Endoscopic ultrasonography as a therapeutic modality

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Purpose of review

Endoscopic ultrasonography (EUS) has taken on more of a therapeutic role in recent years. This review will focus on the therapeutic applications of EUS.

Recent findings

Multiple studies on the therapeutic applications of EUS have been published. EUS facilitates endoscopic drainage of pancreatic fluid collections (PFCs) including walled-off pancreatic necrosis, management of refractory gastrointestinal bleeding from gastric varix or vasculature by fine-needle injection and decompression of obstructive pancreatic or biliary ductal systems following failed access by standard endoscopic or radiological techniques.

Summary

The indications and role of therapeutic EUS have expanded rapidly in recent years. The procedures can be technically challenging, requiring expertise in both endosonography and endoscopic retrograde cholangiopancreatography. Refinement in echoendoscope design and dedicated accessories are required to further expand the applications of therapeutic EUS.

Keywords

biliary drainage, endoscopic ultrasonography, endoscopic retrograde cholangiopancreatography, pseudocysts, walled-off pancreatic necrosis

INTRODUCTION

Evolution of endoscopic ultrasonography (EUS) is the result of improvement in echoendoscope designs, imaging and accessories. Another main reason for this progression is the recent leap into minimally invasive approaches for treatment and palliation of gastrointestinal and pancreaticobiliary diseases. This review focuses on the recent developments in the field of therapeutic EUS, including EUS-guided drainage procedures, EUS-guided treatment of gastrointestinal bleeding, and EUS-guided pancreaticobiliary access and drainage. Other therapeutic indications, such as EUS-guided oncologic interventions [1] and EUS-guided pancreatic cyst ablation, are discussed elsewhere [2].

ENDOSCOPIC ULTRASONOGRAPHY-GUIDED DRAINAGE PROCEDURES

Pancreatic fluid collections (PFCs) are categorized into acute fluid collections, pseudocysts, and walled-off pancreatic necrosis (WOPN). Acute collections lack a well-defined wall and usually require no intervention. However, well-encapsulated and symptomatic collections warrant therapy. Indications for drainage of PFCs include pain, obstruction of the gastrointestinal or biliary tract, infection, or fistula formation [3]. Although surgery is traditionally considered the gold standard for treatment, endoscopic transmural drainage is increasingly recognized as a minimally invasive alternative to surgery. One major limitation of an endoscopic approach is that PFCs not causing a luminal compression cannot be treated endoscopically. This limitation is overcome with the performance of drainage procedures under EUS guidance [4], as long

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KEY POINTS

- Therapeutic endoscopic ultrasonography (EUS) has flourished during recent years and its indications are expanding.
- EUS facilitates endoscopic drainage of pancreatic fluid collections, including walled-off pancreatic necrosis.
- EUS may have an important role in managing patients with refractory gastrointestinal bleeding.
- EUS-guided drainage has been reported as a safe alternative technique for biliary and pancreatic ductal obstruction after failed endoscopic retrograde cholangiopancreatography.
- Improvement in devices and accessories tailored specifically for interventional EUS is needed.

as the collection is within 1.5 cm from the gastrointestinal tract. One randomized trial compared the rate of technical success between EUS and esophagogastroduodenoscopy (EGD) for transmural drainage of pancreatic pseudocysts in 30 patients [5]. EUS had significantly higher success rate than EGD (100 vs. 33%, $P < 0.001$). The authors recommended that EUS should be considered as the first-line treatment modality for endoscopic drainage of pancreatic pseudocysts given its high technical success rate.

We have described EUS-guided pseudocyst drainage as a one-step procedure using graded catheter and balloon dilation of the cystgastrostomy tract and a novel multiple wire insertion technique facilitated by a modified, double-lumen, biliary cytology brush catheter [6▪,7]. Ten patients with 11 pseudocysts underwent EUS-guided pseudocyst drainage using the novel multiple wire insertion technique. Technical success, defined as successfully achieving access and drainage of pseudocysts, was achieved in all cases (100%) with no procedural complications. Clinical success was achieved in all cases with complete resolution of pseudocysts. The novel method of using a modified, double-lumen, biliary cytology brush catheter allows a simple and safe one-step EUS-guided drainage of pseudocysts [6▪,7].

