Interventional Endoscopic Ultrasound

Douglas G. Adler
Editor

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For Harriet and Stanley & Karen and Joel

Preface

Technology progresses at an uneven rate. Since I first started performing endoscopy almost 20 years ago, some procedures have remained fairly static, while others have changed dramatically. ERCP, the first therapeutic procedure I ever fell in love with, despite significant advances in endoscopes, catheters, and wires, is still very similar today, i.e., we still use catheters and wires to access the biliary tree and pancreatic ducts, we still perform sphincterotomy much the way we did back then, and we still use largely the same tools (balloons and baskets) to remove stones. While much of the practice of ERCP has changed, including which patients we select for ERCP, how we perform the ERCP, and what steps we take to prevent pancreatitis, much of the mechanics of ERCP today would look very familiar to someone who performed the procedure in the 1980s.

The evolving practice of EUS, however, represents quite a different story. EUS has undergone what can only be considered a radical transformation over the past few years. From its inception and widespread dissemination in the early 1990s until just a few years ago, EUS was comprised almost entirely of a set of diagnostic procedures, with the vast majority of examinations being used to look at and sample lesions or organs of concern. The idea of EUS being used for therapeutic interventions was slow in coming. Concerns about the mechanical limitations of echoendoscopes, fear of adverse events, and a lack of commercially available accessories to perform these maneuvers significantly hampered progress and development.

Only in the last few years has the idea of using EUS to perform interventional procedures been embraced on a wide scale, and the pace of development has been rapid. Centers around the globe are now actively working to both develop new procedures and devices and to modify old procedures heretofore performed by surgeons or interventional radiologists to be performed by interventional endosonographers.

While much of interventional EUS is still performed with ERCP accessories in an off-label manner, the development and introduction of lumen-apposing metal stents (LAMS) that are supplied on catheters specifically designed to be used with echoendoscopes represents the first true interventional EUS accessory that was not simply a modified needle. LAMS have seen a rapid and widespread dissemination into clinical practice. Although intended for, and widely used, to drain pancreatic fluid collections, the development of LAMS has also led to the development of a plethora of interventional EUS procedures including transmural gallbladder drainage, gastrojejunostomy creation, conduit creation in patients

who have undergone Roux-en-Y gastric bypass to facilitate ERCP, and a host of other procedures.

Beyond LAMS and their applications, interventional EUS has shown the power of using needle-based technologies to do more than sample tissue or fluid from target lesions. Modified needle devices can be used to measure portal pressures, deliver therapeutic agents to treat solid and cystic tumors, implant fiducials to facilitate targeted radiation therapy, and deliver analgesic medications to treat benign and malignant conditions.

The time seems ripe for a single, comprehensive text on interventional EUS and its myriad applications. This book contains 17 chapters that cover the entire depth and breadth of interventional EUS, both with regard to how it is currently practiced and with an eye toward future areas of investigation and development. Each chapter is lavishly illustrated with endoscopic and ultrasonographic images. In addition, each chapter is also accompanied by one or more narrated video segments to allow readers to see how these procedures are performed in real time by experts in the field.

I perform interventional EUS procedures of all manner in my daily therapeutic endoscopy practice and truly enjoy the work. It is my hope that readers use the knowledge contained in this text to expand the range of therapeutic and interventional EUS procedures that they feel comfortable adding to their daily practice. In addition, I hope that readers will someday contribute to the growing body of knowledge on these topics to promote the care of our patients and the development of interventional EUS as a whole in the years to come.

Salt Lake City, UT, USA Douglas G. Adler

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Douglas G. Adler, MD, FACG, AGAF, FASGE attended SUNY Binghamton as an undergraduate and received his medical degree from Cornell University Medical College. He completed his residency in internal medicine at Beth Israel Deaconess Medical Center/Harvard Medical School. Dr. Adler completed both a general gastrointestinal fellowship and a therapeutic endoscopy/ERCP fellowship at Mayo Clinic in Rochester, MN. He then returned to the Beth Israel Deaconess Medical Center for a fellowship in endoscopic ultrasound. Dr. Adler is currently a tenured Professor of Medicine and Director of Therapeutic Endoscopy at the University of Utah School of Medicine in Salt Lake City, UT. Dr. Adler is also the GI Fellowship Program Director at the University of Utah School of Medicine. Working primarily at the University of Utah School of Medicine's Huntsman Cancer Institute, Dr. Adler focuses his clinical, educational, and research efforts on the diagnosis and management of patients with gastrointestinal cancers and complex gastrointestinal disease, with an emphasis on therapeutic endoscopy. He is the author of more than 300 scientific publications, magazine articles, and book chapters. This is Dr. Adler's seventh textbook on gastroenterology.

1 Endoscopic Ultrasound-Guided Drainage of Pancreatic Fluid Collections

Jeffrey S. Bank and Douglas G. Adler

Introduction

In the modern era, pancreatic fluid collections (PFCs) are most commonly diagnosed and treated by gastroenterologists. PFCs occur in the setting of pancreatic ductal injury after episodes of acute pancreatitis and are also seen in patients with chronic pancreatitis, iatrogenic causes (e.g., pancreatic injury during surgery), trauma, or in patients with disconnected duct syndrome [1, 2]. They are divided into pancreatic pseudocysts (PP) or walled-off necrosis (WON). This review will discuss the diagnosis and management of PFCs with an emphasis on endoscopic drainage utilizing double pigtail plastic stents (DPPSs), fully covered self-expanding metal stents (FCSEMS), and lumen-apposing metal stents (LAMS). In addition, we cover the technique used for placement of each stent, compare the advantages/disadvantages, efficacy, and appropriate indications for each stent, and discuss adverse event rates.

Electronic supplementary material: The online version of this chapter (https://doi.org/10.1007/978-3-319-97376-0_1) contains supplementary material, which is available to authorized users.

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Background

Definitions of Pancreatic Pseudocysts (PPs) and Walled-Off Necrosis (WON)

Pancreatic fluid collections (PFCs) have been generally classified as being pancreatic pseudocysts (PPs) and walled-off necrosis (WON). Per the 2012 Atlanta classification criteria, a PP is an "encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with minimal or no necrosis." They usually form more than 4 weeks after the onset of edematous pancreatitis. They have the following contrast-enhanced computerized tomography (CECT) criteria: (1) well circumscribed, usually round or oval, (2) homogeneous fluid density, (3) no non-liquid component, and (4) well-defined wall aka completely encapsulated. PPs most commonly occur as a result of disruption of the main pancreatic duct or its intrapancreatic branches. Another less common etiology is disconnected duct syndrome, where pancreatic parenchymal necrosis of the neck or body of the gland damages a viable distal pancreatic remnant [3, 4].

A WON is a "mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall." WON usually form more than 4 weeks after the onset of necrotizing pancreatitis. They have the following CECT criteria: (1) heterogeneous with liquid and non-liquid density with varying

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degrees of loculations, (2) well-defined wall aka completely encapsulated, and (3) location—intrapancreatic and/or extrapancreatic. WON occurs as a result of necrotic pancreatic parenchyma and/or necrotic peripancreatic tissues and may be infected, may be multiple, and may be present at distant sites from the pancreas [2].

Differences Between PPs and WON

PPs are typically homogeneous in appearance and composed entirely of liquid components, whereas WON are heterogeneous in appearance with at least some solid component. PPs occur due to disruption of the main pancreatic duct without pancreatic parenchymal necrosis; WON arise from necrotic pancreatic parenchyma.

Despite the Atlanta criteria, it remains a challenge to definitively distinguish PPs from WON. In reality, many lesions thought to be PP on CT scans are found to contain solid debris on magnetic resonance imaging (MRI) or EUS. For distinguishing which type of PFC is present, MRI has been shown to be better at detecting solid debris than either CT or ultrasound [5, 6]. In a series of 47 patients who developed PFCs, CT scans performed within 3 days of onset of acute necrotizing pancreatitis (ANP) demonstrated evidence of greater than 50% necrosis in 57% of the patients. Upon repeat evaluation with EUS at 6 weeks, 87% had evidence of solid debris in their PFCs, which slowly decreased on follow-up EUS exams at 3 and 6 months. Over half of PFCs had no evidence of solid debris at 6 months. This was felt to be due to breakdown of the solid debris over time [7].

Under the current Atlanta classification criteria, both pseudocysts and WON can connect with the pancreatic duct, which also makes it difficult to distinguish between the two. Patients with PFCs that contain solid debris tend to have poorer outcomes and more adverse events compared to those with PFCs with only fluid [8]. In clinical practice, many PFCs do not nicely fit into either the PP or WON categories. Due to these gray areas with the Atlanta criteria, it has been proposed that PP and WON should be called "mature PFCs" with a clarifying comment describing the presence or absence of solid material within the collection [9].

Brief Overview of Endoscopic Approaches to PFC

Endoscopic ultrasound (EUS)-guided drainage is currently the most commonly used endoscopic method of drainage of PFCs, and at many centers has largely replaced surgical or interventional radiology approaches in these patients. It has a high clinical success rate, similar to surgical and percutaneous approaches, but with decreased morbidity and costs [10, 11]. EUS allows the endoscopist to identify and drain PFCs without endoluminal bulging, as compared to non-EUS-guided approaches. Transmural drainage alone allows for resolution of PFCs in the majority of patients. Direct endoscopic necrosectomy (DEN) is sometimes necessary for WON. In the past, double pigtail plastic stents (DPPSs) were used for management of PFCs. Recently, fully covered self-expandable metal stents (FCSEMS) and lumen-apposing metal stents (LAMS) are increasingly utilized, especially with WON, owing to their large diameter, which allows for direction insertion of the endoscope into the WON for DEN [12].

EUS-Guided Access

Standard Approaches

There is no universally agreed upon technique of PFC drainage, but some general approaches are widely utilized. EUS-guided drainage of PFCs can be performed with or without fluoroscopy, of note, depending on operator desire.

Once a PFC is visualized endosonographically, a 19-gauge fine needle aspirate (FNA) needle is used for initial transmural puncture. The aspirated fluid is sometimes sent for cell count, gram stain, culture, and cytology—at some centers this step is obviated if the lesion is obviously a PFC. If desired, contrast can then be

injected inside the PFC to ensure the needle is in the correct position. A 0.025″ or 0.035″ guidewire is advanced through the lumen of the needle until it coils in the PFC. This forms extra wire loops in the PFC cavity and helps solidify the endoscope/needle/guidewire position. With the wire left in place, the needle is removed over the wire, and a cystostome, needle knife, or dilation balloon can be threaded over the wire. The fistula tract is dilated either by balloon dilation or via a combination of a cystostome and/or diathermy needle/needle knife. Once the tract is felt to be sufficiently dilated, a stent can be placed over the guidewire. Freely flowing fluid through the stent and into the gastrointestinal cavity indicates successful stent placement [13].

Double Pigtail Plastic Stents (DPPSs)

Typically, multiple DPPSs were used for transmural drainage of PFCs (Fig. 1.1). When multiple DPPSs are placed into a cyst cavity, several guidewires can be placed into the cyst prior to insertion of the first to allow for easier stent placement or a single wire can be used serially with each new stent placement. The stents maintain the fistula tract between the gastric or duodenal wall and the PFC, allowing for continued drainage of the PFC. Of note, when multiple stents are placed the PFC can drain *through* and *between* the stents. Placement of multiple stents also decreases the risk of stent dislodgement and migration. Stent occlusion rates increase with smaller diameter stents, such as 7 Fr, so larger sizes are typically used, but it is not wrong to use a 7 Fr stent [11].

EUS has been used for drainage of PFCs since 1996, with several case series reporting technical success rates of 83–100% [14–16]. Most endoscopists use fluoroscopy as it optimizes visualization and access into PFCs as well as maintenance of the position of various devices used, although fluoroscopy is not mandatory or required for successful PFC drainage. As most previous studies had utilized fluoroscopy to aid with drainage of PFCs, Seicean et al. evaluated the safety of EUS-guided drainage of PFCs without fluoroscopy. Most DPPSs do not migrate in or out of the cyst as they are coiled at their proximal and distal ends. Seicean et al. used DPPSs over a guidewire in a prospective study of 24 patients (9 with abscesses, 15 with PPs) and achieved technical success in 20 patients (83.3%) with complete resolution after a median follow-up time period of 18 months. The four patients (16.7%) in whom failure occurred had diameter <6 cm and wall thickness >2 mm [17]. Seicean et al. felt that the lack of fluoroscopy likely contributed to the technical failure of drainage of PFCs with a diameter <6 cm. All technical failures in their study were due to instability of a cystostome on the wall of a small pseudocyst, in which the absence of fluoroscopy played a role.

A retrospective review of 93 patients with symptomatic PFCs reported clinical success rates of 93.6% using a single plastic stent and 97.4% using multiple plastic stents (P = 0.309). The authors found that the secondary infection rate for drainage utilizing a single stent was 18.4% versus 5.3% for multiple stent drainage (P = 0.134). Surprisingly, the secondary infection rate for smaller diameter stents (8.5 Fr or less) was less than that for larger diameter stents (10 Fr or larger), 3.4% versus 17.2%, respectively (P = 0.138) [18]. It should be emphasized, as mentioned above, that drainage through the stents (when multiple stents are used) contributes to the lower rate of infection.

Two studies have demonstrated high technical success rates (93–94%) utilizing DPPSs for the drainage of PFCs. Clinical success rates were 74.2% and 82%. PFC recurrence with DPPSs typically occurs as a result of stent clogging and/or migration and has been reported at a rate of 12–25%. Procedure-related complication rates were 5.4–15% and included perforation, bleeding, obstruction, migration, recurrence, secondary infection, and asymptomatic pneumoperitoneum [19, 20].

Metal Biliary Stents

Another option for transmural drainage of PFCs are fully covered self-expanding metal stents (FCSEMS) (Fig. 1.2). These devices have larger

