. Another systematic review and meta-analysis by the same author evaluated outcomes of cold snare resection of polyps larger than 10 mm, including 8 trials. The overall adverse event rate was 1.1% with a delayed bleeding rate of 0.5%; no perforations were found. Authors reported a complete resection rate of 99.3%, with an overall recurrence rate of 4.1% at follow-up colonoscopy[42]. Furthermore, a very recent randomized multicenter controlled trial, including 286 colorectal polyps of 6-15 mm, reported cold approach was safer, less time-consuming and had lower incomplete resection rates than hot snare techniques[20].

Therefore, even though larger randomized controlled comparative trials are still required for validation, cold snare techniques are now widely acknowledged to be just as effective as hot snare techniques for larger colorectal polyps while carrying a significantly lower risk of delayed bleeding and perforation because electrocautery is not used.

CSP IN DUODENUM

Given the remarkable achievements of cold snaring for colorectal lesions and the lower rate of complications compared with hot techniques, the cold approach may also be valuable for ER in duodenum, where the risk of perforation and delayed bleeding is considerable. Although current guidelines suggest CSP for small (< 6 mm) duodenal lesions[16], this recommendation is mostly derived from studies on diminutive colorectal polyps[37], as data on CSP for SNADETs were very limited. To address these drawbacks, over the very last few years, several studies have been carried out to assess efficacy and safety of cold resection as a novel therapeutic technique for SNADETs (Table 1).

In a case series of 15 patients, who underwent cold EMR for duodenal lesions ranging from 10 to 60 mm in size (mean size was 24 mm), no perforation and post-polypectomy syndrome were reported and only one case of delayed bleeding occurred in a patient who was on warfarin[43].

A retrospective single center pilot feasibility study by Hamada *et al*[44] evaluated CSP for small multiple duodenal adenomas in 4 patients with FAP. 126 lesions ranging from 2 to 16 mm were removed with CSP without any complications[44]. Further, the same group carried out a single center prospective study to investigate the safety of CSP in an analogue cohort. 10 patients with FAP underwent CSP with removal of 332 duodenal adenomas; most of these lesions were ≤ 10 mm[45]. No adverse event was reported; one case of intra-procedural bleeding occurred and was easily controlled with hemoclips[45].

However, these above mentioned studies lacked efficacy outcomes and follow-up endoscopy data, such as adenoma recurrence rates.

Maruoka *et al*[46] performed a single center prospective study to assess the safety and efficacy of CSP for sporadic SNADETs. In 22 patients, 25 duodenal adenomas that had a median size of 4.3 mm (range was 2–6 mm), were resected using CSP[46]. No adverse event was reported. The *en bloc* and R0 resection rates were 96% and 68.0%, respectively, with no evidence of recurrence at 3 mo follow-up endoscopy [46].

A study with similar design and goals was later carried out by Takizawa *et al*[47] enrolling 21 patients. CSP was attempted on 21 sporadic SNADETs ranging from 3 to 10 mm (median size 8 mm) [47]. CSP was completed in 18 lesions (86%), while three SNADETs could not entirely be removed with CSP and, thus, were resected using conventional HSP. Among the group with complete CSP, the *en bloc* resection rate was 94%. Only 1 recurrent adenoma was detected at follow-up endoscopy 3 mo after CSP. Neither intra-procedural nor delayed complications were observed[47].

On the basis of the increasing evidence of good cold snaring outcomes for large colorectal polyps, Dang *et al*[48] conducted a single center retrospective study for assessing efficacy and safety of cold EMR for small bowel adenomas ≥ 10 mm; 39 adenomatous lesions (37 duodenal, 2 jejunal) that had a mean size of 26.5 mm (range 10-70 mm) were removed with piecemeal cold EMR[48]. Follow-up endoscopy showed an adenoma recurrence rate of 46% (18/39), which was significantly associated with polyp size. Regarding safety, 12% of patients suffered from cold EMR-related adverse events; the only case of delayed bleeding (2.6%) occurred 11 days after the procedure in a patient who was in warfarin and had an international normalized ratio of 4.6 and it was easily managed with hemoclips. 3 post-treatment strictures (7.7%) were reported. All these patients had lesions ≥ 30 mm involving more than half of the small-bowel circumference; when symptomatic, the strictures were treated successfully with endoscopic dilation[48].

Furthermore, a multicenter retrospective comparative study by Repici *et al*[49] assessed efficacy and safety outcomes of cold EMR in comparison with conventional hot EMR for removal of large (≥ 20 mm) sporadic duodenal adenomas. Data from 33 consecutive patients, who were treated with cold EMR, were analyzed and compared with an historical cohort of 101 patients who underwent hot EMR[49]; mean lesion size for cold and hot EMR groups was 31.5 mm and 37.7 mm, respectively. The *en bloc*

Table 1 Cold snaring for superficial non-ampullary duodenal epithelial tumours; study outcomes

Ref.	Center	Design	Group	Patients (*n*)	Age (mean)	Gender (M)	Polyposis (*n*)	Lesions (*n*)	Size (mean, mm)	En-bloc (*n*)	Recurrence (*n*)	Follow up (mean, months)	Adverse events (*n*)	Delayed bleeding (*n*)	Perforation (*n*)	Strictures (*n*)
Choksi *et al* [43], 2015	Single	Retrospective	Cold	15	64	9	NA	15	24	NA	NA	0.5	1	1	0	0
Hamada *et al* [44], 2016	Single	Retrospective	Cold	4	45	2	4	126	NA	NA	NA	2.75	0	0	0	0
Maruoka *et al* [46], 2017	Single	Prospective	Cold	22	64.7	16	0	25	4.3	24	0	3	0	0	0	0
Hamada *et al* [45], 2018	Single	Prospective	Cold	10	39.3	6	10	332	NA	328	NA	NA	0	0	0	0
Repici *et al* [49], 2022	Multi	Retrospective	Cold	33	63	18	0	33	31.5	0	4	3.8	0	0	0	0
			Hot	101	66.4	42	0	101	37.7	9	21	13	26	17	6	2
Trivedi *et al* [50], 2022	Multi	Retrospective	Cold	41	72	28	0	46	12	22	7	5.8	0	0	0	0
			Hot	69	68	34	0	74	15	35	7	5.8	7	6	1	0
Takizawa *et al* [47], 2022	Single	Prospective	Cold	21	NA	16	0	21	NA	17	1	3	0	0	0	0
Dang *et al*[48], 2022	Single	Retrospective	Cold	39	66.8	12	NA	39	26.5	0	18	5.09	5	1	0	3
Okimoto *et al* [51], 2022	Single	Retrospective	Cold	29	66.6	24	0	37	4.4	36	1	39.2	0	0	0	0

NA: Not available.

resection rate was 8.9% for hot EMR, while all lesions in the cold EMR group were removed piecemeal. Both groups achieved similar technical success rates (94% and 89.1% for cold and hot EMR, respectively, $P = 0.42$). At the first follow-up endoscopy (mean follow-up time was 3.8 mo), adenoma recurrence rates were comparable (12.1% *vs* 20.8% for cold and hot EMR, respectively, $P = 0.27$)[49]. Instead, procedural mean time was significantly lower for cold EMR (48 min *vs* 96.9 min, $P < 0.01$). Of note, no intra-procedural or delayed adverse events were reported in the cold EMR group. Whereas, in the hot EMR cohort 17 intra-procedural major complications (16.8%), including 4 perforations and 13 cases of severe bleeding, were reported. Moreover, 26 post-procedural major complications (25.7%) occurred, encompassing 17 cases of delayed bleeding and 6 perforations with 1 procedure-related death[49].

Another multicenter retrospective comparative study, carried out by Trivedi *et al*[50], compared efficacy and safety of CSP with HSP for treatment of sporadic SNADETs; of the 120 adenomatous lesions included, 74 were treated by HSP and 46 by CSP[50]. All polyps were ≥ 5 mm with a similar

mean size (12 and 15 mm for the cold and the hot group, respectively, $P = 0.27$). The *en bloc* resection rate was comparable (47.8% *vs* 47.3% for CSP and HSP, respectively). Of the 110 patients enrolled, a follow-up endoscopy 174 days after polypectomy was available only for 54 patients (49.1%); 19 in the CSP group (35.2%) and 35 in the HSP group (64.8%). The two techniques did not differ significantly in recurrent adenoma rates (20% and 36.8% in HSP and CSP group, respectively, $P = 0.18$), which were statistically correlated with polyp size[50]. While intra-procedural bleeding was similar between the two groups, 7 delayed major complications were reported after HSP (10.1%) and none after CSP. These adverse events included 6 cases of delayed bleeding and 1 perforation[50].

While no long-term follow-up data were available for these above reported studies, Okimoto *et al*[51] performed a single center retrospective study to evaluate long-term outcomes of CSP for SNADETs. 29 patients underwent CSP for 37 sporadic duodenal adenomatous lesions; mean size was 4.4 mm[51]. The *en bloc* and R0 resection rates were 97.3% and 70.3%, respectively. The mean follow-up time was 39.2 mo (range 3-64 mo). The observation period was ≥ 12 mo after CSP for almost all lesions (94.6%). During this follow-up period, only one adenoma recurrence (2.7%) was detected 12 mo after CSP; this recurrent adenoma was successfully resected with CSP. The relapse free survival rate per lesion after 12 mo was 97.1%. Neither delayed bleeding no perforation was reported and no procedure-related death occurred [51].

CURRENT STATE OF ART

The use of electrocautery-based snare techniques is widely regarded as the standard of care for resection of duodenal polyps ≥ 6 mm[16]. This assumption is based on the rationale that HSP provides transection through thick tissue and prevents immediate bleeding through instant vascular coagulation of small arterial and venous branches. Moreover, as electrocautery also allows for the *en bloc* resection of larger polyps and ablates residual dysplastic tissue, it is believed to reduce the risk of recurrent adenoma. However, the use of electrosurgical current also induces submucosal and deeper thermal injury to the bowel wall and, thus, can result in adverse events such as perforation, postpolypectomy syndrome, and delayed bleeding due to coagulum sloughing off exposing an incompletely coagulated submucosal artery[15]. Furthermore, delayed bleeding and perforation after HSP occur more frequently in duodenum in comparison to other bowel tracts according to available data in literature[27]. Indeed, the duodenum has a thin, highly vascularized wall and a high concentration of digestive secretions such as pancreatic enzymes and bile. Particularly, in a recent prospective study delayed bleeding and perforation occurred in 18.6% and 4.2%, respectively, of cases after duodenal hot EMR[26].

CSP does not require use of electrosurgical current and has been demonstrated safer than conventional HSP, avoiding deep thermal injury. Due to a similar efficacy and a better safety profile than HSP [18,19], CSP has become the gold standard treatment for nonpedunculated colorectal polyps < 10 mm [37-39]. Furthermore, CSP and cold EMR are being recently extended to larger nonpedunculated colonic polyps, showing comparable efficacy outcomes with cautery-based techniques but with a significant safety advantage[20,40,41].

Nevertheless, some concerns have been raised for this approach. Cold snare techniques had been historically regarded as inferior to hot snare methods for curability. Indeed, HSP allows an *en bloc* resection for larger polyps than CSP and the absence of electrosurgical current does not provide eradication of neoplastic tissue around the snare. Moreover, it has been shown that CSP has a lower depth of resection and higher rates of incomplete resection than conventional polypectomy for colorectal polyps[52,53]. However, a recent prospective randomized controlled trial reported CSP has enough resection width and depth to enable complete polyp resection[54]. Furthermore, assessment of complete histologic resection, and thereby, curability is often challenging after CSP. In fact, specimen's margins can be damaged by suction through the operative channel or are not visible due to lack of thermal effect. Thus, even if the polyp was pathologically judged to be completely resected, an adenomatous component may remain and vice versa. Since assessment of complete histologic resection is tough for pathologists, it is believed that the most reliable efficiency outcome after CSP is the adenoma recurrence rate at follow-up endoscopy[55].

In the light of his safety superiority over conventional hot techniques for resection of colorectal polyps, in the very last few years cold snaring approach has been increasingly regarded as a potential optimal endoscopic treatment for duodenal adenomas (Figure 1).

The above-mentioned in-depth research on the use of cold snaring techniques for SNADETs substantially support the approach's high level of safety by demonstrating a very low occurrence of negative outcomes. Dang *et al*[48], indicated a noteworthy rate of complications (12%) following cold EMR. The sole patient to experience delayed bleeding while taking warfarin had an INR of 4.6; in contrast, three post-treatment strictures formed following the removal of polyps that were bigger than 30 mm in diameter and covered more than half of the wall circumference. Notably, both comparative trials reported a significant higher adverse event rates after hot snaring comparing with cold snaring techniques; most frequent complications were delayed bleeding and perforation, as expected. Indeed, immediate bleeding is common after CSP as the result of small capillary bleeding and venous oozing,

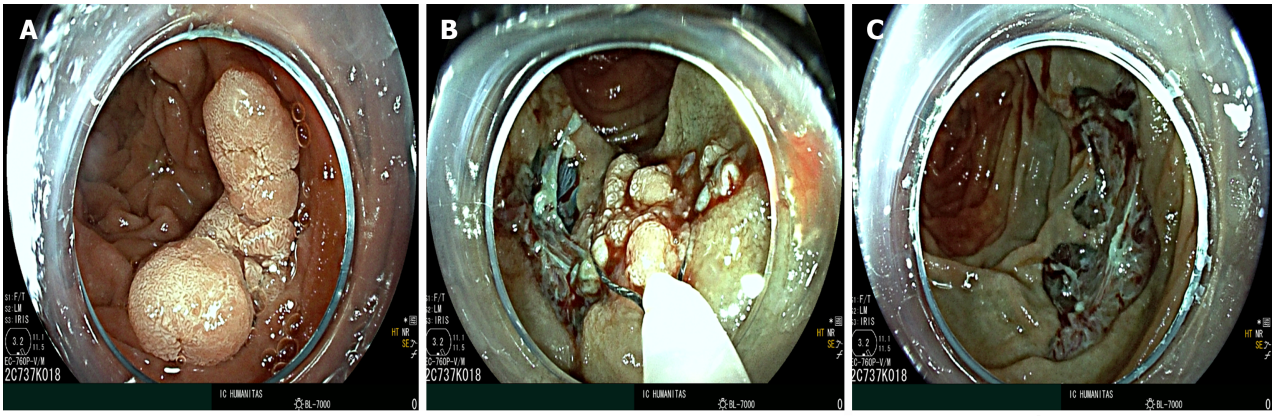

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Figure 1 Cold snare piecemeal resection of a large non-ampullary duodenal adenoma. A: Assessment of the lesion; B: Piecemeal cold snare polypectomy; C: Post-polypectomy scar evaluation.

but resolves spontaneously in almost all patients and it is not considered a real adverse event. Whereas, the effect of cautery and coagulation used during HSP reduces immediate bleeding providing a false feeling of security, but increases the risk of more dangerous delayed bleeding from sloughing coagulated eschar.

As far as the efficiency outcomes are concerned, findings of these studies on cold approach for SNADETs are very amazing. In fact, adenoma recurrence rates were mostly low. Additionally, cold snaring and hot snaring techniques did not significantly differ in recurrence rates in both comparative trials. Furthermore, the only study reporting long-term follow-up data showed a very low incidence of recurrence. Notably, recurrence rates were not statistically associated with resection technique, but with polyp size. These promising results could increase the use of cold approach, which has been historically judged as less curative than hot snare techniques. However, these preliminary data together with the remarkable recurrence rate observed in the largest retrospective study on duodenal hot EMR[15] may even challenge the superiority of hot snare techniques over cold resection in terms of efficacy.

Since delayed bleeding and perforation are linked to hospital stays, blood transfusions, and more invasive operations, CSP can result in economic savings in addition to reducing adverse events and morbidity. Furthermore, due to low rate of delayed bleeding and perforation, the use of cold snare does not necessitate prophylactic clipping of the mucosal defect, which is a costly and time-consuming measure. As a result, a recent study found that treating big sessile colorectal polyps with cold EMR instead of hot EMR resulted in a $955 per case cost savings[56].

Nevertheless, despite the fact that these results point to a safety benefit of CSP *vs* HSP with comparable adenoma eradication success, these studies were influenced by a number of limitations that make it difficult to draw firm conclusions.

First off, the majority were retrospective studies with a single center and a limited patient population. Furthermore, while follow-up data was available, it was almost typically only for a few months. The likelihood of underreporting problems rises in the absence of long-term follow-up results; particularly, the lack of trials with longer follow-up periods may significantly affect those recurrence rates reported. Additionally, the nature of retrospective studies might distort efficacy findings, which can be impacted by the initial patient selection for CSP. Additionally, cold snare resections were mainly performed by expert endoscopists in polyp resection at tertiary centers. Whether these findings can be extended to less experienced endoscopists in various environments have to be shown.

Thus, waiting for further randomized studies comparing cold snare technique with hot snare methods, endoscopists may strongly consider CSP for treatment of SNADETs, especially for subjects at increased risk of delayed bleeding or frail patients, in whom surgery would be hardly tolerated in case of perforation.

CONCLUSION

Overall, despite preliminary, the efficacy and safety outcomes reported by these studies were highly promising and show that cold snaring can lead to significant safety and financial advantages over hot snare-based techniques for treatment of SNADETs, without an impairment in terms of curability. However, as cold resection can be considered a real paradigm shift from the standard of care for duodenal adenomas, larger multicenter prospective randomized comparative trials with long-term follow up are required to better assess safety and efficacy outcomes of this approach and compare to conventional hot snare options.

The cold snare technique is likely to overtake other methods as the preferred method for SNADETs in the near future as we are currently in standpoint revolution where the safety and effectiveness of CSP and cold EMR are being increasingly demonstrated for both colonic and duodenal polyps.

FOOTNOTES

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MINIREVIEWS

Two traction methods that can facilitate esophageal endoscopic submucosal dissection

Mitsuru Nagata

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Abstract

Different traction devices that can provide a visual field and attain appropriate tension at the dissection plane during endoscopic submucosal dissection (ESD) have been developed. Clip-with-line (CWL) is a classic traction device that can offer per-oral traction toward the direction where the line is drawn. A multicenter randomized controlled trial (CONNECT-E trial) comparing the conventional ESD and CWL-assisted ESD (CWL-ESD) for large esophageal tumors was conducted in Japan. This study showed that CWL-ESD was associated with a shorter procedure time (defined as the time from initiating submucosal injection to completing tumor removal) without increasing the risk of adverse events. Multivariate analysis revealed that whole-circumferential lesion and abdominal esophageal lesion were independent risk factors for technical difficulties, which were defined as a procedure time of > 120 min, perforation, piecemeal resection, inadvertent incision (any accidental incision caused by the electrosurgical knife within the marked area), or handover to another operator. Therefore, techniques other than CWL should be considered for these lesions. Several studies have shown the usefulness of endoscopic submucosal tunnel dissection (ESTD) for such lesions. A randomized controlled trial conducted at five Chinese institutions showed that compared with the conventional ESD, ESTD had a significantly reduced median procedure time for lesions covering ≥ 1/2 of the esophageal circumference. In addition, a propensity score matching analysis conducted at a single Chinese institution showed that compared with the conventional ESD, ESTD had a shorter mean resection time for lesions at the esophagogastric junction. With the appropriate use of CWL-ESD and ESTD, esophageal ESD can be performed more efficiently and safely. Moreover, the combination of these two methods may be effective.

Key Words: Endoscopic submucosal dissection; Traction; Clip-with-line; Endoscopic submucosal tunnel dissection

Core Tip: Clip-with-line (CWL) was developed to overcome the challenges faced in endoscopic submucosal dissection (ESD). A multicenter randomized controlled trial comparing the conventional ESD and CWL-assisted ESD (CWL-ESD) for large esophageal tumors was conducted in Japan. Results showed that CWL-ESD had a shorter procedure time without increasing the risk of adverse events. However, this study revealed that there were issues with the use of CWL-ESD for whole-circumferential and abdominal esophageal lesions. Endoscopic submucosal tunnel dissection may be a promising option for treating these lesions.

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INTRODUCTION

Endoscopic submucosal dissection (ESD) can allow the *en bloc* resection of superficial gastrointestinal neoplasms, thereby obtaining a reliable pathological diagnosis and decreasing the risk of recurrence. However, ESD is a challenging procedure, and a long procedure time and perforation remain an issue. Unlike surgeons, endoscopists cannot use their hands to obtain traction for lesions in the gastrointestinal tract, which results in a poor visual field and insufficient tension in the dissection plane in ESD. Clip-with-line (CWL) is among the most classical traction devices developed to address these issues. A single-center randomized controlled trial (RCT) reported the usefulness of CWL-assisted ESD (CWL-ESD) *vs* the conventional ESD for esophageal lesions. Meanwhile, this study had some limitations. That is, it has a small sample size and few operators, and it included patients with a small lesion[1].

CONNECT-E TRIAL

The CONNECT-E trial was the first multicenter RCT conducted at seven institutions in Japan. It aimed to compare the conventional ESD and traction-assisted ESD for treating large esophageal cancers[2]. In this study, CWL was used (Figure 1), and board-certified endoscopists who performed ≥ 40 gastric ESD procedures were included as operators. Patients endoscopically diagnosed with esophageal squamous cell carcinoma or basal cell carcinoma with a tumor diameter ≥ 20 mm and clinically diagnosed with intramucosal cancer (cT1a) or slightly invasive submucosal cancer (cT1b-SM1) were randomly assigned to the conventional ESD (n = 116) and CWL-ESD (n = 116) groups. Due to prolonged ESD (procedure time of > 120 min) or perforation, six patients in the conventional ESD group required conversion to CWL-ESD.

Although a statistical comparison of the baseline characteristics of the patients, including age, sex, tumor diameter, tumor location, and macroscopic type, was not performed, the characteristics of all patients were well balanced. The median tumor diameter was 30 mm in the conventional ESD and CWL-ESD groups. There were no significant differences in histologic depth of the tumor between the groups. The median ESD procedure time (primary endpoint; defined as the time from initiating the submucosal injection to completing tumor removal) of the CWL-ESD group was significantly shorter than that of the conventional ESD group (44.5 *vs* 60.5 min, $P < 0.001$). Although not significant, the rate of perforation was considerably lower in the CWL-ESD group (0% *vs* 4.3%, $P = 0.060$). Hence, CWL can secure the visual field and prevent blind submucosal dissection. The conventional ESD group required handover to another operator more frequently than the CWL-ESD group (6.0% *vs* 0.9%, $P = 0.066$).

In the subgroup analysis, the procedure time of the CWL-ESD group was significantly shorter than that of the conventional ESD group for lesions occupying < 50% and ≥ 50% but < 100%. However, it was not significant for lesions covering the entire circumference.

Approximately 16.4% of patients in the CWL-ESD group had CWL slip-off during ESD, and traction-related damage to the specimen was observed in 1.7% of patients. However, there were no significant differences in the rate of horizontal margin involvement (10.3% *vs* 6.9%, $P = 0.484$) and R0 resection rate (87.2% *vs* 91.4%, $P = 0.30$) between the conventional ESD and CWL-ESD groups.

Further, the CONNECT-E trial evaluated the risk factors of technical difficulties, which were defined as a procedure time of > 120 min, perforation, piecemeal resection, inadvertent incision (any accidental incision caused by the electrosurgical knife within the marked area), or handover to another operator. Multivariate analysis revealed that lesions occupying the full circumference of the esophagus and those

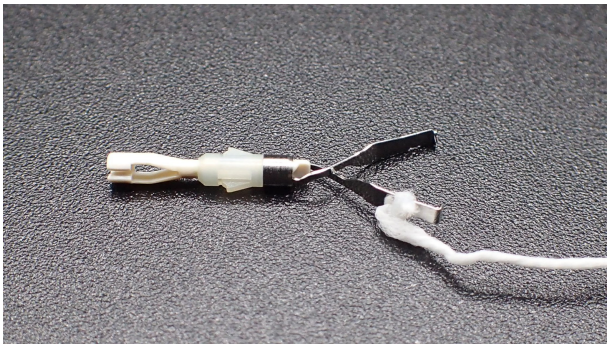

Figure 1 A clip-with-line was made by tying a commercially available dental floss to the arm section of the hemoclip. Reprinted from Mitsuru Nagata. Optimal traction direction in traction-assisted gastric endoscopic submucosal dissection. *World J Gastrointest Endosc* 2022; 14: 667-671. Copyright © Mitsuru Nagata 2022. Published by Baishideng Publishing Group Inc[10].

located at the abdominal esophagus were independent risk factors for technical difficulties. Therefore, techniques other than CWL should be considered for these lesions.

ENDOSCOPIC SUBMUCOSAL TUNNEL DISSECTION–A PROMISING OPTION FOR MANAGING CHALLENGING ESOPHAGEAL LESIONS

Endoscopic submucosal tunnel dissection (ESTD) is a traction method that does not use a specific device [3,4], as it utilizes the mucosal tension for traction.

