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Endoscopic applications of cryospray ablation therapy-from Barrett's esophagus and beyond

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Abstract

In the last decade, the treatment of dysplastic Barrett's esophagus has evolved into primarily endoscopic therapy. Many techniques have become well-established to destroy or remove the mucosal lining of Barrett's esophagus. One of the newest therapies, cryospray ablation, has become a modality to treat both dysplastic Barrett's esophagus as well as esophageal carcinoma. In endoscopic applications, the cryogen used is either liquid nitrogen or carbon dioxide which causes tissue destruction through rapid freeze-thaw cycles. Unlike other endoscopic ablation techniques, its unique mechanism of action and depth of tissue injury allow cryoablation to be used effectively in flat or nodular disease. It can be combined with other modalities such as endoscopic mucosal resection or radiofrequency ablation. Its esophageal applications stem well-beyond Barrett's into ablation of early carcinoma, palliative debulking of advanced carcinoma and reduction of tumor ingrowth into stents placed for dysphagia. Although there are fewer reported studies of endoscopic cryoablation in the literature compared to other endoscopic ablation methods, emerging research continues to demonstrate its efficacy as a durable ablation technology with a variety of applications. The aim of this review is to examine the pathophysiology of endoscopic cryospray ablation, describe its outcomes in Barrett's with dysplasia and esophageal carcinoma, and examine its role in other gastrointestinal applications such as hemostasis in the stomach and rectum.

Key words: Barrett's esophagus; Dysplasia; Esophageal carcinoma; Endoscopic cryoablation; Cryotherapy

Core tip: The current standard of care in treatment of dysplastic Barrett's esophagus is endoscopic ablation. Cryospray ablation, the newest modality can achieve complete eradication of dysplasia and intestinal metaplasia in over 90% of patients. Unlike other endoscopic methods, its unique mechanisms and depth of injury enable successful ablation of early esophageal

carcinoma, palliative debulking of advanced carcinoma and reduction of tumor ingrowth into stents. The applications of cryospray ablation beyond the esophagus include control of bleeding from gastric antral vascular ectasia, portal hypertensive gastropathy, and radiation proctitis. This modality continues to evolve as an important tool of therapeutic endoscopy.

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INTRODUCTION

The treatment of Barrett's esophagus with dysplasia or intramucosal cancer has evolved in the past decade from a primarily surgical management into endoscopic therapy as the initial modality. Many endoscopic techniques have become well established to destroy or remove the mucosal lining of Barrett's esophagus. One of the newest therapies, cryospray ablation, continues to evolve as a method for treatment of dysplastic Barrett's esophagus as well as esophageal carcinoma. This technology was first introduced commercially to gastroenterologists in 2007 but has been based on methods used for over thirty years in fields such as dermatology, gynecology and urology to apply liquid nitrogen in the destruction of superficial lesions. In endoscopic applications, the cryogen used is either liquid nitrogen or carbon dioxide that are applied to cause rapid freezing and thawing of a target area with resulting tissue sloughing and subsequent growth of normal mucosa in its place. As one of the newest modalities for endoscopic ablation of Barrett's, several studies have been reported and more are still underway to demonstrate its efficacy.

After its introduction in treatment of esophageal disease, endoscopic applications of cryospray ablation have continued into other areas of the gastrointestinal tract. FDA approval of the technology has been granted for a broad range indication of "cryosurgical tool for destruction of unwanted tissue in the field of general surgery, specifically for endoscopic applications". With this charge, cryospray ablation has been applied in treatment of a variety of conditions such as palliation of obstructive esophageal cancer, gastric antral vascular ectasia and radiation proctitis. This review will describe the pathophysiology as well as the clinical applications of cryospray ablation in mainly the esophagus but also other areas of gastrointestinal endoscopy.

PATHOPHYSIOLOGY OF CRYOSPRAY ABLATION

Introduced first in the 1960's, liquid nitrogen cryosurgery was used to destroy lesions with applications of -20 ℃. Since then, it has been shown that cellular apoptosis is achieved after reaching temperatures less than -50 ℃[1]. Carbon dioxide cryospray ablation has been shown to reach temperatures of -78 ℃ while liquid nitrogen cryospray can reach temperatures of -196 ℃. Freezing is usually performed at two to three cycles with applications ranging between 10 to 30 s each. The mechanism of action of thermal injury has two modalities. Flash freezing and thawing cycles that are repeatedly applied to a tissue causes immediate effects of slowing cellular metabolism and freezing intracellular water. Subsequently, ice formation results in disruption of cellular membranes and organelle dysfunction. Repeat freeze-thaw cycles add to the injury and cellular apoptosis ensues. The stromal intracellular collagen matrix remains intact and so the injury is not seen by endoscopic view during the immediate phase except for hyperemia of the mucosal surface. There is an immediate vasoconstriction followed later by vasodilation of the microcirculation and thus bleeding is not a major component of the early cellular injury. Delayed effects of the freeze-thaw cycles begin within hours to days with mucosal edema, anoxia, microthrombi formation, and apoptosis of the remaining surrounding tissue. This inflammatory response results in a cytokine mediated response involving Th1 cells following cellular apoptosis[2]. As the cellular scaffolding remains intact, healthy tissue regeneration follows over several weeks.

DEVICES FOR CRYOSPRAY ABLATION

There are two main devices available commercially for the endoscopic application of cryospray ablation. First is liquid nitrogen cryospray known as Trufreeze (CSA Medical, Baltimore, MD) and the other is carbon dioxide cryospray known as Polar Wand (GI Supply, Camphill, PA). Another device that is currently undergoing clinical testing is the Coldplay Focal Cryoballoon Ablation System (C2 Therapeutics, Redwood City, CA).

Liquid nitrogen cryospray ablation

The Trufreeze liquid nitrogen system has become the most widely used of the endoscopic cryospray ablation systems with over 11000 treatments performed. This technology uses a generator that delivers cold liquid nitrogen at -196 ℃ through a flexible spray catheter with a low-flow (2-4 psi) continuous delivery in a noncontact method. Due to the potential for rapid expansion of the liquid nitrogen into 4 to 6 L of gas during a 20 s treatment, a multiport orogastric decompression catheter is placed with constant suction during the delivery of liquid nitrogen (Figure 1). The new generation flexible catheter permits retroflexion applications in the stomach or rectum up to 180°.

The treatment is performed with direct visualization of the mucosa to spray large areas of up to 4 cm length at a time. The depth of injury is dependent on

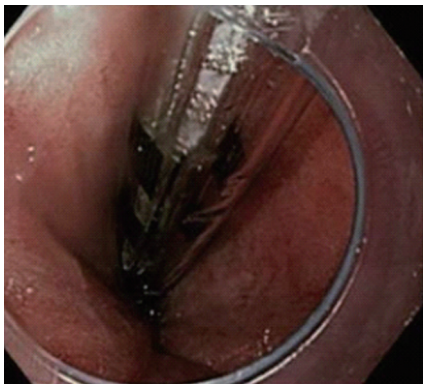

Figure 1 Decompression catheter placement for liquid nitrogen cryospray.

the dosimetry of liquid nitrogen spray time. Traditional applications use 20 s cycles performed twice at each site for dysplastic Barrett's mucosa. In the setting of intramucosal carcinoma, treatment may be performed for longer cycles of 30 s.

The depth of treatment is not limited to the mucosal surface. In contrast, radiofrequency ablation (RFA) has a set dosimetry and ablation depth of 500 microns which will not penetrate below the mucosal surface. Studies into the depth of penetration have been performed with cryospray liquid nitrogen application in the esophagus. Ribeiro prospectively studied a group of patients who were to undergo esophagectomy and applied liquid nitrogen cryospray preoperatively. Using 20 s cycles twice in the same area showed that 93% of patients had cell necrosis into the submucosal layer[3]. If applied in the same area long-enough, esophageal perforation can result as a combination of deep ablation as well as increased esophageal wall tension from rapid gas expansion[4].

Polar wand ablation

This technology uses a through-the-scope spray catheter to deliver compressed liquid carbon dioxide that rapidly expands during spray and reaches -78 ℃ as it exits the catheter. This temperature has been shown to be effective for inducing cellular apoptosis. It has been given FDA clearance for use throughout the GI tract for focal mucosal ablation. Due to the lower flow volume compared to the liquid nitrogen cryospray, a separate decompression catheter is not required. However, a suction channel is directly connected to the spray catheter as it requires a flow of 6 to 8 L/min CO_2 to achieve a temperature of less than -70 ℃. Rapid expansion from a high pressure liquid to a low pressure gas results in a significant drop in temperature as explained by the Joule-Thomson effect.

Focal cryoballoon ablation

While the vast majority of endoscopic ablation of Barrett's mucosa is performed by either RFA or spray cryotherapy, both have their limitations such as the need for sizing, multiple deployment steps, large consoles, and decompression catheter placement. The new Coldplay Focal Cryoballoon Ablation System aims to overcome some of these restrictions. It uses a combination of an inflatable balloon passed through the accessory channel of the endoscope and applies liquid carbon dioxide. The balloon is highly compliant and conforms to the esophageal lumen without excessive tension of the esophageal wall and does not require special decompression catheters. Unlike the inflatable balloon device of RFA, pretreatment sizing is not required with this system. The device has received United States FDA 510 (k) clearance and is undergoing clinical study.

APPLICATIONS IN BARRETT'S ESOPHAGUS

Endoscopic ablation of dysplastic Barrett's has become well established and validated by many studies within the past decade. As per AGA guidelines, endoscopic ablation of Barrett's esophagus is indicated in high-grade dysplasia (HGD) and possibly persistent low-grade dysplasia (LGD) but not in nondysplastic Barrett's epithelium[5]. The ACG practice guidelines of 2015 confirm these same recommendations and also recommend endoscopic mucosal resection (EMR) initially for nodules followed later by endoscopic ablation therapy[6]. The vast majority of recent studies have examined a different modality, RFA. In a meta-analysis of 18 studies in 3802 patients examining RFA for Barrett's, the results show a complete response in eradication of intestinal metaplasia of 78% and overall dysplasia of 91%[7]. However, there are several important studies examining the efficacy of cryospray therapy. Most of these are in regard to liquid nitrogen therapy and show results that are equal to the outcomes of RFA (Figure 2).

Most patients undergoing esophageal cryoablation will require treatment in multiple sessions that are usually separated by 6 to 8 wk intervals to allow for healing of the mucosa. Contraindications to treatment include mucosal breaks such as active esophagitis, erosions, and ulcerations seen at the time of endoscopy due to potential perforation. A tight stricture of the esophagus through which a decompression catheter as well as endoscopic spray catheter cannot both be placed together will also preclude safe treatment. Altered anatomy such as bariatric surgery is a contraindication for therapy due to difficulty in ventilating gas safely from the gastrointestinal tract. The safety of this procedure has been shown in several studies below.