Endoscopic therapy of WOPN is more technically challenging than standard transluminal drainage. Solid contents inside the cavity do not readily drain through small-caliber transluminal stents. This results in stent clogging and infection of sterile WOPN (as a result of contamination during endoscopic procedure). Other minimally invasive techniques for drainage of WOPN include endoscopic necrosectomy [8▪▪] or hybrid techniques (combination of laparoscopy, transcutaneous radiologic drainage, and endoscopy) [9]. Recently, a new EUS-based drainage technique of WOPN was described and entails creating multiple transluminal gateways to facilitate effective drainage of necrotic contents [10▪▪].

Multiple transluminal gateways technique

The WOPN is punctured with a 19-gauge needle (site 1) and a 0.035-inch guidewire is advanced and coiled inside the cavity (Fig. 1). An aspirate from the WOPN is obtained and sent for gram staining and culture for guidance of antibiotic coverage. The transmural tract is dilated to 8 mm (using either bougie or balloon dilation). Initially, one 7F, 4-cm, double-pigtail stent is deployed through the cystgastrostomy or cystduodenostomy. Subsequently, a second area (site 2) in the same necrotic cavity that is distant from site 1 is identified for drainage by using EUS guidance (with the aid of fluoroscopy), and the same process is repeated (Fig. 2) but with dilation of the transmural tract to 15 mm and placement of multiple (2–4), 7F, double-pigtail stents. The procedure is completed with placement of an additional 7F, nasocystic catheter adjacent to the previously placed transmural stent at site 1. This is done by coiling a guidewire within the necrotic lesion and then passing the nasocystic catheter over the wire under fluoroscopic guidance. The rationale for dilating only up to 8 mm

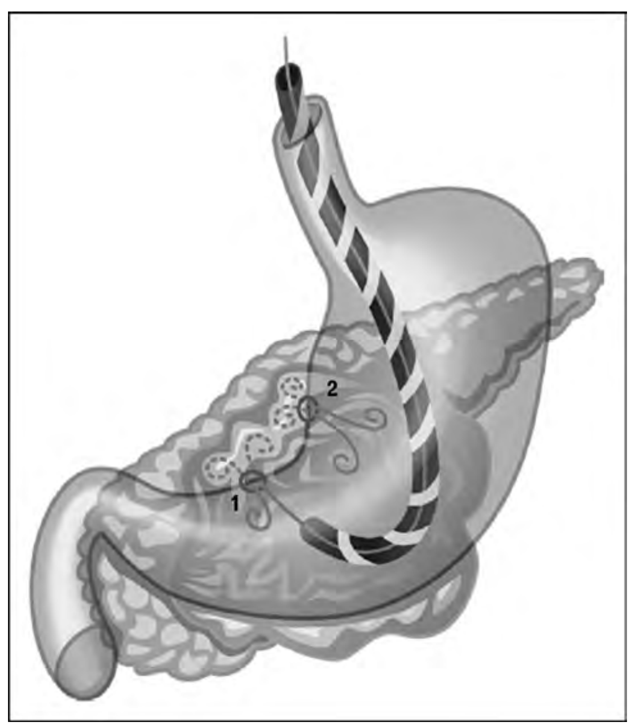

FIGURE 1. Schematic illustration of multiple transluminal gateway technique (MTGT) for EUS-guided drainage of walled-off pancreatic necrosis (WOPN). Data from [10▪▪].