In ESTD, a mucosal incision is first made on the distal side and then on the proximal side of the lesion to enter into the submucosal layer. Next, the submucosal layer under the lesion is dissected from the proximal to the distal side, creating a submucosal tunnel. During submucosal dissection, the lateral position of mucosa prevents the lesion from falling distally. The endoscope inside the tunnel space thrusts the lesion, offering traction for the dissection plane and facilitating submucosal dissection. After creating a submucosal tunnel, the mucosa and submucosa around the tunnel space are dissected to attain *en bloc* resection. It was found to be useful for lesions covering the esophageal lumen and those located at the esophagogastric junction (EGJ). An RCT conducted at five Chinese institutions showed that compared with the conventional ESD, ESTD was significantly associated with a reduced median procedure time for lesions covering ≥ 1/2 of the esophageal circumference (85.5 *vs* 56.0 min, $P < 0.001$) [5]. In addition, muscular injury was less frequent in ESTD than in the conventional ESD (18.4% *vs* 38.2%, $P = 0.007$). In ESTD, the submucosal tunnel can hold the endoscope tip, thereby stabilizing the endoscope and facilitating a parallel approach to the muscularis layer. Moreover, the endoscope can provide sufficient tension at the dissection plane by pushing up the lesion from inside the submucosal tunnel by itself. ESTD had several advantages. That is, it may have a shorter procedure time and a lower muscle injury rate. Further, all operators in this study performed > 200 ESD procedures, and ESTD is different from the conventional ESD. Nevertheless, further studies should be performed to evaluate the feasibility of ESTD by low-experienced operators and its usefulness for whole-circumferential lesions.

A propensity score matching analysis conducted at a single Chinese institution showed that ESTD had a shorter mean resection time (71.59 *vs* 111.00 min; $P = 0.008$) for superficial neoplasms at the EGJ compared with the conventional ESD. Meanwhile, none of the patients who underwent ESTD had complications[6]. The EGJ and the abdominal esophagus are not similar. Nevertheless, ESTD may be a promising method for abdominal esophageal lesions. This study had limitations. For example, it had a small sample size ($n = 17$ for each group) and few operators (only two experienced endoscopists who had completed > 100 ESD procedures). Hence, a large-scale study must be performed to evaluate the feasibility of ESTD for abdominal esophageal lesions.

A recent study showed the efficacy of the combined use of traction devices and the pocket creation method in colorectal ESD[7]. The pocket creation method has the same principle as ESTD. Therefore, CWL-ESD can be combined with ESTD, which might facilitate esophageal ESD.

DIFFERENCE IN THE EFFECT OF CWL IN ESOPHAGEAL AND GASTRIC ESD

CWL-ESD was not significantly associated with a reduced gastric ESD procedure time in the CONNECT-G trial, unlike in the CONNECT-E trial, which aimed to compare the conventional ESD and CWL-ESD for superficial gastric neoplasms[8]. Based on this finding, the effects of CWL can differ according to the conditions where it is used. Nevertheless, it is important to discuss the causes of this

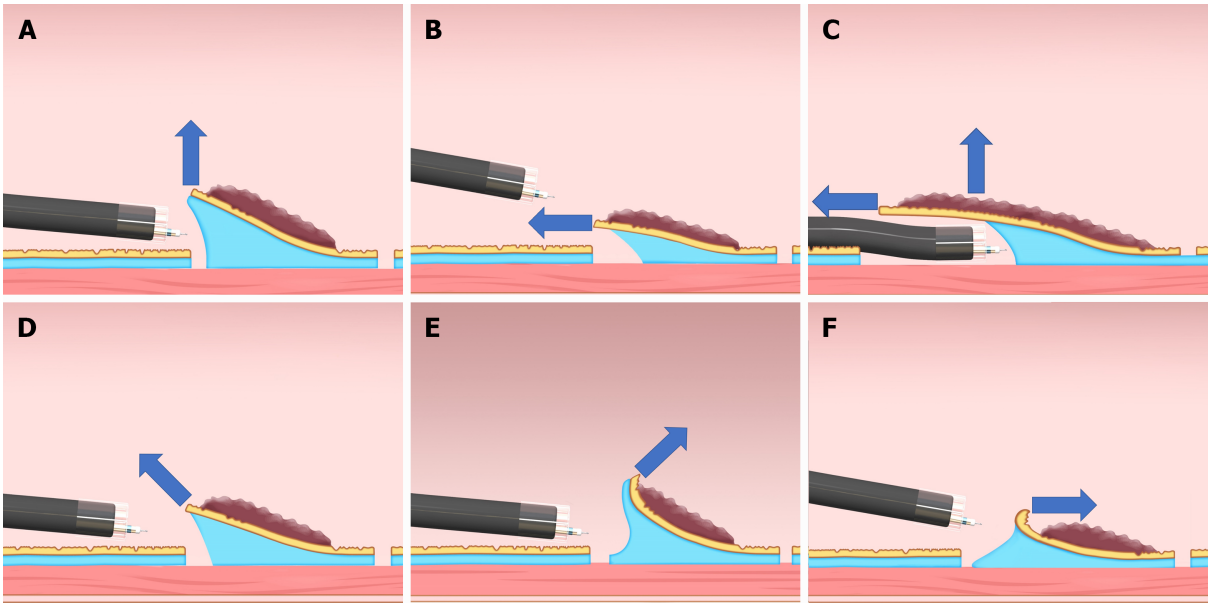

Figure 2 Classification of the traction direction. A: Vertical traction; B: Proximal traction; C: Proximal traction combined with hood traction; D: Diagonally proximal traction; E: Diagonally distal traction; F: Distal traction. Citation: Reprinted from Mitsuru Nagata. Advances in traction methods for endoscopic submucosal dissection: What is the best traction method and traction direction? *World Journal of Gastroenterology* 2022; 28: 1–22. Copyright © Mitsuru Nagata 2022. Published by Baishideng Publishing Group Inc[9].

difference to achieve the most out of CWL.

Traction direction may be the most significant factor affecting the effect of CWL in the esophagus and stomach. It can be classified into five categories (vertical, proximal, diagonally proximal, diagonally distal, and distal traction; Figure 2) based on its association with the endoscope tip and gastrointestinal wall[9]. Since the stomach lumen is large and CWL can provide the lesion with traction toward the cardia, the direction of traction of CWL is naturally restricted to the direction in which the line is drawn; therefore, the direction of traction in CWL-ESD for gastric lesions varies among the abovementioned five directions based on the lesion location (Figure 3). Among these five directions, vertical traction (Figure 2A) was found to be the most effective in the CONNECT-G trial[10]. Moreover, a single-center RCT that compared the conventional and multidirectional traction device (S–O clip; Zeon Medical, Tokyo, Japan)-assisted ESD for superficial gastric neoplasms found that vertical traction reduces the procedure time for gastric ESD[11]. Although few studies have investigated the effectiveness of traction-assisted ESD according to the traction direction, a propensity score matching analysis (42 pairs) comparing S–O clip-assisted ESD and CWL-ESD in the stomach demonstrated that the S–O clip-assisted ESD significantly could reduce the median ESD procedure time (28.3 min *vs* 51.0 min; $P = 0.022$) and accelerated the median dissection speed (24.8 mm^2/min *vs* 17.1 mm^2/min, $P = 0.001$)[12]. In this study, all traction directions in the S–O clip-assisted ESD were vertical whereas only 16.7% directions in the CWL-ESD were vertical, indicating that vertical traction facilitated the gastric ESD better than the other traction directions.

In contrast, the esophageal lumen is narrow and cylindrical. Therefore, endoscope position has a limited forward view, and the traction direction is naturally limited to the proximal traction (Figure 2B). Proximal traction may cause the mucosal flap to fall down toward the endoscope tip, which makes it difficult for the endoscope tip to get under the mucosal flap in some cases. However, in esophageal ESD, the tip of the endoscope can be parallel to the esophageal wall and can smoothly approach the submucosal layer, even with the proximal traction. After the endoscope tip reaches under the mucosal flap, CWL traction can be combined with the traction by the hood attached to the endoscope tip, thereby making vertical traction for the dissection plane (Figure 2C). Due to the abovementioned reasons, CWL can be effective in esophageal ESD. Meanwhile, it cannot be useful in gastric ESD in some cases. Further studies should be performed to assess the impact of traction direction in traction-assisted ESD.

CONCLUSION

Compared with the conventional method, CWL is associated with a reduced esophageal ESD procedure time, decreasing the risk of perforation. CWL slip-off is frequently observed. However, its effect on horizontal margin involvement is not significant. CWL-ESD can be the primary option for superficial esophageal neoplasms, except for lesions covering the whole circumference of the esophageal lumen and abdominal esophageal lesions. ESTD can be a promising strategy for these lesions. Moreover,

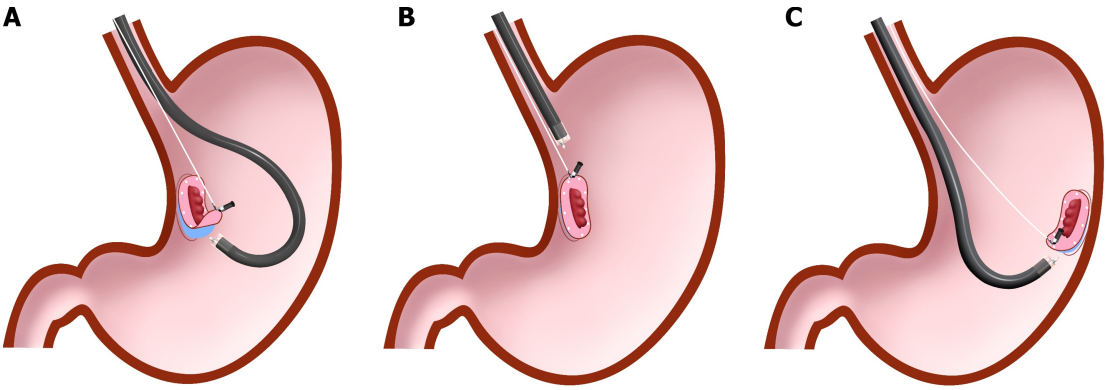

Figure 3 Difference in traction direction depending on the lesion location in the clip-with-line method. A: Distal traction; B: Proximal traction; C: Vertical traction. Citation: Reprinted from Mitsuru Nagata. Advances in traction methods for endoscopic submucosal dissection: What is the best traction method and traction direction? *World Journal of Gastroenterology* 2022; 28: 1–22. Copyright © Mitsuru Nagata 2022. Published by Baishideng Publishing Group Inc[9].

combined CWL-ESD and ESTD can be feasible and facilitate esophageal ESD procedures.

FOOTNOTES

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MINIREVIEWS

Device-assisted traction methods in colorectal endoscopic submucosal dissection and options for difficult cases

Mitsuru Nagata

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Abstract

Endoscopic submucosal dissection (ESD) procedure has a longer procedure time and higher perforation rate than endoscopic mucosal resection owing to technical complications, including a poor field of vision and inadequate tension for the submucosal dissection plane. Various traction devices were developed to secure the visual field and provide adequate tension for the dissection plane. Two randomized controlled trials demonstrated that traction devices reduce colorectal ESD procedure time compared with conventional ESD (C-ESD), but they had limitations, including a single-center fashion. The CONNECT-C trial was the first multicenter randomized controlled trial comparing the C-ESD and traction device-assisted ESD (T-ESD) for colorectal tumors. In the T-ESD, one of the device-assisted traction methods (S–O clip, clip-with-line, and clip pulley) was chosen according to the operator's discretion. The median ESD procedure time (primary endpoint) was not significantly different between C-ESD and T-ESD. For lesions ≥ 30 mm in diameter or in cases treated by nonexpert operators, the median ESD procedure time tended to be shorter in T-ESD than in C-ESD. Although T-ESD did not reduce ESD procedure time, the CONNECT-C trial results suggest that T-ESD is effective for larger lesions and nonexpert operators in colorectal ESD. Compared with esophageal and gastric ESD, colorectal ESD has some difficulties, including poor endoscope maneuverability, which may be associated with prolonged ESD procedure time. T-ESD may not effectively improve these issues, but a balloon-assisted endoscope and underwater ESD may be promising options and these methods can be combined with T-ESD.

Key Words: Endoscopic submucosal dissection; Traction; Traction direction; Balloon-assisted endoscope; Underwater endoscopic submucosal dissection

Core Tip: Various traction devices were developed to overcome the challenges faced in endoscopic submucosal dissection (ESD). A multicenter randomized controlled trial in Japan compared the conventional ESD and traction device-assisted ESD (T-ESD) for colorectal tumors. Although T-ESD did not reduce ESD procedure time, the results of this study suggest that T-ESD is effective for larger lesions and nonexpert operators. A balloon-assisted endoscope and underwater ESD may be promising options and these methods can be combined with T-ESD.

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INTRODUCTION

In endoscopic submucosal dissection (ESD), obtaining traction for lesions by hand is difficult. Gravity and the hood attached to the endoscope tip can be used to achieve traction while securing the visual field and tension for the dissection plane. However, these methods are occasionally insufficient, resulting in a prolonged procedure time and high perforation risk. Many traction devices have been developed to resolve these issues. Single-center randomized controlled trials (RCTs) reported that the colorectal ESD procedure time is shorter in traction device-assisted ESD (T-ESD) than in conventional ESD (C-ESD)[1,2]. However, no multicenter RCTs have been conducted to evaluate the effectiveness of T-ESD against C-ESD in colorectal ESD.

CONNECT-C TRIAL

The CONNECT-C trial was the first multicenter RCT conducted at 10 institutions in Japan[3]. This study aimed to compare the C-ESD and T-ESD for treating colorectal lesions endoscopically diagnosed as early colorectal cancer (Tis-T1a) and measuring > 20 mm in diameter preoperatively. After excluding ineligible patients, 128 patients in the C-ESD group and 123 patients in the T-ESD group were finally included in the analysis.

In the T-ESD group, one of the traction methods such as the clip-with-line (with modified preparation to omit the endoscope reinsertion)[4], S–O clip (Zeon Medical, Tokyo, Japan)[1], or the clip pulley[5] was chosen according to the operator's discretion.

Endoscopists with an experience of 50 or more gastric or esophageal ESD cases were qualified as ESD operators, and those with an experience of 50 or more colon ESD cases were defined as experts. Handover to an expert was permitted if the ESD procedure was prolonged (≥ 60 and ≥ 90 min for lesions measuring < 40 and ≥ 40 mm, respectively).

The primary endpoint was the median ESD procedure time (from the start of the local injection to the end of lesion resection), which was 61 min in the C-ESD group and 53 min in the T-ESD group, showing no significant difference (P = 0.18). The secondary endpoints included the handover to an expert, *en bloc* resection rate, R0 resection rate, and adverse events; all of them were also not significantly different between the C-ESD and T-ESD groups.

Although not significant, the median ESD procedure time was shorter in the T-ESD group than in the C-ESD group for lesions ≥ 30 mm in diameter (69 *vs* 89 min, P = 0.05). In patients treated by nonexpert operators, the median ESD procedure time tended to be shorter in the T-ESD group than in the C-ESD group (64 *vs* 81 min, P = 0.07). These results suggest that T-ESD is effective for larger lesions and nonexpert operators.

IMPACT OF TRACTION DIRECTION IN TRACTION-ASSISTED COLORECTAL ESD

In Japan, the multicenter RCTs CONNECT-E and CONNECT-G trials compared C-ESD and T-ESD in the esophagus and stomach, respectively. In the CONNECT-E trial, unlike C-ESD, T-ESD significantly reduced the esophageal ESD procedure time[6]. In the CONNECT-G trial, the gastric ESD procedure time showed no significant difference between the two procedures[7]. These discrepancies indicate that the effectiveness of T-ESD may differ according to how it works. Traction is a force, but it can be described as a vector, which includes size and direction. Therefore, traction direction is important for T-ESD efficiency. In addition, endoscopists need to perform a complicated procedure to change the traction direction during T-ESD. Thus, the impact of traction direction should be discussed.

Traction direction can be divided into five categories: Proximal, diagonally proximal, vertical, diagonally distal, and distal direction (Figure 1)[8]. Although studies focusing on traction direction are limited, some study results indicated that traction direction affects T-ESD efficiency. The CONNECT-G trial implied that the vertical traction (Figure 1A) is the most efficient among the five traction directions [9]. A single-center RCT compared C-ESD with T-ESD, which used a multidirectional traction device (S–O clip) for superficial gastric neoplasms; results showed that the vertical traction can reduce the gastric ESD procedure time[10]. The CONNECT-E trial suggested that when the endoscope tip can approach the lesion parallel to the gastrointestinal wall, the esophageal ESD procedure time is shorter in the proximal traction (Figure 1B) than in the C-ESD[6].

Although the effectiveness of diagonally proximal traction (Figure 1C), diagonally distal traction (Figure 1D), and distal traction (Figure 1E) is unclear due to a lack of research on these traction directions, distal traction might be the most ineffective option, because it can make the submucosal dissection plane fall distally when the submucosal dissection progresses and result in thinner submucosa; this may result in accidental dissection of the muscle layer or mucosa due to misrecognition of the layer. Furthermore, distal traction may decrease the effective tension for submucosal dissection, thereby decreasing the dissection speed and prolonging the ESD procedure time. Diagonally distal traction could be advantageous during the initial stages of submucosal dissection, as the traction force aids in widening the incised mucosa and exposing the submucosa, thereby facilitating submucosal dissection. Nevertheless, as submucosal dissection progresses, the dissection plane slowly falls distally from the endoscope tip and becomes thin, making it difficult to provide proper tension for the dissection plane. Diagonally proximal traction may be as effective as the vertical traction, because the dissection plane does not fall distally even when the submucosal dissection progresses, which help in maintaining appropriate tension on the dissection plane.

In the CONNECT-C trial, the three different traction methods, namely, S–O clip (Figure 2), clip-with-line (Figure 3), and clip pulley (Figure 4), were applied in T-ESD according to the operator's discretion, with 75, 31, and 22 cases analyzed and a corresponding procedure time of 52, 64, and 51 min, respectively. Although not significant, the clip-with-line method tended to have a longer ESD procedure time than the two other methods (P = 0.25). These methods are the same in terms of pulling definition, but they differ in the manner of pulling. The S–O clip and clip pulley can control traction direction. In contrast, the clip-with-line cannot control the traction direction, thereby making submucosal dissection efficiency worse in some cases. Indeed, propensity score matching analysis (42 pairs) showed that the S–O clip method had a shorter median ESD procedure time (28.3 min *vs* 51.0 min; P = 0.022) and higher dissection speed (24.8 mm^2/min *vs* 17.1 mm^2/min, P = 0.001) compared with the clip-with-line method, although this study was conducted in gastric ESD[11]. All traction directions in the S–O clip method were vertical in this study, whereas only 16.7% tractions were vertical in the clip-with-line method. These findings indicate that vertical traction can reduce the gastric ESD procedure time and increase the dissection speed compared with other traction directions. Traction direction may influence the effectiveness of device-assisted traction methods in colorectal ESD, and its impact in traction device-assisted colorectal ESD should be investigated.

FACTOR ASSOCIATED WITH DIFFICULTY IN COLORECTAL ESD: POOR ENDOSCOPE MANEUVERABILITY

Colorectal ESD occasionally faces endoscope maneuverability difficulty (*e.g.*, paradoxical movement) compared with esophageal and gastric ESD. Poor endoscope maneuverability can be a risk factor for ESD interruption, piecemeal resection, and perforation[12]. Moreover, poor endoscope maneuverability may cause a prolonged colorectal ESD procedure time. The three device-assisted traction methods (clip-with-line, S–O clip, and clip pulley) cannot improve endoscope maneuverability. Therefore, other options should be considered.

The balloon-assisted endoscope (BAE) is reportedly effective for colorectal ESD with poor endoscope maneuverability. A single-center retrospective study evaluated 83 deep-colon (from descending colon to cecum) ESD cases showing poor endoscope maneuverability preoperatively and treated with BAE (BAE group; n = 54) or without BAE (non-BAE group; n = 29)[13]. The ESD procedure time or dissection speed showed no significant differences between the two groups, but subgroup analysis showed the dissection speed in cecum and ascending colon cases was significantly faster in the BAE group than in the non-BAE group (22.3 and 11.3 mm^2/min, respectively; P = 0.037). BAE can improve the endoscope maneuverability; thus, the endoscope can approach the target lesion stably and improve ESD efficiency despite poor endoscope maneuverability. BAE may reduce the risk of intraoperative perforation. A propensity score matching analysis comparing BAE-ESD and C-ESD in the proximal colon revealed that BAE-ESD significantly decreased intraoperative perforation for lesions ≥ 40 mm in diameter (0% *vs* 24%, P = 0.0188), although there were no significant differences in the en bloc resection rate (95% *vs* 99%, P = 0.17), R0 resection rate (92% *vs* 96%, P = 0.30), mean dissection speed (16 mm^2/min *vs* 16 mm^2/min, P = 0.53), and intraoperative perforation (5% *vs* 6%, P = 0.73) between BAE-ESD and C-ESD[14]. Combining T-ESD with BAE may improve procedure-related outcomes in colorectal ESD cases with poor endoscope

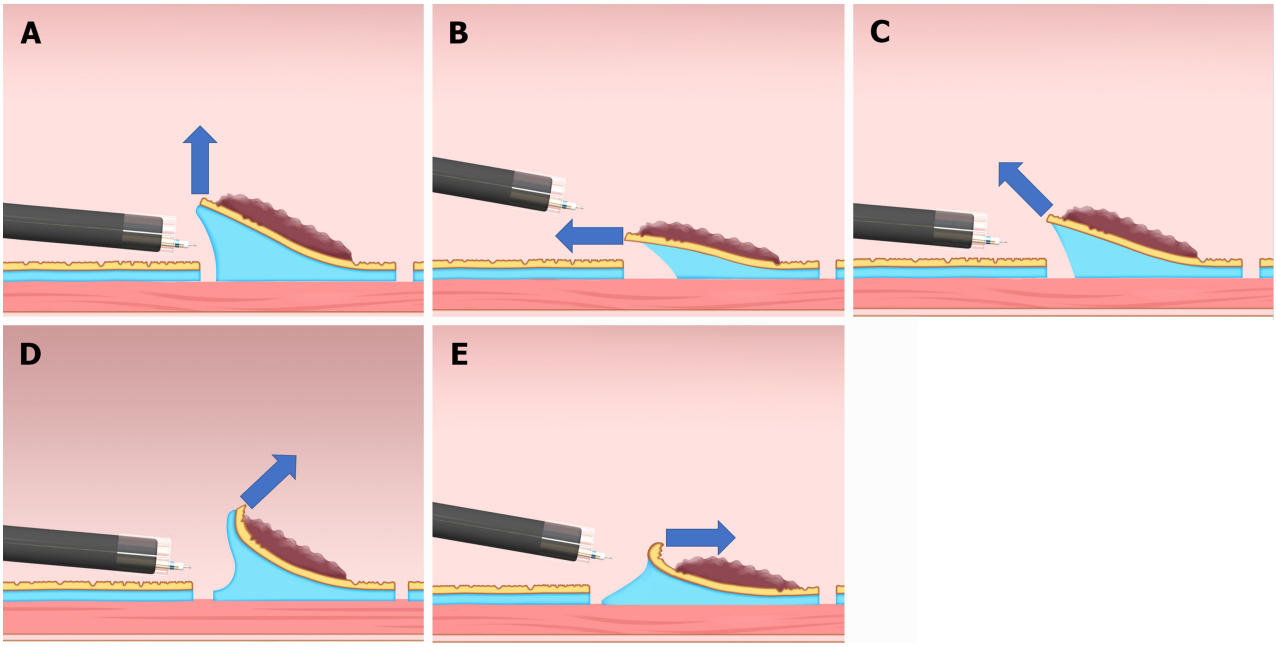

Figure 1 Classification of the traction direction. A: Vertical traction; B: Proximal traction; C: Diagonally proximal traction; D: Diagonally distal traction; E: Distal traction. Citation: Reprinted from Mitsuru Nagata. Advances in traction methods for endoscopic submucosal dissection: What is the best traction method and traction direction? *World Journal of Gastroenterology* 2022; 28: 1-22. Copyright ©Mitsuru Nagata 2022. Published by Baishideng Publishing Group Inc[8].