Shaheen *et al*[6] examined 98 patients with HGD with a mean age of 65.4 years and mean Barrett's length of 5.3 cm. In this group of 87% males, an average of 3.4 treatments per patient was performed with liquid nitrogen cryospray to achieve complete ablation. HGD was eradicated in 97% of all patients while 87% had complete eradication of all dysplasia. No perforations occurred and a stricture rate of 3% was identified

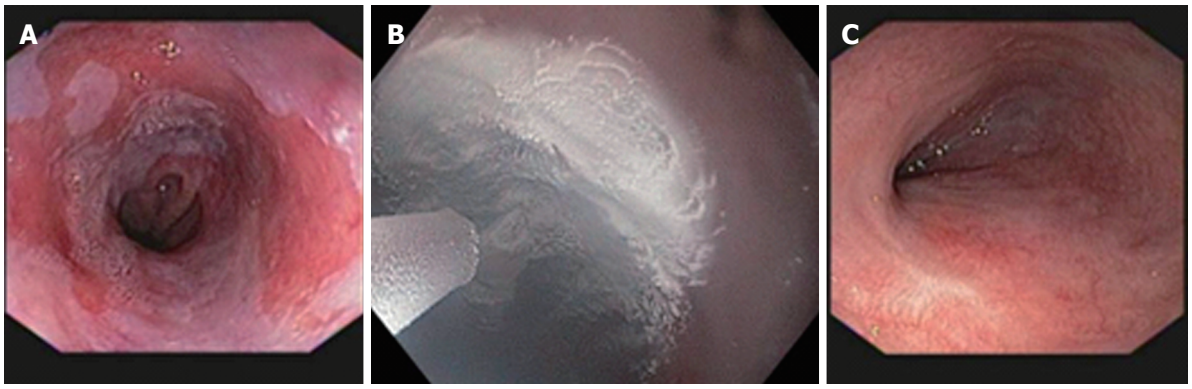

Figure 2 Results that are equal to the outcomes of radiofrequency ablation. A: Barrett's esophagus with high grade dysplasia; B: Liquid nitrogen cryospray ablation; C: Complete eradication of dysplasia and intestinal metaplasia.

and treated easily with endoscopic balloon dilation in all cases[8]. Additionally, this study showed a 1%-2% incidence of chest discomfort that required outpatient narcotic use. This is in contrast to RFA therapy which has been shown to have a significantly higher incidence of chest discomfort sometimes requiring hospitalization up to day 8 following the procedure compared to a sham treatment group and an overall esophageal stricture rate of 6%[9].

Greenwald *et al*[10] further demonstrated in a group of 7 patients with stage Ⅰ esophageal adenocarcinoma that complete response was achieved in 100% with liquid nitrogen cryospray ablation alone. The same group demonstrated recently in a cohort of 33 patients followed long-term for at least 24 mo that a durable response can be achieved. Complete response for HGD was 97% and complete response for intestinal metaplasia was 87% at 24 mo[11].

Recurrence of disease after cryoablation for HGD achieved a complete response has also been evaluated. Halsey *et al*[12] prospectively examined a group of 36 patients who had HGD and underwent liquid nitrogen cryospray therapy. In 11 (30%) patients, recurrent disease was identified at a median of 6.5 mo. In 70% of these patients, recurrences occurred below the neosquamocolumnar junction including a variety of histology such as HGD, LGD, and intestinal metaplasia. In one patient, recurrent disease was esophageal carcinoma within the previously treated esophagus. This patient as well as a total of 33 patients (92%) ultimately achieved complete response to retreatment with cryotherapy[12]. This demonstrates the importance of follow-up surveillance biopsies after completion of cryoablation therapy not only within the previously treated esophagus but also at the gastric cardia immediately below the squamocolumnar junction.

While the cryoballoon focal ablation system is not commercially available, it has been studied for feasibility and efficacy in ablation of Barrett's mucosa. In a prospective, non-randomized trial of 39 patients, 62 ablations were performed between 6-10 s. No adverse events occurred and no strictures resulted from the treatment. Mild pain was noted in 27% of patients. Full squamous regeneration was noted in 47 treated areas (60 % of 6-s cycles, 82% of 8-s cycles, and 100% of 10-s areas). Long-term follow-up of these patients as well as durable responses for HGD or LGD is being examined in ongoing studies[13].

APPLICATIONS IN ESOPHAGEAL NEOPLASIA

The presentation of esophageal neoplasia can range from a small nodule or flat area of intramucosal carcinoma to a large bulky obstructing tumor with ulceration, bleeding and metastases. The standard of care in management of nodular mucosa within Barrett's esophagus is endoscopic mucosal resection. However, larger flat areas of intramucosal cancer may be difficult to treat with EMR alone as well as difficulty with overlapping areas for complete treatment[14]. The combination of cryoablation therapy with EMR has been reported to be effective.

Liquid nitrogen cryoablation has been performed safely prior to and following EMR, as well as during the same session[15]. As described above, cryoablation causes destruction of cellular contents but maintains the intracellular collagen matrix. The structural injury is delayed and enables further therapy to the treated tissue. This may explain how this treatment can be easily combined with endoscopic mucosal resection which alone may be challenging if there is scarring or adherence of esophageal wall layers (Figure 3).

While the data for liquid nitrogen as the cryogen for ablation of esophageal neoplasia seems promising, the use of carbon dioxide has not been shown to achieve similar results. In a recent study of 30 patients with Barrett's and early neoplasia, CO_2 cryoablation therapy was performed. In 9 patients, nodular areas were first treated with EMR. With a mean of 2.5 cryoablation sessions and a six-month follow up of 10 patients, early termination of the study occurred due to the disappointing results with eradication of dysplasia in only 44% and persistence of neoplasia in a large portion. This study suggests that CO_2 cryoablation combined with EMR may not be an effective modality for treatment of

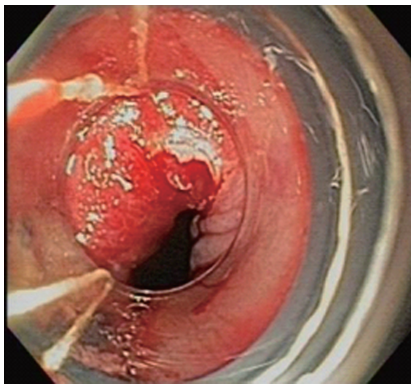

Figure 3 Endoscopic mucosal resection following liquid nitrogen cryoablation.

Barrett's associated neoplasia[16].

Debulking of esophageal cancer for palliation of swallowing has been shown to be feasible (Figure 4). Tumor ingrowth into a palliative metal esophageal stent can also be treated[17]. No outcome studies of cryoablation for palliation of dysphagia have been published. In a recent report, a 63-year-old patient with esophageal squamous cell carcinoma who had recurrence of disease had tumor ingrowth at the ends of a previously placed metal stent resulting in dysphagia. Liquid nitrogen cryotherapy was used to recanalize the lumen of the metal stent successfully[18]. Cash *et al*[19] reported the first application of liquid nitrogen cryotherapy for recurrent esophageal squamous cell cancer that occurred 3 years after definitive chemotherapy. This patient was disease-free at two year follow-up. In another study, 7 patients with superficial esophageal adenocarcinoma had complete response to cryoablation therapy in all patients at a range of follow-up between 3 to 18 mo[10]. Greenwald *et al*[20] reported liquid nitrogen cryoablation treatment of 79 patients with adenocarcinoma (tumor stage included T1-60, T2-16, and T3/4-3). Complete response of intraluminal disease was achieved in 61% and in 75% of patients with intramucosal (T1) disease. Mean follow up was 10.6 mo overall and 11.5 mo for T1 disease.

Hemostasis of bleeding from advanced esophageal carcinoma has been shown to be feasible with endoscopic cryoablation. Shah *et al*[21] reported a case of a 62-year-old male with locally advanced unresectable adenocarcinoma of the esophagus with bleeding that did not respond to chemotherapy, radiation therapy, brachytherapy, or photodynamic therapy. Liquid nitrogen cryospray ablation was used with three 20 s applications and resulted in reduction of blood transfusions from 30 units over the preceding two weeks to one unit over the following two weeks. Immediate post-procedural hemostasis as well as a durable response was noted.

TREATMENT OF GASTRIC ANTRAL VASCULAR ECTASIA

Gastric antral vascular ectasia (GAVE) is a well-recognized entity that causes chronic blood loss from the upper gastrointestinal tract. It is often associated with connective tissue disease, liver cirrhosis, and renal failure but may also be of idiopathic origin[22]. The most common type is also known as "water-melon stomach" due to its classic endoscopic appearance of striped mucosa radiating from the pylorus. The other type is characterized by diffuse punctate erythematous angiomas of the antrum that is often associated with portal hypertension and cirrhosis[23].

Traditional endoscopic therapies of GAVE include the gold-standard of argon plasma coagulation (APC) which is a non-contact thermal method that can cause mucosal ablation and perhaps deeper injury as well. It often requires multiple sessions and has been shown to be very effective in mild to moderate disease but bleeding may be refractory in underlying cirrhosis or severe mucosal involvement[24]. Other treatments that have been tried with some limited success include thermal heater probe therapy, YAG laser ablation, and band ligation. In small studies, RFA has recently been demonstrated to be effective in reducing the blood transfusion requirements within the 6 mo period following treatment for those patients with GAVE refractory to initial APC therapy[25,26].

Cryospray ablation can be used as a secondary line of endoscopic therapy for refractory GAVE as it may be able to cover a larger area through spray therapy than other modalities. However, it is limited by gas flow and potential air entrapment in the small intestine. While it has been described, very few studies are available to show its efficacy. Kantsevoy showed in a pilot study of 7 patients with GAVE and recurrent bleeding that nitrous oxide cryoablation was effective in 71% for cessation of bleeding[27]. Carbon dioxide cryoablation was examined in a study of 12 patients with refractory GAVE and significant iron-deficiency anemia. All of these patients had undergone APC therapy with a median of 6 sessions. In this group, 50% achieved complete response with a mean of 3 sessions of cryoablation and 50% had a partial response manifest by incomplete ablation but stable hemoglobin. The entire group had a mean increase in hemoglobin from 9.9 to 11.3 g/dL. No adverse events were noted in any patient[28]. Liquid nitrogen spray cryotherapy has also been examined in treatment of GAVE and portal hypertensive gastropathy with refractory bleeding. It was shown to be very effective in cessation of bleeding from portal hypertensive gastropathy that did not respond to either APC or transjugular intrahepatic portosystemic shunt placement[29].

TREATMENT OF RADIATION PROCTITIS

Chronic radiation proctitis occurs in up to 15% of patients within months to even decades following radiation therapy for pelvic malignancies. Most patients will present with recurrent rectal bleeding and often have rectal pain and tenesmus. Traditional medical therapies

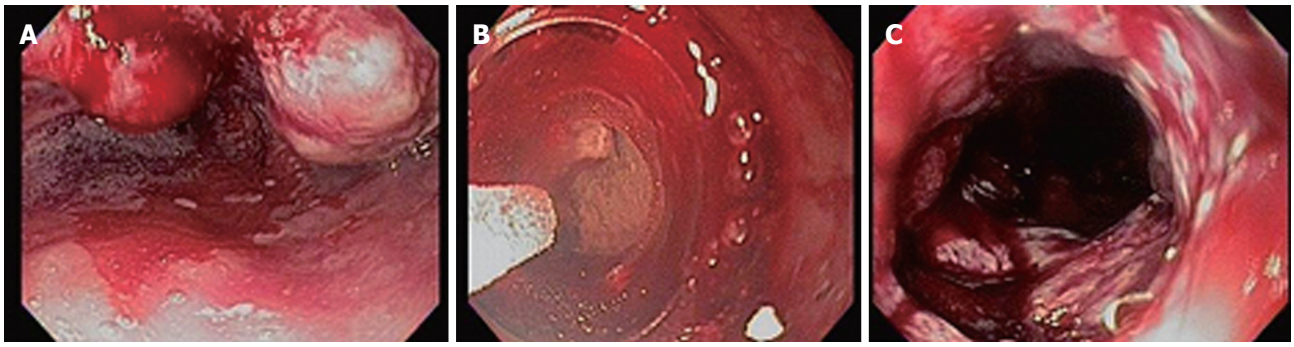

Figure 4 Debulking of esophageal cancer for palliation of swallowing. A: Bulky friable esophageal adenocarcinoma causing dysphagia and bleeding; B: Liquid nitrogen cryospray ablation of tumor for palliation; C: Post-ablation appearance of tumor at 8 wk.

for radiation proctitis include enemas with salicylates, sucralfate, and corticosteroids which may help short-term symptoms but have not been shown to have long-term effects[30]. Endoscopic therapy has traditionally included APC which is very effective in mild to moderate radiation proctitis requiring several sessions to achieve ablation. In more severe mucosal damage, refractory proctitis is present in up to 50% of patients[31]. Recent reports demonstrate RFA with the Halo90 system to be effective in moderate radiation proctitis with 1 to 2 sessions and effective control of lower gastrointestinal bleeding[32].