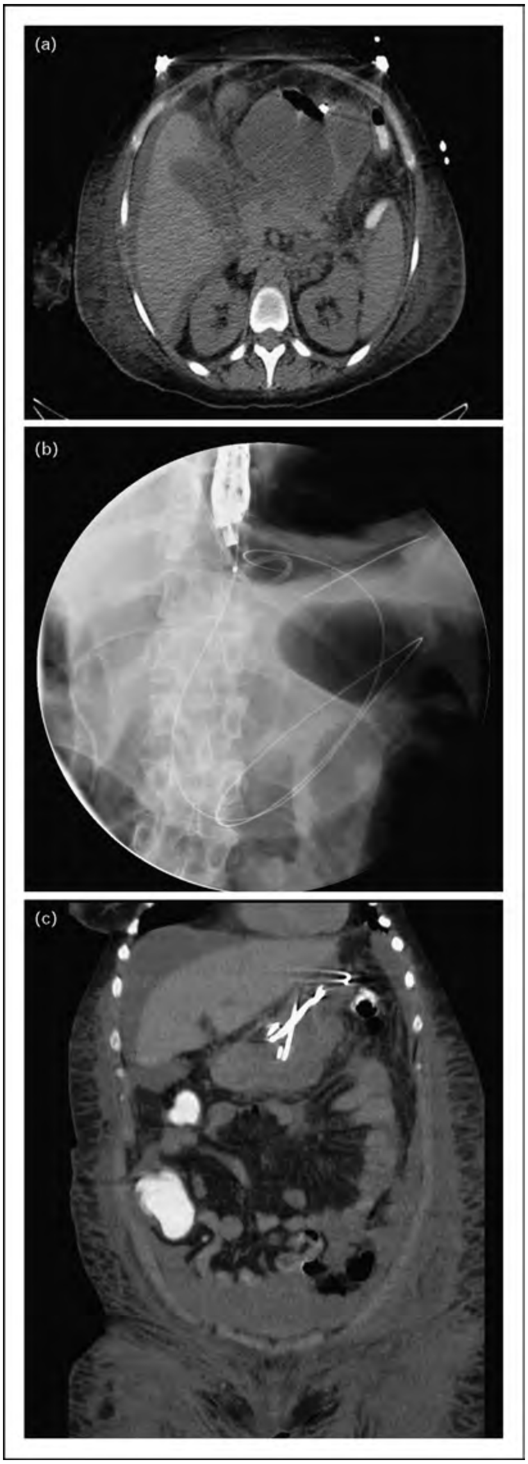

FIGURE 2. Endoscopic ultrasonography-guided drainage of walled-off pancreatic necrosis (WOPN) using multiple transluminal gateways technique (MTGT). (a) A computed tomography (CT) of the abdomen revealing a large WOPN. (b) Fluoroscopic image revealing passage of a guidewire into a different site (site #2) in the WOPN following initial placement of a transmural stent (site #1). (c) Following drainage by MTGT, CT of the abdomen at 72 h reveals marked resolution in size of the WOPN. The multiple stents are better visualized on coronal view.

and placing a single stent at site 1 is to facilitate localization of another site for transmural drainage because rapid evacuation of necrotic fluid (after multiple stent placements) may preclude such localization. Also, site 1 is reserved for deployment of a nasocystic catheter before completion of the procedure. For patients with very large WOPN (>15 cm), creation of three separate transmural tracts may be necessary to optimize drainage [10▪▪].

Outcomes of multiple transluminal gateways technique

Varadarajulu *et al.* [10▪▪] studied 60 patients with symptomatic WOPN, 12 of whom were managed by multiple transluminal gateways technique (MTGT) and 48 with conventional transmural drainage. Drainage was successful in 92% of patients managed by MTGT compared with 52% of patients managed with conventional approach ($P = 0.01$). One patient in the MTGT group required endoscopic necrosectomy. In the conventional group, 17 required surgery, three underwent endoscopic necrosectomy, and three died of multiple-organ failure [10▪▪].

Recommendations for endoscopic management of patients with pancreatic fluid collections

It is preferable that patients with PFCs obtain magnetic resonance cholangiopancreatography (MRI/MRCP) prior to endoscopic therapy. MRCP may suggest pancreatic duct leak and need for endoscopic retrograde cholangiopancreatography (ERCP). MRI (as opposed to computed tomography) enables quantification of solid necrotic material inside the cyst. This can be later confirmed during EUS. If no solid material is identified (pseudocyst), then only conventional transmural drainage is required. If a limited (<40%) percentage of cyst contents is solid, then MTGT is recommended. Although endoscopic necrosectomy or hybrid techniques could be performed in this setting, these techniques are associated with a nontrivial risk of morbidity and mortality [11]. However, these latter approaches are mandatory for PFCs with extensive solid necrotic contents (>40–50%). Placement of a nasocystic catheter with intermittent irrigation of the cyst cavity should be performed in patients with WOPN to ensure continuous irrigation and drainage. The irrigation catheter may be removed after resolution of infection and organ failure (if present), significant decrease in size of WOPN on repeat imaging, in association with absence of necrotic fluid on aspiration of drainage catheter. Subsequent imaging is usually obtained 6–8 weeks afterwards. If WOPN is resolved, transmural stents are removed by endoscopy. For patients with disconnected pancreatic ducts, the transmural stents are left in place indefinitely [12].