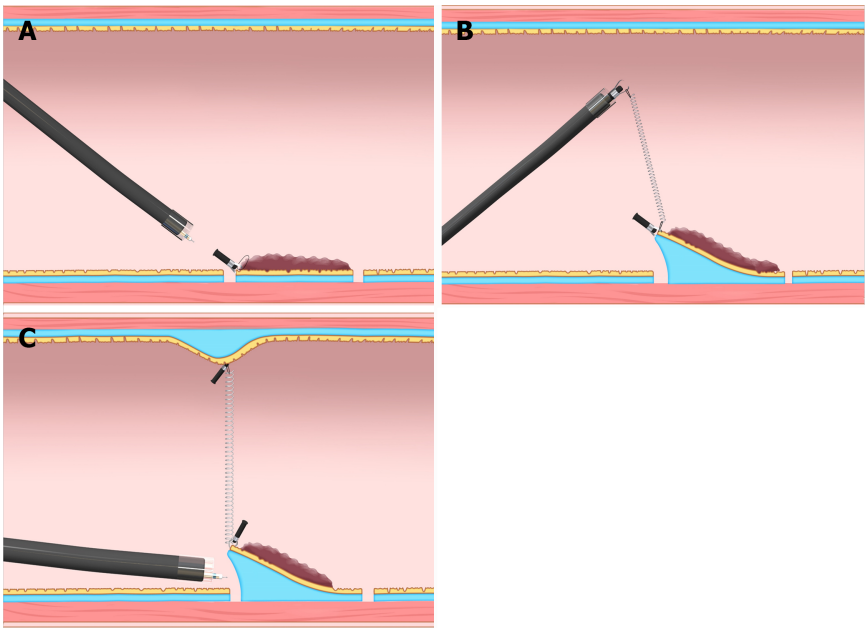

Figure 2 Internal traction method using the spring-and-loop with clip (Zeon Medical, Tokyo, Japan). A: The spring-and-loop with clip (S–O clip) is attached to the lesion; B: The regular clip anchors the loop part of the S–O clip on the gastrointestinal wall; C: The extension of the spring provides traction on the lesion. The traction direction can be controlled by the anchor site. Citation: Figure 2 reprinted from Nagata M, Fujikawa T, Munakata H. Comparing a conventional and a spring-and-loop with clip traction method of endoscopic submucosal dissection for superficial gastric neoplasms: a randomized controlled trial (with videos). *Gastrointestinal Endoscopy* 2021; 93: 1097-1109. Copyright ©2021 American Society for Gastrointestinal Endoscopy. Published by Elsevier Inc[10].

maneuverability. However, the effectiveness of this combination has not been comprehensively investigated. Therefore, future studies should focus on counteracting this issue.

UNDERWATER ESD (U-ESD): AN OPTION FOR DIFFICULT COLORECTAL ESD

The advantages of U-ESD are as follows: A clear visual field without halation; buoyancy; easy use of water pressure for opening the mucosal cutting edge; and the heat-sink effect, which can be useful for

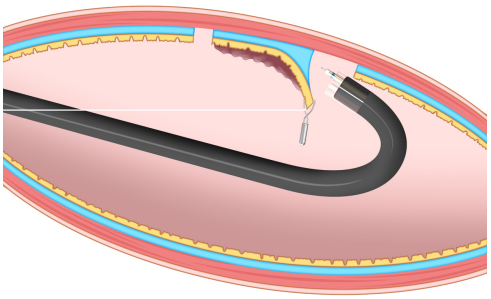

Figure 3 Clip-with-line method. This method provides traction for the lesion by pulling the line. The traction direction is limited to the direction in which the line is pulled. Citation: Figure 3 reprinted from Mitsuru Nagata. Advances in traction methods for endoscopic submucosal dissection: What is the best traction method and traction direction? *World Journal of Gastroenterology* 2022; 28: 1–22. Copyright ©Mitsuru Nagata 2022. Published by Baishideng Publishing Group Inc[8].

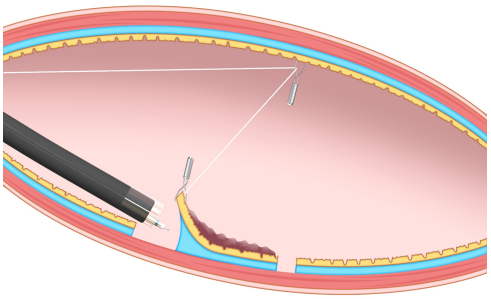

Figure 4 Pulley method. This method is the modified clip-with-line method, which can provide traction in any direction depending on the pulley site. Citation: Reprinted from Mitsuru Nagata. Advances in traction methods for endoscopic submucosal dissection: What is the best traction method and traction direction? *World Journal of Gastroenterology* 2022; 28: 1–22. Copyright ©Mitsuru Nagata 2022. Published by Baishideng Publishing Group Inc[8].

cases with severe fibrosis, abundant fat tissue, and gravitational lower side (Figure 5)[15]. U-ESD may also improve the endoscope maneuverability. A single-center retrospective study reported that U-ESD is beneficial for difficult colorectal lesions, including lesions with poor endoscope maneuverability[16]. In U-ESD, even in a collapsed colorectal lumen resulting from degassing, an underwater condition can help secure the field of vision, improving the operability of the endoscope. Moreover, U-ESD can be combined with T-ESD[17-19]. However, commercially available devices for ESD (*e.g.*, hood, electrosurgical knife, and hemostatic forceps) are basically designed to be used under gas insufflation, and some of them are not suitable for use in underwater conditions. In most U-ESD reports, a straight needle knife (*e.g.*, Dual Knife; Olympus, Tokyo, Japan) was used as the electrosurgical knife. A long bent-type knife (Hook Knife; Olympus, Tokyo, Japan) can also be used with U-ESD, but the setting of the electrosurgical unit needs to be changed appropriately for use in underwater conditions[20].

Conversely, U-ESD has two major disadvantages: visual field loss due to air bubble formation and active bleeding. In most U-ESD reports, a tapered hood, *e.g.*, ST Hood Short Type (Fujifilm Medical, Tokyo, Japan), was used to facilitate the endoscope tip entering into the submucosal space. Air bubbles can be generated during the U-ESD procedures and accumulated in the tapered hood attached to the endoscope tip, resulting in visual field impairment (Figure 6). Recently, a novel tapered hood was reported to be efficient in removing air bubbles from the inside of the tapered hood, thereby maintaining the visual field during U-ESD (Figure 7)[21]. Regarding active bleeding, gel immersion endoscopy can be used to secure the visual field[22,23]. However, most of the U-ESD reports are mainly case reports and case series studies. The feasibility of U-ESD needs further investigation. Moreover, devices that are suitable for use in U-ESD should be developed.

CONCLUSION

The CONNECT-C trial suggests that T-ESD is effective for larger lesions and nonexpert operators in colorectal ESD. Compared with esophageal and gastric ESD, colorectal ESD faces some difficulties, such as poor endoscope maneuverability and strong angulated lumen, which are possibly associated with a prolonged ESD procedure time. These issues may not be effectively improved by device-assisted traction methods, but BAE and U-ESD may be promising options and these methods can be combined with T-ESD.

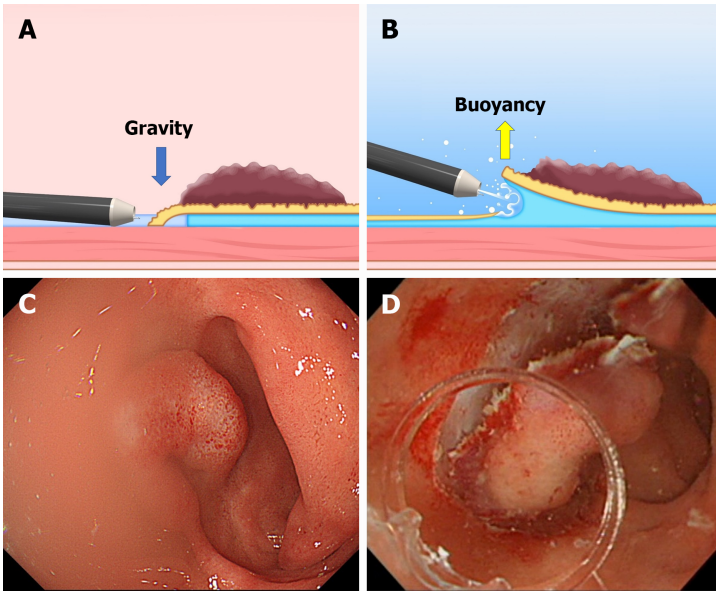

Figure 5 The difference between the conventional endoscopic submucosal dissection and the underwater endoscopic submucosal dissection. A and C: The conventional endoscopic submucosal dissection for the lesion is located at the gravitational lower side. Gravity obstructs the opening of the mucosal flap. Incomplete submersion deteriorates the visual field; B and D: The underwater condition aids the opening of the mucosal flap by buoyancy. Water pressure from the endoscope (using its water supply function) also assists in opening the mucosal flap. Complete submersion improves the visual field. Citation: Figure 5A and B reprinted from Mitsuru Nagata. Advances in traction methods for endoscopic submucosal dissection: What is the best traction method and traction direction? *World Journal of Gastroenterology* 2022; 28: 1–22. Copyright ©Mitsuru Nagata 2022. Published by Baishideng Publishing Group Inc[8]. Figure 5C and D reprinted from Mitsuru Nagata. Underwater endoscopic submucosal dissection in saline solution using a bent-type knife for duodenal tumor. *VideoGIE* 2018; 3: 375–377. Copyright ©2018 American Society for Gastrointestinal Endoscopy. Published by Elsevier Inc[20].

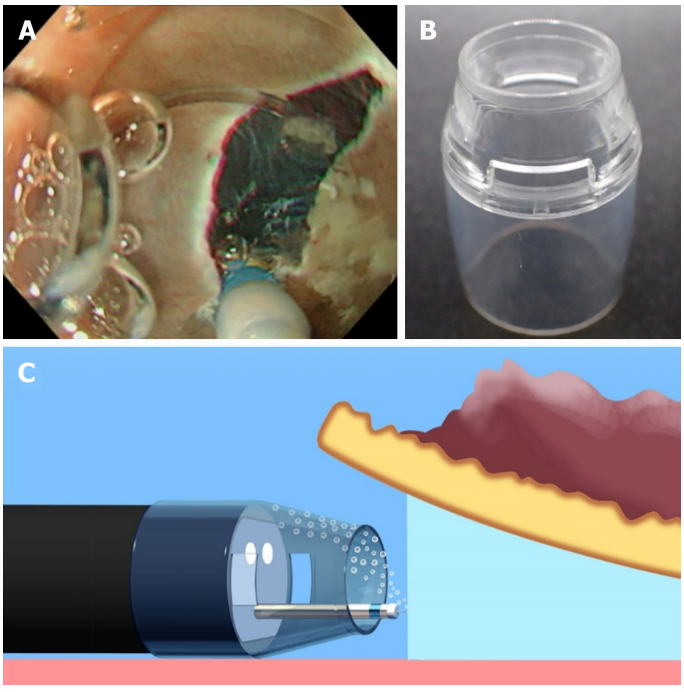

Figure 6 Underwater endoscopic submucosal dissection with a conventional tapered hood. A: Accumulation of air bubbles in the hood causes visual field impairment during underwater endoscopic submucosal dissection; B: A conventional tapered hood (ST Hood Short Type; Fujifilm Medical, Tokyo, Japan). This hood has narrow holes in its sides to remove the liquid *via* the capillary phenomenon, which is inversely proportional to the cross-sectional area of the hole; C: When a conventional tapered hood is used, removal of air bubbles can sometimes be difficult due to the narrow hood tip opening and holes in its sides. Citation: Reprinted from Mitsuru Nagata. Tapered hood with wide holes in its sides for efficient air bubble removal during underwater endoscopic submucosal dissection. *Digestive Endoscopy* 2022; 34: 654. ©2022 Japan Gastroenterological Endoscopy Society. Published by John Wiley & Sons Australia, Ltd[21].

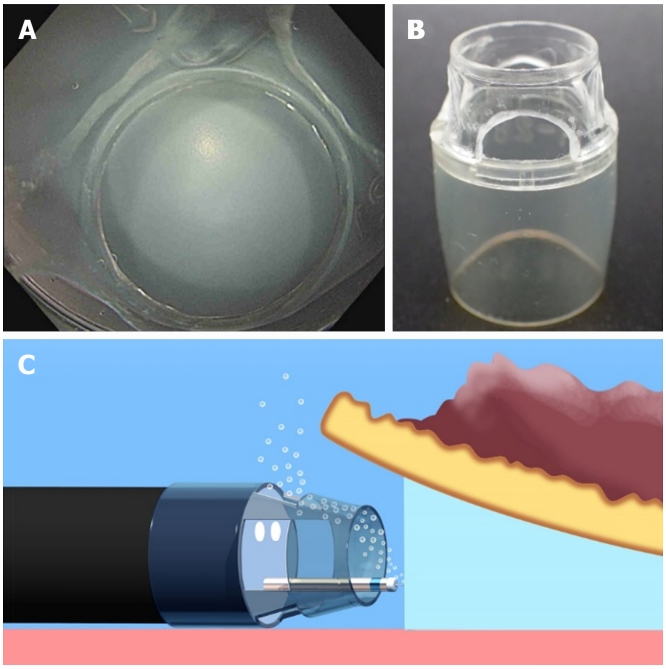

Figure 7 A tapered hood with wide holes in its sides for efficient air bubble removal during underwater endoscopic submucosal dissection. A: An endoscopic view when a tapered tip hood with wide holes in its sides is attached; B: A tapered hood (ST Hood Short Type; Fujifilm Medical) with wide holes in its sides for air bubble removal during underwater endoscopic submucosal dissection. As the tip of an ST Hood Short Type is made of polycarbonate resin, wide holes in its sides can be made by hand using a commercially available router (RTD35ACL; TACKLIFE); C: Wide holes in the sides of the tapered hood can facilitate air bubble removal. Citation: Reprinted from Mitsuru Nagata. Tapered hood with wide holes in its sides for efficient air bubble removal during underwater endoscopic submucosal dissection. *Digestive Endoscopy* 2022; 34: 654. ©2022 Japan Gastroenterological Endoscopy Society. Published by John Wiley & Sons Australia, Ltd[21].

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ORIGINAL ARTICLE

Retrospective Cohort Study

Role of endoscopic ultrasound in the characterization of solid pseudopapillary neoplasm of the pancreas

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Abstract

BACKGROUND

Solid pseudopapillary neoplasm (SPN) is an uncommon pathology of the pancreas with unpredictable malignant potential. Endoscopic ultrasound (EUS) assessment plays a vital role in lesion characterization and confirmation of the tissue diagnosis. However, there is a paucity of data regarding the imaging assessment of these lesions.

AIM

To determine the characteristic EUS features of SPN and define its role in preoperative assessment.

METHODS

This was an international, multicenter, retrospective, observational study of prospective cohorts from 7 large hepatopancreaticobiliary centers. All cases with postoperative histology of SPN were included in the study. Data collected included clinical, biochemical, histological and EUS characteristics.

RESULTS

One hundred and six patients with the diagnosis of SPN were included. The mean age was 26 years (range 9 to 70 years), with female predominance (89.6%). The most frequent clinical presentation was abdominal pain (80/106; 75.5%). The mean diameter of the lesion was 53.7 mm (range 15 to 130 mm), with the slight predominant location in the head of the pancreas (44/106; 41.5%). The majority of lesions presented with solid imaging features (59/106; 55.7%) although 33.0% (35/106) had mixed solid/cystic characteristics and 11.3% (12/106) had cystic morphology. Calcification was observed in only 4 (3.8%) cases. Main pancreatic duct dilation was uncommon, evident in only 2 cases (1.9%), whilst common bile duct dilation was observed in 5 (11.3%) cases. One patient demonstrated a double duct sign at presentation. Elastography and Doppler evaluation demonstrated inconsistent appearances with no emergence of a predictable pattern. EUS guided biopsy was performed using three different types of needles: Fine needle aspiration (67/106; 63.2%), fine needle biopsy (37/106; 34.9%), and Sonar Trucut (2/106; 1.9%). The diagnosis was conclusive in 103 (97.2%) cases. Ninety-seven patients were treated surgically (91.5%) and the post-surgical SPN diagnosis was confirmed in all cases. During the 2-year follow-up period, no recurrence was observed.

CONCLUSION

SPN presented primarily as a solid lesion on endosonographic assessment. The lesion tended to be located in the head or body of the pancreas. There was no consistent characteristic pattern apparent on either elastography or Doppler assessment. Similarly SPN did not frequently cause stricture of the pancreatic duct or common bile duct. Importantly, we confirmed that EUS-guided

biopsy was an efficient and safe diagnostic tool. The needle type used does not appear to have a significant impact on the diagnostic yield. Overall SPN remains a challenging diagnosis based on EUS imaging with no pathognomonic features. EUS guided biopsy remains the gold standard in establishing the diagnosis.

Key Words: Solid pseudopapillary neoplasm; SPN; Frantz tumor; Endoscopic ultrasound features; EUS-guided biopsy; Fine needle aspiration/biopsy

Core Tip: Solid pseudopapillary neoplasm (SPN) presented primarily as a solid lesion on endosonographic assessment. The lesion tended to be located in the head or body of the pancreas. There was no consistent characteristic pattern apparent on either elastography or Doppler assessment. Similarly SPN did not frequently cause stricture of the pancreatic duct or common bile duct. Importantly, we confirmed that Endoscopic ultrasound (EUS) -guided biopsy was an efficient and safe diagnostic tool. The needle type used does not appear to have a significant impact on the diagnostic yield. Overall SPN remains a challenging diagnosis based on EUS imaging with no pathognomonic features. EUS guided biopsy remains the gold standard in establishing the diagnosis.

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INTRODUCTION

Solid pseudopapillary neoplasm is a rare tumor of the pancreas which may demonstrate both solid and cystic imaging characteristics. In contrast to other cystic tumors such as serous or mucinous cystic neoplasms that contain a true epithelial lining or intraductal papillary mucinous neoplasm with cystically dilated pancreatic duct or branches filled with mucin, Solid pseudopapillary neoplasm (SPN) is a low-grade malignant tumor, histologically forming solid and pseudopapillary structures with an absence of specific line pancreatic epithelial differentiation[1].

Historically, most SPN were detected in patients presenting with abdominal pain or non-specific abdominal symptoms. At present, due to the wider application of advanced imaging techniques, the majority of these lesions are recognized incidentally[2]. As a result, the incidence of SPN is increasing, now equating to approximately 6% of all exocrine pancreatic neoplasms[2]. Although SPN usually demonstrates indolent behavior, higher grades of malignancy may be encountered and metastases have been reported in up to 20% of cases[2]. Therefore, detection and diagnosis of SPN mandate surgical referral, for consideration of resection. Importantly, SPN are cured by complete surgical resection alone [3].

Despite advances in imaging, pseudocysts, cystic neuroendocrine tumors and other cystic neoplasms may demonstrate similar imaging characteristic, making a pre-operative diagnosis challenging[4]. Furthermore, differentiation of SPN from other pancreatic neoplasms, such as pancreatic neuroendocrine tumors, acinar cell carcinomas, or ductal adenocarcinomas is important because SPN have a significantly improved prognosis compared with other malignant pancreatic tumors[5].

Traditionally computed tomography and magnetic resonance imaging have been considered the key preliminary diagnostic imaging tools for SPN. However, obtaining a final diagnosis remains dependent on cytohistological analysis[6]. The proximity of the pancreas to the stomach and duodenum facilitates endoscopic ultrasound (EUS) examination and the ability to obtain tissue through the fine needle aspiration/biopsy (FNA/FNB), in assessment of SPN. However, given the relative rareness of SPN, there remains a relative paucity of data regarding the role of EUS-guided biopsy rather than pre-operative assessment of the imaging features[7-9]. Therefore, we sought to define the characteristic EUS findings and their role in the preoperative assessment of SPN.

MATERIALS AND METHODS

Participating centers

This was an international, multicenter, retrospective observational, open-label study involving seven endoscopy units from India, Egypt, Poland, United Kingdom, France, Romania, and Pakistan. The data has been collected by high-volume endoscopy centers, performing in the region of 1000 diagnostic and interventional EUS procedures per year, including EUS-guided biopsy. In all centers, the evaluation was performed by an expert endosonographer who was defined as having performed at least 1000 hepato-pancreaticobiliary (HPB) EUS procedures.

Population data collection

All patients who underwent EUS during a ten year period who ultimately were diagnosed with SPN, (2010-2022), confirmed by histopathological assessment were enrolled in the study. Anonymized data was collected including patient demographics, symptoms, endosonographic features and histological results including EUS-guided biopsy result and surgical confirmation.

Endosonography of SPN

All patients were referred to EUS evaluation due to the non-metastatic, growing locally pancreatic tumor recognized in computed tomography for establishing the diagnosis. Information on EUS, images, EUS-guided biopsy including the number of passes, type of needle and fluid biochemistry analysis (amylase, CA 19.9 and mucin stain) from cystic component were recorded using a collective database. In all cases, surgical resection was the treatment of choice, providing definitive histological SPN confirmation.

The study was conducted and carried out in accordance with the Helsinki declaration as revised in 1989. Based on the anonymized data collection, the Institutional Review Board of Pomeranian Medical University in Szczecin granted approval. The study was conducted in the line with the STROBE guidelines.

Statistical analysis

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) version 28. Numerical data was summarized using mean and standard deviations or medians and/or ranges as appropriate. Categorical data was summarized as numbers and percentages. Estimates of the frequency were done using the numbers and percentages. Numerical data was explored for normality using Kolmogrov-Smirnov test and Shapiro-Wilk test. Chi square or Fisher's tests were used to compare between the independent groups with respect to categorical data as appropriate. Comparisons between two groups for normally distributed numeric variables were done using the Student's *t*-test while for non-normally distributed numeric variables, comparisons were done by Mann-Whitney test. Comparison between more than 2 groups was performed by Kruskal-Wallis for non-normally distributed variables. All tests were two tailed & Probability (*P* value) ≤ 0.05 was considered significant.

RESULTS

Clinical characteristics of SPN patients

One hundred and six cases with SPN were included. The median age was 26 years (range 9 to 70), with similar incidence in both genders when compared by age, but with general female predominance (95 females, 89.6%) (Table 1). The majority of patients presented symptomatically (82.1%), among which the most frequent was abdominal pain (75.5%). However, a history of previous acute pancreatitis episodes was only recorded in one patient. Other symptoms included obstructive jaundice (3.8%), vomiting (1.9%) and weight loss (0.9%) (Table 2). In all patients the tumor marker CA 19.9 was normal.

EUS characteristics of solid pseudopapillary tumors: The mean size of the lesion was 52.8 mm (range 15-130 mm), with the predominant location in the head of the pancreas (44/106; 41.5%). Detailed endoscopic ultrasound evaluation was performed identifying lesions with solid (60/106; 56.1%), mixed (43/106; 40.2%), and cystic (3/106; 2.8%) morphology (Figure 1). In terms of endosonographic echotexture, the tumors considered as solid were mainly hypoechoic, heterogeneous, well-demarcated with regular border (Figure 2A). In three cases presented as a solid mass, hyperechoic echotexture corresponding to calcification was observed (Figure 2B). Also, one tumor with pancreatic head location caused a portal vein confluence thrombosis due to external compression and expansile growth. Cystic lesions presented mainly with a multilocular appearance with septations but without mural nodules or honeycomb pattern (Figure 2C). In one case, circumferential calcification was observed. Mixed tumors included both components; however, the solid part demonstrated soft-tissue stiffness on EUS elastography assessment (Figure 3). In addition, Doppler assessment did not demonstrate significant intralesional vascularity or hypervascular infiltration of surrounding structures. Dilation of the main

Table 1 Sociodemographic characteristics, *n* (%)

	***n* = 106 (%)**
Age	
mean ± SD	26.4 ± 13
Sex	
Female	95 (89.6)
Male	11 (10.4)
Country	
Egypt	48 (45.3)
India	39 (36.8)
Poland	5 (4.7)
France	4 (3.8)
United Kingdom	5 (4.7)
Romania	3 (2.8)
Pakistan	2 (1.9)

Table 2 Clinical manifestation

	***n* (%)**
Symptoms	
Yes	87 (82.1)
No	19 (17.9)
Presentation	
Asymptomatic	19 (17.9)
Abdominal pain	80 (75.5)
Weight loss	1 (0.9)
Obstructive jaundice	4 (3.8)
Vomiting	2 (1.9)

pancreatic duct (MPD) was reported in 2 cases (2/106; 1.9%) of solid SPN (mean size 46 mm; pancreatic head location) measuring up to 10 mm (mean 8.5 mm), while the common bile duct was dilated in 5 cases (5/106; 54.7%) of solid tumors (mean size 61.4 mm; pancreatic head location) with no previous cholecystectomy. Also, there was no correlation between size of the tumor, consistency and anatomical location. The results are summarized in Tables 3-4 and Figure 1.

Technical aspects of EUS-guided biopsy, therapeutic strategy: EUS guided biopsy was performed using three different types of needle: FNA in 67 (63.2%), FNB in 37 (34.9%), Trucut in 2 (1.9%) lesions. For the later, the size 18G and 22G were selected. The 22G and 19G size was mainly selected (94.0%) for the FNA needle type, and 22G for the FNB needle (89.2%). The mean number of passes was 2 and 3 for FNA and FNB needle respectively. Data regarding the needle type used are presented in Table 5.

Cythopathological results

The tissue samples were conclusive in 103 (97.2%) cases (Figure 4). The mucin stain was negative in all cases. Three lesions without conclusive FNA (diagnosed nonspecifically as hemorrhagic material, inflammatory cells and neuroendocrine tumor suspicion) were definitively validated by surgical resection. Consequently a histological diagnosis was reached in all cases (Table 6).

