Therapeutic Endoscopic Ultrasound

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Keywords
Advanced endoscopy, endoscopic ultrasound, biliary access, pancreatic access, gastrojejunostomy, ablative therapy, hemostasis

Abstract: Endoscopic ultrasound (EUS) technology has evolved dramatically over the past 20 years, from being a supplementary diagnostic aid available only in large medical centers to being a core diagnostic and therapeutic tool that is widely available. Although formal recommendations and practice guidelines have not been developed, there are considerable data supporting the use of EUS for its technical accuracy in diagnosing pancreaticobiliary and gastrointestinal pathology. Endosonography is now routine practice not only for pathologic diagnosis and tumor staging but also for drainage of cystic lesions and celiac plexus neurolysis. In this article, we cover the use of EUS in biliary and pancreatic intervention, ablative therapy, enterostomy, and vascular intervention.

Over the past 2 decades, endoscopic ultrasound (EUS) has evolved dramatically. Once a supplementary diagnostic aid available only to those in larger, well-funded centers, it is now a core diagnostic and therapeutic tool that is widely available and indispensable to a developed pancreaticobiliary service.

There are considerable data to support the use and technical accuracy of EUS for the diagnosis of pancreaticobiliary and gastrointestinal (GI) pathology. Since linear-array echoendoscopes were developed, the diagnostic boundaries have been pushed further by the use of fine-needle aspiration to acquire tissue samples from within and around the GI tract. Along with pathologic diagnosis and tumor staging, most endosonographers routinely perform drainage of cystic lesions, fiducial placement, and celiac plexus neurolysis.

As the horizon for EUS continues to expand, we review evolving therapeutic uses for EUS in this article.

Endoscopic Ultrasound–Guided Biliary Drainage

The standard of care for biliary decompression is endoscopic retrograde cholangiopancreatography (ERCP). Biliary access may not be possible in up to 10% of cases, usually due to difficult cannulation, inability to access the papilla, or postsurgical anatomy.[1] Alternate modalities for biliary drainage in this setting include percutaneous transhepatic cholangiography (PTC), surgical bypass, or common bile duct exploration. PTC is a well-established intervention both

for biliary access and for therapy following failure to respond to ERCP. Although morbidity associated with PTC has decreased over the past few decades, the potential risk for infection, hemorrhage, and bile leak persists.[2,3] Patients also receive an external drainage catheter, which is potentially painful, uncomfortable, and cumbersome.

Wiersema and colleagues first introduced the concept of EUS-guided biliary drainage (EUS-BD) in 1996, when 8 of 11 patients (73%) with disease that previously failed to respond to ERCP underwent successful EUS-guided cholangiography.[4] A decade later, Kahaleh and colleagues published a case series of 23 patients who successfully underwent EUS-BD over a 3-year period in an academic institution.[5]

Several factors need to be considered prior to using EUS-BD, the most important being the indication. In 2011, a group of expert endoscopists proposed that generally acceptable indications for EUS-BD include the following settings: failed conventional ERCP, altered anatomy, a tumor preventing access to the biliary tree, and the presence of a contraindication for PTC (such as large-volume ascites).[6] The same consortium also deemed that, due to its complexity, this relatively novel, advanced procedure should be performed only by experienced endoscopists with a high-volume practice (200-300 EUS and ERCP procedures per annum) in centers with appropriate surgical and interventional radiology support.[6]

EUS-guided biliary access is possible from an intrahepatic or extrahepatic approach; the choice is largely predicated on the reason for failed biliary access and the underlying disease process. The subsequent plan for the drainage modality (retrograde vs antegrade) needs to be considered and planned prior to any intervention being made. The intrahepatic approach typically involves a transgastric needle puncture into the left hepatic system, followed by advancement of a wire toward, and ideally through, the papilla. A transpapillary wire generally facilitates a retrograde (rendezvous) drainage technique. In the case where transpapillary wire access is achieved, but rendezvous drainage is not possible due to duodenal obstruction, antegrade transpapillary stenting may be considered.

