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REVIEW

Percutaneous endoscopic gastrostomy and jejunostomy: Indications and techniques

Alessandro Fugazza, Antonio Capogreco, Annalisa Cappello, Rosangela Nicoletti, Leonardo Da Rio, Piera Alessia Galtieri, Roberta Maselli, Silvia Carrara, Gaia Pellegatta, Marco Spadaccini, Edoardo Vespa, Matteo Colombo, Kareem Khalaf, Alessandro Repici, Andrea Anderloni

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Abstract

Nutritional support is essential in patients who have a limited capability to maintain their body weight. Therefore, oral feeding is the main approach for such patients. When physiological nutrition is not possible, positioning of a nasogastric, nasojejunal tube, or other percutaneous devices may be feasible alternatives. Creating a percutaneous endoscopic gastrostomy (PEG) is a suitable option to be evaluated for patients that need nutritional support for more than 4 wk. Many diseases require nutritional support by PEG, with neurological, oncological, and catabolic diseases being the most common. PEG can be performed endoscopically by various techniques, radiologically or surgically, with different outcomes and related adverse events (AEs). Moreover, some patients that need a PEG placement are fragile and are unable to express their will or sign a written informed consent. These conditions highlight many ethical problems that become difficult to manage as treatment progresses. The aim of this manuscript is to review all current endoscopic techniques for percutaneous access, their indications, postprocedural follow-up, and AEs.

Key Words: Percutaneous endoscopic gastrostomy; Enteral nutrition; Gastrostomy;

Percutaneous endoscopic jejunostomy; Indications and techniques

Core Tip: Percutaneous endoscopic gastrostomy (PEG) represents the first choice for long-term enteral nutrition support. The aim of this manuscript is to provide a comprehensive overview of PEG placement, including indications, contraindications, preprocedural clinical assessment, endoscopic techniques, adverse events, and postprocedural follow-up. Furthermore, endoscopic procedures for jejunal nutrition are also addressed. In consideration with the increasing frequency with which PEG placements are requested, this review may be a useful tool for clinical guidance both for endoscopists and physicians in different fields, with a particular focus on appropriateness of the indications and safety of this procedure.

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INTRODUCTION

Nutritional support is essential in patients who have a limited capability to maintain their body weight with a normal diet. In best practice, oral feeding is the main approach to choose for these patients[1]. Many patients cannot consume food by mouth. In some cases, oral intake can even be dangerous for patients with neurological conditions or obstructive causes, although their gastrointestinal (GI) tract is functional[2]. In these cases, physicians can support alimentary intake by positioning a nasogastric or nasojejunal tube or creating a direct access into the stomach through a percutaneous endoscopic gastrostomy (PEG)[3]. This allows the maintenance of normal physiological activities of the GI tract in order to avoid alterations in the intestinal barrier functions and long-term complications related to intravenous nutritional support[4,5].

The choice between whether the feeding tubes are placed *via* oral route over a PEG needs to be evaluated case-by-case by a multidisciplinary team, considering there are multiple factors related to procedural indications, such as patient condition, clinical scenario, and risk of adverse events (AEs) for the patient. However, when the GI tract does not work properly, such as in cases of obstruction, intravenous nutritional support should be preferred.

Parenteral nutrition (PN) is a nutritional support therapy that is provided through the intravenous administration of nutrients such as glucose, electrolytes, amino acids, lipids, and vitamins. Moreover, PN can be associated with AEs and is poorly tolerated, especially in patients with heart failure, renal insufficiency, and diabetes mellitus[6]. A recent systematic review with meta-analysis based on oncologic patients reported no differences between enteral nutrition (EN) and PN with regards to nutritional outcomes, with a higher incidence of infections in the PN group [risk ratio = 1.09, 95% confidence interval: 1.01-1.18; P = 0.03][7]. For these reasons, the recent European Society for Clinical Nutrition and Metabolism guidelines recommended administering total PN only when patients are unable to reach their nutritional outcomes with oral nutrition or EN[6]. Although the benefit of percutaneous access for EN have been reported for a while, several controversies and major concerns still exist regarding these procedures and the related AEs. The aim of this manuscript is to review all current techniques for percutaneous access for EN, their indications, postprocedural follow-up, and AEs.

INDICATIONS

Nowadays, many diseases result in long-term reduction of caloric intake. For this reason, placement of a percutaneous endoscopic access is needed in order to improve nutritional conditions. Percutaneous endoscopic nutrition can be achieved by either a transgastric approach through PEG or a transjejunal approach, namely percutaneous endoscopic jejunostomy (PEJ).

Ever since the first endoscopic insertion of a gastrostomy[8], there has been a worldwide diffusion of these techniques and an increase in indications for this medical approach. A summary list of indications for PEG placement is reported in Table 1. However, nutritional support is often only necessary for a short period, such as less than 1 mo, in case of stroke with fast recovery, mild head trauma, acute

pancreatitis, post-head and neck surgery, post-upper GI surgery, and other temporary diseases. In these patients, a nasogastric tube is easier to insert and to manage directly at bedside. On the other hand, some patients need nutritional support for longer periods of time.

In the recently published European Society of Gastrointestinal Endoscopy guidelines regarding endoscopic management of enteral tubes in adult patients, it is recommended to consider EN by percutaneous access when nutritional support is needed for more than 4 wk on a case-by-case basis[3]. The 4-wk cut-off is arbitrary and has been chosen to avoid many AEs that are related to percutaneous access (*e.g.*, infections). When indicated, the gastric route through a PEG is more desirable than the jejunal approach, due to its better tolerance, ease of procedure, and its possibility to be performed bedside[9]. In the case of altered anatomy, delayed gastric emptying, gastric outlet obstruction, duodenal obstruction, severe gastroesophageal reflux, or increased risk of aspiration pneumonia, PEJ must be considered[9].

Benign diseases

Neurological diseases often need nutritional support, especially in patients that cannot consume food orally due to neurological injury. Specifically, dementia is a common disease that needs EN. Patients with dementia often cannot or will not swallow. This condition mainly occurs later in the course of the disease when patients are in an advanced stage[10] and when they cannot express their will[11]. Currently, studies about EN in patients with dementia are scarce. A systematic review regarding patients with final stage dementia did not show differences between EN and no nutritional support in terms of survival, quality of life, nutritional status, function, behavior, or psychiatric symptoms[12]. For these reasons, the recently published European Society of Gastrointestinal Endoscopy guidelines recommend avoiding PEG placement in patients with advanced dementia, especially if they have a life expectancy of less than 4 wk[3].

Stroke is another common neurological cause of dysphagia, with an incidence of 23%-50%[13]. Some patients recover slowly or do not have the capability to consume food through the oral route, leading to a high risk of aspiration pneumonia and low nutritional intake. Motor neuron diseases often involve varying swallowing functions[14]. A recent cohort study on 957 patients (278 with PEG) affected by amyotrophic lateral sclerosis showed that PEG nutrition support improved overall survival expectancy (21 mo *vs* 15 mo, $P < 0.001$)[15]. Moreover, dysphagia can be present after head injury with neurological damage. A review focused on randomized controlled trials of nutrition in patients with head injury showed that survival expectancy and disability were improved by early PN or EN[16]. Patients with Parkinson's disease can develop motor alteration like dysphagia, and EN should be considered due to the increased risk of aspiration pneumonia and difficulties in oral intake[17].

There is poor evidence to support PEG placement in patients with other benign diseases such as cerebral palsy, anorexia, frailty, burn patients, and hypercatabolic diseases, even though each case must be evaluated individually. Furthermore, cases of PEG placement are reported in patients with benign esophageal strictures such as caustic stricture, Zenker diverticulum, post endoscopic therapy (endoscopic mucosal resection, endoscopic submucosal dissection, radiofrequency ablation), and achalasia[18,19].

Malignant diseases

Head and neck malignancies can lead to dysphagia in 35%-50% of cases[20]. The reported high-risk factors are hypopharyngeal localization, advanced neoplasia (T4), and combined chemoradiation. In these settings, the main indications for PEG are the onset of dysphagia, low nutritional intake, and loss of body weight[21]. A recent published study evaluated 130 patients with a head-neck tumor who underwent chemoradiotherapy. Of these, only 69 patients received a prophylactic PEG placement. The authors showed that prophylactic PEG improved nutritional parameters and unexpected hospitalization [22]. Esophageal cancer is another indication for EN if patients present symptoms of severe dysphagia and when palliation by placement of an endoscopic stent is not feasible[23]. In general, all oncological diseases that imply hypercatabolism that is not compensated by oral intake may require EN by nasogastric tube or PEG[3].

Other indications

Other indications of PEG that are not for nutritional purposes have also been described. An endoscopic gastrostomy may be placed in patients with gastric outlet obstruction or intestinal strictures that cannot be managed through the usual endoscopic approach, by placement of an endoscopic stent, or creating an endoscopic ultrasound (EUS)-guided gastroentero-anastomoses[24-27]. These conditions can benefit from gastric decompression by PEG[28]. This technique aims to improve the patient's symptoms and reduce GI distension. Primarily, it can be connected to an aspirator to quickly relieve symptoms. Later, it can be connected to a drop bag to improve compliance. This also allows patients to eat small quantities of food in order to guarantee a better quality of life, although some poor nutritional benefits may remain.

In a recent systematic review with 1194 cases, 90% of technique success rate had been reported. However, it showed minor AEs (leak 6.7%; peristomal infections 5.1%; device malfunction 2.8%, and

Table 1 Indications for percutaneous endoscopic gastrostomy placement

Benign	Malignant	Pediatric
Neurological diseases and psychomotor retardation. Cerebrovascular disease. Motor neuron disease (amyotrophic lateral sclerosis). Multiple sclerosis. Parkinson's disease. Dementia. Psychomotor retardation. Reduced level of consciousness. Head injury. Intensive care patients. Prolonged coma. Burns. Short bowel syndromes (Crohn's disease). Facial surgery. Polytrauma. Benign esophageal strictures. Other causes of malnutrition (anorexia)	Cerebral tumor. Cancer with catabolic status. Head and neck cancer. Esophageal cancer. Gastric decompression	Cerebral palsy. Congenital anomaly (*e.g.*, trachea esophageal fistula). Cystic fibrosis. Short bowel syndrome

Table 2 Contraindications to percutaneous endoscopic gastrostomy placement

Relative	Absolute
Peptic ulcer bleeding with high risk of rebleeding. Ascites. Ventriculoperitoneal shunts. Abdominal scars. Large intrathoracic hiatal hernia	Coagulation disorders (INR > 1.5, PTT > 50 s). Platelet count < 50000 mm^3. Sign of sepsis. Peritonitis. Peritoneal carcinomatosis. Lack of a safe tract for percutaneous insertion. History of total gastrectomy

INR: International normalized ratio; PTT: Partial thromboplastin time.

dislodgement 2.1%) in 19.8% of patients and major AEs (2 deaths for sepsis and bleeding) in 1.9% of patients[29]. Moreover, Baron *et al*[30] described the use of a surgical gastrostomy (SG) as access for a duodenoscope in order to perform an endoscopic retrograde cholangiopancreatography[30]. This technique can be used effectively in patients with biliary diseases and previous bariatric Roux-en-Y gastric bypass surgery[31].

A percutaneous intragastric trocar was designed to serve as a trocar for the endoscopist's introduction of rigid laparoscopic instruments in order to better aid endoscopic therapeutic procedures. This device was placed following PEG placement and was successfully used in pigs to perform endoscopic submucosal dissection, full-thickness resections, and intragastric stapling[32]. The PEG could also be used as an access route to perform combined antegrade and retrograde dilations in esophageal strictures that cause complete obstruction and are difficult to dilate with standard endoscopic techniques[18,33,34].

Pediatric indications

PEG is also indicated in the pediatric setting when there is a low nutritional intake, malabsorption, and dysphagia that leads to malnutrition[35]. This procedure is considered safe in a pediatric population weighing less than 6 kg, with complex neurologic disability, congenital heart disease, cancer, or other complex medical comorbidities[36]. Down syndrome is regarded as an indication for PEG placement in the pediatric setting when there is poor nutritional intake[37]. Likewise, cerebral palsy may represent an indication for EN, but substantial evidence to support this indication is scarce[3]. Other indications for PEG placement are congenital malformations, such as congenital heart failure, which can lead to chronic malnutrition[38]. In a pediatric oncological setting, PEG placement results in improvement of body weight, malnutrition, and oncological outcome[39,40].

PRE-EVALUATION AND CONTRAINDICATIONS TO PEG PLACEMENT

All patients must be evaluated carefully prior to undergoing a PEG. A complete visit with medical history, physical examination, and current therapy must be completed[41]. Observational studies showed that a multidisciplinary team can select patients that are suitable for PEG placement[42]. Indeed, a gastroenterologist, a PEG specialist nurse, a dietician, and a speech and language therapist must evaluate the situation on a case-by-case basis. The time of observation of the patient by the nutritional team could require up to 7 d prior to deciding whether the procedure is appropriate or not. This period, defined as the "cooling-off period," is reported as a high-risk phase, where 43% of patients pass away. For this reason, waiting a week could avoid inappropriate procedures in patients with a short life expectancy[43]. However, there are some conditions that represent relative or absolute contraindications for PEG placement. The most common are reported in Table 2.

Recent peptic ulcer bleeding with high risk of rebleeding and hemodynamic and respiratory instability are considered relative contraindications[44]. There are also controversial studies about PEG placement in patients with ascites. In a retrospective study of 29 patients with advanced cirrhosis, Baltz *et al*[45] reported high mortality in patients with ascites who underwent PEG placement. Another case control study evaluated 583 cirrhotic patients, 107 of whom had ascites. It showed no difference in terms of mortality, infections, and bleeding after PEG insertion[46].

Furthermore, particular attention must be paid in patients with ventriculoperitoneal shunts (VPS). In a systematic review, a high incidence of infections and PEG malfunctions were reported (12% and 4%, respectively) in these patients[47]. VPS infections are more frequently reported in cases of PEG placement before the shunt procedure (21.8%) or when a simultaneous PEG and VPS placement were performed (50.0%). For these reasons, the authors of this study suggest performing PEG placement 7-10 d after the VPS. Since many patients that require gastrostomy placement suffer from chronic constipation, which can predispose the transverse colon to move in front of the anterior gastric wall, enemas or a macrogol solution through a nasogastric tube should be given to decompress the colon and reduce the risk of colonic interposition during the endoscopic procedure (Figure 1).

Moreover, anatomical alterations of the abdominal wall (*e.g.*, ostomy, scars, and adhesions) can make PEG insertion difficult. When these conditions are present, PEG placement must be carried out at least 2 cm away from the scar[44]. PEG placement should not be performed in cases of fever, abdominal wall infection, or other signs of sepsis in order to reduce the risk of PEG site infection.

Additionally, PEG placement is considered a high bleeding risk procedure[3,48]. Preprocedural blood tests, with platelet count and coagulation tests, should be done. Indeed, a platelet count < 50000 mm^3 and an international normalized ratio > 1.5 are considered contraindications for PEG placement[48].

Moreover, home antiplatelet and anticoagulant therapy should be evaluated, as all patients are stratified in high or low thrombotic risk. Patients with low thrombotic risk who take antiplatelet (anti-P2Y12) should discontinue the medication 5 d prior to PEG placement. On the other hand, patients with a high thrombotic risk must continue cardioaspirin monotherapy, while other antiplatelet medications are to be assessed by a cardiologist. Traditional anticoagulants should be discontinued 2-5 d prior to the procedure, depending on patient comorbidities and renal function and should be replaced by low molecular weight heparin with an international normalized ratio below 1.5. New anticoagulant should be discontinued 2-3 d prior, based on the different drug subtypes and renal function[48]. However, all antiplatelet and anticoagulant drugs should be resumed 2 d after PEG placement[48].

ENDOSCOPIC *VS* RADIOLOGIC *VS* SURGICAL

Gastrostomy tube placement can be performed by three different techniques: Endoscopic (PEG), radiologic, and surgical[49]. Frequently, PEG is considered the standard procedure, but other techniques are often performed, mainly in patients that are unable to undergo the endoscopic approach[50,51]. Several AEs were reported after all subtypes of gastrostomy placement[52,53]. The most common AEs were device malfunction (52%) and infections (19%)[54]. Some comparative studies on PEG *vs* radiologic gastrostomy (RG) reported results that were univocal. One meta-analysis of 5680 patients reported fewer major AEs in patients undergoing RG than in those undergoing PEG [success rate RG: 99.2% *vs* PEG: 95.7%, $P < 0.001$; major complications RG: 5.9% *vs* PEG: 9.4% *vs* SG: 19.9%, $P < 0.001$][55].

Moreover, another systematic review and meta-analysis evaluated 934 PEG and 1093 RG, indicating that PEG was safer than RG[56]. However, many studies report no statistical differences between these techniques[57,58]. A retrospective study including 184068 patients comparing PEG, RG, and SG was recently published. The authors of this study reported that PEG was safer than RG and SG procedures. In particular, when compared to RG and SG, PEG showed a low rate of infections (RG: 1.28; $P = 0.006$ and SG: 1.61; $P < 0.001$), bleeding [odds ratio (OR) RG: 1.84; $P = 0.002$ and SG: 1.09; $P < 0.001$), perforation (OR RG: 1.90; $P = 0.002$ and SG: 6.65; $P < 0.001$), readmission (OR RG: 1.07; $P = 0.002$ and SG: 1.13; $P = 0.01$), and mortality (OR RG: 1.09; $P = 0.01$ and SG: 1.55; $P < 0.001$)[54]. In conclusion, it is not clear which technique is better among the three mentioned above. Nevertheless, PEG seems to have a lower rate of AEs reported. Moreover, not all hospitals have tools and staff dedicated to performing these procedures. For this reason, it seems reasonable to use the safest method available in the facility.

PEG TECHNIQUES

Different endoscopic techniques for PEG placement have been proposed during the years, including the pull technique, the introducer technique, and the push technique.

Pull technique

The pull technique is the most used procedure for PEG placement[59]. This technique was first described in 1980 by Gauderer *et al*[8]. Two operators are needed: One to manage the endoscopic part of the procedure and one to manage the percutaneous site of the procedure. With the patient placed in the supine position, the abdomen is draped in a sterile fashion, and the gastroscope is inserted perorally into the stomach under conscious sedation or deep sedation. Gastric distension with endoscopic air insufflation brings the anterior gastric wall in contact with the abdominal wall. The lights in the room should be dimmed so that the puncture site can be localized on the abdominal wall by endoscopic transillumination and by clear endoscopic visualization of the indentation of the stomach by external

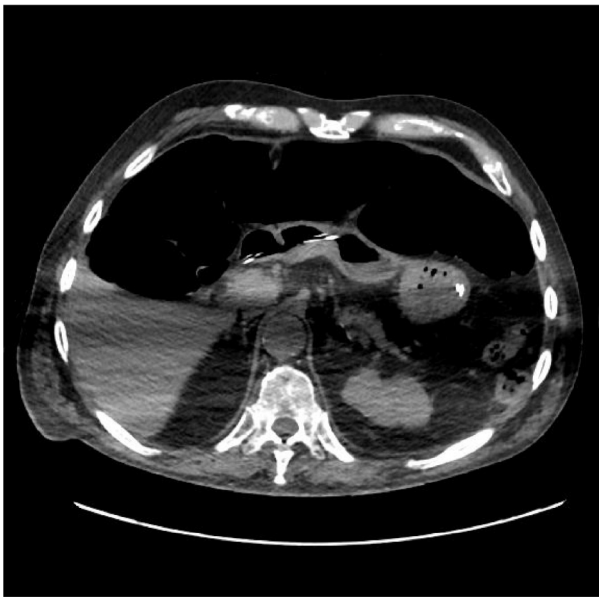

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Figure 1 Case of percutaneous endoscopic gastrostomy failure. Subsequent computed tomography scan showed colonic interposition between the stomach with nasogastric tube and the anterior abdominal wall due to fecal stasis.

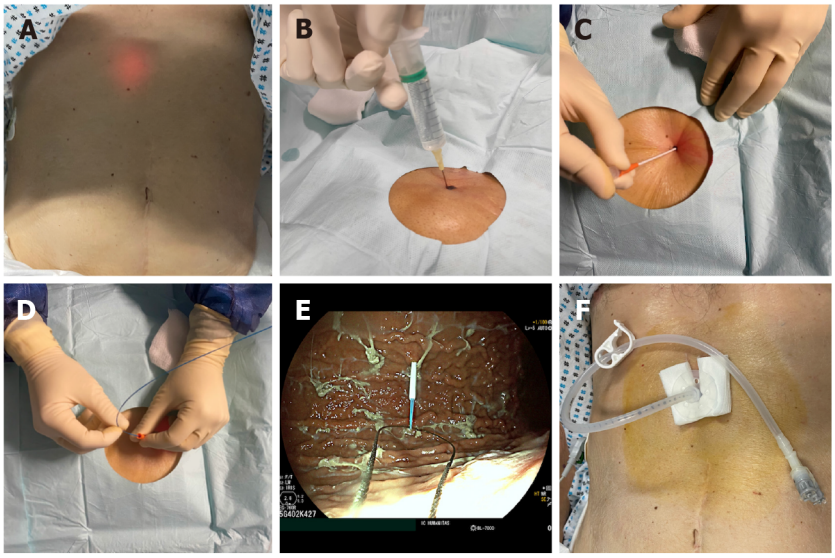

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Figure 2 Steps of percutaneous endoscopic gastrostomy placement with "pull" technique. A: Location of the puncture site *via* transillumination; B: Avoidance of bowel interposition confirmed by the absence of bubbles at aspiration; C: Introduction of the trocar; D: Introduction of the guidewire; E: Grasping the guidewire with an endoscopic snare; F: Final result.

palpation on the marked point.

Then, the "safe track technique"[60] is performed by inserting a 25 G needle attached to a 10 mL syringe that is partially filled with saline solution at the marked point. If bubbles appear in the syringe while aspirating immediately before the needle passes into the stomach, there may be an intervening loop of bowel present. This maneuver could also be performed while withdrawing the needle. Once the puncture site is identified, local anesthesia is given and a skin incision with a surgical blade of 3-5 mm is made so that a 14 G trocar can be inserted under direct endoscopic visualization while keeping constant endoscopic air insufflation of the stomach. Endoscopically a snare, passed through the gastroscope, is looped around the sheath. A dedicated gastrostomy kit wire is then passed through the sheath and into the stomach. It is grasped by the snare and is brought out through the mouth, together with the endoscope.

Thereafter, the gastrostomy kit tube is attached to the wire, and they are pulled back together through the mouth, the esophagus, the stomach, and out through the cutaneous puncture site until the internal

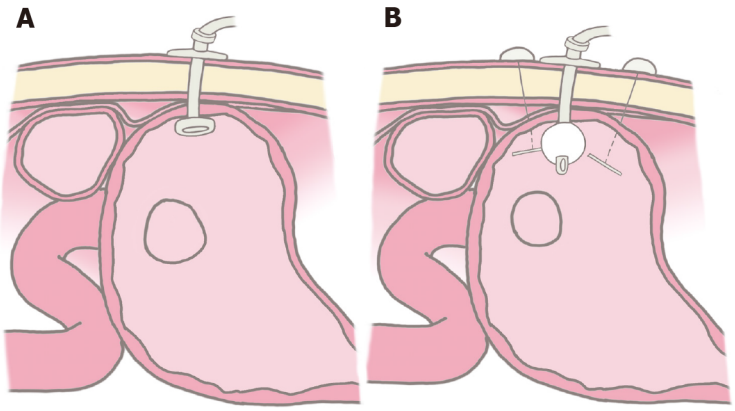

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Figure 3 Graphic representation of percutaneous endoscopic gastrostomy placement technique. A: "Pull" technique; B: "Introducer" technique.

bumper reaches the anterior wall of the stomach. Finally, the external bumper must be fixed against the skin (Figure 2). The described technique can also be done by passing an ultra slim endoscope and the gastrostomy probe transnasally. This variant of the procedure has been described to be well tolerated even in non-sedated patients.

Introducer technique

The direct percutaneous technique, namely the introducer, was first described in 1984 by Russell *et al* [61] and then revised by Brown *et al*[62] in which the stomach is fastened to the abdominal wall with T-fastener sutures. In this technique, two operators are needed, and the gastrostomy site is identified in the same manner as in the "pull" technique. However, while maintaining full gastric endoscopic insufflation, a gastropexy is made by placing two to four T-fasteners circumferentially over the anterior abdominal wall under endoscopic guidance. Within the area between the T-fasteners lies the site for the gastrostomy tube placement[63]. A horizontal incision is made at the identified site so that a trocar can be inserted, and a guidewire introduced into the stomach.

Then, the tract is dilated using dilators that are introduced over the guidewire. Finally, a gastrostomy balloon-type probe is placed over the guidewire through the dilator peel-away sheath and into the stomach (Figure 3). Using this technique, the gastrostomy probe is introduced directly from the exterior through the abdominal wall percutaneously, avoiding contamination of the probe during the passage in the upper digestive tract. This technique should be preferred in patients with esophageal strictures or head and neck cancer to reduce the risk of tumor seeding[3]. In the literature, various cases of gastrostomy site metastasis in patients with upper aerodigestive tract malignancies have been reported, and a recent meta-analysis found that the incidence rate increases particularly in patients with advanced-stage disease[64,65].

Other percutaneous gastrostomy techniques

The "push method" or Sacks-Vine[66] technique is similar to the "pull" method except that the gastrostomy probe is passed over a guidewire from the mouth to the cutaneous side of the gastrostomy. This requires that the tube needs to be much longer and is made of two pieces connected together with a small dilator. EUS-guided PEG placement has also been described[67,68]. In the Baile-Maxía *et al*[67]'s case series, a EUS target was created by filling a sterile glove with saline and was placed over the abdomen of the patient. A linear echoendoscope was passed perorally into the stomach and was positioned against the anterior gastric wall where the EUS target was identified. The abdominal wall was then punctured from inside the stomach with a 19 G needle, and a guidewire was advanced. The guidewire was tied to a string that was passed into the stomach and taken out through the mouth. The following passages are the same of the pull technique. This variation of the pull technique could be selected in obese patients or in patients with previous abdominal surgeries where transillumination could be absent.

AES

Aspiration

This is the most common periprocedural AE[69,70], which has been reported to be around 1%. Risk factors for aspiration are advanced age, need for sedation, and neurologic impairment[71].

Pneumoperitoneum

Transient subclinical pneumoperitoneum is commonly found after the procedure and generally does not have clinical relevance[72].

Injury to adjacent viscera

Under transillumination, if the indentation site is identified and the "safe track technique" is used during the PEG placement, there is a very low risk of injury to the organs adjacent to the anterior abdominal wall, such as colon or liver. If the patient presents severe postprocedural hypotension, liver laceration should be suspected, and urgent computed tomography scan is required. Transhepatic insertion of a gastrostomy tube is a rare and serious AE. Cases reported in the literature have been managed conservatively if the patient remained asymptomatic[73] or surgically if a life-threatening complication such as severe hemorrhage occurred[74]. Colonic injury can present a few days after the procedure, with leakage of the intestinal contents around the gastrostomy tube, abdominal pain, and fever[75]. A computed tomography scan using a hydrosoluble contrast agent should be performed. If no leak into the peritoneal cavity is detected, then the complication can be managed with endoscopic closure of the fistulous tracts[76]. If the patient develops generalized peritonitis, then surgical revision is mandatory. However, in most cases, a gastro-colonic-cutaneous fistula remains clinically silent until months after the gastrostomy placement the first implanted probe is removed, and the replacement tube is placed into the colon (Figure 4). Once nutritional feeding is resumed, diarrhea develops. If a new gastrostomy placement is needed, then laparoscopic gastrostomy should be considered[77,78].

Bleeding

Mild intraprocedural oozing from capillaries could be encountered during the procedure, but they are usually self-limiting or managed with endoscopic therapy. Major bleeding is a rare AE and is usually caused by the puncture of the left gastric or gastroepiploic arteries or one of their branches[79].

Wound infection

The systematic use of prophylactic antibiotic therapy has drastically reduced the incidence of this complication[80]. It generally manifests in redness, edema, and leakage of pus from the gastrostomy site and is usually managed with systemic antibiotic therapy and local wound care (Figure 5). If not treated adequately it can result in necrotizing fasciitis, a rare but potentially fatal complication.

Granulation tissue

Re-epithelialization of gastric mucosa could cause the development of excessive granulation tissue at the gastrostomy site. Treatment consists of avoiding occlusive dressings, and if the mucosa causes persistent minor bleeding, then topical silver nitrate or argon plasma coagulation can be applied to the tissue[81].

Buried bumper syndrome

Buried bumper syndrome is defined by the migration of the internal bumper along the gastrostomy fistula tract. It is generally related to excessive traction from the outside of the internal bumper, which perpetuates over time, leading to a local tissue pressure necrosis and subsequent progressive migration of the internal bumper. To avoid this AE, it is recommended to keep the outer bumper loose from the skin and to periodically check that the gastrostomy tube remains easily rotatable. When the internal bumper has reached the subcutaneous plane, a bulging on the skin is visible at the gastrostomy site, which is hard to the touch, and the gastrostomy tube is not moveable. If, on the other hand, the internal bumper is in the gastric wall, the peristomal skin may appear regular, but the gastrostomy tube will still not be moveable.

Based on the depth of the buried bumper, different extraction techniques can be applied[82,83]. When part of the internal bumper is still endoscopically visible, the buried bumper, after inserting a wire through the gastrostomy tube from the outside, can be effectively pushed back into the stomach with a dilator (*e.g.*, Savary bougie size 15 Fr in 20 Fr gastrostomy tube). Totally or near-totally ingrown bumpers can be removed by cutting the overlying mucosa with an endoscopically guided application of electrosurgical current using a sphincterotome, a needle-knife, or a hook knife. In cases of clear extragastric localization, surgical treatment may be needed.

In a recent study, Costa *et al*[84] reported the use of a novel endoscopic dedicated device, the Flamingo device, for buried bumper syndrome management. The Flamingo device is inserted over the guidewire into the stomach through the external insertion of a partially cut gastrostomy probe. The distal part of the Flamingo device is flexed to 180° using its dedicated handle, exposing the bowstring, sphincterotome-like cutting wire. External traction is then applied to the Flamingo device from the cutaneous side of the gastrostomy, pulling the flexed cutting wire toward the granulomatous tissue through direct endoscopic visualization until apposition is achieved, and the overgrown tissue is then incised.

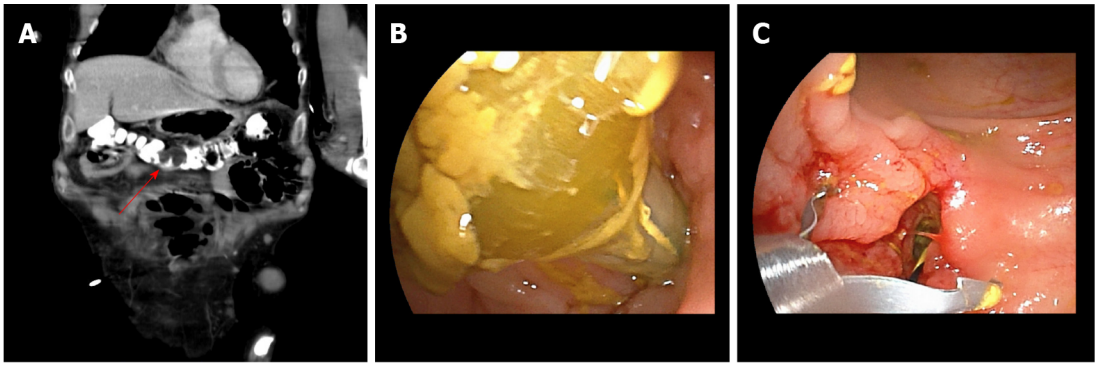

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Figure 4 Percutaneous endoscopic gastrostomy displacement and development of colocutaneous fistula. A: Computed tomography scan image showing percutaneous endoscopic gastrostomy balloon located in the transverse colon (red arrow); B: Endoscopic view of the percutaneous endoscopic gastrostomy balloon within the colon; C: Endoscopic closure of the colonic fistulous orifice with clips.

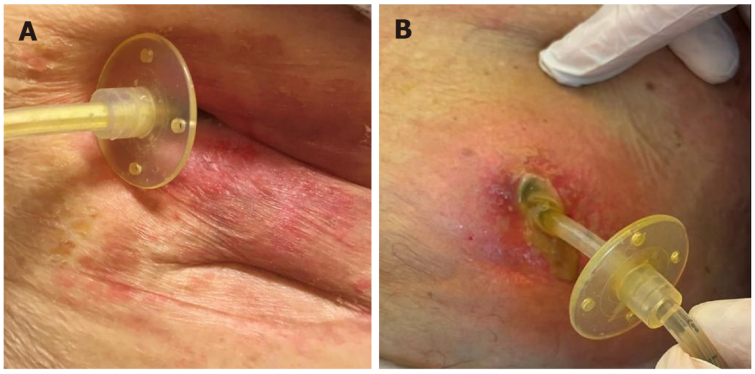

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Figure 5 Wound infections. A: Superficial infection of the abdominal wall; B: Wound infection with abscess formation within the anterior abdominal wall.

Tube displacement

If probe removal occurs earlier than 4 wk after the gastrostomy placement, the fistula may not have consolidated. Therefore, a percutaneous replacement should not be attempted. After the probe removal, the patient must be placed under broad antibiotic coverage and must fast for at least 24 h. The placement of a new endoscopic gastrostomy should be scheduled after complete wound healing. In the case of a probe removal after 4 wk, the attempt to percutaneously place a replacement probe is indicated and should be done quickly because in the absence of a tube in the gastrostomy tract, the gastrocutaneous fistula tends to close spontaneously within 12-24 h[85]. Our advice is that if a replacement probe is not available at the time of displacement, another tube (*e.g.*, 18-20 Fr Foley catheter) should be placed temporarily as soon as possible in order to avoid the risk of closure of the fistulous tract.

Peristomal leakage of gastric content

This is generally linked to a patient's clinical condition that led to a delayed gastric emptying, which may be due to either pre-existing conditions such as gastroparesis or to the presence of fecal impacts that alter intestinal transit leading to sub-occlusive symptoms. It can be managed by trying to improve gastric emptying with the use of prokinetics in order to reduce gastric secretions with the use of protein-protein interactions and to improve intestinal canalization with the periodic administration of macrogol through the gastrostomy tube. Local skin irritation can be prevented by stoma adhesive powder or zinc oxide application. When the condition does not resolve with the optimization of medical therapy, the positioning of a jejunal extension is indicated to prevent the feeding solution remaining in the stomach and for the gastric tube to be used as a drainage of gastric secretions to progressively reduce the peristomal leakage.

Gastrocutaneous fistula

Once the probe has been removed, the gastrostomy usually closes within 12-24 h. The nonclosure of the fistula is often caused by severe malnutrition and a reduced thickness of the fistulous tract. If the external bumper is positioned too close to the skin, the continuous compression of the skin leads to tissue ischemia with reduction of the thickness of the fistulous tract. When the thickness of the fistulous

tract is 1-2 mm, the closure of the fistula by a secondary intervention becomes very difficult and it is often necessary to perform an endoscopic closure, using techniques similarly to GI perforation[86-90] (Figure 6).

POST-PROCEDURAL CONSIDERATIONS

At the gastrostomy site, the PEG tube can be used for infusion after 12-24 h of placement. To start, begin with water followed by regular EN with progressive increase in the infusion rate. In the first 72 h, the external bumper must be fixed against the skin to allow adequate attachment of the abdominal wall to the gastric wall, which is fundamental for a correct maturation of the fistula. After 72 h the external bumper should be detached from the skin by at least 0.5-1.5 cm to avoid compression of the skin as the patient's position changes. This compression would increase the risk of developing subcutaneous infections and, in the long term, would lead to ischemia of the wall itself, with a progressive reduction in the thickness of the fistula wall. At least 4 wk after the PEG creation, the gastrocutaneous fistula is considered to be fully consolidated. In very undernourished patients, the maturation of the fistula may take longer. The peristomal skin should be kept clean daily by using only mild soap and water, and the gastrostomy site should be left open without occlusive dressings, which may lead to peristomal skin maceration.