Ninety-seven (91.5%) patients were treated surgically (Figure 5). Whipple's/pancreatoduodenectomy was performed in 47 (44.3%), central pancreatectomy in 29 (27.4%) and distal pancreatosplenectomy in 21 (19.8%). Post-surgical SPN confirmation was determined in all cases. Follow up varied according to local protocol and within the 2 year research period, no cases of recurrence or metastatic disease were recorded.

Table 3 Endoscopic ultrasound characteristic of solid pseudopapillary tumors

	n (%)
Location	
Head	44 (41.5)
Body	43 (40.6)
Tail	19 (17.9)
Consistency	
Solid	60 (56.1)
Mixed	43 (40.2)
Cystic	3 (2.8)
Additional findings	
Calcification	4 (3.8)
CBD dilation	
Yes	5 (4.7)
No	101 (95.3)
PD dilation	
Yes	2 (1.9)
No	104 (98.1)
Size	
mean ± SD	52.8 ± 23.1
Median (range)	50 (15-130)

CBD: Common bile duct; PD: Pancreatic duct; SD: Standard deviation.

Table 4 Correlation between size of the tumor, consistency and location

	Size	*P* value
Consistency/appearance		0.365
Cystic, median (range)	52.5 (36-130)	
Solid, median (range)	45 (15-120)	
Mixed, median (range)	54 (17-95)	
Location		0.4
Head, median (range)	51.5 (15-130)	
Body, median (range)	45 (19-100)	
Tail, median (range)	60 (17-125)	

SD: Standard deviation, *P* value < 0.05 is considered significant.

DISCUSSION

In this study, we found that SPN presented as moderately large lesions without other clinically specific features or typical endosonographic appearance including the size, echotexture, impact on the main ducts (CBD and MPD), and growth pattern. In addition there was no consistent pattern evident in the ancillary EUS features of calcification, vascularity or stiffness (elastography).

The distribution of SPN was in all anatomic components of the pancreas, with a slight dominance in the pancreatic head (41.5%), followed by pancreatic body (40.6%), consistent with the previous published work which has been unable to conclusively demonstrate atypical location for SPN[2,10,11]. Interestingly, of the 44 cases presenting in the head of the pancreas, only four led to a local complication

Table 5 Endoscopic ultrasound needle characteristic

	n (%)
Needle type	
FNA	67 (63.2)
FNB	37 (34.9)
Tru cut	2 (1.9)
Needle size	
19 G	9 (8.5)
22 G	88 (83)
18 G	1 (0.9)
20 G	2 (1.9)
25 G	6 (5.7)
No of passes	
Median (range)	3 (1-3)
FNA	*n* = 67 (%)
Needle size	
19 G	9 (13.4)
22 G	54 (80.6)
25 G	4 (6)
No of passes	
Median (range)	2 (1-3)
FNB	*n* = 37 (%)
Needle size	
22 G	33 (89.2)
20 G	1 (2.7)
25 G	3 (8.1)
No of passes	
Median (range)	3 (1-3)
Trucut	*n* = 2 (%)
Needle size	
22 G	1 (50)
18 G	1 (50)
No of passes	2

FNA: Fine needle aspiration; FNB: Fine needle biopsy.

resulting in jaundice and double duct sign was only evident in one case. Importantly, some lesions grew to a significant size without significant symptoms. We performed logistic regression analysis and could not find any correlation between size and symptoms or tumor appearance. Additionally, even the largest tumor with pancreatic head location (130 mm) did not cause double duct sign and most of them did not infiltrate surrounding structures despite such large size, which was in agreement with previous literature[2,11].

In our study group, only one tumor located in the pancreatic head with the size of 42 mm had an expansile growth pattern leading to the compression of portal vein confluence and thrombosis, but without an impact on the bile duct or pancreatic duct. In our cohort, we did not observe infiltrative SPN nature. We believe that the lack of ductal changes may be due to the inherent parenchymal localization of the tumor, with specific growth dynamics that induces a preferential growth away from the pancreas and not towards the main pancreatic duct or bile duct.

Table 6 Cytopathology

	n (%)
Cytopathology	
Non-diagnostic	3 (2.8)
SPN (conclusive)	103 (97.2)
Surgery	
Yes	97 (91.5)
No	9 (8.5)
Surgery	
Central pancreatectomy	29 (27.4)
Distal pancreatosplenectomy	21 (19.8)
Whipple's panceatoduodenectomy	47 (44.3)
Refused	9 (8.5)

SPN: Solid pseudopapillary neoplasm.

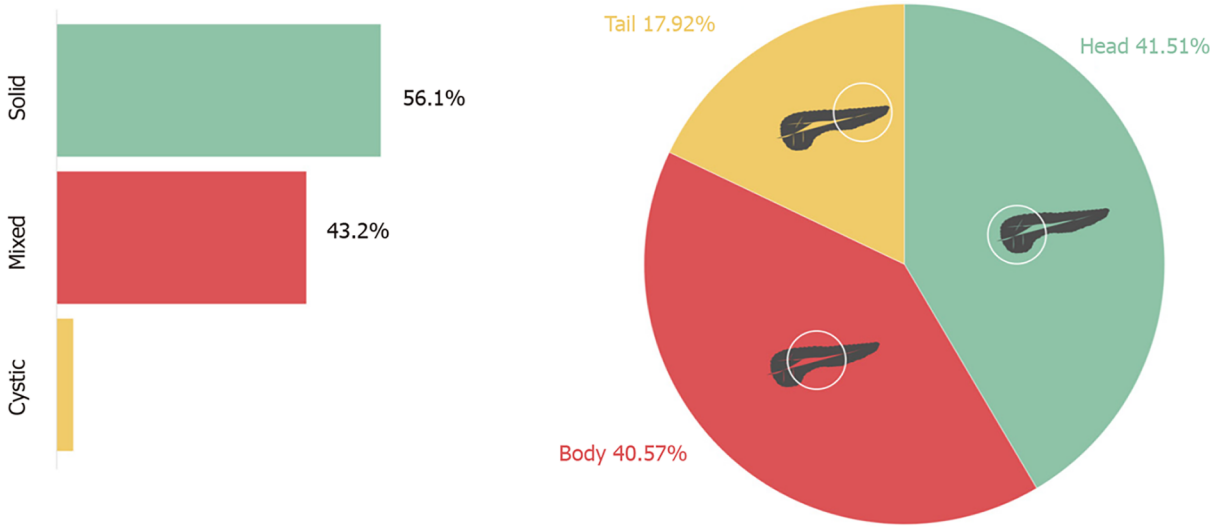

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Figure 1 Endoscopic ultrasound characteristic of solid pseudopapillary tumors.

Also, there were no typical findings regarding EUS imaging ancillary features such as elastography and Doppler assessment.

Confirming previous reports, we found that the majority of patients were female with a 9:1 ratio[12]. Other features, age, size, and tumor appearance were similar, with no statistical significance. Although variation was demonstrated between genders and lesion location (male – head, female – body predominance), these results were not statistically significant.

Previously, Marchegiani *et al*[13] found that expansive growth pattern had a statistically significant association with recurrence of SPN. However, during our period of assessment, no cases of local recurrence or metastatic disease were identified. Clearly ongoing surveillance of this group will be of interest.

Importantly, we found that EUS-guided tissue acquisition was an efficient and safe diagnostic tool regardless of biopsy needle type. Consistently a high preoperative diagnostic yield was achieved. We were able to reach a preoperative diagnosis in 97% the patients, confirmed by resected specimen.

Our study has potential shortcomings, including its retrospective design. In addition we did not perform a comparison between the needle type, size and number of passes in terms of the efficiency.

Finally, to our knowledge, this represents the largest multicenter study of SPN to date, with the advantage of varied international geographic location.

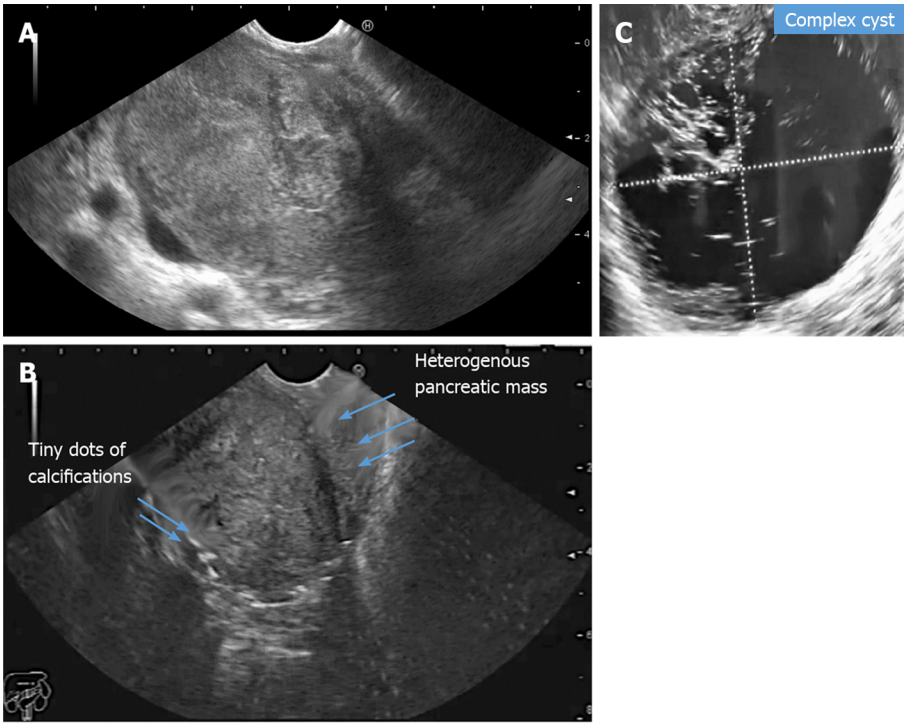

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Figure 2 Endoscopic ultrasound. A: A large heterogeneous solid pseudopapillary neoplasm in the pancreatic head; B: A large heterogeneous solid pseudopapillary neoplasm with calcific spots in the pancreatic head; C: A cystic solid pseudopapillary neoplasm in the pancreatic body.

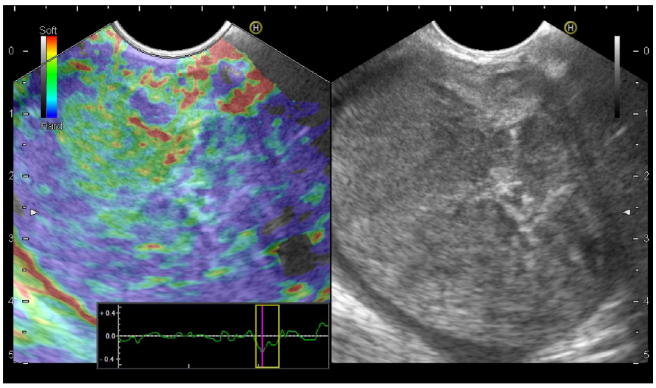

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Figure 3 A large heterogeneous firm solid pseudopapillary neoplasm in the pancreatic head with dominant blue color denoting grade 3 Elasticity score.

CONCLUSION

In conclusion, we found that SPN presented mainly as solid endosonographic lesions, with slight dominance of pancreatic head location without pathognomonic EUS features that would permit a definitive imaging diagnosis. Despite their large size, SPN do not tend to impinge on the pancreatic duct and more frequently demonstrate a parenchymatous growth. Importantly, we confirmed that EUS-guided biopsy is an efficient and safe diagnostic tool, regardless of needle type, with high preoperative diagnostic yield. We propose that a prospective international study of SPN would further improve our understanding of this rare tumor.

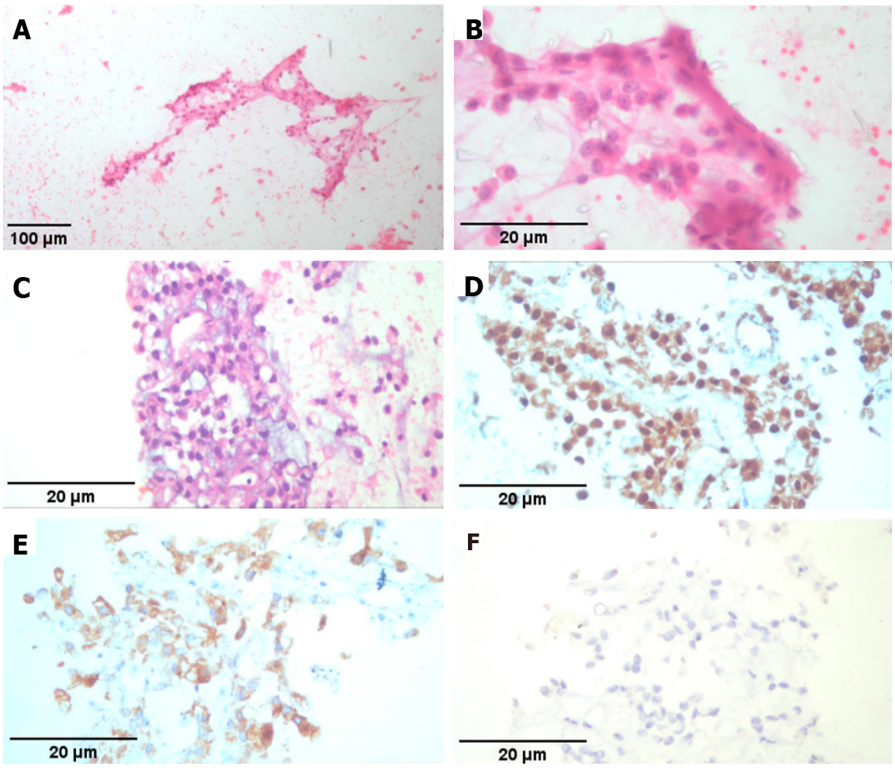

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Figure 4 Smears of solid pseudopapillary pancreatic tumor. A and B: Clusters of uniform epithelioid cells arranged in a vague papillary like formation (Hematoxylin & Eosin × 40); C: Cell block of same tumor (Hematoxylin & Eosin × 400); D: Positive nuclear B-Catenin immunoreaction in tumor cells (Hematoxylin & Eosin × 400); E: Positive cytoplasmic Synatophysin immunoreaction in tumor cells (Hematoxylin & Eosin × 400); F: Negative Chromogranin immunoreaction (Hematoxylin & Eosin × 400).

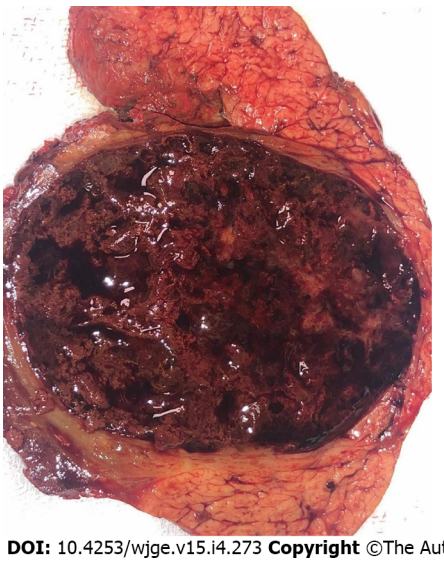

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Figure 5 A post-operative specimen of mixed solid pseudopapillary neoplasm with solid and cystic areas.

ARTICLE HIGHLIGHTS

Research background

Solid pseudopapillary neoplasm (SPN) is an uncommon pathology of the pancreas with unpredictable malignant potential. Endoscopic ultrasound (EUS) assessment plays a vital role in lesion characterization and confirmation of the tissue diagnosis.

Research motivation
There is a paucity of data regarding the imaging assessment of these lesions.

Research objectives
To determine the characteristic EUS features of SPN and define its role in preoperative assessment.

Research methods
This was an international, multicenter, retrospective, observational study of prospective cohorts from 7 large hepatopancreaticobiliary centers. All cases with postoperative histology of SPN were included in the study. Data collected included clinical, biochemical, histological and EUS characteristics.

Research results
One hundred and six patients with the diagnosis of SPN were included. The mean age was 26 years (range 9 to 70 years), with female predominance (89.6%). The most frequent clinical presentation was abdominal pain (80/106; 75.5%). The mean diameter of the lesion was 53.7 mm (range 15 to 130 mm), with the slight predominant location in the head of the pancreas (44/106; 41.5%). The majority of lesions presented with solid imaging features (59/106; 55.7%) although 33.0% (35/106) had mixed solid/cystic characteristics and 11.3% (12/106) had cystic morphology. Calcification was observed in only 4 (3.8%) cases. Main pancreatic duct dilation (MPD) was uncommon, evident in only 2 cases (1.9%), whilst common bile duct dilation was observed in 5 (11.3%) cases. One patient demonstrated a double duct sign at presentation. Elastography and Doppler evaluation demonstrated inconsistent appearances with no emergence of a predictable pattern. EUS guided biopsy was performed using three different types of needles: FNA (67/106; 63.2%), FNB (37/106; 34.9%), and Sonar Trucut (2/106; 1.9%). The diagnosis was conclusive in 103 (97.2%) cases. Ninety-seven patients were treated surgically (91.5%) and the post-surgical SPN diagnosis was confirmed in all cases. During the 2-year follow-up period, no recurrence was observed.

Research conclusions
SPN presented primarily as a solid lesion on endosonographic assessment. The lesion tended to be located in the head or body of the pancreas. There was no consistent characteristic pattern apparent on either elastography or Doppler assessment. Similarly SPNs did not frequently cause stricture of the pancreatic duct or common bile duct. Importantly, we confirmed that EUS-guided biopsy was an efficient and safe diagnostic tool. The needle type used did appear to have a significant impact on the diagnostic yield. Overall SPN remains a challenging diagnosis based on EUS imaging with no pathognomonic features. EUS guided biopsy remains the gold standard in establishing the diagnosis.

Research perspectives
We propose that a prospective international study of SPN would further improve our understanding of this rare tumor.

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FOOTNOTES
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Institutional review board statement: The study was conducted and carried out in accordance with the Helsinki declaration as revised in 1989. Based on the anonymized data collection, the Institutional Review Board of Pomeranian Medical University in Szczecin granted approval. SVU, MED018.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Relationships of hospitalization outcomes and timing to endoscopy in non-variceal upper gastrointestinal bleeding: A nationwide analysis

Simcha Weissman, Muhammad Aziz, Ayrton I Bangolo, Dean Ehrlich, Arnold Forlemu, Anthony Willie, Manesh K Gangwani, Danish Waqar, Hannah Terefe, Amritpal Singh, Diego MC Gonzalez, Jayadev Sajja, Fatma L Emiroglu, Nicholas Dinko, Ahmed Mohamed, Mark A Fallorina, David Kosoy, Ankita Shenoy, Anvit Nanavati, Joseph D Feuerstein, James H Tabibian

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Abstract

BACKGROUND

The optimal timing of esophagogastroduodenoscopy (EGD) and the impact of clinico-demographic factors on hospitalization outcomes in non-variceal upper gastrointestinal bleeding (NVUGIB) remains an area of active research.

AIM

To identify independent predictors of outcomes in patients with NVUGIB, with a

particular focus on EGD timing, anticoagulation (AC) status, and demographic features.

METHODS

A retrospective analysis of adult patients with NVUGIB from 2009 to 2014 was performed using validated ICD-9 codes from the National Inpatient Sample database. Patients were stratified by EGD timing relative to hospital admission (≤ 24 h, 24-48 h, 48-72 h, and > 72 h) and then by AC status (yes/no). The primary outcome was all-cause inpatient mortality. Secondary outcomes included healthcare usage.

RESULTS

Of the 1082516 patients admitted for NVUGIB, 553186 (51.1%) underwent EGD. The mean time to EGD was 52.8 h. Early (< 24 h from admission) EGD was associated with significantly decreased mortality, less frequent intensive care unit admission, shorter length of hospital stays, lower hospital costs, and an increased likelihood of discharge to home (all with $P < 0.001$). AC status was not associated with mortality among patients who underwent early EGD (aOR 0.88, $P = 0.193$). Male sex (OR 1.30) and Hispanic (OR 1.10) or Asian (aOR 1.38) race were also independent predictors of adverse hospitalization outcomes in NVUGIB.

CONCLUSION

Based on this large, nationwide study, early EGD in NVUGIB is associated with lower mortality and decreased healthcare usage, irrespective of AC status. These findings may help guide clinical management and would benefit from prospective validation.

Key Words: Upper gastrointestinal bleeding; Esophagogastroduodenoscopy; Outcomes; Mortality; Anticoagulation

Core Tip: Patients are often admitted for nonvariceal upper gastrointestinal bleeding (NVUGIB). There is not enough data on the importance and timing of esophagogastroduodenoscopy (EGD) in those scenarios. We investigated a nationally representative database to identify independent predictors of outcomes in patients with NVUGIB, with a particular focus on EGD timing, anticoagulation (AC) status, and demographic features. We found that early EGD in NVUGIB is associated with lower mortality and decreased healthcare usage, irrespective of AC status.

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INTRODUCTION

Non-variceal upper gastrointestinal bleeding (NVUGIB) is responsible for approximately 300000 hospital admissions in the United States (US) annually[1,2]. NVUGIB can range from mild to life-threatening, with a mortality rate of 3%-14% despite the best available care[3-5], and places a substantial burden on the healthcare system, with annual costs surpassing $1 billion[2]. The timing of endoscopy in acute NVUGIB has long been an area of discussion and research[4-12]. While multiple guidelines recommend early esophagogastroduodenoscopy (EGD) (within 24 h of admission) for NVUGIB, existing evidence regarding the benefit of early endoscopy remains unclear[1,4,6-10,13,14]. Several studies have revealed mortality benefits with early endoscopy; however, they included variceal hemorrhage in their cohort, were limited by small sample size, single-center experiences, and/or did not examine healthcare usage amongst the study outcomes[5,7,11].

While numerous scoring systems—such as the Rockall score, Blatchford score, and AIMS65—have been proposed to help risk stratify patients presenting with UGIBs, none of them have been adopted widely. Moreover, few large-scale studies have assessed variables such as anticoagulation (AC) use and/or demographic features for adverse hospitalization outcomes in NVUGIB.

The purpose of this study was to analyze a large, nationwide database to identify risk factors that predict differences in outcomes in patients hospitalized for NVUGIB—with a particular focus on timing to EGD, anticoagulation status, and demographic features.

MATERIALS AND METHODS

Data source

The National Inpatient Sample (NIS) is the largest publicly available all-payer inpatient database in the United States with more than seven million hospital stays each year, as a part of the Healthcare Cost and Utilization Project. As such, this database contains de-identified data on nationwide hospital admissions including demographic information, clinical data, comorbidities, discharge diagnoses, procedures, outcomes, and hospitalization costs. It lists patients based upon a primary discharge diagnosis, up to 29 sary diagnoses, and is associated with 15 different procedural codes.

Study population

In this retrospective cohort study, using the NIS data from 2009 to 2014, adult (> 18 years old) patients with a primary diagnosis of NVUGIB were identified *via* validated International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes[15].

Exclusion criteria: Patients admitted electively, below the age of 18, with a history of liver cirrhosis, and/or admitted for anything other than NVUGIB were excluded from this study.

Inclusion criteria: Adult patients (> 18 years old), no past medical history of liver cirrhosis with or without varices, primary admission diagnosis of upper gastrointestinal (GI) bleed were included in our study.

Patients who had an esophagogastroduodenoscopy (EGD) during the hospitalization were identified and linked with the time and/or day the procedure was performed. Subsequently, those that underwent an EGD were stratified into 2 groups: (1) Early, defined as EGD performed within 24 h of admission; and (2) late, defined as EGD performed after 24 h from admission[12,13]. A subgroup analysis was performed by further stratifying these patients based on timing of EGD: (1) EGD performed within 24 h after admission; (2) EGD performed 24-48 h after admission; (3) EGD performed 48-72 h after admission; and (4) EGD performed more than 72 h after admission. Additionally, to determine the association between EGD timing and mortality, another subgroup analysis was performed to identify the AC status (warfarin, dabigatran, rivaroxaban, or apixaban) for all patients who underwent an EGD (due to the limited granularity of the NRD dataset, anti-platelet therapy use was unable to be determined). Thereafter, a sensitivity analysis was performed, for the most common etiology of bleeding, to determine the independent association between EGD timing and mortality. The validated ICD-9-CM diagnostic and procedural codes used in this study are presented in Supplementary Table 1[15]. Institutional Review Board approval was not required for this study as it was performed using de-identified and nationally available data.

Study variables

Patient demographics were age, sex, race, primary expected payer, hospital bed size (small, medium, and large), teaching status, and hospital location (urban *vs* rural). Burden of comorbidities was assessed using the chronic condition indicator originating from the Elixhauser comorbidity index and Hwang's method[16,17]. These are medical conditions that last 12 mo or longer, resulting in ongoing need for the use of medical services or products, and place undue limitations on self-care, independent living, and social interactions.