ENDOSCOPIC ULTRASONOGRAPHY-GUIDED TREATMENT OF GASTROINTESTINAL BLEEDING

Endoscopic management of gastrointestinal bleeding is insufficient in about 10% of cases and leads to early recurrence of bleeding. The source of bleeding occasionally cannot be identified using conventional endoscopy. The initial experience with EUS to manage gastrointestinal bleeding was described in a report that included five patients, four of whom had severe refractory bleeding that resulted from hemosuccus pancreaticus, a Dieulafoy's lesion, duodenal ulceration, or gastrointestinal stromal tumor (GIST) [13]. EUS-guided therapy was performed by injecting alcohol or cyanoacrylate (CYA). Power and pulse Doppler revealed complete cessation of blood flow and occlusion of the vessel of interest, thereby indicating a successful endpoint of angiotherapy. None of the patients re-bled after EUS-guided therapy. A more recent study reported on EUS-guided sclerotherapy using CYA or polidocanol 2% to treat refractory gastrointestinal bleeding in eight patients (varices, aneurysms, and Dieulafoy's) [14]. The procedure was successful in seven (87.5%) patients with immediate cessation of Doppler signal at the end of procedures.

Binmoeller *et al.* [15■■] recently described the technique of EUS-guided transesophageal treatment of gastric fundal varices (GFVs) with combined coiling and CYA injection.

Description of technique of transesophageal endoscopic ultrasonography-guided therapy of gastric fundal varices

The echoendoscope is positioned in the distal esophagus and GFVs are visualized after filling the stomach with water. The hypoechoic diaphragmatic crus muscle is identified between the esophageal wall and the GFV. The GVF is then punctured with a 19-gauge needle using a transesophageal approach. An embolization coil is then deployed into the varix through the fine-needle aspiration (FNA) by advancing the stylet. Subsequently, 1 ml of CYA is injected by using normal saline solution to flush the glue through the catheter. Color Doppler is then used to confirm absence of flow in the treated varix. Repeat injection of CYA and coils is performed for persistent flow. Medium or large esophageal varices are then treated by band ligation (Fig. 3).

Outcomes of endoscopic ultrasonography-guided therapy of gastric fundal varices

All ($n = 30$) included patients underwent successful EUS-guided transesophageal treatment of GFVs [15■■]. The mean number of GFVs treated was 1.3 per patient, and the mean volume of CYA injected was 1.4 ml per varix. Hemostasis of acute bleeding was 100%. The majority (96%) of patients attained GFV obliteration after a single treatment session. Rebleeding occurred in four patients, with none attributed to GFVs. There were no procedure-related complications and no symptoms or signs of CYA embolization.

This approach for treating bleeding due to GFV has multiple advantages and deserves attention and further studying at other centers to determine its efficacy and safety. Advantages of EUS-guided transesophageal treatment of gastric fundal varices using a combination of coiling and CYA (glue) injection are as follows:

(1) straight position of echoendoscope in the esophagus, which allows easy passage of 19-gauge needle and subsequent advancement of the coil using the stylet;
(2) retroflexion in gastric fundus is not required to access fundal varices;
(3) treatment is not affected by gastric blood that typically pools in the fundus;
(4) no disruption of gastric mucosa overlying the varix;
(5) access to feeder vessels;
(6) initial coiling acts as scaffold to retain glue and prevent embolization;
(7) coiling contributes to variceal obliteration and decreases the volume of glue needed for variceal obliteration.

ENDOSCOPIC ULTRASONOGRAPHY-GUIDED PANCREATICOBILIARY ACCESS AND DRAINAGE

Failure to achieve bile duct and main pancreatic duct (MPD) access during ERCP occurs because of either failed cannulation or an inaccessible papilla from altered anatomy or gastric outlet obstruction (GOO) caused by tumor invasion. Percutaneous transhepatic biliary drainage or surgical interventions are often required in these cases, but are associated with significant morbidity [16,17]. EUS-guided drainage has been reported as a safe alternative technique for biliary and pancreatic ductal drainage. Considerable attention has been given to this promising EUS-guided interventional approach in the last year and has yielded publication of multiple case