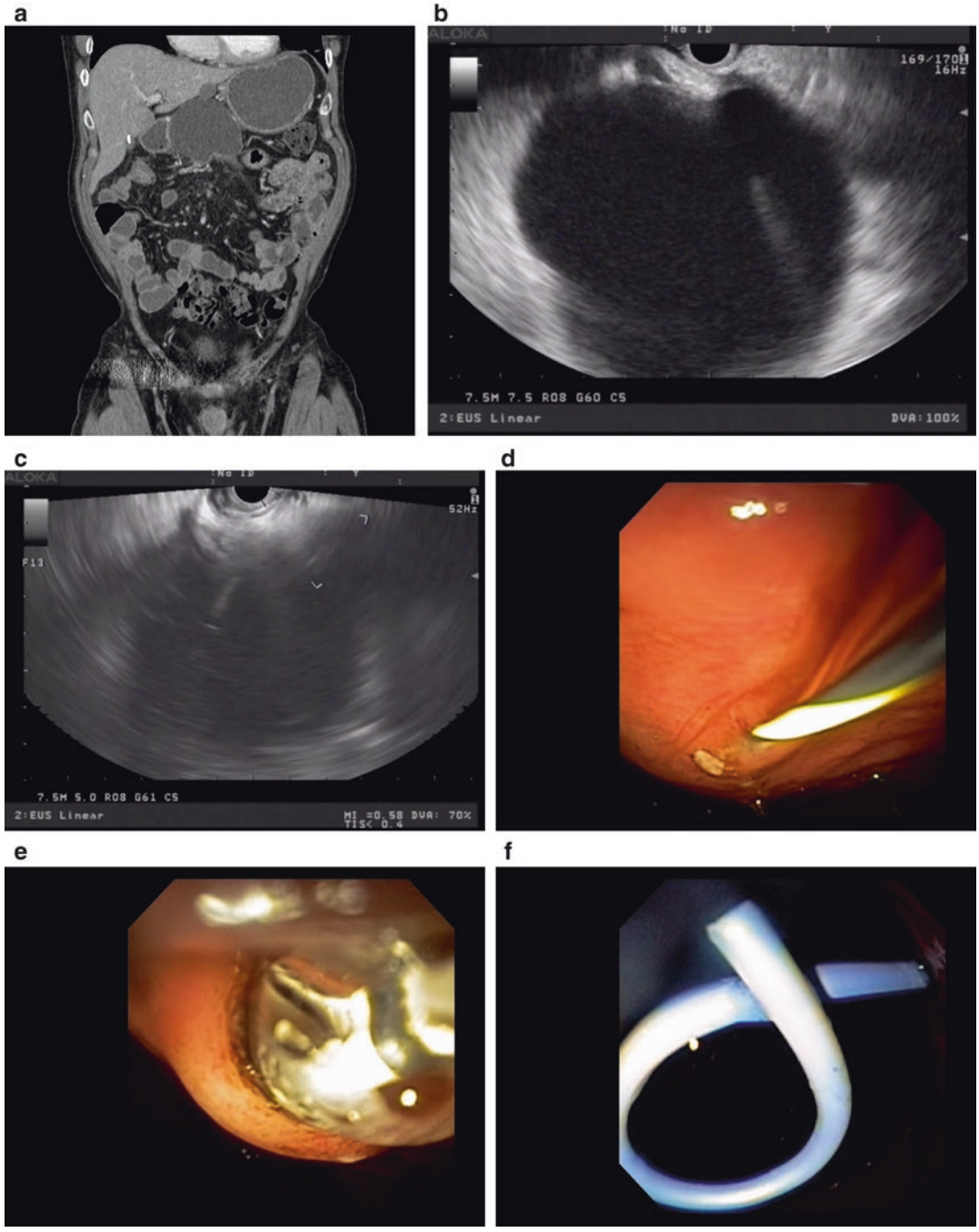
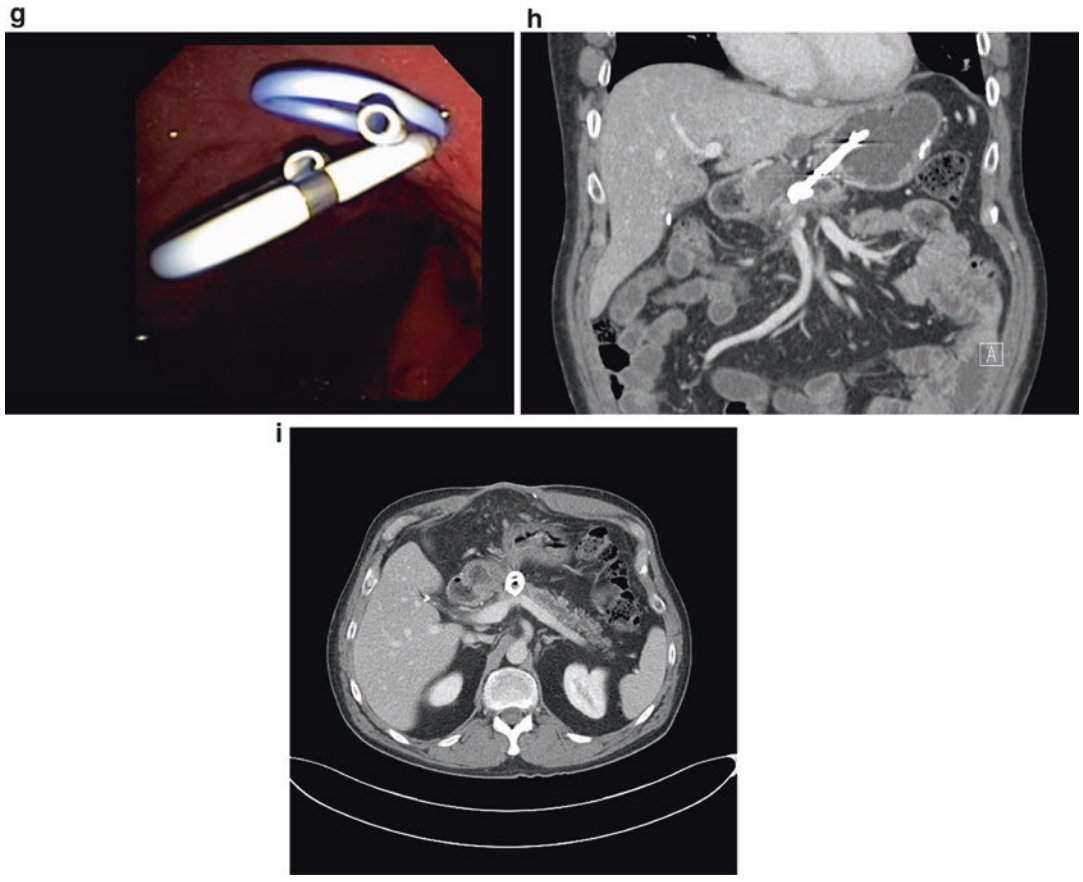


Fig. 1.1 Use of double pigtail stents to drain a pancreatic fluid collection (PFC). (**a**) CT image of a large PFC abutting the stomach. (**b**) Linear EUS image of the PFC showing largely fluid contents. (**c**) A 19-gauge needle has been passed into the PFC. (**d**) A biliary guidewire is advanced into the PFC through the needle and the needle is removed over the wire providing guidewire access to the PFC. (**e**) The cystgastrostomy is dilated to 10 mm using an over-the-wire biliary dilation balloon catheter. (**f**) A double pigtail stent is placed across the cystgastrostomy into the PFC. (**g**) A second double pigtail stent is placed across the cystgastrostomy next to the first stent. (**h**) Coronal CT image of double pigtail stents in the PFC. (**i**) Sagittal CT image of the double pigtail stents in the fully collapsed PFC shortly before they were removed. The PFC did not recur



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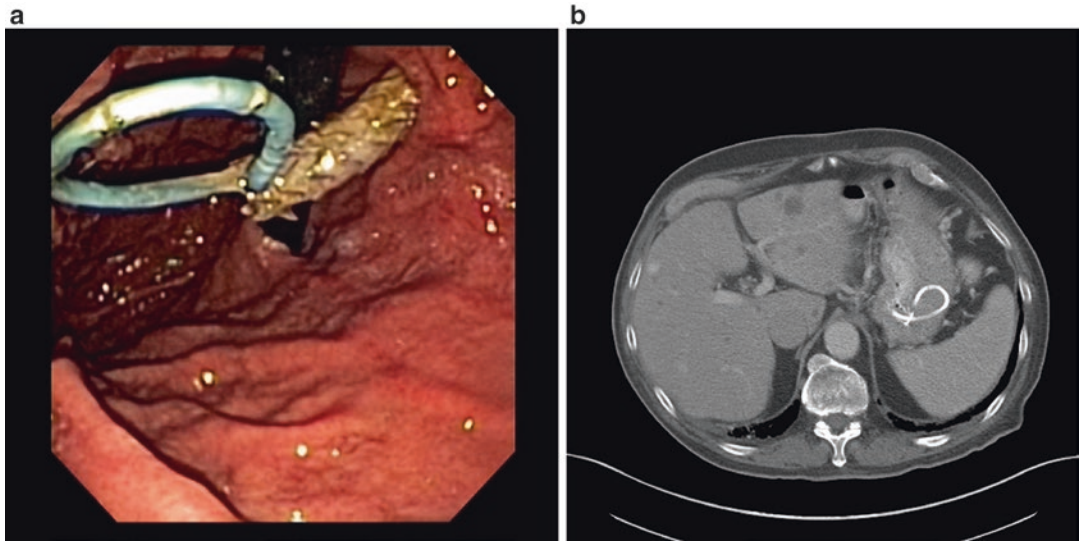

Fig. 1.2 Fully covered metal biliary stent used to drain a PFC. (**a**) Endoscopic image of fully covered metal biliary stent across a cystgastrostomy. A double pigtail stent has been placed through the metal stent to reduce the risk of migration. (**b**) CT image of the same patient showing the position of the stents across the cystgastrostomy

diameters (6, 8, or 10 mm) and placement of a single stent can provide a wide drainage opening, as opposed to DPPSs, which typically require placement of multiple stents. Owing to their larger diameter, they have a decreased risk of occlusion, especially for PFCs that contain a significant amount of solid material [11].

It should be noted that FCSEMSs are designed for drainage related to a luminal stricture and not to a transluminal route and devices used in this manner should be considered off-label. When a biliary metal stent is utilized for drainage of a PFC, the ends of the stent protrude into both the gastric or duodenal lumen and the PFC cavity, which can cause contact ulceration and increase the risk of stent migration and bleeding. These devices may not be the best option for PFCs that are not firmly adherent to the gastrointestinal wall as they do not have flanges to provide an anchoring force; in addition, they may migrate just like DPPSs. Many endoscopists place DPPSs through a FCSEMS to decrease the risk of migration and help maintain stent patency [11].

Overall, the technical and clinical success rates of FCSEMSs have been reported at 78–100% and 81–94%, respectively [21–25]. Biliary FCESMSs have been used for drainage of symptomatic PFCs in multiple case series in addition to two prospective, single-center studies [26–28]. Talreja et al. utilized FCSEMSs in 18 patients for drainage of PFCs and placed DPPSs alongside (n = 4) or through the FCSEMS (n = 14) to further promote drainage and to prevent migration. At a mean follow-up time period of 77 days, 14 (78%) patients had complete resolution of their PFC [29]. Penn et al. used FCSEMSs in 20 patients for drainage of PPs and found that 14 (70%) patients had resolution of their PPs after stent placement without known recurrence, adverse events, or the need for surgical intervention. One (5%) patient required surgery for primary failure of endoscopic drainage and another two (10%) patients developed pseudocyst infection, requiring surgery. Three (15%) patients initially had resolution of their PP, but had recurrence after stent removal [30].

The adverse event rate was higher (44%) in Talreja et al. as opposed to Penn et al. (15%), likely in part due to the inclusion of patients with higher-risk WON. The most common adverse events between the two studies were superinfection, bleeding, stent migration, and fever. This rate of adverse events is similar to Sharaiha et al., whose adverse event rate was 16% in those patients with PPs treated with FCSEMSs, although multivariate analysis demonstrated patients with plastic stents were 2.9 times more likely to experience adverse events than those treated with FCSEMSs [31]. A large retrospective review of 211 patients treated with FCSEMSs for PFCs had an adverse event rate of 21%, which included infection (11%), bleeding (7%), and stent migration and/or perforation (3%) [21].

Lumen-Apposing Metal Stents (LAMS)

Lumen-apposing metal stents (LAMS) have a saddle-shaped design and larger inner lumen diameter than either plastic or metal biliary stents, which theoretically decreases the risk of migration and allows for an endoscope to pass into PFCs as well as the ability to perform DEN (Fig. 1.3 and Video 1.1). There are three different LAMSs available at this time around the globe (AXIOS, NAGI, and Niti-S Spaxus). The AXIOS stent (Xlumena Inc., Mountain View, CA, USA) consists of double-walled flanges perpendicular to the lumen that hold the tissue walls in apposition [32]. The NAGI stent (Taewoong-Medical Co.) comes in 3 different lengths, 4 diameters and has flared ends of 20 mm [33]. The Niti-S Spaxus stent (Taewoong Medical Co., Ltd., Ilsan, Korea) consists of nitinol wire and is fully covered with a silicone membrane [34]. Currently available LAMSs range in diameter from 8 to 20 mm.

Advances in endoscopy over the last 10 years with endoscopic ultrasound (EUS)-guided drainage of PFCs via transmural stent

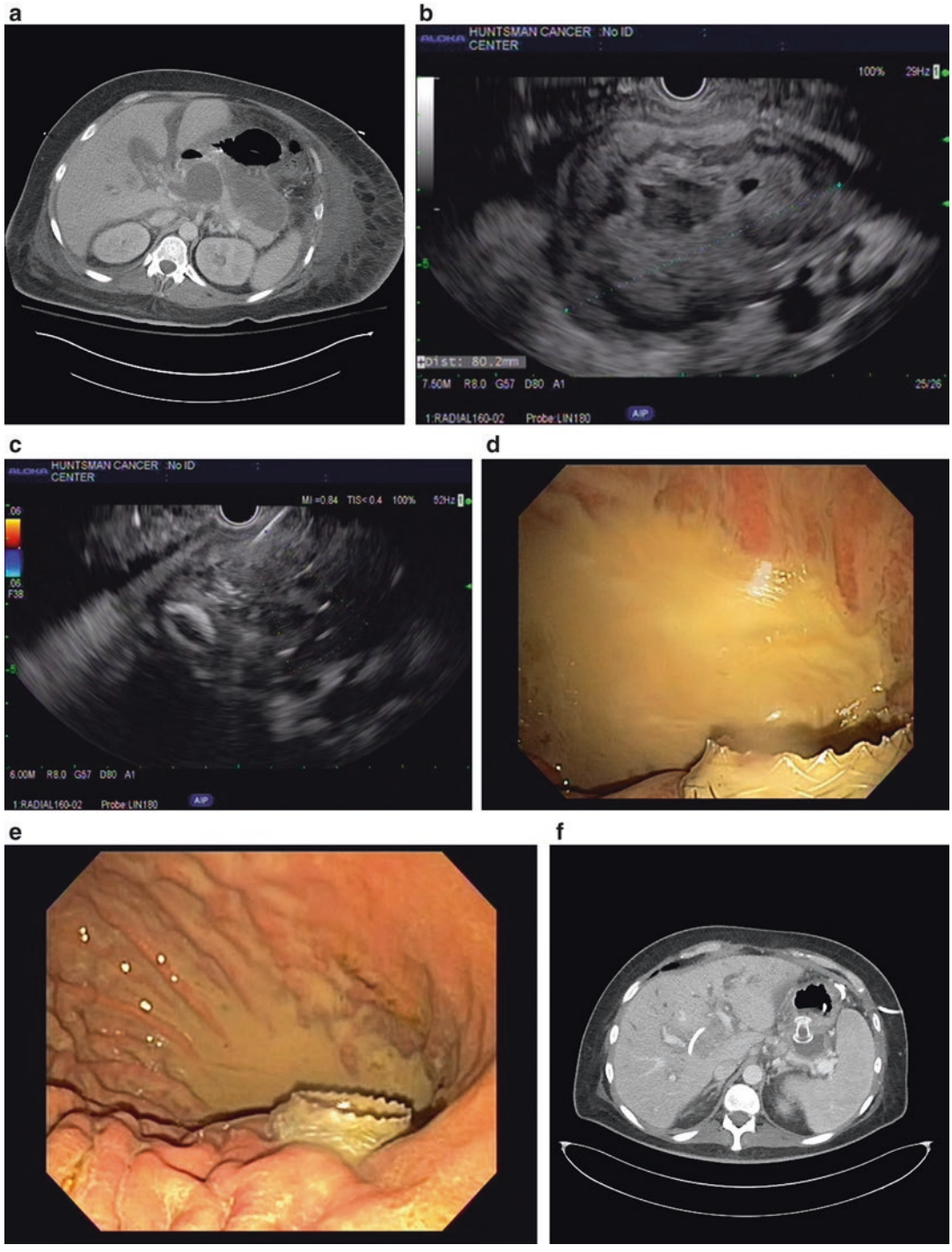

Fig. 1.3 Use of a 15 mm diameter lumen-apposing metal stents (LAMS) to treat a patient with infected walled-off pancreatic necrosis (WON). (**a**) CT scan image of a large WON occupying much of the pancreatic bed. (**b**) EUS image of the WON with copious turbid solid contents. (**c**) The electrocautery-enhanced LAMS has been advanced into the PFC and half of the LAMS has been deployed. (**d**) Endoscopic image after the LAMS has been fully deployed showing WON contents spilling into stomach. (**e**) LAMS in good position after stomach aspirated. (**f**) CT scan showing LAMS in position across the cystgastrostomy. (**g**) Contents of WON seen during endoscopic necrosectomy 1 week later. (**h**) Solid necrosis being grabbed with an endoscopic net. (**i**) A large piece of necrotic tissue has been grasped and is being pulled through the LAMS to be deposited in the stomach. (**j**) Appearance of the WON cavity after total debridement. Note the absence of any further necrotic tissue. (**k**) Final appearance of fully collapsed WON cavity at 8 weeks. (**l**) The LAMS is removed using a rat-tooth forceps

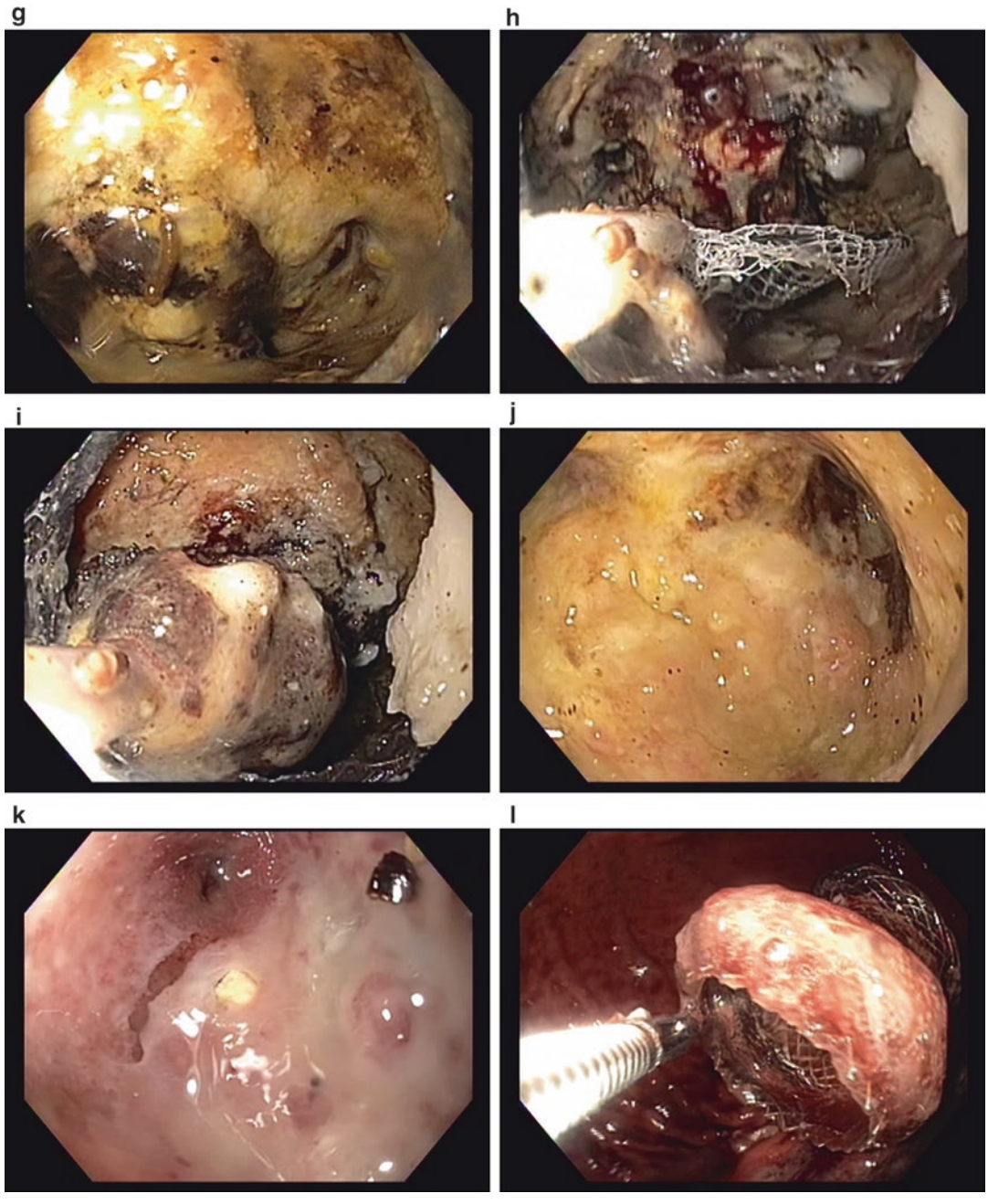

Fig. 1.3 (continued)

placement has become the first-line management of PFCs at most tertiary care centers [35]. Over the last few years, LAMSs have been shown to be both safe and efficacious for endoscopic transmural drainage of PPs and WONs [19–21, 36–38].