Enteral tube replacement

There are no exact evidence-based guidelines regarding the replacement of PEG tubes. Therefore, each center adopts its own protocol based on the management of these patients, which is very complex because they are generally very fragile and undernourished and may have neurological diseases that compromise their autonomy. We can certainly distinguish the timing of replacement of the first implanted probe based on the probe material[91]. There are probes, generally those that can only be removed perorally, that are manufactured using resistant materials and remain functional even after 1 year or 2 years. On the other hand, there are probes which can be removed percutaneously using traction, which are made of more flexible materials. However, these tend to wear out more quickly over time. The deterioration of the probe becomes evident externally, which then corresponds to the deterioration of the internal bumper and becomes more rigid, compromising the flexibility necessary for removal by percutaneous traction. Therefore, the removable traction probes should be removed usually about 6 mo after placement at bedside without endoscopic control.

However, when the attempt of removal of this type of tube is made after many months, the percutaneous traction removal becomes more and more difficult, requiring a different approach. In this situation, the probe is removed by cutting the tube from the external skin margin and the internal bumper is left in the stomach. Endoscopic retrieval of the bumper in the stomach is recommended in patients at risk of intestinal occlusion[3]. The balloon-type gastrostomy probes[92], which are applied during the procedure of direct percutaneous gastrostomy and are used as replacement after removal of the first implanted probes, have a balloon as an internal bumper. This balloon, after the percutaneous insertion of the tube and when the gastric cavity is reached, is filled with sterile water. The advantage of a balloon-type probe is that it can be easily removed by just deflating the internal balloon. The disadvantages are that they tend to wear out quite quickly over time and that they can be easily removed accidentally. The substitution of this type of probe should be made every 3-6 mo.

Follow-up of patients with a gastrostomy tube

The management of patients after gastrostomy placement varies according to local protocols. It is generally a multidisciplinary management that involves home care nursing, nutritional planning, and specialized medical support. Training courses are held for the relatives of the patients who will play a fundamental role in caring for these patients. The balloon type tubes can be easily replaced at home by dedicated staff with a low risk of AEs[93]. The home management of these patients is essential because they are very fragile and, in most cases, not mobile or independent. Therefore, staying in the hospital is risky and difficult to manage[94].

PEG WITH JEJUNAL EXTENSION

Percutaneous endoscopic transgastric jejunostomy (PEG-J) is a gastrostomy with a jejunal extension tube. The jejunal extension tube can be positioned "beneath the scope," grasped endoscopically with forceps in the stomach lumen, and dragged into the jejunum or "over the wire" that is advanced over an endoscopically or radiologically placed guidewire. The placement of the jejunal extension tube should be attempted in patients with gastrostomy feeding-related AEs, such as aspiration pneumonia due to gastroesophageal reflux of the gastric feed and uncontrolled peristomal leakage[9]. The feeding solution can be administered from the jejunal extension tube, and the gastric tube can perform the gastric

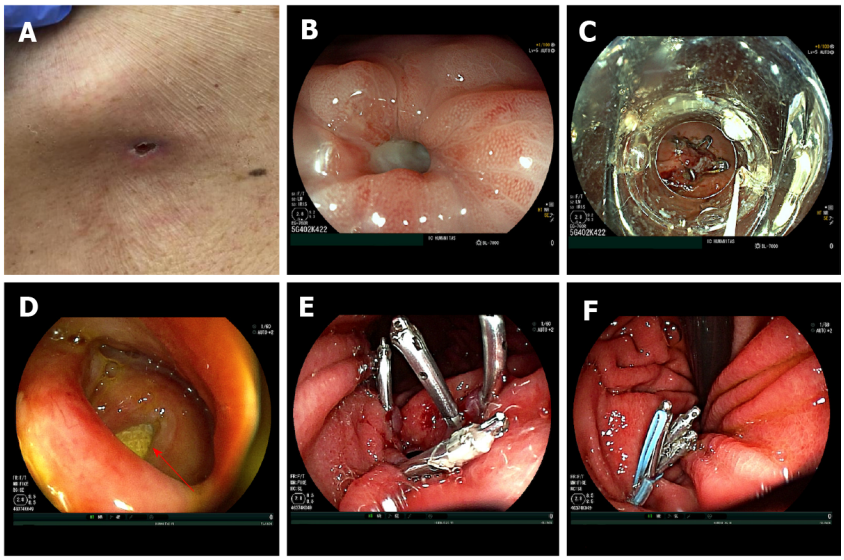

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Figure 6 Gastrocutaneous fistula. A: External appearance of a gastrocutaneous fistula in the first case; B: Endoscopic appearance of the gastrocutaneous fistulous orifice; C: Endoscopic closure of the gastric fistulous orifice with an over-the-scope metal clip in the first case (OTSC – Ovesco Endoscopy AG, Tubingen, Germany); D: Endoscopic appearance of a large gastrocutaneous fistula, with detection of the gauze placed from the outside at the cutaneous end of the tract (red arrow) in the second case; E: Endoscopic placement of four metal clips at the margins of the fistulous orifice; F: Placement of an endoloop over the metal clips to achieve complete closure of the fistulous orifice.

decompression function. PEG-J is also used in Parkinson's disease patients for delivering the levodopa-carbidopa intestinal gel[95]. In this case, the jejunal extension tube allows a continuous delivery of the drug into the small bowel[95] (Figure 7). The disadvantages of these probes are that the jejunal extension tubes are usually long (median length of 55 cm) and small in diameter (median diameter of 9-10 Fr) and are more prone to occlusion, kinking, or dislocation[96]. These tubes also have limited longevity and tend to wear out after 3-6 mo, especially if they are used as EN feeding devices.

DIRECT PEJ

Direct PEJ (DPEJ), described in 1996 by Shike *et al*[97], is an alternative method of EN feeding in patients that cannot undergo gastrostomy placement because of previous resection of the esophagus or stomach, or in patients with frequent clogging or migration of PEG-J extension. In these circumstances, DPEJ placement is performed using the same passages of the gastrostomy technique. Likewise, this technique is needed to achieve the proximal or medium jejunum under endoscopic visualization by a push enteroscopy, single-balloon or double-balloon enteroscopy, or underwater enteroscopy[98]. The use of ultrasonography, fluoroscopy, or anchoring a needle to the jejunum can be used to facilitate correct placement. Jejunal probes placed through DPEJ are shorter and greater in diameter compared to jejunal tubes placed through PEG-J, making them less prone to tube dysfunction.

However, DPEJ is a challenging technique with a successful placement between 68% and 83%, which is highly variable based on local expertise. Endoscopic access up to the jejunum is not straightforward, and once obtained, the major difficulty is to identify the target jejunal puncture site. Serious periprocedural AEs have been reported, such as bowel perforation (up to 2.5%) and volvulus. A frequently reported post-procedure AE is peristomal leakage with fistula enlargement, which is aggravated by leakage of pancreatic juice and bile causing peristomal irritation and severe dermatitis[99,100]. DPEJ is a useful technique in order to avoid the need for surgery when long-term nutritional jejunal access is needed. However, it is associated with a moderate or severe complication risk in up to about 10% of the cases, which physicians should be aware of (Figure 8).

FUTURE PERSPECTIVES

The data within this paper confirms that PEG placement is a safe procedure. The selection of patients requiring PEG will be of paramount importance to understanding which individuals may benefit more from this nutritional support than others, maximizing the outcomes, and reducing the AEs. Considering the complexity of these patients, a dedicated multidisciplinary team for pre- and post-procedural management are required for patient care. Moreover, the development of a home health care service for

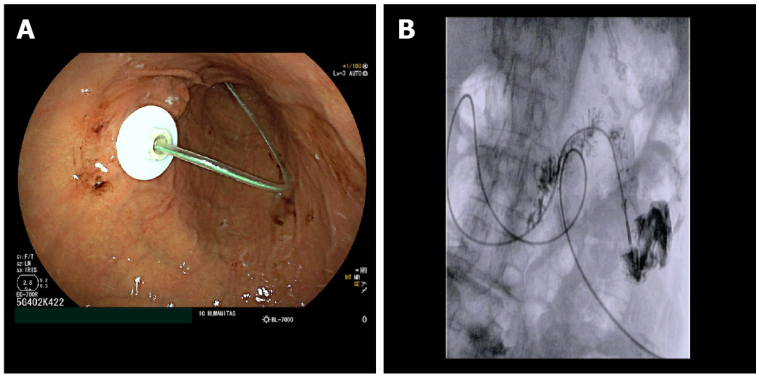

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Figure 7 Percutaneous endoscopic transgastric jejunostomy placement. A: Endoscopic appearance of the percutaneous endoscopic transgastric jejunostomy with jejunal extension entering from the percutaneous endoscopic transgastric device towards the jejunum; B: Final fluoroscopic appearance of the percutaneous endoscopic transgastric jejunostomy with distal end of the jejunal extension into the proximal jejunum after injection of contrast medium.

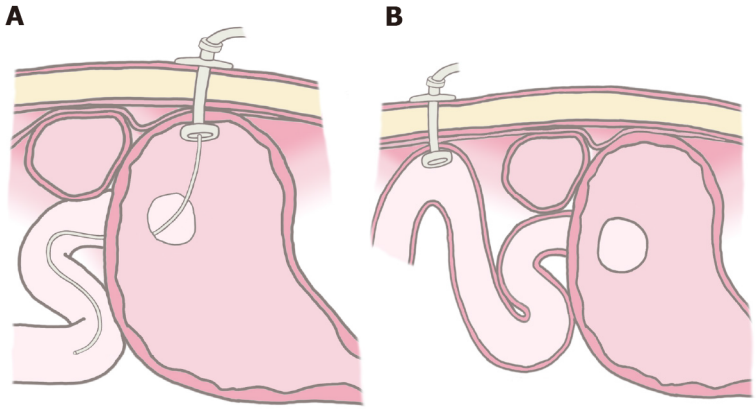

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Figure 8 Graphic representation. A: Percutaneous endoscopic gastrostomy with jejunal extension; B: Direct percutaneous endoscopic jejunostomy.

nutrition support and device management, consisting of a gastroenterologist, nurse, and nutritionist is fundamental to avoid patient transportation. In particular, the coronavirus disease 2019 outbreak has significantly impacted our clinical practice, and we have established infection prevention measures in order to protect both patients and personnel[101-104]. Moreover, the pandemic definitively underlined the importance to reduce hospital visits, especially for such fragile patients[27]. Currently, the main purpose of PEG placement is for nutritional support. However, other ingenious gastrostomy-related procedures have been described in the literature that are not for nutritional purposes, including gastric decompression in GI malignancies, access for endoscopic retrograde cholangiopancreatography in patient with surgically altered anatomy, and access of the trocar for therapeutic procedures. The introduction of dedicated devices into clinical practice for therapeutic procedures through a PEG will expand the possible indication for PEG placement.

CONCLUSION

PEG is a safe and effective procedure even if performed in fragile patients. The selection of patients and the creation of a dedicated team for pre- and post-procedural care is fundamental to obtain good outcomes and reduce AEs. Moreover, careful selection of the best approach used over the different endoscopic approaches is required. Finally, the stoma can be used not only for nutritional purposes but also as an access route for advanced endoscopic procedures.

FOOTNOTES

Author contributions: Fugazza A, Capogreco A, and Cappello A drafted the manuscript; Rosangela Nicoletti R, Da Rio L, Galtieri PA, Maselli R, Carrara S, Pellegatta G, Spadaccini M, Vespa E, Colombo M, and Khalaf K contributed

to the acquisition, analysis, or interpretation of data for the work; Repici A and Anderloni A contributed to the critical revision of the manuscript; All authors approved the final version to be published.

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REVIEW

Current updates and future directions in diagnosis and management of gastroenteropancreatic neuroendocrine neoplasms

Andrew Canakis, Linda S Lee

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Abstract

Gastroenteropancreatic neuroendocrine neoplasms are a heterogenous group of rare neoplasms that are increasingly being discovered, often incidentally, throughout the gastrointestinal tract with varying degrees of activity and malignant potential. Confusing nomenclature has added to the complexity of managing these lesions. The term carcinoid tumor and embryonic classification have been replaced with gastroenteropancreatic neuroendocrine neoplasm, which includes gastrointestinal neuroendocrine and pancreatic neuroendocrine neoplasms. A comprehensive multidisciplinary approach is important for clinicians to diagnose, stage and manage these lesions. While histological diagnosis is the gold standard, recent advancements in endoscopy, conventional imaging, functional imaging, and serum biomarkers complement histology for tailoring specific treatment options. In light of developing technology, our review sets out to characterize diagnostic and therapeutic advancements for managing gastroenteropancreatic neuroendocrine tumors, including innovations in radiolabeled peptide imaging, circulating biomarkers, and endoscopic treatment approaches adapted to different locations throughout the gastrointestinal system.

Key Words: Gastroenteropancreatic neuroendocrine neoplasms; Neuroendocrine tumors; Neuroendocrine carcinoma; Gastrointestinal; Pancreas; Small intestine

Core Tip: Diagnostic technology for neuroendocrine tumors continues to advance. Radiomics promises to enhance morphologic imaging. Gallium-68 DOTA-peptide positron emission tomography/computed tomography has replaced Octreoscan as the preferred functional imaging modality. Newer radiolabeled peptides may further improve detection. A novel liquid biopsy biomarker (NETest) has proven more accurate than chromogranin A in monitoring treatment response and predicting disease activity. Therapy has also progressed with treatment adapted based on the predicted behavior of the tumor. Advanced endoscopic resection techniques have revolutionized treatment. Preliminary evidence suggests endoscopic ultrasound guided radiofrequency ablation may prove useful in treating pancreatic lesions. Multimodality therapy continues to evolve for metastatic pancreatic tumors.

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INTRODUCTION

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are a heterogenous group of rare neoplasms with a wide clinicopathologic spectrum of disease activity[1]. These neoplasms arise from the secretory cells of the neuroendocrine system and can occur anywhere along the gastrointestinal tract[2]. Nearly 95% occur sporadically, though genetic testing should be considered for patients less than 40 years old, family history of NENs, features concerning for multiple endocrine neoplasia type 1, von Hippel-Lindau disease, tuberous sclerosis or neurofibromatosis type 1[3]. Traditional terminology including carcinoid tumor and APUDoma were replaced by neuroendocrine neoplasm in 2010 by the World Health Organization (WHO), which also discouraged using the terms benign and malignant. NENs are grouped as well-differentiated neuroendocrine tumors (NET) or poorly differentiated neuroendocrine carcinomas (NEC)[4]. NECs are highly aggressive with significantly worse prognosis. Nearly 80%-90% of GEP-NENs are NETs, which are slow growing and graded from G1 (low), G2 (intermediate), to G3 (high)[2].

With the advent of high-resolution cross-sectional imaging, GEP-NENs are increasingly being discovered-notably without any significant change in rates of metastasis[5]. In a large population-based study of 64971 patients, the age-adjusted incidence rate of NETs increased from 1.09 per 100000 in 1973 to 6.98 per 100000 in 2012, with the greatest increase occurring in localized NETs and G1 NETs[6]. These observations suggest that many of these lesions are incidental and/or asymptomatic at the time of discovery. Incidence of gastric and rectal NETs has increased the greatest unlike small bowel NETs, which likely correlates with greater use of endoscopic procedures. Similar trends have been noted in Europe and Asia[7].

GEP-NENs are divided into gastrointestinal and pancreatic NENs with the most common being rectal (29%) and small intestinal (28%) (Figures 1 and 2)[8,9]. These tumors exhibit a wide range of behavior with varying degrees of disease activity including growth rate, grade, differentiation and metastatic potential[10]. Generally speaking, small intestinal NENs have high malignant potential while gastric, duodenal, appendiceal, and rectal NETs are less likely to metastasize[11]. A recent cohort of 43751 patients in the United States noted that the majority of GEP-NENs were localized (51.7%) and grade 1 (71.7%)[9]. This study also found that the most lesions (73%) occurred in whites, followed by black (16.2%) and Asian (7.3%) populations with no difference in three or five year survival based on race.

The majority of GEP-NENs are non-functional while functional NENs secrete hormones and substances that lead to clinical symptoms. Functioning gastrointestinal NENs are not classified separately from nonfunctioning gastrointestinal NENs and manifest with carcinoid syndrome while functioning pancreatic NENs are classified distinctly according to the hormone secreted by the tumor. Nonhormonal products are also produced by both non-functional and functional NENs, which include chromogranin A, pancreastatin and pancreatic polypeptide, and may offer aid in diagnosis and follow-up.

DIAGNOSIS

Diagnosis relies on morphological imaging, functional imaging, endoscopic procedures, biomarkers, and pathology. All patients should undergo computed tomography (CT) and/or magnetic resonance imaging (MRI). Functional imaging serves as an adjunct to conventional imaging in advanced NETs and is helpful for identifying primary tumors and staging. Endoscopic procedure with biopsy diagnoses gastric, duodenal and colorectal NENs while endoscopic ultrasound (EUS) aids in identification of

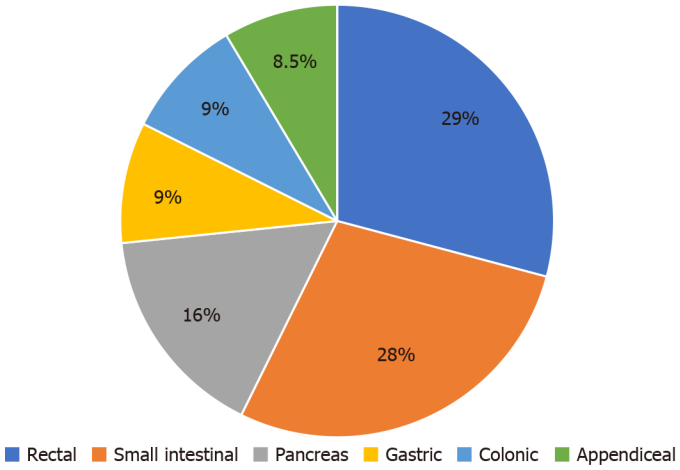

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Figure 1 Epidemiology of gastroenteropancreatic neuroendocrine neoplasms.

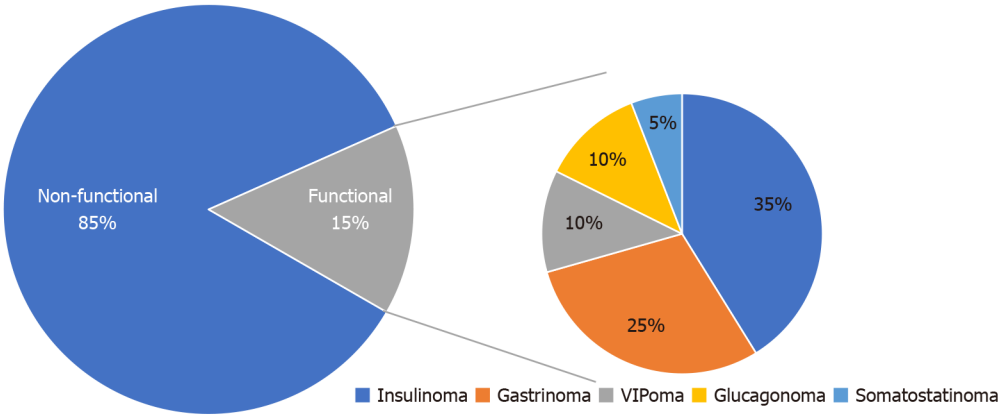

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Figure 2 Epidemiology of pancreatic neuroendocrine neoplasms.

pancreatic NENs. The mainstay of biomarkers is chromogranin A although newer markers have been identified, which may expand the role of biomarkers in post-treatment surveillance and detection of recurrence.

Pathology (staging and grading)

Tumor staging and grading are essential to assess prognosis and disease activity as reflected in the 2019 WHO classification based on tumor differentiation and grading (mitotic rate or Ki-67 index) (Table 1)[2, 4]. The degree of differentiation is based on the extent the tumor cells resemble their endocrine cell counterparts[11]. Grading is based on the proliferative rate from either mitotic counts or Ki-67 labeling index with higher values associated with more aggressive behavior, independent of stage[2]. Mitotic counts rely on the number of mitotic figures in 10 consecutive high-power fields while Ki-67 Labeling index is the percent of positive tumor cells. Small biopsy samples and heterogeneity within the tumor all pose challenges to accurate assessment of tumor grade of the entire lesion. Whether there is incremental benefit from larger core samples obtained during EUS-fine needle biopsy and whether artificial intelligence technology will help partially automate calculating Ki-67 index require further study[12]. Radiomics may supplant or supplement histologic diagnosis by assessing the whole lesion and will be discussed further below.

Morphologic imaging

NETs typically are highly vascular, hyperenhancing in the early arterial phase with washout during the delay portal venous phase of CT (Figure 3). Differentiating liver metastases from hepatocellular carcinomas may be aided by exploiting the fact that hepatocellular carcinomas have higher attenuation levels with contrast and higher iodine uptake with a threshold value of 0.22 for normalized iodine uptake having 100% sensitivity and 90% specificity[13]. Attenuation assessment of lymph nodes on CT

Table 1 World Health Organization 2019 Classification

Terminology, grade	Differentiation	Mitotic count (HPF²)	Ki-67 index (%)
NET, G1	Well-differentiated	< 2/10	< 3
NET, G2	Well-differentiated	2-20/10	3-20
NET, G3	Well-differentiated	> 20/10	> 20
NEC, G3 (small or large cell type)	Poorly differentiated	> 20/10	> 20

NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma; HPF: High powered field.

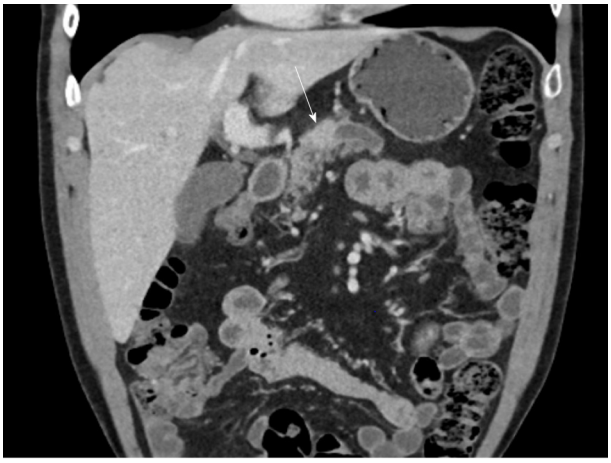

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Figure 3 Computerized tomography scan of hyperenhancing pancreatic neuroendocrine tumor (white arrow).

may also help identify malignant nodes with a cutoff value of 7.5 Hounsfield units distinguishing 96% of positron emission tomography (PET) positive and 89% of PET negative lymph nodes[14]. Limitations of CT include lower sensitivity with a recent study suggesting only 76% of CT scans identified the primary tumor in patients with metastatic GEP-NETs, and difficulties with identifying small (< 1 cm) lesions especially in the small bowel where only 21% of small intestine NETs were identified in one study[15-17]. CT enteroclysis has been used for localization of small bowel tumors[18] with luminal distension using neutral contrast aiding in defining small mucosal features with a positive predictive value of 95%[18].

MRI with contrast enhancement is superior in detecting lesions in the liver and pancreas[15]. With higher tissue resolution, MRI is also better for evaluating bone and liver metastases[19,20]. NENs typically have low T1 and high T2 signal on imaging (Figure 4). Adding diffusion weighted MRI to standard MRI imaging increased metastatic findings in 71% of patients, which changed patient management in 19% of patients[21]. A comparative study showed that while contrast enhanced MRI is superior, adding diffusion weighted to non-contrast MRI imaging may suffice for everyday practice[22].

Radiomics appears to augment the ability of MRI to differentiate pancreatic NET from adenocarcinoma and solid pseudopapillary neoplasms[23,24].

Grading pancreatic NETs by CT or MRI is challenging and relies on assessing tumor margins, pattern of venous phase contrast washout, and enhancement pattern[10,18]. Irregular margins on CT have 71% sensitivity and 82% specificity for predicting grade 2/3 tumors while a model incorporating margins and fusion signature had 0.90 AUC for differentiating grade 1 from grade 2/3 tumors. Tumor texture analysis of CT and MRI images suggests entropy may be most useful in differentiating the different grades with 91% sensitivity and 85% specificity for distinguishing grade 1/2 NET from grade 3 NEC on CT and 83% sensitivity and 61% specificity for separating G2/3 from G1 tumors on MRI[25,26]. Whole tumor apparent diffusion coefficient histogram analysis may help predict the aggressiveness of pancreatic NET with kurtosis being the most useful marker[26]. While exciting, further studies are needed to understand the capabilities and role of radiomics in diagnosing, grading, and potentially prognosticating and guiding treatment.

Functional imaging

Somatostatin receptor imaging provides whole body imaging for NETs based on the wide expression of somatostatin receptors in most well-differentiated NETs. Nearly 70%-90% of gastrointestinal NETs and

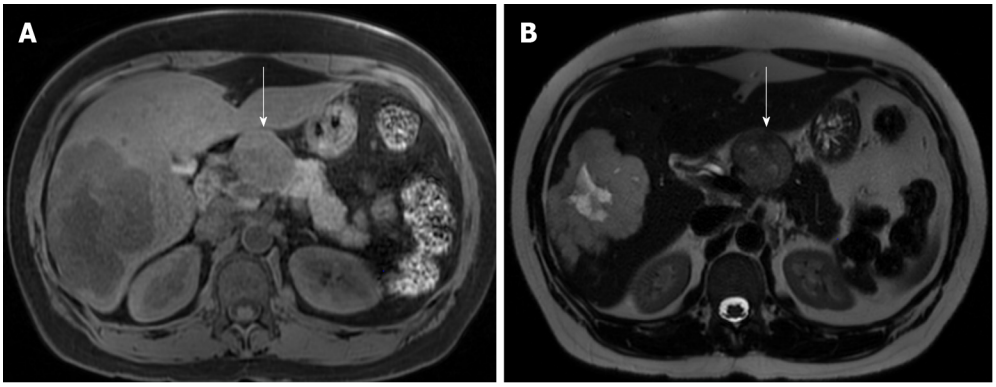

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Figure 4 Magnetic resonance imaging with T1 hypointense and T2 mildly hyperintense well-defined peri-pancreatic neuroendocrine tumor. A: T1 hypointense; B: T2 mildly hyperintense.

50%-70% of pancreatic NETs express somatostatin receptors[27]. Quantification of somatostatin receptor expression can diagnose, stage, and assess response to therapy with somatostatin analogues (SSAs) or peptide receptor radionuclide therapy (PRRT)[15]. Gallium (Ga)-68 DOTA-peptides with PET/CT have replaced traditional Octreoscan [octreotide single-photon emission computed tomography (SPECT)/CT or 111-Inpentetreotide with SPECT] as the preferred modality due to its higher accuracy and shortened procedure time, which reduces radiation exposure (Figure 5)[28]. The sensitivity and specificity to detect NET is 92% and 95%, respectively[29]. Of note, there are different labeled peptides that can be used (DOTA-TOC, DOTA-NOC, and DOTA-TATE), but they are regarded as equally efficient[30]. One meta-analysis of 1561 patients found that using 68-DOTATATE changed management in one third of patients who previously had an Octreoscan[31]. Another study of 101 patients with well/moderately differentiated NETs showed that 68-DOTATATE imaging altered management in 36 patients, which included avoiding the need for biopsy (n = 4), initiating systemic therapy (n = 14), and altering operative plans in half of patients referred to surgery (n = 14)[32]. When available, this modality is preferred due to its high sensitivity and ability to influence management strategies in more than 70% of cases[33,34].

However, it should be noted that the accuracy of Ga-DOTA-peptides PET-CT imaging declines as NET tumor grading increases due to decrease in somatostatin receptor expression[15]. As NETs lose somatostatin receptors, their cells increase glucose utilization[35]. In this context, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT may be the preferred method for identifying high grade lesions. In a large study with 104 biopsy proven NETs where both Ga-DOTATATE and ^{18}F-FDG PET/CT were performed, ^{18}F-FDG PET/CT was most useful in changing management of G3 tumors while not helpful for G1 tumors[36]. Therefore, these authors suggested only limited use of ^{18}F-FDG PET/CT for tumors with Ki-67 ≤ 12%. Ga-DOTATATE and ^{18}F-FDG PET/CT may be complementary imaging modalities. Other studies have suggested this as well with FDG PET-CT being 100% sensitive for identifying poorly differentiated G3 tumors while Ga-DOTATATE had 83% sensitivity for well-differentiated G2/3 tumors[37]. A retrospective study of pathology-proven NENs demonstrated increased sensitivity (94%) for diagnosing NENs when both tracers were used compared to either alone (Ga-DOTATATE 63.8% and ^{18}F-FDG 74.7%)[37]. Ki-67 index also negatively correlated with Ga-DOTATATE while positively correlated with ^{18}F-FDG. Another group developed a NETPET grade from 0 to 5: P0 is negative for both ^{18}F-FDG and 68Ga-DOTA-peptide scans, P1 is 68Ga-DOTA scan positive and ^{18}F-FDG negative, P2-4 are positive for both with varying intensity of uptake, P5 is ^{18}F-FDG positive and 68Ga-DOTA scan negative. This grading system correlated with tumor grade and survival with P5 having lowest median overall survival (11 mo)[38]. NETPET may allow selection of patients for PRRT which relies on the presence of somatostatin receptors to uptake therapeutic radionuclide into the NET cells. Patients with significant ^{18}F-FDG positivity and 68Ga-DOTA negative disease may not respond well to PRRT alone and likely would benefit greater from systemic chemotherapy.

64Cu-DOTA is a new tracer with longer half-life and potentially superior spatial resolution compared to 68Ga[39]. The longer half-life (12.7 h *vs* 1.1 h) would potentially allow 64Cu-DOTA to be used more routinely and readily compared with 68Ga-DOTA. In 59 patients who underwent both 64Cu-DOTATATE and 68Ga-DOTATOC PET/CT, more patients had more lesions detected using 64Cu-DOTA than with 68Ga-DOTA (13 *vs* 3, respectively, P = 0.013)[40]. A phase III US study confirmed the safety and high accuracy of 64Cu-DOTA PET/CT[41].

^{18}F (fluoro-dihydroxyphenylalanine)-DOPA is another radiopharmaceutical that has high sensitivity of 97% and specificity of 90% for small intestinal NETs, and alters management in 50% of small intestinal NETs[42]. In a comparative prospective study, ^{18}F-DOPA outperformed combined CT and somatostatin-receptor scintigraphy imaging in localizing low grade small intestinal NETs[43]. However, other studies have suggested 68Ga-DOTA is superior to ^{18}F-DOPA for detecting well-differentiated

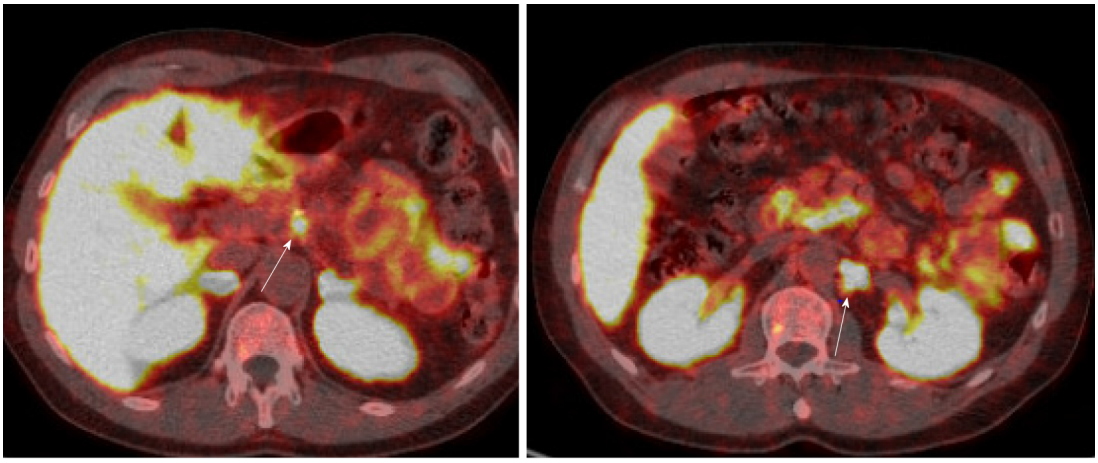

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Figure 5 Gallium-68 DOTATATE positron emission tomography/computed tomography demonstrating avid lymph nodes.

NETs, including small intestinal NETs. ^{18}F-DOPA is not readily available in Western countries, but may be complementary in the evaluation of small intestinal NETs[39,44].

Insulinomas are notoriously difficult to detect using morphological and somatostatin receptor imaging. Because they over-express glucagon-like peptide-1-receptors (GLP-1R), these offer targets for PET-based imaging[39]. 68Ga-DOTA-exendin-4 is a PET agent targeting GLP-1R. In a prospective randomized crossover study of 52 patients with suspected insulinoma, patients underwent 68Ga-DOTA-exendin-4 PET/CT, SPECT/CT and MRI with 68Ga-DOTA-exendin-4 imaging being more accurate than MRI for detecting insulinomas (93.9% and 67.6%, respectively)[45].

There is little literature on the value of PET-MRI, however, one small study demonstrated comparable image quality between 68Ga-DOTA-TOC PET/CT with PET/MRI while another suggested more lesions were identified with PET/MRI[46,47]. Advantages of PET/MRI include use in patients with renal insufficiency and better detection of liver lesions.

Biomarkers

Functional NETs secrete hormones that lead to various clinical symptoms and syndromes. These hormone levels should only be checked in patients with clinical symptoms and syndromes suggestive of a functional NET. Hormone levels may be followed in patients with functional pancreatic NETs to monitor response to treatment and recurrence[48].

Carcinoid syndrome may occur with metastatic NETs, typically from the small intestine. Twenty four hours measurement of urinary 5-hydroxyindoleacetic acid (5-HIAA), an end product of serotonin metabolism, has a specificity and sensitivity of over 90%[49]. Patients should avoid tryptophan-rich foods and certain medications for several days before urine collection. Urinary 5-HIAA may also help predict patients at risk for carcinoid heart disease and carcinoid crisis during surgery as well as those who may respond to SSAs and PRRT[50]. If urine collection is difficult, plasma testing may be more convenient. Compared to urinary measurements, plasma 5-HIAA has a sensitivity and specificity of 89% and 97%, respectively, in diagnosing carcinoid patients[51]. Its widespread use is limited by institutional preferences and lack of validation in clinical studies.

Nonhormonal secretory products are also produced by both functional and nonfunctional NETs and can serve as biomarkers. Chromogranin A, a nonhormonal serum glycoprotein, is the main biochemical marker. However, its use has been deemphasized with the National Comprehensive Cancer Network and North American Neuroendocrine Tumor Society (NANET) not recommending its routine use due to limitations in accuracy, lack of standardization across laboratories (differing assays and isoforms), and unclear added value beyond imaging findings[48,52,53]. It should be measured fasting and at least 2 wk after discontinuation of proton pump inhibitors[54]. Sensitivity is lower in localized disease[55], and chromogranin A levels may drop with use of SSAs due to decreased production of hormones from cells rather than reduction in tumor burden[56].

Consequently, other biomarkers have been investigated. Genetic mutations in DAXX and ATRX expression (which interact with centromeric and telomeric regions) have recently been associated with well-differentiated NENs and poor survival in pancreatic NETs[57]. DNA hypermethylation has been associated with worse prognosis in pancreatic NETs. There is also interest in a new biomarker that measures cell-free DNA which circulates in the plasma following apoptosis, necrosis or active secretion, whereby it may have the potential to differentiate metastatic *vs* localized pancreatic NETs[57,58].

A novel liquid biopsy biomarker (NETest) measures 51 different RNA transcripts relevant to NET using quantitative real-time polymerase chain reaction[59]. Scores range from 0%-100% with 0-20 normal, 4-80 intermediate and ≥ 80 high activity. NETest has recently been reported with favorable

results compared to chromogranin A for monitoring treatment response following both surgery and PRRT[60,61]. In a cohort of 253 GEP-NENs, NETest out performed chromogranin A in terms of accuracy (99% *vs* 53%) and also proved reliable in correlating the grade, stage and progression of GEP-NENs[62]. Another prospective study confirmed high diagnostic accuracy (91%) of NETest, ability to differentiate metastatic from local disease, 91% concordance with CT/MRI/ Ga 68-DOTA peptide PET, correlation with curative *vs* palliative surgeries, and higher diagnostic accuracy compared with chromogranin A [63]. NETest predicted postoperative recurrence at postop day 30 with 94% accuracy while chromogranin A was not helpful[64]. No patients with R0 resection and normal NETest developed recurrence while all R1/R2 patients had elevated NETest. This would allow early identification of patients with residual disease postoperatively who need to be followed more intensely while those with R0 resection and normal NETest likely can have fewer follow-up imaging studies. These exciting results need further confirmation in larger studies, and the utility of using this blood test rather than imaging to adjust treatment in advanced disease requires study as well.