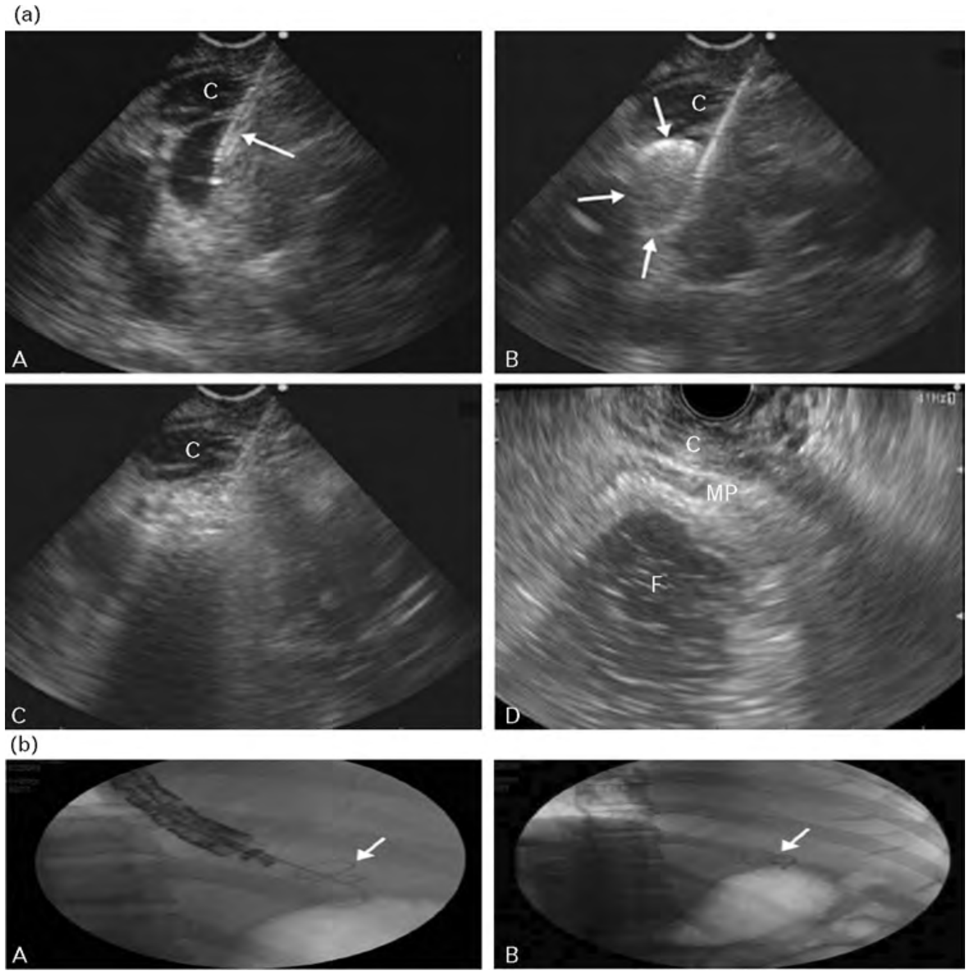

FIGURE 3. (a) Transesophageal EUS showing fundal varix targeted with a 19-gauge needle (arrow) (A); deployment of coil (arrows) through the 19-gauge needle (B); injection of 1 ml of cyanoacrylate glue through the 19-gauge needle to obliterate the varix lumen (C); eradication of fundal varices (D). (b) Fluoroscopic view showing A, coil (arrow) insertion into a gastric varix and B, appearance after intravariceal deployment. C, crus muscle; F, fundus; MP, muscularis propria of stomach wall. Data from [15▪▪].

series [18▪▪,19–24,25▪], case reports [26–29], and review papers [30–33].

Endoscopic ultrasonography-guided biliary drainage

EGBD can be performed entirely transgastrically or transduodenally without accessing the papilla (direct transluminal technique) or via rendezvous whereby the wire must pass through the papilla (rendezvous technique). The rendezvous approach is our preferred approach as it avoids the need for a permanent bilioenteric fistula and the need to dilate the fistulous tract, which may lead to complications such as bleeding, pneumoperitoneum and pneumomediastinum. However, this approach may not be possible if the wire cannot pass through the ampulla because of difficult angulation or tight distal biliary stricture. A third approach that has not been extensively reported is EUS-guided antegrade biliary stent placement (transpapillary). This is the technique of choice in cases of malignant biliary strictures and an endoscopically inaccessible papilla or bilioenteric anastomosis [34].

Technique

A linear echoendoscope is used to achieve initial biliary access within a segment of dilated bile duct proximal to the site of obstruction. The tip of the echoendoscope is positioned in the gastric fundus or duodenal bulb when accessing the intrahepatic and extrahepatic bile duct, respectively. A transesophageal access approach (Fig. 4) [26] should be avoided unless absolutely necessary because of risk of pneumomediastinum and mediastinitis. A 19-gauge needle is used to puncture the bile duct with access confirmed by contrast injection and fluoroscopic