Due to their large diameter, AXIOS, Nagi, and Spaxus LAMSs are preferable when DEN is

required as it allows the endoscopist to pass the scope directly through the stent into the PFC to remove the necrotic material [23, 24].

The graded dilation technique is the most common technique utilized for the drainage of PFCs using cold LAMSs. A 19-gauge access needle is inserted into the PFC and a 0.035-in. guidewire is then advanced through the needle into the collection and coiled under fluoroscopic guidance. The needle is then removed. The tract is subsequently enlarged by passing a dilating catheter, balloon dilator (4, 6, or 8 mm), or needle-knife catheter over the guidewire. In some centers, a larger caliber balloon dilator (range, 8–15 mm) is used to further expand the cystenterostomy tract, but this step is optional. After dilation, a LAMS is then deployed across the cystenterostomy. The endoscopist may then choose to perform DEN, balloon dilation of the LAMS, or to place DPPSs through the LAMS as needed and based on patient and physician needs and preferences. If a DPPS (7F or 10F) is placed through the LAMS, it is placed in an over-the-wire manner under endoscopic and/or fluoroscopic guidance into the PFC with the internal pigtail inside the PFC and the external pigtail in the lumen of the stomach or duodenum. Some endoscopists choose to place DPPSs through the LAMS to decrease the risk of migration and to help break up solid contents inside a PFC through mechanical processes [39].

Comparison Between DPPSs and Metal Stents (Both FCSEMSs and LAMSs)

In a systematic review of 17 studies with 881 patients with PFCs who underwent EUS-guided drainage with plastic versus metal (including both FCSEMS and LAMS) stents, there were similar clinical success rates (defined as a decrease in PFC size and/or resolution of symptoms) for plastic stents (81%) and metal stents (82%) for both PPs (85% vs 83%, respectively) and WON (70% vs 78%, respectively). In addition, there were no statistically significant differences in the rates of adverse events (e.g., bleeding, secondary infection, and stent migration) with plastic versus metal stents (16% vs 23%, respectively) or recurrence (10% vs 9%, respectively). The overall high adverse event rate is likely due to the high-risk nature of endoscopic PFC drainage [40].

A large retrospective study of 103 patients with PFCs examined the efficacy of, and adverse events from, LAMSs versus DPPSs. They reported 80 cases with PP (70 DPPSs, 10 LAMSs) and 23 cases of WON (14 DPPSs, 9 LAMSs). In patients for whom follow-up data was available, clinical success rates were 67/70 (96%) with DPPSs and 16/17 (94%) with LAMSs, as defined by resolution of PFCs within 6 months ($p = 0.78$). PFC recurrence occurred in four (3.9%) patients (3 DPPSs, 1 LAMS). The overall adverse event rate was 18%. Adverse events occurred in nine (12%) patients treated with DPPSs and ten (53%) patients treated with LAMSs ($p = 0.0003$). There were more bleeding episodes in the LAMS group than in the DPPS group (21% vs 1%, $p = 0.0003$). In addition, unplanned repeat endoscopy occurred more frequently in the LAMS group (10% vs 26%, $p = 0.07$) [41].

An additional retrospective review of 49 patients (31 with PP and 18 with WON) examined clinical success rates, cost, and adverse events for drainage of PFCs utilizing LAMSs (Nagi stent) versus DPPSs. Inadequate drainage occurred in 10 cases treated with DPPS compared to zero with LAMS. Clinical success was achieved in 25/38 (64.9%) for DPPS versus 11/12 (91.7%) for LAMS. Placement of DPPS was associated with an increased frequency of repeat drainage (34.2% vs 6.3%, $p = 0.032$) compared to LAMS, which is different than the previous study. DPPSs were significantly cheaper for drainage of non-infected PPs; costs were similar for infected PP and WON. Overall adverse event rate was 13.5% for DPPS and 0% for LAMS [42].

Siddiqui et al. examined by the efficacy of DPPSs, FCSEMSs, and LAMSs for the drainage of WON in 313 patients (106 with DPPSs, 121 with FCSEMSs, and 86 with LAMSs). There were no differences in technical success rates between the three stents, however, complete resolution of WON at 6-month follow-up seen in significantly fewer patients treated with DPPSs as opposed to FCSEMSs and LAMSs (81% vs 95% s 90%; $P = 0.001$). The average number of endoscopic sessions for WON resolution was significantly lower in the LAMS group compared with the FCSEMS and DPPS groups (2.2 vs 3 vs 3.6; $P = 0.04$). Adverse events occurred in 27 (8.6%) of 313 patients and included perforation ($n = 6$), bleeding ($n = 8$), suprainfection ($n = 9$), and other ($n = 7$). Early adverse events occurred less often in the FCSEMS group compared with the DPPS and LAMS groups (1.6% vs 7.5% vs 9.3%; $P < 0.01$). Overall, drainage of WON was felt to be most efficacious with FCSEMSs or LAMSs as opposed to DPPSs [25].

In a retrospective case-control study, Bang et al. compared the efficacy of LAMSs versus DPPSs for PFC drainage in 21 patients undergoing PP drainage (7 via LAMS, 14 via conventional plastic double pigtail stents) and 39 patients undergoing WON drainage (14 via LAMS, 26 via plastic stents). To be considered a treatment success, the pseudocyst or WON had to be ≤2 cm on CT/MRI in combination with resolution of the patient's symptoms at 8 week follow-up. With regard to hospital costs, there was no difference seen between WON treated with plastic stents vs LAMS, but hospital costs were significantly decreased for pseudocysts drained with plastic stents ($18,996 vs $58,649, $p = 0.03$). The authors achieved treatment success in 80.9% of patients (17/21); of the four patients who had treatment failure, three had WON and one had a PP. This study did not demonstrate improved clinical outcomes for LAMS over plastic stents for the treatment of pseudocysts or WON. The major advantage of LAMS was decreased procedure time, while the major disadvantage of LAMS was increased cost [43].

Electrocautery-Enhanced LAMS (EC-LAMS)

Recently, an electrocautery-enhanced LAMS (EC-LAMS) has been made available for EUS-guided drainage of PFCs. EC-LAMS allows endoscopists to perform drainage of PFCs in a more efficient manner by decreasing the number of steps needed, and in many cases completely obviating the need for the use of a wire at all. EC-LAMS procedures also should not require the use of a dilating catheter as well, further saving time and the cost of additional supplies.

Three studies have examined the use of an electrocautery-enhanced LAMS for the drainage of PFCs in a total of 131 patients. In a retrospective study of 25 patients who underwent EC-LAMS drainage of PFCs (3 with PP and 22 with WON), technical success was achieved in 25 (100%) patients and PFCs resolved in 24 (96%) patients at an average follow-up of 7.8 months. The resolution failure occurred in a patient with WON. Adverse event rate was 8% and included stent occlusion ($n = 1$), and spontaneous migration into enteral lumen after resolution ($n = 1$) [44]. In a large retrospective study of 93 patients (80% with complex collections) with PFCs at 13 European centers, Rinninella et al. achieved a technical success rate of 99%. Overall clinical success occurred in 86/93 patients (92%) without evidence of recurrence during average follow-up of 320 days. Treatment failure occurred in 6/93 patients (6%) due to persistent infection requiring surgery ($n = 3$), perforation and significant bleeding caused by nasocystic drainage catheter ($n = 2$), and the need for a larger opening to extract large necrotic tissue ($n = 1$). Major adverse events occurred in 5/93 patients (5%) and included perforation and massive bleeding caused by the nasocystic drainage catheter ($n = 2$), pneumoperitoneum ($n = 1$), stent dislodgement during DEN ($n = 1$), and postdrainage infection ($n = 1$) [45].

In a recent retrospective, multicenter study of 13 patients with PFCs (69% with WON) who underwent drainage with EC-LAMS, Adler et al. had technical and clinical success rates of

100%. Of note, DEN was carried out in all 9 patients with WON and there was no evidence of recurrence during an average follow-up time period of 2.5 months. There was one procedure-related adverse event. In one patient, the LAMS was dislodged immediately after deployment, falling into the stomach where it was removed. A second electrocautery-enhanced LAMS was placed in this patient immediately afterward [46]. Overall, EC-LAMS has been shown to be safe and highly effective for drainage of PFCs based on early data, although EC-LAMS has now progressed to widespread adoption.

Adverse Events

Metal (LAMS and FCSEMS) Versus DPPS

With regard to the safety of LAMSs versus DPPSs, a recent small randomized trial for drainage of PFCs via LAMSs versus DPPSs demonstrated stent-related adverse events in 50% (6/12) patients who received LAMSs and no adverse events in patients who received DPPSs [47]. Similar results were seen in a previous study using both LAMSs and DPPSs for drainage of PFCs where stent-related adverse events occurred in 10% (2/20) of patients who received LAMS and 2.5% (1/40) patients who received DPPSs [36]. Other studies using LAMSs for drainage of PFCs with larger numbers of patients (n = 47 to n = 124) have reported adverse event rates of 5–20% [6, 43, 48–50]. Performing a CT scan 3 weeks post-procedure for all patients who received a LAMS followed by stent removal of evidence of PFC resolution may be reasonable as proposed by Bang et al. [44]. The optimal time frame to remove a LAMS after placement remains unknown.

In 230 patients with PPs treated with DPPSs (n = 118) or FCSEMSs (n = 112), Sharaiha et al. found a procedural adverse event rate of 31% in those treated with DPPSs and 16% with FCSEMSs (P = 0.006). Multivariate analysis demonstrated patients with plastic stents were 2.9 times more likely to experience adverse events than those treated with FCSEMSs (95% confidence interval, 1.4–6.3) [29]. A large retrospective review of 211 patients treated with FCSEMSs for PFCs had an adverse event rate of 21%, which included infection (11%), bleeding (7%), and stent migration and/or perforation (3%) [21].

The literature is conflicting on whether adverse events occur more frequently with metal stents (LAMS and FCSEMS) versus DPPSs. A systematic review of 17 studies with 881 patients with PFCs found there to be no statistically significant differences in the rates of adverse events (e.g., bleeding, secondary infection, and stent migration) between metal vs plastic stents [38], whereas another retrospective study of 103 patients with PFCs found that LAMSs have an increased adverse event rate when compared with DPPSs (53% versus 12%, P = 0.0003), specifically with regard to more bleeding episodes and unplanned repeat endoscopy [39]. A retrospective review of 49 patients (31 with PP and 18 with WON) found that inadequate drainage occurred in 10 cases treated with DPPSs compared to zero with LAMSs; in addition, the overall adverse event rate was 13.5% for DPPSs and 0% for LAMSs [40]. A prospective study utilized DPPSs, FCSEMSs, and LAMSs for the drainage of WON in 313 patients had an overall adverse event rate of 8.6%, which included perforation (n = 6), bleeding (n = 8), suprainfection (n = 9), and other (n = 7) [41].

EC-LAMS

Overall, adverse event rates for EC-LAMS are low at 5–8%. The most common events reported include stent occlusion, stent migration, perforation and bleeding, and infection [25, 43, 44].

Infection

Infected pancreatic necrosis typically occurs within the first 2–3 months after the initial episode of necrotizing pancreatitis, but is rare during the first week [51, 52]. The rates of secondary infection after placement with each stent type is highly

variable in clinical studies, ranging 2.7–12% of DPPSs, 0–28% of FCSEMSs, and 0–15.2% in LAMSs [16, 25, 28, 49, 51, 53, 54].

Guo et al. examined risk factors for infection after EUS-guided drainage of PFCs in 83 patients and found evidence of infection in 7 (8.4%) patients. All 7 of these patients had a history of acute pancreatitis and the cyst diameters were all greater than 15 cm. They concluded that cyst diameter is an independent risk factor for infection and that cysts with a diameter greater than 15 cm should be drained with either a large diameter FCSEMS or multiple DPPSs to decrease the risk of infection [53].

One retrospective study of 93 patients found that the secondary infection rate for smaller diameter stents (8.5 Fr or less) was surprisingly less than that for larger diameter stents (10 Fr or larger), 3.4% versus 17.2%, respectively ($P = 0.138$) [16]. The reasons for this are unclear and somewhat difficult to reconcile.

One case report described a case of infected pancreatic necrosis that developed 2 years after necrotizing pancreatitis. The infected pancreatic necrosis was treated using a LAMS with subsequent endoscopic necrosectomy to remove solid debris [54]. This case represents the longest time ever documented from the onset of pancreatic necrosis to documented infection.

Stent Migration and Occlusion

There is a wide range of migration rates with each stent type reported in the literature, including 0.7–18% with plastic stents, 0–10% with FCSEMSs, and 3–6.7% with LAMSs [25, 27, 28, 55–60].

A retrospective study of 31 patients with PPs treated with DPPSs had 6 (25%) symptomatic recurrences due to stent clogging or migration, with 2 secondary infections during a mean follow-up time period of 12.6 months. Both were treated with new DPPSs stents [17]. In DPPSs, occlusion rates increase with smaller diameter stents, such as 7 Fr, so larger sizes are typically used [11].

Conclusion

Interventional endoscopists can choose from DPPSs, FCSEMSs, and LAMSs for endoscopic drainage of PFCs. DPPSs have high technical and clinical success rates and are less expensive than FCSEMSs and LAMSs, but are more prone to stent occlusion, especially in the setting of WON. We recommend that they primarily be used for drainage of PPs as opposed to WON for this reason. FCSEMSs also have high technical and clinical success rates. They have a decreased risk of occlusion compared to DPPSs, but have similar rates of stent migration. FCSEMSs should be utilized for drainage related to a luminal stricture as opposed to LAMSs, which are designed for a transluminal route. LAMSs have higher technical and clinical success rates for drainage of WON as compared to both DPPSs and FCSEMSs. This is likely due to their larger diameter, which allows for DEN. Endoscopists have many safe and effective stent options for EUS-guided drainage of PFCs with high clinical success rates.

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2 Endoscopic Ultrasound-Guided Bile Duct Access and Drainage: Antegrade Approaches

Nan Ge and Siyu Sun

Introduction

EUS-BD

Endoscopic ultrasound (EUS), which couples endoscopy with ultrasound in examining the GI tract and adjacent structures, has improved our understanding of many disease states [1–3]. EUS-guided fine needle aspiration (FNA) was first reported in 1992. Its use has proved superior to EUS alone in accurately diagnosing and staging malignancies, thus aiding in treatment selection. EUS is also a unique, effective, and minimally invasive therapeutic technique [4], enabling bile duct drainage as well [5].

Since the advent of EUS-guided biliary drainage (EUS-BD) in 2001, [6, 7] the efficacy and safety of this type intervention has been amply demonstrated. A recent meta-analysis has shown that EUS-BD has a pooled technical success rate of 90–95% in therapeutic applications, with a relatively low (14–17%) cumulative rate of adverse events after failed endoscopic retrograde cholangiopancreatography (ERCP) [8]. These data are supported by a new prospective international multicenter study citing comparable technical (95.7%) and clinical (95%) success rates in an intention-to-treat analysis, with an adverse event rate of 10.5% for patients with malignant distal biliary obstruction [6]. Compared with percutaneous transhepatic biliary drainage (PTBD), EUS-BD is deemed superior in terms of possible catheter dislodgement, recurrent infection, acute cholangitis, pneumothorax, and cosmetic problems (due to external drainage) [9].