Endoscopy

For gastrointestinal NETs, endoscopy with biopsy should be performed to obtain pathological diagnosis [20]. Endoscopic imaging is insufficient for definitive diagnosis as differential diagnosis includes other subepithelial lesions, such as gastrointestinal stromal tumor especially in the stomach and duodenum and cysts and Brunner's gland hyperplasia also in the duodenum. When imaging modalities fail to localize a small bowel tumor, video-capsule endoscopy (VCE) and device-assisted enteroscopy (DBE) are often needed[10]. VCE has a diagnostic yield of 45% for detecting tumors in the small intestine[65]. A retrospective study conducted over a seven year period found that small bowel tumors were detected in 1.5% of patients undergoing VCE (with a mean number of 4.7 tests used prior to VCE)[66]. In a study of 390 patients with metastatic NETs, radiology failed to localize a primary tumor in 2.8% whereas VCE identified NETs in 8/10 patients, which were confirmed histologically. As such, VCE should be used in select patients to identify small intestine NETs. While more invasive, antegrade and retrograde DBE may serve as an adjunctive tool prior to surgery by providing a histologic diagnosis and allowing tattooing areas of interest for surgeons[65]. Its diagnostic yield for detecting small intestine NETs ranges from 33%-80%[67,68]. Multifocal small intestinal NETs occur in 20%-30% of patients. CT and MRI have low accuracy for detecting these, and while CT or MR enterography, VCE, and DBE improve detection, the gold standard remains digital palpation of the small bowel intraoperatively[69].

EUS is valuable for diagnosing pancreatic NETs and differentiating from pancreatic adenocarcinoma or metastatic disease with 87.2% sensitivity of 87.2% and 98% specificity (Figure 6)[70]. Mean detection rate of pancreatic NET for EUS is 90% while about 73% for both CT and MRI[71]. EUS identified pancreatic NET in 26% of cases where CT and other radiology studies including MRI and PET were negative[72]. EUS is particularly helpful for detecting small pancreatic NETs < 10 mm, 68% of which were missed by CT[73]. EUS also provides more accurate size estimate than CT (11.2% *vs* 46.5% inaccurate, respectively). Therefore, in patients with suspected pancreatic NET and negative imaging, EUS should be performed.

A limitation of EUS sampling is inaccurate assessment of grade and Ki67 index compared with surgical specimens. This discordance is accentuated in tumors > 2 cm because Ki-67 immunoreactivity can be focal and therefore, potentially missed by EUS sampling[74]. EUS-FNB may improve assessment of Ki-67 as well as diagnostic yield compared with EUS-FNA[75,76]. Diagnostic yield of EUS-FNA in cystic pancreatic NETs is lower at 73% compared with solid NETs although higher than mucinous cysts. Cystic pancreatic NETs may have thick wall with low carcinoembryonic antigen levels (< 5 ng/mL)[77].

Adjunctive EUS technologies include elastography and contrast harmonic EUS (CH-EUS). Elastography assesses the relative stiffness of tissue qualitatively and semi-quantitatively with strain elastography and more recently shear wave elastography. It may help differentiate pancreatic ductal adenocarcinoma from pancreatic NET, but was unable to distinguish NET from benign lesions in one study[78]. Another study suggested modest ability to diagnose malignant *vs* benign pancreatic NETs (67% sensitivity and 71% specificity)[79]. Further studies are needed with shear wave elastography, which may lead to improved results. CH-EUS uses intravenous microbubble-based contrast agents to assess microvasculature in lesions. With pancreatic NETs being hypervascular, they appear hyperenhancing on CH-EUS with sensitivity 79% and specificity 99%[80]. CH-EUS may be particularly helpful in assessing tumor grade as microvasculature density inversely correlates with grade. Therefore, higher grade tumors have more heterogeneous enhancement with 90% accuracy for predicting malignancy and > 95% negative predictive value for tumor aggressiveness[81]. Quantitative CH-EUS may allow accurate differentiation of G1/G2 pancreatic NET from G3 pancreatic NEC[82].

MANAGEMENT

The next sections will highlight updates and controversial areas needing further research for the various GEP-NETs.

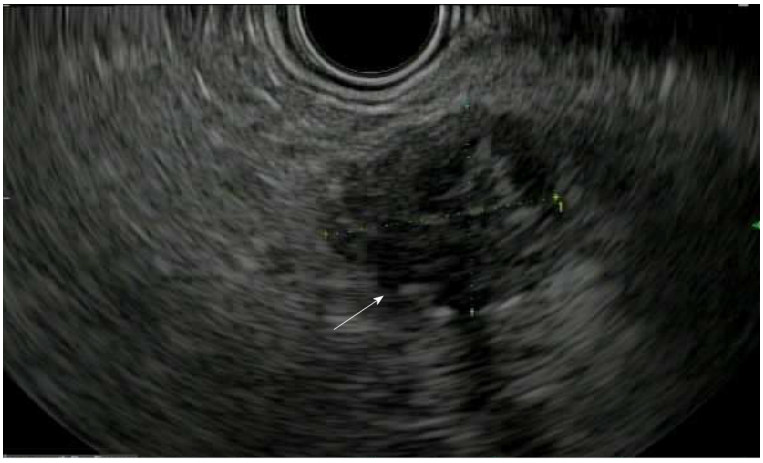

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Figure 6 Endoscopic ultrasound of pancreatic neuroendocrine tumor appearing well-defined and hypoechoic.

Stomach

Gastric NETs are typically diagnosed incidentally during endoscopy, and it is important to understand the subtypes of gastric NETs and their corresponding treatment recommendations (Table 2). Metastases occur in less than 10% of type I gastric NETs ≤ 2 cm (Figure 7), but in nearly 20% greater than 2 cm[83,84]. A long-term study of small (< 1 cm) type I gastric NETs followed endoscopically over an average of 7 years found that none developed advanced disease or significant growth of the tumor[85]. For larger lesions, EUS should be performed to assess depth of invasion and presence of lymph node metastases before performing endoscopic or surgical resection. Regarding endoscopic resection, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) can be considered although ESD should be reserved for larger lesions with superficial submucosal invasion[86]. A retrospective study of 87 Lesions less than 1 cm resected by ESD or EMR found that while complete resection rates trended higher with ESD (94.9% *vs* 83.3%, $P = 0.174$), it was associated with increased procedural time (26.1 min *vs* 9.5 min) and a tendency towards higher complications (15% *vs* 6%, $P = 0.28$)[87]. For rare type 1 gastric NETs with invasive disease, regional metastases, or grade 3 Lesions, surgery may be considered [88]. Antrectomy is an option in patients with numerous tumors, which may be curative with decreased recurrence compared to endoscopic resection (11% *vs* 44%)[89]. The role of medical therapy with SSAs (lanreotide and octreotide) to suppress gastrin levels as a means to reduce tumor progression remains to be determined[86].

Because type III gastric NETs behave differently from type I and II and are very aggressive tumors, traditionally surgical resection was recommended (Table 3)[90,91]. However, for small < 1 cm well-differentiated lesions without EUS evidence of deep invasion or regional metastases, endoscopic resection may be feasible[92]. A Japanese multi-center study of 144 Lesions (90 G1 and 54 G2) with median size 8 mm compared surgical (81 patients) and endoscopic (63 patients) resection outcomes during long-term follow-up[93]. Patients undergoing endoscopic resection had smaller lesions confined to the mucosa or submucosa, and 24% of these patients needed subsequent surgical resection. Overall, 5-year survival was similar for both groups, and in the endoscopic resection alone cohort, only one patient developed recurrence with no mortality over median 32-mo follow-up. Another recent study comparing 45 patients undergoing surgical or endoscopic resection found that tumor size greater than 1 cm was associated with lymph node metastases[94]. In a cohort of 50 patients undergoing endoscopic resection (41 EMR and 9 ESD) with a median follow up of 46 mo, mean size was 10 mm with nonsignificant trend towards larger lesions resected with ESD (14.2 mm *vs* 9.3 mm) and greater lymphovascular invasion in ESD patients (22.2% *vs* 2.4%). However, there was no evidence of tumor recurrence in either group. Of note, all lesions were no deeper than the submucosa layer and well-differentiated[95]. Given the more aggressive biology of type III gastric NETs, ESD may be favored over EMR although further study is needed. The resection approach should be carefully tailored to a patient's tumor size, depth of invasion, grade and presence of regional metastases[71].

Duodenum

Table 3 summarizes evaluation and management of small intestinal (duodenal, ampullary, and jejuno-ileal) NETs[96,97]. Nearly 90% of duodenal NETs are non-functional, well-differentiated and incidentally discovered as small, polypoid lesions in the first and second portion of the duodenum (Figure 8)[88]. For small duodenal NETs undergoing EMR, the optimal EMR technique remains unclear (standard, underwater, ligation, ligation without resection) with the main complications being bleeding in up to 20% of patients and perforation. For lesions greater than 2 cm without evidence of metastatic

Table 2 Gastric neuroendocrine tumors[88,90,91]

	Type 1	Type 2	Type 3	Type 4
Proportion of gastric neuroendocrine tumors	70%-80%	5%	15%-25%	Very rare
Associated conditions	Atrophic gastritis	Zollinger-Ellison and MEN-1	Sporadic	Sporadic
Location	Gastric fundus and body	Gastric fundus and body	Antrum	Anywhere
Endoscopic findings	Multiple, small polyps	Multiple, small polyps	Solitary, larger	Solitary, larger
Gastrin level	Increased	Increased	Normal	Normal
pH	Increased	Decreased	Normal	Normal
Prognosis	Excellent	Good	Poor	Very poor
Metastasis	10%-20%	10%-30%	30%-80%	80%-100%
Evaluation	Gastric pH, gastrin, EUS 1-2 cm lesions	Gastric pH, gastrin, EUS 1-2 cm lesions, abdominal imaging	Gastric pH, gastrin, EUS, abdominal imaging	Gastric pH, gastrin, EUS, abdominal imaging
Treatment	Endoscopic resection for larger lesions and surveillance for lesions < 2 cm	Similar to type 1	Surgery, endoscopic resection for superficial, well-differentiated lesions < 1 cm	Surgery for local disease, systemic chemotherapy for metastatic
Surveillance	EGD every year	EGD every 6-12 mo, abdominal imaging every year	EGD every 6-12 mo, abdominal imaging every 3 mo	

EUS: Endoscopic ultrasound; EGD: Esophagogastroduodenoscopy; MEN1: Multiple endocrine neoplasia type 1.

Table 3 Small intestinal neuroendocrine tumors[96,97,101,102,104,108,109]

	Duodenal	Ampullary	Jejuno-ileal
Epidemiology	2%-3% GEP-NETs	0.3%-1% GEP-NETs	1.2 cases/100000 incidence quadrupled over past 30 yr
Evaluation	> 2 cm: CT and EUS	CT, EUS	Chromogranin A, urine 5-HIAA, CT/MRI, gallium-DOTATATE PET CT, colonoscopy into terminal ileum
5-yr survival	No metastases: 80%-95%; Regional metastases: 65%-75%; Zollinger-Ellison or MEN-1: > 90%	59%	Local disease: 80%-100%; Regional disease: 70%-80%; Distant metastases: 35%-80%
Treatment	< 1 cm: Endoscopic resection; 1-2 cm: Endoscopic or surgical resection; > 2 cm: EMR or ESD, surgical resection for regional disease	< 2 cm superficial without metastases: Pancreaticoduodenectomy or consider endoscopic ampullectomy; > 2 cm: Pancreaticoduodenectomy	Surgery; Carcinoid syndrome: Long-acting SSA (octreotide LAR 20-30 mg IM)
Surveillance	EGD at least every 2 yr	EGD at 1-2 yr interval	NANETS: Curative surgery-CT every 3-6 mo then 6-12 mo for 7 yr; Advanced disease- CT every 6 mo; ENETS: Curative surgery: Chromogranin A, urine 5-HIAA, CT every 6-12 mo; Slow-growing treated without curative intent: every 3-6 mo

EUS: Endoscopic ultrasound; EGD: Esophagogastroduodenoscopy; GEP-NETs: Gastroenteropancreatic neuroendocrine tumors; PET: Positron emission tomography; CT: Computed tomography; MRI: Magnetic resonance imaging; SSAs: Somatostatin analogues; LAR: Long-acting release; HIAA: Hydroxyindoleacetic acid.

disease, ESD should be reserved for larger lesions because perforation and bleeding appear higher than with EMR or ESD[20,86,98].

The optimal strategy for duodenal NETS between 1 and 2 cm remains unclear. A multicenter study of 60 patients found that lesions larger than 11 mm had significantly higher rates of lymphovascular invasion and incomplete endoscopic resection with none having complete pathologic resection compared with smaller lesions[99]. Therefore, the authors suggested surgical resection for lesions larger than 11 mm. However, a recent study suggested EMR is efficacious and safe for 1-2 cm lesions without regional or distant metastases with similar overall survival to surgical resection during median 56-mo follow-up[100]. As expected, patients undergoing EMR were older (72.6 years *vs* 59.2 years,

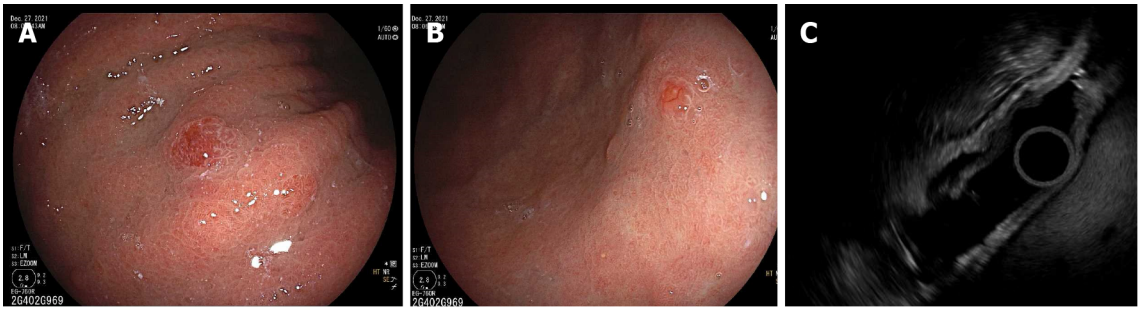

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Figure 7 Endoscopic and endoscopic ultrasound views of type 1 small, superficial neuroendocrine lesions in gastric body. A and B: Endoscopic; C: Endoscopic ultrasound.

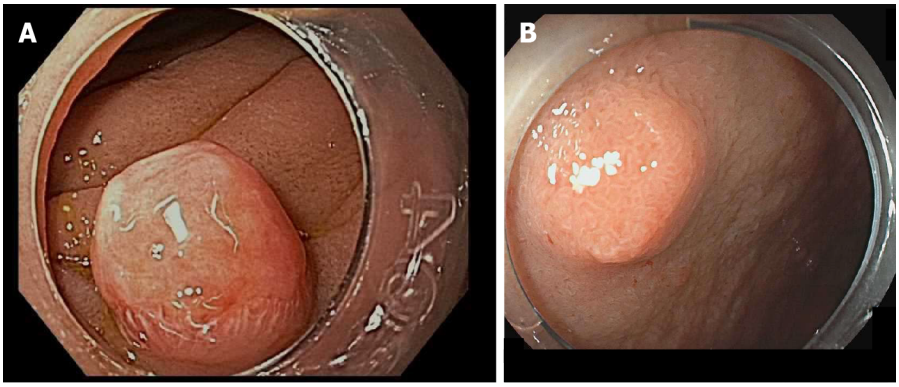

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Figure 8 Endoscopic imaging of duodenal neuroendocrine tumors.

respectively) with more node negative disease (89.5% *vs* 50%, respectively). The decision to pursue endoscopic or surgical resection should be considered based on local expertise and the individual case.

Ampullary NETs (Table 3) appear different in nature than non-ampullary duodenal NETs, and are often more advanced at presentation (G3 in 17% *vs* 2% for duodenal NETs) with higher incidence of lymph node metastasis (34% *vs* 10% for duodenal NETs)[101,102]. In a large pathology series of 203 duodenal NETs, most of the 27 NECs occurred in the ampullary region[103]. While pancreaticoduodenectomy is recommended regardless of size, its morbidity and mortality make endoscopic resection an attractive option. Small ampullary NETs less than 2 cm without muscularis propria invasion or lymph node metastases were completely resected endoscopically in one small study, and 71% had no recurrence during median 56 mo follow-up[104]. Further studies are needed to understand which patients may be managed with endoscopic ampullectomy.

Jejuno-ileal tumors

The true incidence of jejuno-ileal NETs (Table 3) likely remains underappreciated as in autopsy studies, the incidence is much higher (1.2 cases per 100000) than in population studies (0.67 cases per 100000)[96,105]. This implies that many early jejuno-ileal NETs remain undiagnosed[106]. Early diagnosis remains challenging as most patients are asymptomatic or have nonspecific symptoms, and carcinoid syndrome occurs in only 20%-30% of patients with metastatic disease[106]. Unlike gastric, duodenal and colorectal NETs, incidental diagnosis of jejuno-ileal NETs is unlikely with 89% found in the ileum[105,107].

Segmental resection and wide lymphadenectomy is the definitive approach for jejuno-ileal NETs with localized and regional metastatic disease[108]. Intraoperative exploration with small bowel palpation is recommended as up to 70% of pre-operative imaging may understage tumors[109]. This is likely due to limitations of diagnostic imaging including VCE and DBE, which may miss small, multifocal lesions[52,110]. For patients with distant metastatic disease, surgical resection of the primary tumor may still be considered to alleviate symptoms resulting from the lesion (for example, obstructive symptoms or bleeding), to achieve potential cure if the distant metastases may be completely resected as well, and to improve outcome although data on this is mixed and further study is needed[106].

Appendiceal tumors

Traditionally appendiceal NETs were the most common appendiceal tumors although recent data

suggests mucinous neoplasms may have surpassed them[111,112]. Most present incidentally and are asymptomatic as the majority are located in the distal one-third of the appendix rather than the base. Because risk of metastases correlates with tumor size, recommendations for evaluation and management vary depending on the size (Tables 4 and 5). However, a study of 418 patients noted that risk of nodal metastases was affected by age, depth of invasion, extent of surgery as well as tumor size with 0.89 area under the curve[113]. Another study analyzing 435 patients found that tumor size > 1.5 cm, G2 grade, lymphovascular infiltration, and mesoappendiceal invasion were associated with nodal metastasis[114]. Therefore, some guidelines suggest right hemicolectomy for 1-2 cm tumors with any of these high-risk features. However, in a study of 916 patients with 1-2 cm NETs, right hemicolectomy was not associated with increased survival despite being associated with larger and higher stage tumors (hazard ratio = 1.14, P = 0.72)[115]. The most appropriate surgical approach for appendiceal NETs especially between 1-2 cm remains unclear as well as the definitive triggers to send a patient for completion right hemicolectomy.

Colonic neuroendocrine tumors

With increased colon cancer screening, the incidence of colonic NETs has increased dramatically from 0.02 to 0.2 per 100000 people in the United States between 1973 to 2004[116]. The majority are high-grade, poorly differentiated lesions that typically occur in the right colon (70%), especially in the cecum [117,118]. Well-differentiated colonic NETs have significantly worse prognosis than well-differentiated NETs anywhere else in the GI tract. A recent study using the SEER database developed a novel nomogram to predict survival incorporating patient's age ≥ 68 years, sex, tumor size, grade, chemotherapy, N stage and M stage. This outperformed the traditional TNM staging system in predicting overall survival[119].

With aggressive behavior and poor survival outcomes, colonic NETs require multidisciplinary care (Table 5). Tumors < 2 cm may be considered for endoscopic resection, however surgery is required for incomplete resection or high-grade pathology[116]. Very little data exists about the efficacy and safety of ESD with one study including only 6 non-rectal, colonic NETs. This study demonstrated that non-rectal NETs were significantly associated with risk of non-R0 resection and while complications were higher, this was not significant compared with ESD of rectal NETs[120]. On the other end of the spectrum in patients with metastatic disease, chemotherapy can also be utilized[117]. Survival improved with chemotherapy alone, surgery alone and even more with the combination of surgery and chemotherapy (5-year survival 37% for combination *vs* 32% surgery alone, P < 0.001)[121]. However, other studies noted that surgery did not provide significant survival benefit in localized and metastatic disease[122, 123]. Further study is necessary to understand the optimal treatment combination as well as role of immunotherapy.

Rectal neuroendocrine tumors

Similar to colonic NETs, rectal NETs have been increasingly diagnosed with improved screening colonoscopy rates, experiencing a 10-fold rise in incidence over the past 30 years[124,125]. They are more common in women in the United States although in Korea men are more likely to have rectal NETs. In the United States, Asian and African American patients have higher incidence than Caucasians [126]. The majority (70%-88%) of rectal NETs are small (< 1 cm) and localized at the time of diagnosis [124,127]. Lymph node metastasis occurs in about 2% and distant metastases in about 8% of rectal NETs at diagnosis. Tumor size, depth of invasion, grade and lymphovascular invasion all affect prognosis. Regarding tumor size, it appears to correlate with metastasis at the time of diagnosis (3%, 66%, and 73% metastases with tumor size ≤ 1 cm, 1-1.9 cm, and ≥ 2 cm, respectively)[128]. A study using the SEER database of 788 patients with T1 rectal NETs noted tumor size and submucosal invasion were predictive of metastasis, and no tumors ≤ 19 mm without submucosal invasion had metastases[129]. At diagnosis, 1.5% of patients had metastases with 1.1% in tumors ≤ 10 mm and 6.6% in NETs 11-19 mm.

Usually, rectal NETs are not recognized before polypectomy by the endoscopist and only later discovered when pathology returns. If the endoscopist is suspicious of a rectal NET during the procedure, biopsies can be obtained with photograph documentation and tattoo adjacent to the lesion. In terms of treatment, endoscopic resection should be performed for lesions smaller than 1 cm without invasion beyond the submucosa. Options include EMR, EMR band ligation, and ESD; however, given the greater procedure time and complications with ESD, EMR or EMR band ligation are preferred. A prospective study comparing EMR band ligation (n = 53) to ESD (n = 24) in lesions ≤ 10 mm demonstrated the superiority of EMR band ligation with higher complete resection rates (100% *vs* 54.2%, P = 0.00)[130]. In addition to 100% negative margins, EMR band ligation was associated with shorter procedure times (5.3 *vs* 17.9 min, P = 0.00). Similarly, a retrospective study of 82 tumors < 10 mm reported higher complete resection rates with EMR band ligation compared to ESD (95% and 75%, P = 0.025) with shorter procedure times[131]. A recent retrospective comparative study of underwater EMR (n = 36) to ESD (n = 79) found no difference in achieving R0 resection for lesions ≤ 10 mm[132]. Yet underwater EMR was associated with a significantly shorter procedure time (5.8 min *vs* 26.6 min, P = 0.0001) and no adverse events while there were two cases of delayed bleeding and minor perforation in the ESD group. Therefore, for small rectal NETs < 1 cm, EMR band ligation is the endoscopic method of choice while underwater EMR may be considered as well.

Table 4 Risk of metastases by tumor size in appendiceal neuroendocrine tumors[169]

Tumor size	Nodal metastases	Distant metastases
≤ 1 cm	0%	0%
1-2 cm	7.5%	4%
≥ 2 cm	33%	12%

Table 5 Colorectal neuroendocrine tumors[103,112,114,121,124,126,170-173]

	Appendiceal	Colonic	Rectal
Epidemiology	1.45% of appendectomies	< 10% NETs	29% GEP-NETs
Presentation	Incidental or acute appendicitis; Carcinoid syndrome rare	Incidental (yellowish polypoid or donut-shaped); 46% advanced at diagnosis	Incidental (small, yellowish polypoid)
Evaluation	(1) Colonoscopy; (2) CT/MRI if > 2 cm, incomplete resection[1], suspected metastases; (3) Gallium DOTATATE PET CT: Incomplete resection[1], suspected metastases, carcinoid syndrome; and (4) Chromogranin A and urine 5-HIAA: liver metastases or carcinoid syndrome	CT, EUS, Gallium DOTATATE PET CT	Colonoscopy; EUS; > 2 cm, invasion beyond submucosa, lymph node disease: Gallium DOTATATE PET CT
5-yr survival	< 2 cm without regional or distant disease: 100%; 2-3 cm with regional nodes or ≥ 3 cm: 78%; Distant metastases: 32%	Stage I: 90%; Stage II: 77%; Stage III: 53%; Stage IV: 14%	Localized: 98%-100%; Regional metastases: 54%-74%; Distant metastases: 15%-37%
Treatment	Right hemicolectomy with lymph node dissection: (1) > 2 cm; and (2) 1-2 cm with high-risk features[2]; Appendectomy: (1) < 1 cm, well-differentiated; and (2) 1-2 cm without high-risk features[2]	Local disease: segmental colectomy and lymphadenectomy; Metastatic disease: chemotherapy	< 1 cm without invasion beyond submucosa: Endoscopic resection; 1-2 cm: Endoscopic resection or transanal resection; > 2 cm without metastatic disease: Radical surgical resection
Surveillance	(1) ≤ 2 cm without high-risk features[2] and confined to appendix: No follow-up; and (2) Larger or node positive, and right hemicolectomy: CT/MRI 3-12 mo post-surgery; consider baseline gallium DOTATATE PET CTAfter first year, annual CT/MRI		< 1 cm: None; 1-2 cm: EUS or MRI at 6 and 12 mo; > 2 cm: CT/MRI at 3 and 12 mo, then every 12-24 mo

[1]Incomplete resection: Positive margin and/or lymph nodes.

[2]High-risk features: Large tumor size, G2, lymphovascular invasion, mesoappendiceal invasion.

NET: Neuroendocrine tumor; EUS: Endoscopic ultrasound; EGD: Esophagogastroduodenoscopy; GEP-NENs: Gastroenteropancreatic neuroendocrine neoplasms; PET: Positron emission tomography; CT: Computed tomography; MRI: Magnetic resonance imaging; HIAA: Hydroxyindoleacetic acid.

If incomplete resection occurs, then salvage therapy with ESD or transanal endoscopic microsurgery should be pursued to minimize recurrence[133,134]. Optimal management for rectal NETs 1-2 cm remains uncertain. NANETS recommends transanal excision although noted this could be considered after endoscopic resection if that resulted in positive margins. ESD may have a role and may be preferred to cap-assisted EMR as higher complete resection (100% *vs* 70%) and lower recurrence (0% *vs* 17%) was achieved with ESD[135]. However, ESD may not be the ideal approach in patients with lymphovascular invasion, grade 2, and/or positive margins as distant metastasis occurred in 2.5% following ESD of small (< 2 cm) rectal NETs[120]. With advanced metastatic disease, palliative surgery and systemic therapies should considered through a multidisciplinary approach considering availability of local resources.

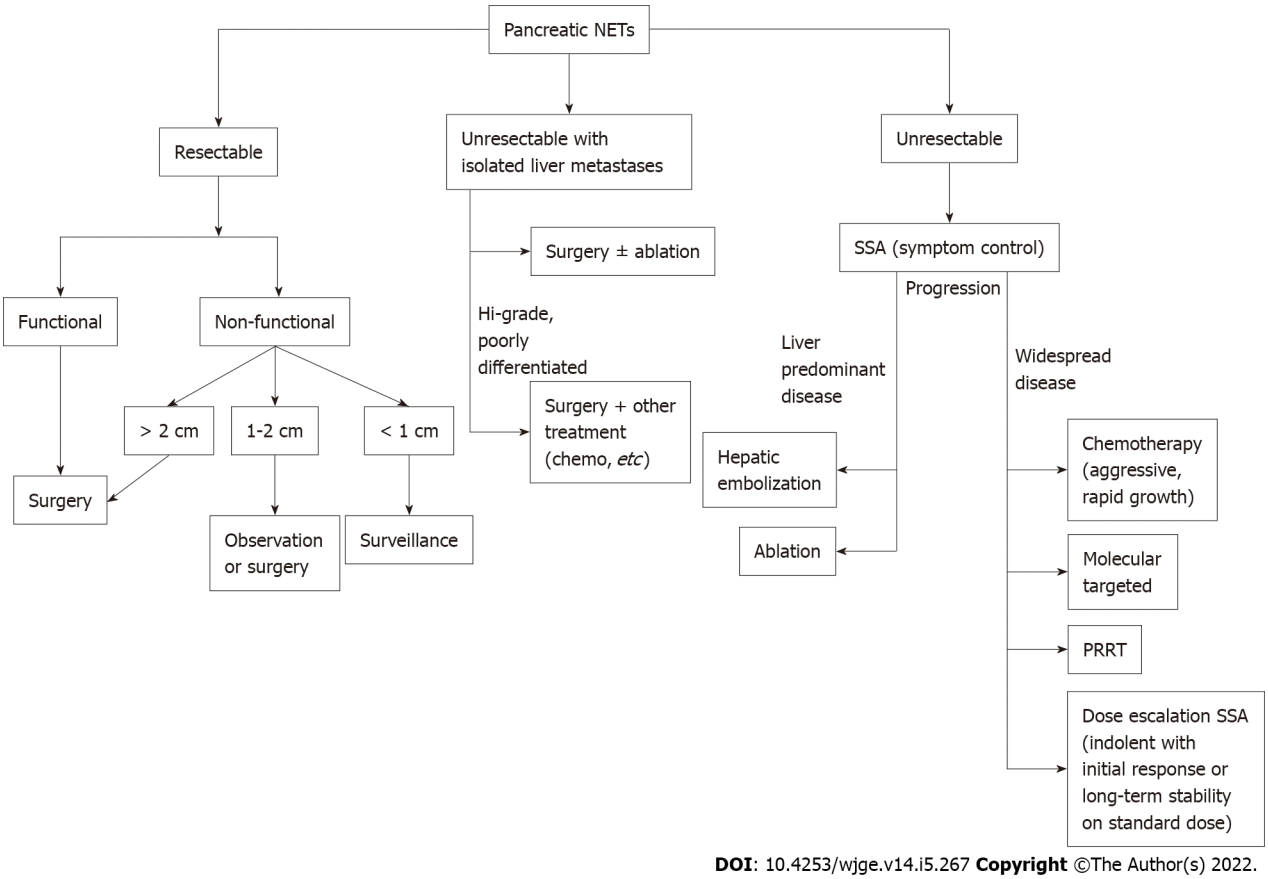
Pancreas

Pancreatic NETs make up 16% of GEP-NETs with annual incidence of 0.5 per 100000 people[6,9]. The majority are sporadic and malignant with metastatic disease present in 60% of patients at the time of diagnosis (Table 6)[96,136]. If there are no distant metastases or if the metastatic disease is resectable (for example, isolated hepatic metastases), surgery is the primary method of treatment for all functioning pancreatic NETS, irrespective of size (Figure 9). It is also recommended for localized (confined to the pancreas and regional lymph nodes) nonfunctioning pancreatic NETs greater than 2 cm. Lesions less than 1 cm can safely undergo surveillance in the absence of symptoms and pancreatic duct dilation [137]. In a cohort comparing nonoperative and operative management of nonfunctioning NETs less than 1 cm, there was no difference in mortality or disease progression over median 45-mo follow up with surgical patients experiencing relatively high 46% rate of complications postoperatively[138].

Table 6 Diagnosing pancreatic neuroendocrine tumors[136,174]

	Diagnostic evaluation
All pancreatic NET	Multiphasic CT/MRI
	If results impact management, gallium DOTATATE PET CTEUS with biopsy
Insulinoma	72 h fast test: Hypoglycemia with elevated insulin
	Oral glucose tolerance test: May be necessary in minority with only postprandial hypoglycemia
Gastrinoma	Fasting gastrin 10 times upper limit of normal + gastric pH < 2
	If gastrin less elevated + gastric pH < 2, measure BAO with secretin test
	BAO > 15 mEq/h or serum gastrin increase > 120 pg/mL
Glucagonoma	Fasting serum glucagon > 500 pg/mL
Somatostatinoma	Fasting plasma somatostatin > 30 pg/mL
VIPoma	Large volume diarrhea + serum VIP > 75 pg/mL

NET: Neuroendocrine tumor; CT: Computed tomography; MRI: Magnetic resonance imaging; PET: Positron emission tomography; EUS: Endoscopic ultrasound; BAO: Basal acid output.



DOI: 10.4253/wjge.v14.i5.267

Figure 9 Treatment algorithm for pancreatic neuroendocrine tumors. NET: Neuroendocrine tumor; SSA: Somatostatin analogue; PRRT: Peptide receptor radionuclide therapy.

However, observation *vs* surgery for nonfunctioning pancreatic NETs measuring between 1-2 cm remains controversial. Several studies have supported observation, as smaller tumor size correlates with lower malignancy potential[138-141]. On the other hand, other studies have suggested surgery is superior[142-145]. One study that followed 39 resected lesions less than 2 cm for a median 34.2 mo found that 7.7% developed late metastasis or recurrence[143]. Two other comparative studies supported surgical resection for pancreatic NETs less than 2 cm, as five-year overall survival rates were greater than the observation group (82.2%-92.8% *vs* 34.3%-67.4%, respectively)[142,145]. Regardless of tumor

size, if surgery is pursued, follow up with cross-sectional imaging is recommended annually for the first three years then every two years for a total of 10 years[146].

EUS-guided radiofrequency ablation (RFA) has recently been studied as a potentially safe and minimally invasive treatment option. Through the use of targeted electromagnetic energy and alternating high-frequency currents, EUS-RFA induces coagulative necrosis, fibrotic changes, and a delayed immune response to the pancreatic tissue of interest[147]. Only a few human studies have investigated treatment outcomes, but have demonstrated feasible and promising results[148,149]. In one study, 18 patients (including seven insulinomas and 11 non-functioning lesions) with a mean diameter of 1.4 cm demonstrated no signs of recurrence during mean follow-up of 8.7 mo[149]. Furthermore, all seven patients with insulinomas had normalization of glucose within 24 h of EUS-RFA. A prospective multicenter study of 14 pancreatic NETs (G1 lesions with median size 1.3 cm) found that 12 (85.7%) lesions completely resolved at 12 mo follow up[148]. The other two lesions were considered treatment failures with one increasing by 3 mm and the other remaining unchanged in size. A recent video case report used EUS-guided microwave ablation to safely and effectively treat a symptomatic inoperable pancreatic neck NET (35 × 32 mm) invading the splenic artery without any complications[150]. Further prospective and longer-term studies are needed to determine how this technology may improve patient outcomes and how it fits into the treatment algorithm.

For patients with isolated liver metastases, optimal management remains uncertain in the absence of randomized controlled studies and ranges from surgical resection of all visible metastatic disease to local therapy with ablation. Candidates for resection of liver metastases include those with isolated unilobar disease, preserved liver function and well-differentiated pathology[151]. However, even patients with bilobar disease could undergo multiple wedge resections and/or hepatectomy provided at least 20 percent of the total liver volume remains preserved. Five-year survival rates ranging from 85% to 90% have been reported with selected patients undergoing curative resection[152,153]. However, recurrence rates are as high as 54% despite negative margins, which implies that preoperative imaging misses small metastatic disease[154].

Whether the primary tumor should be resected as well in these patients remains debated although retrospective studies suggest improved survival with this approach[155].

Ablation is mainly effective for small (< 3 cm) lesions and includes RFA, cryoablation and microwave ablation with a more favorable morbidity profile than surgery or hepatic arterial embolization. The optimal use of this technique remains unclear although it is often used as an adjunct to surgical resection especially when complete resection of multifocal or bilateral disease is not feasible or in patients who have already undergone hepatic resection. Comparative studies remain limited with one nonrandomized study suggesting high overall 5-year survival (84%) following RFA compared to surgery (90%)[152]. If RFA is contraindicated (especially for lesions near the liver surface or adjacent to vital structure) or technically not possible, cryoablation can be used[156]. While cryoablation is relatively underutilized, a small case series demonstrated 77.8% complete response and 22.2% partial response in 9 patients undergoing ablation with a median follow of 7 mo[157]. Cryoablation may be considered in technically challenging tumor locations. Further studies are needed to delineate its role relative to other ablative techniques.