While both APC and RFA require a contact method of treatment and may be limited by blood or tissue adherence, cryoablation has been used as noncontact application for treatment of chronic radiation proctitis. In a recent study, treatment was applied for 5 s applications to reduce the risk of proximal gas entrapment and perforation. Patients required between 1 and 4 sessions. In all patients, significant response was seen in endoscopic score of proctitis, and improvement in rectal pain and bleeding[33].

CONCLUSION

Cryoablation therapy has become well-established as a modality for treatment of dysplastic Barrett's esophagus. Due to its potential for deeper tissue injury, it has evolved into successful applications of ablation of nodular Barrett's and early esophageal carcinoma with or without combined EMR therapy. This modality also serves as an alternative when other endoscopic ablation modalities such as RFA or APC are refractory or contraindicated in high risk settings such as chronic anticoagulation, implanted cardiac defibrillators, esophageal strictures, radiation therapy, or within esophageal stents. Other applications of cryoablation in the stomach or rectum to treat bleeding angioectasia have been shown to be feasible. As the newest modality of endoscopic mucosal ablation, more efficacy studies as well as novel applications within the gastrointestinal tract are continuing to emerge, ensuring that cryotherapy will remain an important tool for therapeutic endoscopy.

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ORIGINAL ARTICLE

Retrospective Study

Bleeding risk with clopidogrel and percutaneous endoscopic gastrostomy

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Data sharing statement: Dataset is available from the corresponding author, Matthew Bechtold at bechtoldm@health.missouri.edu. Given that is a retrospective study, informed consent was not obtained for data sharing but data was anonymized and project approved by the IRB.

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Abstract

AIM

To compare bleeding within 48 h in patients undergoing percutaneous endoscopic gastrostomy (PEG) with or without clopidogrel.

METHODS

After institutional review board approval, a retrospective study involving a single center was conducted on adult patients having PEG (1/08-1/14). Patients were divided into two groups: Clopidogrel group consisting of those patients taking clopidogrel within 5 d of PEG and the non-clopidogrel group including those patients not taking clopidogrel within 5 d of the PEG.

RESULTS

Three hundred and nineteen PEG patients were found. One hundred and sixty-eight males and 151 females with mean body mass index 28.47 ± 9.75 kg/m^2 and mean age 65.03 ± 16.11 years were identified. Thirty-three patients were on clopidogrel prior to PEG with 286 patients not on clopidogrel. No patients in either group developed hematochezia, melena, or hematemesis

within 48 h of percutaneous endoscopic gastrostomy (PEG). No statistical differences were observed between the two groups with 48 h for hemoglobin decrease of > 2 g/dL (2 *vs* 5 patients; P = 0.16), blood transfusions (2 *vs* 7 patients; P = 0.24), and repeat endoscopy for possible gastrointestinal bleeding (no patients in either group).

CONCLUSION

Based on the results, no significant post-procedure bleeding was observed in patients undergoing PEG with recent use of clopidogrel.

Key words: Percutaneous endoscopic gastrostomy; Clopidogrel; Bleeding; Complications; Antiplatelets

Core tip: Percutaneous endoscopic gastrostomy (PEG) is a common but invasive procedure. In the past, many medications were held prior to the procedure to reduce the risk of potential bleeding complication, such as clopidogrel. Much debate has been performed regarding the need for cessation of clopidogrel prior to PEG placement with little evidence found in the literature. This manuscript showed that clopidogrel use in patients undergoing PEG placement had no increased early post-procedure bleeding risk.

Sohail U, Harleen C, Mahdi AO, Arif M, Nguyen DL, Bechtold ML. Bleeding risk with clopidogrel and percutaneous endoscopic gastrostomy. *World J Gastrointest Endosc* 2016; 8(16): 553-557 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i16/553.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i16.553

INTRODUCTION

Percutaneous endoscopic gastrostomy (PEG) is most commonly performed to provide nutritional support to patients who fail to swallow for a long time requiring tube feeding support[1]. This procedure was first reported by Gauderer *et al*[2] in 1980. Since then PEG has become an important technique for inserting feeding tubes in patients with swallowing difficulties who require long term nutritional support without undergoing laparotomy[2,3]. The placement of PEG tube is classified among high-risk endoscopic procedure because of the risk of associated clinically significant bleeding. The enteric tube can be placed surgically, under radiological guidance or by endoscopic technique. When compared, the endoscopic technique has the least overall risk[4]. Due to having the least overall risk, it is considered to be the technique of choice. However, endoscopic procedures may be low or high risk procedures. High risk endoscopic procedures are ones which are associated with the risk of bleeding being > 1%. PEG is considered a high risk procedure and carries a 2.5% risk of complications[3]. PEG tube is usually required in patients who are elderly and have multiple comorbidities. These patients are usually on antithrombotic agents or anticoagulants and hence are at increased risk of procedure-related bleeding. At the same time, holding the antiplatelet or anticoagulant agents could have potential thromboembolic complications from the underlying pro-thrombotic state. These medications for various cerebrovascular, cardiovascular, and hematological disorders has drastically increased[3]. These agents significantly increase gastrointestinal (GI) bleeding risk. However, a recent study revealed that the incidence of bleeding after a PEG placement appears to be similar at 2.8%[5]. Based on literature review, PEG post-procedure bleeding risk is estimated to be 2%-2.5%[6,7]. According to current guidelines, clopidogrel discontinuation for 7-10 d prior to PEG in patients with underlying low thromboembolic risks is recommended[6-8].

In case of high underlying thromboembolic risk, it is recommended to consider postponing the procedure until it is safe to hold the thienopyridines (clopidogrel, *etc*.). They should be held for 7-10 d when the underlying risk is low. In patients taking dual antiplatelet therapy, it is safe to continue aspirin while holding the clopidogrel. In cases where patients are on monotherapy with thienopyridines, these patients can be started on aspirin during peri-procedure period.

The patterns of clinical practice for the management of these medications differ from these recommendations. Differences also exist in the patterns of practice among gastroenterologists themselves in the use of these agents. An international survey that was conducted in 2008 revealed that differences exist between Western and Eastern countries with regards to management of these agents[9].

To further evaluate the use of clopidogrel in PEG placement, we performed a retrospective study examining the potential post-procedure risks of bleeding.

MATERIALS AND METHODS

A retrospective study was conducted at a single tertiary-care center on all adult patients having PEG placement (January 2008-January 2014). Institutional review board approval was obtained. PEG was performed by using the standard push or pull technique[2]. The procedure was performed by the attending gastroenterologist and the gastroenterology fellow at our tertiary-care center. All patients were nothing per mouth from midnight to the procedure and received a prophylactic antibiotic 30 min prior to the procedure (if not already receiving antibiotic treatment at the time of PEG insertion for any other reason).

The data pertaining to the several parameters was collected. These included patient demographics, indication for PEG placement, comorbid illnesses, and laboratory data, including hematology profile (hemoglobin, platelets, and coagulation values). The use of each

Table 1 General demographics of patients included in the study

All patients	
Patients (*n*)	320
Age (mean years ± SD)	65.03 ± 16.11
BMI (mean years ± SD)	28.47 ± 9.75
Gender	
Male (*n*)	169
Female (*n*)	151

BMI: Body mass index.

Table 2 Demographics and complications in patients taking clopidogrel *vs* patients not on clopidogrel

Outcome	No plavix	Plavix	*P* value
Patients (*n*)	286	33	-
Age (mean years ± SD)	64.37 ± 16.44	71.21 ± 11.43	0.02
BMI (mean years ± SD)	28.30 ± 9.59	29.25 ± 10.66	0.60
Hgb drop < 48 h	5	2	0.16
Local complications < 48 h	8	2	0.28
Transfusions < 48 h	7	2	0.24
Rescope < 48 h	1	1	0.20

BMI: Body mass index; Hgb: Hemoglobin.

antiplatelet drug was noted and data regarding the timing of the last dose prior to PEG placement and the first dose following PEG was also recorded. Patients were divided into two groups: Clopidogrel group consisting of those patients taking clopidogrel within 5 d prior to the PEG and the non-clopidogrel group including those patients not taking clopidogrel within 5 d of the PEG.

Procedure-related complications, repeat endoscopy, and blood transfusions < 48 h of PEG was collected. The complications were classified as early (< 48 h of PEG placement) *vs* late (> 48 h). GI bleeding was defined as hemoglobin (hgb) drop > 2 g/dL from baseline, observation of GI bleeding (hematochezia, melena, hematemesis), required blood transfusion, and endoscopic hemostasis. The severity of bleeding was defined as mild (clinical evidence of bleeding, no transfusion required), moderate (transfusion required, less than 4 units, but no surgery required) and severe (transfusion of more than 5 units, radiological or surgical intervention).

Statistical analysis was conducted using the following: Descriptive statistics (demographics), two-tailed unpaired *t* test (continuous data), and Fisher's exact test (categorical data). Statistical significance was significant at $P < 0.05$. Statistics were reviewed by two biostatisticians (Matthew L Bechtold and Doug L Nguyen).

RESULTS

Three hundred and nineteen patients with PEG placement were identified, consisting of 168 males, 151 females, mean age 65.03 ± 16.11 years, and mean BMI 28.47 ± 9.75 kg/m^2 (Table 1). Thirty-three patients were using clopidogrel (mean age 71.21 ± 11.43 years). Thirty patients out of these 33 patients received a dose of clopidogrel within 5 d prior to the actual day of the procedure, whereas three patients out of 33 received a dose of Plavix within 7 d prior to the procedure. Two hundred and eighty-six patients were not taking clopidogrel (mean age 64.37 ± 16.44 years). Within 48 h of PEG, no patients in either group developed hematochezia, hematemesis, or melena (Table 2). Within 48 h of PEG, decrease in hgb of > 2 g/dL was identified in 2 patients (clopidogrel group) *vs* 5 patients (non-clopidogrel group) ($P = 0.16$). Blood transfusion within 48 h was necessary in 2 patients (clopidogrel group) *vs* 7 patients (non-clopidogrel group) ($P = 0.24$). No patients underwent repeat endoscopy for GI bleeding.

DISCUSSION

PEG over the years has emerged as a popular method to provide long-term enteral nutrition to patients. A PEG is required in those with inadequate intake of nutrition but have a normally functioning GI tract[1].

Some of the common indications for placement of a PEG include: Neurological disorders that impair the normal physiology of swallowing, malignancies involving the oropharynx or the esophagus and facial trauma[10-12]. There are several options available when considering placement of a gastrostomy tube. However, the endoscopic technique is preferred due lower incidence of complications and is more cost effective than open surgical gastrostomy[13]. Even though the incidence is less, there are still several complications reported that are secondary to PEG placement[14-17]. In a meta-analysis performed by Wollman *et al*[18], the procedure-related mortality was noted as 0.5% and the 30-d all-cause mortality was 15%. Bleeding is one of the complicating factors contributing to mortality.