EUS-BD by rendezvous technique and EUS-guided choledochoduodenostomy (EUS-CDS); hepaticogastrostomy (EUS-HGS) or hepaticoduodenostomy; and antegrade (EUS-AG) stenting technique are the most common interventions in this context.

EUS-AG

EUS-AG stenting is a viable treatment option for patients with bile duct stones (BDS) or obstruction (BDO) in whom ERCP has failed, primarily as a consequence of surgically altered anatomy [10], duodenal obstruction, or inability to cannulate the papilla.

EUS-AG procedures may have several advantages over other EUS-guided techniques, especially in patients whose surgically altered anatomy precludes ready choledochoduodenostomy access. Likewise, EUS-AG may reduce the occurrence of stent migration compared with

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HGS. Long-term influx of intestinal content into the biliary system is then a potential risk. The EUS-AG approach confers clinical benefits of durable stent patency and fewer adverse events, such as bile peritonitis. EUS-AG holds promise as a safe and effective alternative in managing biliary disorders (Table 2.1).

Indications

- Obstructive jaundice and failed ERCP or non-access to ampulla of Vater
  (a) Surgically altered anatomy
  (b) Upper intestinal obstruction
  (c) In situ enteral stents
  (d) Problematic bile duct intubation (periampullary diverticular or infiltrative tumor impingement)
- Common bile duct stones and failed ERCP or non-access to ampulla of Vater
  (a) Surgically altered anatomy
  (b) Upper intestinal obstruction
  (c) In situ enteral stents
  (d) Problematic bile duct intubation (periampullary diverticular or infiltrative tumor impingement)

Contraindications

- Contraindication to EUS, including ERCP
- Normal coagulation studies and platelet count
- Severe organ failure
- Failure to obtain consent

Devices (Table 2.2)

The following list included suggested devices for EUS-AG biliary drainage procedures. Many different devices from multiple manufacturers could potentially be used for these procedures.

- Fine Needles
  (a) 19G EchoTip Needle or EchoTip Access Needle (Cook Medical, Bloomington, IN, USA). The EchoTip Access Needle may help deter guide wire shearing during interventions. In studies conducted by Godat et al. [11], both the 19G EchoTip Needle and 19G EchoTip Access Needle were used for intrahepatic bile duct (IHBD) puncture, culminating in a higher success rate for the 19G EchoTip Needle (16/16, 100% vs. 5/7, 71%). No instances of interventional guide wire shearing were recorded in this study.
  (b) Boston 19G Flexible Needle (Boston Scientific Corp, Marlborough, MA, USA)
  (c) SonoTip Pro Control 19G Fine Needle (Medi-Globe GmbH, Rosenheim, Germany; Medico's Hirata Inc, Osaka, Japan)
  (d) Dilators (hepaticogastric tract dilation)
  (e) 6Fr cystotome (ENDO-FLEX GmbH) for dilation of hepaticogastric tract or biliary stenosis
  (f) 6Fr, 8Fr Soehendra biliary dilation catheter (Cook Medical)
  (g) 6Fr diathermic dilator (Cysto-Gastro-Set; Endo-Flex, Voerde, Germany)
  (h) Balloon for dilatation biliary stenosis
  (i) 6Fr, 7Fr Bougie dilator (PD-SS6F180C; Gadelius Medical, Tokyo, Japan)
- Guide wires
  (a) 0.035-in (Tracer Metro Direct Wire Guide, Cook Medical or Radiofocus, Terumo, Tokyo, Japan)
  (b) Cyst guide wire (nitinol uncoated; Medi-Globe GmbH)
  (c) 0.025-in (VisiGlide, Olympus, Tokyo, Japan or Revowave, Piolax Medical Devices, Kanagawa, Japan)
  (d) 0.018-in guide wire with 22G fine needle is also a choice for some operators

Approaches

- EUS-AG bile duct stones removal (Fig. 2.1)
  (a) EUS scan of left hepatic lobe for dilated IHBDs.
  (b) Color Doppler identification of intervening vessels to avoid during puncture.

Table 2.1 Summary of EUS-AG stenting trials

Study	Author	Treatment	Cause	Technical success	Clinical success	Adverse event	Puncture site closure
1 [11]	Godat	SEMS placement 20/20	Malignant biliary obstruction 1/20	20/20	17/20	Persistent obstructive cholangitis 1/20	N
			Benign biliodigestive anastomotic stenosis 19/20			Infection 2/20	
2 [12]	Iwashita	SEMS placement 1/6	Malignant biliary obstruction 1/6	6/6	6/6	Mild pancreatitis 1/6	N
		Balloon dilation (1–15 mm) and stone removal 5/6	Choledocholithiasis 4/6			Mild abdominal pain 1/6	
			Anastomotic stricture 1/6				
3 [13]	Ogura	SEMS placement	Malignant biliary obstruction	42/49	40/49	Hyperamylasemia 4/49	N
						Bleeding 1/49	
4 [14]	Iwashita	SEMS placement	Malignant	19/20	19/20	Mild pancreatitis 3/20	N
			Biliary obstruction			Mild fever 1/20	

Table 2.2 Device usage in EUS-AG stenting trials

	Needles	Guide wire (in)	Dilator	ENBD	Stent
1	19G EchoTip (16/20)	0.035	Cystotome 6Fr		Non-covered metal stents
	19G EchoTip Access (7/20)				
2	19G EchoTip (7/7)	0.025	Bougie dilator 7Fr	5/6	Non-covered metal
3	19G SonoTip Pro Control	0.025	Dilation catheter (23/49)		Partly covered metal
	19G EchoTip Ultra		Balloon catheter (24/49)		
			Diathermic dilator (1/49)		
4	19G SonoTip Pro Control	0.025	Bougie dilator 6Fr	3/19	Uncovered SEMS

(c) EchoTip Ultra Endoscopic Ultrasound Needle introduced via working channel of echoendoscope, puncturing bile duct under EUS guidance.
(d) Sample aspirate obtained (after withdrawal of stylet) to confirm bile duct puncture.
(e) Radiopaque contrast injected into bile duct for detecting common duct stones.
(f) Guide wire inserted into bile duct.
(g) Maneuvering of guide wire antegrade for passage along common bile duct and through papilla (minimizing withdrawal movements to avoid damaging surface of guide wire).
(h) Once guide wire traverses papilla, puncture needle is withdrawn, using cystotome (6Fr) to dilate needle path (hepaticogastric tract).
(i) Via newly made hepaticogastric tract, balloon dilator is placed in papilla under X-ray surveillance (diameter of dilator dependent on stone size).
(j) Stone balloon serves to push calculi along guide wire, through papilla, and into GI lumen under fluoroscopic guidance.
(k) Nasobiliary drainage (NBD) tube placed as warranted in fistula between stomach and liver; to be removed after 48 h, ensuring proper functioning of biliary self-expandable metal stent (SEMS).

- EUS-AG bile duct drainage (Fig. 2.2 and Video 2.1)
  (a) EUS scan of liver for dilated IHBDs.
  (b) Color Doppler identification of intervening vessels to avoid during puncture.
  (c) Stylet withdrawn upon needle tip entry of bile duct.
  (d) Endoscopic Ultrasound Needle introduced via working channel of echoendoscope, puncturing bile duct under EUS guidance.
  (e) Sample aspirate obtained (after withdrawal of stylet) to confirm bile duct puncture.
  (f) Radiopaque contrast injected into bile duct to characterize stenosis.
  (g) Guide wire inserted into bile duct, maneuvering past stenosis (minimizing withdrawal movements to avoid damaging surface of guide wire).
  (h) Once guide wire moves past stenosis, puncture needle is withdrawn, using cystotome (6Fr) to dilate needle path.
  (i) After successful dilation, SEMS placement proceeds (along guide wire) under fluoroscopic guidance, deployed at stenotic site (preferably in transpapillary position).
  (j) Nasobiliary drainage (NBD) tube placed as warranted in fistula between stomach and liver, if necessary.

Success Rate

Although data is still limited, the technical and clinical success rates of EUS-AG procedures are relatively high (technical success: 85.7–100%; clinical success rate: 81.6–100%). Guide wire shearing may occur during manipulation and is one reason for failed attempts. Some interventionists may use small-caliber guide wires (0.025 in) or the 19G EchoTip Access Needle to avoid this problem. Disadvantages of the 19G EchoTip Access Needle are the risk of submucosal parabiliary insertion and

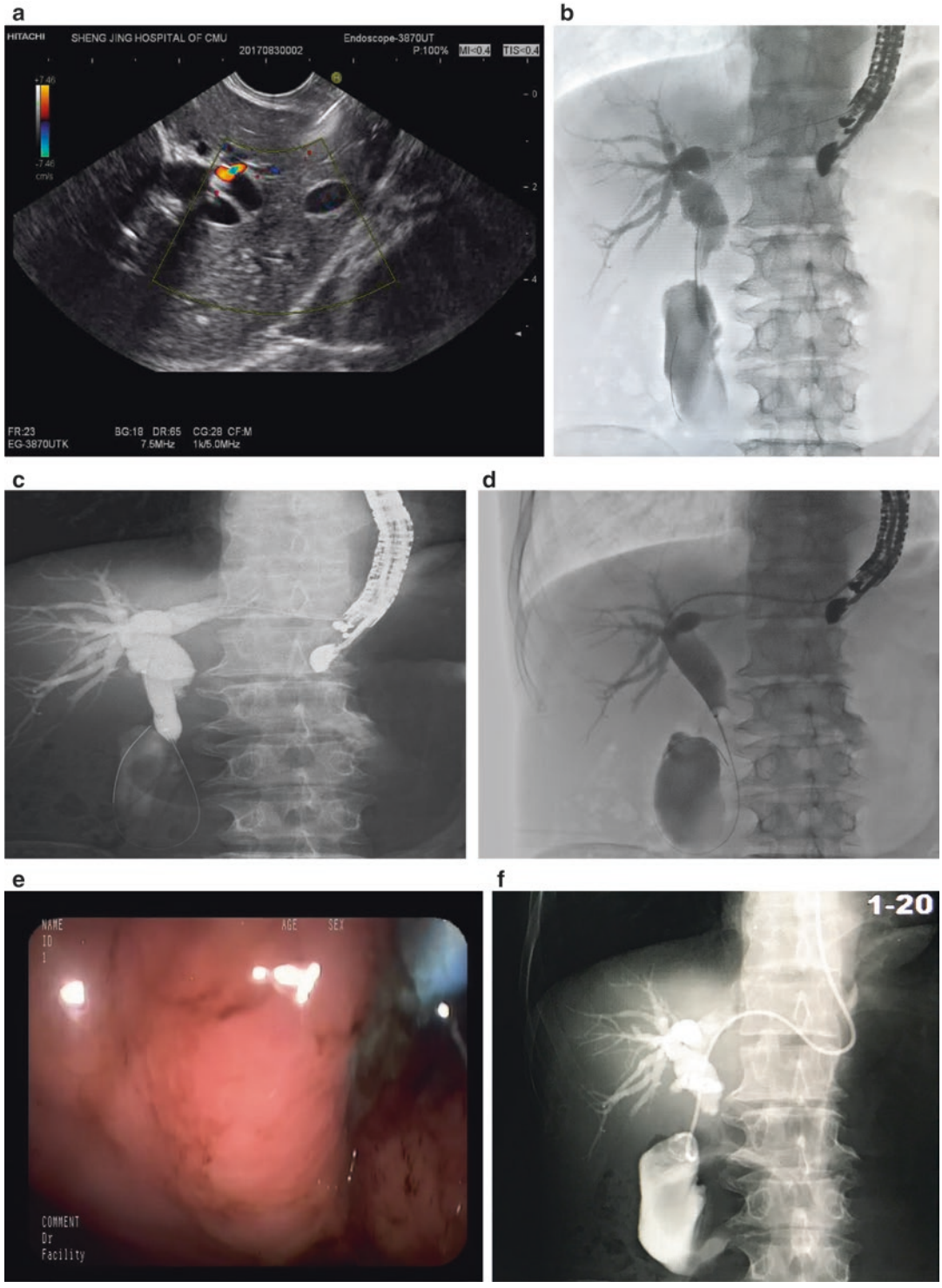

Fig. 2.1 61-year-old man with common bile duct stones and duodenal bulb stenosis, due to duodenal bulb ulcer (**a**) EUS scanning of dilated IHBD (left lobe), punctured by 19G needle. (**b**) Guide wire entry of common bile duct and passage through papilla, enabling contrast agent injection within bile duct. (**c**) Dilatation of papilla achieved via balloon. (**d**) Lithotomy balloon enabling delivery of stone into duodenal cavity. (**e**) ENBD inserted into common bile duct (endoscopic view). (**f**) X-ray image of NBD passage through papilla

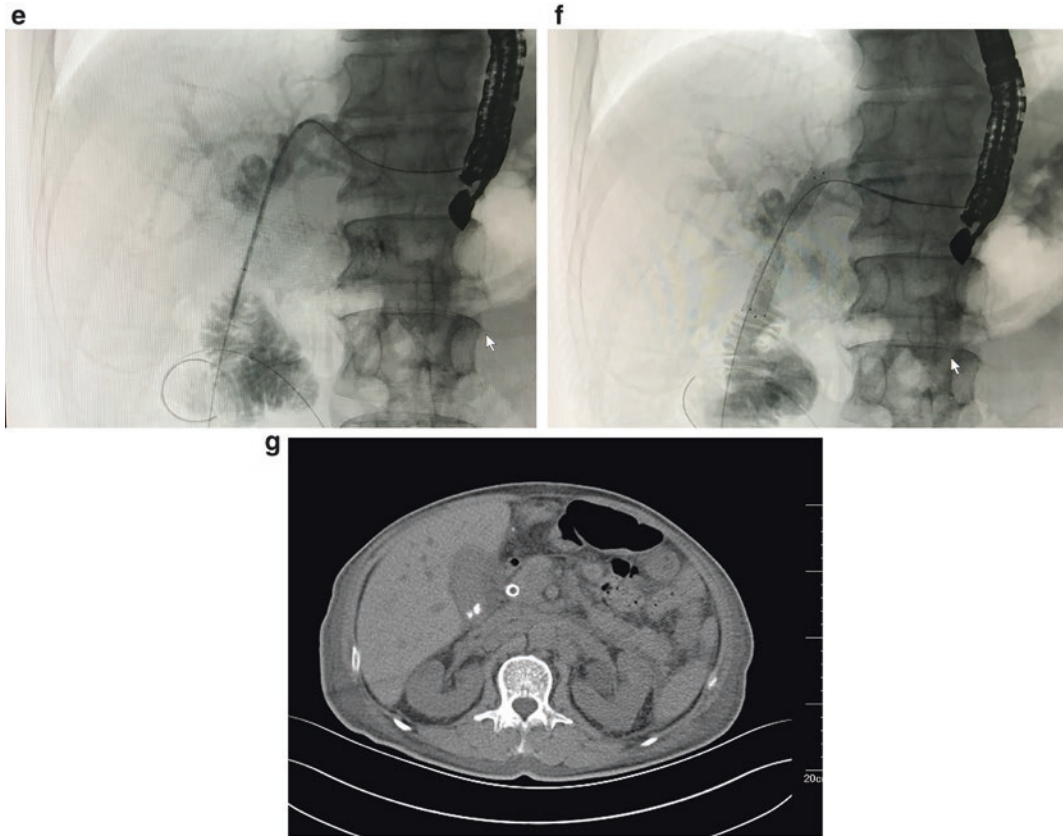

Fig. 2.1 (continued)

a lesser rate of IHBD puncture, compared with the 19G EchoTip Needle. In other instances, the extent of biliary obstruction may prohibit guide wire advancement into the intestine.

Complications

Severe complications of EUS-AG stenting have not been reported. Other minor complications, including obstructive cholangitis, infection, pancreatitis, mild abdominal pain, and fever, have ranged from 10 to 33%. As mentioned, biliary SEMS should be placed in transpapillary position to ease any resistance to bile flow. Certain researchers [11] have extended the process, placing a second non-covered SEMS through one-step interventions in 15% (3/20) of patients and ensuring SEMS patency by maintaining a protective nasobiliary catheter in 10% (2/20) of patients. In this particular trial, EUS-AG was deemed inadequate in 10% (2/20) of the patients treated, although drainage was achieved by concurrent EUS-HGS in one patient and by percutaneous drainage of right IHBD in another.

Bile peritonitis has not been reported in any of the studies. Clinically, the patency of EUS-AG stenting is durable, with little risk of adverse events, although there is a potential for acute pancreatitis due to obstruction of pancreatic duct orifice.