Hospital bed size was reported as small for hospitals in the northern region that had 1-49 beds (rural), 1-124 beds (Urban, nonteaching) and 1-249 beds (Urban, teaching); in the Midwest region that had 1-29 (rural), 1-74 (Urban, nonteaching) and 1-249 (Urban, teaching); southern region 1-39 (rural), 1-99 (Urban, nonteaching) and 1-249 (Urban, teaching); and western region 1-24 (rural), 1-99 (Urban, nonteaching) and 1-199 (Urban, teaching). Hospital bed size was reported as medium hospitals in the northern region that had 50-99 beds (rural), 125-199 (Urban, nonteaching) and 250-424 (Urban, teaching); Midwest region 30-49 (rural), 75-174 (Urban, nonteaching) and 250-374 (Urban, teaching); southern region 40-74 (rural), 100-199 (Urban, nonteaching) and 250-499 (Urban, teaching); and western region 25-44 (rural), 100-174 (Urban, nonteaching) and 200-324 (Urban, teaching). Hospital bed size was reported large for hospitals in the northern region that had 100+ beds (rural), 200+ (Urban, nonteaching) and 425+ (Urban, teaching); Midwest region 50+ (rural), 175+ (Urban, nonteaching) and 375+ (Urban, teaching); southern region 75+ (rural), 200+ (Urban, nonteaching) and 450+ (Urban, teaching); and western region 45+ (rural), 175+ (Urban, nonteaching) and 325+ (Urban, teaching).

Thirty comorbidities were taken into account among which: Congestive heart failure, Cardiac arrythmias, Valvular disease, Pulmonary circulation disorders, peripheral vascular disorders, Hypertension, paralysis, neurodegenerative disorders, uncomplicated diabetes, complicated diabetes,

hypothyroidism, renal failure, liver disease, peptic ulcer disease excluding bleeding, acquired immunodeficiency syndrome/human immunodeficiency virus, lymphoma, metastatic cancer, solid tumor without metastasis, rheumatoid arthritis/collagen vascular diseases, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, blood loss anemia, deficiency anemia, alcohol abuse, drug abuse, Psychoses, and depression.

Study outcomes

Our primary outcome was in-hospital all-cause mortality: (1) Based upon ethno-racial/socioeconomic disposition; (2) per EGD timing; and (3) based upon long-term anticoagulation status. Our secondary outcomes included: (1) Intensive care unit (ICU) admission; (2) mean length of stay (LOS); (3) mean hospitalization charges and costs; and (4) patient disposition; discharge to home *vs* short- or long-term rehabilitation facilities. All these outcomes were defined using validated ICD-9 diagnostic and procedural codes, as shown in Supplementary Table 1[15].

Statistical analysis

Statistical analyses were performed using IBM SPSS statistics for windows software, version 24.0 (IBM Corp., Armonk, NY, United States). This software facilitates analysis to produce nationally representative unbiased results, variance estimates and *P* values. A weight for patient-level observations was implemented. Proportions were compared using the Chi square test and continuous variables were compared using the student t-test (for outcomes with two levels) and ANOVA (for outcomes with more than two levels). Univariate analysis was initially performed to calculate unadjusted odds ratio and determine confounders significantly associated with the outcomes. The multivariate regression analysis was performed to adjust for gender, race category, age category, insurance payer, hospital details (region, size, location, ownership), comorbidities and EGD within 1 d of admission. A significant association was determined with a cutoff *P* value of 0.2. Regression models were then built by including all confounders that were found to be significant by univariate analysis, to calculate adjusted odds ratio. Logistic regression was used to model in-hospital mortality with and without regard to anticoagulant use, ICU admission status, and patient disposition upon discharge. Linear regression was used to model hospital LOS and total charges. All *P* values were two sided, with 0.01 as threshold for statistical significance.

RESULTS

Patient and hospital characteristics

1082516 adult patients with a diagnosis of NVUGIB were included in the study. The mean age was 66.1 years, the majority of patients were female (50.3%), white (69.6%), and had 4 or more comorbidities (81.1%). Medicare was the primary payer insurance of the patients (62.2%) and patients were predominantly admitted to non-teaching hospitals (80.1%). The complete patient and hospital characteristics are presented in Table 1.

EGD during hospital admission

Of the 1082516 patients admitted for NVUGIB, 553,186 patients (51.1%) underwent EGD during hospital admission. Early (< 24 h) EGD was performed in 265529 patients (48%). The mean time to EGD was 52.8 h. Peptic ulcers represented the most common etiology of NVUGIB (62%). Figure 1 summarizes the pattern of EGD timing by gastroenterologists. Figure 2 summarizes the etiology of NVUGIB. Table 2 offers data on demographic/ethno-racial predictors of hospitalization outcomes.

EGD timing and mortality

Our primary outcome, total all cause in-hospital mortality for patients admitted with NVUGIB, was 5.9%. There was a significantly increased likelihood of mortality in patients who underwent EGD after 24 h compared to those whom had it done within 24 h of admission (aOR 2.94, $P < 0.001$). Additionally, compared to those who underwent EGD within the first 24 h, there was a significantly increased likelihood of mortality if EGD was done 48-72 h (aOR 1.54, $P < 0.001$) or > 72 h of admission (aOR 1.63, $P < 0.001$); however, there was no mortality difference if EGD was performed 24-48 h of admission (aOR 1.01, $P = 0.805$) (Figure 3). Upon subgroup analysis, examining the most common etiology of bleeds, for both peptic ulcer bleeds and bleeding gastritis/duodenitis there was a significantly increased likelihood of in-hospital mortality in patients who underwent EGD after 24 h compared to those who had it done within 24 h of admission [(aOR 1.20, $P < 0.001$), and (aOR 1.15, $P = 0.001$) respectively].

EGD timing and mortality stratified by anticoagulation use

Total all-cause in-hospital mortality for patients on long-term AC (either warfarin, dabigatran, rivaroxaban, or apixaban) (of note, anti-platelet therapy use was unable to be determined) admitted with NVUGIB was 7.0% as compared to 5.1% [aOR 2.02, $P = 0.001$] in patients that were *not* on AC. Total

Table 1 Patient, hospital, and clinical characteristics of all admissions for non-variceal upper gastrointestinal bleeding

Variable	Number (%) or mean ± SD
Mean age	66.10 yr ± 16.45 yr
Age group	
18 to 49 yr	199875 (18.5)
50 years or more	882641 (81.5)
Sex	
Female	544506 (50.3)
Male	538010 (49.7)
Race	
White	692345 (69.6)
Black	145949 (14.7)
Hispanic	95736 (9.6)
Asian/pacific islander	26569 (2.7)
Native American	7082 (0.7)
Other	26982 (2.7)
Payment method/insurance type	
Medicare	653964 (62.2)
Medicaid	118107 (11.2)
Private insurance	213404 (20.3)
Self-pay	59962 (5.7)
Other insurance	5932 (0.6)
Hospital location	
Urban	288087 (81.8)
Rural	63972 (18.2)
Hospital teaching status	
Non-teaching hospital	334 (80.1)
Teaching hospital	83 (19.9)
Hospital bed size	
Small	188 (45.1)
Medium	105 (25.2)
Large	124 (29.7)
Comorbidities	
None	12361 (1.1)
One	45456 (4.2)
Two	61930 (5.7)
Three	84763 (7.8)
Four or more	878006 (81.1)

all-cause in-hospital mortality for patients on long-term AC who underwent EGD was 1.5% as compared to 2.5% [aOR 1.83, $P = 0.001$] in patients on long-term AC who did *not* undergo EGD. There was no significant difference in mortality between patients on long-term anticoagulation who underwent EGD within 24 h compared to those whom had it done after 24 h from admission (aOR 0.88, $P = 0.193$). Additionally, there was no significant difference in mortality for those on long-term anticoagulation if EGD was done 24-48 h (aOR 0.78, $P = 0.015$), 48-72 h (aOR 1.01, $P = 0.907$), or > 72 h from admission (aOR 1.35, $P = 0.036$), compared to those who underwent EGD within the first 24 h.

Table 2 Demographic/Ethno-racial predictors of hospitalization outcomes

Factor	Mortality	LOS	Discharge home	ICU admission
Gender				
Male (*vs* female)	aOR: 1.32, 95%CI: 1.26-1.38[a]	aOR: -0.25, 95%CI: -0.30-0.1[a]	aOR: 1.22, 95%CI: 1.19-1.24[a]	aOR: 1.36, 95%CI: 1.32-1.40[a]
Ethnicity				
Black (*vs* White)	aOR: 0.95, 95%CI: 0.89-1.01	aOR: 1.13, 95%CI: 1.05-1.21[a]	aOR: 0.96, 95%CI: 0.93-0.98[a]	aOR: 1.04, 95%CI: 0.99-1.09
Hispanic (*vs* White)	aOR: 1.15, 95%CI: 1.07-1.24[a]	aOR: 0.62, 95%CI: 0.53-0.72[a]	aOR: 1.29, 95%CI: 1.24-1.35[a]	aOR: 1.10, 95%CI: 1.05-1.16[a]
Asian (*vs* White)	aOR: 1.30, 95%CI: 1.15-1.46[a]	aOR: 0.84, 95%CI: 0.67-1.01	aOR: 1.21, 95%CI: 1.13-1.30[a]	aOR: 1.28, 95%CI: 1.18-1.40[a]
CCI				
4 *vs* 0	aOR: 4.71, 95%CI: 3.02 -7.35[a]	aOR: 2.82, 95%CI: 2.57–3.07[a]	aOR: 0.32, 95%CI: 0.26-0.38[a]	aOR: 5.35, 95%CI: 4.00-7.14[a]

[a]*P* = 0.001. aOR: Adjusted odds ratio; CCI: Charlson comorbidity index; CI: Confidence interval; ICU: Intensive care unit; LOS: Length of stay.

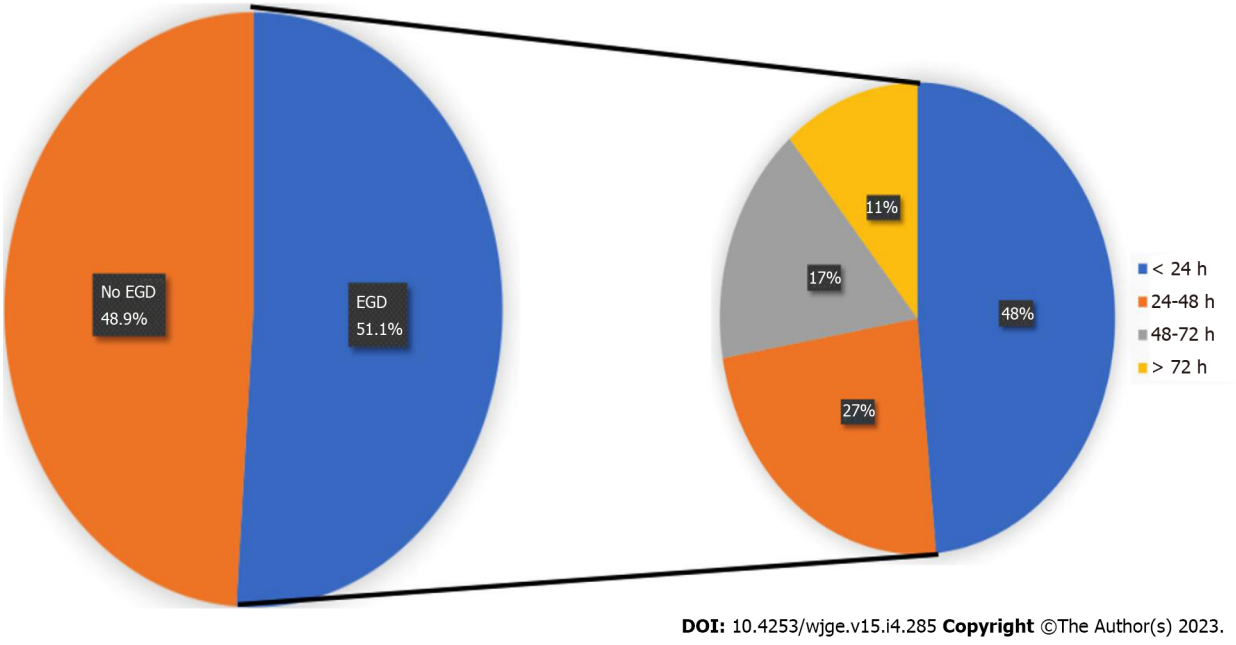

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Figure 1 Pie chart illustrating the performance and timing of esophagogastroduodenoscopy in patients hospitalized with non-variceal upper gastrointestinal bleeding relative to admission. EGD: Esophagogastroduodenoscopy.

EGD timing and ICU admission

Of patients admitted for NVUGIB, 7.9% were admitted to the ICU at some point during the hospital stay. Patients who underwent EGD after 24 h had a significantly increased likelihood of ICU admission compared to those who underwent EGD within 24 h from admission (aOR 1.51, $P = 0.001$). Additionally, compared to those who underwent EGD within the first 24 h of admission there was a significant increased likelihood of ICU admission if EGD was performed 48-72 h (aOR 1.59, $P = 0.001$) or > 72 h (aOR 1.21, $P = 0.001$) from admission; however, there was no significant difference in ICU admission if EGD was performed within 24-48 of admission (aOR 1.03, $P = 0.045$) (Figure 3).

EGD timing and healthcare usage

The mean LOS for patients admitted with NVUGIB was 6.55 d. Patients who underwent EGD within 24 h had a significantly lower LOS (adjusted coefficient: -2.19 d, $P < 0.001$) compared to those who underwent EGD after 24 h from admission. Additionally, compared to patients who underwent EGD within the first 24 h, there was a significantly increased LOS if EGD was performed 48-72 (adjusted coefficient: 2.90, $P < 0.001$) or > 72 h (adjusted coefficient: 4.43, $P < 0.001$) from admission; however no significant difference was found in LOS for EGD performed between 24-48 h (adjusted coefficient: 0.96, $P = 0.08$) (Figure 4).

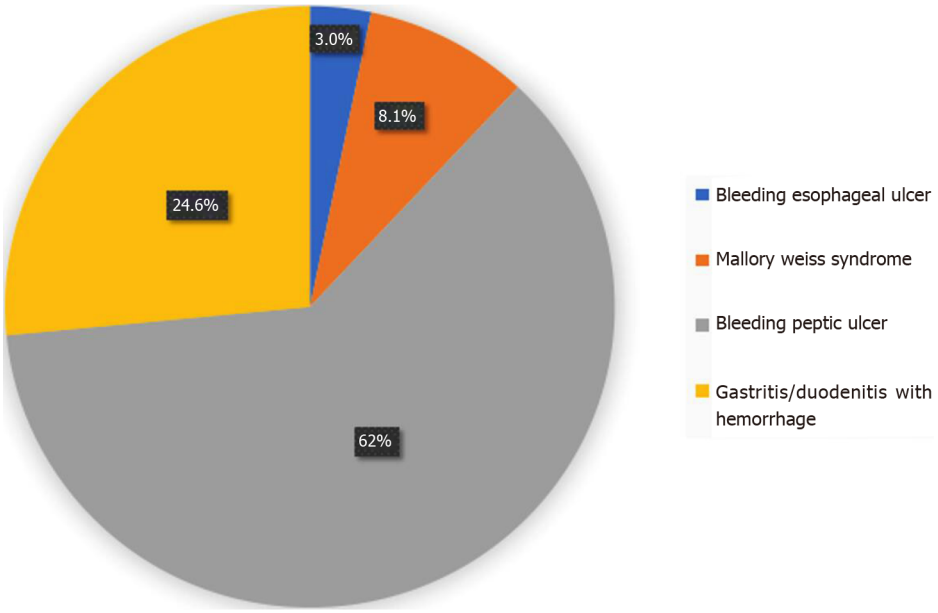

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Figure 2 Various etiologies of non-variceal upper gastrointestinal bleeding in the study sample.

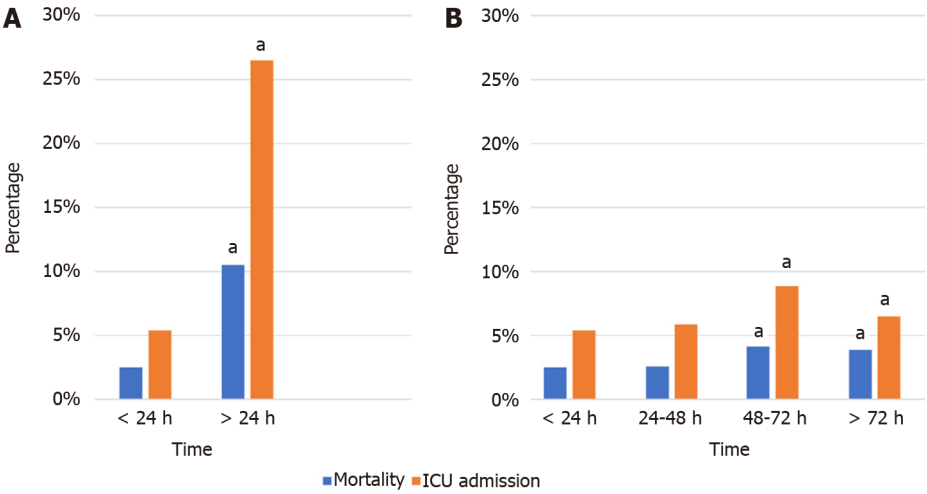

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Figure 3 Hospital mortality and intensive care unit admissions among patients who underwent esophagogastroduodenoscopy (EGD) for non-variceal upper gastrointestinal bleeding as a function of time to EGD. A: < 24 h *versus* > 24 h of admission; B: At all time strata. [a]*P* < 0.001. ICU: Intensive care unit.

Mean hospitalization charges for all patients admitted with NVUGIB was $56195. Patients who went through EGD in the first 24 h of admission had significantly lesser mean hospitalization charges compared to those who had it done post 24 h (adjusted coefficient: $-9021, $P < 0.001$). Additionally, compared to patients who underwent EGD within the first 24 h of admission, there were significantly higher hospitalization charges if EGD was performed 24-48 h (adjusted coefficient: $8441), 48-72 h (adjusted coefficient: $27341), or after 72 h (adjusted coefficient: $26216) from admission (all with $P < 0.001$) (Figure 5).

Overall, 56.9% of patients were discharged to home as opposed to a rehabilitation facility. Patients who had EGD after 24 h were significantly less likely to be discharged home than those who underwent EGD within 24 h from admission (aOR 0.69, $P < 0.001$). Additionally, there was a significantly decreased likelihood of discharge to home if EGD was performed 24-48 h (aOR 0.44), 48-72 h (aOR 0.60), or > 72 h (aOR 0.86) from admission, compared to patients who underwent EGD within the first 24 h of admission (all with $P < 0.001$) (Figure 6).

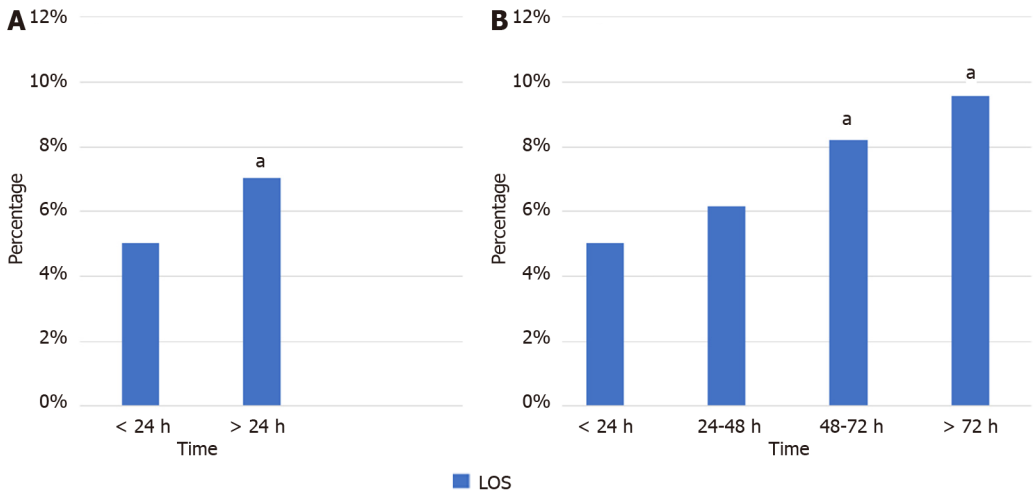

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Figure 4 Hospital length of stay among patients who underwent esophagogastroduodenoscopy (EGD) for non-variceal upper gastrointestinal bleeding as a function of time to EGD. A: < 24 h *versus* > 24 h of admission; B: At all time strata. [a]*P* < 0.001. LOS: Length of stay.

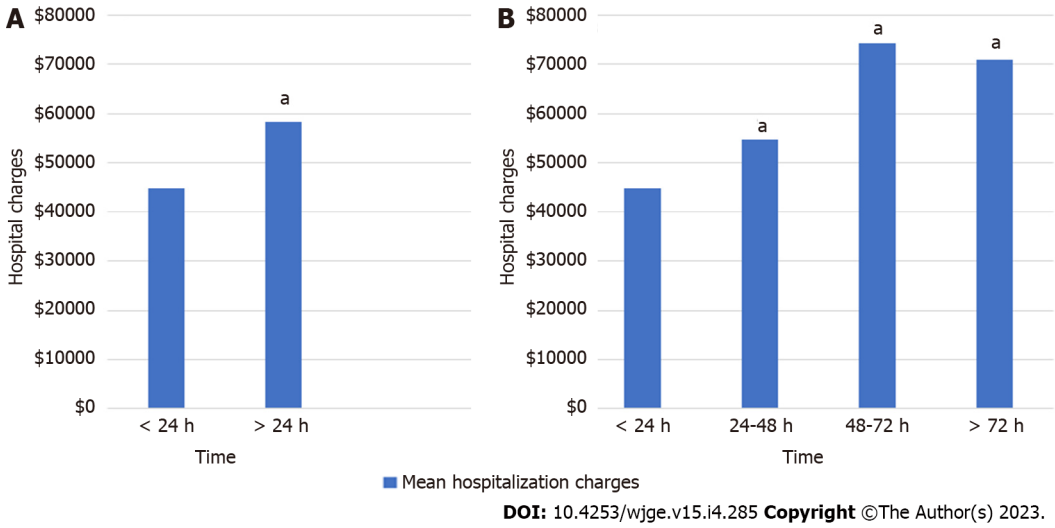

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Figure 5 Hospital charges among patients who underwent esophagogastroduodenoscopy (EGD) for non-variceal upper gastrointestinal bleeding as a function of time to EGD. A: < 24 h *versus* > 24 h of admission; B: At all time strata. [a]*P* < 0.001.

DISCUSSION

Using a large, nationally representative database, we found that mortality was significantly affected by the timing of endoscopic intervention in patients admitted with NVUGIB. Patients who underwent an EGD within the first 24 h had lower mortality than those who had it performed after 24 h of admission. Interestingly, there was no mortality difference if EGD was performed 24-48 h of admission as compared to within the first 24 h, despite current guidelines that suggest EGD within the first 24 h of hospital admission. In addition, we found that patients on long-term AC who did *not* undergo EGD had higher mortality than those who did, which appears to be unaffected timing. Moreover, we were able to identify numerous other factors such as-Male sex, Hispanic or Asian race, and those with more numerous comorbidities, to help predict patients at high risk for adverse hospital outcomes in NVUGIB.

Although prior studies have aimed to determine the appropriate timing of EGD in patients hospitalized for UGIB, the current study demonstrates some unique and important differences[4-14]. Including variceal hemorrhage amongst the etiology of bleeding, as done in prior studies, limits the value of extrapolating the data to NVUGIB in particular[11]. As variceal bleeding is thought to spontaneously cease (without endoscopic intervention) in up to 50% of cases and most other causes of upper GI bleeding in up to 80% of cases, variceal bleeding is of higher acuity[18,19]. While specifically examining NVUGIB (as opposed to all UGIB), as well as subgrouping by etiology of NVUGIB, we were able to identify the benefits/advantages of early endoscopy in this setting.

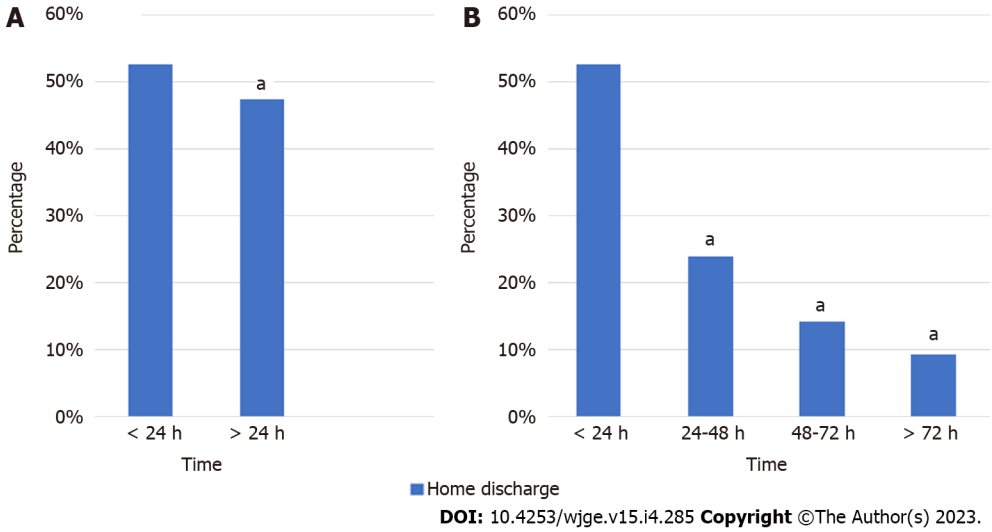

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Figure 6 Home discharge (as opposed to discharge to a rehabilitation facility) among patients who underwent esophagogastroduodenoscopy (EGD) for non-variceal upper gastrointestinal bleeding as a function of time to EGD. A: < 24 h *versus* > 24 h of admission; B: At all time strata. [a]*P* < 0.001.