Our study focused on the risk of post-PEG placement early bleeding in patients that were already on clopidogrel as compared to those not taking clopidogrel. The study did not reveal any significant increase in the risk of early post-procedure bleeding (occurring within 48 h after the procedure) in patients who were taking clopidogrel. When the data was analyzed according to age (above and below the age of 60) and body mass index (BMI) (more than or less than BMI of 30), there was also no significant differences in the bleeding risks or need for blood transfusions. With this data, the use of clopidogrel should not be considered a contraindication to PEG placement. However, other parameters must be considered prior to PEG in this patient population.

First, prior to performing any endoscopic procedure, the risks and benefits should be thoroughly reviewed, including risk of bleeding[6,7]. Second, careful consideration to the clinical impact of withholding an antithrombotic agent must be performed. Hence, each case

should be individually evaluated and the decision made after evaluating the pros and cons of proceeding with procedure and holding any antithrombotic agents.

As with any study, strengths and limitations were observed. The strengths include a large amount of patients undergoing PEG placement at a single tertiary-care center over 6 years. However, limitations are observed as well and should be considered when interpreting the results. First, this is retrospective study and not a randomized controlled trial. Certain biases may be involved in accordance to a retrospective study but efforts were done to try to minimize those biases. Second, given the small sample size of patients undergoing PEG while on clopidogrel (n = 33), a type II statistical error may be present which indicates the study lacked the power to detect a significant difference between the two groups. However, given that PEG placement has traditionally been withheld on patient who have been on recent clopidogrel, a limited number of patients underwent PEG with clopidogrel over the 6-year period and all of those patients were included in the study. Based on this possibility, results should be interpreted with caution and further larger studies are required to evaluate the overall effect of clopidogrel and PEG placement.

In conclusion, bleeding is a potential complication of PEG placement. Our retrospective study demonstrated no statistically significant increase in bleeding risk or requirement of blood transfusions in patients who were on clopidogrel for PEG placement. Therefore, clopidogrel did not increase bleeding risk despite cessation for a shorter time period as recommended by current guidelines.

COMMENTS

Background

Percutaneous endoscopic gastrostomy is a common procedure for patients who require enteral supplemental nutrition. In the past, any medications that could lead to increased bleeding risk were held prior to the percutaneous endoscopic gastrostomy (PEG) placement. However, recently, this practice has been challenged, especially with clopidogrel with little evidence in the literature.

Research frontiers

Little evidence is in the literature regarding the use of clopidogrel during PEG placement. This retrospective study evaluates the use of concomitant clopidogrel and PEG placement in a tertiary-care hospital in regards to post-procedure bleeding. Very few publications are available in the literature to evaluate this subject. Two publications that are related are below. Lucendo AJ, Sánchez-Casanueva T, Redondo O, Tenías JM, Arias Á. Risk of bleeding in patients undergoing PEG tube insertion under antiplatelet therapy: a systematic review with a meta-analysis. *Rev Esp Enferm Dig* 2015; 107: 128-136; Richter JA, Patrie JT, Richter RP, Henry ZH, Pop GH, Regan KA, Peura DA, Sawyer RG, Northup PG, Wang AY. Bleeding after percutaneous endoscopic gastrostomy is linked to serotonin reuptake inhibitors, not aspirin or clopidogrel. *Gastrointest Endosc* 2011; 74: 22-34.e1.

Innovations and breakthroughs

This is a rare study evaluating the use of clopidogrel with PEG placement. Very few studies have evaluated this subject. This study shows that clopidogrel may not require cessation prior to PEG placement which is a change in current and past practice.

Applications

For PEG placement, clopidogrel does not require cessation prior to procedure. This will allow patients to continue their much needed clopidogrel for PEG placement.

Terminology

PEG placement is a common procedure performed on patients who require supplemental enteral nutrition. Clopidogrel is also a common medication for antiplatelet properties.

Peer-review

The manuscript is provided useful information that clopidogrel discontinuation before PEG is not necessary in case of urgent need for such procedure.

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ORIGINAL ARTICLE

Retrospective Study

What types of early gastric cancer are indicated for endoscopic ultrasonography staging of invasion depth?

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at (watarij@hyo-med.ac.jp). Consent for data sharing was not obtained from the participants but the presented data are anonymized and risk of identification is low.

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Abstract

AIM

To clarify the diagnostic efficacy and limitations of endoscopic ultrasonography (EUS) and the characteristics of early gastric cancers (EGCs) that are indications for EUS-based assessment of cancer invasion depth.

METHODS

We retrospectively investigated the cases of 153 EGC patients who underwent conventional endoscopy (CE) and EUS (20 MHz) before treatment.

RESULTS

We found that 13.7% were "inconclusive" cases with low-quality EUS images, including all nine of the cases with protruded (0-I)-type EGCs. There was no significant difference in the diagnostic accuracy

between CE and EUS. Two significant independent risk factors for misdiagnosis by EUS were identified-ulcer scarring [UL(+); odds ratio (OR) = 4.49, P = 0.003] and non-indication criteria for endoscopic resection (ER) (OR = 3.02, P = 0.03). In the subgroup analysis, 23.1% of the differentiated-type cancers exhibiting SM massive invasion (SM2) invasion (submucosal invasion $\geqslant$ 500 μm) by CE were correctly diagnosed by EUS, and 23.1% of the undifferentiated-type EGCs meeting the expanded-indication criteria for ER were correctly diagnosed by EUS.

CONCLUSION

There is no need to perform EUS for UL(+) EGCs or 0-I-type EGCs, but EUS may enhance the pretreatment staging of differentiated-type EGCs with SM2 invasion without UL or undifferentiated-type EGCs revealed by CE as meeting the expanded-indication criteria for ER.

Key words: Gastric cancer; Endoscopic ultrasonography; Invasion depth diagnosis; Conventional endoscopy; Endoscopic submucosal dissection

Core tip: With the increasingly expanded indications of endoscopic resection for early gastric cancer (EGC), the accurate diagnosis of the invasion depth has become more important in the pretreatment strategy. Although there have been many investigations comparing the efficacy of endoscopic ultrasonography (EUS) and conventional endoscopy (CE) for invasion depth diagnosis of EGCs, much controversy remains. Our results revealed that there is no need to perform EUS for EGCs that are protruded type or those that have an ulcer scar, but EUS may have an add-on effect in the pretreatment staging of differentiated-type EGCs diagnosed as SM2 (submucosal invasion $\geqslant$ 500 μm) and undifferentiated-type EGCs diagnosed by CE as meeting the expanded-indication criteria for endoscopic resection.

Watari J, Ueyama S, Tomita T, Ikehara H, Hori K, Hara K, Yamasaki T, Okugawa T, Kondo T, Kono T, Tozawa K, Oshima T, Fukui H, Miwa H. What types of early gastric cancer are indicated for endoscopic ultrasonography staging of invasion depth? *World J Gastrointest Endosc* 2016; 8(16): 558-567 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i16/558.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i16.558

INTRODUCTION

Until recently, the Japanese Gastric Cancer Treatment Guidelines[1] stipulated that mucosal lesions < 2 cm in size and without ulceration are indicated for endoscopic resection (ER). However, in response to a report by Gotoda *et al*[2] on the low incidence of lymph node metastasis from early gastric cancers (EGCs), the indications for ER described in those Guidelines have been expanded to include EGCs with a very low risk of lymph node metastasis. Another part of the rationale behind this decision was that endoscopic submucosal dissection (ESD), which was developed in Japan[3-7], has made *en bloc* resection possible for lesions of all sizes. Along with the expanded indications for the ER of EGCs, therefore, the accurate diagnosis of invasion depth has become a very important component of pretreatment strategies.

Conventional endoscopy (CE) remains a useful modality for detecting EGCs and gauging their invasion depth. Although there have been many investigations, mostly in Japan, of the ability of CE to gauge the invasion depth of mucosal (M) and submucosal (SM) invasive cancers, collectively the rate of successful depth measurement has ranged from 62% to 80%[8-10]. Thus it is sometimes difficult to establish diagnostic criteria for differentiating M from SM cancers by CE alone. Endoscopic ultrasonography (EUS) permits a more objective assessment by providing a tomographic image, and is thus sometimes used as an adjunct diagnostic tool for determining the depth of gastric cancer invasion.

Several studies have compared the accuracy of invasion depth measurement between CE and EUS, and some of these reports clearly demonstrated the superiority of EUS for diagnosing EGC invasion depth[11-14] whereas others did not[9,15]. Two recent meta-analyses showed that EUS has relatively low accuracy for staging the depth of EGC invasion, and thus EUS may not be indispensable in the staging of EGCs[16,17]. It has also been reported that the accurate determination of invasion depth is difficult in cases with a large tumor size[11,15,18-21], upper location[15,18,20], depressed-type lesion[11,20], undifferentiated histology[15,21] or ulcerous finding (UL)[15,19,21,22].

There are also a number of practical technical difficulties that impede the production of suitable EUS images, and the use of poor-quality EUS images to determine the depth of EGCs may lead to incorrect results[23]. Unfortunately, most of the previous comparative studies (with the exception of the study by Tsujii *et al*[24]) analyzed only cases in which good-quality EUS images were obtained, and thus their findings may not show the true diagnostic capability of EUS in actual practice.

Along with the expanded indications for EGC dissection, it is expected that the number of ESDs of EGCs will increase, and the precise invasion depth staging of EGCs will therefore be important. Accordingly, the aims of the present study were to clarify: (1) the comparative diagnostic efficacies and limitations of EUS and CE for the pre-operative staging of EGC; and (2) the characteristic(s) of EGCs that are indications for the use of EUS as an adjunct diagnostic tool for measuring invasion depth.

MATERIALS AND METHODS

Patients

Between April 2012 and March 2015, 452 consecutive patients with a total of 510 neoplasias comprised of gastric adenomas and EGCs were treated with ESD (360 neoplasias) and surgery (150 neoplasias) at Hyogo College of Medicine Hospital in Nishinomiya, Japan. Among them, 153 EGCs in 140 patients were examined using both CE and EUS. Both the absolute-indication and the expanded-indication criteria for the ER of EGCs followed the Japanese Gastric Cancer Treatment Guidelines[1]. The absolute-indication criteria for ER are: M cancer, differentiated-type adenocarcinoma, UL(-), and < 2 cm in dia. The proposed extended-indication criteria for ER are as follows: (1) M cancer, differentiated-type adenocarcinoma, UL(-) and any tumor size; (2) M cancer, differentiated-type adenocarcinoma, UL(+) and < 3 cm in size; (3) minute submucosal cancer (< 500 μm invasion into the submucosa, SM1), differentiated-type adenocarcinoma and < 3 cm in size; and (4) M cancer, undifferentiated-type carcinoma, UL(-) and < 2 cm in size.

Written informed consent was obtained from all patients prior to the procedures and treatment, and the study design was approved by the Ethics Committee of Hyogo College of Medicine (No. 2109).

The CE and EUS diagnoses of the invasion depth of EGCs

When the invasion depth of an EGCs is being diagnosed, close endoscopic observation is necessary to adjust the air volume in the patient's stomach. The endoscopic criteria for cancer invasion in the present patient series were judged based on previous reports[8-10,15,24-26]. Briefly, in the CE diagnosis, the presence or absence of the following CE findings of SM massive invasion was determined: (1) irregular surface including nodules in the depressed area; (2) submucosal tumor-like elevation without flexibility; (3) abnormal converging folds such as clubbing and fusion; and (4) deep ulceration with marked marginal elevation. All endoscopic observations were performed by chromoendoscopy using an endoscope (GIF-Q260, H260, H260Z, H290Z, H290 or HQ290; Olympus Medical Systems, Tokyo) followed by EUS.