For unresectable liver disease in symptomatic patients, hepatic arterial embolization is suggested for palliation as an alternative to medical treatment alone. Techniques include injection of different substances [bland embolization (gel foam powder), chemoembolization (chemotherapy), radioembolization (radioactive isotopes)]. In liver predominate disease, chemoembolization is associated with a tumor response rate over 50%, which appears comparable to the other techniques[158]. A randomized trial is underway to compare liver progression-free survival and complications of these three techniques.

For unresectable widespread disease, treatment options include systematic therapy with SSAs to treat symptoms and control disease, chemotherapy, molecular targeted therapy, PRRT, and immunotherapy. SSAs suppress hormone release in pancreatic NETs by binding somatostatin receptors, which prevents the release of hormonal peptides, and is thus most helpful for VIPomas, glucagonomas, and somatostatinomas and less helpful for insulinomas and gastrinomas. When used to control disease by exploiting the ability of SSAs to decrease proliferation in nonfunctioning NETs, SSAs are administered to patients with high tumor burden[159]. The CLARINET study, a randomized, double blind placebo trial, provided support for lanreotide in preventing disease progression in advanced well to moderately differentiated nonfunctioning pancreatic NETs (prolonged progression-free survival 65% *vs* 33% at 24 mo)[160]. Short-acting octreotide may be used and if effective, changed to long-acting depot with monthly injections.

Chemotherapy is particularly helpful in aggressive disease with rapidly growing metastases[10]. Compared to temozolomide, the use of combination chemotherapy with capecitabine and temozolomide (CAPTEM) demonstrated high response, progression free survival, and manageable toxicity in patients with well-differentiated intermediate to high grade pancreatic NETs[161,162]. Given its favorable toxicity profile as an oral regimen, CAPTEM is typically favored over streptozocin-containing regimens. Expression of methylguanine DNA methyltransferase (MGMT) may predict response to alkylating chemotherapeutics as studies suggested that patients without MGMT had better response [163]. However, prospective studies are necessary.

Molecular targeted therapy has a role in patients with disease progression on SSAs by inhibiting the mammalian target of rapamycin or tyrosine kinase with everolimus and sunitinib, respectively[164]. Compared to placebo, everolimus was able to prolong progression free survival (11 mo *vs* 4.6 mo) in a cohort of 410 patients with advanced, progressive low and intermediate grade pancreatic NETs[165]. Sunitinib has also demonstrated safe and reliable results in progressive, well-differentiated pancreatic NETs where progression free survival was double placebo (11.4 mo *vs* 5.5 mo)[161]. with a response rate of 24.5%[166]. Other promising agents include tyrosine kinase inhibitors sorafenib, pazopanib, vascular endothelial growth factor receptor inhibitor cabozantinib and lenvatinib, which all require further prospective study.

PRRT uses radiolabeled SSAs (^{90}Yttrium or ^{177}Lutetium) to bind somatostatin receptors as a means to emit localized radiation in advanced pancreatic NETs[164]. Therefore, it is an option in patients who have progressed through SSAs. A phase III trial compared ^{177}Lu-Dotatate (116 patients) to long acting octreotide (113 patients) and found longer progression free survival (65.2% *vs* 10.8%) and higher response rates (18% *vs* 3%) with ^{177}Lu-Dotatate[167]. A larger study of 610 patients (which included bronchial NETs) also reported a favorable survival and response rate, especially in the pancreatic NET group[168]. Despite encouraging results, concern remains over potential long-term toxicity including acute leukemia (0.7%) and myelodysplastic syndrome (1.5%)[168]. As such, risk and benefits of treatment should be carefully discussed with patients before embarking on PRRT. Further studies are needed to understand the role and safety of PRRT as well as whether combination therapy with SSAs is more efficacious.

Although immunotherapy has revolutionized oncology, its utility in treating pancreatic NETs remains unclear. Early trials evaluating anti-programmed cell death 1 antibodies including spartalizumab and pembrolizumab have not been encouraging with minimal response in pancreatic NETs. Further studies are certainly needed.

CONCLUSION

GEP-NENs represent a complex and diverse physiologic and pathologic spectrum of neoplasms with varying disease activity that benefit from multidisciplinary care. With advancements in functional imaging, serum biomarkers, and endoscopic techniques for diagnosis including EUS as well as therapy with EMR, ESD and EUS-RFA, identification and management of these protean lesions continue to improve and allow for tailored treatment plans based on prognostic information and location throughout the gastrointestinal tract.

FOOTNOTES

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MINIREVIEWS

Endobiliary biopsy

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Abstract

The differential diagnosis between benign and malignant biliary strictures is challenging and requires a multidisciplinary approach with the use of serum biomarkers, imaging techniques, and several modalities of endoscopic or percutaneous tissue sampling. The diagnosis of biliary strictures consists of laboratory markers, and invasive and non-invasive imaging examinations such as computed tomography (CT), contrast-enhanced magnetic resonance cholangiopancreatography, and endoscopic ultrasonography (EUS). Nevertheless, invasive imaging modalities combined with tissue sampling are usually required to confirm the diagnosis of suspected malignant biliary strictures, while pathological diagnosis is mandatory to decide the optimal therapeutic strategy. Although EUS-guided fine-needle aspiration biopsy is currently the standard procedure for tissue sampling of solid pancreatic mass lesions, its diagnostic value in intraductal infiltrating type of cholangiocarcinoma remains limited. Moreover, the "endobiliary approach" using novel slim biopsy forceps, transpapillary and percutaneous cholangioscopy, and intraductal ultrasound-guided biopsy, is gaining ground on traditional endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography endobiliary forceps biopsy. This

review focuses on the available endobiliary techniques currently used to perform biliary strictures biopsy, comparing the diagnostic performance of endoscopic and percutaneous approaches.

Key Words: Biliary strictures; Endoscopic retrograde cholangiography; Cholangioscopy; Endobiliary forceps biopsy; Intraductal ultrasound-guided biopsy; Percutaneous transhepatic

Core Tip: Invasive imaging modalities combined with tissue sampling are almost always required to confirm the diagnosis of suspected malignant biliary strictures. The "endobiliary approach" using novel slim biopsy forceps, transpapillary and percutaneous cholangioscopy, and intraductal ultrasound-guided biopsy is gaining ground over traditional endoscopic retrograde cholangiopancreatography and percutaneous endobiliary forceps biopsy. Nevertheless, both endoscopic and percutaneous interventional radiology modalities are today considered safe and effective tissue sampling options, providing histologic identification of biliary strictures with satisfactory sensitivity and specificity rates.

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INTRODUCTION

The diagnosis of biliary strictures remains a challenge, even in an era of considerable technologic advances regarding our current diagnostic tools. A biliary stricture is an area of stenosis in the intrahepatic or extrahepatic biliary tree (Figure 1). It can be the result of either malignant or benign pathologies, with a high prevalence of malignancy (two-third of cases)[1]. Malignant strictures of the biliary system (MBS) are commonly divided into distal strictures (involving the common bile duct) and proximal strictures (involving the hepatic hilum and right and left hepatic ducts). Pancreatic ductal adenocarcinoma is the most common cause of distal malignant stenosis, followed by cholangiocarcinoma, and, less commonly, ampullary or metastatic cancer. Proximal malignant strictures are due to cholangiocarcinoma, hepatocellular and gallbladder cancer or lymphoproliferative disorders, and metastatic lesions. The most common causes of a benign stricture include iatrogenic injury, chronic pancreatitis, primary sclerosing cholangitis, autoimmune diseases, and others. Biliary strictures are defined indeterminate when a clear diagnosis cannot be obtained after a non-invasive diagnostic work-up and an endoscopic retrograde cholangiopancreatography (ERCP) with biliary sampling. Their evaluation should be extremely careful given the noteworthy false-positive preoperative diagnosis of cancer, resulting in a 13%-24% resection rate of benign lesions[2].

Differentiating between the nature of strictures and diagnosing the relative aetiology often require a complex diagnostic approach. The evaluation of biliary strictures consists of laboratory markers and invasive and non-invasive imaging examinations including focused abdominal ultrasound (US), computed tomography (CT), contrast-enhanced magnetic resonance cholangiopancreatography, and endoscopic ultrasonography (EUS).

Nevertheless, invasive imaging modalities combined with tissue sampling are almost always required to support the diagnosis of a suspected MBS. If a histological diagnosis is obtained through the first procedure, further invasive diagnostic modalities can be avoided and appropriate treatment can be started. Both endoscopic retrograde cholangiography (ERC) and percutaneous transhepatic cholangiography endobiliary forceps biopsy (PTHC-EFB) have been valid procedures for a while for histological assessment of intrahepatic and/or extrahepatic biliary strictures.

EUS-guided fine-needle aspiration biopsy (FNAB) is nowadays the standard procedure for tissue sampling of solid pancreatic lesions because of its high diagnostic rate: In this setting, previous meta-analyses reported that the sensitivity rates of EUS-FNAB ranged from 85% to 89%[3]. However, EUS-FNAB has some limitations in cases of MBS other than pancreatic lesions, such as the frequent intraductal infiltrating type of cholangiocarcinoma. Furthermore, over the past 20 years, the technique of EUS-guided biliopancreatic lesion sampling has not gained widespread availability.

Currently, other endobiliary techniques for biliary tissue acquisition are increasing the possibility to obtain a definitive diagnosis: In fact, the "endobiliary approach" to suspect MBS is expanding past the more traditional ERCP and PTHC, through the use of novel slim biopsy forceps, to include transpapillary and percutaneous cholangioscopy, and intraductal ultrasound-guided biopsy (IDUS-G biopsy).

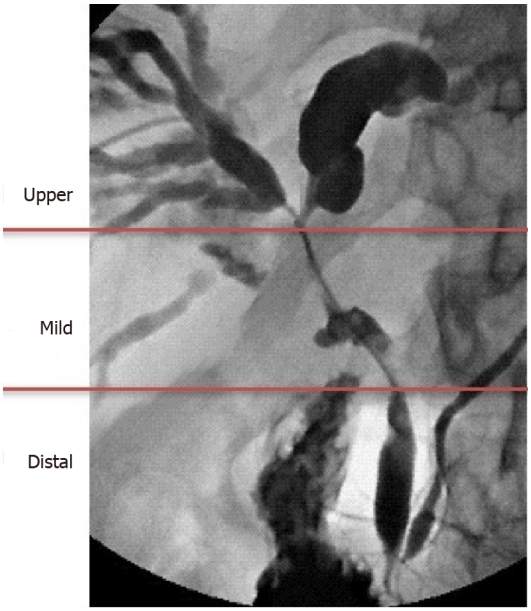

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Figure 1 Biliary stricture levels.

ENDOSCOPIC TECHNIQUES

Endoscopic retrograde cholangiopancreatography

ERCP is a diagnostic and therapeutic invasive imaging modality that provides an "indirect" radiological visualization of the biliopancreatic ductal system. ERCP with endobiliary brushing and/or forceps biopsy is often the first endoscopic approach for tissue sampling of biliary strictures because of its wide availability. According to several studies, the forceps biopsy sampling method has slightly better performance in comparison to brush cytology: A systematic review and a meta-analysis (9 studies; n = 730 patients) by Navaneethan *et al*[4] reported a pooled diagnostic odds ratio in detecting malignant biliary strictures of 43.18 (95% confidence interval [CI]), with a 48.1% pooled sensitivity and 99.2% pooled specificity, for intraductal biopsies, compared to a pooled diagnostic odds ratio of 33.43 (95%CI), with a 45% pooled sensitivity and 99% pooled specificity, for brushing. Combining the two sampling methods only modestly increased the sensitivity to 59.4%.

Theoretically, sufficient biliary tissue sampling provides adequate identification of the tissue's specific features such as superficial intraductal spread and/or wall invasion, details that cannot be obtained by brush cytology. Despite a low-diagnostic sensitivity, brush cytology is still the first line ERCP sampling modality, because of its feasibility and safety. However, as trans-papillary forceps biopsy has got a higher sensitivity rate in comparison to brush cytology, it may play an important role in the pathological confirmation of MBS.

Several series reported malignancy detection rates with ERCP endobiliary forceps biopsy ranging from 33% to 71 % for pancreatic cancer and 44% to 89 % for cholangiocarcinoma[5]. A more recent review by Korc and Sherman[6] reported detection rates for pancreatic cancers and cholangiocarcinoma of 37% and 63%, respectively. The poor sensitivity of endobiliary forceps biopsy is likely due to the blind modality of sampling under fluoroscopic guidance. In addition, MBS that mainly infiltrate the wall of the duct or incite extrinsic compression are challenging to be targeted through the ERCP tissue sampling modality. ERCP with trans-papillary biopsies are performed using forceps designed for standard endoscopes[6] that should provide an adequate sample of bile duct tissue deep to the epithelium. The biopsy forceps are introduced into the bile duct after sphincterotomy of the papilla, even though some studies described the forceps insertion modality without previous sphincterotomy [7]. The forceps are pushed under fluoroscopic guidance to the level of the stricture to grasp specimens from the lower part of the stricture. The ideal number of specimens to perform has not been standardized, although several studies[5-8] suggest that at least three specimens should be obtained.

To optimize the unsatisfying sensitivity of trans-papillary forceps biopsy, in 2011 Wright *et al*[9] proposed a method of rapid on-site cytopathological evaluation (ROSE) through the cytologic preparation and analysis of forceps biopsy sampling made by an onsite cytopathologist (Smash protocol). In total, 133 patients were enrolled in the study. A "smash" specimen sensibility of 72% was reported.

Another work[10] valued the yield of ERCP biliary biopsy sampling subjected to ROSE and reported that sensitivity for cancer diagnosis increased to 76%-97%. This gain suggests that ROSE modality may improve the sensitivity of ERCP forceps biopsy sampling. However, this resource is available only to a

few tertiary referral centres. Adverse events related to endobiliary forceps biopsy sampling are rare: To date, the same minor and only a few major cases of haemobilia[8] and perforation of the common hepatic duct[11] have been described.

Novel slim biopsy forceps

To overcome the difficulty of common bile duct cannulation that is related to the thickness and the hardness of the standard biopsy forceps, some novel biopsy forceps have been developed. In 2017, Inoue *et al*[11] published a study about the diagnostic yield of controllable biopsy-forceps (C-BF) in MBS. C-BF (MTW Endoskopie, Wesel, Germany) allows the tip's angle to be adjusted by up to 90°. In that study, 110 patients with biliary strictures were retrospectively evaluated. A high technical success rate (99%) of biliary biopsies sampled was reported.

That study reported different performances of the biopsies performed with C-BF depending on the target site: Adequate samples were respectively obtained in 96% (22/23) of specimens from the intrapancreatic common bile ducts, 92% (11/12) of those from the upper common bile ducts, 80% (12/15) from the carrefour of the hepatic ducts, 75% (9/12) from the right intrahepatic bile ducts, and 31% (5/16) from the left intrahepatic bile ducts.

Moreover, the diagnostic sensitivity for biliary strictures reported was just 60%, which is similar to those reported from studies carried out on conventional forceps biopsy. The benefits of using C-BF may be limited because of its lack of rotation torque ability; thus, only a curvature to the patient's right-hand side can be performed: This feature leads to an adequate sampling of lesions located to the right intrahepatic bile duct (75%), in contrast to a poor success rate in procedures that involved selecting the left intrahepatic bile duct (31%).

Another novel slim biopsy forceps, with a soft and thinner shaft of 1.8 mm (Radial Jaw 4P, Boston Scientific, Boston, MA, United States), has been developed to enable the jaws to pivot onto the targeted biopsy site for better tissue grasping. To evaluate the feasibility and efficacy of this novel biopsy device in the diagnosis of MBS, in 2017, Yamamoto *et al*[12] tested it on a cohort of 360 patients who underwent ERCP for biliary strictures. That study showed a higher sensitivity than previous studies of trans-papillary bile duct biopsies: In fact, the overall sensitivity and accuracy were 69.6% and 78.8%, respectively. The sensitivity was 75.6% in cholangiocarcinoma, 64% in pancreatic cancer, and 57.1% in metastasis. In cholangiocarcinoma, a lower sensitivity was observed for perihilar lesions (68.7%) rather than for distal stricture (83.1%). A better sensitivity has been reported for longer stenosis of pancreatic cancer and metastasis. These results suggest that trans-papillary forceps biopsy should be performed in consideration of the stricture level, stricture length, and cancer type. Actually, a lower sensitivity was observed for the perihilar MBS rather than for the distal one. This may be due to the features of the strictures: Narrow, smooth, and angled lesions could lower the biopsy forceps ability to hit the targeted area. Moreover, the distance of the MBS from the papilla could reduce the possibility of precisely grasping the lesion. In contrast, a better sensitivity was observed for the distal MBS. Regarding the lower bile duct, a better sensitivity was observed for the strictures in which an adequate space to open enough the biopsy forceps jaws was present.

In 2017, Kwon *et al*[13] reported a single experience of MBS sampling with the use of a custom-made prototype guide-wire assisted endobiliary forceps biopsy: Targeted sampling from the central area of the mass was easy and successful.

Peroral cholangioscopy

Peroral cholangioscopy (POCS) modalities provide direct visualization of the biliary ductal system. Those procedures are important diagnostic tools in cases of suspect MBS in which other available invasive/non-invasive imaging modalities (*e.g.*, EUS, CT, MRI, and ERCP with transpapillary biopsy sampling) cannot provide a definitive diagnosis. Three different cholangioscopic techniques are currently available: The "mother-baby" dual-operator cholangioscopy (DOC), the "mother-baby" single-operator cholangioscopy (SOC), and the direct cholangioscopy[14]. DOC is necessarily performed by two endoscopists with the use of a very slim endoscope passed through the working channel of a duodenoscope up to cannulating the common bile duct, usually over a guide-wire. POCS with optical image manipulation using narrow-band imaging (NBI) allows emphasizing the imaging of certain features of the bile duct tissue, such as mucosal structures and capillary vessels (*e.g.*, irregular and tortuous vessels, papillogranular or nodular elevated surface), enabling to target biopsy onto the suspect lesion.

A prospective multicentre study on indeterminate bile duct lesions and preoperative mucosal cancerous extension diagnosis by DOC plus NBI was conducted by Osanai *et al*[15] in 2013. This work was conducted on a cohort of 87 patients of whom only 35 underwent endobiliary forceps biopsy sampling *via* DOC for indeterminate lesions. In 34/35 patients, NBI was useful in differentiating benign from malignant lesions. Collected data showed an accuracy rate of 85.7 % for indeterminate biliary lesion diagnosis using endobiliary forceps biopsy *via* DOC. That study also reported additional accuracy for detection of mucosal cancerous extension in the bile duct with POCS: In fact, the accuracy rate of ERCP alone in verifying the presence or absence of mucosal cancerous extension was 73.5%, in comparison to an accuracy rate of 92.9% for ERCP with POCS plus biopsy. However, as the authors acknowledged, that prospective study had the same bias concerning the non-randomized selection of

patients and the fact that most of the targeted patients had already a bile duct cancer diagnosis: Those aspects could explain the high rate of accurate diagnosis of the study. A video endoscope and a disposable access catheter using fiberoptics (SpyGlass system; Boston Scientific, MA, United States) enable the SOC modality[16].

Since the launch of the first-generation SpyGlass system, in 2007, several studies have reported increasing sensitivity and accuracy with the addition of its direct endoscopic visualization of the bile duct to ERCP or tissue sampling [17-19]. However, the mean sensitivity of biliary sampling, using the dedicated biopsy forceps (SpyByte), for discriminating between malignant and benign biliary lesions was only slightly superior (68%) to that of the other conventional sampling modalities (Figure 2).

The initial version of SpyGlass was fiberoptic and the optical probe was reusable. Since 2015, a new digital single-operator/single-use instrument (SpyGlass DS; Boston Scientific, MA, United States) has been available. This 2nd generation system does not require to be reprocessed to avoid the issue of potential image degradation with repeated use. In 2016, a prospective multicenter study in Japan enrolled 148 patients with a collection of pancreaticobiliary diseases (124 with biliary disease). This work reported a SpyGlass targeted biopsy sensitivity of 81.4% and an accuracy of histologic diagnosis in indeterminate biliary strictures of 70.7%[20].

Direct cholangioscopy employing is questionable because of the same safety issue related to the occurrence of rare but life-threatening adverse events such as stroke caused by leakage of air into the portal or hepatic venous system[21], biliary perforation, and slightly higher incidence of postprocedural cholangitis[22].

Intraductal ultrasound-guided biopsy

IDUS involves the insertion into the bile duct of a high-frequency ultrasound ultrathin probe, generally over a wire. It provides high-resolution images of the ductal wall and periductal tissues[23]. Potentially, IDUS could be an important diagnostic tool in the evaluation of the indeterminate biliary strictures in whom is not possible to obtain a diagnosis despite previous evaluations. ERCP with IDUS examination, if performed by an expert endoscopist trained in both EUS and ERCP, helps to identify patients with a high suspicious of MBS[1] better than EUS does, particularly for lesions located at the hilum or mid-bile duct[23,24]. Several studies[25-28] reported high diagnostic sensitivity and specificity of IDUS during ERCP in differentiating malignant from benign strictures. Since IDUS provides real-time, high-resolution images of the bile duct wall and the adjacent structures[27], it is an ideal tool to use before biliary stenting. Unfortunately, this modality is not widely used because of the lack of ERCP operators who are also skilled in EUS. IDUS is also limited by the lack of a specific sampling modality.

Consequently, based on those aspects, two studies have investigated the performance of IDUS-guided biopsy sampling[29,30]. In these two works the ultrasonic probe is inserted into the bile duct over the wire after endoscopic sphincterotomy until IDUS recognize the suspected MBS. While maintaining the ultrasonic probe on the narrowest position to the stricture, a conventional biopsy forceps is inserted into the orifice of the papilla to the tip of the placed ultrasonic probe under fluoroscopic guidance. During the trans-papillary biopsy forceps sampling the scanning ultrasonic probe is keep at the nearest intraductal position.

Jong *et al*[29] reported a higher sensitivity for cancer diagnosis of indeterminate biliary strictures (87% with IDUS-guided biopsy in comparison to 67% with fluoroscopically trans-papillary guided biopsy).

Similarly, Kim *et al*[30] designed a prospective randomized study on the accuracy of IDUS-guided trans-papillary biopsy and conventional biopsy on fluoroscopy in suspected MBS and 65 out of 72 patients enrolled in the study underwent ERCP with IDUS.

The accuracy of IDUS-guided trans-papillary biopsy for MBS is significantly higher than conventional trans-papillary biopsy (90.8% *vs* 76.9%) in cases with intraductal infiltrating lesions, which were the most common findings on IDUS (47.5%). There was no significant difference in cancer detection rate according to the location of the stricture, as well as any significant improvement of cancer detection rates was reported in cases with extrinsic compressed lesions. This study reported no significant procedure-related adverse events (only two mild cases of hemobilia after trans-papillary forceps biopsy).

However, to date, there are no dedicated accessories that combine IDUS and forceps biopsy, thus IDUS-guided trans-papillary forceps biopsy is more challenging than conventional sampling modalities for the risks of bile-duct trauma. New types of IDUS probes or accessories for IDUS-guided trans-papillary forceps biopsy, as well as larger studies for validation, are expected.

Interventional radiology techniques

In cases in which the endoscopic approach to biliary strictures has failed or is deemed difficult or impossible due to unfavourable anatomy (*e.g.*, in cases of surgical interventions as hepatico-jejunostomy), their cyto-histological assessment can be performed with percutaneous transhepatic endobiliary brushing and/or forceps biopsy (PTEFB)[31].

Percutaneous transhepatic endobiliary sampling of biliary strictures/obstructions is usually performed after local anaesthesia and during conscious sedation, under fluoroscopic guidance, through a biliary drainage access, before drainage positioning, both from the right or left liver lobe based on stricture/obstruction location, even though right intercostal approach is preferred for positional

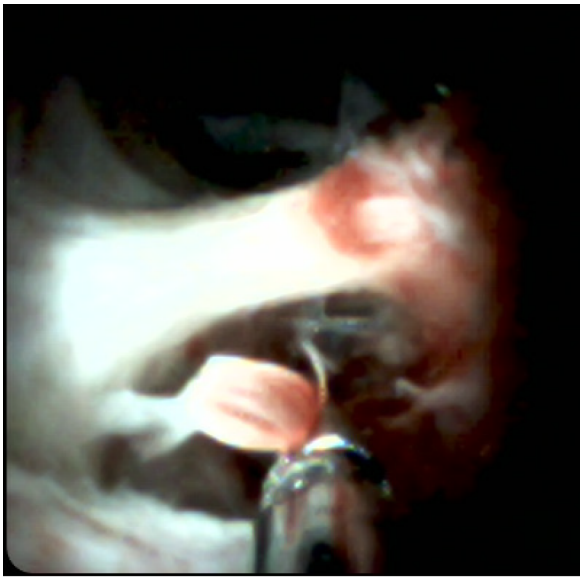

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Figure 2 Endobiliary biopsy performed using the dedicated biopsy forceps (SpyByte™), under PerOral Cholangioscopy.

advantage and operator easiness. Periprocedural broad-spectrum antibiotic coverage is recommended. In cases of occurrence of hemobilia or cholangitis after percutaneous transhepatic biliary access, the sampling should be delayed 24-48 h[32,33]. Cholangiography-guided detection of the stenosis/obstruction is obtained and, after passing through the stricture with a guide-wire and positioning a 6-8F introducer sheath in the biliary ducts, the sampling procedure can be performed.

In cases of brushing, a flexible probe with a brush on an atraumatic tip is introduced through the sheath up to the stricture and then is pushed and pulled and rotated under fluoroscopic guidance multiple times[34].

In case of PTEFB, a careful and accurate forceps biopsy is performed advancing the forceps through the introducer sheath. Patel *et al*[35] described a variant of this technique, the so-called "cross and push", in which the introducer sheath is advanced on a guidewire into the stricture/obstruction and is used to push the biopsy forceps granting greater stability of the forceps and allowing to obtain a larger lesion sample. Multiple samples should be taken, if possible, to obtain greater true-positive rates[36]. A bile sample after the brushing/biopsy (as much as 10 milliliters) should be always taken for bile cytology, as it demonstrated to have up to a 34% of sensitivity, which increases to 52% in case of multiple and seriate samplings[37,38]. In the case of forceps biopsy, a transhepatic cholangiography should be always performed to evaluate contrast medium leak from the bioptic site.

Cyto-histologic diagnosis of the sample obtained with the biopsy must always be confirmed after the surgical excision or, in case of benign disease diagnosis or non-specific findings, after dimensional stability of the lesion at a close follow-up. Redo-sampling should be performed in cases of a negative histological result, particularly in patients with high suspicion of malignancy, and in cases in which the operator deemed the first histological specimen inadequate for evaluation, as the fibrotic and scirrhous tissue which associates to cholangiocarcinoma and pancreatic carcinoma, in addition to necrotic and inflammatory changes, can hinder a correct diagnosis, even though Rabinovitz *et al*[436] reported that biopsies repeated three or more times yielding only negative results should reduce the probability of malignancy to 0%; it is mandatory, however, to perform a strict imaging and laboratory follow-up in these patients.

Percutaneous transhepatic endobiliary brushing demonstrates sensitivity rates ranging from 26 to 67%, and low negative predictive values (around 12.5%). Noticeably, Xing *et al*[39] reported a superior sensitivity value of 75% with greater sensitivity in cases of cholangiocarcinoma *vs* other strictures ($P < 0.05$) while stricture location had no effect on brushing sensitivity[32,34,40-43].

Overall percutaneous biliary forceps biopsy sensitivity has been attested between 55.8 and 93.3%, with a higher sensitivity for cholangiocarcinoma (up to 94%)[33,35,40,41,44-47]. Augustin *et al*[44] performed PTEFB in 13 patients, with at least 3 samples of 1-2 mm per patient, and in 92.3% of cases the material was deemed sufficient for histological analysis; PTEFB had sensitivity and accuracy rates of 88.9% and 92.3% respectively.

Jung *et al*[33] performed 130 PTEFB obtaining a 78.4% sensitivity rate. Park *et al*[48] retrospectively reviewed 271 PTEFB, finding 77.2% of sensitivity and 78.9% of accuracy. Patel *et al*[35] with their abovementioned "cross and push" technique performed in 52 patients obtained a sensitivity of 93.3%. Inchingolo *et al*[47] prospectively performed 30 PTEFB in 29 patients, with the "cross and push" technique, obtaining a sensitivity rate of 91.67% and an accuracy rate of 92.59%. Boos *et al*[40] described

better sensitivity rates when forceps biopsy and brush cytology were combined in a tandem approach (55.8% *vs* 40.6% of forceps biopsy alone); while this procedure can be considered expensive when compared to the use of forceps biopsy alone, it is cost-effective when compared to performing two separate procedures in case of an initial negative histological sample; however randomized studies comparing the sensitivity of the two approaches (single and tandem) should be performed. The tandem approach must be distinguished from obtaining a smear from forceps biopsy for cytological analysis [41].

PTEFB can be also performed under cholangioscopic/choledochoscopic guidance, which gives the operator the ability to directly visualize and target the pathologic tissue (Figure 3). After adequate sequential dilation of the transhepatic tract (with an introducer sheath of up to 11-16 F *vs* 7-8 F of fluoroscopy-guided PTEFB) a scope is positioned over a stiff guidewire and the forceps are inserted through its working channel. This approach has sensitivity and specificity exceeding 95% for diagnosing biliary malignancies despite its greater costs when compared to fluoroscopy-guided PTEFB and the need for specialized equipment and expertise[32,42,49,50]. Due to the diameter of the cholangioscope and the risk of hemobilia after first puncture of the biliary ducts, percutaneous tract "maturation" for one week or more after placement of a 8-10 French biliary drainage is recommended to avoid hemorrhage and prevent peritonitis due to extra-hepatic bile leak, as well as progressive oversizing of the biliary tube reduces the subsequent trauma from cholangioscope insertion[51]. Flexible endoscopes are preferred over the rigid ones due to their smaller diameter, better control and wider view; in addition, long endoscopes should be preferred, particularly in case of lesions in the distal common bile duct or in the contralateral ducts. Complication of transhepatic cholangioscopy include cholangitis, hemobilia, biloma or abscess formation, but in half of cases are related to the initial access and tract dilation, and can be avoidable with tract maturation[52].

Among percutaneous transhepatic biopsy approaches, Schechter *et al*[55] reported the use of the Simpson atherectomy catheter, with a sensitivity of 79% but 11% of hemorrhages, high costs, and difficulties in passing through angled transhepatic tracts.

On the other hand, Rossi *et al*[34] described the diagnostic yield of sampling the balloon surface in patients with strictures which needed bilioplasty, reporting a sensitivity of 87.5%.

Various authors reported great diagnostic sensitivity of PTEFB in strictures of the upper biliary tree (up to 92%), whereas Ierardi *et al*[56] reported lower sensitivity for lesions of the hilum and common bile duct as compared to the common hepatic bile duct and ampulla[33,35,42,54,55]. Overall, the PTEFB procedure does not have severe technical difficulties, therefore the learning curve is reported to be steep, with only a few cases needed to master the technique[47].

In terms of safety, PTEFB yielded low rates of complications, the most common being transient hemobilia, postprocedural cholangitis, transient bile leakage, and less often, the formation of biloma in the bioptic site, which were promptly treated with percutaneous drainage[33,35,44,45,47].

Other complications were related to the percutaneous puncture and not to the sampling procedure itself, ranging from subcapsular biloma to hepatic hematoma to pseudoaneurysm formation[35,56].

The main limitation of PTEFB is linked to the diagnosis of extra-biliary neoplasms determining biliary obstruction and which have not infiltrated yet the biliary duct walls (*e.g.*, hepatic hilum lymph-nodal metastasis, tumor infiltration/compression), due to the limited tissue samples, determining false-negative results both during surgical inspection or at follow-up[57]. Among metastatic tumor-related extrinsic biliary compression, the prospective analysis from Estrella *et al*[58] demonstrated that metastases from colorectal cancer more commonly present with intrabiliary growth when compared to other tumors (10.6 *vs* 1.9%). Another limitation is represented by the intrinsic characteristics of the forceps, which can cause "crush" artifacts of the bioptic specimen, represented by the degradation of the specimen during the bioptic maneuver, that can hinder the diagnosis[35].

Discussion

The diagnostic approach (Table 1) and correct histologic identification of a biliary stricture can be a demanding issue, while first-line non-invasive diagnostic methods alone cannot confirm the diagnosis of MBS in most of the cases. Moreover, pathological diagnosis is mandatory for the decision on the therapeutic approach. Therefore, it is crucial to establish the optimal sampling modality to confirm the diagnosis. According to current literature, both PTC and ERCP forceps biopsy are sensitive and accurate sampling modalities for suspected MBS.

Chang *et al*[45] retrospectively compared a group of 38 patients undergoing PTEFB and brushing with a group of patients undergoing endoscopic trans-papillary biopsy; PTEFB had a sensitivity of 86.7% compared to the 77.1% of endoscopic biopsy, especially for biliary strictures located at the hilum. Mohkam *et al*[46] retrospectively compared 75 PTEFB with patients who underwent endoscopic trans-papillary biopsy and PTEFB demonstrated sensitivity rate of 69%, similar to endoscopic biopsy (75%, P = 0.45). The choice of biliary strictures that more suitable for endoscopic rather than a percutaneous biopsy seems to mainly depend on the anatomical location and type of stricture.

Several studies[45,54] demonstrated that PTEFB is correlated with high diagnostic sensitivity for strictures located in the upper biliary tree, distant from the papilla – where endoscopic biopsy has better sensitivity. Particularly, Chang *et al*[45], reported higher sensitivity for PTEFB in hilum lesions than those located within the common bile duct. According to the authors, sensitivity was higher for

Table 1 Tools for endobiliary biopsy sampling

Endoscopic techniques		
	Advantage	Disadvantage
ERC + TPB	Safeness, feasibility and large availability; better sensibility for MBS versus brushing	Low sensitivity for MBS (48%), difficulty of cannulation with standard biopsy forceps, not easy targeting of the lesion
ERC + TPB with C-BF	Slight better sensibility (60%) for MBS respect to conventional biopsy forceps	Sampling benefits limited to lesions located to the right intrahepatic bile duct (75%)
Cholangioscopy + endobiliary biopsy	Gain in accuracy for diagnosis of malignancy in indeterminate lesions (85-92%) versus ERCP + TPB	Same safety; issue with direct cholangioscopy related to rare adv events (leakege of air in to portal vein)
IDUS + TPB	Higher sensitivity for malignancy in indeterminate intraductal lesiones (87-91%) versus ERCP + TPB	Advanced experience in both ERCP/EUS requested, lack of standardized procedure and specific devices, time-consuming technique
Interventional radiology techniques		
	Advantage	Disadvantage
PTE endobiliary brushing	Safe, cheap and large availability;	Low sensitivity for MBS
PTE endobiliary biopsy	High sensitivity; Larger biopsy cup comapred to ERC + TPB	Indirect visualization of the lesion
Colangioscopy + PTEFB	Direct visualization of the lesion;	Combined procedure with endoscopist; Expensive procedure; small size specimen

TPB: Trans papillary biopsy; IDUS: Intraductal ultrasound; ERC: Endoscopic retrograde cholangiography; PTEFB: Percutaneous transhepatic endobiliary brushing and/or forceps biopsy; C-BF: Controllable biopsy-forceps; EUS: Endoscopic ultrasonography.