EUS-AG has the potential to be an effective and safe alternative management method for biliary disorders in patients with surgically altered anatomies or failed papilla cannulation. At present, it shows some possible advantages over other approach routes (ERCP, PTBD, or EUS-HGS),

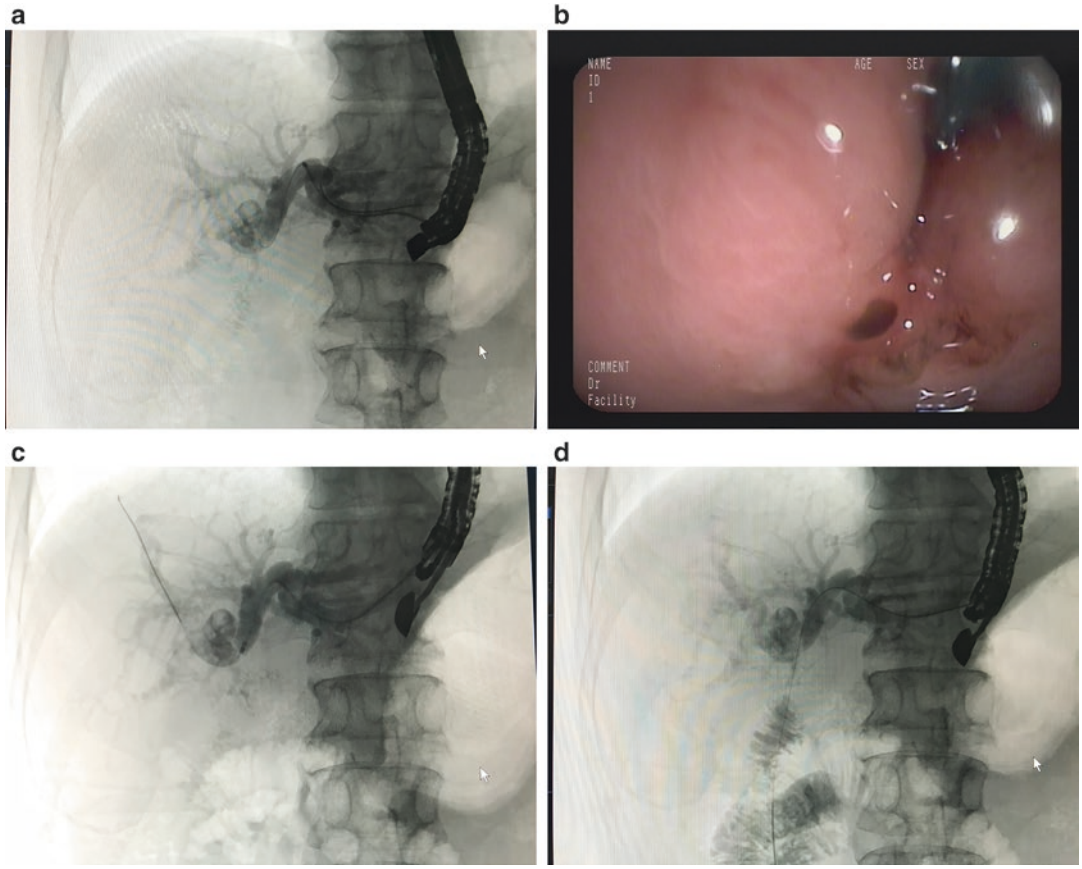

Fig. 2.2 55-year-old patient with unresectable malignant bile duct obstruction; 4 years ago, he had the surgery of pancreaticoduodenectomy; initial ERCP attempt unsuccessful due to surgically altered anatomy (**a**) Guide wire entry of intrahepatic bile duct. (**b**) Needle path dilated by cystotome (6Fr). (**c**) Guide wire maneuvered into common bile duct with cystotome. (**d**) Guide wire passed through stenotic site, entering duodenal cavity. (**e**) Stent placement in common bile duct, past stenosis. (**f**) Uncovered metal stent deployed at stenosis. (**g**) CT revealed the stent

however, there is not enough evidence to conclude that any one procedure is superior to another, and further comparisons among the approaches are required.

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3 Endoscopic Ultrasound-Guided Biliary Drainage: Retrograde Approaches

Constantine Melitas and Douglas G. Adler

Introduction

Endoscopic ultrasound (EUS) has several advantages over luminal procedures as it allows for access to structures which typically have no direct communication. Furthermore, adjacent structures may have altered anatomy based on disease infiltration making typically simple luminal procedures difficult and sometimes impossible. Thus, in biliary obstruction, where endoscopic retrograde cholangiopancreatography (ERCP) has failed or is not technically possible due to post-surgical anatomy or malignant gastric outlet obstruction, EUS can be used to directly access the biliary system through the intestinal wall to assist with biliary drainage [1–3].

If the ampulla is not able to be reached endoscopically and/or the level of biliary obstruction is very proximal (most commonly at the level of the bifurcation), then an EUS antegrade approach, typically via hepaticogastrostomy, may be used to gain access into the intrahepatic biliary system to assist with drainage. If the ampulla is accessible and standard ERCP cannulation techniques have failed or the intrahepatic bile ducts are not dilated, a retrograde EUS-guided approach is more favorable [4].

Accessing the common bile duct (CBD) directly has been shown to be a more favorable approach when compared to accessing the intrahepatic bile ducts as the CBD has much thicker walls, closer apposition to the bowel lumen, and allows for greater stabilization of instrumentation, and is a much more widely utilized target for EUS-guided biliary drainage leading to higher success rates [5].

EUS-Guided Rendezvous

There are two main methods of retrograde biliary drainage via EUS. The first method is also known as a "rendezvous" procedure which has also been performed with the assistance of interventional radiologists in the past [6]. Endoscopically, this procedure can be performed via intrahepatic approach or extrahepatic approach [7]. The intrahepatic approach is a transgastric method whereas the extrahepatic method is a transduodenal (either via the first or second portion of the duodenum, known as D1 and D2). In the retrograde approach, the bile duct is accessed by using

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a 19-gauge FNA needle. To further ensure that the biliary system has been successfully penetrated, bile should be aspirated. It is at this point that contrast should be injected to outline the anatomy of the biliary system. A long guidewire can then be manipulated and passed down the needle into the CBD and out through the ampulla into the duodenum. Most commonly, the needle and wire are inserted retrograde via D1 or D2 and the wire is then manipulated in an antegrade direction.

Manipulation of the guidewire is by far the most challenging aspect of the procedure as it often may coil in the bile duct or begin to advance away from the desired direction. Getting the wire to advance into the desired location can be a cumbersome and sometimes a tedious process. This is often the point of the procedure that takes the most time. However, it is the most crucial aspect of the procedure [4, 8, 9].

Recent studies have shown that use of a hydrophilic guidewire and positioning as close to the ampulla as possible, such as D2, allow for easier manipulation and minimize the challenges associated with passing the guidewire [10]. This guidewire can then be used to cannulate the biliary system in retrograde fashion by means of ERCP. Cannulation can either be achieved by simply entering the papilla next to the previously passed wire, which acts as a guide for a 2nd wire to be passed retrograde, or by grasping the first wire and pulling it through a duodenoscope so a catheter can be advanced over it. The decision on which of these two techniques to choose is left to the operator.

Extrahepatic Versus Intrahepatic EUS-Guided Rendezvous

The extrahepatic approach first involves proper positioning of the echoendoscope. The positions for retrograde access have been termed the "push" or "pull" positions [11, 12]. The push position is similar to the long access in ERCP in which the echoendoscope travels along the greater curvature of the stomach. This often places the tip of the echoendoscope in the bulb or 2nd portion of the duodenum with an orientation looking towards the common bile duct. The FNA needle in this position will exit the scope and penetrate the CBD cephalad towards the liver hilum. Alternatively, the pull position is similar to the short access positioning in ERCP. In the pull/short position, the tip of the echoendoscope is flush with the duodenal wall and the ultrasound transducer can be more easily oriented towards the distal common bile duct. The needle in this position will exit caudally and towards the ampulla.

When draining the biliary system using transduodenal approaches, the push/long positioning has more scope stability but may limit FNA needle maneuverability [4]. Needle maneuverability is sometimes easier in the push/long position, however, endoscopic stability is often compromised. Therefore, scope positioning should be based on individualized clinical and anatomical conditions. When accessing the biliary system through the intrahepatic bile duct, the endoscope is in a straight position which allows both effective needle maneuverability and a high degree of endoscope stability [4]. However, given the increased distance from the ampulla, an increase in difficulty with guidewire maneuverability may be encountered with this endoscopic position [10, 11, 13].

Many patients require biliary decompression due to the presence of biliary strictures. The cholangiogram is therefore a crucial step once biliary access has been obtained in order to identify the presence, location, and extent of these strictures. Gaining access through the left intrahepatic bile duct is ideal as this access point allows for a more direct guidewire passage to the liver hilum and across a stricture [14]. The EUS needle must be withdrawn while guidewire manipulation is being performed as this may sheer or cut the guidewire [15]. After the guidewire has been successfully manipulated through the stricture of interest, a 4 mm balloon may be used to dilate the papilla and biliary system to allow for advancement of a stent over the guidewire to traverse both ends of the stricture adequately [15].

Choledochoduodenostomy

The second method of performing EUS-guided retrograde biliary dilation is by means of transmural stenting. Transmural stenting can be performed by four methods: choledochoduodenostomy, hepaticogastrostomy, choledochoantrostomy, and hepaticoduodenostomy, with the latter two being very rarely performed [16–19]. Retrograde drainage is primarily done by means of choledochoduodenostomy (Fig. 3.1). This method entails transluminal stenting between the duodenal bulb (D1) and the CBD. This method was first described in 2001 and is most often used in patients with distal bile obstruction and normal gastrointestinal anatomy [20]. Patients with abnormal anatomy from surgery can undergo other forms of retrograde access including choledochojejunostomy (Video 3.1).

To perform the choledochoduodenostomy, the push/long position of the echoendoscope is preferred with the needle directed towards the liver hilum [21]. The echoendoscope should be advanced to the first portion of the duodenum to adequately visualize the extrahepatic bile duct, which is usually quite dilated and easy to identify. Ideally, the penetration point into the bile duct should be at a point at which the CBD is dilated to at least 5 mm in diameter and the length of the bile duct segment should be 1–3 cm to allow for successful stenting [21]. A 19-gauge FNA needle is usually used to gain access into the biliary system in an angle which will allow for easy passage of the guidewire into the biliary system. To confirm adequate positioning, bile should be aspirated and contrast can be injected to outline the biliary anatomy. Some authors suggest that the tract should then be dilated by means of balloon, bougie, cautery dilator, or fine-gauge balloon dilator, but this maneuver is not performed universally [22, 23].

The selected stent should then be deployed within the dilated iatrogenic fistula which connects the duodenum to the CBD. Traditionally, self-expanding metal stents (SEMS) which are greater than 4 cm in length and are either fully covered or partially covered are most often used as these stents have been used in most studies and have been shown to decrease the risk of stent migration [4, 24–29]. However, the success rates, ease of the procedure, and procedure length have all been significantly improved with the introduction on lumen apposing metal stents (LAMS) [30] (Fig. 3.2).

Success Rates

Several meta-analyses have reported success rates for EUS-guided biliary drainage procedures in over 90% of patients [24–26, 31]. The overall success rate with EUS-guided rendezvous procedures has been found to be about 81% and the overall success rate of transluminal stenting has been shown to be higher, nearing 95% [25, 32]. It has been shown that success rates have improved since the introduction of EUS-guided biliary drainage and also have improved with the cumulative experience of each operator over time, demonstrating that these are complex, high risk procedures with their own learning curve [31]. The rates of procedure related deaths have also significantly decreased due to these reasons as well [33]. Success rates have also been impacted by an experienced assistant as they become more familiar with guidewire manipulation, stent deployment, and other portions of the procedure which help increase the desired procedural outcomes [34].

There has yet to be a consensus as to which biliary draining modality is superior when comparing EUS-guided rendezvous and transluminal stenting. Many operators are strongly influenced by their own experience with one or both techniques. However, in comparing EUS-guided hepaticogastrostomy and choledochoduodenostomy, there have been no significant differences in success rates and adverse events [25]. Despite this, choledochoduodenostomy may be more beneficial as it is often technically more straightforward, has been associated with lower rates of stent dysfunction, and greater 3-month stent patency rates [35].

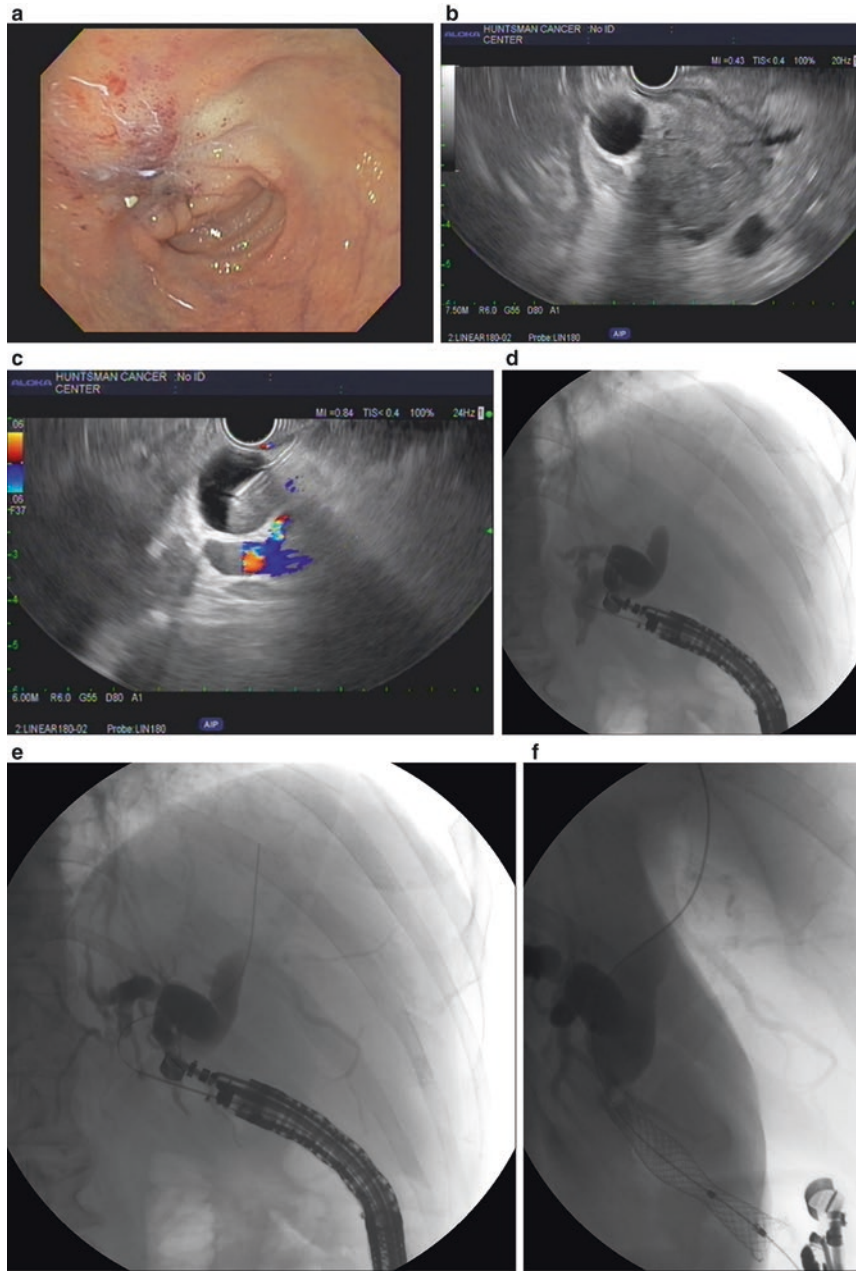

Fig. 3.1 EUS-guided choledochoduodenostomy and treatment of simultaneous malignant gastric outlet obstruction. (**a**) Endoscopic image of gastric outlet obstruction at the level of the duodenal bulb. The ampulla is thus not accessible for standard ERCP. (**b**) EUS image showing a large, solid pancreatic head mass obstructing the CBD, which is markedly dilated. (**c**) Using a 19-gauge EUS FNA needle, the CBD is accessed in a transduodenal manner. (**d**) Injection of dye through the FNA needle results in a cholangiogram showing a distal CBD stricture. (**e**) A guidewire is passed through the FNA needle and into the proximal biliary tree. (**f**) Fluoroscopic image of a fully covered metal biliary stent after deployment over the wire and across the choledochoduodenostomy. (**g**) Endoscopic image of a fully covered metal biliary stent after deployment over the wire and across the choledochoduodenostomy. (**h**) Using a biliary balloon catheter, a guidewire is advanced across the gastric outlet obstruction. (**i**) A 22 × 60 mm uncovered enteral stent is advanced over the wire and across the gastric outlet obstruction. (**j**) Duodenal stent after deployment. The patient has now had his biliary obstruction and gastric outlet obstruction relieved in a single outpatient procedure