Extrahepatic drainage typically involves direct puncture of the common bile duct (using a transgastric or duodenal approach). This may be advantageous due to better visualization of the larger duct. It may also be safer in patients with ascites, as the common bile duct is retroperitoneal. Once biliary access is achieved, retrograde, antegrade, or transmural (choledochoenteric) drainage may be considered. Transmural or antegrade stenting from an extrahepatic access point requires dilation of the tract to allow passage of the stent, typically by a balloon, dilating catheter, or needle knife. The majority of published data for EUS-BD has involved use of a 19-gauge needle.[7] This preference is likely due to needle stiffness and tip visibility on EUS and fluoroscopy. The larger needle will also facilitate passage of a standard 0.035-inch guidewire.

High success rates have been reported for EUS-guided biliary cholangiography (97%-100%). Failure of biliary access is most commonly attributed to the inability to access peripheral hepatic ducts, lack of biliary dilation, and postsurgical anatomy. Once biliary access has been achieved, drainage rates are variable in the published data, ranging from 44% to 100%.[8-13] Failure to achieve successful drainage is usually due to nontraversable biliary strictures, tortuous intrahepatic ducts, or difficulty dilating the transmural tract. Transpapillary access for rendezvous procedures appears to be more successful with an extrahepatic biliary approach[8,14]; however, both intrahepatic and extrahepatic approaches appear satisfactory in achieving transmural drainage.[11,15]

Difficult biliary strictures and limited ability for wire manipulation in the relatively inflexible needle used in EUS needle aspiration may make transpapillary biliary rendezvous access challenging. Therefore, transmural biliary access and the formation of a choledochoduodenostomy may be preferred. Giovannini and colleagues first described successful EUS-guided transmural placement of a 10-Fr (10-gauge, French scale) plastic biliary stent in 2001.[16] Since then, several series have shown the efficacy of self-expanding metal stents (SEMS) for transmural drainage. Park and colleagues performed a prospective feasibility study on EUS-BD using fully covered SEMS.[12] Fourteen patients with malignant biliary obstruction were included, 9 of whom had drainage achieved by an intrahepatic approach. The technical success rate was 100%, and 2 patients had self-limited pneumoperitoneum (both in the intrahepatic approach group). Only 1 patient required re-intervention due to a distally migrated stent over a 6-month follow-up period.

Once EUS-BD has been achieved, stent patency appears adequate and is probably equitable to that of stents placed during ERCP for similar indications. Park and colleagues noted no problems with 41 stents at a mean follow-up of 165 days (range, 30-275 days).[12] In a prior study of transmural stenting, the same group noted mean stent patency rates for intrahepatic and extrahepatic access of 132 and 152 days, respectively.[11] It is difficult to make recommendations about this issue, however, due to the lack of homogeneity within these data in terms of stent type, disease process, and access routes. Nevertheless, it seems intuitive that using fully covered SEMS for transmural drainage (via either an intrahepatic or extrahepatic approach) would serve to minimize bile leakage and stent occlusion.

Until recently, EUS-BD had not been compared with ERCP for biliary drainage. Dhir and colleagues recently published data from a multicenter comparative analysis of

the placement of SEMS for the management of malignant distal biliary strictures using EUS-BD or ERCP.[17] The study included 208 patients, 104 of whom were treated by ERCP and 104 by EUS-BD (68 via direct transmural drainage and 36 via rendezvous). Technical success rates and adverse events were similar in both groups (93% and 8%, respectively). The risk of pancreatitis was higher in the ERCP group (4.8% vs 0%, respectively).