During the years of data collection (2009-2014), we noted that the mean time to EGD was 52.8 h, less than half of patients underwent EGD within 24 h of admission, and 11% of patients underwent EGD greater than 72 h after admission, even though current guidelines suggest EGD within the first 24 h of hospital admission.

Notably, the timing of EGD did not affect mortality in patients on long-term anticoagulation. Endoscopic hemostasis was notably safe and effective in a study where patients were anticoagulated with warfarin and international normalized ratio (INR) was observed to be 1.5-2.5. A limitation of this analysis was the low number of study sample (n = 23 patients)[20]. More studies are needed to assess the impact of elevated INR and/or use of direct oral anticoagulants and the risk of increased adverse outcomes (worsening bleeding, failure of hemostasis, need for transfusion, and/or mortality) in patients undergoing early endoscopy *i.e.*, within 24 h of presentation. This will help formulate guidelines and assist the endoscopist in taking informed decisions for their patients that are on anticoagulants and presenting with NVUGIB.

Healthcare utilization was significantly affected by EGD timing. ICU admission rates were significantly higher in patients who had a delayed EGD (> 24 h from time of admission). Overall healthcare costs and LOS were also significantly affected by EGD timing. Additionally, discharge disposition was directly related to the timing of EGD, with those patients having an EGD within 24 h from admission being more likely to be discharged to home. Retrospective studies have shown the benefit of decreasing the length of stay in patients undergoing early EGD. Chak *et al*[21] demonstrated significantly decreased length of hospital stay in patients undergoing early EGD within 24 h of admission *vs* after 24 h (median 5 *vs* 7 d, $P < 0.005$). Similarly, Jairath *et al*[22] demonstrated that patients that underwent delayed endoscopy *i.e.* after 24 h remained 1.7 d longer in the hospital compared to those that underwent endoscopy within 12 h. Our study demonstrated a significant decrease in healthcare utilization, including ICU admission, data which has not been previously found on a national level[5]. Nevertheless, we acknowledge that perhaps patients whom went to the ICU were too hemodynamically unstable for an early EGD, thus it cannot be determined, based on this observation, what the causality was.

Our results are consistent with previous studies in terms of increasing age and comorbidities causing increased mortality rates in patients presenting with an upper GI bleed[23,24]. We further found that male sex, Hispanic or Asian race and persons on Medicaid insurance were also at increased risk of mortality. These findings may partially be explained by hormonal differences in (male) sex, and/or limited access to healthcare for patients of Hispanic/Asian race or those with Medicaid insurance.

Some limitations should be taken into account when interpreting the data of the current study. First, we used a database that relies on billing codes to generate diagnoses limited to the inpatient setting. Second, akin to many other national databases, a few important pieces of information might not be available in the NIS database. This missing data prevents the determination of the clinical severity or contraindications to EGD (*e.g.*, severe coagulopathy). Third, the specific reason for EGD timing (24 h *vs* 48 h *vs* 72 h) remains unknown. While early EGD could be associated with hospital teaching status, patient comorbidity, age, and/or socioeconomic status, other factors not possible to quantify—such as endoscopist or patient preference-may have contributed. Lastly, incorrect ICD coding (and consequently erroneous inclusion of patients with variceal bleeding, for example) could have skewed data in favor of

early EGD; however, with such a large dataset, we believe that such patients would be unlikely to significantly affect the overall results, especially since we have used validated codes[15].

Despite such limitations, our study has several strengths. The primary strength is the large sample size and breadth of the population studied. This is significantly more expansive than other studies on this topic, which tend to be smaller. Within the limits of making associations from a coding database, the large sample size and variety of patients lessen the risk of making unwarranted conclusions based on outliers. In addition, we were able to provide meaningful information on both well-studied endpoints such as all-cause inpatient mortality, as well as other less-studied outcomes such as ICU admission, health care utilization, and home discharge. Further, we were able to stratify based on several time strata to predict the appropriate time frame for EGD in NVUGIB.

CONCLUSION

To conclude, early EGD (within 24 h) is associated with several benefits including less mortality, irrespective of anticoagulation status. Insofar as high-quality RCTs examining the timing of EGD in NVUGIB are unlikely to be conducted, the findings of this large, nationwide study may serve as a useful clinical resource to effectively help guide patient care. Additionally, we identified numerous other factors such as-Male sex, Hispanic or Asian race, and those with more numerous comorbidities, all of which may help predict patients at high risk for adverse hospital outcomes in NVUGIB.

ARTICLE HIGHLIGHTS

Research background

Patients are often admitted for nonvariceal upper Gastrointestinal bleeding (NVUGIB). However, there is not enough data on the importance and timing of esophagogastroduodenoscopy (EGD) in those scenarios.

Research motivation

The main motivation of this study was to identify independent predictors of outcomes in patients with NVUGIB, with a particular focus on EGD timing, anticoagulation (AC) status, and demographic features.

Research objectives

The purpose of this study was to analyze a large, nationwide database to identify risk factors that predict differences in outcomes in patients hospitalized for NVUGIB—with a particular focus on timing to EGD, anticoagulation status, and demographic features.

Research methods

This was a retrospective analysis of patients with NVUGIB from 2009 to 2014, using validated ICD-9 codes from the National Inpatient Sample database. Patients were stratified by EGD timing relative to hospital admission (≤ 24 h, 24-48 h, 48-72 h, and > 72 h) and then by AC status (yes/no). The primary outcome was all-cause inpatient mortality. Secondary outcomes included healthcare usage.

Research results

553186 (51.1%) patients underwent EGD between 2009-2014. The mean time to EGD was 52.8 h. Early (< 24 h from admission) EGD was associated with significantly decreased mortality, less frequent ICU admission, shorter length of hospital stays, lower hospital costs, and an increased likelihood of discharge to home (all with $P < 0.001$). AC status was not associated with mortality among patients who underwent early EGD (aOR 0.88, $P = 0.193$). Male sex (OR 1.30) and Hispanic (OR 1.10) or Asian (aOR 1.38) race were also independent predictors of adverse hospitalization outcomes in NVUGIB.

Research conclusions

Early EGD (within 24 h) is associated with lower mortality, less hospital cost and less healthcare utilization; regardless of the consumption of anticoagulants.

Research perspectives

Randomized clinical trials examining the timing of EGD in NVUGIB will be difficult to conduct. Thus, the data of our study can shed some light on this clinically important subject. Additionally, we identified numerous other factors such as-Male sex, Hispanic or Asian race, Medicaid insurance, age > 50, and those with more numerous comorbidities, all of which may help predict patients at high risk for adverse hospital outcomes in NVUGIB.

FOOTNOTES

Author contributions: Weissman S, Aziz M, and Bangolo A searched the literature, wrote, and revised the manuscript; Ehrlich D, Forlemu A, Willie A, Gangwani MK, Waqar D, Terefe H, Singh A, Gonzalez DMC, Sajja J, Emiroglu FL, Dinko N, Mohamed A, Fallorina MA, Kosoy D, Shenoy A, and Nanavati A revised and edited the manuscript; Feuerstein JD and Tabibian JH approved the final version and are the article's guarantors; All authors certify that they contributed sufficiently to the intellectual content and data analysis; Each author has reviewed the final version of the manuscript and approved it for publication.

Conflict-of-interest statement: All the authors have no potential conflict of interest to disclose.

Data sharing statement: The National Inpatient Sample is a publicly available dataset.

STROBE statement: The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Causes of gastrointestinal bleeding in children based on endoscopic evaluation at a tertiary care center in Bahrain

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Abstract

BACKGROUND

Gastrointestinal bleeding (GIB) is a serious health problem worldwide, particularly during childhood. This can be an alarming sign of an underlying disease. Gastrointestinal endoscopy (GIE) is a safe method for the diagnosis and treatment of GIB in most cases.

AIM

To determine the incidence, clinical presentation, and outcomes of GIB in children in Bahrain over the last two decades.

METHODS

This was a retrospective cohort review of the medical records of children with GIB who underwent endoscopic procedures in the Pediatric Department at Salmaniya Medical Complex, Bahrain, between 1995 and 2022. Demographic data, clinical presentation, endoscopic findings, and clinical outcomes were recorded. GIB was classified into upper (UGIB) and lower (LGIB) GIB according to the site of bleeding. These were compared with respect to patients' sex, age, and nationality using the Fisher's exact, Pearson's χ^2, or the Mann-Whitney U tests.

RESULTS

A total of 250 patients were included in this study. The median incidence was 2.6/100000 per year (interquartile range, 1.4-3.7) with a significantly increasing

trend over the last two decades (P < 0.0001). Most patients were males (n = 144, 57.6%). The median age at diagnosis was 9 years (5–11). Ninety-eight (39.2%) patients required upper GIE alone, 41 (16.4%) required colonoscopy alone, and 111 (44.4%) required both. LGIB was more frequent (n = 151, 60.4%) than UGIB (n = 119, 47.6%). There were no significant differences in sex (P = 0.710), age (P = 0.185), or nationality (P = 0.525) between the two groups. Abnormal endoscopic findings were detected in 226 (90.4%) patients. The common cause of LGIB was inflammatory bowel disease (IBD) (n = 77, 30.8%). The common cause of UGIB was gastritis (n = 70, 28%). IBD and undetermined cause for bleeding were higher in the 10–18 years group (P = 0.026 and P = 0.017, respectively). Intestinal nodular lymphoid hyperplasia, foreign body ingestion, and esophageal varices were more common in the 0–4 years group (P = 0.034, P < 0.0001, and P = 0.029, respectively). Ten (4%) patients underwent one or more therapeutic interventions. The median follow-up period was two years (0.5-3). No mortality was reported in this study.

CONCLUSION

GIB in children is an alarming condition, whose significance is increasing. LGIB, commonly due to IBD, was more common than UGIB, commonly due to gastritis.

Key Words: Pediatric; Gastrointestinal bleeding; Endoscopy; Causes; Outcome; Bahrain

Core Tip: The incidence, clinical presentation, cause, and outcomes of gastrointestinal bleeding (GIB) in children in Bahrain are unknown. We observed a significant increase in the annual incidence of GIB. Lower GIB (LGIB) was more common than upper GIB (UGIB). The most common cause of LGIB was inflammatory bowel disease. The most common cause of UGIB was gastritis. Causes of GIB varied with patient's age and differed from that reported in other countries. No mortality was observed in any patient. These findings are essential to tailor management based on the most common causes and patient age.

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INTRODUCTION

Gastrointestinal (GI) bleeding (GIB) is a serious health problem worldwide, particularly during childhood. It is defined as any kind of hemorrhage or blood loss in the digestive tract, from the mouth to the anus[1], which can range from nearly undetectable to acute, massive, or life-threatening[1]. It is divided into three main clinical forms: Upper GIB (UGIB), lower GIB (LGIB), and bleeding of obscure origin[2]. UGIB and LGIB are defined based on their relationship with the ligament of Treitz[3]. The source of bleeding in UGIB is proximal to the ligament of Treitz (from the upper part of the esophagus to the duodenojejunal flexure), whereas that of LGIB is distal to the ligament (small bowel and colon)[3]. GIB can also be occult, that is, not visible to the patient or physician, leading to either a positive fecal occult blood test or iron-deficiency anemia[3].

GIB can cause anxiety in children, caregivers, and healthcare providers[4] and can be an alarming sign of an underlying disease[5]. GIB has a variety of causes; a good elicitation of patients' medical history and physical examination can adequately differentiate between macroscopic and microscopic forms of bleeding[5].

GI endoscopy (GIE) is a safe method for the diagnosis and treatment of GIB[4]. GIE can reveal the underlying etiology of GIB in most cases[3]. However, it requires the experience and coordination of the medical team to provide specialized patient care[6].

According to the Italian Society of Pediatric Gastroenterology, the incidence rate of GIB in children is 6.4%[3]. However, there is a paucity of studies regarding the incidence and causes of GIB in the pediatric population in the Middle East. Thus, we aimed to determine the incidence, clinical presentation, causes, and outcomes of GIB in children at the main tertiary hospital in Bahrain over the last two decades. Additionally, we aimed to stratify the causes of GIB based on patient age.

MATERIALS AND METHODS

Study design and setting

We conducted a retrospective cohort review of all medical records of children diagnosed with GIB in the Pediatric Department at Salmaniya Medical Complex (SMC), Manama, Bahrain, between January 1995 and October 2022. SMC is the only tertiary hospital in Bahrain to where children with GIB are referred for diagnosis and management. Endoscopic procedures were performed in either the endoscopy unit or the main operating theatre. The endoscopy unit in SMC consists of three rooms, in which three pediatric gastroenterology consultants and one chief resident can perform endoscopic procedures. Two types of endoscopic equipment were used: Olympus (PCF-230 and XQ230, Olympus Cooperation, Shinjuku, Tokyo, Japan) and Pentax (EG-2901 and EC-380IF, Pentax Ricoh Imaging Company Ltd, Tokyo, Japan).

Study participants

All children who were admitted to the pediatric department for GIB and underwent GIE were included in the study. Patients who were discharged from the emergency department and those who did not undergo endoscopic procedures were excluded. Patients were classified as having upper, lower, or both GIB according to their presenting symptoms.

Data collection

From 1995 to 2010, the data were retrieved from archived paper-based medical records, while from 2010 to 2022, the data were retrieved from the I-Seha electronic medical records. The following demographic data were collected: Year of presentation, sex, nationality, age at diagnosis, and history of associated chronic diseases.

Presenting symptoms, such as hematemesis, melena, and rectal bleeding (hematochezia), were noted. Additional symptoms, including recurrent vomiting or abdominal pain, chest pain, diarrhea, constipation, weight loss, and history of foreign body or caustic ingestion, were noted. Physical findings such as oral ulcers, pallor, jaundice, perianal fistula or fissure, hemorrhoids, and failure to thrive were recorded. A perianal fistula was defined as a small passage that connects an infected gland inside the anus to an opening on the skin around the anus. A perianal fissure is a tear in the anal mucosa. Failure to thrive (thinness) was defined as a weight for age z-score of < 2 standard deviations according to the World Health Organization growth references[7].

Endoscopy data on the type, upper (UGIE) or lower (LGIE) GIE, and the total number of procedures performed were collected. The causes of GIB were based on endoscopic findings, such as Mallory–Weiss syndrome, esophagitis, esophageal ulcer or varices, foreign body ingestion, gastritis, peptic or duodenal ulcer, gastroenteritis, inflammatory bowel disease (IBD), nodular lymphoid hyperplasia, Meckel's diverticulum, rectal ulcers or polyps, and anal fissures. Data on therapeutic interventions, as well as number of patients who required repeat endoscopic interventions, follow-up duration, and patient outcomes were collected.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) (version 21; IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp, United States). The annual incidence of GIB was calculated. The 28-year study period was divided into four periods (1995–2001, 2002–2008, 2009–2015 and 2016–2022), which were compared in terms of the mean annual incidence of GIB using a one-way analysis of variance test. Bonferroni post-hoc analysis was used for pairwise multiple comparisons between the four periods. Patient ages were classified into three groups: 0–4, 5–9, and 10–18 years. Categorical variables are presented as frequency and percentage. Continuous variables are presented as median and interquartile range (IQR). UGIB and LGIB were compared with respect to sex, age, and nationality. The causes of GIB were compared according to age group. Fisher's exact test or Pearson's χ^2 test was used to compare categorical variables, while the Mann–Whitney U test was used to compare continuous variables with a skewed distribution. P values < 0.05 were considered statistically significant.

Ethical approval

This study was conducted in accordance with the principles of Helsinki Declaration, and it was ethically approved by the Research and Research Ethics Committee, Salmaniya Medical Complex, Government hospitals, Kingdom of Bahrain (IRB number: 6170122, January 17, 2022).

RESULTS

During the study period, 250 children were admitted to the hospital for GIB and underwent a GIE procedure. All the patients were included in this study. According to the 2020 Bahrain Health Statistics, the total population in Bahrain was 1472204, with 481819 people within the pediatric age group (up to

18 years). The median incidence was 2.6/100000 per year (IQR, 1.4–3.7) with an increasing trend (Figure 1). A significant difference in the mean GIB incidence was found between the four periods, [F (3, 24) =10.280, P < 0.0001]. The mean incidence in 2009–2015 was significantly higher (4.9 ± 1.9) than that in 1995–2001 (1.7 ± 0.8), 2002-2008 (1.5 ± 0.9) and 2016-2022 (2.7 ± 1.9) (P = 0.001, P < 0.0001, P = 0.028, respectively). The demographic data of the included patients are shown in Table 1. Most of the patients were males (n = 144, 57.6%). The majority were Bahraini (n = 224, 89.6%), while the rest were non-Bahraini (n = 24, 9.6%) [eight (3.2%) were from India, three (1.2%) from Pakistan, two (0.8%) from Iraq, two (0.8%) from Egypt, one (0.4%) from Oman, one (0.4%) from Qatar, one (0.4%) from Yemen, one (0.4%) from Sudan, one (0.4%) from Syria, one (0.4%) from Sweden, one (0.4%) from Bangladesh, one (0.4%) from China, and one (0.4%) from Philippines]. Two patients (0.8%) were of unspecified nationality. The median age at the time of endoscopic diagnosis was 9 years (IQR, 5–11). The most commonly affected age group was the 10–18 years group (n = 107, 42.8%). Thirty-nine (15.6%) patients had one or more associated diseases that were not considered as a direct cause of GIB. The common associated diseases were gastroesophageal reflux disease (GERD) (n = 7, 2.8%) and celiac disease (n = 7, 2.8%), followed by sickle cell disease (n = 5, 2%), and autoimmune hepatitis (n = 4, 1.6%). Other associated diseases were cerebral palsy (n = 3, 1.2%), mental retardation (n = 3, 1.2%), biliary atresia (n = 2, 0.8%), Wilson's disease (n = 2, 0.8%), sclerosing cholangitis (n = 2, 0.8%), chronic liver disease with portal hypertension (n = 2, 0.8%), trisomy 21 (n = 2, 0.8%), Ehlers Danlos syndrome (n = 1, 0.4%), familial Mediterranean fever (n = 1, 0.4%), cholecystitis (n = 1, 0.4%), intestinal worms (n = 1, 0.4%), tracheoesophageal fistula (n = 1, 0.4%), liver cirrhosis (n = 1, 0.4%), Turner's syndrome (n = 1, 0.4%), insulin-dependent diabetes mellitus (n = 1, 0.4%), hydrocephalus (n = 1, 0.4%), glucose-6-phosphate dehydrogenase deficiency (n = 1, 0.4%), congenital heart disease (n = 1, 0.4%), hiatal hernia (n = 1, 0.4%), autoimmune hemolytic anemia (n = 1, 0.4%), food allergy (n = 1, 0.4%) and anorexia nervosa (n = 1, 0.4%).

LGIB was more frequent (n = 151, 60.4%) than UGIB was (n = 119, 47.6%). Out of the 250 patients, 20 (8%) patients underwent both UGIB and LGIB. Children with LGIB were older [median age of 9 years (IQR, 5–12)] than those with UGIB [median age of 8 years (IQR, 4–11)]. This difference was not statistically significant (P = 0.185). There was also no significant difference in sex (P = 0.710) and nationality (P = 0.525) between the two groups (Figure 2).

The clinical presentations are shown in Table 2. The most common presenting symptom was per rectal bleeding (n = 151, 60.4%), followed by hematemesis (n = 117, 46.8%). Some patients presented with more than one symptom. Physical examination was unremarkable in most of the patients (n = 218, 87.2%). However, 32 (12.8%) patients had positive findings on physical examination (Table 2).

Most patients (n = 206, 82.4%) required one GIE; the remaining 44 (17.6%) required more than one GIE. The median number of endoscopies was one, ranging from one to seven. Abnormal endoscopic findings were detected in 226 (90.4%) patients; twenty-four (9.6%) patients had a normal GIE. Examples of patients with positive findings are shown in Figure 3.

The different causes of GIB according to age group are shown in Table 3. The most common cause of LGIB was IBD (n = 77, 30.8%); thirty-four (44.1%) had ulcerative colitis, 33 (42.9%) had Crohn's disease, and 10 (13%) had unspecified IBD. The most common cause of UGIB was gastritis (n = 70, 28%); nonspecific gastritis (n = 55, 78.6%), Helicobacter pylori infection (n = 14, 20%), and eosinophilic gastritis (n = 1, 1.4%). In patients with both UGIB and LGIB, the causes of bleeding were gastritis (n = 6, 3.5%), gastroenteritis (n = 4, 2%), ulcerative colitis (n = 3, 1.5%), Crohn's disease (n = 2, 1%), unspecified IBD type (n = 1, 0.5%), esophageal ulcer (n = 1, 0.5%), gastric ulcer (n = 1, 0.5%), duodenal ulcer (n = 1, 0.5%), and esophagitis with gastritis (n = 1, 0.5%).

IBD and unclear cause for bleeding were significantly higher in the 10–18 years group (P = 0.026 and P = 0.017, respectively), while intestinal nodular lymphoid hyperplasia, ingestion of foreign bodies, and esophageal varices were more frequent in the 0–4 years age group (P = 0.034, P < 0.0001, and P = 0.029, respectively). There were no significant differences between other causes according to age groups.

Ten (4%) patients underwent one or more therapeutic interventions [polypectomy (n = 4, 1.6%), injection sclerotherapy (n = 3, 1.2%) where one required two sessions, clipping (n = 2, 0.8%), and banding of esophageal varices and dilatation of esophageal stricture (n = 1, 0.4% each)]. Forty-five (18%) patients underwent follow-up endoscopy for disease reassessment. The median follow up period was two years (IQR, 0.5–3). No mortality was reported in this study.

DISCUSSION

This study revealed that the median incidence of GIB in children was 2.6/100000 per year, which has significantly increased over the last two decades. This increase could be attributed to the overall increase in some of the underlying etiologies, such as IBD. The burden of IBD is rising worldwide[8]. In the Middle East, the incidence of GIB in children is not well established[9,10]. However, in the United States, it accounts for 1% of all pediatric hospitalizations[11]. Romano *et al*[3] reported a higher incidence reaching 6.4% in Italy.

Table 1 Demographic data of children presented with gastrointestinal bleeding

Variables	*n* (%)
Sex	
Male	144 (57.6)
Female	106 (42.4)
Nationality	
Bahraini	224 (89.6)
Non-Bahraini	24 (9.6)
Unspecified	2 (0.8)
Age group (yr) (*n* = 247)	
0-4	58 (23.2)
5–9	82 (32.8)
10–18	107 (42.8)
Type of endoscopy performed	
Upper gastrointestinal endoscopy	98 (39.2)
Lower gastrointestinal endoscopy	41 (16.4)
Both types of gastrointestinal endoscopies	111 (44.4)

Data are presented as numbers and percentages.

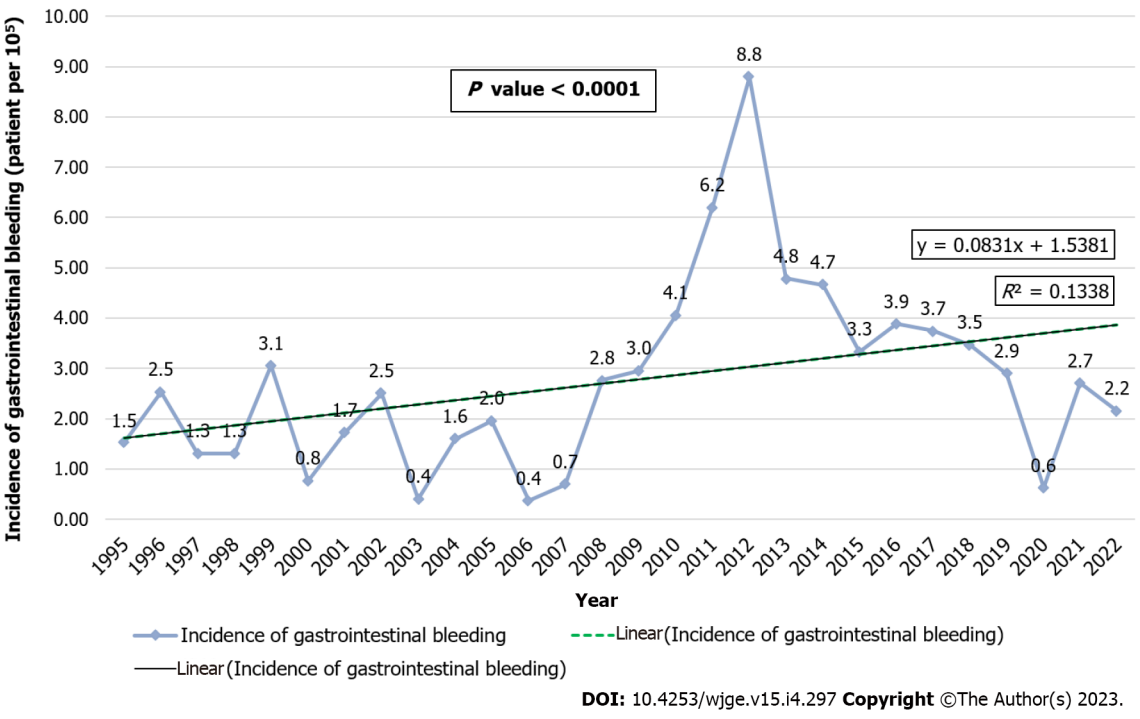

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Figure 1 Incidence of gastrointestinal bleeding in children, 1995-2022.