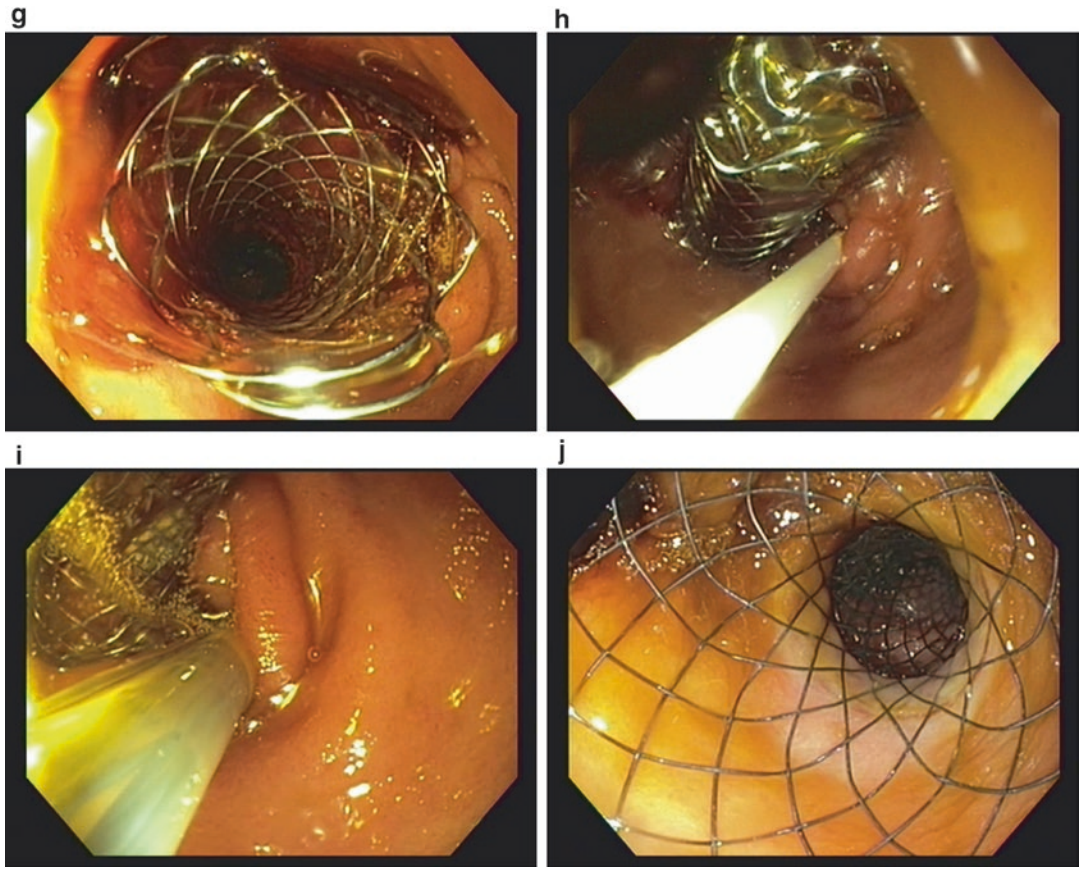

Fig. 3.1 (continued)

Adverse Events

Systematic reviews have shown complication rates associated with EUS-guided biliary drainage as a whole to be between 16.5% and 23.3% [24–26]. In a large systematic review consisting of over 1100 patients, the most common complications included: bleeding (4.03%), bile leakage (4.03%), pneumoperitoneum (3.02%), stent migration (2.68%), cholangitis (2.43%), abdominal pain (1.51%), and peritonitis (1.26%) [24–26]. Most complications were treated conservatively. The type of complication is often related to the approach used, devices used, disease process, and experience of the endoscopist [33, 34].

The reported rates of complication associated with EUS-guided rendezvous specifically are approximately 15%. These complications include bile leaks, pneumoperitoneum, subcapsular hematoma, and pancreatitis (most often associated with the ERCP portion of the procedure) [36].

When comparing approaches of EUS-guided biliary drainage, the extrahepatic approach has been found to be safer with adverse events occurring in about 14% of cases as compared to 18% of cases via the intrahepatic approach [37]. However, in one compilation of almost 30 studies, the complication rate seen with transmural stenting was 24%. The most common adverse events were stent migration (5.4%), pneumoperitoneum (3.4%), peritonitis (3%), cholangitis (3%), bleeding (2.8%), and bile leakage (1.5%) [25]. Similar rates of these complications have been seen in patients undergoing transduodenal and transgastric transmural approaches.

When comparing the use of biliary stents, plastic stents have been shown to have a significantly higher rate of bile leakage at 11% as

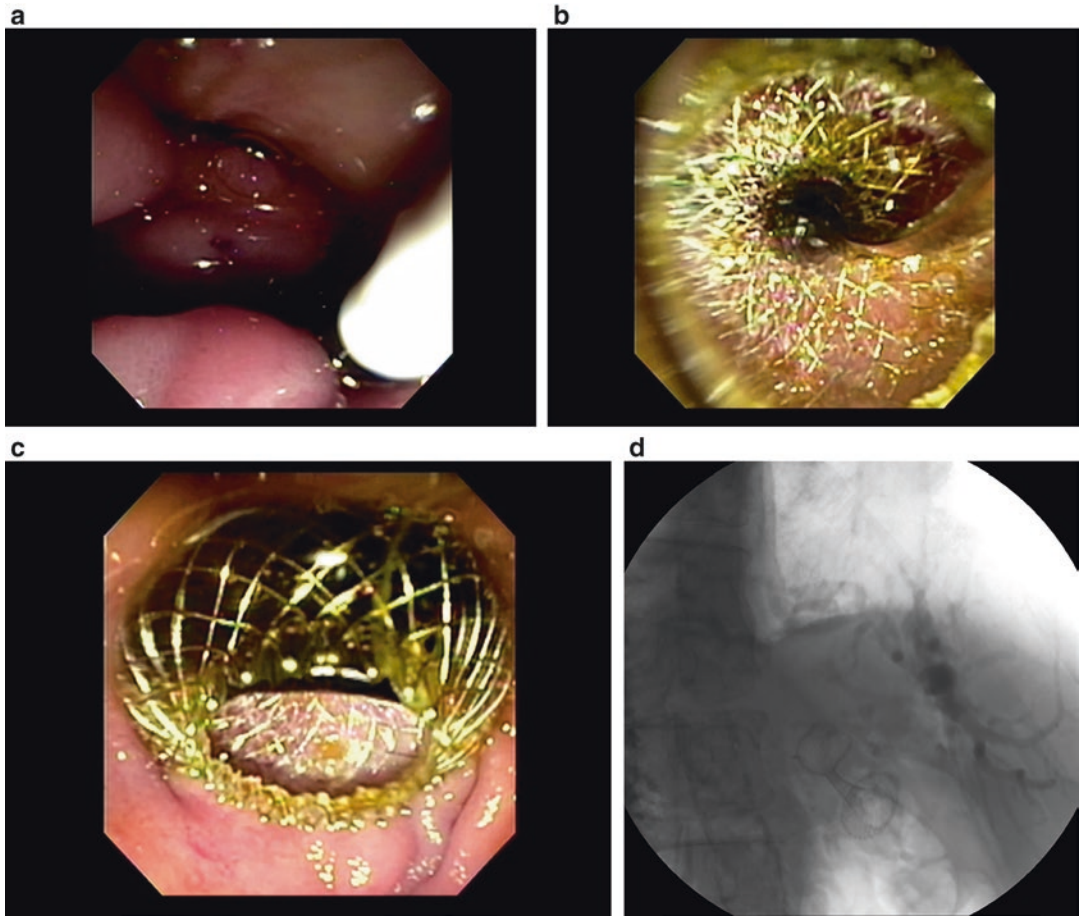

Fig. 3.2 Use of a lumen apposing metal stent (LAMS) to create a choledochoduodenostomy. (**a**) After guidewire access to the CBD has been obtained in a manner similar to that used in Fig. 3.1, a 10 mm Axios stent (Boston Scientific, Natick, MA) is advanced across the choledochoduodenostomy. (**b**) Axios stent immediately after deployment across the choledochoduodenostomy. (**c**) Axios stent in good position after deployment draining copious bile. (**d**) Fluoroscopic image demonstrating the patient's cholangiogram as well as the Axios stent in good position with functional choledochoduodenostomy

opposed to 4% in cases that utilized covered metal stents [35]. Studies on newer equipment specific to these procedures such as LAMS, hybrid metal stents (which consist of uncovered proximal portions and covered distal portions), hook stents (metal stents with anchoring hooks), and plastic pigtail stents with four flanges have shown promise in further decreasing stent related complications [30, 38–43]. Given that most of the tools and devices used are adapted from ERCP, there are very few devices specific to EUS-guided biliary drainage. The development of more devices specific to these procedures may very well likely continue to decrease the procedural complications even further.

Other Biliary Drainage Methods Versus EUS-Guided Biliary Drainage

A commonly used alternative method for draining the biliary system when ERCP has failed or is not possible is the percutaneous approach. Many studies and systematic reviews have compared the percutaneous approach to the EUS-guided approach and have shown similar success rates

and adverse event rates [44]. However, the percutaneous route has been found to require frequent reinterventions and higher costs [45]. Also, when considering all reinterventions, a higher rate of complications has been appreciated with the percutaneous approach [45]. Despite higher overall costs, the percutaneous method has several other disadvantages such as its affect on lifestyle. This is an external drain which can interfere with daily activities, intimacy, physical appearance, difficulty with sleeping, and can even interfere with getting dressed.

Other studies have compared EUS-guided biliary drainage to ERCP as primary interventions for biliary decompression. Success rates for primary biliary interventions in the setting of malignant biliary obstructions between ERCP and EUS-guided approaches are similar, however, the EUS-guided approach, especially transmural stenting, is also associated with decreased procedure times [46, 47]. Furthermore, EUS-guided biliary drainage after failed ERCP has been compared to EUS-guided biliary drainage without failed ERCP and has been found to have similar success rates and adverse events as well [48].

Conclusion

EUS-guided retrograde approaches for biliary drainage are exciting revolutionary methods for accessing the biliary tree, especially in patients with failed ERCP, altered anatomy, and in patients in whom the ampulla is inaccessible. Both methods of EUS-guided retrograde biliary drainage have been found to be very safe and efficacious with high success rates and acceptably low rates of complication. Studies evaluating these procedures as first-line biliary decompressive strategies have shown promising results. However, further prospective investigations will need to be performed. As the majority of the tools used for these procedures have been originally developed for ERCP, the development of more devices specific to these procedures as well as having these procedures performed by endoscopists experienced in these procedures may very well likely decrease the procedural complications even further. Furthermore, the decrease in procedural times, especially seen with transluminal stenting, and the decrease in overall cost, when compared to percutaneous biliary drainage, may further assist in these procedures becoming routine methods of biliary decompression.

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EUS-Guided Gallbladder Drainage

4

Sunil Amin and Amrita Sethi

Introduction

For most patients, acute cholecystitis is a surgical disease. Laparoscopic cholecystectomy is the standard of care for operative candidates, while poor surgical candidates typically receive percutaneous cholecystostomy tube placement [1, 2]. Endoscopic transpapillary cystic duct stenting, while feasible, requires a high degree of technical expertise and necessitates that an endoscopic retrograde cholangiopancreatography (ERCP) be performed, thereby exposing the patient to additional procedural-related risks. As such, cystic duct stenting is often reserved for patients in which the transhepatic approach is contraindicated or anatomically impossible [3, 4]. In recent years, however, transmural gallbladder drainage via an endoscopic ultrasound-guided approach (EUS-GBD) has emerged as a feasible and potential equally efficacious option that obviates the need for an external drainage catheter or ERCP. Early adopters of EUS-GBD used plastic or fully covered metal self-expandable metal biliary stents (FCSEMS), but more recently the use of a lumen-apposing metal stent (LAMS) has become widespread [5–8]. The most recent 2018 Tokyo Guidelines on the management of acute cholecystitis recognize EUS-GBD as an appropriate treatment for high-risk surgical patients when performed in high-volume tertiary care centers by skilled endoscopists [9]. This inclusion in the treatment algorithm is a paradigm shift as EUS-GBD was not recommended in earlier versions of the text [10]. This review will address the rationale, indications, technique, complications, outcomes, and controversies regarding EUS-GBD.

Indications/Contraindications

Several requirements must be met prior to consideration of EUS-GBD. First, the patient should have a diagnosis of acute cholecystitis and either should be a high-risk surgical candidate (with an estimated mortality >10%) or should have refused surgical treatment. The authors of the 2018 Tokyo Guidelines recommend percutaneous transhepatic gallbladder drainage (PT-GBD) as the first alternative to cholecystectomy in high-risk surgical patients, but state that endoscopic drainage including EUS-GBD may be considered in high-volume centers when performed by skilled endoscopists [9]. Grade III

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disease, defined by the 2013 Tokyo Guidelines (TG13) as acute cholecystitis associated with organ dysfunction, is particularly suited for EUS-GBD [10]. In these patients, PT-GBD is associated with higher mortality, higher readmission rates, and prolonged hospital stay [10, 11].

Although not absolute contraindications, the presence of ascites or severe coagulopathy should be met with caution. In these circumstances, endoscopic transpapillary drainage either with placement of a cystic duct stent or naso-biliary catheter may be more appropriate.

Technique/Procedure

EUS-GBD should, in general, only be performed in tertiary care centers where the full cadre of surgical and interventional radiological expertise is available to the endoscopist should complications occur. Although slight variations in procedural technique are described, EUS-GBD is sequentially performed as follows. Prior to the start of the procedure, the patient is sedated (often via general anesthesia), placed in a supine or left lateral decubitus position, and given intravenous antibiotics.

A therapeutic linear echoendoscope is then advanced into the pre-pyloric antrum or the duodenal bulb, and the gallbladder is identified endosonographically. A suitable access point must be chosen so that the distance between the gastrointestinal lumen and the gallbladder wall is equal to or less than the saddle length of the available LAMS and no intervening vessels are present. Either a one-step or two-step procedure is then performed in order to create a cholecystogastrostomy or cholecysto-duodenostomy and subsequently deploy a metal stent trans-luminally.

In the one-step procedure, an electrocautery tipped 10.8F catheter containing a 15 mm inner-diameter lumen-apposing metal stent (LAMS) (AXIOS-EC, Boston Scientific, Natick, MA) is used to simultaneously puncture the body or neck of the gallbladder and deploy the LAMS (Fig. 4.1, Video 4.1). Whereas this method may be performed in a wire-guided fashion as well (in which the cautery-enhanced catheter is placed over a pre-inserted guidewire), in general, it is felt that the placement of the wire can potentially push the GB wall away from the gastric or duodenal wall, subsequently increasing the risk of misdeployment or bile leak. Therefore, the free-hand techniques appear to be the favored approach.

In the two-step procedure, a 19-gauge needle is first used to puncture the gallbladder, bile is aspirated, and a 0.035-in guidewire is advanced through the needle and coiled in the gallbladder lumen. A long-wire exchange is then performed under endosonographic guidance and flash dilation of the fistulous tract is performed with a 6 mm dilating balloon. This dilation, though necessary, must not be too aggressive in order to minimize the risk of peritoneal leakage during the long-wire exchange [12, 13]. The 10.8F LAMS delivery catheter is then advanced over the wire into the gallbladder lumen, where the distal flange is deployed in the gallbladder and the proximal flange is deployed in the gastrointestinal lumen.

With both methods, the LAMS can be dilated using a standard through-the-scope balloon dilator if so desired. At this point, certain endoscopists place a short double pig stent through the LAMS prior to concluding the procedure or bring the patient back several days later to perform this step. Again, there is variability among endoscopists in procedural specifics such as patient positioning, whether to dilate the LAMS post-deployment (and if so, to what size), and the need for and timing of the placement of a double pigtail stent.