EUS was performed with a 20-MHz miniature probe UM-3R (Olympus Medical Systems), which was connected to an endoscopic ultrasonic observation unit (EU-M2000; Olympus Medical Systems). Approximately 200-500 mL of deaerated water was instilled in the stomach to improve the transmission of the ultrasound beam. In the EUS diagnoses, lesions confined to the 1st and 2nd sonographic layers were considered mucosal cancer. Massive submucosal invasion was defined as obvious irregular narrowing or budding into the 3rd sonographic layer as shown in previous reports[9-11,14,15,20,21,23-26].

In the UL(+) lesions, the previous criteria for EUS diagnosis were used[13,27]; namely, if a fan-shaped hypoechoic area was demonstrated in the 3rd layer, the lesion was defined as M/SM1, and when an arch-shaped hypoechoic area was observed in the 3rd layer, the lesions were regard as SM massive invasion (SM2). In the cases in which at least five layers of the gastric wall, including the lesion, were unclear and an assessment by EUS was difficult due to the low-quality image, the lesions were judged to be "inconclusive"[24].

It is very difficult to discriminate SM1 from M cancer even by CE or EUS, and the therapeutic strategies for these lesions are also similar. We therefore clinically divided these lesions into two groups: The M/SM1 group, for which ER may be suitable, and the SM2 group, for which surgery was indicated.

In this retrospective study, two endoscopists (Jiro Watari and Shigemitsu Ueyama) with 29 and 17 years of endoscopic practice experience, respectively and board certification from the Japan Gastroenterological Endoscopy Society independently reviewed the CE and EUS images without any pathologic information. The results were used for the calculation of interobserver agreement (κ value).

Histological evaluation

Resected specimens were sectioned at 2-mm intervals for ESD and 5-mm intervals for surgical resection. The histology, tumor location, gross morphologic type, and depth of invasion fulfilled the criteria of the Japanese Research Society for Gastric Cancer[28]. We histologically classified the specimens into two groups based on their depth of submucosal invasion: Invasion into the SM1 (invasion < 500 μm) or SM2 (invasion ≥ 500 μm) layer. The largest measured tumor size of the resected specimen was recorded histologically as the tumor dia.

Statistical analysis

We assessed the data by performing the Mann-Whitney *U* test for comparisons between two independent groups, and the χ^2 test or Fisher's exact test was used to examine differences between two proportions. Statistical significance was defined as a P value < 0.05. Risk factors for the misdiagnosis of the depth of cancer invasion by EUS that were found to be significant with a P value of < 0.05 in a univariate analysis were entered into a multiple logistic regression model and analyzed using a backward approach. Odds ratios (ORs) and 95%CIs were calculated for each risk factor.

The interobserver agreement for the CE imaging and the EUS imaging evaluations was calculated by κσ statistics, which were interpreted as follows: Poor (≤ 0.2), mild (0.2-0.4), moderate (0.4-0.6), good (0.6-0.8), and excellent (0.8-1.0). Differences at P < 0.05 were considered significant. All statistical analyses were performed using the StatView software program, ver. 5.0 (SAS Institute, Cary, NC).

Table 1 Patient characteristics

Total no. of lesions (patients)	153 (140)
Mean (± SD) age, years	68.7 ± 10.4
Sex, male/female	102/38
Macroscopic type	
0-I /0-IIa/0-IIb /0-IIc	9/51/1/92
Location	
Upper/middle/lower	45/69/39
Mean (± SD) tumor size, mm	20.5 ± 14.4
Depth of invasion	
M/SM1/SM2	93/17/43
Histology	
Differentiated/undifferentiated	118/35
Ulcer scar	
Positive/negative	29/124
Criteria for endoscopic resection	
Absolute/expanded/non-indication	51/38/64

M: Mucosal cancer; SM1: Submucosal invasive cancer invaded into the submucosal layer < 500 μm from the muscularis mucosa; SM2: Submucosal invasive cancer with invasion of ⩾ 500 μm into the submucosal layer.

Table 2 Clinical characteristics of the 21 inconclusive cases

Tumor-related factors		No. of inconclusive cases (%)	*P* value
Macroscopic type			< 0.0001
I	(*n* = 9)	9 (100)	
IIa	(*n* = 51)	7 (13.7)	
IIc	(*n* = 92)	5 (5.4)	
Location			0.03
Upper	(*n* = 45)	3 (6.7)	
Middle	(*n* = 69)	8 (11.6)	
Lower	(*n* = 39)	10 (25.6)	
Histology			0.16
Differentiated	(*n* = 118)	19 (16.1)	
Undifferentiated	(*n* = 35)	2 (5.7)	
Ulcer scar			0.37
Positive	(*n* = 29)	2 (6.9)	
Negative	(*n* = 124)	19 (15.3)	
Criteria for ER			0.58
Absolute	(*n* = 51)	9 (17.6)	
Expanded	(*n* = 38)	5 (13.2)	
Non-indication	(*n* = 64)	7 (10.3)	

ER: Endoscopic resection.

RESULTS

Patient characteristics and clinicopathological data of EGCs

Table 1 shows the characteristics of the 140 patients and a summary of the 153 studied EGCs. The mean age of the patients was 68.7 ± 10.4 years (range 23-87 years), and women accounted for 27.1% of the patients. The mean tumor size was 20.5 ± 14.4 mm in dia. The numbers of lesions that met the absolute- and expanded-indication criteria for ER were 51 and 38 lesions, respectively. The lesions were located mainly in the middle portion of the stomach.

Clinical characteristics of the "inconclusive" cases

Twenty-one (13.7%) of the 153 EGCs were judged as "inconclusive". As shown in Table 2, all nine of the protruded-type (0-I) cancers yielded low-quality images. The inconclusive rate was significantly higher in the lower portion of the stomach than in other portions (P = 0.03). There was no significant difference in the inconclusive rate between the lesions with and without UL.

Comparison of EGC invasion-depth diagnoses between EUS and CE

The κ-values for the interobserver agreement for the invasion depth diagnosis between the two endoscopists were 0.78 (95%CI: 0.68-0.89) for EUS and 0.82 (95%CI: 0.72-0.92) for CE. Thus the interobserver agreement for invasion depth diagnosis by EUS and CE was good to excellent. When the results of the diagnostic accuracy by one endoscopist whose accuracy rate was higher than that of the other endoscopist were used in both modalities, the accuracy rate of EUS was 71.2% (109 of 153 lesions) (Table 3), and when the accuracy was calculated in 132 lesions (omitting 21 inconclusive cases), the rate increased to 82.6% (109 of 132).

The sensitivity of EUS for diagnosing M/SM1 lesions was 85.3% (81 of 95 cases), the specificity was 75.7% (28 of 37), the positive predictive value (PPV) was 90.0% (81 of 90), and the negative predictive value (NPV) was 66.7% (28 of 42). The diagnostic accuracy of EUS was not significantly different among the three macroscopic types or the three tumor locations, or between the histological types, *i.e.*, the differentiated type and the undifferentiated type.

However, UL(+) and the non-indication criteria for ER were significantly associated with the incorrect diagnosis of tumor invasion depth by EUS (P < 0.0001 and P = 0.0004, respectively). In addition, UL(+) (OR = 4.49; 95%CI: 1.68-11.97; P = 0.003) and the non-indication criteria for ER (OR = 3.02; 95%CI: 1.14-8.00; P = 0.03) were significant and independent risk factors affecting misdiagnosis by EUS in our multivariate logistic regression analysis.

There were no significant differences in the accuracy or other parameters between EUS and CE; the sensitivity of CE diagnosis for M/SM1 was 88.2% (97 of 110 cases), the specificity was 58.1% (25 of 43), the PPV was 84.3% (97 of 115), and the NPV was 65.8% (25 of 38). As shown in Table 3, the accuracy rate obtained for the absolute-indication criteria lesions was very high for both modalities, and was significantly higher than that of the non-indication criteria lesions (P < 0.0001 in EUS and P = 0.01 in CE). There were also significant differences in the accuracy between the lesions with the expanded-indication criteria and those with the non-indication criteria for ER (P = 0.02 in both EUS and CE). However, no significant differences in diagnostic accuracy between the two modalities were observed within the expanded-indication criteria group or the

Table 3 Comparison of the invasion depth diagnosis between endoscopic ultrasonography and conventional endoscopy

	Clinical diagnosis	Histologic diagnosis		EUS diagnosis		P^2	Histologic diagnosis		Accuracy	P (*vs* EUS)
		M/SM1	SM2	Overall accuracy	Accuracy[1]		M/SM1	SM2		
Diagnosis	M/SM1	81	9	71.2	82.6		97	18	79.7	0.54
	SM2	14	28				13	25		
Macroscopic type						0.30				
I	M/SM1	-	-	-	-		5	1	88.9	-
	SM2	-	-				0	3		
IIa/IIb	M/SM1	26	4	67.3	77.8		32	5	78.8	0.90
	SM2	6	9				6	9		
IIc	M/SM1	55	5	80.4	85.1		60	12	79.3	0.32
	SM2	8	19				7	13		
Location						0.55				
Upper	M/SM1	21	2	74.4	80		24	4	80.0	> 0.99
	SM2	6	11				5	12		
Middle	M/SM1	40	7	69.9	78.5		44	11	78.3	0.98
	SM2	7	11				4	10		
Lower	M/SM1	19	2	62.2	85.2		29	3	82.1	> 0.99
	SM2	2	4				4	3		
Histology						0.79				
Diff.	M/SM1	71	10	70.4	83		77	12	80.5	0.63
	SM2	8	17				11	18		
Undiff.	M/SM1	9	1	75.0	84		20	6	77.1	> 0.99
	SM2	4	12				2	7		
Ulcer scar						< 0.0001				
Positive	M/SM1	3	2	46.7	50		7	4	58.6	0.51
	SM2	12	11				8	10		
Negative	M/SM1	77	7	75.6	89.4		90	14	84.7	0.29
	SM2	4	16				5	15		
Indication for ER						< 0.0001				
Absolute	M/SM1	37	-	80.4	97.4[b]		43	-	84.3[f]	0.07
	SM2	1	-				8	-		
Expanded	M/SM1	28	-	75.7	87.5[d]		33	-	86.8[h]	> 0.99
	SM2	4	-				5	-		
Non-indication	M/SM1	12	13	56.1	62.7[b,d]		16	18	64.1[f,h]	> 0.99
	SM2	9	25				5	25		

Accuracy[1] was calculated with the exception of 21 inconclusive cases of EUS; P^2 indicates a significant difference in Accuracy[1]. [b]$P < 0.0001$; [d]$P = 0.02$; [f]$P = 0.02$; [h]$P = 0.01$. EUS: Endoscopic ultrasonography; CE: conventional endoscopy; Diff: Differentiated-type; Undiff: Undifferentiated-type; ER: Endoscopic resection.

non-indication criteria group (Table 3).

Diagnostic concordance between EUS and CE

As shown in Table 4, the number of lesions that showed a correct diagnosis by CE and an incorrect diagnosis by EUS was almost the same as the number of lesions that showed an incorrect diagnosis by CE and a correct diagnosis by EUS in both the expanded-indication criteria group and the non-indication criteria group, irrespective of histology. This result may indicate that there is no additive effect of EUS in the diagnosis of invasion depth.