Despite the data supporting the use of EUS-BD and its technical improvements, mainstream adoption of this technique as a second-line strategy for biliary access following unsuccessful ERCP has not been recommended. Data from high-volume centers demonstrate procedural challenges, including wire shearing and failure of rendezvous drainage, the latter of which results in a potentially riskier transluminal approach.[18] Varadarajulu and Hawes commented in 2013 that the technique is not yet ready for widespread use.[19]

However, in a recent comparative analysis of EUS-BD vs percutaneous drainage after failed ERCP, the authors found no significant difference in clinical success between the 2 modalities.[20] Interestingly, the percutaneous drainage group had a higher rate of adverse events, a higher rate of re-intervention, and significantly higher costs compared with EUS-BD. These data support the view that in centers with experienced interventional endosonographers, consideration should be given to EUS-BD as the intervention of choice in the setting of failed biliary cannulation during ERCP.

Endoscopic Ultrasound–Guided Gallbladder Drainage

Surgical management of acute cholecystitis may not be feasible due to patient comorbidities or may not be appropriate due to advanced cancer. ERCP may play a role in transpapillary gallbladder drainage; however, this procedure is often challenging and unsuccessful. That may be due to locally advanced pancreaticobiliary pathology, or an inaccessible cystic duct. These patients are often managed with percutaneous drainage, which is associated with several morbidities, including bile leak and subsequent peritonitis, hemorrhage, pneumoperitoneum, pneumothorax, and of course patient discomfort/inconvenience due to the external drain.

There are mounting data to support the technical success and safety of EUS-guided gallbladder drainage (EUS-GBD). A recent review by Widmer and colleagues demonstrated a 96.7% success rate in 90 documented cases.[21] However, the review also highlighted the potential risks, showing that 11 of 90 patients (12.2%) had complications that included biliary peritonitis, pneumoperitoneum, and stent migration.[21] In order to limit these risks, newer stents that appose the stomach wall to the gallbladder have been studied. The Axios stent (Boston Scientific) has shown promise both for gallbladder drainage and for pancreatic cyst gastrostomy.[22,23] Having SEMS in situ can also facilitate cholecystoscopy, during which the lumen of the gallbladder can be directly visualized endoscopically.

The available data suggest that EUS-GBD is as effective as percutaneous drainage, with no significant difference in risk. Jang and colleagues compared percutaneous gallbladder drainage to EUS-GBD in 59 patients.[24] In this randomized, noninferiority study, gallbladder drainage was successful in 97% in both groups, with no significant difference in morbidity. Interestingly, the patients who underwent EUS-GBD had significantly lower pain scores. This is of particular importance when considering this modality as a palliative technique.

Endoscopic Ultrasound–Guided Pancreatography and Drainage

EUS-guided pancreatic access is challenging and has not been as successful as EUS-BD to date. There are fewer than 300 cases in the literature, all of which were part of retrospective reviews. The overall reported technical success rate was 78%, with the main challenge being posed by scope positioning and optimal orientation for pancreatic duct access. Complications have included pancreatitis, hemorrhage, and perforation.[25]

A significant challenge in pancreatic drainage is optimal stent choice. Plastic stents may obstruct more readily, whereas covered metal stents may occlude pancreatic side branches and cause pancreatitis. Uncovered metal stents are unfavorable in this setting due to the potential for pancreatic juice leakage.

In patients with true pancreatic pathology in whom standard transpapillary pancreatic access has been unsuccessful, options are limited to surgical intervention. Fujii and colleagues demonstrated that 32 of 43 patients (74%) had successful EUS-guided pancreatic intervention.[26] Many of these patients had altered surgical anatomy. Eighty-three percent (24 of 29 patients) experienced resolution of their symptoms following EUS-guided pancreatic access and stent placement. These findings indicate that this technique may have a role to play in this challenging subset of patients.

Endoscopic Ultrasound–Guided Gastrojejunostomy

The palliation of malignant gastric outlet obstruction has traditionally consisted of surgical gastrojejunostomy (SGJ) in fit patients, and metal stent placement in patients with a less optimal functional status. Stent placement leads to