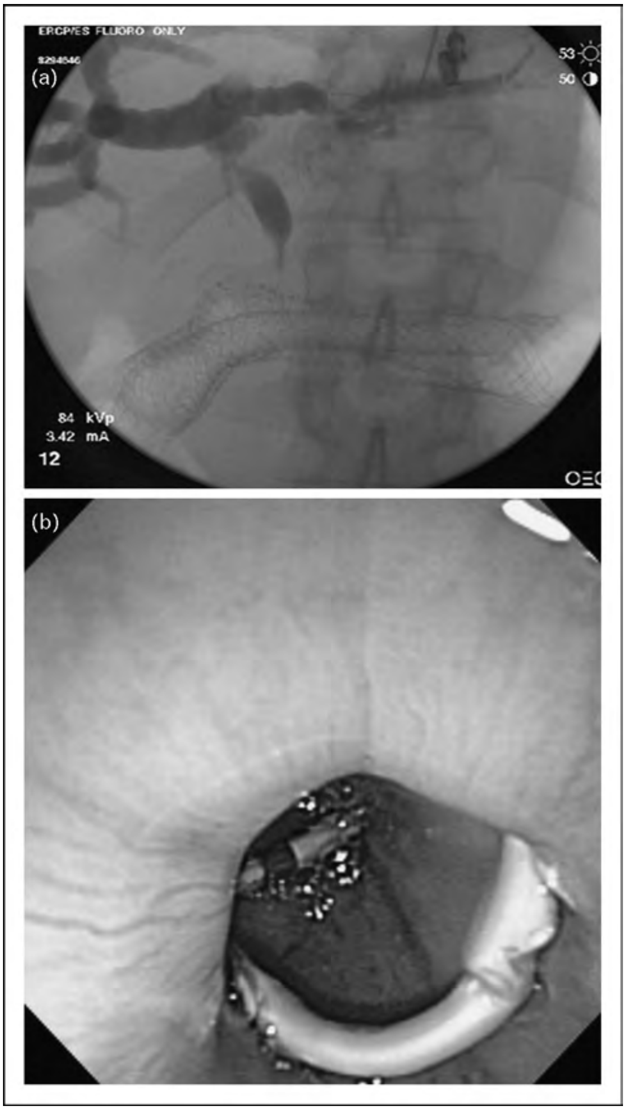

FIGURE 4. Endoscopic ultrasonography-guided hepatoesophagostomy for transesophageal biliary drainage in a patient with diffuse gastric cancer and gastric outlet obstruction. (a) Transesophageal puncture of left intrahepatic duct was performed using 19-gauge needle and antegrade cholangiogram was obtained. This revealed dilated intrahepatics and severe extrahepatic biliary stricture. (b) Transesophageal plastic stent placement was performed after tract dilation.

imaging. A 0.035-inch guidewire is advanced into the bile duct. The echoendoscope and needle should be angled to facilitate antegrade guidewire passage through the site of obstruction and across the papilla and coiling of the wire within the duodenum. Self-expandable metal stent (SEMS) insertion is performed via either a retrograde (rendezvous) or an antegrade approach. For the latter approach, the entire tract from the access puncture site through the obstruction to the duodenal lumen is catheter and balloon dilated to facilitate stent placement [25▪].

For the retrograde approach, a rendezvous is performed after withdrawing the echoendoscope and leaving the guidewire in place. A duodenoscope is passed to the papilla and a snare or biopsy forceps is used to grasp the guidewire and withdraw it through the endoscope with subsequent stent placement. In contrast, for the transluminal or transpapillary antegrade methods of stent insertion, the procedure is performed entirely via the echoendoscope. The transpapillary antegrade approach involves stent passage through the gastric or duodenal wall access site, then through the biliary obstruction and papilla into the duodenum. A third option is transluminal antegrade stenting (direct transluminal technique), in which a stent is advanced antegrade into the bile duct but not beyond the site of biliary obstruction. The biliary stent extends from the obstructed portion of the biliary tree to the intestinal lumen via the gastric or duodenal access site (Fig. 5). This approach is performed when transpapillary stenting (antegrade or retrograde) is not possible.

Endoscopic ultrasonography-guided pancreatic duct drainage in patients with preexisting duodenal stents

Patients with GOO resulting from duodenal tumor compression and infiltration present a particular challenge during ERC, especially in the presence of a duodenal SEMS. Although ERCP can be accomplished by fenestration of a duodenal stent in some cases, alternative approaches for biliary access and drainage are needed when the papilla is unable to be reached or visualized [25▪].