In the subgroup analysis of a total of 13 differentiated-type cancers without UL and with SM2 invasion diagnosed by CE, three (23.1%) cases that were misdiagnosed by CE were correctly diagnosed as M/SM1 lesions by EUS (Table 5 and Figure 1). We identified two cases (20.0%, 2 of 10) lesions that were ⩽ 2 cm and three cases (25.0%, 3 of 12) that were 3 cm in size. These cases were subsequently treated with ESD, avoiding surgery. The reverse phenomenon, *i.e.*, cases misdiagnosed by EUS but correctly diagnosed by CE - was not seen.

Similarly, in our subgroup analysis of 13 undifferentiated-type cases that met the expanded-indication criteria for ER, which were judged endoscopically as M/SM1 lesions, UL(-) and ⩽ 2 cm in size, three cases (23.1%) were correctly diagnosed by EUS as having SM2 invasion (Table 6 and Figure 2). These three cases were thus adequately treated with surgery.

DISCUSSION

Although there have been many investigations comparing the efficacy of EUS and CE for the pretreatment staging of EGCs, much controversy remains. In our present study, the overall accuracy of EUS for diagnosing invasion depth was lower than that of CE, but not significantly so. The accuracy of EUS was 82.6% (71.1% in overall accuracy), which was similar to the values reported in previous studies[13,14,19,22-25,27] but higher than the values obtained in other studies[9,11,12,15,20,21,26]. In recent meta-analyses, most of the cited studies showed that EUS has only a limited effect on determining the

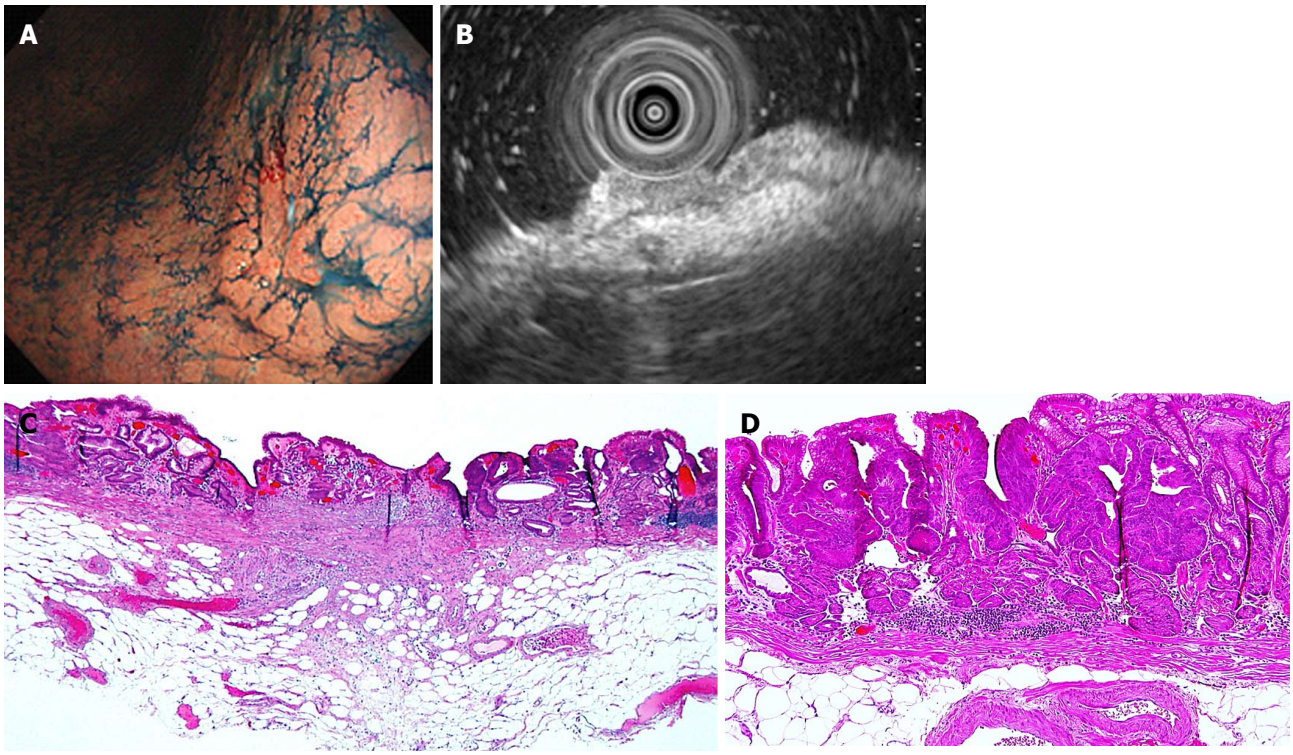

Figure 1 Case diagnosed correctly by endoscopic ultrasonography but misdiagnosed by endoscopy. A: Chromoendoscopy shows an irregular surface in a depressed lesion diagnosed as SM2; B: On this EUS image, irregular narrowing of sonographic layer 3 was not observed, and thus this lesion was considered an M/SM1 lesion; C: The histology by endoscopic submucosal dissection showed a differentiated-type intramucosal cancer with slightly fibrosis by biopsy; D: Histologic specimen of the lesion shows well differentiated-type adenocarcinoma limited to the mucosae (× 200). EUS: Endoscopic ultrasonography.

Table 4 Diagnostic concordance between endoscopic ultrasonography and conventional endoscopy

Diagnosis		Indication for endoscopic resection		
		Absolute criteria	Expanded criteria	Non-indication
Differentiated-type cancer (n = 99)				
EUS	CE	(n = 42) (%)	(n = 25) (%)	(n = 32) (%)
Correct	Correct	39 (92.9)	19 (76)	20 (62.5)
Incorrect	Incorrect	0 (0)	3 (12)	11 (34.4)
Correct	Incorrect	1 (4.8)	1 (4)	1 (3.1)
Incorrect	Correct	1 (2.4)	2 (8)	0 (0)
Undifferentiated-type cancer (n = 33)				
EUS	CE		(n = 8) (%)	(n = 25) (%)
Correct	Correct	-	8 (100)	15 (60)
Incorrect	Incorrect	-	0 (0)	1 (4)
Correct	Incorrect	-	0 (0)	5 (20)
Incorrect	Correct	-	0 (0)	4 (16)

EUS: Endoscopic ultrasonography; CE: Conventional endoscopy.

optimal therapeutic strategy[15,18-20,25]. Our present findings clearly demonstrated the limitations of EUS and the characteristics of EGCs that make them suitable for analysis by EUS.

In the present study, all nine of the 0-I-type cancers (protruded-type) yielded low-quality EUS images and were thus judged as inconclusive cases, as mentioned above[11,22]. The main cause of inconclusiveness was ultrasound attenuation due to the use of a high-frequency ultrasound probe (20 MHz); the submucosal layer could not be clearly visualized. If a low-frequency EUS or probe had been used, the number of inconclusive cases among those types of cancers might have been lower. However, in 0-I-type cancer the mucosa is thick and the muscularis mucosae elevates toward the mucosa from the submucosa, and it may thus be difficult to make an accurate diagnosis even if low-frequency EUS is performed.

In addition, the accuracy rate of EUS in the UL(+) lesions was extremely low (≤ 50%), and significantly lower than that in the UL(-) lesions (P < 0.0001). Regarding the reason for this finding, most of the lesions (80%, 12 of 15) of M/SM1 cancers with UL were over-diagnosed due to submucosal fibrosis,

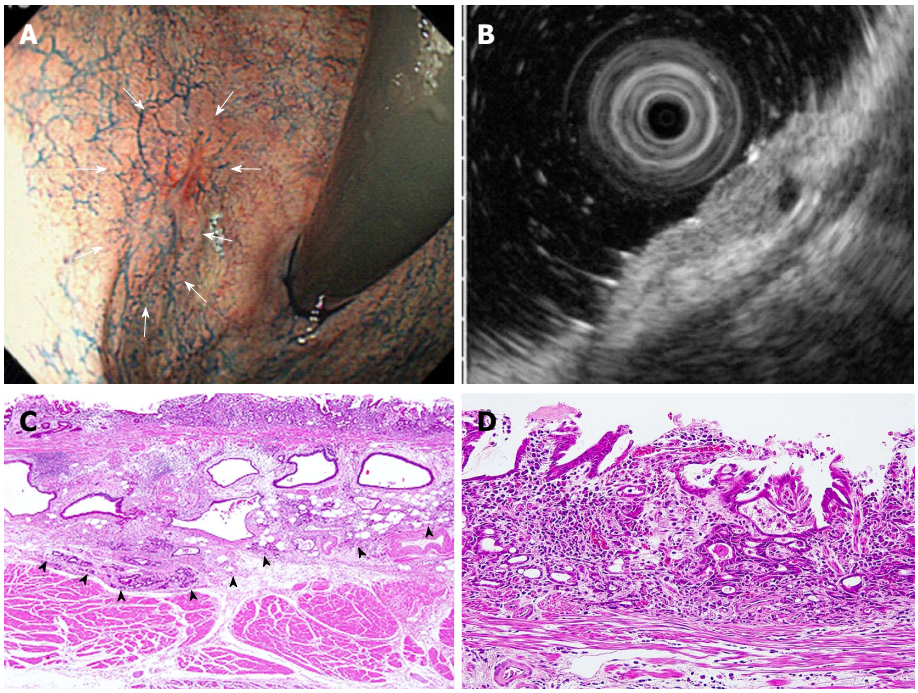

Figure 2 Case diagnosed correctly by endoscopic ultrasonography but misdiagnosed by endoscopy. A: Chromoendoscopy shows a reddish and smooth surface in a shallow depressed lesion diagnosed as M/SM1 (arrows). Histologically, the biopsy sample indicated a moderately to poorly differentiated adenocarcinoma; B: EUS image showing that a hypoechoic mass invaded the submucosal layer (sonographic layer 3). This lesion was diagnosed as SM2; C: Histology revealed that undifferentiated type adenocarcinoma massively invaded the submucosal layer (arrowheads); D: Moderately to poorly differentiated adenocarcinoma cells were observed in the gastric mucosae (× 200). EUS: Endoscopic ultrasonography.

Table 5 Subgroup analysis of 13 differentiated-type cancers without UL and with SM2 diagnosed by conventional endoscopy[1]

EUS	CE	*n* (%)
Correct	Correct	10 (76.9)
Correct	Incorrect	3 (23.1)
Incorrect	Correct	0 (0)
Incorrect	Incorrect	0 (0)

SM2 indicates invasion ⩾ 500 μm into the submucosal layer. [1]The lesions with an ulcer scar or 0-I macroscopic type were excluded from this analysis because the diagnostic capability for those lesions was extremely low. EUS: Endoscopic ultrasonography; CE: Conventional endoscopy.

Table 6 Subgroup analysis of 13 undifferentiated-type cancers diagnosed as meeting the expanded criteria for endoscopic treatment by conventional endoscopy[1]

EUS	CE	*n* (%)
Correct	Correct	10 (76.9)
Correct	Incorrect	3 (23.1)
Incorrect	Correct	0 (0)
Incorrect	Incorrect	0 (0)

[1]One 0-I macroscopic type lesion was excluded from this analysis because the diagnostic capability of this type of lesions was extremely low. EUS: Endoscopic ultrasonography; CE: Conventional endoscopy.

which is in agreement with previous reports[12,15,19,21,23]. In the report by Mandai *et al*[21], the accuracy rate of EUS decreased from 86.5% to 28.9% in the UL(-) lesions. Although a few studies have introduced a method that distinguishes cancer invasion from ulcer fibrosis[13,27], it may be difficult in practice to differentiate between those two conditions. In our multivariate logistic regression analysis, UL was a significant and independent risk factor affecting misdiagnosis by EUS, and thus it may be futile to perform EUS for UL(+) lesions.