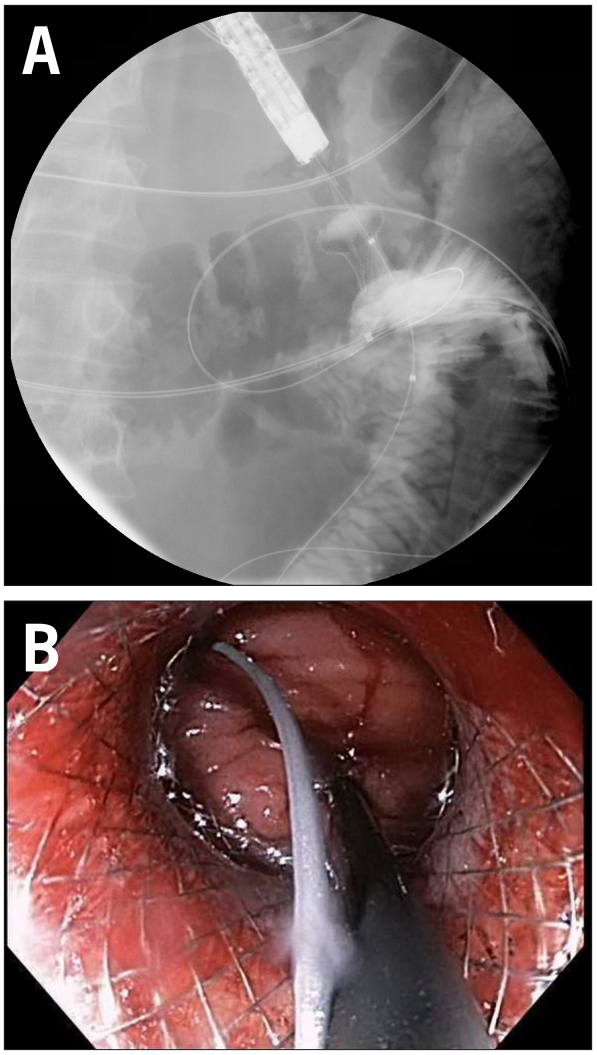

Figure. Fluoroscopic (**A**) and endoscopic (**B**) views of stent deployment in an endoscopic ultrasound–guided gastrojejunostomy.

Photos courtesy of Dr Todd Baron, The University of North Carolina at Chapel Hill.

faster improvement of symptoms compared with SGJ, but SGJ has a longer patency period. For patients in whom a stent is placed, the main complication is stent obstruction due to tumor/granulation tissue overgrowth. However, this can be treated with further stenting. If life expectancy is a few months or longer, then SGJ is recommended.

Endoscopically created gastrojejunostomies have been reported and performed without need for EUS guidance.[27] In 2002, Fritscher-Ravens and colleagues reported on the use of EUS to create a gastrojejunostomy using T fasteners.[28] Two recent studies in pigs have been successful at creating gastrojejunostomies under EUS guidance. Binmoeller and Shah reported on novel tools to create a gastrojejunostomy in 5 pigs.[29] These included a new anchor wire, a new access device, and a fully covered lumen-apposing stent (Axios stent, Boston Scientific). A jejunal loop was instilled with water and was found with a linear-array echoendoscope located in the stomach. The access device was used to enter the jejunal loop, and the anchor wire was used to secure the jejunal loop wall against the gastric wall. The lumen-apposing stent was then deployed. One animal was sacrificed immediately, and the stent caused good apposition of the gastric and jejunal walls. The stents were removed from the other 4 animals 5.5 weeks later; the gastrojejunostomy was noted to be open, and there was complete fusion of the gastric and jejunal walls on necropsy (Figure).

Itoi and colleagues also used EUS to access the small bowel from the stomach in 5 pigs, but the researchers used a double-balloon enteral tube to instill water into a loop of the bowel (in the segment between the 2 balloons) for more consistent identification via EUS from the stomach.[30] The lumen-apposing stent (Spaxus, Taewoong Medical Co) was then placed. In this study, the stents were removed 4 weeks later, and necropsy showed good fusion of the gastric and jejunal loops in all animals. All animals in both studies exhibited normal eating behavior. No human studies of EUS-guided gastrojejunostomy have been reported as of yet.