We performed EGBD in nine patients with preexisting duodenal and inaccessible ampulla [25▪]. The bile duct was accessed via a transgastric ($n = 3$) or transduodenal ($n = 6$) approach, requiring needle passage through the interstices of the duodenal stent in five patients. Biliary access was achieved using a 19-gauge FNA via an extrahepatic ($n = 7$) or an intrahepatic approach ($n = 2$). Following guidewire passage through the site of obstruction and papilla, catheter dilation was performed. Dilation included the gastric or duodenal wall, intervening tissues between the lumen wall and bile duct, site of obstruction, and duodenal stent interstices. Inserted biliary SEMS were fully covered or uncovered, measured 10 mm in diameter, and ranged from 40 to 80 mm in length. Antegrade bypass stent insertion (direct transluminal access) was required in two patients because of inability to advance the guidewire antegrade through the obstruction and to the duodenum,

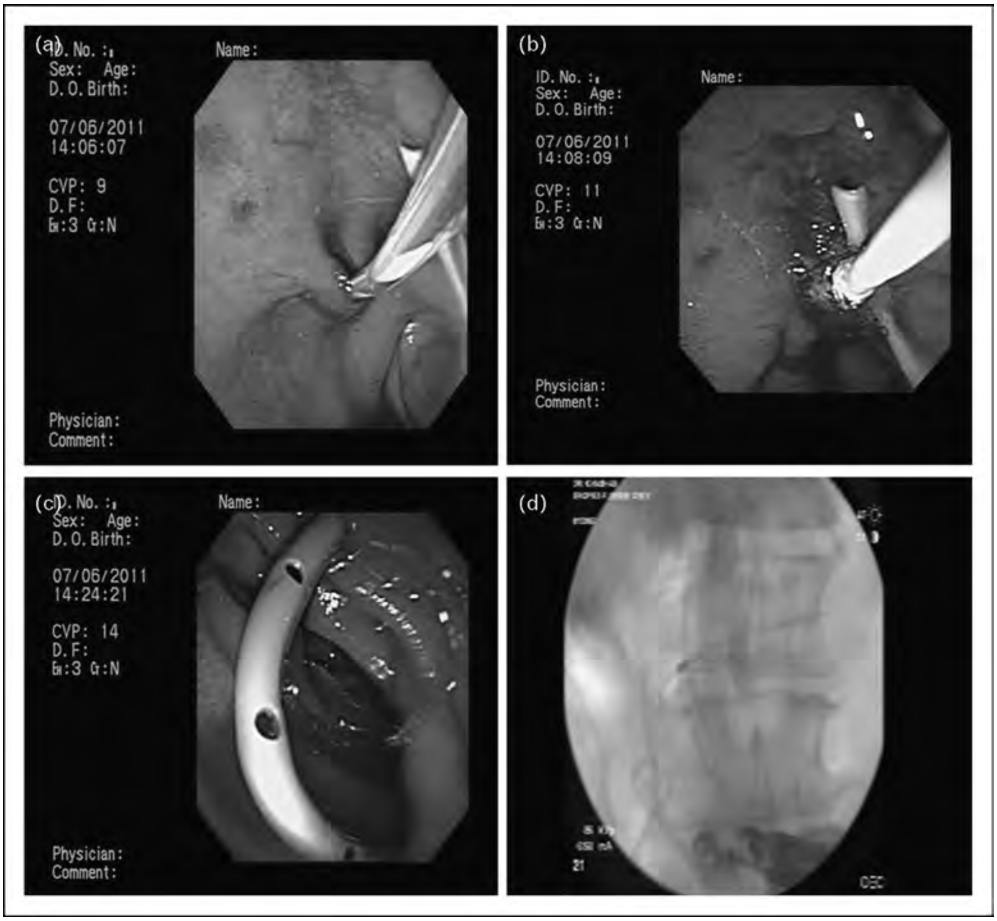

FIGURE 5. Endoscopic ultrasonography-guided biliary drainage using direct transluminal approach. (a). Choledochoduodenostomy was initially established with puncture of the bile duct with 19-gauge needle and then dilation with an endoscopic retrograde cholangiopancreatography catheter (a sphincterotome in this case). (b) Tract was then balloon dilated. (c) A stent was placed across the choledochoduodenostomy. (d) Fluoroscopic image showing a double-pigtail stent with its proximal end in the bile duct and distal end in the duodenal bulb. In this particular case, a pancreaticoduodenostomy was also established.

thereby prohibiting transpapillary drainage (Fig. 6). All patients had clinical resolution of their jaundice.