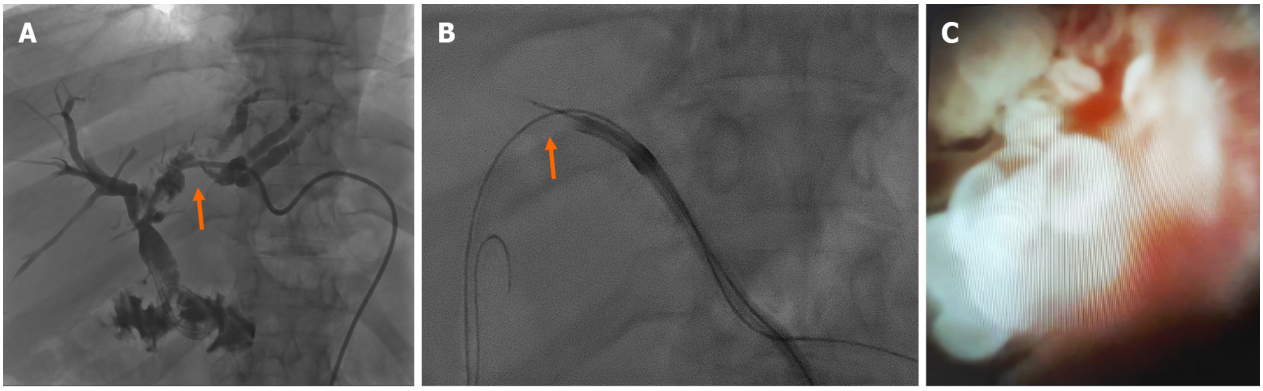

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Figure 3 Endobiliary biopsy performed using the dedicated biopsy forceps (SpyByte™), under Perctaneous Cholangioscopy. A 63 year female, with history of Whipple's procedure 20 years before. A: Cholangiography revealed multiple endoluminal defects (red arrow); B: Endobiliary biopsy using SpyByte, under fluoroscopy and cholangioscopy; C: Histological examination revealed intestinal metaplasia of the biliary mucosa.

strictures located close to the hilum. On the contrary, compared to PTC, ERCP resulted in higher accuracy for lower strictures. In this setting, the distance between the site of biliary stricture and the device used to push and maneuver the biopsy forceps seems to play a key role: the greater the distance, the lesser the precision of sampling. Therefore, specimen sampling of the biliary strictures located proximal to the hilum should ideally be performed *via* PTEFB, while for strictures located at the hilum or more distally, ERCP should be preferred. Other factors influencing the effectiveness of endobiliary biopsy are insufficient space for forceps opening noted in cases of severe strictures, lesions located at sites with marked angulation, lesion shape, and of course local expertise, and device availability.

CONCLUSION

Both ERCP and PTC endobiliary biopsy remain valid methods for tissue identification demonstrating satisfactory diagnostic accuracy, especially in properly selected lesions. Novel slim biopsy forceps and new endobiliary sampling modalities such as POCS, and IDUS-guided biopsy, currently under investigation, seem to improve the efficacy of histologic characterization.

FOOTNOTES

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MINIREVIEWS

Lessons learned: Preventable misses and near-misses of endoscopic procedures

Alla Turshudzhyan, Houman Rezaizadeh, Micheal Tadros

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Abstract

Endoscopy is a complex procedure that requires advanced training and a highly skilled practitioner. The advances in the field of endoscopy have made it an invaluable diagnostic tool, but the procedure remains provider dependent. The quality of endoscopy may vary from provider to provider and, as a result, is not perfect. Consequently, 11.3% of upper gastrointestinal neoplasms are missed on the initial upper endoscopy and 2.1%-5.9% of colorectal polyps or cancers are missed on colonoscopy. Pathology is overlooked if endoscopic exam is not done carefully, bypassing proper visualization of the scope's entry and exit points or, if exam is not taken to completion, not visualizing the most distal bowel segments. We hope to shed light on this issue, establish areas of weakness, and propose possible solutions and preventative measures.

Key Words: High-quality colonoscopy; Esophagogastroduodenoscopy; EGD; Cancer screening; endoscopy; Missed lesions

Core Tip: Endoscopy has become a widely used diagnostic tool and plays an instrumental role in screening and surveillance of gastrointestinal pathology. Despite its wide acceptance, it remains provider dependents and, as a result, is not perfect. Both upper and lower endoscopy have weaknesses and shortcomings unless executed flawlessly. A high-quality endoscopy includes a complete examination of the bowel, including distal segments that are difficult to visualize, as well as scope's entry and exit points. Better understanding of the shortcomings of endoscopy may help change training and improve physician awareness.

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INTRODUCTION

Today, endoscopy is considered one of the best diagnostic tools for screening and surveillance of gastrointestinal pathology. Since the beginning of the 21st century, endoscopy use has risen by more than 50%[1]. With wider utilization of endoscopy, it has become more and more evident that the procedure quality is multifactorial and operator dependent[2]. Consequently, lesions may be missed depending on the level of provider training, procedural skills, and attentiveness to subtle pathology. This prompted development of several quality metrics to provide guidance for operators[3-7]. Despite proposed quality metrics, there is still a significant number of missed gastrointestinal cancers. A meta-analysis by Menon *et al*[8] suggested that 11.3% of upper gastrointestinal (UGI) neoplasms are overlooked on the initial upper endoscopy (EGD). Around 2.1%-5.9% of colorectal polyps or cancers are missed on colonoscopy[9]. The difference likely stems from the fact that endoscopic training has historically put emphasis on colorectal cancer prevention and screening, while there is usually less awareness around UGI neoplasms.

It should be noted that aside from neoplastic lesions, bleeding sources can be missed on endoscopy and only seen on repeat examination in patients with unexplained occult GI bleed or iron deficiency anemia with negative diagnostic work up[10]. Missed lesions on endoscopy are a common reason for malpractice lawsuits[11], which further emphasizes the importance of quality improvement. Some of the common reasons for why pathology is overlooked are a hastily performed endoscopy that bypasses proper visualization of the scope's entry and exit points, not taking endoscopic exam to completion, and not visualizing more distal bowel segments.

REVIEW

Using our personal experience with 4 patients who had lesions missed or near missed on endoscopy, we hope to expose some of the weaknesses and shortcomings of endoscopy. Our goal is to bring the attention of other gastroenterologists to these commonly missed areas that may go undetected.

Case 1

The first patient was a 72-year-old male who presented with symptoms of dysphagia. The initial EGD was unrevealing. It was only after the second EGD that a flat squamous cell carcinoma was appreciated 2 cm below the upper esophageal sphincter (UES) (Figure 1A, Figure 2A). The lesion was missed on the initial scope insertion and was likely missed because of a rapid scope withdrawal.

Case 2

The second patient was a 40-year-old female with iron deficiency anemia requiring multiple blood transfusions. The patient had undergone multiple upper and lower endoscopies and a capsule study, all of which were unrevealing. It was only after the 4th portion of the duodenum was examined that a malignant gastrointestinal stromal tumor was identified, diagnosed, and resected (Figures 1B and 2B).

Case 3

The third patient was a 50-year-old female who presented with ongoing diarrhea. Stool studies revealed cryptosporidium. Fortunately, the patient's colonoscopy included examination of the terminal ileum and was able to detect a small submucosal carcinoid tumor (Figures 1C and 2C). It was successfully resected with metastatic disease noted in only one lymph node.

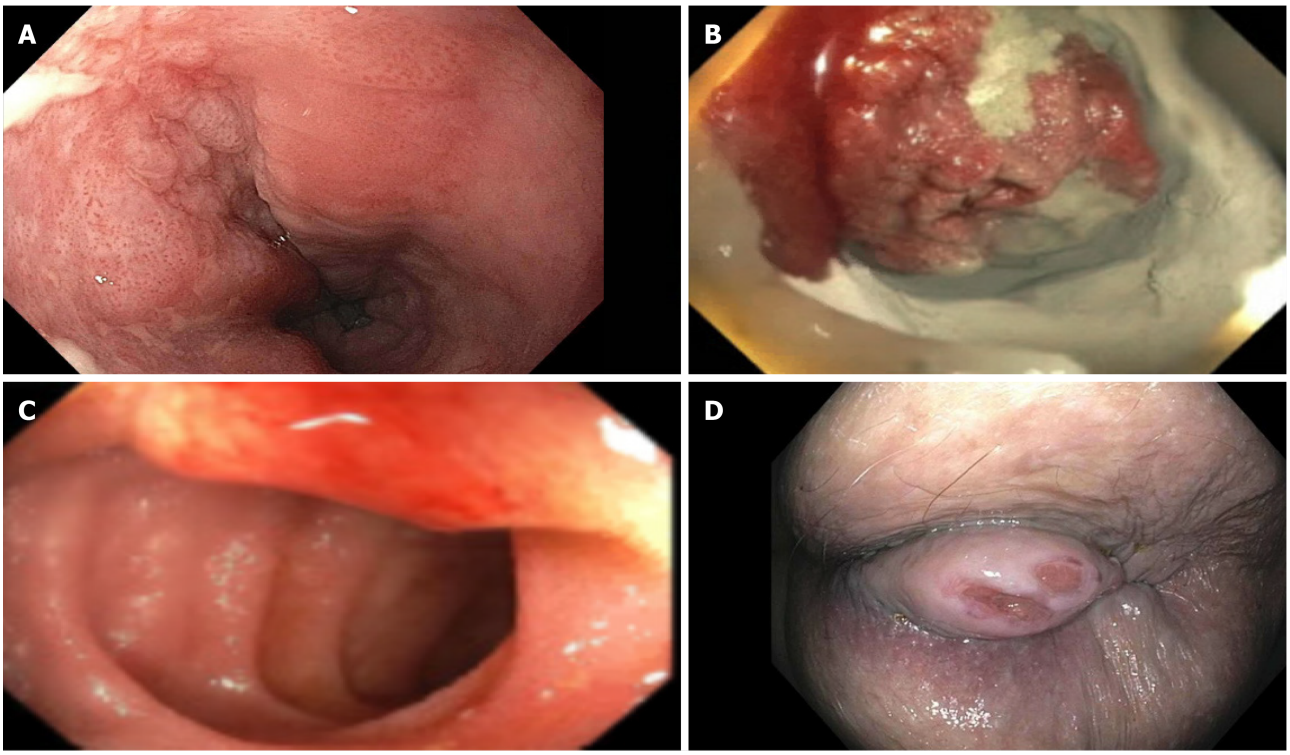

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Figure 1 Endoscopic visualization of the lesions near missed. A: Subtle flat squamous cell carcinoma was appreciated 2 cm below the upper esophageal sphincter; B: Malignant gastrointestinal stromal tumor treated with hemospray in proximal jejunum; C: Small submucosal carcinoid tumor in terminal ileum; D: 2 cm anal squamous cell cancer noted on rectal exam.

Case 4

Our last patient was a 68-year-old with a history of cirrhosis and recurrent bright red blood per rectum. She had 2 colonoscopies done to find the bleeding source, both were unrevealing. It was months later that the patient had a 2 cm anal growth examined and diagnosed on careful retroflexion. The anal lesion was then seen on a reinspection of the anal area. (Figures 1D and 2D).

DISCUSSION

Increasing awareness of the bowel segments at risk for being missed on endoscopy is important. Similarly, it is important to incorporate technical maneuvers that could help identify these challenging lesions into fellowship training and post-graduate courses to help practicing endoscopists (Tables 1 and 2)[10]. Lastly, following the most recent endoscopy quality metrics will help improve the detection of challenging lesions.

Colonoscopy

A complete colonoscopy should include a thorough exam of the endoscope's entry point (anal canal), all segments of the colon, and, if possible, the distal ileum. We are going to discuss distal to proximal bowel segments as visualized on colonoscopy and use it as a framework to go over commonly missed lesions for each segment along with maneuvers and techniques that can help detect them.

Anorectum: Some of the commonly missed lesions in anorectum are anal and rectal cancer, anal fissures, recto cutaneous fistulas, anal warts (Table 1)[10]. This is likely because of the scopes entry point being overlooked or not property visualized at the beginning of the procedure. The importance of anal examination by a skilled endoscopist if further emphasized by the fact that anorectal lesions can have a non-specific presentation and may go undiagnosed by patient's primary care physician. Chiu *et al*[12] found that only 54% of patients have a rectal examination by their primary care provider when they present with a non-specific anal complaint. Another study indicated that only 23% of patients presenting with anal complaint were diagnosed correctly by their primary care provider; the remaining patients were erroneously diagnosed with hemorrhoids[13]. As a result, this leads to delay in diagnosis and management of anal and rectal cancers. As proposed by quality metrics, digital rectal exam needs to be performed and thoroughly documented prior to colonoscopy (Table 2)[11]. Another maneuver that

Table 1 Commonly missed lesions requiring second-look colonoscopy[10,14-16] or upper endoscopy[10,20,24]

Bowel segment	Lesions missed	Intervention to improve lesion detection
Anorectum	Anal/rectal cancers	Careful anorectal exam before and on scope insertion with retroflexion
	Anal fissures	
	Recto-cutaneous fistulas	
	Anal warts	
Colon	Lesions in colonic folds (particularly sigmoid)	Careful exam between the folds of the colon, especially in sigmoid segment, consider using a cap
		Excellent, good, or adequate bowel preparation, supported by photography
	Right colon	Second look
		Retroflex in right colon
	Cecum (especially behind IC valve)	Document examination
		Examine behind the ileocecal valve
		Cecal intubation rate
Terminal ileum	Lesions in ileum	Intubate in the terminal ileum
Esophagus	Below UES lesions, *i.e.*, squamous cell carcinoma	Careful examination of upper esophagus, slow scope withdrawal
	Distal esophagus, collapsed varices in volume depleted patient	Careful examination of distal esophagus and awareness of patient's volume status
	Subtle lesions of Barrett segment	Adequate time for examination of the segment
Stomach	Cameron lesions, gastro-esophageal junction (especially challenging to detect/examine with large hiatal hernias)	Careful examination of gastro-esophageal junction and diaphragmatic hiatus with retroflexion of the scope
	Arteriovenous malformation, Dieulafoy's lesions	Careful inspection between the gastric folds using a cap
Small bowel	Duodenal bulb	Examine all 4 walls of the duodenal bulb and
	Duodenal sweep	May need to use of a side view scope
	3rd and 4th part of the duodenum	Advance scope by reducing the loop into 3rd and 4th parts of duodenum

UES: Upper esophageal sphincter.

could be used to enhance detection of challenging lesions in anorectum is retroflexion. It allows for a better visualization of distal rectum and distal anus (Table 1)[14]. Retroflexion needs to be photographed and documented[11].

Colon: Some of the commonly missed lesion of colonic segment include lesions found inside the colonic folds (especially in sigmoid colon), right-sided colon, cecum [especially behind the ileocecal (IC) valve], and distal ileum (Table 1). There are a few techniques that can be implemented to facilitate detection of these challenging lesions (Table 1). Endoscopists should do a thorough examination between the haustral folds to avoid missing even large polyps that can hide inside the folds. Cap-assisted colonoscopy is another acceptable option as it involves a transparent attachment at the end of the scope that can improve adenoma detection rate (ADR) by flattening of the haustral folds and improving visualization of mucosa, especially on scope withdrawal[15].

Second look examination of the right side of the colon can help reduce the rate of cecal lesions missed [16]. Retroflexion in the right colon is another maneuver that can enhance visualization of right-sided lesions and improve ADR[14,16]. It entails bending of the scope in a *U*-turn such that viewing lens is facing backwards[14].

Cecum intubation is a very important skill and a quality measure that can enhance visualization of the cecum and identify lesions that are oftentimes missed. Additionally, endoscopists should pay particular attention to the mucosa behind the IC valve. Documentation of cecal landmarks is crucial.

All maneuvers discussed need to be thoroughly photographed and documented in the procedure description per the colonoscopy quality metrics (Table 2). Quality metrics further require bowel preparation to be excellent, good, or adequate and supported by photography and withdrawal time

Table 2 Quality metrics for endoscopic procedures[11,20,21,23,24]

Colonoscopy	EGD
High quality bowel preparation (excellent, good, or adequate), documented with photos	At least 1 min of inspection per centimeter of circumferential segment of Barrett's esophagus
Digital rectal examination prior to colonoscopy with results documented	NDR record should be considered
	When evaluating for gastric intestinal metaplasia, 5 or more biopsies need to be taken
Cecal intubation performed, landmarks noted in documentation and photos recorded	Overall, EGD evaluation for gastric intestinal metaplasia has to last 7 min or more
Withdrawal time is 6 min or more	
Retroflexion, if performed, is thoroughly documented (with photographs)	
Endoscopists ADR exceeds recommended thresholds. Physician participates in quality-improvement and continues to measure individual ADR	

EGD: Endoscopy; NDR: Neoplasia detection rate; ADR: Adenoma detection rate.

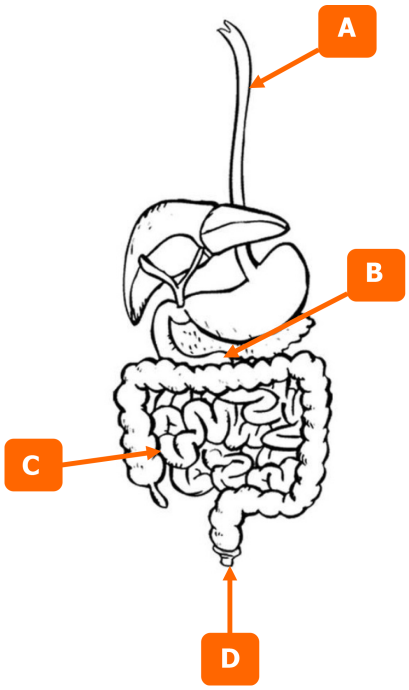

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Figure 2 Gastrointestinal tract segments at risk for having lesions missed. A: Upper esophageal sphincter; B: Proximal jejunum; C: Terminal ileum; D: Anus.

should be noted in documentation and exceed 6 minutes[11]. It is also encouraged that practicing endoscopist's adenoma detection rate (ADR) exceeds recommended thresholds. Physicians should routinely measure their ADR and participate in quality improvement programs[11].

The optimal withdrawal time for colonoscopy remains an important topic. A 6-minute withdrawal time was accepted, but a recent meta-analysis by Bhurwal *et al*[17] of 69551 patients compared withdrawal time of 6 *vs* 9 min in its ability to detect adenomas. They found that odds ratio for ADR was significantly higher at 1.54 for colonoscopies with withdrawal time of 9 min or more[17].

Terminal ileum: Lesions can be missed in terminal ileum as many colonoscopies do not investigate this bowel segment. It is important to note that the ileum is the most common site for development of carcinoid tumors (57%) and that even primary ileal tumors are missed on computer tomography (CT) scans in 64% of cases[18-20].This emphasizes the importance of a thorough and complete endoscopic exam that may detect primary ileal tumors early and allow for timely intervention[20]. Endoscopists should try to intubate the terminal ileum whenever feasible.

Upper endoscopy

A complete EGD should entail a thorough exam of the esophagus, including the UES, point of entry into the stomach, other poorly visualized areas of the stomach, along with all segments of the duodenum. We are going to discuss distal to proximal bowel segments as visualized on EGD and use it as a framework to go over commonly missed lesions for each segment along with maneuvers and techniques to help detect them.

Esophagus: Some of the most commonly missed esophageal lesions are immediately below the UES and lesions in the distal esophagus (such as collapsed varices in a volume depleted patient or subtle changes of Barrett's segment) (Table 1)[10]. Some possible interventions to facilitate detection of challenging lesions are careful examination of the full length esophagus paying particular attention to upper and lower most segments, being aware of patient's volume status, and allotting adequate time for examination of the segment (Table 1). Quality metrics for Barrett's segment inspection time call for 1 minute inspection time per cm of circumferential length[21]. Longer inspection time results in a more careful visualization of the mucosa and subsequently increase chances of detecting pathology[21]. Another quality metric that is being proposed when examining esophagus is neoplasia detection rate (NDR)[22]. Like ADR for colonoscopy, it is important to keep track of NDR for EGD when examining for Barrett's segment, because it reflects the quality of inspection[22].

Stomach: Some of the common gastric lesions missed on EGD are Cameron lesions, lesions around gastro-esophageal (GE) junction (especially with large hiatal hernias), arteriovenous malformations, Dieulafoy lesions (Table 1). Some interventions that can be done are careful inspection of GE and diaphragmatic hiatus with retroflexion of the scope, inspection between gastric folds using the previously discussed cap-assisted endoscopy (Table 1)[23]. One of the EGD quality metrics that is important to remember is adequate number of gastric biopsies, which should be greater or equal to 5 [24]. Timing is another important quality metric. Examination time during EGD when looking for intestinal metaplasia should be longer than 7 min, because longer inspection implies a more careful exam and results in a higher rate of neoplasia detection[25]. Park *et al*[25] observed that slow endoscopists (defined as withdrawal time of more than 3 min) were better at detecting neoplastic lesions (0.28%) compared to fast endoscopists (0.20%). As a result, they proposed that examination time could be a surrogate measure for the procedure quality[25]. Another study identified that endoscopist who takes more than 7 min to complete exams is more likely to detect a high-risk gastric lesion when compared to a fast endoscopist[26]. Given heterogeneity of data between the two studies, it is difficult to draw conclusions regarding the optimal examination time. This is further complicated by the fact that longer endoscopic times are associated with cardiac arrythmias, esophageal tears, aspiration, and bacterial translocation[27].

Incidence of gastric pathology varies in different countries. There is higher prevalence of gastric cancer in Eastern countries. Consequently, this led to increased awareness of gastric lesions and a more robust screening protocols in countries like Japan[28]. In Japan, it is recommended to undergo annual upper endoscopy for anybody over the age 40. As a result, there are more early-stage gastric lesions (53%) identified when compared to United States (27%)[29,30]. This shows that increased awareness and adequate training can improve subtle lesion detection.

Duodenum

Some of the commonly missed segments of the small bowel are duodenal bulb, duodenal sweep, and 3rd and 4th parts of the duodenum (Table 1). Some of the maneuvers that can help detect these challenging lesions are careful examination of all 4 walls of the duodenal bulb, use of a side view scope for the duodenal sweep, advancement of the scope by reducing the loop into the 3rd and 4th parts of duodenum (Table 1). Many upper endoscopies do not go past the 2nd part of the duodenum. Lesions in more distal segments of the duodenum (3rd and 4th) are usually more challenging to visualize and require an extra-long fiber optic scope and a trained endoscopist[31]. Interestingly, 60% of benign duodenal lesions and 50% of malignant duodenal lesions are only diagnosed on autopsy and missed on the endoscopic exam [32].

TRAINING

As we learn more about common pitfalls and shortcomings of endoscopy, training fellows to recognize them becomes the next key step. It is important to standardize best practices and shed light on the areas commonly missed in colonoscopy training[33]. One of the studies even suggested that pre-fellowship exposure to best practices of endoscopy, can improve the learning period and procedural skill of fellows [34].

ARTIFICIAL INTELLIGENT in ENDOSCOPY

Endoscopy continues to be an operator dependent procedure. As such, it presents a growing opportunity for development of machine learning technology and computer algorithms to assist endoscopists with lesion detection. Artificial intelligent (AI) has a promise to improve accuracy of endoscopic procedures, reduce inter-operator variability, and compensate for human error and factors contributing to it such as fatigue or limited experience[35]. Thus far, computer-aided detection algorithms of AI have been trained to detect lesions both macroscopically and by optical biopsy/microscopically[36]. Recent studies demonstrated that AI performed better than endoscopists in esophageal cancer and neoplasm detection in pooled sensitivity 94% *vs* 82%, respectively[37]. The specificity of AI-based endoscopy had specificity of 85% for esophageal cancer and neoplasms[37]. AI-based endoscopy provided a 26.5% increase in sensitivity for detection of early gastric cancer when compared to endoscopists (sensitivity of 95%)[38]. The specificity of AI-based endoscopy had specificity of 87.3% for early gastric cancer[38]. AI algorithms have also been targeted towards colorectal cancer detection. Recent reports suggest that AI-assisted colonoscopy has sensitivity of 94% [39,40]. While some reports suggest that AI may not show significant improvement in larger polyp detection rate (38.8% *vs* 26.2%), AI-based colonoscopy showed significant improvement in detection of small and flat polyps that are easily missed (76.0% *vs* 68.8% and 5.9% *vs* 3.3%, respectively)[41].

CONCLUSION

Endoscopy has developed into a sophisticated diagnostic tool that provides great accuracy in lesion detection, but it is not perfect and remains operator dependent. The cases we presented expose weaknesses and shortcomings of endoscopic examination for both the upper and lower gastrointestinal tract, providing an opportunity for improvement. Commonly missed areas and the reason for why they were missed need to be communicated to currently practicing gastroenterologists. Additionally, educating fellows during their training on the possible shortcomings and weaknesses of endoscopy may help improve the quality of procedures in the future.

FOOTNOTES

Author contributions: Turshudzhyan A wrote the letter, Rezaizadeh H and Tadros M critically revised the manuscript.

Conflict-of-interest statement: Rezaizadeh H has financial interest associated with AstraZeneca and research funding/interest associated with Celgene/Bristol Meyers Squibb.

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ORIGINAL ARTICLE

Retrospective Study

Recognition of esophagitis in endoscopic images using transfer learning

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Abstract

BACKGROUND

Esophagitis is an inflammatory and damaging process of the esophageal mucosa, which is confirmed by endoscopic visualization and may, in extreme cases, result in stenosis, fistulization and esophageal perforation. The use of deep learning (a field of artificial intelligence) techniques can be considered to determine the presence of esophageal lesions compatible with esophagitis.

AIM

To develop, using transfer learning, a deep neural network model to recognize the presence of esophagitis in endoscopic images.

METHODS

Endoscopic images of 1932 patients with a diagnosis of esophagitis and 1663 patients without any pathological diagnosis provenient from the KSAVIR and HyperKSAVIR datasets were splitted in training (80%) and test (20%) and used to develop and evaluate a binary deep learning classifier built using the DenseNet-201 architecture, a densely connected convolutional network, with weights pretrained on the ImageNet image set and fine-tuned during training. The classifier model performance was evaluated in the test set according to accuracy, sensitivity, specificity and area under the receiver operating characteristic curve (AUC).

RESULTS

The model was trained using Adam optimizer with a learning rate of 0.0001 and applying binary cross entropy loss function. In the test set (n = 719), the classifier achieved 93.32% accuracy, 93.18% sensitivity, 93.46% specificity and a 0.96 AUC. Heatmaps for spatial predictive relevance in esophagitis endoscopic images from

the test set were also plotted. In face of the obtained results, the use of dense convolutional neural networks with pretrained and fine-tuned weights proves to be a good strategy for predictive modeling for esophagitis recognition in endoscopic images. In addition, adopting the classification approach combined with the subsequent plotting of heat maps associated with the classificatory decision gives greater explainability to the model.

CONCLUSION
It is opportune to raise new studies involving transfer learning for the analysis of endoscopic images, aiming to improve, validate and disseminate its use for clinical practice.

Key Words: Esophagitis; Endoscopy; Artificial intelligence; Deep learning; Transfer learning

Core Tip: Considering the clinical relevance of esophagitis, we proposed a deep learning model for its diagnosis from endoscopic images of the Z-line, *via* binary classification of the images according to the presence or absence of esophageal inflammation signs. The excellent accuracy and area under the receiver operating characteristic curve achieved demonstrate the potential of the adopted strategy, consisting of the conjunction of densely connected neural networks and transfer learning. With this, we contribute to the improvement and methodological advancement in the development of automated diagnostic tools for the disease, which reveal great potential in optimizing the management of these patients.

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INTRODUCTION

Esophagitis is an inflammatory and damaging process of the esophageal mucosa, that can be the outcome of different pathological processes, which share, however, the same clinical presentation: retrosternal pain, dysphagia, odynophagia and heartburn[1,2]. Different pathological processes may lead to esophagitis, with possible etiologies embracing gastroesophageal reflux disease (GERD), infectious processes, in eosinophilic esophagitis, medications or even radiation. In extreme cases, it can result in stenosis, fistulization and esophageal perforation[3]. These complications, however, may be prevented with precoce diagnosis.

Esophagitis can be suspected based on the clinical history, with a confirmation performed through endoscopic visualization. The differentiation of its etiopathogenesis may be determined from endoscopic and histological study of the esophagus. The endoscopic presentation of eosinophilic esophagitis is characterized by exudates, strictures and concentric rings. In colonization by *Candida sp.* there are small and diffuse yellow-white plaques; in cytomegalovirus infection there are large ulcerations; Herpes Virus, in turn, may cause multiple small ulcerations[3-5]. GERD, on the other hand, has a better-defined endoscopic classification with the Los Angeles classification, which has four gradations based on the presence, size and distribution of esophageal[6].

Machine learning, main exponent of artificial intelligence, has gained space and attention in healthcare and medical research, especially after the development and validation by Beam and Kohane [7] and Gulshan *et al*[8] of a deep learning algorithm capable of detecting the presence of diabetic retinopathy in studies of the retina[7,8]. In the context of esophagitis, the use of machine learning, especially deep learning, may be considered to determine, among others, the presence of esophageal lesions compatible with esophagitis.

Deep learning - which comprehends deep artificial neural network-based algorithms capable of learning from large amounts of data - is considered the state of the art in the field of artificial intelligence for computer vision[9]. Among the possible uses of such applications, there is the binary classification of images according to the presence or absence of a given finding. In these cases, a dataset comprising examples of the image type to be classified is divided into two distinct subsets: one to train the model (from which the weights will be learned) and the other to evaluate its performance[10]. It is important that the two subsets obtained are representative, in terms of labels proportion, of the original dataset.

Traditionally, algorithms for deep learning use large volumes of data for training. However, obtaining databases large enough to accurately train them can prove to be a highly expensive process. As a way of mitigating this situation, one can choose to apply a technique called transfer learning, which is based on the use of external data to perform a training step mentioned above[10]. The use of this technique makes it possible to obtain a scale of pretrained weights in computational models for analyzing, among others, medical images. It should be noted, however, that the use of pretrained weights does not exempt the need to carry out a training stage with data that are representative of the base to be tested, with this second training step (called fine tuning) aiming to improve, principally, the deep layers of the algorithm in order to obtain results with greater accuracy[11].

This study aims to develop a supervised deep learning model using a fine-tuned transfer learning dense convolutional neural network (DCNN) to recognize, in a binary way, the presence of changes compatible with esophagitis in images from endoscopic studies. Thus, it seeks to contribute to the advancement and methodological improvement of a cost-effective and accurate automated technology for the diagnosis of esophagitis, optimizing the management of patients who present this condition.

MATERIALS AND METHODS

Data acquisition

Endoscopic images of 1932 patients with a diagnosis of esophagitis and 1663 patients without any pathological diagnosis (in both cases being z line the image topography) were obtained from the publicly available KSAVIR Dataset[12] and HyperKSAVIR Dataset[13]. Were included in this study the images in both datasets labeled as "normal z line" and the images labeled as "esophagitis". From these data, we set out to develop a binary deep learning classifier using the DenseNet-201 architecture, a densely connected convolutional network which connects each layer to every other layer in a feed-forward fashion[14], pretrained on the ImageNet image set.

The top layer of the DenseNet-201 architecture was not included in our model, and its output (that is, the output of the final convolutional block) was converted from a 4 dimensional to a 2 dimensional tensor using global average pooling. As the final layer, we added a dense layer with one unit and sigmoid activation. The structure of the final deep neural network predictive model is summarized in Table 1, and its architecture is illustrated in Figure 1.

Model development, training, and validation

For this purpose, the images were converted to arrays of dimension 256 × 305 × 3, whose units were rescaled using the *densenet* preprocessor, and divided into training set (80%) and test set (20%). The training set (n = 2876) was divided in batches of size 16 and used to train, throughout 80 epochs, the transfer learning based neural network whose structure is shown in Table 1. The test set (n = 719) was used to evaluate the model according to the following metrics: accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC).

The adopted methodology is schematically summarized in Figure 2. All steps of the predictive model development were performed in Python (version 3.6.9), using Keras library.

Ethical disclosure

As previously stated, all the imaging data was obtained from the public datasets KSAVIR Dataset[12] and HyperKSAVIR Dataset[13] that were released for both educational and research purposes. Therefore, it was not necessary to submit this study to the ethics committee, being in accordance with all the established precepts by the Committee on Publication Ethics.

RESULTS

The model was trained using Adam optimizer with a learning rate of 0.0001 and applying binary cross entropy loss function. All layers of the DenseNet architecture incorporated in the model were set as trainable (that is, we fine-tuned all weights).

In the test set, which was designated to model evaluation, the classifier achieved 93.32% accuracy, 93.18% sensitivity, 93.46% specificity and a 0.96 AUC. The confusion matrix between true labels and labels predicted by the model is presented in Figure 3, while its receiver operating characteristic curve is presented in Figure 4.

In order to identify the imagery aspects related to the predictive decision, it is possible to plot heatmaps that indicate, colorimetrically, the areas with the greatest influence on the prediction. Examples of such heatmaps for esophagitis images contained in the test set are shown in Figure 5.

Table 1 Synthesis of the model's structure

Type of layer	Brief description	Number of parameters
Functional	Instantiates the DenseNet-201 architecture with average pooling of the output	18321984
Dense	One unit with sigmoid activation	1921

The functional layer instantiates the DenseNet-201 architecture, thus aggregating all its layers. The dense layer outputs the final binary classification of the model.

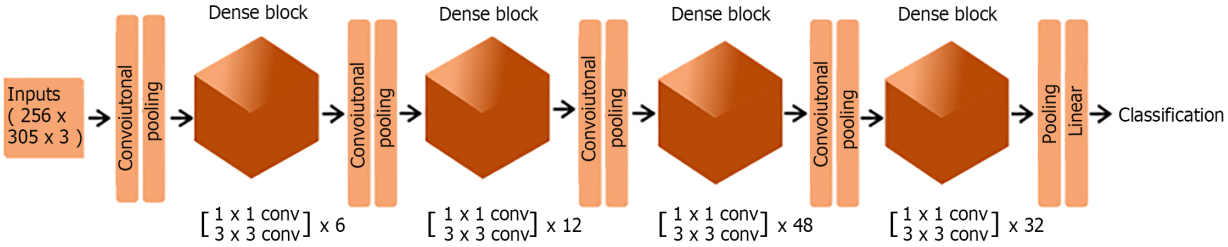

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Figure 1 Representation of model's final architecture. In the proposed model, each image is used as an input for a deep neural network composed of four blocks of densely connected convolutional layers, together with convolutional and pooling transition layers. The network output is a binary classification.

DISCUSSION

This study understands that transfer learning associated with DCNN has great potential to aid and improve the quality and rate of esophagitis diagnosis through endoscopic imaging. Improving workflow, providing faster preliminary reports, relieving the burden of the increasing patient population associated with the intensive and repetitive mechanical work is some of the promises of the integration of CNN-based algorithms to medical practice[15].

Once the mark of at least 93% in the parameters of accuracy, sensitivity, and specificity has been reached, we were able to demonstrate the potential of these algorithms to assist in the premature recognition of pathological predecessor endoscopic abnormalities, and as a consequence, to intervene positively in the management of these. Thus, the use of DCNN with pretrained and fine-tuned weights proves to be a good strategy for predictive modeling of this type (and potentially other types) of medical images. In addition, adopting the classification approach combined with the subsequent plotting of heat maps associated with the classificatory decision gives greater explainability to the model.

In consistency with findings described by Wimmer *et al*[16], when they established the potential of the association of transfer learning with CNN in the classification of endoscopic images, previously used focused on celiac disease, or also described by Song *et al*[17] when they reported a deep learning-based model with the ability to histologically classify polyps with a higher accuracy than trained endoscopists, the performance of our algorithmic model reaffirms the potential of deep learning for computer vision in the field of gastrointestinal diagnostics. In line with the mentioned studies, our study demonstrates the already defended potential of CNN-based artificial intelligence systems to diagnose esophageal disease, and can contribute with methodological insights for the development and improvement of such systems[18].

By recognizing changes in the mucosa of the esophageal Z-line, the binary transfer learning classifier presented in this study aims to demonstrate the effectiveness of these algorithms to differentiate endoscopic images of the same topography with and without changes characteristic of esophagitis. Unlike other studies that aimed at automatic detection of anatomical landmarks and diverse diseases affecting different anatomical sites using the KVASIR database[19-22], we employed state-of-the-art deep learning to specifically target Z-line related changes, bringing great accuracy to its analysis.

However, as it is well settled in applications of deep learning in medical image analytics[23], a major limitation of the technical capability of the proposed classifier is the lack of large-scale labeled data. As already shown by Sun *et al*[24], the performance on artificial intelligence in visual tasks increases logarithmically based on volume of training data size. Coupled with this factor, we cannot ensure how the binary classifier would behave in patients with the presence of other diseases. In both cases, however, training on more plural datasets should optimize performance on the parameters evaluated.