Endoscopic Ultrasound–Guided Ablative Therapy

The use of EUS to provide therapy for locally advanced pancreatic malignancy is a rapidly developing field. Several techniques have been studied, and some have been incorporated into practice. The data, however, are still quite limited.

Endoscopic Ultrasound–Guided Radiofrequency Ablation

Radiofrequency ablation (RFA) enables local tissue destruction by thermally induced coagulative necrosis. The goal of RFA is to minimize damage to nonneoplastic tissue while maximizing its effect on the target tumor. Maintaining a temperature range between 50 and 100 degrees Celsius within the target tumor maximizes protein coagulation and results in irreversible mitochondrial damage. Temperatures above 100 degrees Celsius can result in tissue vaporization and gas formation, which may actually impede the formation of a radiofrequency field.[31] There are extensive data supporting the efficacy and safety of RFA for the treatment of small primary and metastatic liver cancers.[32] Ablative therapy in the pancreas, which is a more friable, noncapsulated organ, has been considered to be a riskier endeavor given the potential for uncontrolled necrosis.

Several series have shown the potential for RFA in treating pancreatic malignancy via an open, percutaneous, or laparoscopic approach.[33,34] Although percutaneous or surgical approaches to the pancreas may be somewhat more

technically challenging due to the retroperitoneal location of the organ, this typically does not pose an issue for EUS. Goldberg and colleagues were one of the first groups to demonstrate the use of RFA in a porcine model.[35] In this study, 16 ablations were performed on 13 anesthetized pigs. RFA was applied to normal pancreatic tissue. The animals were sacrificed immediately, 2 days, or 2 weeks after the procedure. Pathology demonstrated a well-demarcated sphere of coagulation necrosis surrounded by a small rim of hemorrhage. The rim of coagulation necrosis was retracted in the animals that were euthanized 2 weeks after the procedure.[35] Several other animal studies showed similar findings of controlled coagulation necrosis with relatively low complication rates.[36,37]

Data on the use of EUS-guided RFA therapy in humans with pancreatic cancer are very limited. A relatively new flexible bipolar hybrid ablation system has been developed. This cryothermal probe (Erbe Elektromedizin) combines cryotherapy with bipolar RFA and is believed to allow for more efficient tissue ablation in the setting of lower temperatures provided by the cooling cryogenic gas.[38] This technique was initially studied in porcine[39] and ex vivo human pancreas models,[40] and it has more recently been demonstrated in patients with locally advanced pancreatic cancer. An Italian study involved 22 patients with locally advanced pancreatic cancer who had received neoadjuvant therapy. RFA at 18 watts and cryogenic cooling at 650 pounds per square inch were performed for durations specific to the tumor size. Cryothermal probe application was only possible in 16 of 22 patients, with failure of probe application related to luminal wall or tumor firmness. There were no clinically significant complications during or immediately after the procedure. Four late complications arose, but they were attributed to disease progression. Disappointingly, only 6 of 16 patients had clearly definable tumor margins on cryotherapy following the procedure. In these patients, the tumors did seem smaller, but the difference was not statistically significant.[41]

Until more human research data, in the form of randomized trials, provide more insight into the efficacy and safety of this technique, it remains experimental.

Endoscopic Ultrasound–Guided Photodynamic Therapy and Brachytherapy

Photodynamic therapy is a modality for producing local tissue necrosis with light after the administration of a photosensitizing agent. Photodynamic therapy may induce apoptosis and necrosis by regulating pancreatic cellular signaling pathways or modulating plasma membrane protein structures.[42] A phase 1 study in the United States demonstrated that this technique was safe and feasible with the ability to provide predictable, localized tissue necrosis with a low incidence of complications.[43] Human randomized, controlled studies have not been performed, however.

Brachytherapy involves placement of radioactive seeds, which emit gamma rays, in and around tumors to provide locally ablative therapy. To date, the literature has not shown impressive clinical results. Sun and colleagues performed EUS-guided radioactive seed placement (mean, 22 per patient) in 15 patients with unresectable pancreatic cancer.[44] Patients had follow-up visits every 2 to 3 months with clinical examination, performance status evaluations, and imaging (computed tomography and/or EUS). At a median follow-up of 10.6 months, 27% of patients had an objective tumor response on imaging. This partial response lasted a median of 4.5 months. Visual pain scores did improve in the patient cohort, but this effect was temporary.