There were no complications of significant bleeding or leakage from the gastric, duodenal, or hepatobiliary area reported following the procedure in any patient. One patient developed pancreatitis and cholecystitis following fully covered transpapillary SEMS placement [25▪].

Recommendations for endoscopic ultrasonography-guided pancreatic duct drainage in patients with preexisting enteral stents

Our experience suggests the safety of EGBD in this patient population. We do not dilate the transluminal tract until acceptable guidewire position for stent placement has been achieved, as the risk of leak is probably increased if biliary obstruction is not relieved. In addition, we aim for sufficient dilatation of the tract to allow stent insertion while avoiding overly aggressive dilatation that may predispose to a biliary leak. Similarly, we avoid cautery-assisted tract dilatation given the potential for complications, particularly bleeding and bile leak [35▪]. It is also our practice to avoid traversal of the pancreas when accessing the bile duct in order to minimize the risk of pancreatitis or a pancreatic duct leak.

Endoscopic ultrasonography-guided pancreatic duct drainage

Endoscopic ultrasonography-guided pancreatic duct drainage (EGPD) is indicated to relieve pancreatic duct obstruction in patients with chronic pancreatitis or stenosed pancreaticojejunostomy after pancreaticoduodenectomy (Whipple resection) who have failed ERCP (e.g. failed retrograde cannulation because of tight pancreatic duct stricture or long afferent limb) [23,36–40]. Principles of EGPD techniques are similar to those of EGBD.

FIGURE 6. Endoscopic ultrasonography-guided biliary drainage in a patient with preexisting duodenal self-expandable metal stent (SEMS) obscuring ampulla. (a) Dilated bile duct was punctured with a 19-gauge needle and dye was injected. (b) Antegrade cholangiography revealed dilated bile duct with distal stricture. (c) Choledochoduodenostomy was catheter dilated to 7Fr. (d) A biliary SEMS was placed across the choledochoduodenostomy through the mesh of the existing enteral SEMS. (e) Fluoroscopic image confirming relative position of enteral and transluminal biliary stent.

Rendezvous and direct transluminal techniques can also be used during EGPD [27]. During the latter approach, use of cautery-assisted tract dilation may be needed as the stent has to traverse pancreatic parenchyma, which is often fibrotic because of chronic pancreatitis or prior surgeries. Ergun *et al.* [23] performed EGPD in 20 patients with post-Whipple symptomatic anastomotic strictures ($n = 10$) and chronic pancreatitis ($n = 10$). Transluminal stenting (transgastric or transbulbar) was performed in 15 patients, while a rendezvous approach was carried out in five patients. Successful ductal drainage was achieved in 18 (90%) patients and long-term pain resolution was noted in 72% of these patients. Stent dysfunction (occlusion or migration) occurred in 50% of patients and was treated with stent exchanges or repeat EGPD. Similar or higher stent dysfunction rates were reported in other studies [38,39]. The high stent occlusion rate is likely because of the small caliber of pancreatic duct stents. The high stent migration rate is likely a result of the limited intraductal length of the stent and expulsive gastric contractions. Placement of double-pigtail stents may be considered to decrease migration risk.

CURRENT LIMITATIONS

The current linear array echoendoscopes have an elongated tip that is sometimes not conducive for traversing strictured gut lumen. Also, once guidewire access is obtained, the scope design limits adequate endoscopic visualization, which makes stent deployment and other endotherapy technically challenging. A forward view echoendoscope is currently under development to overcome this technical challenge. This new device has a blunt tip, similar to a standard gastroscope, and preliminary data for performing interventions appears promising [41].

Another hindrance to the progress of therapeutic EUS is the absence of dedicated accessories. Currently, most interventions are being performed using ERCP accessories, some of which are not conducive for use with a curvilinear echoendoscope. Also, endosonographers not proficient with ERCP can find therapeutic EUS technically challenging to perform. Although some advances have been made with respect to drainage of PFCs [42], a single-step device for this indication is still not fully developed.

CONCLUSION

Therapeutic EUS has flourished during recent years and its indications are expanding. Therapeutic EUS procedures are technically demanding and challenging and frequently require skills in both endosonography and ERCP. Improvement in devices and accessories tailored specifically for interventional EUS is needed. This is essential to expand the horizons of therapeutic EUS, such as carrying on EUS-guided cardiac and intrauterine interventions.

Acknowledgements

None.

Conflicts of interest

M. A. K. is a consultant for Boston Scientific. S. V. is a consultant for Boston Scientific and Olympus Medical Systems Corporation.

REFERENCES AND RECOMMENDED READING

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