Complications

Pooled analyses report adverse events rates of EUS-GBD between 8% and 17% [6, 14, 15]. Potentially serious procedure-related complications may include bile leakage, perforation, stent migration, and recurrent cholecystitis due to stent occlusion. When stratified by stent type, Anderloni et al. report an adverse rate of 18.2% for plastic stents, 12.3% for SEMS, and 9.9% for LAMS [14]. Not surprisingly, their data suggest

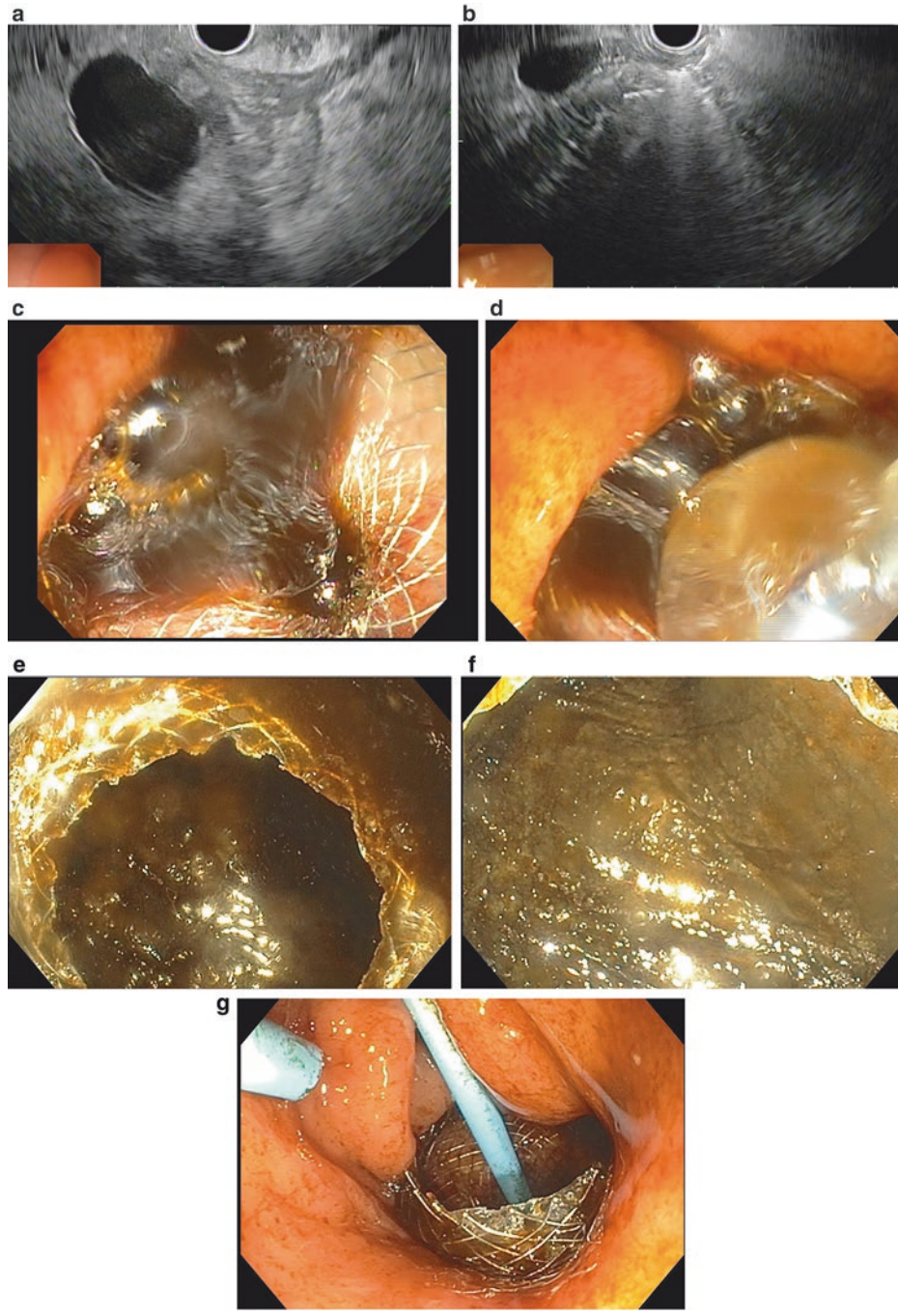

Fig. 4.1 EUS-guided transgastric gallbladder drainage in a 64-year-old female with metastatic breast cancer. (**a**) EUS image of GB with thickened wall and sludge-filled. (**b**) EUS image of deployed distal flange within gallbladder during step 3 of AXIOS deployment (pulling back on catheter to pull flange up to GB wall and create apposition). (**c**) Post-deployment of proximal flange (gastric side) of AXIOS stent with drainage of GB contents. (**d**) Post-deployment dilation of lumen of deployed stent with CRE balloon. (**e**) View of GB wall through deployed and dilated AXIOS stent. (**f**) Endoscopic view of GB wall after passing diagnostic endoscope through deployed and dilated AXIOS stent. (**g**) Gastric view of deployed AXIOS stent with 7F double pigtail placed through lumen of LAMS. Courtesy of Doug Adler, MD, Amrita Sethi, MD, and Reem Z. Sharaiha, MD

pros and cons to each approach. Bile leakage was only associated with the use of plastic stents (in which that GB wall can easily separate from the gastric or duodenal wall), while stent migration and stent occlusion only occurred with SEMS. LAMS was associated with higher rates of bleeding, infection, and pain. In a separate meta-analyses looking at LAMS only, the most common early adverse events were bleeding (3.9%, 7/181), stent migration (1.1%, 2/181), and recurrent cholecystitis due to stent occlusion (1.7%, 3/181) [15].

Peri-Procedural Care

There is no standardized approach to the peri-procedural management of patients undergoing EUS-GBD. The majority of these patients are high-risk surgical patients that may not be candidates for percutaneous transhepatic drainage either due to ascites or coagulopathy. As such, the nuances of managing these critically ill patients is individualized. In general, however, patients should remain NPO and intravenous antibiotics initiated once the diagnosis of acute cholecystitis is made. Post-procedurally, patients are often kept hospitalized, kept NPO until clinical resolution of symptoms begins, and maintained on broad-spectrum antibiotics for at least several days. Some practitioners place patients on a traditional enteral stent (low residue) diet to reduce the risk of stent occlusion but others allow patients to consume a full diet.

Outcomes

The technical and clinical success rates of EUS-GBD are consistently reported at greater than 90%. In their systematic review and pooled analysis of 166 high-risk surgical patients with acute cholecystitis who underwent EUS-GBD, Anderloni et al. report a pooled technical success rate of 95.8% and clinical success rate of 93.4% [14]. Peñas-Herrero et al. report even higher numbers (97% and 99%, respectively) in their pooled analysis of 155 patients (8 series and 12 case reports) [6]. Most recently, a meta-analysis looking exclusively at the use of LAMS in 181 EUS-GBD procedures computed a pooled technical success rate of 95% (CI 91–99%) and clinical success rate of 93% (CI 90–97%) [15].

Several studies have favorably compared outcomes for EUS-GBD versus percutaneous gallbladder drainage (PC-GBD) [5, 16–19]. Tyberg et al. retrospectively analyzed 155 patients who either underwent EUS-GBD ($n = 42$) or PC-GBD ($n = 113$) across seven international tertiary centers [16]. Whereas technical success was slightly higher in the PC-GBD group (99% vs. 95%), clinical success was higher in the EUS-GBD group (95% vs. 86%). Nevertheless, neither of these differences reached statistical significance ($p = 0.179$ and $p = 0.157$, respectively). Interestingly, significantly more patients in the PC-GBD group required repeat interventions ($n = 28$, 24%) compared to the EUS-GBD group ($n = 4$, 10%). There was no difference in adverse events between the two groups. The authors conclude therefore that EUS-GBD and PC-GBD have similar safety and efficacy; however, EUS-GBD results in significant cost savings.

A follow-up study by Irani et al. compared 45 patients with EUS-GB to 45 patients with PC-GBD but looked exclusively at LAMS [5]. The authors similarly found no difference in technical or clinical success between the two groups. However, EUS-GBD was associated with a lower mean post-procedural pain score (2.5 vs. 6.5, $p < 0.05$), shorter average length of stay in the hospital (3 days vs. 9 days, $p < 0.05$), and fewer repeat interventions per patient (0.2 vs. 2.5, $p < 0.05$). Furthermore, there was a trend towards fewer adverse events in the EUS-GBD group (11% vs. 32%, $p = 0.065$).

In a slightly larger study, Teoh et al. looked specifically at adverse events between EUS-GBD and PT-GBD [17]. Among 118 patients with acute cholecystitis deemed unfit for surgery, the 59 patients who received EUS-GBD suffered significantly fewer serious (23.7% vs. 74.6%, $p < 0.001$) and overall (32.2% vs. 74.6%, $p < 0.001$) adverse events than the 59 patients who underwent percutaneous cholecystostomy.

Current Controversies/Future Considerations

Although most experts performing EUS-GBD achieve high clinical and technical success rates (>90%), EUS-GBD remains in its infancy and optimal technique and best practices are still being defined.

At present, there is no current consensus regarding optimal type of drainage stent (plastic, FCSEMS, and LAMS) or location of puncture site. Both transgastric and transduodenal routes appear to be technically viable and safe (Fig. 4.2). Theoretically, LAMS results in better lumen apposition and thus might reduce risk of bile leak and stent migration. Furthermore, the larger caliber of the drainage stent may result in quicker symptom resolution. In a recent systematic review and pooled analysis of 21 studies and 166 patients, Anderloni et al. report the technical success rate of 100% with plastic stents, 98.6% with SEMS, and 91.5% with LAMS [14]. Clinical success was 100%, 94.4%, and 91.5%, respectively. In their sub-group analysis of 42 patients who underwent EUS-GBD, Tyberg et al. found no difference in adverse events (p = 0.895) or clinical failure (p = 0.978) between plastic, FSCEMS, or LAMS [16]. There was also no difference in adverse events (p = 0.289) or clinical failure (p = 0.432) based on the location of the stent (transgastric vs. transduodenal vs. transjejunal). Regardless, a head-to-head trial of plastic vs. FCSEMS vs. LAMS with regard to technical success, clinical success, and adverse events would certainly help guide future efforts.

A second consideration for which there is no clear agreement is the optimal time for stent removal, or whether the stent should be removed at all. Given the frailty of many patients undergoing EUS-GBD, certain experts argue against planned removed of the stent, thus mitigating the risk and cost associated with further procedures [5]. This strategy makes EUS-guided gallbladder drainage so-called destination therapy. The risk associated with this strategy, however, is stent occlusion and recurrent cholecystitis. As an alternative approach, Kamata et al. performed a retrospective study of 12 patients who received EUS-GBD and had their SEMS removed at 4 weeks after resolution of symptoms [20]. The SEMS was removed without replacement in 8 patients, and replaced with a 7F pigtail stent in 4 patients. Recurrence of cholecystitis was seen in only 1 patient who did not receive a pigtail stent. Thus, the authors conclude that 4 weeks is a reasonable interval to remove the stent to prevent migration and recurrence due to food impaction.

A third point of controversy, as in management after PT-GBD [10], is whether patients should be referred for cholecystectomy upon clinical resolution of symptoms after EUS-GBD and the timing of such an intervention. While one study reported significantly lower rates of completion cholecystectomy for patients undergoing EUS-GBD vs. PT-GBD (5% vs. 27%, p = 0.003) [16], no substantial data is available comparing outcomes for the two groups. Furthermore, there are no long-term data regarding whether ultimately undergoing cholecystectomy results in improved clinical outcomes in this sick population of patients or whether EUS-GBD affects outcomes of cholecystectomy.

A final concern associated with EUS-GB is gastric reflux into the gallbladder lumen that may result in delayed pain, stent occlusion, or even gallbladder perforation requiring surgical revision. Kim et al. describe two such patients [21]. Although both patients experienced initial clinical success, the first patient was re-admitted with intractable right upper quadrant pain with cross-sectional imaging confirming a large amount of gastric reflux into the gallbladder. This patient was managed with repeat outpatient endoscopic drainage. The second patient developed a stent occlusion that required a repeat endoscopic procedure, an infected biloma, and, ultimately, intraperitoneal free air requiring surgical exploration.

With regard to future considerations, the use of a large bore LAMS for EUS-GBD provides repeated access to the gallbladder for per-oral cholecystoscopy and other advanced interventions [22–24]. In their feasibility study of 27 cholecystoscopies following EUS-GBD, Chan et al. demonstrate the safety and efficacy of a number of practical applications [23]. First, the endoscopist is able to confirm clearance of stones prior to

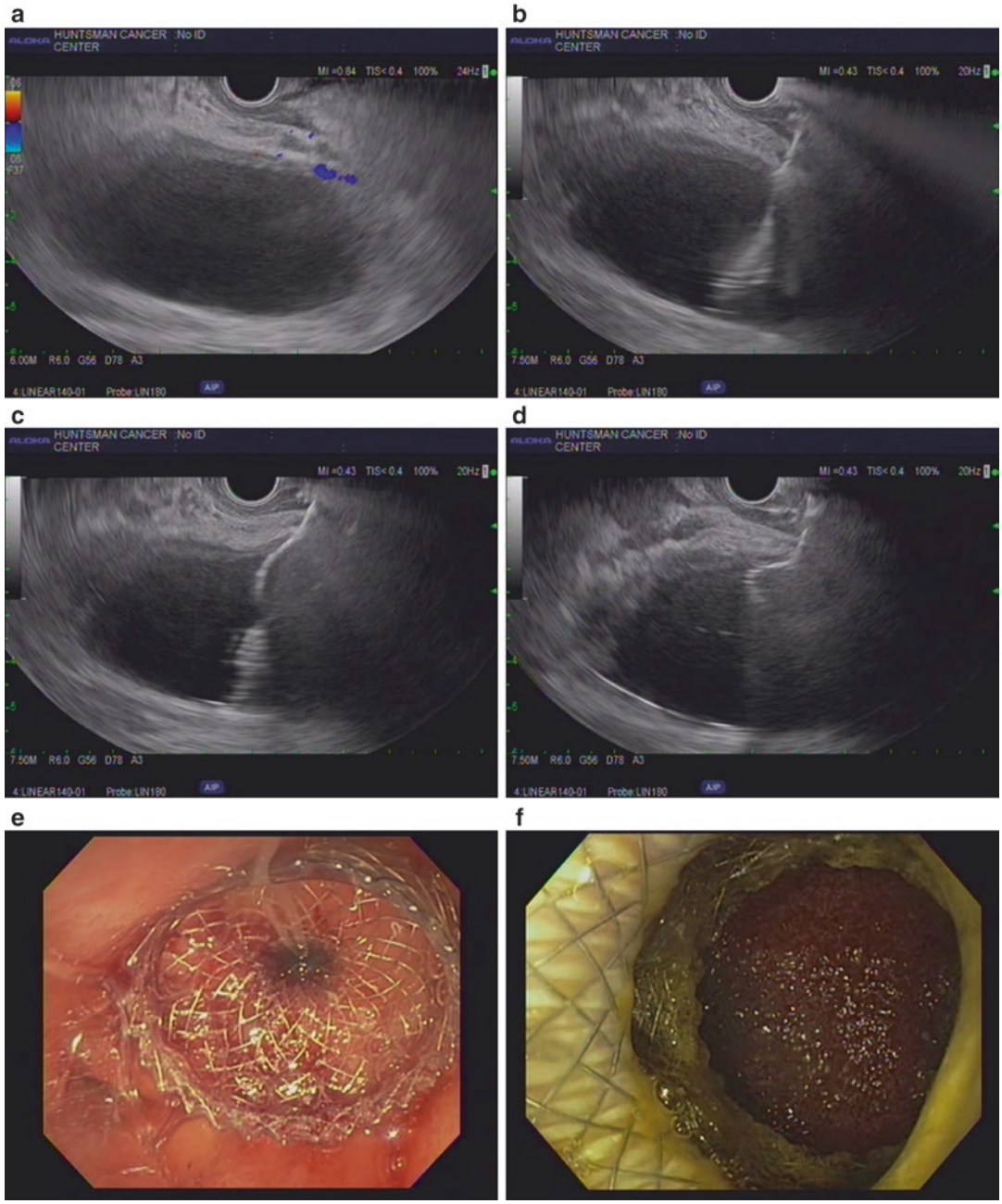

Fig. 4.2 EUS-guided transduodenal gallbladder drainage in a male with inoperable IPMN. (**a**) EUS image of a large, distended gallbladder with a very thickened wall. (**b**) EUS image of the electrocautery-enhanced LAMS catheter during passage through the duodenal wall into the gallbladder. (**c**) EUS image of deployment of the distal end of the LAMS within the gallbladder lumen. (**d**) EUS image of the fully deployed LAMS across the duodenal bulb into the gallbladder. (**e**) Endoscopic image of the proximal end of the LAMS after deployment. Note purulent drainage. (**f**) Endoscopic view through the LAMS into the gallbladder 1 week after initial deployment. (**g**) Endoscopic image of a guidewire being passed through the LAMS into the gallbladder. (**h**) Endoscopic image of a double pigtail stent through the lumen of the LAMS. Note descending duodenum on the left side of image. (**i**) Fluoroscopic image of LAMS after deployment. Note patient has a metal biliary stent as well as the LAMS. (**j**) Fluoroscopic image of guidewire being passed into the gallbladder through the LAMS. (**k**) Fluoroscopic image of double pigtail stent through LAMS. Courtesy of Douglas G. Adler, MD