There was no significant difference in the accuracy rate of EUS among the three tumor locations of the stomach, but inconclusive cases were observed significantly more frequently in the lower third of the stomach than in the other portions (P = 0.03). Several studies showed that the diagnostic accuracy of the invasion depth was diminished for lesions in the upper portion of the stomach[8,12,14,15,19,23]. Tsuzuki *et al*[25] reported that the submucosal layer in the upper third of the stomach is relatively thin and tends to have fibrosis and many vessels, making signs of submucosal invasion difficult to diagnosis and leading to incorrect staging. For other reasons, it is considered that it is difficult to fill this region with deaerated water[8,19,25]. However, this problem can be overcome by adjusting the volumes of air and deaerated water. In our patient population, it was often difficult to achieve the necessary pool of deaerated water in the lower third of the stomach, and there were technical problems with scanning this portion.

The diagnostic accuracy of EUS has been reported to be low for undifferentiated-type lesions[10-12,14,18,22] and

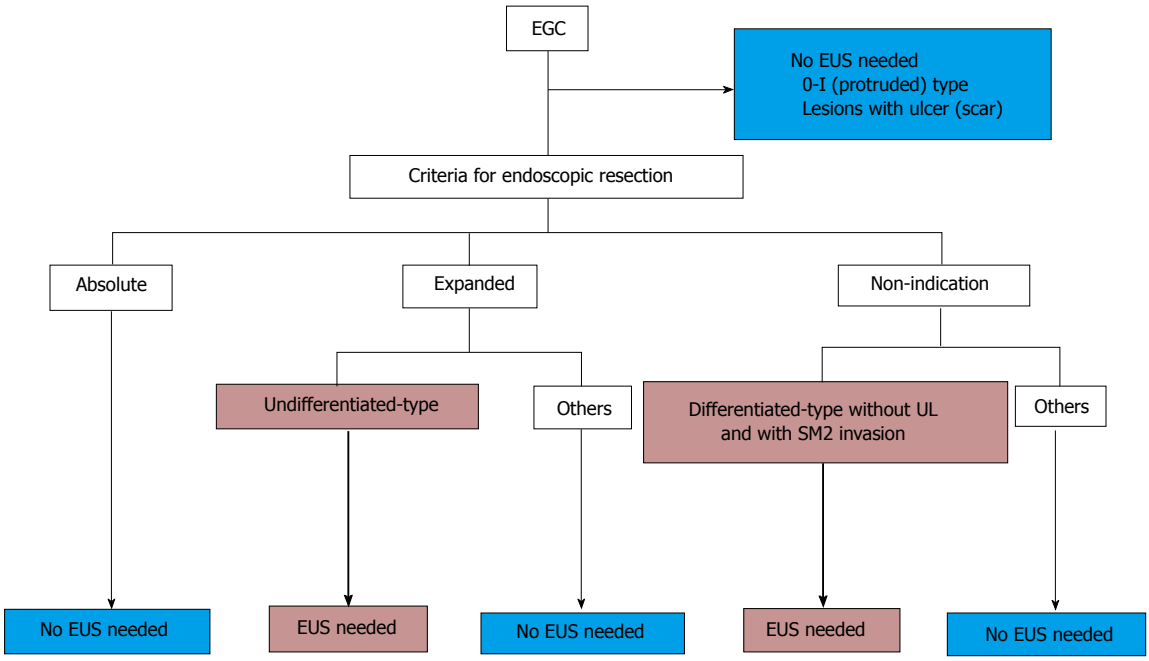

Figure 3 Flowchart of endoscopic ultrasonography diagnostic strategy for early gastric cancer. EUS should be considered performing the following lesions: (1) differentiated-type cancers without UL diagnosed as invading to SM2; and (2) undifferentiated-type cancers diagnosed by conventional endoscopy as meeting the expanded-indication criteria for endoscopic resection. In cases rather than those lesions, however, EUS may not be needed for the preoperative determination of the depth of EGCs. SM2 indicates invasion ⩾ 500 μm into the submucosal layer. EGC: Early gastric cancer; EUS: Endoscopic ultrasonography.

larger-size lesions[11,12,18,19,21], which were categorized mainly as meeting the expanded-indication criteria or non-indication criteria for ER. In the present study, the diagnostic accuracy for the lesions meeting the absolute-indication criteria for ER was very high for both EUS (97.4%) and CE (84.3%) as expected, whereas the accuracy rates of EUS and CE were significantly lower for the lesions that met the non-indication criteria for ER compared to those that met other criteria for ER.

If EUS is going to be performed for many lesions meeting the absolute-indication criteria for ER, the overall accuracy of EUS may naturally increase, but not to a clinically significant degree. It has been reported that magnifying endoscopy with narrow-band imaging (ME-NBI) is useful for determining the invasion depth diagnosis of EGC[29,30]; however the diagnostic criteria for SM2 are complex[29] and the diagnostic specificity of ME-NBI may be relatively low[30]. Actually, when the staging of an EGC is doubtful by CE, EUS is likely to provide helpful information to stage the EGC, *i.e.*, to determine the M/SM1 or SM2 status[16]. In such cases EUS may correct a misdiagnosis by CE, especially with respect to the expanded-indication and non-indication criteria for ER.

Taking past findings into consideration along with our present results, we propose that EUS may be considered for the following lesions: (1) differentiated-type cancers without UL diagnosed as invading to SM2; and (2) undifferentiated-type cancers diagnosed by CE as meeting the expanded-indication criteria for ER. When EUS is performed for these lesions, the additive effect of EUS will increase the accuracy by 23.1%. It should be noted, however, that we studied only a small number of either type of lesions, *i.e.*, three lesions of type (1) and three lesions of type (2). In contrast, it should also be emphasized that there were no lesions of either type which were correctly diagnosed by CE and incorrectly diagnosed by EUS. Based on our conclusion, we have summarized the indications of EUS for the pretreatment diagnosis of EGCs in Figure 3.

Our study has several potential limitations. First, it was a retrospective study at a single institution. Second, the sample size was relatively small. However, we did not perform EUS for most of the lesions that met the absolute-indication criteria, which could be definitely diagnosed as mucosal cancer by CE as mentioned above. Indeed, of the 186 EGCs that met the absolute-indication criteria for ER and that were treated with ER during this study period, only 50 lesions (26.9%) underwent EUS. This result may thus have resulted in a selection bias because there were no eligibility criteria for performing EUS in this study. Third, only the patients with histologically confirmed EGC who underwent EUS and ESD or surgery were evaluated, which might also have introduced a potential selection bias. Fourth, since EUS was performed under CE by an endosonographer, the construction of EUS images may have been affected by the endoscopic appearance of the lesions and the experience of the endosonographer[31]. In addition, one observer might have been involved in both of the examinations, *i.e.*, CE and EUS, in some cases. In general, the observer who validates the criteria should not have been involved in the evaluation of the EUS and CE images[24].

In conclusion, our analyses revealed that: (1) EUS may not be necessary to determine the pretreatment staging of 0-I type and UL(+) or absolute-indication criteria lesions; and (2) EUS may be considered for the following lesions: (1) differentiated-type cancers diagnosed without UL and with invasion to SM2; and (2) undifferentiated-type cancers diagnosed as meeting the expanded-indication criteria for ER by CE.

COMMENTS

Background

It is sometimes difficult to establish diagnostic criteria for differentiating mucosal cancer from submucosal invasive cancer by conventional endoscopy (CE) alone. Although endoscopic ultrasonography (EUS) permits a more objective assessment by providing a tomographic image, recent meta-analyses showed that EUS has relatively low accuracy for staging the depth of early gastric cancer (EGC) invasion.

Research frontiers

According to the previous studies, some of these reports clearly demonstrated the superiority of EUS for diagnosing EGC invasion depth whereas others did not. The authors retrospectively investigated the application of EUS in the pre-treatment staging of EGD.

Innovations and breakthrough

All protruded-type EGCs were "inconclusive" cases with low-quality EUS images. There was no significant difference in the diagnostic accuracy between CE and EUS. The lesions with ulcer scar (UL) and non-indication criteria for endoscopic resection (ER) were significant independent risk factors for misdiagnosis by EUS. In the subgroup analysis, however, the additive effect of EUS was found in the lesions with the differentiated-type cancers exhibiting SM2 invasion (submucosal invasion $\geqslant$ 500 μm) by CE and the undifferentiated-type EGCs meeting the expanded-indication criteria for ER.

Applications

EUS may not be necessary to determine the pretreatment staging of protruded (0-I)-type and the lesions with UL or absolute-indication criteria for ER; and EUS may be considered for the following lesions: (1) differentiated-type cancers diagnosed without UL and with invasion to SM2; and (2) undifferentiated-type cancers diagnosed as meeting the expanded-indication criteria for ER by CE.

Terminology

EUS is a reliable method for predicting the invasion depth diagnosis of EGC. However, there is no need to perform EUS for the EGCs with the absolute-indication criteria, UL(+) or 0-I-type. The modality should be considered performing the limited lesions.

Peer-review

This is a good article to describe the indications for EUS staging of invasion depth in EGCs.

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CASE REPORT

Small bowel Dieulafoy lesions: An uncommon cause of obscure bleeding in cirrhosis

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Abstract

Dieulafoy lesions (DLs) are an uncommon cause of gastrointestinal bleeding, accounting for up to 2% of cases overall. They are largely under recognised and difficult to treat. Up to 95% occur in the stomach, and only case reports document their occurrence in the small bowel (SB). Little is known about their pathophysiology, although there have been associations made previously with chronic liver disease, thought to be due to the erosive effects of alcohol on the mucosa overlying the abnormally dilated vessels. We present a case series of 4 patients with a long duration of obscure gastrointestinal bleeding, who were diagnosed with small intestinal DLs and incidentally diagnosed with chronic liver disease. The histories describe the challenges in both diagnosis and treatment of small intestinal DLs. Our case series suggest a previously unreported link between chronic liver disease and SB DLs which may be due to anatomical vasculature changes or a shift in angiogenic factors as a consequence of portal hypertension or liver cirrhosis.

Key words: Obscure gastrointestinal bleeding; Dieulafoy lesions; Cirrhosis; Portal hypertension; Capsule endoscopy; Double balloon enteroscopy

Core tip: Patients with advanced liver disease are known to have a high rate of obscure gastrointestinal bleeding, the cause of which is often left undetected. Our case series suggests that there may be an increased risk of small intestinal Dieulafoy lesions (DLs) in patients with cirrhosis. Although the pathophysiology of DLs is unknown, our case series of jejunal lesions in patients with cirrhosis raises the question of a potential alteration in the vasculature secondary to portal hypertension, as either an anatomical abnormality or due to a shift in angiogenic factors in these patients.

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INTRODUCTION

Dieulafoy lesions (DLs) are an uncommon cause of gastrointestinal bleeding (GIB), accounting for up to 2%, and are largely under recognised and difficult to treat. Endoscopically they are characterised by the following diagnostic criteria: Active bleeding from a mucosal defect < 3 mm in size, an isolated protruding vessel with or without a minute mucosal defect, or an adherent clot with a narrow point of attachment to a tiny mucosal defect or occasionally normal appearing mucosa[1]. The majority, up to 95%, of DLs are found in the stomach, generally within 6 cm of the oesophagogastric junction, with over 60% on the lesser curvature of the stomach, however they also occur in the colon, duodenum, and rarely in the small bowel (SB). The presentation of bleeding is usually acute overt haemorrhage, and due to the intermittent nature of bleeding, rates of diagnosis at initial endoscopy can be as low as 70%[2]. Endoscopic treatment with argon plasma coagulation (APC), clipping, injection of adrenaline or banding is successful in up to 90% of cases, with angiographic embolization or surgical resection reserved for cases unresponsive to endoscopic therapy[3]. Although the initial response is very high, recurrence is common, and up to 10% of patients present with massive acute GIB, and despite advances in endoscopic treatment mortality rates are as high as 8%[4]. DLs in the SB are rare, however with the increasing availability of SB endoscopy, there have been a number of case series in recent years, understandably suggesting that SB lesions are more difficult to treat[5,6]. Several hypotheses have been put forward as to the cause of bleeding from these DLs, and although an association has been suggested between the use of non-steroidal anti-inflammatories (NSAIDs) and anticoagulants, no causal link or pathophysiological basis for their development has been established. Interestingly a number of small studies have identified an association between advanced liver disease and DLs, suggesting a similarity of these lesions to spider naevi, however the numbers in each study have been small[7-9]. We present a case series of 4 patients with SB DLs who were found incidentally to have advanced liver disease during their workup for obscure GIB. These patients presented consecutively to our institution over approximately a two year time period.