Concerning the predictive behavior towards other possible esophageal Z-line abnormalities, assuming that the algorithm was able to differentiate with high accuracy normal images from images with different degrees of inflammation - and consequently different mucosal lesion configurations - it is

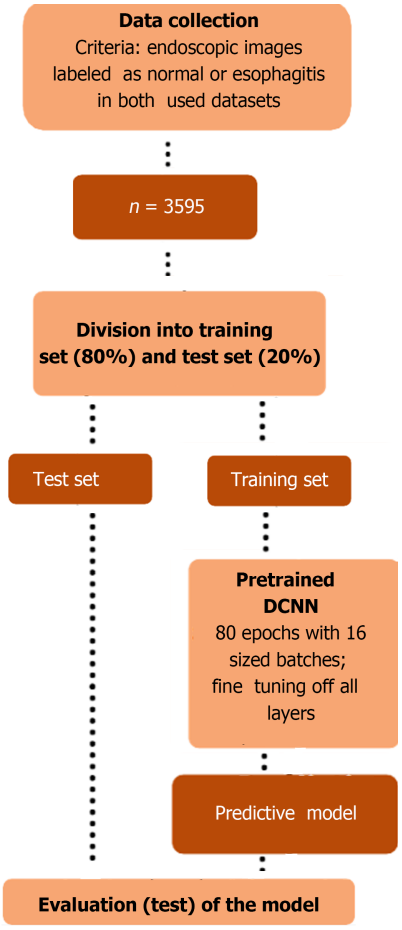

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Figure 2 Methodological design of the study. The proposed workflow encompasses selective collection of endoscopic images from the datasets, splitting and pre-processing of the data, iterative training of the classificatory model, and finally evaluation of its performance. DCNN: Dense convolutional neural network.

reasonable to assume that other esophageal lesions would be differentiated from the healthy aspect, and thus categorized together with the esophagitis images. Among the possible clinical differential situations, esophageal and esophagogastric junction cancers are of particular relevance. Upper endoscopies are considered by the Society of Thoracic Surgeons and the National Comprehensive Cancer Network as the initial diagnostic evaluation to exclude esophageal cancer[25]; although techniques such as chromoendoscopy and narrow band imaging are often used to increase the sensitivity of detection of lesions suggestive of malignancy, traditional endoscopic imaging still plays an important role in the investigational flowchart, and can demonstrate suspicious findings incidentally [26].

In view of this, in order to extend the clinical utility of our proposed algorithm to the investigation of potentially malignant endoscopic findings, two main approaches are possible: (1) Propose an adaptation of the model to multiclass classification and, to this end, retrain the model including endoscopic images of esophageal cancer, fine-tuning, if necessary, only the final layers, making appropriate changes in the final dense layer and in the loss function to accommodate 3 classes (thus, the final layer would now have 3 neurons with softmax activation function, and the sparse categorical crossentropy loss function would be adopted); and (2) Preserve the binary classification structure, but proposing to change the labels for normal and abnormal findings (thus, the model would be used to triage any endoscopic abnormalities, ranging from inflammatory findings to lesions suggestive of malignancy) and, for this purpose, retrain the model including endoscopic images representative of other types of lesions (including neoplastic lesions). In either situation, the incorporation of images representative of lesions suspicious for malignancy would be necessary, and the weights derived from training with normal endoscopic images and with esophagitis findings already performed would be used (same domain fine-tuning).

Convolutional neural networks with transfer learning for automated analysis of endoscopic images, as proposed in this study, may be incorporated into daily practice as a clinical decision support tool - screening abnormalities and indicating the need for further specialized evaluation or double checking medical reports. This application would add value especially in contexts of scarce resources, in which the number of endoscopists is limited and they are often poorly trained - increasing, thus, the likelihood

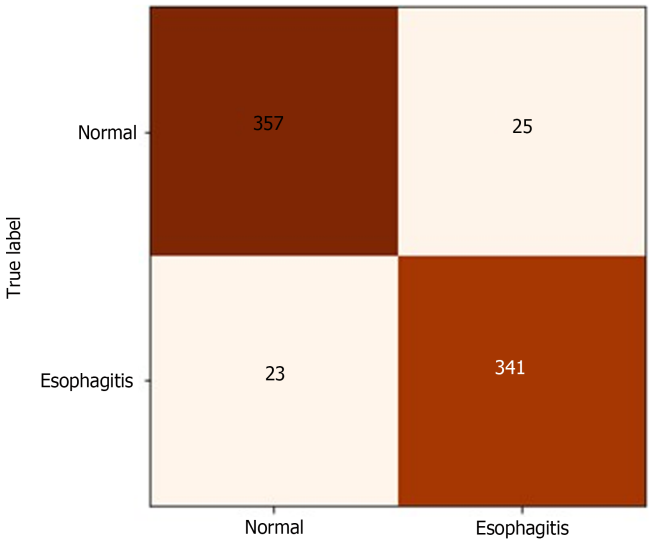

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Figure 3 Confusion matrix for the predictive model. As illustrated, the model was able to accurately classify 314 of 337 esophagitis images and 357 of 382 normal images, with true positive and false positive rates of 93.2% and 93.5%, respectively.

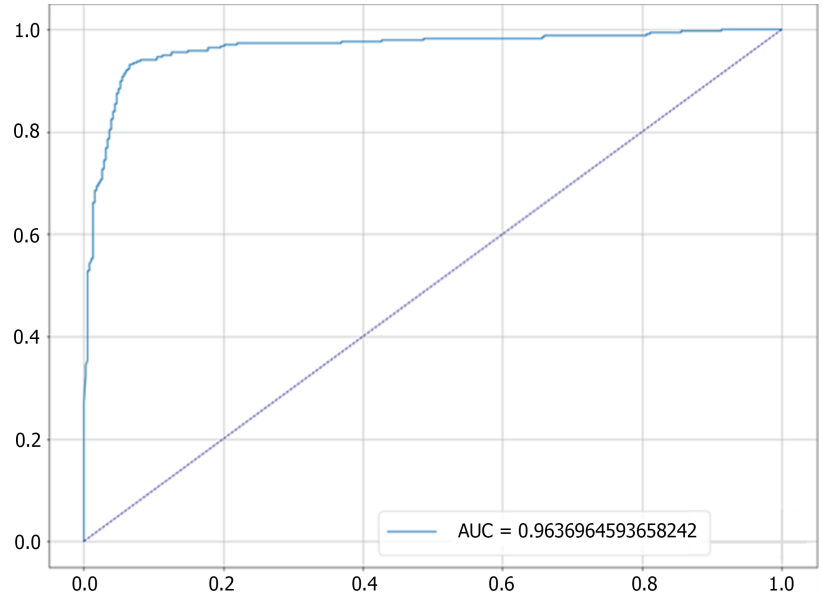

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Figure 4 Receiver operating characteristic curve for the proposed predictive model. The graph shows the resulting curve relating the true and false positive rates, giving an area on the curve of 96.4%. AUC: Area under the receiver operating characteristic curve.

of diagnostic errors. Moreover, it is especially promising as an adjunct tool to telemedicine, favoring rural and remote areas.

CONCLUSION

The use of deep learning, especially the transfer learning technique, has great potential field for the analysis of clinical images, including endoscopic records. Observing this great potential, this paper applied such technique, associated with retraining of all layers, to classify, with a 93.3% accuracy, esophageal mucosa images obtained from endoscopic studies according to the presence or absence of esophagitis. It then becomes evident the potential of transfer learning with fine-tuning for the analysis of images obtained by endoscopic method and recognition of esophageal lesions.

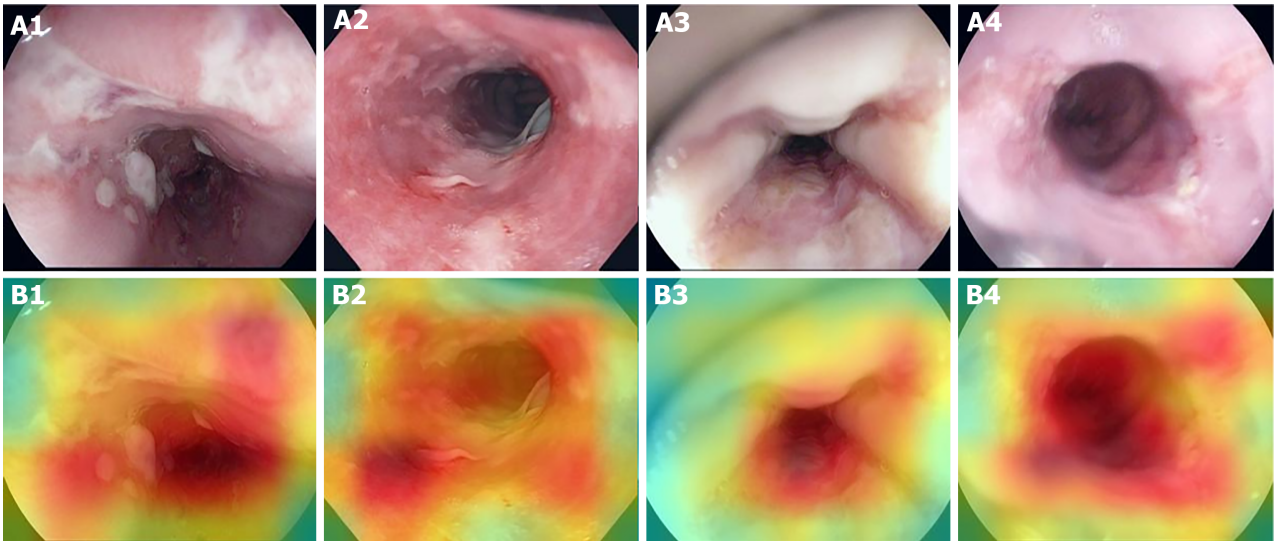

Figure 5 Heatmaps for spatial predictive relevance in esophagitis endoscopic images from test set. A and B: Images A1-A4 represent examples esophagitis endoscopic images used to test our predictive model, while images B1-B4 represent the corresponding heatmaps indicating, for each image, the areas with the greatest influence on the prediction. A1-A4: Citation: Pogorelov K, Randel K, Griwodz C, Eskeland S, Lange T, Johansen D, Spampinato C, Dang-Nguyen D, Lux M., Schmidt P, Riegler M, Halvorsen P. Kvasir: A Multi-Class Image Dataset for Computer Aided Gastrointestinal Disease Detection. MMSys'17 Proceedings of the 8th ACM on Multimedia Systems Conference (MMSYS); 2017 June 20-23; Taipei, Taiwan. New York: Association for Computing Machinery, 2017: 164-169. Copyright © Simula Research Laboratory 2017. Published by Association for Computing Machinery[12]. The authors have obtained the permission for figure using from the Simula Research Laboratory (Supplementary material). Citation: Borgli H, Thambawita V, Smedsrud PH, Hicks S, Jha D, Eskeland SL, Randel KR, Pogorelov K, Lux M, Nguyen DTD, Johansen D, Griwodz C, Stensland HK, Garcia-Ceja E, Schmidt PT, Hammer HL, Riegler MA, Halvorsen P, de Lange T. HyperKvasir, a comprehensive multi-class image and video dataset for gastrointestinal endoscopy. *Sci Data* 2020; 7: 283. Copyright © Simula Research Laboratory 2020. Published by Nature Publishing Group[13]. The authors have obtained the permission for figure using from the Simula Research Laboratory (Supplementary material).

In view of this, it is opportune to raise new studies involving transfer learning for the analysis of related data, with the aim of improving, disseminating and validating its use for the daily routine of clinical practice. Furthermore, the composition and dissemination high-quality endoscopic image sets representative of various clinical conditions (especially esophageal cancer, given its high clinical and epidemiological relevance) is essential for new studies to be developed and algorithms already proposed to be improved.

ARTICLE HIGHLIGHTS

Research background

Computer vision allied with deep learning, especially through the use of deep convolutional neural networks, has been increasingly employed in the automation of medical image analysis. Among these are endoscopic images, which are of great importance in the evaluation of a number of gastroenterological diseases.

Research motivation

Endoscopic findings constitute the diagnostic definition for esophagitis, a multietiological condition with significant impacts on quality of life and the possibility of evolution to a series of complications. Automating the identification of findings suggestive of esophageal inflammation using artificial intelligence could add great value to the evaluation and management of this clinical condition.

Research objectives

To identify whether a densely connected convolutional neural network with pre-trained and fine-tuned weights is able to binary classify esophageal Z-line endoscopic images according to the presence or absence of esophagitis.

Research methods

Endoscopic images of 1932 patients with a diagnosis of esophagitis and 1663 patients were splitted in training (80%) and test (20%) and used to develop and evaluate a binary deep learning classifier built using a pre-trained DenseNet-201 architecture. The classifier model performance was evaluated in the test set according to accuracy, sensitivity, specificity and area under the receiver operating characteristic

curve.

Research results

The proposed model was able to diagnose esophagitis in the validation set with sensitivity of 93.18 and specificity of 93.46, demonstrating the feasibility of using deep transfer learning to discriminate normal from damaged mucosa in endoscopic images of the same anatomical segment. It remains to be investigated whether, by means of a more diverse set of images, this technique can be proposed to identify different types of esophageal abnormalities, and potentially in other organs.

Research conclusions

Convolutional neural networks with transfer learning for automated analysis of endoscopic images, as proposed in this study, demonstrate potential for incorporation into clinical practice as a clinical decision support tool, mainly benefiting scarce resources settings.

Research perspectives

Sets of endoscopic images representative of various clinical conditions should be published, in order to allow the findings of this study to be externally validated and for new models with different classificatory approaches to emerge.

FOOTNOTES

Author contributions: Caires Silveira E proceeded the data collection/entry, performed data analysis and data interpretation, developed the proposed predictive model and participated in preparation and review of manuscript; Santos Corrêa CF and Madureira Silva L participated in preparation of manuscript and wrote the literature analysis/search; Mattos Pretti S and Almeida Santos B participated in review of manuscript; Freire de Melo F designed the research and participated in review of manuscript.

Institutional review board statement: For this study, there was no need for an appraisal by an ethics committee, since only publicly available anonymized data were used.

Informed consent statement: The present manuscript used anonymous images to produce its analyzes and results, in a method that obeys the norms of medical bioethics. Thus, there was no direct or even indirect contact between researchers and patients, with no necessity for "Signed Informed Consent Form" to carry out our study.

Conflict-of-interest statement: The authors have no financial relationships to disclose.

Data sharing statement: No additional data are available.

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Retrospective Study

Why is endosonography insufficient for residual diagnosis after neoadjuvant therapy for esophageal cancer? Solutions using muscle layer evaluation

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Abstract

BACKGROUND

The diagnosis of residual tumors using endoscopic ultrasound (EUS) after neoadjuvant therapy for esophageal cancer is considered challenging. However, the reasons for this difficulty are not well understood.

AIM

To investigate the ultrasound imaging features of residual tumors and identify the limitations and potential of EUS.

METHODS

This exploratory prospective observational study enrolled 23 esophageal squamous cell carcinoma patients receiving esophagectomy after neoadjuvant therapy [15 patients after neoadjuvant chemotherapy (NAC) and 8 patients after chemoradiotherapy (CRT)] at the Department of Surgery, Chiba University Hospital, between May 2020 and October 2021. We diagnosed the T stage for specimens using ultrasound just after surgery and compared ultrasound images with the cut surface of the fixed specimens of the same level of residual tumor. The ratio of esophageal muscle layer defect measured by ultrasound was compared with clinicopathological factors. Furthermore, the rate of reduction for the muscle layer defect was evaluated using EUS images obtained before and after neoadjuvant therapy.

RESULTS

The accuracy of T stage rate was 61% (n = 14/23), which worsened after CRT

(38%, n = 3/8) than after NAC (73%, n = 11/15) because of overstaging. Moreover, pT0 could not be diagnosed in all cases. The detection rate of residual tumor for specimens using ultrasound retrospectively was 75% (n = 15/20). There was no correlation between after-NAC (79%, n = 11/14) and after-CRT (67%, n = 4/6) detection rate. The detection of superficial and submucosal types was poor. The pathologic tumor size and pathological response were correlated. Tumor borders were irregular and echogenicity was mixed type after CRT. There was a correlation between the pT stage (pT0/1 *vs* pT2/3) and the length of muscle layer circumference (P = 0.025), the length of muscle layer defect (P < 0.001), and the ratio of muscle layer defect (P < 0.001). There was also a correlation between the pT stage and the rate of muscle layer defect reduction measured by EUS (P = 0.001).

CONCLUSION

Compared to pathological images, some tumors are undetectable by ultrasound. Focusing on the esophageal muscle layer might help diagnose the depth of the residual tumor.

Key Words: Esophageal cancer; Esophageal squamous cell carcinoma; Neoadjuvant therapy; Endoscopic ultrasound; Residual tumor; Endosonography

Core Tip: This exploratory prospective observational study evaluated the effectiveness of endoscopic ultrasound (EUS) in diagnosing residual tumors after neoadjuvant therapy for esophageal squamous cell carcinoma. It is well known that the diagnosis using EUS after neoadjuvant therapy is inaccurate. The results of ultrasound for surgical specimens are not satisfactory as well. Our study found that the inability to distinguish scar tissue from the tumor made detection and diagnosis impossible in some residual tumors. Esophageal muscle layer defect as an indirect finding correlated with the depth of the residual tumor. These insights could help improve the diagnosis of residual tumors.

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INTRODUCTION

Esophageal cancer is the seventh most common cancer worldwide in terms of incidence and the sixth most common in terms of mortality. Especially in Asia, esophageal squamous cell carcinoma (ESCC) accounts for more than 90% of all esophageal cancers[1]. There is strong evidence supporting the superiority of neoadjuvant chemoradiotherapy (CRT) and neoadjuvant chemotherapy (NAC) plus surgery over surgery alone for locally advanced esophageal cancer[2]. In ESCC patients, pathological complete response (pCR) was 62% after CRT and 2%-7% after NAC[3-5]. While patients with pCR may have avoided unnecessary esophagectomy, the residual tumor must be accurately identified to justify not performing a surgical resection.

In contrast, residual tumors after CRT and NAC are often present only at a depth of the esophageal wall, without any exposure to the superficial mucosa[6,7]. Although Endoscopic ultrasound (EUS) has a well-established role in the initial staging of esophageal cancer[8], the diagnosis of esophageal cancer after neoadjuvant therapy has been controversial. EUS sensitivity for residual tumors at the primary site after neoadjuvant CRT is as high as 0.96; however, the specificity is as low as 0.08, and thus it does not seem to be sufficiently accurate to detect residual tumor[9]. In addition, the accuracy of staging after NAC is not sufficient[10]. Several studies have correlated EUS measurements with tumor regression grade and survival. However, it is unclear whether the echogenic lesions detected using EUS are indeed residual tumors and how they appear on ultrasound. The purpose of this study was to characterize the ultrasound images of residual tumors, explore the limitations of EUS, and assess its potential in residual diagnosis.

MATERIALS AND METHODS

Patient population

This exploratory prospective observational study was conducted in two steps. The first step (study 1) aimed to investigate the limitations and characteristics of residual tumor diagnosis using ultrasound. Based on study 1, the second step (study 2) aimed to implement EUS to detect remanent tumors deep in the muscle layer. Study 1 enrolled 23 ESCC patients undergoing esophagectomy after neoadjuvant therapy, including NAC or CRT in the Department of Surgery, Chiba University Hospital, between May 2020 and October 2021. All patients were histologically proven to have ESCC based on biopsy specimens. The clinical stage was determined by endoscopy, barium esophagography, chest and abdominal computed tomography (CT) scans, and 18F-fluorodeoxyglucose positron emission tomography, based on the 11th Edition of the Japanese Classification of Esophageal Cancer[11]. Study 2 enrolled 20 out of the initial 23 participants in the first study who underwent EUS for staging and were diagnosed with cT2 or deeper. Our Institutional Review Board (IRB No. 3550) approved this study. We obtained written informed consent from patients for all examinations and treatments.

Preoperative and surgical treatment

As recommended by the Japanese Clinical Oncology Group (JCOG) 9907 Study, we performed preoperative chemotherapy postoperatively for patients with clinically UICC stage II/III resectable ESCC in our department's criteria[5]. NAC was composed of two cycles of 5-fluorouracil (800 mg/m^2 infusion for five consecutive days) and cisplatin (80 mg/m^2 on day 1). Some patients received three cycles of docetaxel (70 mg/m^2 on day 1), cisplatin (70 mg/m^2 on day 1) and 5-fluorouracil (750 mg/m^2 infusion for five consecutive days) based on the JCOG 1109 study[12]. After NAC, all patients were evaluated by CT, PET, and endoscopy, and underwent radical esophagectomy with three-field lymphadenectomy, including cervical, mediastinal, and abdominal lymph node dissection. CRT was composed of 2 Gy/fraction at a total dose of 40 Gy with a long-T radiation field from the cricoid cartilage to the upper abdomen, including the gross tumor volume. Concurrent chemotherapy was performed with 5-fluorouracil (500 mg/m^2 infusion on day 0-4) and cisplatin (15 mg/m^2 on day 1-5). After receiving a 40 Gy dose, all patients were evaluated by CT, PET, and endoscopy. An additional 20 Gy dose was delivered to patients with potentially resectable tumors, making the total irradiation dose 60 Gy (definitive CRT), and concurrent chemotherapy with the same regimen was also provided. After CRT, patients with resectable tumors underwent radical esophagectomy with three-field lymphadenectomy four weeks after CRT. The criteria for the pathological response of primary tumor were categorized as ineffective (Grade 0); viable cancer cells accounted for 1/3 or more of tumor tissue (Grade 1); viable cancer cells accounted for less than 1/3 of tumor tissue (Grade 2); no viable cancer cells (Grade 3).

Procedure of ultrasound for surgical specimens

In study 1, the surgical specimens of all patients were collected from the operation room, and an ultrasound was performed immediately. The unfixed specimens immersed in saline solution were scanned vertically and horizontally using 15 MHz electronic linear ultrasound. The imaging procedure was recorded on video. We used LOGIQ S8 (GE Healthcare Japan Corporation, Tokyo, Japan) ultrasound platform in all studies. The ultrasound for specimens showed the mucosal layer, submucosal layer, inner muscle layer, intermuscular connective tissue layer, and outer muscle layer, as shown in EUS. We diagnosed the presence and depth of the tumor on the day of surgery before pathology results were known. We assessed the accuracy of diagnosing residual tumor depth using ultrasound. The prefix "u" indicates ultrasound diagnosis. Furthermore, to clarify the characteristic features of residual tumor, we compared ultrasound images with the cut surface of the fixed specimens at the same level of tumor site in the esophageal wall.

Measurements of muscle layer defect

In study 1, in addition to the direct finding of the tumor, we focused on the esophageal muscle layer as an indirect finding, which is the most visible on ultrasound. We set up a cross-sectional image vertical to the esophagus at the center of the tumor. We measured the length of muscle layer circumference and the length of muscle layer defect. We calculated the ratio of muscle layer defect and compared each pathological factor.

Muscle layer defect angle

Study 2 aimed to evaluate the muscle layer defect using EUS. However, the EUS and ultrasound findings for specimens were different since the specimens were fully stretched. Keeping the esophageal wall stretched *in vivo* and measuring the circumference of the muscle layer by EUS would be challenging. Therefore we substituted the ratio of muscle layer defect with the total circumference of the muscle layer by the angle and named it as muscle layer defect angle (MDA). MDA was defined as the angle between the center of the lumen and the two points where EUS could not help visualize the inner muscle and intermuscular connective tissue layer. Using MDA, we measured the percentage of

improvement in muscle layer defect caused by neoadjuvant therapy using the still images as well as video images of EUS. EUS was performed before and after neoadjuvant therapy by three or more skilled endoscopists. We calculated the MDA reduction rate using Pre-MDA and Post-MDA. MDA reduction rate was expressed using the following equation:

MDA reduction rate (%) = {[PreMDA(°) - PostMDA(°)] / PreMDA(°)} × 100

We compared each MDA factor with the pathological T stage. The echo images were analyzed using ImageJ software (National Institutes of Health, available at http://rsb.info.nih.gov/ij) specialized for morphological evaluation.

Statistical analysis

This study compared the results of prospectively collected data after confirming pathology. All statistical analyses were conducted with the JMP® Pro software program, version 13.2 (SAS Institute Inc., Cary, NC, United States). Continuous variables were expressed as median (min–max) or mean (± SD). Fisher's exact test was used to compare and analyze categorical variables. Continuous variables were analyzed using Wilcoxon's signed-rank sum test. P values of < 0.05 were considered statistically significant. Receiver operating characteristics (ROC) analysis was performed to assess the highest diagnostic values to determine the optimal cut-off points.

RESULTS

Patients' characteristics

From May 2020 to October 2021, 61 patients underwent esophagectomy for esophageal cancer, and 37 patients underwent neoadjuvant therapy in our department. Of these, we excluded 5 patients with adenocarcinoma, 2 patients with neuroendocrine carcinoma, and 7 patients whose surgical specimens could not be analyzed using ultrasound. The clinical characteristics and pathological examination are summarized in Table 1. Fifteen patients received NAC, of which 13 patients received cisplatin plus 5-fluorouracil (CF), and 2 patients received docetaxel plus cisplatin plus 5-fluorouracil (DCF). Eight patients received CRT, of which 6 patients received 38-40 Gy irradiation, and 2 patients received additional irradiation to the total of 60 Gy as their tumors were considered unresectable by the end of 40 Gy irradiation. These two patients underwent salvage surgery after the additional irradiation. Three patients achieved pathological pCR (pathological grade 3); of these, 2 patients received CRT, and 1 patient received NAC only.

The diagnosis of uT stage with ultrasound for specimens

We diagnosed uT stage by ultrasound for specimens just after surgery (Table 2). There was poor agreement between uT and pT stages. The overall accuracy uT stage rate was 61% (n = 14/23). The respective accuracy uT stage rate was 0% (n = 0/3) for pT0, 0% (n = 0/3) for pT1a, 67% (n = 4/6) for pT1b, 67% (n = 2/3) for pT2, and 100% (n = 8/8) for pT3. All pT0 and pT1a patients could not be diagnosed. Regarding comparison with NAC and CRT, the overall accuracy of uT stage rates were 73% (n = 11/15) and 38% (n = 3/8), respectively. The overall accuracy of overstaging uT stage rates was 13% (n = 2/15) and 62% (n = 5/8), respectively.

Detect for residual tumor retrospectively

Among 20 patients, excluding 3 patients who achieved complete response, we compared ultrasound images with the cut surface of the fixed specimens of the same level of residual tumor site in the esophageal wall to examine whether the residual tumor itself could be detected (Table 3). The overall detection rate for residual tumors was 75% (n = 15/20), with no correlation between after NAC (79%, n = 11/14) and after CRT (67%, n = 4/6). The macroscopic types after neoadjuvant therapy were classified into two groups; 11 patients had ulcerative and protruding tumor types, while 9 patients had superficial and submucosal tumors. The superficial and submucosal types were poorly detected (P = 0.008). In addition, pathologic tumor size and the pathological response showed a significant correlation (P = 0.008, 0.127). Echoic characteristics of the residual tumor are shown in Table 4.

The tumor borders were relatively regular, and echogenicity was hypoechoic after NAC. In contrast, tumor borders were irregular, and echogenicity was hypo and iso (mixed) echoic type in all patients after CRT (Figure 1).

Relationship between muscle layer measurements and pathological characteristics

We measured the muscle layer using ultrasound images (Figure 2). Ultrasound showed a clearly defined disruption of the muscle layer. We compared muscle layer factors with pathological characteristics (Figure 3). There was a significant correlation between pT stage (pT0/1, n = 12 *vs* pT2/3, n = 11) and length of muscle layer circumference (36.2 ± 5.9 mm *vs* 44.3 ± 8.9 mm, P = 0.025), length of muscle layer defect (22.5 ± 8.0 mm *vs* 7.1 ± 7.2 mm, P < 0.001), and the ratio of muscle layer defect (63.0 ± 22.8% *vs* 16.1 ± 16.0%, P < 0.001).

Table 1 Patients' characteristics

	All population (*n* = 23)	NAC (*n* = 15)	CRT (*n* = 8)
Age (yr)			
Median (range)	72 (43-81)	72 (43-78)	72 (49-81)
Sex			
Male	19	12	7
Female	4	3	1
Tumor location			
Ut	2	2	0
Mt	15	8	7
Lt	4	4	0
Ae	2	1	1
Clinical T stage			
cT1b	1	1	0
cT2	3	3	0
cT3	11	11	0
cT4a	1	0	1
cT4b	7	0	7
Chemotherapy regimen			
CF	21	13	8
DCF	2	2	
Total irradiation dose			
38-40Gy	6		6
60Gy	2		2
Time of surgery after therapy (d)			
Median (range)	37 (31-61)	36 (31-61)	40 (35-57)
Pathological T stage			
pT0	3	1	2
pT1a	3	1	2
pT1b	6	6	0
pT2	3	1	2
pT3	8	6	2
Pathological response			
Grade1	13	11	2
Grade2	7	3	4
Grade3	3	1	2

Ut: Upper thoracic esophagus; Mt: Middle thoracic esophagus; Lt: Lower thoracic esophagus; Ae: Abdominal esophagus; CF: Cisplatin plus 5-fluorouracil; DCF: Docetaxel plus cisplatin plus 5-fluorouracil; NAC: Neoadjuvant chemotherapy; CRT: Chemoradiotherapy.

There was no correlation between pathological response (Grade 1/2, n = 20 *vs* Grade 3, n = 3) and length of muscle layer circumference (40.0 ± 9.0 mm *vs* 42.6 ± 4.9 mm, P = 0.438), length of muscle layer defect (14.5 ± 11.5 mm *vs* 14.6 ± 4.5 mm, P = 1.00), and the ratio of muscle layer defect (39.2 ± 32.9% *vs* 33.8 ± 6.8%, P = 0.927).

Table 2 Comparison Ultrasound for specimens uT stage to histological pT stage

Ultrasound T stages	pT0	pT1a	pT1b	pT2	pT3	Total
	Pathological T stages after NAC and CRT					
uT0	0	1	1	0	0	2
uT1a	0	0	0	0	0	0
uT1b	0	0	4	0	0	4
uT2	1	1	1	2	0	5
uT3	2	1	0	1	8	12
Total	3	3	6	3	8	23
Accuracy (%)	0	0	67	67	100	61
Overstaging (%)	100	67	17	33	0	30
Understaging (%)		33	16	0	0	9
	Pathological T stages after NAC					
uT0	0	1	1	0	0	2
uT1a	0	0	0	0	0	0
uT1b	0	0	4	0	0	4
uT2	1	0	1	1	0	3
uT3	0	0	0	0	6	6
Total	1	1	6	1	6	15
Accuracy (%)	0	0	67	100	100	73
Overstaging (%)	100	0	17	0	0	13
Understaging (%)		100	17	0	0	13
	Pathological T stages after CRT					
uT0	0	0	0	0	0	0
uT1a	0	0	0	0	0	0
uT1b	0	0	0	0	0	0
uT2	0	1	0	1	0	2
uT3	2	1	0	1	2	6
Total	2	2	0	2	2	8
Accuracy (%)	0	0	0	50	100	38
Overstaging (%)	100	100	0	50	0	62
Understaging (%)		0	0	0	0	0

NAC: Neoadjuvant chemotherapy; CRT: Chemoradiotherapy.

Relationship between MDA and pathological T stage

In study 2, we measured MDA using EUS images (Figure 4). To confirm the reduction of muscle layer defect after adjuvant therapy compared to before, we excluded 3 patients (EUS before therapy did not show muscle layer invasion in 2 patients, and 1 patient did not undergo EUS before therapy). The clinical characteristics and pathological examination results are summarized in Table 5. There was no significant difference between pT0/1 and pT2/3 in terms of clinical characteristics. MDA factors were compared with pathological T stage (Figure 5). There was no correlation between preoperative treatment (NAC, n = 12 *vs* CRT, n = 8), pre-MDA (50.0 ± 35.3° *vs* 70.0 ± 27.9°, P = 0.137), post-MDA (30.5 ± 33.6° *vs* 43.2 ± 28.4°, P = 0.279), and MDA reduction rate (51.4 ± 34.9% *vs* 40.4 ± 25.7%, P = 0.589). There was a significant correlation between pT stage (pT0/1, n = 10 *vs* pT2/3, n = 10), pre-MDA (142.5 ± 110.6° *vs* 274.0 ± 91.7°, P = 0.039), post-MDA (45.9 ± 49.3° *vs* 210.0 ± 98.7°, P < 0.001), and MDA reduction rate (68.9 ± 24.4% *vs* 25.1 ± 20.3%, P = 0.001).

Table 3 Relationship between detection of residual tumor and clinicopathological factors

	Detection of residual tumor		
	Possible	Impossible	*P*
All, *n* (%)	15 (75)	5 (25)	
Preoperative treatment, *n* (%)			
NAC	11 (79)	3 (21)	
CRT	4 (67)	2 (33)	0.613
Macroscopic type after neoadjuvant therapy, *n* (%)			
Ulcerative and protruding type	11 (100)	0 (0)	
Superficial and SMT type	4 (44)	5 (56)	0.008
Pathologic tumor size (mm)			
Median (range)	42 (5-65)	4 (2-34)	0.008
Pathological T stage, *n* (%)			
pT1a/1b	5 (56)	4 (44)	
pT2/3	10 (91)	1 (9)	0.127
Pathological response, *n* (%)			
Grade1	12 (92)	1 (8)	
Grade2	3 (43)	4 (57)	0.031

NAC: Neoadjuvant chemotherapy; CRT: Chemoradiotherapy.

Table 4 Echoic characteristics of the detected residual tumor

	All population (*n* = 15)	NAC (*n* = 11)	CRT (*n* = 4)	*P*
Border				
Regular	10	10	0	
Irregular	5	1	4	0.004
Echogenicity				
Hypoechoic	5	5	0	
Hypo and isoechoic (mixed)	10	6	4	0.231

NAC: Neoadjuvant chemotherapy; CRT: Chemoradiotherapy.

We conducted ROC analysis to determine the optimal MDA reduction rate cut-off points that could yield the maximum difference between the two groups (Figure 6). From this ROC curve analysis, 57.0% was determined as the best cut-off rate to detect the patients in the pT0/1 group with the highest accuracy. Based on the optimal cut-off values of the MDA reduction rate, that could distinguish the pT0/1 group with a sensitivity of 0.80, specificity of 0.90, and accuracy of 0.93.

DISCUSSION

We conducted two studies; study 1 was performed to investigate the limitations and characteristics of residual tumor diagnosis using ultrasound and study 2 aimed to implement EUS to detect remanent tumors deep in the muscle layer. The first study revealed the limitations and potential of ultrasound for residual tumors. After cross-referencing ultrasound images with the correct pathological diagnosis, some residual tumors were found to be undetectable on ultrasound. In contrast, the ratio of the esophageal muscle layer defect, which was not focused upon so far, was considered helpful in diagnosing the depth of the residual tumor. In the second study, muscle layer defect was measured using EUS. The results showed that the rate of muscle layer defect reduction in neoadjuvant therapy

Table 5 Patients' characteristics in study 2

	pT0/1 (*n* = 10)	pT2/3 (*n* = 10)	*P*
Age (yr)			
Median (range)	73 (52-79)	72 (43-81)	0.94
Sex			
Male/Female	9/1	7/3	0.582
Tumor location			
Ut, Mt, Lt/Ae	10/0	8/2	0.473
Clinical T stage			
cT2, 3/cT4a, b	6/4	6/4	1
Preoperative treatment			
NAC/CRT	6/4	6/4	1
Chemo regimen			
CF/DCF	9/1	9/1	1
Total irradiation dose			
38-40Gy/60Gy	2/2	4/0	0.429
Time of EUS after therapy (d)			
Median (range)	37 (21-49)	29 (14-50)	0.172
Time of surgery after therapy (d)			
Median (range)	41 (34-57)	37 (31-61)	0.471

Ut: Upper thoracic esophagus; Mt: Middle thoracic esophagus; Lt: Lower thoracic esophagus; Ae: Abdominal esophagus; CF: Cisplatin plus 5-fluorouracil; DCF: Docetaxel plus cisplatin plus 5-fluorouracil; NAC: Neoadjuvant chemotherapy; CRT: Chemoradiotherapy.

correlated with the pathological depth of the tumor. Our findings can help improve EUS diagnosis and provide more treatment options for ESCC patients after neoadjuvant therapy.

We considered comparing pathological and ultrasound images. However, using only EUS was considered unreliable for the following reasons. First, it was difficult to compare the measured level of tumor site in the esophagus with the level of the fixed specimens. Second, EUS was good for evaluating targeted areas but not for scanning large areas. In contrast, ultrasound for surgical specimens allowed us to compare pathological and ultrasound images with the same level of ultrasound images and scans of the entire lesion. This could help clarify whether the modality of echo itself contributes to the residual diagnosis after neoadjuvant therapy.