In the current study, most patients who presented with GIB were males (*n* = 144, 57.6%). This is comparable to several other studies, with a male predominance ranging between 54% and 59.2%[2,6,9,12,13]. However, Kalyoncu *et al*[14], Banisalamah *et al*[15], and Almadi *et al*[16] reported a higher percentage, ranging from 66.8% to 74.2%. The cause of this male predominance in children with GIB remains unclear.

In this study, the median age at the time of endoscopic diagnosis was 9 years (IQR, 5–11), with no significant difference according to the type of bleeding. Similarly, Cleveland *et al*[4] reported a median

Table 2 Clinical presentation of children with gastrointestinal bleeding

Clinical presentation	Patients' *n* (%)
Presenting symptom[a]	
Per rectal bleeding	151 (60.4)
Hematemesis	117 (46.8)
Melena	25 (10)
Associated symptom	
Recurrent abdominal pain	59 (23.6)
Diarrhea	23 (9.2)
Constipation	19 (7.6)
Recurrent vomiting	17 (6.8)
Weight loss	10 (4)
Chest pain	8 (3.2)
History of foreign body ingestion	7 (2.8)
Caustic ingestion	1 (0.4)
Nausea	1 (0.4)
Physical finding	
Normal	218 (87.2)
Pallor	11 (4.4)
Perianal fissure	11 (4.4)
Perianal fistula	4 (1.6)
Jaundice	3 (1.2)
Failure to thrive	2 (0.8)
Oral ulcers	1 (0.4)

[a]Some patients presented with more than one symptom. Data are presented as number and percentage.

age of 10.1 years with a mean age of 9.3 ± 5.7 years. However, Gimiga *et al*[6], Rafeey *et al*[10], and Kalyoncu *et al*[14] reported GIB in younger children (1.3, 6.1 ± 3.9, and 7.6 ± 2.4 years, respectively). Nonetheless, the most commonly affected age group in our study was 10–18 years. However, Jafari *et al*[2] and Hassoon *et al*[9] reported that children aged 6–12 years were more frequently affected, with percentages of 31.8% and 24%, respectively. Gimiga *et al*[6] and Zahmatkeshan *et al*[12] reported that the 2–10 and 3–10 years age groups were the most commonly affected, representing 63.7% and 55.1% of their patient samples, respectively. This variation in age at diagnosis could be attributed to the differences in the study settings, inclusion criteria, and site and causes of bleeding in each study.

In the current study, the most common associated diseases were GERD and celiac disease (n = 7, 2.8%). Attard *et al*[13] reported a higher percentage of GERD in children with GIB (12.2%). Almadi *et al*[16] also reported a high percentage of GERD (38.13%) in adult patients with GIB. Celiac disease can cause occult GIB; it rarely presents as frank GIB[1].

In the present study, LGIB was more frequent than UGIB was, accounting for 60.4% (n = 151) and 47.6% (n = 119) of cases, respectively. However, Jafari *et al*[2] determined that UGIB was more common than LGIB. Apart from the Jafari *et al*[2] study, all the other published studies tackled either UGIB or LGIB alone. Thus, our findings cannot be compared with those of other studies.

In this study, per rectal bleeding was the most frequent presenting symptom (n = 151, 60.4%). Gimiga *et al*[6] and Zahmatkeshan *et al*[12] reported similar findings, with hematochezia as the most common symptom in 54.2% and 80.2% of their patients, respectively.

In our study, 117 (46.8%) patients presented with hematemesis. This percentage is higher than those reported by Jafari *et al*[2] (40.7%) and Rafeey *et al*[10] (26.9%). However, Cleveland *et al*[4] and Hassoon *et al*[9]. reported higher percentages of 58.5% and 73.4%, respectively. This might be related to the fact that hematemesis is bright red and usually alarms the child and family to seek early medical advice[9].

In the present study, melena was the third most common symptom. However, Jafari *et al*[2] (17.73%), Cleveland *et al*[4] (20.8%), and Rafeey *et al*[10] (13.42%) reported higher percentages of melena. In

Table 3 Causes of gastrointestinal bleeding in children in relation to age group

Causes[a]	Age group (yr)			Total, *n* (%)	*P* value[b]
	0-4, *n* = 58 (23.2)	5-9, *n* = 82 (32.8)	10-18, *n* = 107 (42.8)		
Inflammatory bowel disease	10 (17.2)	27 (32.9)	40 (37.4)	77 (30.8)	**0.026**
Gastritis	16 (27.6)	23 (28)	31 (29)	70 (28)	0.980
Unclear cause (normal)	3 (5.2)	4 (4.9)	17 (15.9)	24 (9.6)	**0.017**
Gastroenteritis	7 (12.1)	9 (11)	6 (5.6)	22 (8.8)	0.275
Duodenal ulcer	5 (8.6)	4 (4.9)	11 (10.3)	20 (8)	0.397
Esophagitis	4 (6.9)	5 (6.1)	6 (5.6)	15 (6)	0.947
Rectal polyp	6 (10.3)	5 (6.1)	4 (3.7)	15 (6)	0.237
Anal fissure	1 (1.7)	5 (6.1)	5 (4.7)	11 (4.4)	0.461
Peptic ulcer	4 (6.9)	4 (4.9)	1 (0.9)	9 (3.6)	0.114
Colonic ulcers	2 (3.4)	5 (6.1)	2 (1.9)	9 (3.6)	0.305
Rectal ulcer	0 (0)	2 (2.4)	7 (6.5)	9 (3.6)	0.078
Intestinal nodular lymphoid hyperplasia	4 (6.9)	4 (4.9)	0 (0)	8 (3.2)	**0.034**
Foreign body ingestion	6 (10.3)	1 (1.2)	0 (0)	7 (2.8)	**< 0.0001**
Esophageal varices	4 (6.9)	0 (0)	2 (1.9)	6 (2.4)	**0.029**
Esophageal ulcer	2 (3.4)	1 (1.2)	2 (1.9)	5 (2)	0.646
Meckel's diverticulum	1 (1.7)	2 (2.4)	1 (0.9)	4 (1.6)	0.717
Mallory Weiss syndrome	1 (1.7)	2 (2.4)	0 (0)	3 (1.2)	0.291
Hemorrhoids	1 (1.7)	0 (0)	1 (0.9)	2 (0.8)	0.524
Duodenal varices	1 (1.7)	0 (0)	0 (0)	1 (0.4)	0.195
Colonic angiodysplasia	0 (0)	0 (0)	1 (0.9)	1 (0.4)	0.518
CMPA	1 (1.7)	0 (0)	0 (0)	1 (0.4)	0.195

[a]Some patients may have more than one cause.
[b]Pearson χ^2. Data are presented as number and percentage. *P* value < 0.05 was considered statistically significant. CMPA: cow's milk protein allergy.

contrast, Hassoon *et al*[9] reported a lower percentage of 5.2%. This variation might be explained by the fact that melena is usually unnoticeable by the patients and their families, especially in older children; it typically appears after hematemesis, which leads to delayed presentation and diagnosis[9].

Recurrent abdominal pain was the most frequent associated symptom with GIB (*n* = 59, 23.6%). This result is comparable to that reported by Gimiga *et al*[6] (26.3%) and Zahmatkeshan *et al*[12] (24.5%), where abdominal pain was the most common accompanying symptom. However, Rafeey *et al*[10] reported a lower percentage (7.4%) of abdominal pain in children over the age of one. Several mechanisms can explain the association between abdominal pain and GIB, depending on the underlying etiology. Peptic or duodenal ulcers can develop due to the loss of the protective mucosal layer, which normally protects against gastric acid[17]. Deep or perforated ulcers irritate the gastric nerves or cause peritonitis, which causes severe abdominal pain[18].

In the current study, physical examination was unremarkable in most of the patients (*n* = 218, 87.2%). However, pallor was documented in 11 (4.4%) patients. Pallor might be related to the severity of bleeding and amount of blood loss. Cleveland *et al*[4] found that esophageal varices and duodenal ulcers are the most common conditions leading to anemia. Persistent or recurrent iron-deficiency anemia is a sign of obscure GIB[3]. Zahmatkeshan *et al*[12] reported iron deficiency anemia in 1.4% of the patients. However, Gimiga *et al*[6] reported a much higher incidence of hypochromic microcytic anemia (61.9%).

The causes of GIB in children vary based on the diagnostic approach used (radiological or endoscopic). Specific causes of GIB can be diagnosed based on imaging findings even before endoscopic intervention, such as foreign body ingestion, esophageal varices, intussusception, Meckel's diverticulum, and IBD[19,20]. The role of radiology in the management of children with GIB differs according to patient age and clinical presentation[19]. Radiological imaging is frequently requested after a negative endoscopic evaluation or for undetermined causes or bleeding sites[19]. Abdominal

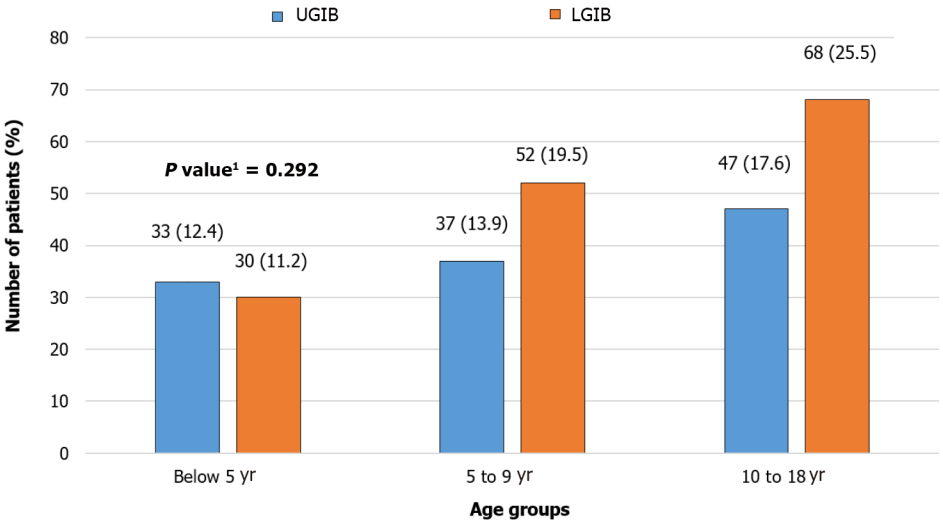

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Figure 2 Comparison between upper and lower gastrointestinal bleeding according to the age groups. [1]Pearson χ^2 Test. UGIB: Upper gastrointestinal bleeding; LGIB: Lower gastrointestinal bleeding. 250 patients had a total of 270 bleeding episodes (20 patients had both UGIB and LGIB).

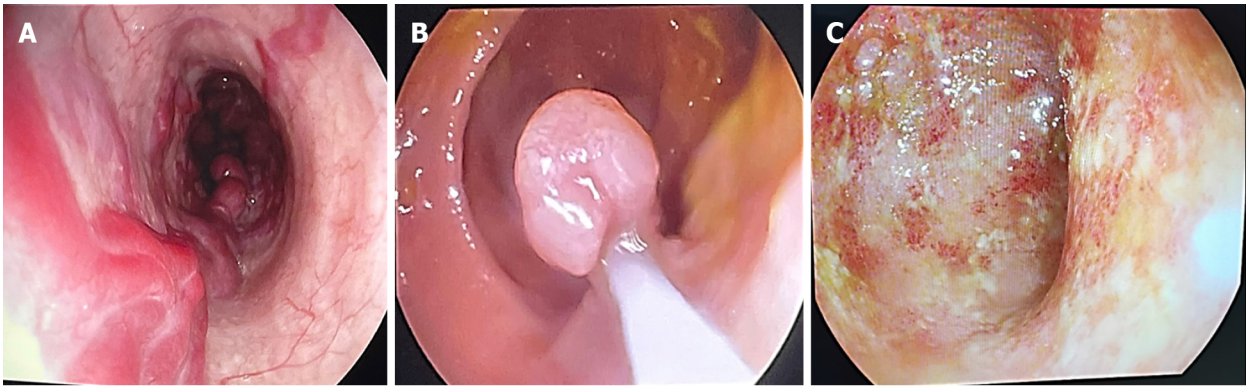

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Figure 3 Endoscopic findings in children presented with gastrointestinal bleeding. A: Esophageal varices; B: Rectal polyp; C: Inflamed ulcerated colonic mucosa in patient with ulcerative colitis.

ultrasonography, barium studies, computed tomography, magnetic resonance imaging, nuclear scintigraphy, and selective angiography may play a role in identifying the underlying pathology and exact source of bleeding[19]. In our study, IBD was the main cause of GIB in adolescents, whereas foreign body ingestion and esophageal varices were the main causes if GIB in preschool children. Çolak recently reported a small bowel intussusception caused by Meckel's diverticulitis in a 10-year-old girl in whom it was diagnosed using radiological images even before endoscopic evaluation[20].

With advancements in the field of medical interventions, endoscopy has become the modality of choice for diagnosing GIB in children[21]. All the patients in this study were diagnosed *via* endoscopic examination. The causes of GIB among the published studies were diverse, which might account for the variation in disease distribution among different countries (Table 4). The most common cause of GIB in this study was IBD. Gimiga *et al*[6] reported ulcerative colitis (22%) as the second-most common cause of GIB. However, Jafari *et al*[2] and Zahmatkeshan *et al*[12] reported IBD to be a rare cause of GIB, accounting for only 4% and 5.8% of the study population, respectively. In patients with IBD, deep ulcers secondary to colitis might be sufficient to disrupt the underlying blood vessels of the inflamed and friable mucosa, causing GIB[11].

The second-most cause of GIB in this study was gastritis, with Helicobacter pylori infection accounting for 20% of the cases. However, Jafari *et al*[2] (7.1%), Rafeey *et al*[10] (14.5%), and Hassoon *et al*[9] (19.6%) reported lower percentages of gastritis in their study population. This difference might be due to the high prevalence of Helicobacter pylori gastritis in our community (57%)[22]. Duodenal ulcers were noted in 20 (8%) of our patients, which is comparable to that reported by Hassoon *et al*[9] (7.4%), Rafeey *et al*[10] (7.6%), and Cleveland *et al*[4] (8.2%). Duodenal ulcers can be caused by mucosal irritation from infections, such as *Helicobacter pylori* infection, or certain medications, such as

Table 4 Summary of previous studies of gastrointestinal bleeding in children from neighboring countries and worldwide

Ref.	Country	*n*	Age (yr)	Sex	Bleeding site	Two most common symptoms (%)	Two most common causes (%)
Isa *et al*, 2023	Bahrain[a]	250	≤ 18	M > F	Both	Per rectal bleeding (60.4); Hematemesis (46.8)	Inflammatory bowel disease (30.8); Gastritis (28)
Jafari *et al*[2], 2018	Iran	113	< 18	M > F	Both	Hematemesis (40.7); Coffee ground vomitus (38)	Prolapse gastropathy (18.6) for UGIB; Polyps (32.5) for LGIB
Rafeey *et al*[10], 2013	Iran	447	< 18	M > F	UGIB	Hematemesis (26.85); Melena (13.42)	Erosive esophagitis (40); Gastric erosion (17)
Zahmatkeshan *et al*[12], 2012	Iran	363	< 18	M > F	LGIB	Hematochezia (80.2); Bloody diarrhea (18.1)	Juvenile polyp (23.1); Lymphoid nodular hyperplasia (18.2)
Hassoon *et al*[9], 2012	Iraq	58	4 d-18	M > F	UGIB	Hematemesis (58.5); Melena or hematochezia (5.2)	Esophageal varices (39); Gastric erosions (19.6)
Gimiga *et al*[6], 2015	Romania	118	< 18	M > F	LGIB	Hematochezia (54.2); Rectorrhagia (40.7)	Solitary colorectal polyps (33); Ulcerative colitis (22)
Cleveland *et al*[4], 2012	USA	158	< 17	M > F	UGIB	Hematemesis (73.4); Melena (20.8)	Prolapse gastropathy syndrome (12.7); gastric erosions/ulcers (10.8)

[a]The present study. UGIB: upper gastrointestinal bleeding; LGIB: lower gastrointestinal bleeding; USA: United states of America.

nonsteroidal anti-inflammatory drugs[23].

Esophagitis occurs due to irritation of the esophageal mucosal lining by gastric acids[11]. In this study, esophagitis was observed in 15 (6%) patients, which is similar to that seen in Khan *et al*[24] (4%) and Hassoon *et al*[9] (4.9%). However, other studies report a higher percentage, ranging between 9.5% and 40%[2,4,10].

Intestinal polyposis is another cause of GIB. In this study, polyps were detected in only 15 (6%) patients. However, Zahmatkeshan *et al*[12], Jafari *et al*[2] and Gimiga *et al*[6], reported polyps as the most common cause of LGIB, representing 23.1%, 32.5%, and 33% of their study population, respectively.

In the present study, 4% of our patients underwent one or more therapeutic interventions. Polypectomy was the commonest (1.6%), followed by injection sclerotherapy (1.2%). Comparably, Lee *et al*[25] reported that 2.3% of their patients underwent polypectomy; however, they reported a higher percentage of injection sclerotherapy (21%).

Like most retrospective studies, this study was limited by missing medical data such as vital signs and hemoglobin levels at GIB presentation. In addition, this was a single-center study that included only patients who were admitted to the hospital and underwent an endoscopic procedure. Subsequently, children with GIB who presented to the pediatric emergency department and were discharged home, such as those with Mallory–Weiss syndrome, and those who were admitted but did not undergo endoscopy, were excluded. Therefore, this study might not reflect the true incidence of GIB in children. Another limitation is that, in 2020, most endoscopic procedures were cancelled due to the coronavirus pandemic. This resulted in a marked reduction in the total number of patients with GIB who underwent endoscopy that year.

Despite these limitations, this study is important because it is the first study from Bahrain to focus on children presenting with GIB. Moreover, this study covers most aspects of GIB, including the incidence, clinical presentation, diagnosis, therapeutic interventions, and outcomes in children. Furthermore, this study covered both types of GIB (upper and lower), which is considered a strength of this study; most previous studies reported only one type of bleeding. The findings of this study are essential for pediatricians or gastroenterologists to tailor their management strategies based on the most frequent causes of GIB according to the patient's age group. Additionally, it forms a strong foundation for future research.

CONCLUSION

Gastrointestinal bleeding in children is an alarming condition that has increased significantly over the last two decades. LGIB was more common in our study population than UGIB was. Additionally, most of the patients presented with bleeding per rectum. Endoscopic procedures are the best modality for diagnosing this condition. IBD was the most frequent cause of LGIB, whereas gastritis was the most frequent cause of UGIB. The causes of GIB varied according to the patients' age group and were different from those reported in neighboring countries and the rest of the world. The children in our study had particularly good outcomes. Further studies that include GIB identified in an emergency

setting and those that assess the effect of GIB on patients' hemodynamic stability, the need for blood transfusion, and the long-term impact of this condition are needed.

ARTICLE HIGHLIGHTS

Research background

Gastrointestinal bleeding (GIB) is a serious health problem worldwide, particularly in childhood. The incidence, clinical presentation, and causes of pediatric GIB vary among countries.

Research motivation

Due to limited data on GIB in the pediatric population in the Middle East, we were motivated to study this health problem in Bahrain.

Research objectives

To assess the incidence, clinical presentation, causes, and outcomes of GIB in children at the main tertiary hospital in Bahrain over the last two decades and to stratify the causes of GIB according to the patients' age group.

Research methods

We retrospectively reviewed and collected the demographic data, clinical presentation, endoscopic findings, and outcomes of children with GIB admitted to the Pediatric Department at Salmaniya Medical Complex, Kingdom of Bahrain, from medical records between 1995 and 2022. The causes of GIB were compared according to patient's age at presentation.

Research results

A total of 250 patients with GIB were included in this study. The median incidence was 2.6/100000 per year (interquartile range, 1.4–3.7) with a significantly increasing trend over the last two decades (P < 0.0001). Most patients were males (n = 144, 57.6%). The median age at diagnosis was 9 years (IQR, 5–11). Ninety-eight (39.2%) patients required upper gastrointestinal endoscopy alone, 41 (16.4%) required colonoscopy alone, and 111 (44.4%) required both. Lower GIB (LGIB) was more frequent (n = 151, 60.4%) than upper GIB (UGIB) (n = 119, 47.6%). There were no significant differences in sex (P = 0.710), age (P = 0.185), or nationality (P = 0.525) between the two groups. Abnormal endoscopic findings were detected in 226 (90.4%) patients. Inflammatory bowel disease (IBD) was the most common cause of LGIB (n = 77, 30.8%), whereas gastritis was the most common cause of UGIB (n = 70, 28%). IBD and undetermined cause for bleeding were higher in the 10–18 years group (P = 0.026 and P = 0.017, respectively), while intestinal nodular lymphoid hyperplasia, foreign body ingestion, and esophageal varices were more common in the 0–4 years group (P = 0.034, P < 0.0001, and P = 0.029, respectively). Ten (4%) patients underwent one or more therapeutic intervention. The median follow-up period by endoscopy was two years (IQR, 0.5-3). No mortality was reported in this study.

Research conclusions

GIB in children is an alarming condition that is increasing significantly. LGIB were more frequent than UGIB. IBD was the most common cause of LGIB, whereas gastritis was the most common cause of UGIB in our children. The cause for GIB varied based on patient age and differed from those reported in neighboring countries and the rest of the world.

Research perspectives

Further studies are needed that include children with GIB from an emergency setting and studies that assess the effect of this bleeding on patients' hemodynamic stability, the need for blood transfusion, and the long-term impact of this condition.

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FOOTNOTES

Author contributions: Isa HM was the main contributor in study design, literature review, data analysis, drafting manuscript, and over-sight for all phases of the project and the final approval of the version to be published; Alkharsi FA was responsible for literature review, data collection, drafting and revising manuscript; Ebrahim HA, Walwil KJ and Diab JA were responsible for literature review, data collection and revising manuscript; Alkowari NM was responsible for literature review, drafting and revising manuscript; All the authors have read and approved the final manuscript.

Institutional review board statement: This study was ethically approved by the Research and Research Ethics Committee, Salmaniya Medical Complex, Government hospitals, Kingdom of Bahrain (IRB number: 6170122, January 17, 2022).

Informed consent statement: Consent was not needed as the study was retrospective without exposure to the patients' data.

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ORIGINAL ARTICLE

Retrospective Study

Outcomes of colon self–expandable metal stents for malignant *vs* benign indications at a tertiary care center and review of literature

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Abstract

BACKGROUND

Endoscopic placement of a self-expandable metal stent (SEMS) is a minimally invasive treatment for use in malignant and benign colonic obstruction. However, their widespread use is still limited with a nationwide analysis showing only 5.4% of patients with colon obstruction undergoing stent placement. This underutilization could be due to perceived increase risk of complications with stent placement.

AIM

To review long- and short-term clinical success of SEMS use for colonic obstruction at our center.

METHODS

We retrospectively reviewed all the patients who underwent colonic SEMS placement over a eighteen year period (August 2004 through August 2022) at our academic center. Demographics including age, gender, indication (malignant and benign), technical success, clinical success, complications (perforation, stent migration), mortality, and outcomes were recorded.

RESULTS

Sixty three patients underwent colon SEMS over an 18-year period. Fifty-five cases were for malignant indications, 8 were for benign conditions. The benign strictures included diverticular disease stricturing (n = 4), fistula closure (n = 2), extrinsic fibroid compression (n = 1), and ischemic stricture (n = 1). Forty-three of the malignant cases were due to intrinsic obstruction from primary or recurrent colon cancer; 12 were from extrinsic compression. Fifty-four strictures occurred on the left side, 3 occurred on the right and the rest in transverse colon. The total malignant case (n = 55) procedural success rate was 95% *vs* 100% for benign cases (P = 1.0, NS). Overall complication rate was significantly higher for benign group: Four complications were observed in the malignant group (stent migration, restenosis) *vs* 2 of 8 (25%) for benign obstruction (1-perforation, 1-stent migration) (P = 0.02). When stratifying complications of perforation and stent migration there was no significant difference between the two groups (P = 0.14, NS).