Endoscopic Ultrasound–Guided Vascular Intervention

The ability of EUS to evaluate vascular flow and deliver precise therapy in real time should confer an advantage over standard endoscopy. The actual clinical utility of this, however, has been varied. Data on EUS-guided therapy in nonvariceal GI hemorrhage are scarce and limited to case reports or anecdotal experience.

Endoscopic sclerotherapy and band ligation have been the mainstay of therapy for bleeding and nonbleeding upper GI tract varices. While generally successful, rebleeding is not infrequent, and subsequent modalities such as emergent portosystemic shunts may be required.[45,46]

Esophageal Varices

In 2006, de Paulo and colleagues postulated that recurrence of esophageal varices after standard treatment may be related to collateral vessels, which could be identified and treated using EUS-guided sclerotherapy.[47] The researchers designed a randomized, controlled trial that compared standard esophageal variceal management to EUS-guided sclerotherapy of collateral vessels in 50 patients with cirrhosis. The patients were followed for at least 6 months. No difference was seen in the rates of eradication, number of procedures, complications, pain, or volume of sclerosant injected. Varices were eradicated in 48 patients who adhered to the study protocol. All patients in both arms underwent EUS to assess for collateral vessels. Thirty-three percent of patients with endoscopically eradicated varices had evidence of collateral vessels, compared with none in the EUS-guided treatment arm. Although this was statistically significant (P=.004), after 6-month follow-up, 2 patients in the EUS-guided sclerotherapy group and 4 patients

in the standard therapy arm experienced recurrence of varices, yielding no significant difference between the groups (*P*=.32). Neither group experienced rebleeding episodes despite the recurrence of varices during the follow-up period.[47]

Gastric Varices

The literature has suggested that a regimen that includes EUS-guided therapy for gastric varices is more effective than as-needed treatment. A study by Lee and colleagues compared 2 groups of patients who presented with gastric variceal bleeding.[48] All patients were treated with bolus therapy of cyanoacrylate (CYA) mixed with lipiodol. The first group (47 patients) had on-demand treatment for recurrent bleeds, whereas the second group (54 patients) underwent biweekly EUS followed by repeat injection until complete obliteration of flow was visualized endosonographically. Although early rebleeding rates (<48 hours) were similar in both groups (7.4% and 12.8%, respectively; *P*=NS), late rebleeding rates were significantly lower in the EUS group, which confirmed variceal obliteration (18.5% vs 44.7%, respectively; *P*=.0053; odds ratio, 0.28).[48]

Vascular coil placement to stop bleeding is well documented in the interventional radiology literature. The challenge and risk of managing gastric varices and the medically complex cohort of patients they are often found in has led to alternative treatment options. Romero-Castro and colleagues have presented a retrospective multicenter study of 30 consecutive patients with gastric varices who received either EUS-guided coil placement (n=11) or the standard CYA injection (n=19).[49] Gastric varix obliteration was achieved in 94.7% of patients in the CYA group and 90.9% of patients in the EUS-guided coil placement group. Interestingly, 12 of 30 patients (40%) had adverse events, although the majority were asymptomatic glue embolisms noted on cryotherapy performed as part of the study protocol. Of these 12 complications, however, only 1 occurred as a result of coil placement (9.1%; *P*<.01).[49] This area needs to be further studied in randomized, controlled studies.

Conclusion

No longer considered solely a diagnostic tool, EUS is proving itself to be a commanding tool in the realm of therapeutic endoscopy. New diagnostic and therapeutic uses for EUS seem to be limited only by the creativity of the advanced endoscopist. The challenge now is to establish robust data from randomized trials, from which formal recommendations and practice guidelines can be made.

The authors have no relevant conflicts of interest to disclose.

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