According to several meta-analyses examining the accuracy of detecting residual tumors for esophageal cancer after CRT, the consensus was that EUS had high sensitivity but low specificity[10,13]. Even after NAC, the concordance rate between EUS and pathological T-stage was reportedly as low as 29%, and the depth was overstaged in more than half of the cases (51%)[14]. It is well known that tumor invasion might be overestimated due to inflammation within and surrounding the tumor[15]. Our study showed 61% accuracy and 30% overstaging of uT, which was better than previous studies. Even though the ultrasound on surgical specimens was performed in a stable environment, these results are not sufficiently accurate. A previous study analyzing the accuracy of EUS in patients with esophageal cancer after NAC or CRT showed that accuracy of uT was significantly worse after CRT (16%) than after NAC (43%)[16]. In line with this previous study, our results showed that the accuracy of uT worsened after CRT (38%) than after NAC (73%). Our study showed that CRT downstaged tumors more effectively than NAC. As a result, there were more tumors with pT0 and pT1a, which were difficult to detect using ultrasound. All pT0 and pT1a patients could not be diagnosed because the scar tissue associated with tumor disappearance was misidentified as a residual tumor, causing overstaging. Diagnosing T3 was easy because the esophageal muscle layer was destroyed or replaced by fibrosis. However, distinguishing between a residual tumor and a fibrosis tissue seemed impossible.

We also examined the retrospective detection rate for residual tumor and the echoic characteristics of the residual tumor by comparing ultrasound images with the cut surface of the fixed specimens of the same level of the esophageal wall. Our results showed no difference in the detection rate after CRT and after NAC; however, the after CRT specimens appeared to have an irregular border and mixed echogenicity. According to a study that classified the echogenicity of gastrointestinal tumors, most

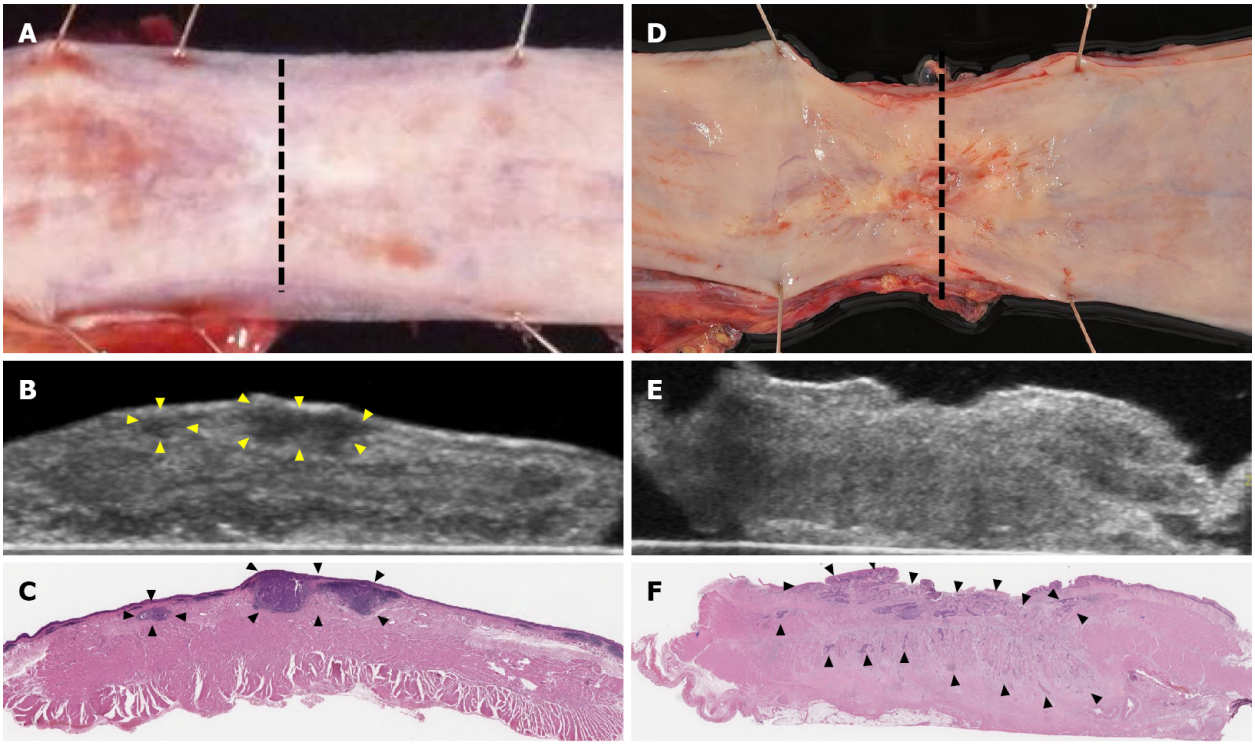

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Figure 1 Ultrasound for specimens. A: In the after neoadjuvant chemotherapy cases, the residual tumor was SMT type with no exposure to the mucosal surface; B: Ultrasound showed the tumor as hypoechoic with regular borders (arrowhead); C: Pathology showed 18 mm × 18 mm, pT1b-SM3 (arrowhead). The pathological response was Grade1; D: After chemoradiotherapy, the residual tumor was ulcerative type; E: Ultrasound showed the tumor as mixed echoic with irregular borders; F: Pathology showed 45 mm × 20 mm, pT3 (arrowhead). The pathological response was Grade1.

esophageal cancers expressed echo levels between the muscularis propria and the deep mucosa[17]. However, our study showed that the residual tumors lost heterogeneity and higher echogenicity after CRT compared to deep mucosa. This result indicated that the preoperative treatment increased the brightness of echogenicity. In a previous pathological study, chemotherapy was found to generally decrease tumor cellularity and cause fragmentation of cell nuclei. Additionally, in squamous cell carcinoma, chemotherapy is known to increase keratinization with the formation of keratin pearls, acellular keratin with islands of nonviable tumor cells, histiocytic giant cells, and lymphocytes surrounding tumor cells in squamous cell carcinoma[18]. Our pathological findings after neoadjuvant therapy, particularly after CRT, showed that the density of collagen fibers increased as the cancer cells disappeared. Consequently, the ratio of cancer cells to stromal components also changed, which might have led to a difference in echo level, such as mixed echogenicity. The increase in the echogenicity of tumors is reportedly related to the positive response to NAC in breast tumors[19]. Although such phenomena correlating echogenicity and treatment effect are not reported for esophageal cancers, and our study could not prove the relationship, some changes in echogenicity of ESCC could be attributed to treatment.

When predicting patient prognosis after CRT or NAC, it is reasonable to measure the reduction in tumor volume using EUS. However, the conventional measurement method involving direct identification and measurement of the tumor is not accurate. Several studies have assessed the predictive value of tumor thickness and area using EUS to determine patient prognosis and tumor regression in patients with esophageal cancer undergoing NAC or CRT[20-23]. Although these studies focused on lesions identified on EUS, our results showed that EUS could not detect the residual tumor. Tumors were either scattered on the esophageal wall, had unclear borders, or were scar tissue that appeared like a tumor.

For this reason, we considered it inappropriate to include EUS-confirmed echo lesions as residual tumors. In our clinical experience, we have observed that the esophageal muscle layer can be clearly visualized using EUS in patients with a good response to neoadjuvant therapy. Therefore, we focused on the esophageal muscle layer as indirect findings instead of the tumor. In the first study, ultrasound findings for specimens in the group with pT0 and pT1 showed that the muscle layer circumference was longer, the length of muscle layer defect was shorter, and the rate of muscle layer defect was lower than in the group with pT2 and pT3. Tissue heterogeneity was noted if residual cancer cells remained in the muscle layer or deeper; in such cases, we could not explore the muscle layer using ultrasound findings. In addition, it was improbable that the muscle layer destroyed by tumor invasion could be regenerated,

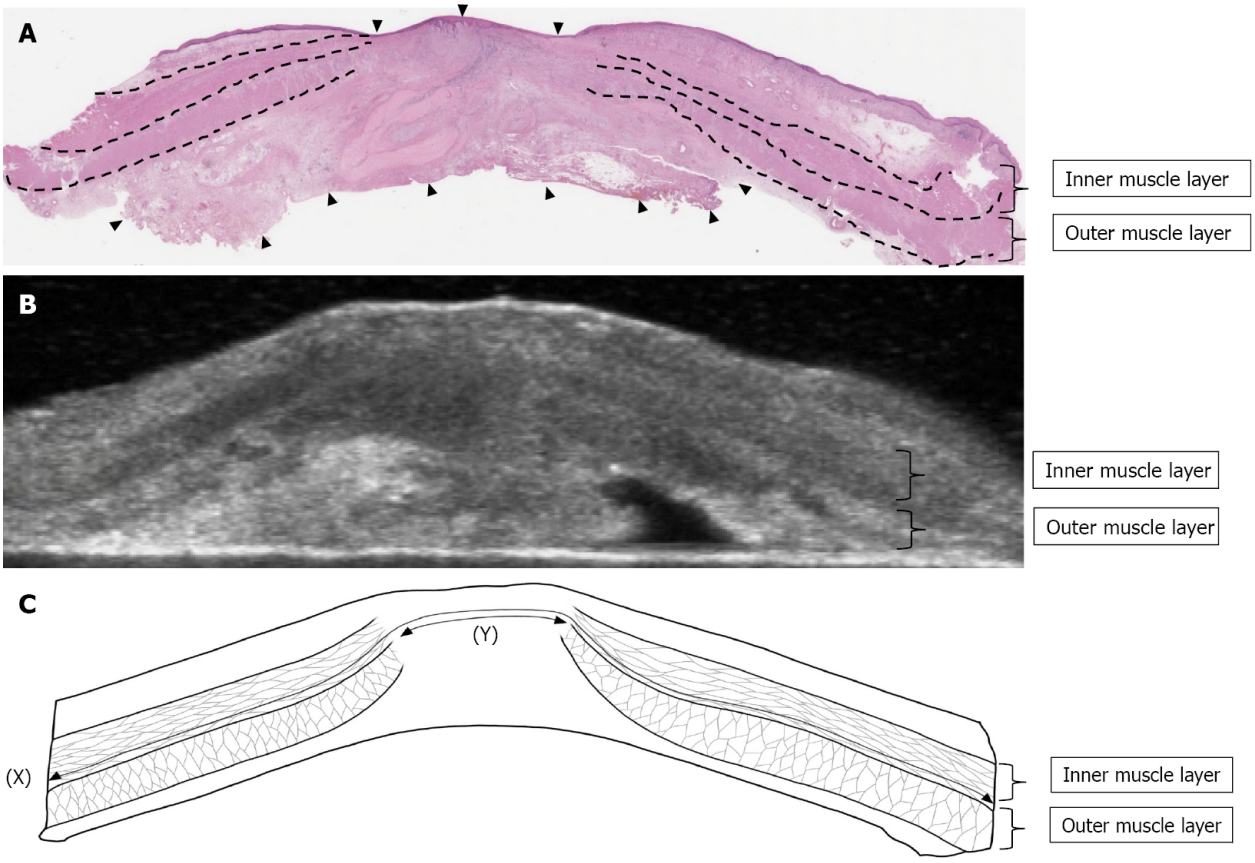

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Figure 2 Measurements of muscle layer defect. A: In this case of cT4b to pT1a after chemoradiotherapy, most of the primary tumors were replaced by degenerative tissue (arrowhead), and the muscle layer was taking over; B: Ultrasound for specimens showed a clearly defined disruption of the muscle layer; C: Length of muscle layer circumference (X) was 45 mm. The length of the muscle layer defect (Y) was 12 mm. In this case, the ratio of muscle layer defect was 27%.

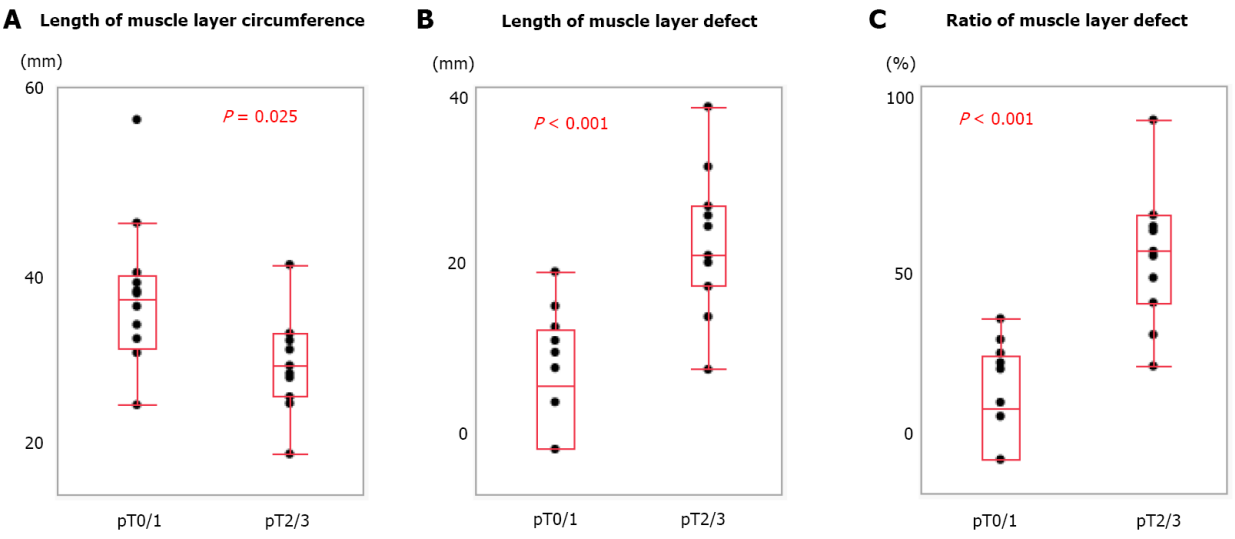

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Figure 3 Relationship between muscle layer measurements and pathological characteristics. A: Length of muscle layer circumference correlated with pT (pT0/1 *vs* pT2/3); B: Length of muscle layer defect correlated with pT; C: Ratio of muscle layer defect correlated with pT.

at least during the observation period. We considered that the reduction in the muscle layer defect in the specimens with stages pT0 and pT1 was because of scar contraction caused by the disappearance of the tumor due to neoadjuvant therapy. In the second study, findings of EUS performed before and after neoadjuvant therapy in the group with pT0 and pT1 showed that pre-MDA was smaller, post-MDA was smaller, and MDA reduction rate was larger in the groups with pT2 and pT3 staging. The improvement

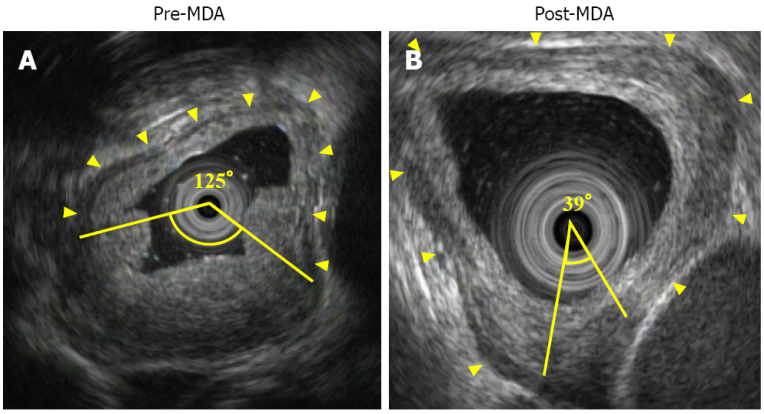

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Figure 4 Measurements of muscle layer defect angle. A: Endoscopic ultrasound showed the normal muscle layer as hypoechoic inner muscle layer, hyperechoic intermuscular connective tissue layer, and hypoechoic outer muscle layer (arrowhead). In this case of cT3 before neoadjuvant chemotherapy (NAC), pre-muscle layer defect angle (MDA) was 125°; B: After NAC, post-MDA was 39°, and thus MDA reduction rate was 34.8%. This case achieved pCR.

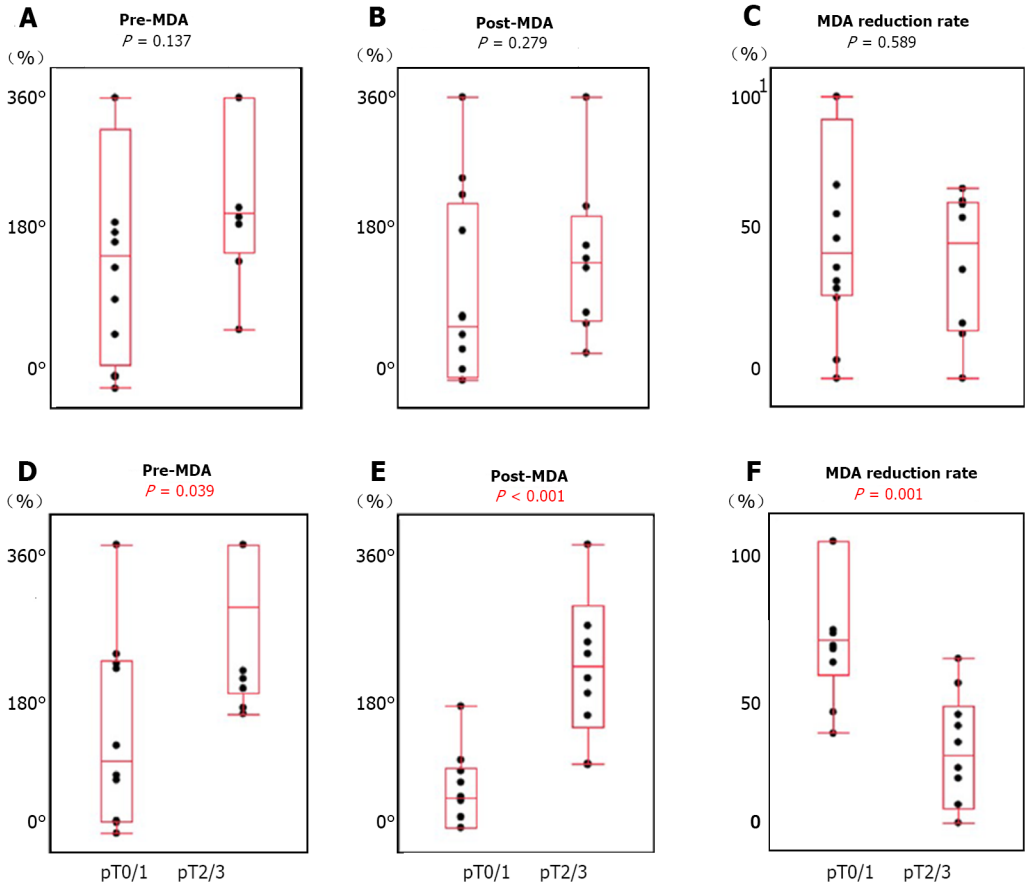

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Figure 5 Relationship between muscle layer defect angle measurements and clinicopathological factors. A: Pre-muscle layer defect angle (MDA) not correlated with preoperative treatment [neoadjuvant chemotherapy (NAC) *vs* chemoradiotherapy (CRT)]; B: Post-MDA not correlated with preoperative treatment (NAC *vs* CRT); C: MDA reduction rate not correlated with preoperative treatment (NAC *vs* CRT); D: Pre-MDA correlated with pT (pT0/1 *vs* pT2/3); E: Post-MDA correlated with pT (pT0/1 *vs* pT2/3); F: MDA reduction rate correlated with pT (pT0/1 *vs* pT2/3).

of the muscle layer defect was considered useful in EUS depth diagnosis.

If EUS helps diagnose pCR or superficial residual tumors and deep remanent tumors in patients after neoadjuvant therapy by focusing on the muscle layer, the clinical treatment options can be expanded significantly. In recent years, endoscopic salvage resection has been preferred over esophagectomy for patients with superficial localized residual tumors after CRT[24,25]. In addition, it was reported that overall, 29% of patients with esophageal cancer achieved pCR after neoadjuvant CRT[26], and 62% of

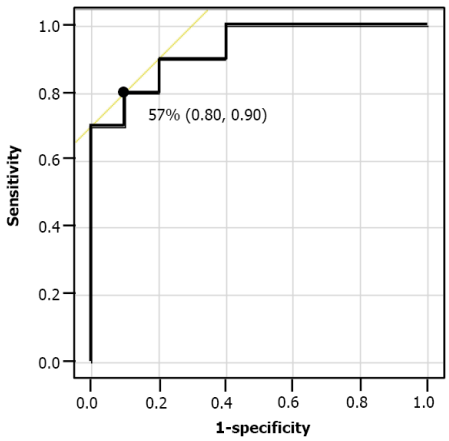

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Figure 6 Receiver operating characteristics curve of the muscle layer defect angle reduction rate. The AUS was 0.93, and 57% was the optimal cut-off value to detect the patients in the pT0/1 group with the highest accuracy.

patients with ESCC achieved pCR according to the JCOG9906 study in Japan[3]. A study reported that 2%-7% of patients with ESCC achieved pCR after NAC; however, they included only a small number of cases[4,5]. Because of such response rates, recent studies have focused on assessing the efficacy of active surveillance to help avoid highly invasive esophagectomy[27]. In addition to the usual endoscopic diagnosis, which mainly involves biopsy, subsequent MDA reduction rate may allow the selection of endoscopic salvage resection instead of esophagectomy.

Our study had some limitations. First, it was a single-center study with a small sample size. The usefulness of EUS must be evaluated in the future by conducting larger prospective studies. Second, it was difficult to seamlessly match the sites measured before and after preoperative treatment with EUS. We attempted to match the measurement sites by recording the scope length from the mouth and comparing it to the surrounding vessels and structures. Third, the value of post-MDA could be different depending on the time since preoperative treatment. We assessed MDA 4 to 6 wk after the last preoperative treatment. However, to determine the effectiveness of neoadjuvant therapy and for active surveillance, it is necessary to examine the differences in MDA according to the time since treatment.

CONCLUSION

This study showed that ultrasound could not detect some residual tumors after neoadjuvant therapy. Meanwhile, focusing on the esophageal muscle layer as indirect findings rather than the residual tumor as direct findings could help diagnose the depth of the tumor. Applying these results in clinical practice may help clinicians provide more treatment options for patients with ESCC after neoadjuvant therapy.

ARTICLE HIGHLIGHTS

Research background

The diagnosis of endoscopic ultrasound (EUS) for esophageal cancer after neoadjuvant therapy is controversial. In addition, it is unclear whether the echogenic lesions detected using EUS are indeed residual tumors and how they appear on ultrasound.

Research motivation

There are few studies that contrast echographic and pathologic images of esophageal cancer after neoadjuvant therapy. In our clinical experience, we have observed that the esophageal muscle layer can be clearly visualized using EUS in patients with a good response to neoadjuvant therapy.

Research objectives

To investigate the ultrasound imaging features of residual tumors and identify the limitations and potential of EUS.

Research methods

Twenty-three patients receiving esophagectomy after neoadjuvant therapy [15 patients after

neoadjuvant chemotherapy (NAC) and 8 patients after chemoradiotherapy (CRT)] were studied. We diagnosed the T stage and compared ultrasound images with pathological findings using ultrasound for surgical specimens. Furthermore, the rate of reduction for the muscle layer defect was evaluated using EUS images obtained before and after neoadjuvant therapy.

Research results

The accuracy of T stage rate was 61%, which worsened after CRT (38%) than after NAC (73%). Moreover, pT0 could not be diagnosed in all cases. The detection rate of residual tumor for specimens using ultrasound retrospectively was 75%. Tumor borders were irregular and echogenicity was mixed type after CRT. There was a correlation between the pT stage and the rate of muscle layer defect reduction measured by EUS.

Research conclusions

Some tumors are undetectable on ultrasound when compared to pathological images. However, focusing on the esophageal muscle layer may improve the accuracy of T stage diagnosis of residual tumors.

Research perspectives

If EUS helps diagnose T stage of residual tumors in patients after neoadjuvant therapy by focusing on the muscle layer, the clinical treatment options can be expanded significantly.

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FOOTNOTES

Author contributions: Yonemoto S performed the research and wrote the paper; Uesato M came up with the study idea and supervised the study; Uesato M, Nakano A, Murakami K, Toyozumi T, Maruyama T, Suito H, Tamachi T, Kobayashi M and Kainuma S collected the data; Matsusaka K provided pathological advice; Matsubara H supervised the report.

Institutional review board statement: The study protocol was approved by Hospital of Chiba University Biomedical Research Ethics Committee, No. 3550.

Informed consent statement: Written informed consent was obtained before treatment for all patients.

Conflict-of-interest statement: All authors declare no conflicts-of-interest related to this article.

Data sharing statement: No additional data are available.

Country/Territory of origin: Japan

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CASE REPORT

Endoscopic ultrasonography drainage and debridement of an infected subcapsular hepatic hematoma: A case report

Theo Doyon, Thibault Maniere, Étienne Désilets

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Peer-review model: Single blind

Peer-review report's scientific quality classification

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Grade B (Very good): B, B, B
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Abstract

BACKGROUND

Endoscopic ultrasonography (EUS) has evolved in the last years making it not only a diagnostic modality but a therapeutic procedure. EUS is now used as an alternative technique to percutaneous and surgical drainage. Even though EUS is a challenging procedure and not always suitable compared to percutaneous drainage, there is a need for developing new therapeutic approaches to the liver for when percutaneous drainage is not feasible.

CASE SUMMARY

We present the case of a 82 years old male who developed an infected subcapsular hepatic hematoma (SHH) of the left lobe following percutaneous biliary drainage. After 2 failed attempts of percutaneous drainage of the SHH and because the patients couldn't withstand surgery, we conducted a EUS drainage and debridement of the SHH. Using a lumen apposing metal stent (LAMS) by a transgastric approach, we were able to gain endoscopic access to the SHH. With our experience in the debridement of walled off pancreatic necrosis using this technique, we were confident it was the right approach. After four debridement sessions, the computed tomography scan showed a clear regression of the SHH.

CONCLUSION

To our knowledge, this is the first case of successful endoscopic debridement of a SHH using a LAMS which appear to be feasible and safe in this specific case.

Key Words: Intervention endoscopic ultrasonography; Complication; Hepatic subcapsular hematoma; Transmural drainage; Lumen apposing metal stent; Case report

Core Tip: We conducted an endoscopic ultrasonography drainage and debridement of a subcapsular hepatic hematoma (SHH). Using a lumen apposing metal stent (LAMS) with a transgastric approach, we were able to gain endoscopic access to the SHH. With our experience in the debridement of walled off pancreatic necrosis using this technique, we were confident it was the right approach. After four sessions of debridement, the computed tomography scan showed a clear regression of the SHH. To our knowledge, this is the first case of successful endoscopic debridement of a SHH using a LAMS which appear to be feasible and safe in this specific case.

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INTRODUCTION

Endoscopic ultrasonography (EUS) has evolved making it more and more a therapeutic procedure[1-3]. For instance, it is now used for drainage of abscesses or hematomas when the first line of treatment that is percutaneous drainage is not feasible or has failed[1,4-7] or for gallbladder drainage for cases of refractory acute cholecystitis in the elderly who can't withstand surgery[8]. EUS is now used as an alternative technique to surgical drainage which is highly invasive, making EUS more favorable in term of procedural complications[1]. Percutaneous drainage, despite its high success rate also has its complications: Bleeding, perforation, peritonitis, fistula, sepsis and hematomas like subcapsular hepatic hematoma (SHH)[4,5,9]. Even though EUS is a challenging procedure and not always suitable compared to percutaneous drainage[5], there is a need for developing new therapeutic approaches to the liver when percutaneous drainage is not feasible[5] thus preventing the use of surgical drainage and its potential complications[1]. SHH can be a life-threatening situation[9-13]. SHH are traditionally managed conservatively with antibiotics and pain management[4,11,12,14]. However, when the SHH is persistent, becomes infected or worsens, it can be treated by percutaneous drainage and in case of failure by surgical drainage[4,5,13].

In walled off pancreatic necrosis (WOPN), debridement of the necrosis can be done surgically or by EUS which is less at risk of complications compared to conventional surgery[3,15,16]. The usual procedure for the drainage and debridement of WOPN is a puncture of the collection under EUS and dilation of the track using a cystotome or a balloon[15,16]. Endoscopic drainage of WOPN is then assured by the placement of multiple double pigtail stents or by installing a lumen apposing metal stent (LAMS) under EUS and use the stent as an access to get inside the necrosis for debridement of the WOPN[15]. Knowing that surgical drainage of SHH is an invasive and risky procedure, that the site of the hematoma can make percutaneous drainage difficult[1,4,5], that EUS drainage of a liver abscess is an effective and successful method to drain difficult to access abscess using a transgastric or transduodenal approach[4,5,7] and that EUS is used in debridement of WOPN[15,16]; we hypothesized that debridement of a SHH using EUS could be successful.

CASE PRESENTATION

Chief complaints

We report the case of a 82 years old male, known for a pancreatic cystic lesion under punctual surveillance by EUS.

History of present illness

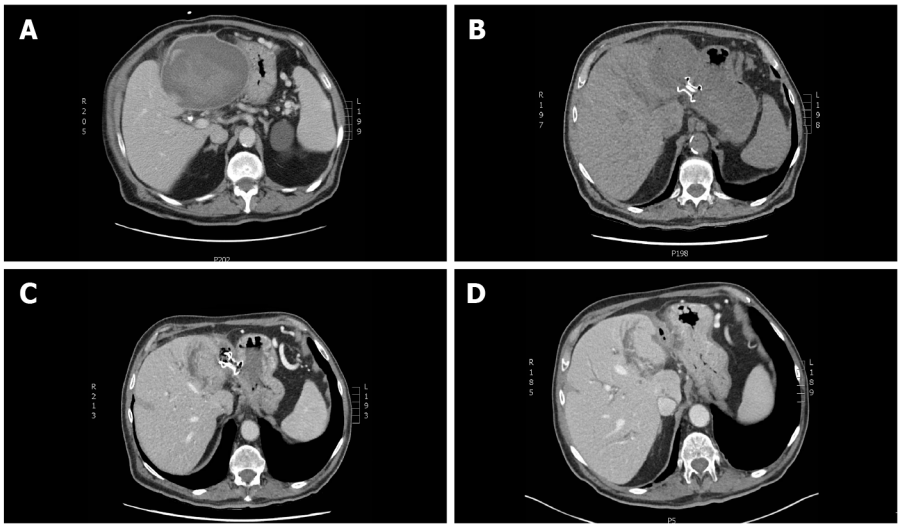
The patient has a pancreatic cystic lesion under punctual surveillance by EUS.

History of past illness

The history of past illness are chronic kidney failure, hypertension, type 2 diabetes, dyslipidemia and coronary artery disease for which he took medication.

Personal and family history

None personal or family history.



DOI: 10.4253/wjge.v14.i5.335 **Copyright** ©The Author(s) 2022.

Figure 1 Computed tomography scan of the upper abdomen showing the left subcapsular hepatic hematoma at different stages of endoscopic treatment. A: At diagnosis, the subcapsular hepatic hematoma (SHH) size was 12.5 cm × 10.5 cm × 12.5 cm and was compressing the stomach; B: At day 1 after endoscopic ultrasonography and lumen apposing metal stent (LAMS) was installed by transgastric approach; C: A month later, a control computed tomography (CT) scan of the upper abdomen showed a resorption of the SHH after 4 debridement sessions; D: Control CT scan of the upper abdomen after the LAMS was removed endoscopically.

Physical examination

During a routine monitoring of the pancreatic cystic lesion, EUS revealed a focal dilatation of the left intrahepatic bile duct.

Laboratory examinations

His laboratory tests showed white blood cells at 10.9 × 10^9/L, hemoglobin at 109 g/L, bilirubin at 23 μmol/L, alkaline phosphatase 231 U/L, aspartate aminotransferase 70 U/L, alanine aminotransferase 134 U/L and CA199 at 315 kU/L. Hours after the percutaneous drainage, the patient developed right upper quadrant pain and the hemoglobin level went down to 62 g/L.

Imaging examinations

Sequential endoscopic retrograde cholangiopancreatography was performed with cytology brushing and dilatation of a left intrahepatic biliary stricture followed by deployment of a 15 cm 8.5 Fr plastic stent in that area. A percutaneous drain in the left intrahepatic bile duct was then added in radiology.

FINAL DIAGNOSIS

The patient developed cholangitis.

TREATMENT

A control computed tomography (CT) scan revealed a 12.5 cm × 10.5 cm × 12.5 cm hypodense lesion compatible with a SHH in the left lobe (segment 3) (Figure 1). The patient was sent back in radiology and there was no active bleeding or pseudoaneurysm during the arteriography. Over the next days the patient developed a fever. A percutaneous 10 Fr catheter was inserted in the hematoma to attempt drainage and was repositioned once. Only a modest amount of bloody fluid was collected (150 mL). After a month of conservative treatment and a failed attempt to wean the patient from antibiotics, a control CT scan showed an expansion of the SHH with air bubbles within. Percutaneous drainage was again performed in radiology using a multiperforated 10 Fr stent and drained 100 cc of bloody liquid. Control CT showed a slow regression of the SHH and a thick wall around it.

Seeing the slow rate of resorption of the infected SHH, a consultation in hepatobiliary surgery was obtained but the patient was deemed too sick to withstand surgery. After consent from the patient, we decided to perform a EUS drainage of the infected SHH with a 10 mm × 15 mm LAMS (Hot-Axios, Boston scientific) by a transgastric approach under conscious sedation. The collection appeared heterogenous, surrounded by a thick wall and very close to the stomach smaller curvature. Considering the

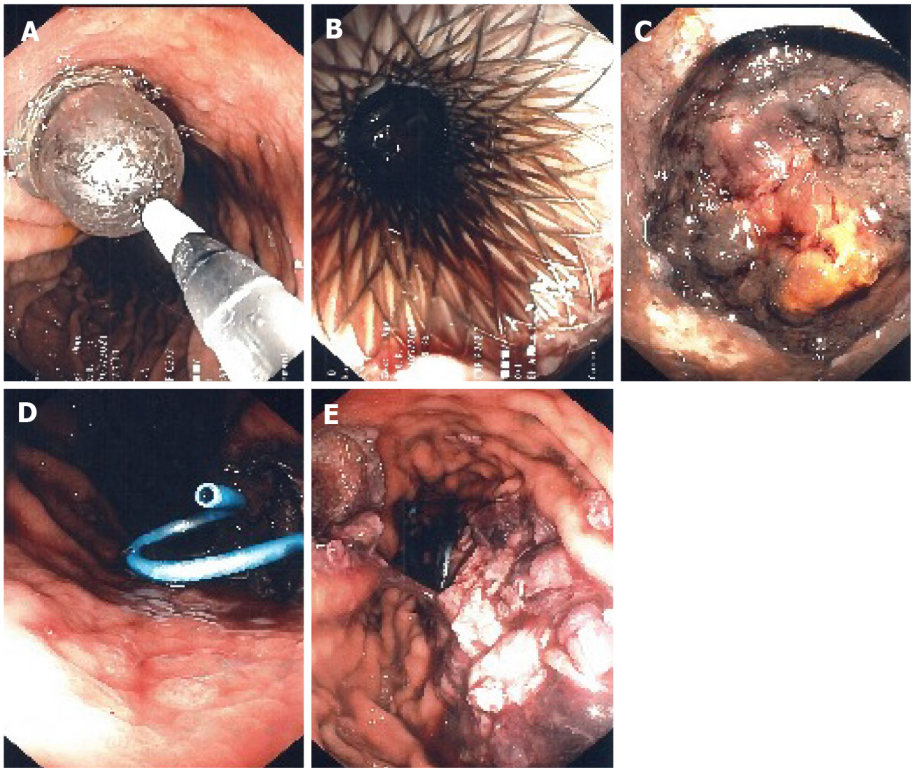


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Figure 2 Endoscopic ultrasonography guided transgastric insertion of fully covered 10 mm × 15 mm lumen apposing metal stent allows endoscopic access to the subcapsular hepatic hematoma for drainage and debridement. A: Dilatation of the lumen apposing metal stent (LAMS) was needed for the first debridement; B: Endoscopic image showing the LAMS after dilatation during the first of four debridements; C: Endoscopic image showing the subcapsular hepatic hematoma (SHH) during the second debridement; D: After each debridement, a double pigtail stent was inserted into the lumen of the LAMS allowing a more complete drainage of the SHH; E: Endoscopic image showing debris of the hematoma inside the stomach after the last debridement.

location of the SHH, the puncture was easy, and deployment of the LAMS was done using the standard Seldinger technique. Pus and blood were drained from the hematoma into the stomach immediately after deployment. After the procedure, the patient recovered well, with no adverse event. The two percutaneous drains were removed. The following day, the first of four debridement sessions under conscious sedation were performed with a standard gastroscope through the LAMS (Figure 2). Dilatation of the LAMS at 18 mm was needed at the first debridement. Each debridement session lasted between 30-35 min. Informed consent was obtained before each session. At the end of each debridement, a double-sided pigtail 7 Fr drain was installed inside the LAMS stent to help drain the SHH and maintain position and patency.