CONCLUSION

Colon SEMS remains a worthwhile option for colonic obstruction related to malignancy and has a high procedural and clinical success rate. Benign indications for SEMS placement appear to have similar success to malignant. While there appears to be a higher overall complication rate in benign cases, our study is limited by sample size. When evaluating for perforation alone there does not appear to be any significant difference between the two groups. SEMS placement may be a practical option for indications other that malignant obstruction. Interventional endoscopists should be aware and discuss the risk for complications in setting of benign conditions. Indications in these cases should be discussed in a multi-disciplinary fashion with colorectal surgery.

Key Words: Colon cancer; Obstruction; malignancy; Stricture; Self-expandable metal stent; Stent migration

Core Tip: Endoscopic self-expandable metal stent placement remains an underutilized option for malignant and benign colonic obstruction. We retrospectively evaluated sixty three patients with colon malignant obstruction. Fifty five patients had malignant obstruction and 8 had benign colonic obstruction. Procedural success rate was 95% for benign and 100% for malignant obstruction. No difference in complications were noted between and malignant obstruction.

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INTRODUCTION

Self-expandable metal stent (SEMS) placement offers a minimally invasive management option for use in malignant colonic obstruction. SEMS placement can be used both, as definitive therapy for palliation in end stage disease as well as for preoperative management as a bridge to primary surgical anastomosis. In a nationwide analysis of patients with large bowel obstruction only 42.6% of patients underwent prompt intervention, colon stent placement was performed only in 5.4% of patients[1,2]. Multiple previous studies have shown significant success with placement of SEMS for malignant obstruction. A recent meta-analysis of 36 studies showed technical success of 92%, clinical success of 82% in left sided malignant colonic obstruction[3]. Smaller studies have shown similar success rate for right sided lesions with technical and clinical success rates of 92.7% and 90.2%[4-8]. Currently, the European Society of Gastroenterology, SEMS are the preferred therapy for malignant colonic obstructions[9]. The American Society of colon and Rectal surgery also recommend that in patients with incurable disease and obstruction, decompressive stent is preferable to colectomy or diversion while in patients with curable disease stent can be used as a bridge to surgery after discussion of risks and

benefits with the patient[10].

While some studies have shown that SEMS can reduce surgical complications including need for stoma formation, length of hospital stay and mortality[11,12]. Others have reported no difference in overall survival, time to progression and disease free survival when compared to emergent surgery[13]. Risk of technical failure has been shown to be higher for longer strictures, strictures in the splenic flexure, extracolonic obstruction and complete obstruction[14]. A randomized controlled trial (RCT) comparing SEMS to surgery found a significantly higher rate of perforation in the SEMS group (60%) and was terminated early[15]. A Cochrane review looking at SEMS placement for malignant obstruction found the procedure to have a perforation rate of 5.88%[16].

Despite all the above supporting data, colon stents continued to remain underutilized as shown in the above mentioned nationwide inpatient sample analysis (performed only in 5.4% of patients)[1]. The aim of this study was to review the procedural and clinical success of both benign and malignant colonic stenting at a tertiary care academic center as well as review the available literature on this topic.

MATERIALS AND METHODS

Patients who underwent colonic stenting over an eighteen-year period (August 2004 through August 2022) were identified using an endoscopy database. Internal review board approval was obtained for chart review. Patients were retrospectively reviewed and pertinent information including age, gender, indication (malignant and benign), technical success, clinical success, complications, follow-up length, death and type of surgical procedure and outcomes were recorded.

SEMS were all placed under fluoroscopic guidance by one of five interventional advanced endoscopists. Each interventionist in the group had been in practice for at least 5 years. Stents on the left side were placed with Therapeutic Upper Endoscope (GIF 1TH190 series, Olympus America *TM*) and for those on the right side adult colonoscope was used. For right sided and transverse colon obstruction patients were sedated with the help of anesthesia services using propofol. For left sided obstruction procedures were performed using moderate conscious sedation. For moderate conscious sedation, low dose diphenhydramine (25-50 mg) fentanyl and versed were used. Fluroscopic guidance was used for all procedures. An endoscope was inserted into the rectum and advanced to the point of obstruction. Contrast was injected using a balloon proximal to the tumor to determine the length of the stricture, guide wire was then passed through stricture. The SEMS was then deployed across the stricture over the guide wire under fluoroscopic guidance (Figure 1). Sixty three of the cases were done with Wallflex (Boston Scientific™) stents. Fifty five with a 22 by 90 mm stent and eight with a 22 by 60 mm stent. In one case, an esophageal covered stent was used for an anastomotic fistula (Figure 2) and the distal end was "clipped" to the mucosa to secure its position and prevent migration.

Technical success was defined as endoscopically successful placement of SEMS with evidence of traversing stricture fluoroscopically, and the presence of immediate stool passage. Clinical success was defined as clinical evidence of obstruction relief with passage of stool. Patients with benign strictures who underwent stent placement were felt to be poor surgical candidates, stent placement was performed after review of the case with surgical services. Preoperative bridging success was defined as ability of surgery to be done *via* laparoscopic approach. Palliative stent success was defined as patients not going on to require a surgical diversion. Major complications including perforations, stent migration and death were recorded. Continuous data are described by mean, standard deviation, and range. Categorical data are presented as numbers and percentages.

RESULTS

Sixty three patients underwent colonic stenting with SEMS over the fourteen-year period. Average age was 65 years old with 66% being female patients. Seventy one percent of colon stents were placed in the sigmoid colon or rectum (Table 1). Fifty five cases were for malignant indications: 23 cases for preoperative bridging and 32 for palliation. Malignant case procedural success was 95% and clinical success was 95%. Complication rate was 1.8% in malignant group. Both the patients with complications had rectal cancer. Complications were related to stent migration in one case, necessitating repeat stenting 7 mo later followed by repeat migration needing stent removal and loop colostomy 7 mo later. Two other patients with rectal cancer needed repeat stent placements in 4-6 mo due to recurrent obstruction secondary to tumor ingrowth. Both of these had sustained clinical remission thereafter. The one patient that did not immediately improve with stent placement, clinically improved that same admission with radiation therapy. Four patients of the 32 patients treated with palliative intent ultimately needed surgery (Table 2). Fifteen of the 23 patient's treated for preoperative bridging were able to have primary laparoscopic operative resections (Table 3). Of the eight benign indications, four were for diverticular disease associated strictures, two stents were placed for fistula closure, one was for extrinsic fibroid compression, and one stent was placed for ischemic stricture. All benign diseases had procedural success and clinical success. Two of the eight patients had stent migration with one of the

Table 1 Patients that underwent colonic stenting with self-expandable metal stent over the fourteen-year period

	Malignant	Benign	*P* value
Number of cases (total *n* = 63)	55	8	
Mean age	63.7	67.6	0.54
Gender (Male:Female)	27:36	2:6	
Intrinsic *vs* Extrinsic	43 *vs* 12	7 *vs* 1	
Procedure success	95%	100%	1.0
Complication rate	1.8%	25%	0.02
Perforation rate	0%	13%	0.14
Migration rate	1.8%	13%	0.14

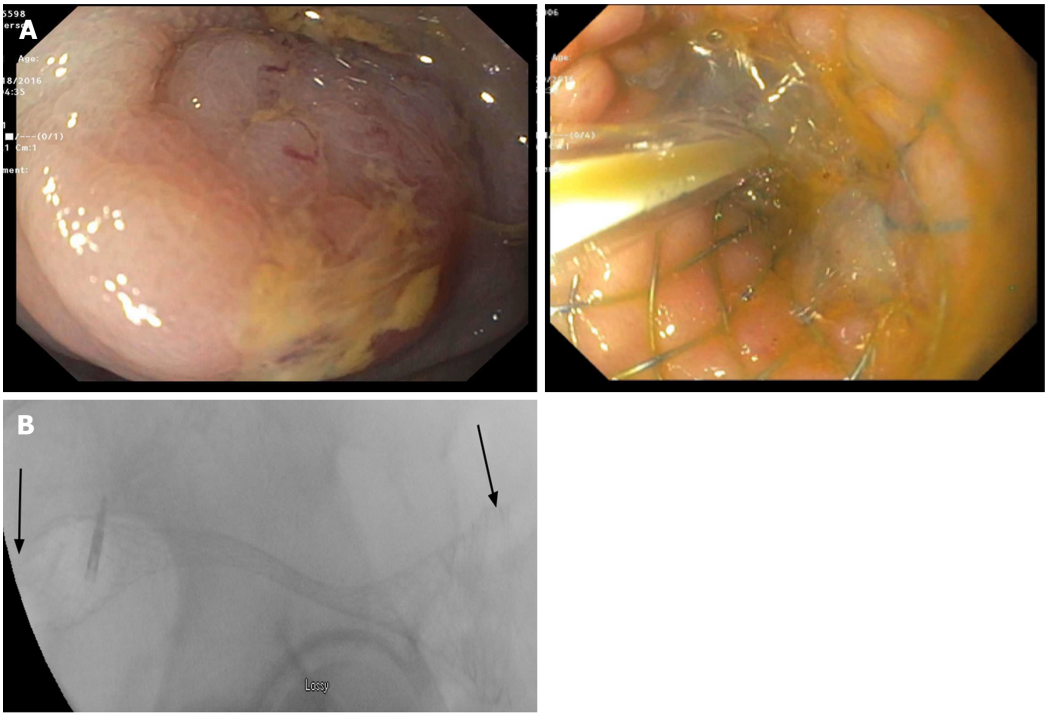

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Figure 1 Malignant colon obstruction. A: Endoscopic image of malignant colon obstruction and successful colon self-expandable metal stent placement across malignant obstruction; B: Fluoroscopic image of successful colon self-expandable metal stent placement across malignant obstruction.

patients having a bowel perforation; this was in a patient with a recent PEA arrest who was not a surgical candidate (Table 4).

DISCUSSION

SEMS remain a viable option for colonic obstruction related to malignancy, with our series confirming high technical and clinical success (90.7% and 87.5% respectively). Our clinical and technical success appears to be much higher, a recent review reported risk of technical and clinical failure as high as 25% [2]. Our clinical success is also higher than previously reported by Aerozoo in their RCT (78.6%)[13]. The higher technical and clinical success noted in our case series could be related to colon stent placements being performed only by advanced endoscopist with all of them having five plus years of experience (range 6–30 years of experience) in the field of advanced endoscopy.

In preoperative bridging for malignant obstruction, colonic stenting improves primary surgical outcomes with the majority of these cases performed *via* a laparoscopic approach (65% of cases). Minimally invasive approaches were considered in 41% of patients by Arezzo *et al*[13] with laparoscopic success being completed only in 30% of SEMS placement cases[13]. Rate of adverse events, colostomy

Table 2 Baseline patient and tumor characteristics of malignant obstruction in cases for palliation

Patient	Age	Sex	Tumor location	Technical success	Clincial success	Complications or surgery	Suvival (days)
1	77	M	Sigmoid	Yes	Yes	None	14
2	71	M	Sigmoid	Yes	Yes	None	NA
3	54	F	Sigmoid	Yes	Yes	None	50
4	42	F	Sigmoid	Yes	Yes	Eventual diversion	NA
5	62	F	Splenic	Yes	Yes	None	NA
6	47	F	Rectum	Yes	Yes	None	33
7	43	M	Sigmoid	Yes	Yes	None	47
8	87	F	Sigmoid	Yes	Yes	None	NA
9	57	F	Sigmoid	Yes	Yes	None	85
10	67	F	Sigmoid	Yes	Yes	None	354
11	70	M	Splenic	Yes	Yes	None	84
12	62	M	Sigmoid	Yes	Yes	Eventual diversion	NA
13	75	F	Sigmoid	Yes	Yes	None	NA
14	54	M	Rectum	Yes	Yes	None	NA
15	42	F	Splenic	Yes	No	Improved w/XRT	38
16	54	F	Sigmoid	No	NA	NA	NA
17	46	M	Sigmoid	Yes	Yes	None	7
18	43	M	Sigmoid	Yes	Yes	Repeat stent 12 mo	689
19	61	F	Sigmoid	Yes	Yes	None	21
20	64	F	Splenic	Yes	Yes	None	76
21	62	F	Splenic	Yes	Yes	None	64
22	52	F	Sigmoid	Yes	Yes	None	271
23	87	M	Sigmoid	Yes	Yes	None	306
24	44	M	Sigmoid	Yes	Yes	None	50
25	61	F	Rectum	Yes	Yes	Repeat stent 6 mo	235
26	80	M	Ascending	Yes	Yes	None	326
27	66	M	Transverse	Yes	Yes	None	454
28	68	M	Transverse	Yes	Yes	None	345
29	76	M	Sigmoid	No	No	None	NA
30	76	M	Ascending	No	No	None	NA
31	62	F	Rectal	Yes	Yes	Repeat stent 4 mo	Open
32	64	M	Rectal	Yes	Yes	Repeat stent in 7 mo, stent migration after 7 mo-removed	420

M: Male; F: Female; NA: No application.

formation were all higher in the surgery group as compared to anastomotic group in their study[13]. Multiple other studies including a systematic review and a meta-analysis of 7 RCTs have also showed stenting as a bridge to surgery to be beneficial in terms of higher rates or primary anastomosis and decreased rates of stoma formation[17,18]. A recent observational cohort looking 345 patients with acute presentations for CRC, found that when comparing outcomes between stoma formation and stenting, patients undergoing stenting had shorter hospital stays, were able to be discharged home and had similar or fewer complications[19]. There were no complications noted in the patients who underwent stent placement as a bridge to surgery in our cohort.

Table 3 Baseline patient and tumor characteristics of malignant obstruction in cases for bridging to surgery

Patient	Age	Sex	Tumor location	Technical success	Clincial success	Complications	Surgery type
1	86	M	Sigmoid	Yes	Yes	None	Open
2	52	F	Sigmoid	Yes	Yes	None	Laproscopic
3	50	F	Decending	Yes	Yes	None	Laproscopic
4	66	F	Sigmoid	Yes	Yes	None	Laproscopic
5	74	F	Sigmoid	Yes	Yes	None	Laproscopic
6	96	F	Sigmoid	Yes	Yes	None	Laproscopic
7	83	M	Sigmoid	Yes	Yes	None	Laproscopic
8	50	F	Transverse	Yes	Yes	None	Laproscopic
9	48	M	Sigmiod	Yes	Yes	None	Open
10	72	M	Sigmoid	Yes	Yes	None	Laprascopic
11	61	M	Sigmoid	Yes	Yes	None	Laprascopic
12	72	M	Rectum	Yes	Yes	None	Open
13	49	M	Sigmoid	Yes	Yes	None	Open
14	81	F	Sigmoid	Yes	Yes	None	Open
15	68	F	Rectal	Yes	Yes	None	Open
16	81	M	Transverse	Yes	Yes	None	Laprascopic
17	72	M	Transverse	Yes	Yes	None	Laprascopic
18	53	F	Trasnverse	Yes	Yes	None	Laprascopic
19	65	F	Sigmoid	Yes	Yes	None	Laprascopic
20	40	M	Sigmoid	Yes	Yes	None	Open
21	61	F	Sigmoid	Yes	Yes	None	Laproscopic
22	66	F	Decending	Yes	Yes	None	Open
23	86	M	Splenic	Yes	Yes	None	Laproscopic

M: Male; F: Female.

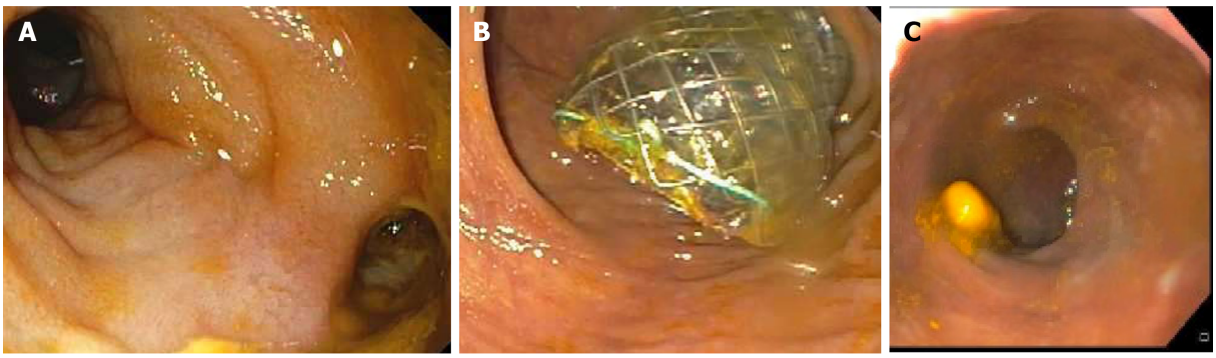

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Figure 2 Anastomotic fistula. A: Patient with anastomotic fistula at recto sigmoid anastomosis causing leak; B: Successful placement of covered self-expandable metal colonic stent across the fistula; C: Two month follow up post stent placement.

In patients undergoing stent placement for palliative purposes our technical and clinical success was slightly lower than those previously reported. Our technical and clinical success rate was 90.7%. In three patients with malignant obstruction, we were unable to safely deploy a stent. The reason for this fail deployment were multifactorial including complete obstruction leading to inability to pass the guide wire, tortuosity of colon at the point of obstruction limiting guide wire passage, failure to reach the area of obstruction in the setting of poor prep. One patient had technical success with failed improvement of

Table 4 Baseline patient and characteristics of benign obstruction

Patient	Age	Sex	Lesion	Location	Technical success	Clincial success	Complications
1	55	F	Fistula	Sigmoid	Yes	Yes	Migration
2	78	F	Extrinisic compression	Sigmoid	Yes	Yes	Perforation
3	76	F	Diverticular	Sigmoid	Yes	Yes	None
4	65	F	Fistula	Ileocolonic	Yes	Yes	None
5	56	F	Ischemic stricture	Rectum	Yes	Yes	None
6	58	F	Diverticular	Sigmoid	Yes	Yes	None
7	66	M	Diverticular	Sigmoid	Yes	Yes	None
8	86	F	Diverticular	Sigmoid	Yes	Yes	None

M: Male; F: Female.

symptoms initially however later symptoms improved with radiation therapy. There are multiple studies showing the success and safety of colonic SEMS for palliation of stage IV colon cancer. One of the largest series had a technical and clinical success rates of 96% and 99%, respectively[20]. Our study demonstrated good technical and clinical success rates and few patients went on to require diversion surgeries (2/32). More recently a meta-analysis of palliative stenting showed shorter time to chemotherapy and lower 30 day mortality[21]. Quality of life has been shown to be improved following colonic stenting for palliative intent[22]. While survival may depend on multiple factor including stage of the disease at time of diagnosis, patient ECOG status, tolerance and response to chemotherapies and other comorboidities. Data for survival was available in 21 patients. The mean survival post stenting was 189 days in our cohort (ranging from 7-689 d). Four patients needed repeat stent placement, 3 of these had rectal tumor while one had sigmoid tumor.

Colonic perforation remains of high concern when placing SEMS. While our series only included one perforation (1.7% perforation rate) other studies have shown a much higher rate. The perforation noted in our cohort was in the group who underwent stent placement for benign indication. One RCT comparing SEMS to surgery found a significantly higher rate of perforation in the SEMS group (60%) and was terminated early[15]. However, another RCT was also terminated early due to a higher mortality in the surgical group compared to the stent group[23]. The majority of studies looking at SEMS placement for malignant obstruction found the procedure to be safe and highly effective with a Cochrane review showing a perforation rate of 5.88%[16]. More recently a meta-analysis looking at perforation risk showed the rate to be 7.4%[24]. Providers should be aware of this risk and be able to provide appropriate informed consent. One particular risk is that of patients on bevacizumab. One study showed that bevacizumab therapy nearly tripled the risk of perforation[20]; while another study showed that bevacizumab therapy increased the risk of perforation by 19.6-fold[25]. More recently a meta-analysis confirmed the risk of perforation for patients on bevacizumab[24]. Chemotherapy agents should be reviewed prior to stent placement for palliation and bevacizumab should be considered a contraindication to SEMS placement. Other than perforation and re-obstruction risks, providers should be aware of other side effects including pain, tenesmus, incontinence and fistula formation[23].

While per literature review the indications and outcomes for malignant obstruction seem clearer, data on benign indications seems limited. Our series had only 8 patients who underwent stent placement for benign indications. In our series, benign indications for SEMS placement appears to have similar success as malignant, however there are significantly higher rates of complication when compared to malignant group (25% in benign group *vs* 1.8% in malignant group (P = 0.02). One patient had stent migration while one had perforation. This risk of migration has also been shown in other series that included benign disease[8,25,26]. A systematic review showed that complication rates are high for benign disease with a perforation rate of 12% and a re-obstruction rate of 14%[27]. Complications for benign indications seem to occur more often if surgical interventions are delayed with one study showing the risk significantly higher if surgery was not performed within 7 d of stent placement[16,28]. Another series showed similarly high risk of complication, especially in diverticular strictures; authors recommended surgery within a month to avoid such complications[29]. Currently there is not enough data to support routine placement of SEMS for benign indications. If SEMS are placed for bridging, surgery should be done within a week to avoid serious complications[30]. Our series included successful treatment of an anastomotic fistula with use of a fully covered esophageal stent. This was after an attempt at fistula closer with over and thru the scope clips which were unsuccessful given likely post-surgical anastomotic fibrosis. Other series have used covered esophageal stents for fistulas with success. This use is off label, and providers should be aware of the migration risk. More recently, a larger retrospective study of 126 patients found that colonic stenting in acute large-bowel obstruction was more likely to be

successful in shorter, malignant strictures than with longer, benign strictures which were associated with an increased risk of perforation[31].

The limitations of this study are inherent to its retrospective nature and small sample size especially for benign disease. Despite this study being completed at a tertiary center, there were only sixty three cases completed over an eighteen-year period. This also reflects the likely underutilization of colon stenting in cases of malignant obstruction. Our results show that the colonic stenting can be performed with high success even in centers with low number of cases per year. Larger multi center studies are needed especially regarding the use of colon stents for benign colonic strictures and their outcomes.

CONCLUSION

Gastroenterologists, internists and surgeons should remain aware that colon stent is a safe and effective option for malignant obstruction and may improve surgical outcomes. They remain a worthwhile option for both palliative and preoperative indications in patients with malignant obstructions. Preoperative bridging needs further investigation into the long term risk of recurrence of disease. Benign indications for SEMS placement appear to have similar success however there was a high rate of stent migration and perforation, our study was however limited by sample size to draw further concrete conclusions. Further larger prospective multi center trails are needed to shed light on the use of colon stent placement especially for benign indications.

ARTICLE HIGHLIGHTS

Research background

Colon obstruction due to benign and malignant etiologies at our tertiary care center is a fairly common problem however the wide spread use of colon stent is limited nationally with a nationwide analysis showing only 5.4% of patients with colon obstruction undergoing stent placement.

Research motivation

This under-utilization of colon stents for patient with colon obstruction prompted us to study the outcomes of patient undergoing colon stent placement for malignant and benign etiologies.

Research objectives

The objective of this study was to review long- and short-term clinical success of self-expandable metal stent (SEMS) use for colonic obstruction at a tertiary care center.

Research methods

We retrospectively reviewed all the patients who underwent colonic SEMS placement over an eighteen year period (August 2004 through August 2022) at our academic center.

Research results

Sixty three patients underwent colon SEMS over an 18-year period. Fifty-five cases were for malignant indications, 8 were for benign conditions. The total malignant case (n = 55) procedural success rate was 95% *vs* 100% for benign cases (P = 1.0, NS). Overall complication rate was significantly higher for benign group: Four complications were observed in the malignant group (stent migration, restenosis) *vs* 2 of 8 (25%) for benign obstruction (1-perforation, 1-stent migration) (P = 0.02).

Research conclusions

SEMS remain a worthwhile option for both palliative and preoperative indications in patients with malignant obstructions. Benign indications for SEMS placement appear to have similar success however there was a high rate of stent migration and perforation, our study was however limited by sample size to draw further concrete conclusions.

Research perspectives

Preoperative bridging needs further investigation into the long term risk of recurrence of disease. Further larger prospective multi center trails are needed to shed light on the use of colon stent placement especially for benign indications.

FOOTNOTES

Author contributions: Walayat S and Johannes AJ did the literature review, wrote and finalized the manuscript; Nelsen E and Akhter A collected the data; Benson M, Kennedy G, Soni A, Reichelderfer M and Pfau P designed the research study; Gopal D designed the study and analyzed the data and reviewed the manuscript; all authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the University of Wisconsin Institutional Review Board.

Informed consent statement: All authors have reviewed the study and are aware of the final material being submitted. The study was also approved by the IRB board at UW Madison.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at dvg@medicine.wisc.edu.

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