CASE REPORT

Case 1

PS: A 67-year-old female was referred for investigation of obscure overt GIB ongoing for 2 years. Her past history included rheumatic fever, with metallic aortic and mitral valve replacements, for which she was anticoagulated, and congestive cardiac failure. She had initially presented with recurrent episodes of melaena and underwent multiple upper and lower endoscopies and a CT mesenteric angiogram which failed to reveal the source of her bleeding. Cross sectional imaging revealed cirrhosis, without significant varices. A serological screen failed to show any cause of cirrhosis and it was presumed to be secondary to her cardiac failure. She was initially treated empirically with iron and red cell transfusions, however her requirements increased and she became dependent on fortnightly transfusions to maintain her haemoglobin above 8 g/dL. At this stage she was admitted electively and underwent SB capsule endoscopy (SBCE) which showed a large volume of fresh bleeding in the proximal jejunum, with melaena and transported clots throughout the SB. Double balloon enteroscopy (DBE) showed no active bleeding but an isolated protruding vessel in the proximal jejunum, consistent with a DL was detected, and APC and endoclips were applied. Following this she was treated with 20 mg of a long-acting intramuscular somatostatin analogue and she remained bleed free for 12 wk. Unfortunately she then suffered an acute haemorrhage, presenting with haemoglobin of 5 g/dL. She underwent repeat SBCE and DBE which again showed active bleeding from the DL in the proximal jejunum which was again treated with APC and endoclips which initially controlled the bleeding. However PS suffered a massive further haemorrhage, a bleeding source could not be identified by CT mesenteric angiography and despite undergoing an emergency jejunal resection; she died post operatively due to cardiac complications.

Case 2

MF: A 74-year-old lady was referred with intermittent melaena ongoing for 18 mo. She had a history of rheumatic fever, a mitral valve replacement, requiring anticoagulation, congestive cardiac failure and a SB resection in the 1990s for angiodysplasia. Similarly, MF had undergone multiple upper and lower endoscopies which had been unyielding and again, she was found to have features of cirrhosis and portal hypertension on cross sectional imaging, the cause of which was idiopathic. Prior to referral to our services she had received over 50 units of red cell transfusions. She underwent SBCE which showed active bleeding and a minute mucosal defect in her proximal jejunum consistent with a DL, with clots of likely transported blood seen more distally. Her DL was treated with APC *via* DBE on 4 occasions due to early re-bleeding, along with 20 mg of long-acting somatostatin analogue. MF developed cholecystitis secondary to choledocholithiasis, which was managed conservatively, requiring her to discontinue the somatostatin analogue. She has been bleed-free for the last 24 mo, with a most recent

haemoglobin level of 12.1 g/dL.

Case 3

MB: A 76-year-old lady was admitted electively for investigation of a 12-mo history of recurrent obscure overt bleeding in the form of melaena. She had a background of a mitral valve replacement requiring anticoagulation, chronic myeloid leukaemia, cirrhosis of unknown aetiology, and hypertension. MB had undergone embolization of a bleeding source in her proximal jejunum *via* mesenteric angiography prior to her referral to our services; however her melaena recurred within 4 mo of the procedure, and she was requiring weekly red cell transfusions. SBCE showed active bleeding in her proximal jejunum; however at DBE although fresh blood was seen in her proximal jejunum no active bleeding or mucosal abnormalities were seen. During her admission she suffered a number of large volume overt bleeds requiring multiple red cell transfusions, again DBE showed active bleeding in the proximal jejunum. However this was not detected by either CT mesenteric angiogram or a formal heparin-provoked angiogram. After prolonged consideration and discussion, MB underwent a laparoscopic resection of her proximal jejunum, with histology findings consistent with that of a DL. Her haemoglobin remained stable without any red cell transfusions for over 9 mo at which point she re-presented with melaena. On this occasion she was not found to have and SB bleeding, however a new DL was found in her gastric fundus.

Case 4

EN: A 75-year-old lady was referred to our institution for investigation of recurrent melaena. She had undergone multiple upper and lower endoscopies which had not revealed a source of bleeding. Her past medical history included congestive cardiac failure, atrial fibrillation for which she was anticoagulated, type 2 diabetes mellitus, hypertension and cirrhosis, again diagnosed incidentally by imaging during her workup for GIB. SBCE showed fresh blood in the proximal jejunum and she underwent a DBE where a small amount of fresh bleeding was noted in the first part of her duodenum, with the visualisation of a pinpoint vessel consistent with a DL. The area was injected with adrenaline and endoclips were applied with initial haemostasis. However due to the need for ongoing anticoagulation the lesion continued to ooze and a definitive treatment was sought. EN underwent a CT mesenteric angiogram which revealed an occluded coeliac artery with retrograde filling of the gastroduodenal artery from the superior mesenteric artery. Due to the anatomical abnormalities in her vasculature, embolization therapy was not possible and an ileohepatic artery bypass was planned. However, despite previously normal imaging, at laparotomy EN was found to have macro nodular cirrhosis with multiple small intra-abdominal varices. The proposed bypass was abandoned and multiple small DLs around D1 were ligated and/or clipped. EN recommenced anticoagulation shortly after her surgery and has not had any recurrent bleeding episodes in over 10 mo.

DISCUSSION

The above 4 cases outline the challenges in both diagnosis and treatment of SB DLs, and they also present a number of potentially new associations with SB DLs. Firstly regarding demographics, in keeping with the published literature, our patients were elderly with multiple comorbidities, however in contrast to the suggested male preponderance, our 4 patients with SB DLs were all female. In addition, all 4 patients had SB without coexistent lesions in the stomach, where 95% of DLs reportedly occur, although the third case was found to have a de novo gastric DL over 9 mo later. There was also no history of NSAID, or alcohol use, although all patients were anticoagulated, which has been proven to increase the risk of bleeding. Each of the cases highlights the difficulties in diagnosis of SB DLs and reiterates the importance of heightened vigilance in patients with obscure GIB. Despite active bleeding causing systemic compromise and large red cell transfusion requirements, none of the DLs were detected by mesenteric angiography, and were only diagnosed by mucosal visualisation with SB endoscopy, either *via* SBCE or DBE.

Previous associations between cirrhosis and DLs have been thought to be due to the erosive effect of alcohol on the mucosa overlying the dilated DL vessel; however alcohol was not a factor in any of our 4 patients. As mentioned in the introduction, comparisons have been made between the appearances of DLs and spider naevi, a known feature of chronic liver disease, with the suggestion that DLs are gastrointestinal forms of spider naevi; however the pathophysiology for the development of spider naevi is also unknown. Cirrhosis can increase the risk of GIB, mainly due to portal hypertension, leading to portal gastropathy and intraluminal varices; however in our case series all patients had undergone multiple endoscopies, out ruling varices as a cause of bleeding. Patients with advanced liver disease are known to have a high rate of obscure GIB, the cause of which is often left undetected, however; our case series suggests that there may be an increased risk of DLs in patients with cirrhosis. In general the most common cause of obscure GIB is SB angiodysplasias, which have a similar clinical presentation to DL; however there were no characteristic endoscopic features of angiodysplasias in the vascular lesions in any of these 4 patients. We have recently identified an association between the abnormalities in the Angiopoietin pathway along with other angiogenic factors, with the presence of SB angiodysplasias[10]. Our finding of jejunal DLs in patients with cirrhosis raises the question of a potential alteration in the vasculature secondary to portal hypertension, as either an anatomical abnormality, as was described in case 4, or potentially due to a shift in angiogenic factors in these patients. As referenced in the case series by Akhras *et al*[9], the examination of biopsies

from DLs is likely to yield more information about their pathophysiology. Finally, 3 of our 4 patients were treated both medically with long-acting somatostatin analogues and endoscopically, due to a combination of their long history of bleeding and its significant burden on their quality of life, and their need for long-term anticoagulation. Somatostatin analogues are known to reduce GIB due to a combination of effects, including reducing the splanchnic and portal pressure and *via* an anti-angiogenic effect on vascular endothelial growth factor. This makes it difficult to determine which treatment modality was effective in controlling further bleeding episodes but the seemingly successful use of somatostatin analogues in these patients would support both a "vascular pressure system" and an "angiogenic disarray" hypothesis in the pathogenesis of SB DLs. Further work in the field of portal hypertension and angiogenic factors in the pathophysiology of SB DLs and other vascular lesions including angiodysplasias will be interesting and could lead to more targeted treatment options in cases of refractory bleeding.

COMMENTS

Case characteristics

All cases had a long history of significant gastrointestinal bleeding from small intestinal Dieulafoy lesions (DLs) and were found to have cirrhosis and portal hypertension, suggesting a potential association between the two conditions.

Clinical diagnosis

Small intestinal DLs were diagnosed by a combination of capsule endoscopy and double balloon enteroscopy in all patients, with a diagnosis of cirrhosis initially suggested by radiological imaging and confirmed by clinical examination ± laboratory features of cirrhosis.

Differential diagnosis

There are a number of other vascular lesions which can affect the small intestine and share similar endoscopic features with DLs including: Angiodysplasias, telangiectasias, arteriovenous malformations, mucosal ulceration and trauma.

Laboratory diagnosis

All patients presented with iron deficiency anaemia, in addition features of cirrhosis including thrombocytopaenia and a low serum albumin were found in 2 patients.

Imaging diagnosis

Small intestinal DLs were diagnosed endoscopically by characteristic visual appearances, using either capsule endoscopy or double balloon enteroscopy.

Pathological findings

When examined histologically, DLs are found to consist of abnormally large calibre sub-mucosal end arteries which lie close to the surface of the mucosa, making them delicate and prone to rupture and bleeding.

Treatment

Treatments included endoscopic; a combination of injection of adrenaline, application of endoclips, and/or thermal coagulation, *via* angiographic embolization, or ultimately *via* surgical resection of the segment of affected bowel, or ligation of the vessels feeding the DLs.

Related reports

Small intestinal DLs are reported only rarely in the literature and are thought to be difficult to treat. An association between patients with advanced liver disease and DLs outside the small intestine has also been made in a few other case reports, although the pathophysiology linking the two conditions is still unknown.

Term explanation

DLs are uncommon causes of gastrointestinal bleeding characterised by tiny defects in the gastrointestinal mucosa.

Experiences and lessons

This case series highlights the difficulties in the diagnosis of DLs and the need for heightened vigilance and repeated investigation in patients with obscure gastrointestinal bleeding, particularly in patients with cirrhosis. It also highlights the difficulties and poor outcomes following treatment, which addresses the need for further research in the area to identify the pathophysiology of DLs and develop targeted therapies.

Peer-review

The paper is a useful addition to the literature concerning this difficult to treat lesion.

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