OUTCOME AND FOLLOW-UP

After the fourth debridement, the endoscopic appearance of the SHH cavity was clean with whitish walls and a CT scan revealed a massive regression of the SHH (2.2 cm × 3.1 cm); showing that the EUS procedure was a success. The LAMS was then removed endoscopically and the fistula between the stomach and the SHH closed immediately. The patient recovered well (Figure 3).

DISCUSSION

SHH is an "accumulation of blood between the Glisson's capsule and the liver parenchyma; rupture into the peritoneum has a 75% mortality rate"[10] which makes it life threatening[11]. In this case, the SHH was present for more than 3 mo, giving it time to organize itself and coagulate making it refractory to percutaneous drainage. Moreover, the SHH was infected, and the patient was under antibiotics for 6 wk without any success. Finally, the patient couldn't withstand surgery, so we had no choice but to try EUS drainage as a therapeutic procedure.

Important factors helped us choose this approach: The patient didn't have any coagulopathy; the encapsulated look and thick walls of the SHH; the anatomy of this region and the proximity of the SHH,

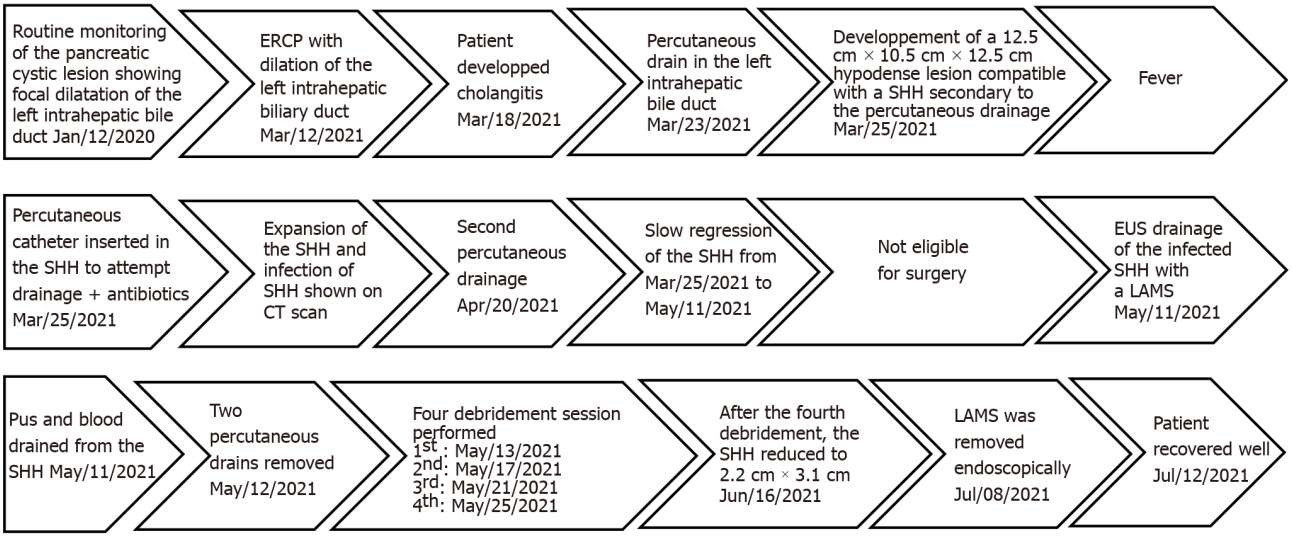

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Figure 3 Timeline of the medical care episode. CT: Computed tomography; SHH: Subcapsular hepatic hematoma; ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasonography; LAMS: Lumen apposing metal stent.

in segment 3 of the liver, with the small curvature of the stomach; the absence of pseudoaneurysm or active bleeding on the arteriogram and our experience in the debridement of WOPN. Altogether, it made us confident that EUS drainage and debridement under conscious sedation was the right approach. This way we were able to use a known and proven technique to a novel situation (*i.e.*, SHH). The procedure was a success, since after drainage and debridement, there was a significant reduction in the volume of the SHH (Figure 1).

This makes it the first EUS drainage and debridement of a SHH to our knowledge in the medical literature. We warn that this technique may be used only in cases where the collection is near the gastric or duodenal wall and when there is an experienced endoscopist who has competence in therapeutic EUS. The use of a naso-cystic tube to improve irrigation and shorten the resolution of SHH is debatable. Those tube are used also for common bile duct infection but are not well tolerated by patients. We decided to keep the LAMS in place for 2 mo to maintain the fistula wide open and make the access to the SHH easier. We removed it after the fourth debridement when the SHH was resolved. It is usually advised to remove those stents after 4-6 wk to avoid potential bleeding due to mucosal erosion[17].

There are many risks associated with the procedure. Aside from the general risks related to endoscopic anesthesia (respiratory failure, aspiration), the specific risk are bile leak, bleeding, infection, perforation, peritonitis and death. To assess and minimize the bleeding risk, doppler was used before the first endoscopic access to avoid any vascular structure in the gastric wall. The SHH was scanned with multiphasic acquisitions to rule out the presence of a pseudoaneurysm. If significant bleeding was to happen, we would have referred to angiography and arterial embolization. For peritonitis, the decision to send the patient to the operating room to proceed with conservative management would have been based on the severity and extent on imaging studies.

Furthermore, since the access to the SHH was in the smaller curvature, there was a potential risk of reflux of digestive flora into the SHH. This is a potential risk of all trans-gastric drainage techniques for which the consequences are unknown to our knowledge. Some have stated that it could be beneficial in the way that stomach acidity can provide a kind of chemical debridement [some even stop proton pump inhibitors (PPIs) between sessions of pancreatic necrosis debridement][18]; others fear potential supra-infection from the digestive flora and food relux from the digestive lumen[19]. In our case, the patient remained on large spectrum IV antibiotics from the first to the last endoscopic intervention to prevent supra-infection. PPIs were maintained.

We did not study the cost effectiveness of this approach compared to surgery. This is certainly an interesting question. Surgery remains for us the gold standard for refractory SHH; we proceeded this way because the risk of surgery was too high in our case. In the future, we think that EUS should be considered along the other modalities (surgery and radiological drainage) for the treatment of all kinds of peri-digestive infections (pseudocyst, pancreatic necrosis, liver and perihepatic abscesses, acute cholecystitis). The choice of the best modality should be based on available scientific data, specific risks for the patient, local expertise, and availability of the technology.

There are many potential advantages to the use of EUS: It is less invasive than surgery, there is no need for a transcutaneous tube or collecting bag, it can be a permanent drainage (*ex*: For gallbladders and pseudocyst) and larger stents allow for potential endoscopic debridement if needed. However, the lack of availability and expertise and the cost of material and technology make using EUS as a

therapeutical option challenging.

CONCLUSION

To our knowledge, this is the first case of successful endoscopic debridement of a SHH using a LAMS which appear to be feasible and safe in this specific case. Thus, EUS drainage of an infected SHH seems like an alternative therapeutic approach to consider, but clinical indications remain to be defined. More experience from other centers around the world will be needed before applying this treatment in a widespread fashion.

FOOTNOTES

Author contributions: Doyon T, Manière T and Désilets E contributed equally to this work.

Informed consent statement: The patient signed an informed written consent form for all the information that is found in this case report, and for all the procedures he went through.

Conflict-of-interest statement: All authors disclosed no financial relationships relevant to this publication.

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CASE REPORT

Intraoperative endoscopic retrograde cholangiopancreatography for traumatic pancreatic ductal injuries: Two case reports

Andrew Canakis, Varun Kesar, Caleb Hudspath, Raymond E Kim, Thomas M Scalea, Peter Darwin

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Provenance and peer review: Unsolicited article; Externally peer reviewed.

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Peer-review report's scientific quality classification

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Abstract

BACKGROUND

In order to successfully manage traumatic pancreatic duct (PD) leaks, early diagnosis and operative management is paramount in reducing morbidity and mortality. In the acute setting, endoscopic retrograde cholangiopancreatography (ERCP) can be a useful, adjunctive modality during exploratory laparotomy. ERCP with sphincterotomy and stent placement improves preferential drainage in the setting of injury, allowing the pancreatic leak to properly heal. However, data in this acute setting is limited.

CASE SUMMARY

In this case series, a 27-year-old male and 16-year-old female presented with PD leaks secondary to a gunshot wound and blunt abdominal trauma, respectively. Both underwent intraoperative ERCP within an average of 5.9 h from time of presentation. A sphincterotomy and plastic pancreatic stent placement was performed with a 100% technical and clinical success. There were no associated immediate or long-term complications. Following discharge, both patients underwent repeat ERCP for stent removal with resolution of ductal injury.

CONCLUSION

These experiences further demonstrated that widespread adaption and optimal timing of ERCP may improve outcomes in trauma centers.

Key Words: Pancreatic ductal injury; Pancreatic leaks; Endoscopic retrograde cholangiopancreatography; Trauma; Endoscopic stenting; Case report

Core Tip: In the acute setting, intraoperative endoscopic retrograde cholangiopancreatography (ERCP) can effectively diagnosis and manage pancreatic duct (PD) injuries with stenting. At our high-volume trauma center, the on call therapeutic endoscopy team allows for quick and effective mobilization of resources. In this series, the time from admission to ERCP occurred within 6.3 and 5.6 h. The pancreatic injuries healed, and both stents were removed. In cases of traumatic PD injury, we believe that advanced gastroenterology care has the opportunity to improve the timing of diagnosis and treatment as a means to potentially reduce the morbidity and mortality associated with such injuries.

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INTRODUCTION

Pancreatic duct (PD) injuries are uncommon (occurring in 3% to 12% of traumas), primarily due its protective retroperitoneal location. They can be difficult to diagnose due to non-specific symptoms and delayed findings on imaging[1]. A delay in diagnosis can result in severe complications, such as a pancreatic fistula, hemorrhage, or abscess by which obtaining a fast and accurate diagnosis is paramount[2,3].

Standard therapy for high grade pancreatic injury with traumatic PD disruption is operative. As the duct itself is not amenable to repair, surgical options are resection and/or simple drainage accepting the inevitable pancreatic fistula. Major pancreatic resection is morbid and can produce nutritional cripples and render patients diabetic. Preoperative imaging is often inaccurate or not feasible. The limited sensitivity (52%) of computed topography (CT) is further complicated by timing, as CT scans performed in less than 24 h of presentation can often miss PD injuries as inflammatory associated changes are yet to manifest[1,4,5]. There is also poor sensitivity associated with magnetic resonance cholangiopancreatography (MRCP) imaging, and many times unstable patients may not be suitable for such imaging[4,6].

The diagnosis of PD transection is often suspected at the time of laparotomy. Knowing whether the PD is actually transected can be difficult. Visual inspection can over diagnose these injuries leading to unnecessary surgery. One would prefer to limit major pancreatic procedures to those patients with hemorrhagic shock or those without other options.

While endoscopic retrograde cholangiopancreatography (ERCP) is the most accurate method for assessing PD integrity and extent of injury, its wide spread use is hindered due to limited resources, local expertise and difficulty performing the procedure itself in an emergent, operative setting[1,7]. ERCP can also be therapeutic as PD stenting can be performed at the time of diagnosis. Stenting a duct that is transected can be challenging but if successful, the duct may heal around the stent and limit the need for major pancreatic resection. In this case series, we present two cases treated at a major urban trauma center where PD injuries were diagnosed with intraoperative ERCP and treated with sphincterotomy and stenting.

CASE PRESENTATION

Chief complaints

Case 1: Multiple gunshot wounds (GSWs).

Case 2: Blunt abdominal trauma.

History of present illness

Case 1: A 27-year-old male presented with four GSWs to the chest and abdomen.

Case 2: A 16-year-old female initially presented to an outside hospital with severe upper quadrant abdominal pain following blunt abdominal trauma. She remained at the hospital for two days with an inability to tolerate per oral intake, nausea, and vomiting.

History of past illness

Both patients had no specific history of past illness.

Personal and family history

No pertinent personal or family history of both patients.

Physical examination

Case 1: Upon arrival he was found to have penetrating GSWs to the left shoulder, left axilla, right flank, and subxiphoid areas.

Case 2: Upon arrival she was afebrile (37 ℃), normotensive (119/71 mmHg) but tachycardic (130 beats per min) with abdominal tenderness to palpation.

Laboratory examinations

Case 1: Labs on admission were notable for a white blood cell (WBC) count 10.9 K/mcL, hemoglobin 12.5 g/dL, platelets 430 K/mcL, international normalized ratio 1, aspartate transaminase (AST) 315, alanine transaminase (ALT) 282, alkaline phosphatase (ALP) 72, total bilirubin 0.2, amylase 127 units/L, lipase 59 units/L and lactate 6.8 nmol/L. He was resuscitated and imaging was obtained.

Case 2: Labs were notable for a WBC 16.6 K/mcL, Hg 11 g/dL, AST 23, ALT 12, ALP 74, total bilirubin 2.3 mg/dL, lipase 1160 units/L and amylase 441 units/L.

Imaging examinations

Case 1: Computed tomography angiography of the chest abdomen and pelvis revealed significant injuries, including but not limited to a left ventricle apex cardiac injury, laceration of liver lobe segments two and six, a pancreatic artery pseudoaneurysm (measuring 1.4 cm), and shrapnel wounds to the gallbladder, duodenum, pancreatic head, and hepatic flexure (Figure 1). There was no mention of pancreatic leak.

Case 2: A CT of the abdomen demonstrated a grade III pancreatic injury (thickness pancreatic transection involving the proximal tail and neck), large hemoperitoneum, and a 1 cm posterior splenic laceration for which she was transferred to our center for surgical care (Figure 2).

Further diagnostics

Case 1: He immediately went to the operating room (OR) for exploratory laparotomy where he underwent a non-anatomic bilateral liver resection, cholecystectomy, colon resection with end colostomy, gastric wedge resection, small bowel resection (20 cm) with anastomosis. He had a high-grade injury to his pancreatic head that would have required a Whipple to treat but it was not clear that he had a major PD injury. An intraoperative ERCP demonstrated a ventral PD leak in the head of the pancreas (Figure 3).

Case 2: She was sent directly to the OR, where an exploratory laparotomy revealed 500 mL of pancreatic ascites which was evacuated from the lesser sac and right upper quadrant. There was concern for PD disruption at proximal aspect of the pancreatic tail. An intraoperative ERCP demonstrated a PD leak in the body (Figure 4).

FINAL DIAGNOSIS

Both patients were diagnosed with PD leaks.

TREATMENT

Following the diagnostic ERCP, the first patient, underwent a pancreatic sphincterotomy followed by plastic pancreatic stent placement (5 Fr by 10 cm) (Figure 5). The main pancreatic duct (MPD) was intact. There were no technical challenges or associated complications from the procedure itself. The time from admission to ERCP was 6.35 h (Table 1). A drain was placed, and output decreased from 600 cc/d to 300 cc/d over two days. The drain amylase level was > 24000 units/L. Six days after the ERCP, his labs improved with an AST 46, ALT 77, ALP 89, and a total bilirubin 0.3. His hospital course was protracted related to non-pancreatic complications. He developed an intra-abdominal abscess communicating with the right abdominal wall wound. A CT abdomen pelvis did not show signs of a leak. However, he underwent a repeat ERCP with PD stent exchange to a larger 7 Fr by 10 cm plastic stent 18 d later due to a persistent leak on pancreatogram, with no further issues.

Similarly, in case 2, a 4 mm ventral sphincterotomy was performed followed by placement of a 5 Fr by 13 cm plastic stent into the dorsal pancreatic duct (Figures 6 and 7). There was no evidence of bile leakage. Her pancreas widely drained. The time from hospital admission to ERCP was 5.65 h. The procedure was technically successful with no adverse events. Her abdomen was left open. The next day,

Table 1 Patient characteristics with traumatic pancreatic duct leak

Patient	Age/sex	Etiology	Prior imaging	ERCP findings	Plastic biliary stent (Fr/cm)	Time from admission to ERCP (h)	Length of hospital stay
1	27/male	Gunshot wound	Yes, CTA	Ventral PD leak in the head of the pancreas	5/10 then upsized to 7/10	6.3	25
2	16/female	Blunt trauma	Yes, CT	Dorsal PD leak	5/13	5.6	22

CTA: Computed topography angiography; CT: Computed topography; ERCP: Endoscopic retrograde cholangiopancreatography; PD: Pancreatic duct.

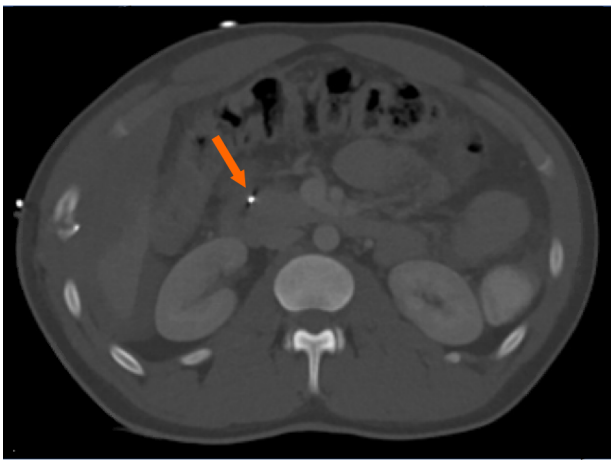

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Figure 1 Computed tomography of the abdomen demonstrating bullet shrapnel involving the proximal duodenum and the pancreatic head (arrow).

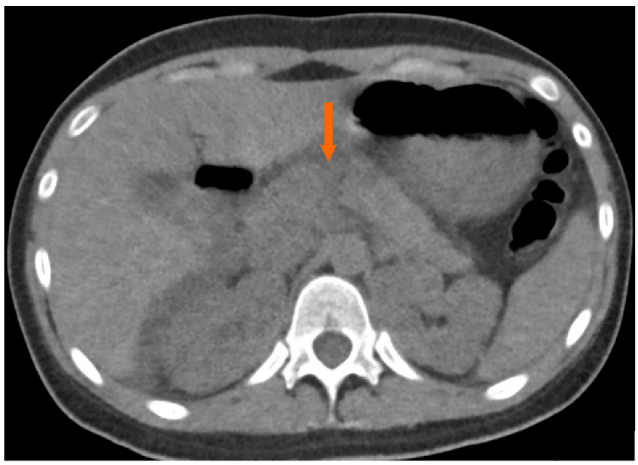

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Figure 2 Computed tomography of the abdomen revealing a full-thickness pancreatic transection involving the proximal tail and neck (arrow).

a MRCP confirmed placement of the pancreatic duct stent, which traversed the area of pancreatic transection with the tip of the stent residing in the tail of the pancreas. Two days after her initial surgery, she returned to the OR for abdominal re-exploration, pancreatic debridement, omentopexy, and primary closure.

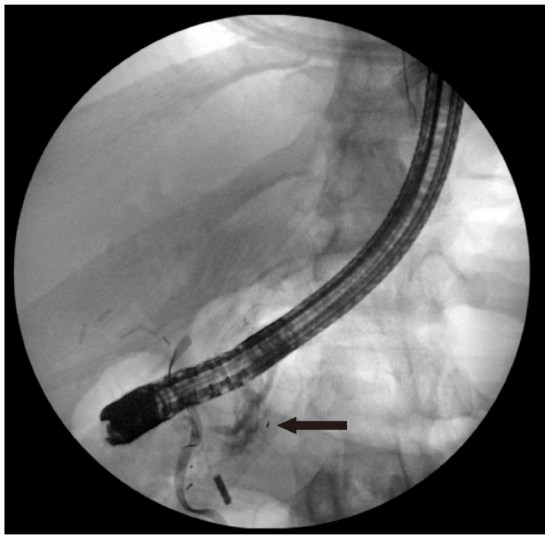

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Figure 3 Endoscopic retrograde cholangiopancreatography fluoroscopy showing a ventral pancreatic ductal leak in the head of the pancreas (arrow).

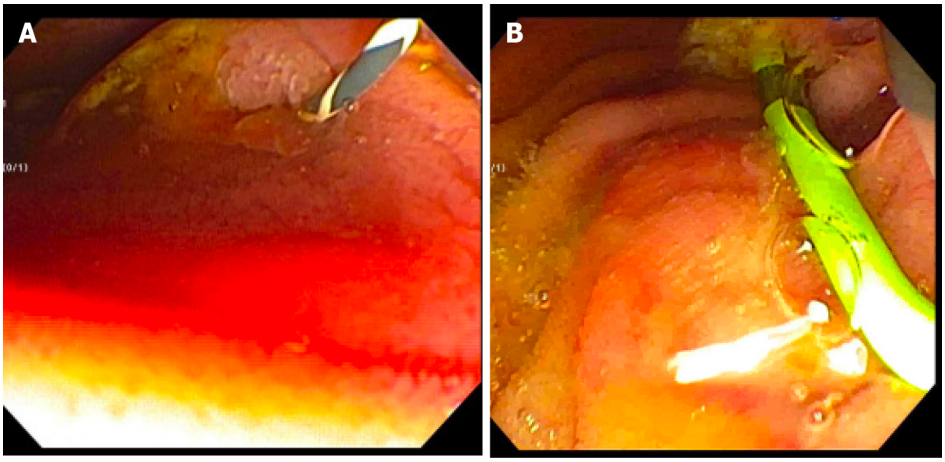

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Figure 4 Intraoperative endoscopic retrograde cholangiopancreatography. A and B: Endoscopic view following placement of an angled Visiglide wire into the ventral pancreatic duct (A) and placement of a plastic stent in the dorsal pancreatic duct (B).

OUTCOME AND FOLLOW-UP

Patient 1 was eventually discharged with a 25 d hospital length of stay. In the outpatient setting he underwent repeat ERCP with stent removal 84 d after discharge, with leak resolution and no further symptoms. The second patient's hospital length of stay was 22 d, and she was discharged without any major ERCP or pancreatic related complications. She underwent a repeat ERCP with stent removal 59 d following its initial placement with resolution of ductal injury.

DISCUSSION

This series demonstrates the efficacy, safety, and feasibility of intraoperative ERCP as a diagnostic and therapeutic tool. In this case series the average time from admission to ERCP occurred within 5.95 h. Both patients also underwent successful stent removal without any post-ERCP complications and resolution in the PD injury.

Clinical manifestations and management of PD leaks are largely dependent on the leak's size and location, where the integrity of the main duct influences prognosis[8]. In the setting of ductal injury, high pressure gradients cause pancreatic juices to flow outwards; as such, transpapillary stenting reduces the pressure gradient with preferential flow through the stent into the duodenum in order for

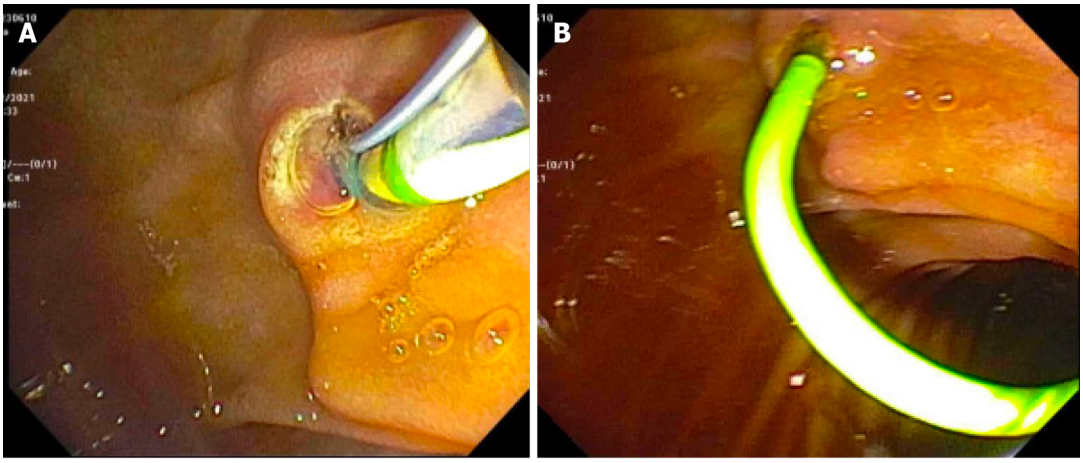

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Figure 5 Endoscopic view of the pancreatic sphincterotomy and pancreatic duct plastic stent placement. A: Pancreatic sphincterotomy; B: Pancreatic duct plastic stent placement.

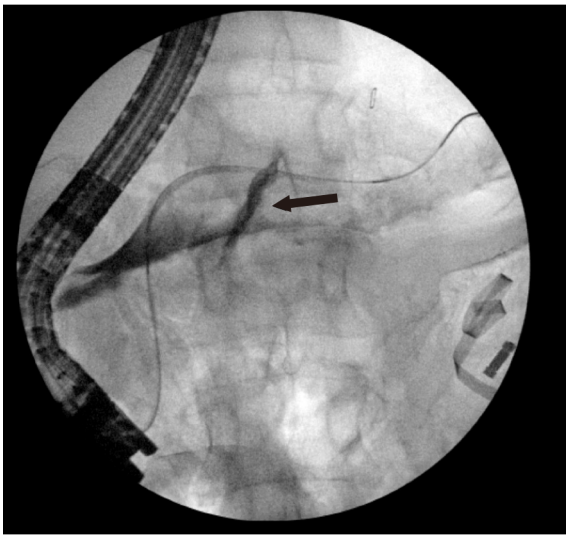

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Figure 6 Endoscopic retrograde cholangiopancreatography fluoroscopic view demonstrating a dorsal pancreatic ductal leak (arrow).

the injury to properly heal. At our center, we always perform a sphincterotomy with stent placement instead of employing nasobiliary catheter, with well documented success in cases of hepatic trauma as well[9].

The role of intraoperative ERCP in the trauma setting is not yet well defined. In a study of 71 patients with pancreatic injury, 50 of whom underwent immediate laparotomy, there was a 14% complication and 20% mortality rate[4]. In that study, intraoperative ERCP was not used. Instead, intraoperative visual inspection was undertaken to investigate for ductal injury. Four patients deemed not to have a leak developed pancreatic leaks with abscess formation. ERCP should be considered in the setting of traumatic pancreatic injury with a questionable PD injury. Its high diagnostic accuracy cannot be matched by any combination of a CT abdomen, serum amylase or peritoneal lavage[10]. In a large PD trauma series, an abdominal CT missed the diagnoses of major PD injury in 40.7% (11/27) of patients [11]. Furthermore, in a prospective study of 14 patients with PD injury, those undergoing ERCP greater than 72 h following trauma had higher rates of pancreatic complications and longer hospital stays[12]. In our series, both patients underwent ERCP immediately with no ERCP related complications or delayed lengths of hospital stays. One could postulate that early intraoperative ERCP effectively contained the leak and contributed to these positive outcomes.

ERCP with early stenting has also proven to be an effective and safe option in pediatric cases[13,14]. Yet, there has been some concern regarding the development of strictures, though it's unclear if such a complication occurs from the trauma itself or stent-induced changes[7]. In a small study analyzing long term outcomes for pancreatic stenting from blunt trauma the authors found that only 50% (3/6) of stents were successfully removed at 12, 19, and 39 mo[15]. Such complications were not seen in our patients,

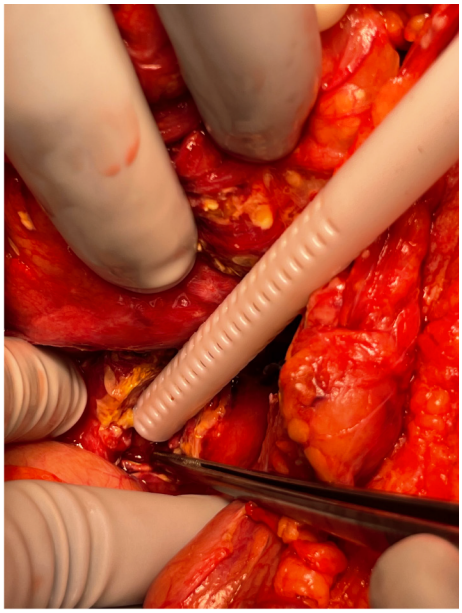

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Figure 7 Intraoperative photo confirming following placement of the pancreatic ductal stent.

likely because the stents were removed significantly earlier with minimal stent exchanges.

Studies exploring pancreatic trauma have not detailed intraoperative timing, which may be an important aspect for reducing complications as well. In a study of 43 patients with major PD trauma, 15 underwent stenting as the first treatment modality with a median time from trauma to ERCP of 6 d[12]. Within this group, there were 17 related complications including pseudocyst formation (8), PD stricture (4), distal pancreatic atrophy from injury site (3), and pancreatic fistulas (2). They also reported two deaths, one of which was related to severe pancreatitis where the stent was removed 8 d after insertion. The other death was attributed to a patient with severe alcoholic liver cirrhosis–unrelated to the stent. In another study of 48 patients with pancreatic trauma (26 blunt and 22 penetrating), the median time from presentation to ERCP was 38 d and only seven patients had a stent inserted for a pancreatic fistula (7) and a MPD stricture (1), whereby all patients avoided surgery[16]. While variable complications have been reported, the heterogeneity of presentations at different centers must be considered. The studies mentioned above did not employ, early intraoperative ERCP.

The logistics of performing intraoperative ERCP can limit its use, especially in cases of poly-trauma. Wise use of this novel technique requires commitment and flexibility from the surgeons and gastroenterologists. In instances of trauma, PD injury, duodenal injury and papilla edema may also increase the difficulty of the procedure itself, thereby increasing the chances of complications such as post-ERCP pancreatitis[17]. In both of our cases, there were no immediate or long term complications from the ERCP. Patient 1 did require upsizing from 5 Fr to 7 Fr stent, which is commonly seen. ERCP may be underutilized due to operator comfortability, lack of awareness of the value of endoscopic treatment in this setting, and equipment availability in the OR. Our high-volume trauma center is unique and is equipped to handle these situations with quick and effective mobilization of resources including on call therapeutic endoscopy.

CONCLUSION

In conclusion, this case series emphasizes the utility of intraoperative ERCP in cases of severe pancreatic trauma. Further studies are needed to clarify the optimal timing and safety outcomes in this setting.

FOOTNOTES

Author contributions: Canakis A reviewed the literature and drafted manuscript; Kesar V, Hudspath C, Kim RE, and Darwin P participated in the therapeutic endoscopic care of the patient; Scalea TM was the patient's trauma surgeon; Darwin P conceptualized the case series idea; Darwin P and Scalea TM provided critical revisions; all authors have read and approve the final manuscript.

Informed consent statement: Informed Consent was obtained for this case series.

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LETTER TO THE EDITOR

Acute upper gastrointestinal bleeding: A stitch on time saves nine

Nishkarsh Gupta, Anju Gupta

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Abstract

Upper gastrointestinal bleeding is common and often needs timely intervention for optimal outcomes. Esophageal bleeding may occur due to local advancement of malignancy or bleeding from an arterio-oesophageal fistula. We discuss the management options available for such cases.

Key Words: Esophageal bronchial artery; Upper gastrointestinal bleeding; Bleeding; Fistula; Gastrointestinal

Core Tip: Esophageal bronchial artery fistula is a rare serious cause of upper gastrointestinal bleeding and needs to be managed appropriately. If unrecognized, it can be catastrophic. We discuss the management options for upper gastrointestinal bleeding due to these fistulas as a response to a previously published article.

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TO THE EDITOR

Acute upper gastrointestinal bleeding (UGIB) is a relatively common medical emergency with approximately 400000 cases/year and corresponding mortality rates of up to 16%[1]. In the index report, authors describe a rare case of UGIB due to an

esophago-bronchial artery fistula, in a patient with carcinoma of the esophagus with an esophageal metallic stent *in situ*[2]. The local advancement of the esophageal malignancy probably contributed to the UGIB as in this case the bronchial artery was non-aneurysmal.

Arterio-esophageal fistula (AEF) is a rare abnormal communication between the aorta and esophagus, with thoracic aortic aneurysm being the commonest association[3]. It can present as massive bleeding which can be potentially life-threatening. It is difficult to be diagnosed by endoscopy and therefore, requires a high index of suspicion. Another type of AEF is subclavian artery-esophageal fistula which has been previously reported in few patients with prolonged nasogastric intubation and such patients should be screened for the possibility of an aberrant aortic arch system to avoid this fatal complication [4,5].

Esophageal bronchial artery fistula is a rare serious cause of UGIB, which can be fatal if unrecognized. Bronchial artery aneurysm/pseudoaneurysm is commonly associated in such cases. Jadeja *et al*[6] reported a case of an esophageal-bronchial artery fistula due to pseudoaneurysm resulting from an endobronchial ultrasound-guided transbronchial needle aspiration. The case was successfully managed by endoscopic therapy and coil embolization.

Any patient with UGIB needs to be resuscitated with intravenous fluids, blood and blood products, vasopressors, and hemostatic agents as appropriate. In patients who become drowsy, confused, or hypoxemic, they would need prompt airway protection with endotracheal intubation to avoid aspiration and respiratory compromise. Antibiotics may be needed especially in patients with variceal bleeding and coexisting ascites or endocarditis.

Studies have shown improved outcomes with an urgent endoscopic management in the critically ill patients with hemodynamic instability or continuing transfusion requirements[7]. Urgent evaluation allows the identification of the type of bleeding, permits targeted therapy, and allows stratification of the sequelae of the bleeding which allows urgent risk stratification, and it also allows the early identification of the patients who would be suitable candidates for an early interventional radiological procedure or surgical intervention. In the index case also, since active bleeding was not seen on endoscopy, the patient could be further evaluated using computed tomography, which revealed signs of fistula between the bronchial artery and the esophagus. Even though there was no active bleeding, bronchial artery embolization was done as the signs of fistula formation were observed. Stent removal and re-stenting were done endoscopically along with embolization. Arteriography can provide a definitive diagnosis of source of bleeding and also yield temporary hemostasis by tamponade[4].

Endoscopy may be done under sedation or general anesthesia with endotracheal intubation depending on patient's sensorium and haemodynamic status. However, in the present report the mode of anesthesia has not been commented upon. Various nonoperative endoscopic hemostatic techniques have been recommended in cases where an active bleeding vessel can be identified as a source of UGIB. These treatment options include esophageal stenting, endoscopic fibrin application, injection therapy, thermal cautery, and endoclip application[8,9,10,11,12,13]. An epinephrine–saline solution injected in four quadrants surrounding the lesion is usually employed for endoscopic injection therapy. Mechanical hemostasis with hemoclips has been found effective for peptic ulcer bleeding with the advantage of minimal tissue disruption, leading to a likely faster ulcer healing. Recently, OverStitch (Apollo Endosurgery Inc., Austin, TX, United States) has been developed as an attractive minimally invasive device for endoscopic suturing which can potentially be useful for closing small perforations and fistulas without the need for surgical intervention[12,13].

Argon plasma coagulation is a technique which appears to be the most effective for broad ill-defined lesions such as vascular ectasias but also has been effectively employed in bleeding ulcer therapy[9].

Hemospray (Cook Medical, Winston-Salem, NC, United States) is a promising new therapy recently introduced for the management of UGIB. It is a hemostatic powder that acts as both a cohesive and an adhesive substance and thereby creates a mechanical barrier[10]. Cryotherapy has gained wider recognition particularly as a management modality for arteriovenous malformation. It allows for tissue destruction *via* freezing by nitric monoxide at a temperature of −89.5°C and creating an ice layer on the surface of the mucosa[9,11].

To conclude, AEF is a rare cause of UGIB and needs a high index of suspicion and interdisciplinary management. Minimally invasive endoscopic or interventional radiology treatment modalities are effective in managing the majority of such cases.

FOOTNOTES

Author contributions: Gupta N devised the concept, collected the data, revised the manuscript, and approved final version; and Gupta A collected the data, wrote the first draft, and approved the final version.

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