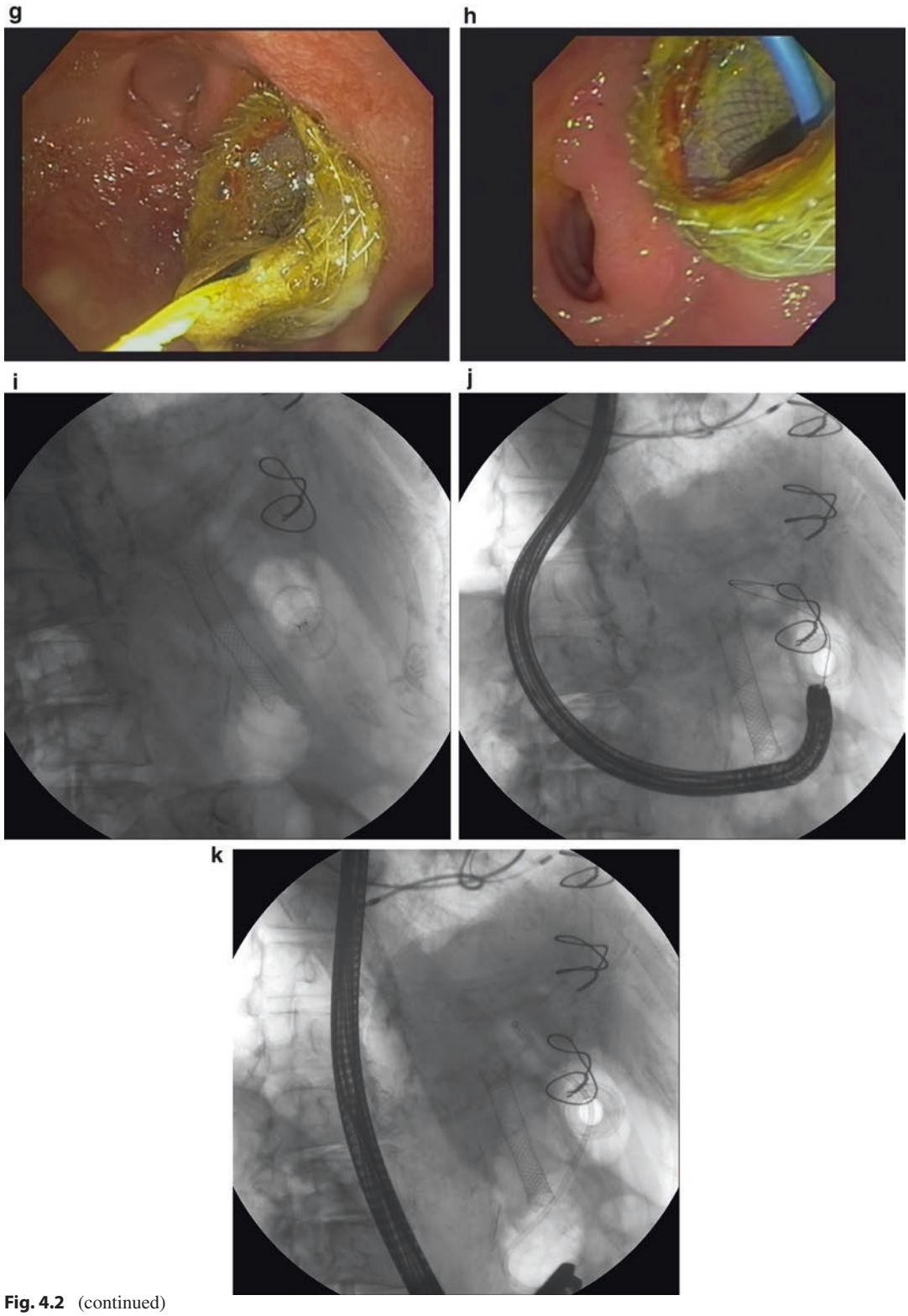

Fig. 4.2 (continued)

removal of the LAMS. Should stones remain, they can be extracted with biliary baskets and lithotripsy can be performed if required. Second, should choledocholithiasis be suspected, the endoscopist can perform a cholecystogram by injecting contrast through the cystic duct opening under fluoroscopy. Finally, narrow band imaging (NBI) and confocal endomicroscopy (nCLE) can be used to examine potential mucosal irregularities in the GB wall. Although not demonstrated to date, EUS-GBD could also provide a portal for removal of large gallbladder polyps as well (>1 cm) that would otherwise require cholecystectomy.

Summary

Endoscopic ultrasound-guided gallbladder drainage (EUS-GBD) is now an accepted treatment option for the high-risk surgical patient with acute cholecystitis. Consensus guidelines suggest that this emerging procedure may be particularly useful among patients with contraindications to percutaneous transhepatic gallbladder drainage, or those with severe Type 3 cholecystitis [9, 10]. Adverse event rates are low (8–17%) but not insignificant, even in expert hands. Potential complications include recurrent cholecystitis due to stent occlusion, stent migration, biliary leakage, or bleeding. As such, EUS-GBD must be performed only at tertiary care centers with surgical and radiological backup. Early comparative studies suggest that compared to PT-GBD, EUS-GBD provides a comparably safe, less invasive, and more cost-effective option for high-risk surgical patients. Further study is needed to determine additional roles for EUS-GBD in the treatment algorithm for acute cholecystitis. While early efforts used plastic and fully covered metal stents, most experts now prefer the LAMS, which provides better luminal apposition, is quicker to deploy, and minimizes the risk of biliary leakage and stent migration. Furthermore, LAMS provides continued access to the gallbladder lumen for cholecystoscopy and other advanced interventions. Future prospective studies with adequate follow-up are needed to clarify optimal stent type, location for drainage, and a standardized management strategy of both the stent and gallbladder itself, after resolution of symptoms.

Disclosure Statement

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5 Endoscopic Ultrasound-Guided Pancreatic Duct Drainage (EUS-PD)

Shawn L. Shah and Amy Tyberg

Introduction

Over the past 25 years, endoscopic ultrasound (EUS) has evolved from a diagnostic endoscopic tool to a versatile therapeutic one [1–3]. One emerging indication is drainage of the pancreatic duct (PD) in patients with symptomatic PD obstruction who fail conventional endoscopic retrograde cholangiopancreatography (ERCP). Until recently, percutaneous or surgical drainage was the primary option for these patients (and these were only rarely attempted); however, EUS-guided pancreatic duct drainage (EUS-PD) has risen as a minimally invasive, efficacious, and safe alternative [4]. The procedure involves visualizing and accessing the PD through EUS, advancing a wire into the duct, creating a fistulous tract, and finally deploying a stent for decompression. While the procedure of EUS-PD remains among the most technically challenging of all therapeutic EUS procedures, the ability to provide successful drainage without percutaneous or surgical intervention makes the procedure an attractive option when conventional approaches fail.

Pancreatic duct opacification using EUS guidance was first described in 1995 by Harada et al. in a patient status post pancreaticoduodenectomy [5]. Since then, there have been multiple case series describing the EUS-PD experience of therapeutic endoscopists around the world, with improvements in technique allowing for therapies such as stricture dilation, calculi extraction, tissue sampling, and long-term drainage [2, 6–8]. In this chapter, we will describe the EUS-PD technique and highlight the current literature on EUS as a modality for pancreatic duct access and drainage, evaluating the strengths and limitations of prior studies, and propose recommendations therapeutic endoscopists can consider when cannulation of the PD fails with conventional ERCP.

Procedural Technique

Patient Selection

The most common indications for EUS-PD are inaccessible ampullas, PD strictures, obstructing calculi, chronic pancreatitis, disconnected PD syndrome, and complex postsurgical PD anatomy

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(e.g., post-pancreaticoduodenectomy) [2]. Common contraindications to EUS-PD include severe uncorrectable coagulopathy or thrombocytopenia, inability to visualize the PD on EUS or find a safe and appropriate access window without interposed vessels, multifocal PD strictures, or any condition preventing endoscopy. The most important aspect of deciding to convert to EUS-PD after a failed conventional approach is the experience of the therapeutic endoscopists as well as appropriate patient selection.

Procedural Prerequisites

In our practice, all EUS-PD procedures are performed under general anesthesia with use of carbon dioxide insufflation and fluoroscopy although MAC may be a viable alternative from a sedation point of view. Intravenous antibiotics are given periprocedurally along with indomethacin per rectum to prevent and decrease the severity of potential post-procedure pancreatitis [9]. Preprocedure imaging with computed tomography or magnetic resonance imaging is necessary for optimizing procedural approach and intervention. A therapeutic channel linear echoendoscope is preferred as it allows for the passage of a variety of accessories and stents. Equipment including fine-needle aspiration (FNA) needles for access, guidewires, PD tract dilators and cautery agents, and stents should be available to the endoscopist as well as a variety of standard ERCP tools and accessories to help manage unforeseen difficulties [10, 11]. In addition, a multidisciplinary team including interventional radiologists and surgeons is required in conjunction with the endoscopy staff to provide full comprehensive care, although they are not needed to be present during the EUS-PD procedure.

Performing the Procedure (Video 5.1)

Once the decision is made to perform EUS-PD, the patient's individual anatomy dictates the approach and guides technique and route of access selected. A therapeutic channel linear echoendoscope is used to access the main PD via two main approaches: transgastrically or transenterically. The optimal access site is often determined by the shortest distance between the bowel lumen and the main PD without interposed vasculature, as well as on the targeted portion of the duct and patient anatomy (Fig. 5.1). In most reported studies, the transgastric approach appears to have the highest technical success [2]. After achieving relative endoscope stability, a puncture is made with a 19 gauge FNA needle and contrast is gently injected to obtain a pancreatogram (Figs. 5.2, 5.3, and 5.4). A guidewire is then advanced through the needle and coiled into the duct (Figs. 5.5 and 5.6). Cautery (Fig. 5.7) of the needle tract followed by balloon dilation (Figs. 5.8 and 5.9) is used to create a fistulous tract to allow for stent placement. Cautery is often applied via needle knife or a cystotome. To avoid the risk of a pancreatic fluid leak, the tract should be ballooned to the smallest diameter to facilitate stent deployment.

Plastic stents are utilized in the majority of cases. Occasionally, metal stents are deployed when the PD is markedly dilated (Figs. 5.10 and 5.11). Stents can be deployed in an antegrade fashion (towards the head of the pancreas) or retrograde (towards the tail of the pancreas) (Fig. 5.12). Crossing the papilla or anastomosis is prioritized whenever possible (Figs. 5.13 and 5.14). When not feasible, transluminal stent placement is performed with the distal end of the stent in the pancreatic duct and the proximal end in the gastrointestinal lumen (Figs. 5.15, 5.16, and 5.17). However, successful crossing can often be achieved on repeat intervention after the duct has been successfully decompressed.

In cases where the papilla/anastomosis is crossed and accessible endoscopically, a rendezvous technique can be used and conventional ERCP can be performed: the guidewire is left in place and coiled into the small bowel as the echoendoscope is removed over the wire. A duodenoscope is then inserted to the ampulla/anastomosis, where the wire is grasped with a biopsy forceps or snare and pulled through the working channel of the scope, followed by performance of a conventional ERCP. Alternatively, the wire can be left in place as a guide and cannulation can be performed with a second wire next to the first

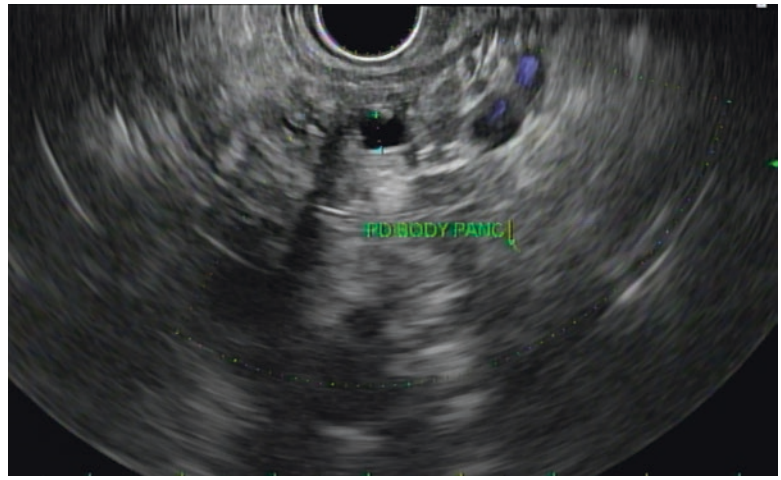

Fig. 5.1 Endosonographic image of the pancreatic duct visualized from the gastric lumen with no interposing vessels

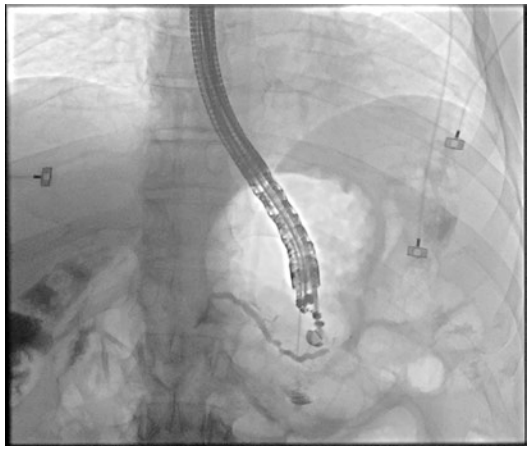

Fig. 5.2 Fluoroscopic image of a pancreatogram obtained via transgastric FNA of the tail of the pancreas

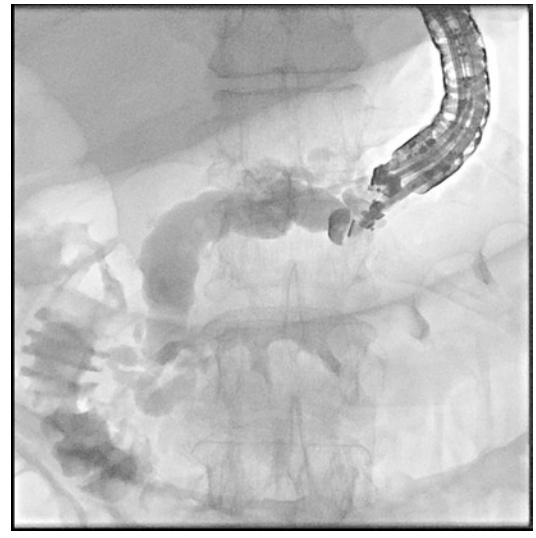

Fig. 5.3 Fluorosocpic image of a pancreatogram obtained via transgastric FNA from the body of the pancreas with filling of the small bowel

wire, often in short order. The defect at the access site is then closed with a hemostatic clip.

In cases where the ampulla/anastomosis is crossed but not reachable endoscopically, transpapillary/anastomotic transluminal stent deployment is preferred in which the distal end of the stent crosses the ampulla/anastomosis, the middle portion traverses the pancreatic duct, and the proximal end terminates in the gastrointestinal lumen (Fig. 5.18). While there are reports of increased technical success with two endoscopists (one trained in ERCP and the other in EUS), most centers performing this procedure have operators trained in both modalities [12].

Procedure times vary widely among the EUS-PD studies with a trend towards shorter procedure times upon completion of a greater number of cases [13]. In Tyberg et al.'s multicenter retrospective study of 80 patients, the procedure success rate was higher than several previously reported studies given the experience of the endoscopists involved. This highlights the learning curve needed prior to developing a proficiency for performing EUS-PD.

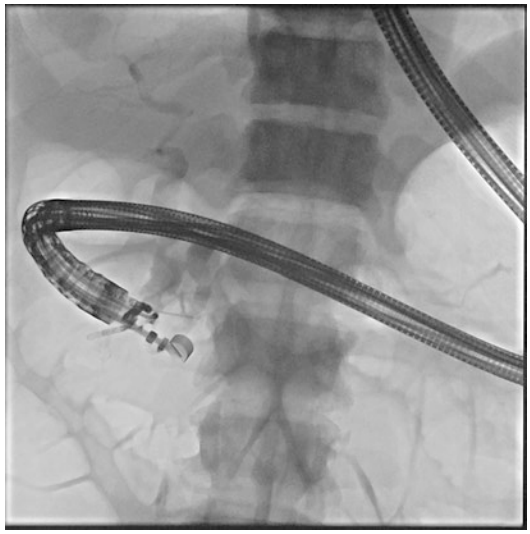

Fig. 5.4 Fluoroscopic image of a pancreatogram obtained via contrast injection through an FNA needle, transduodenal access

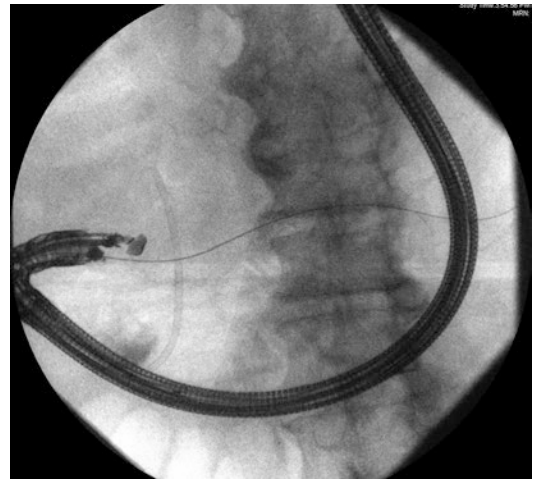

Fig. 5.6 Fluoroscopic image of wire advanced into the pancreatic duct, retrograde orientation

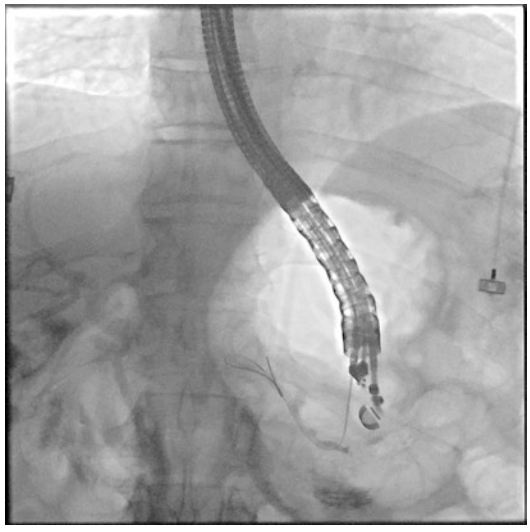

Fig. 5.5 Fluoroscopic image of wire advanced into the pancreatic duct, antegrade orientation

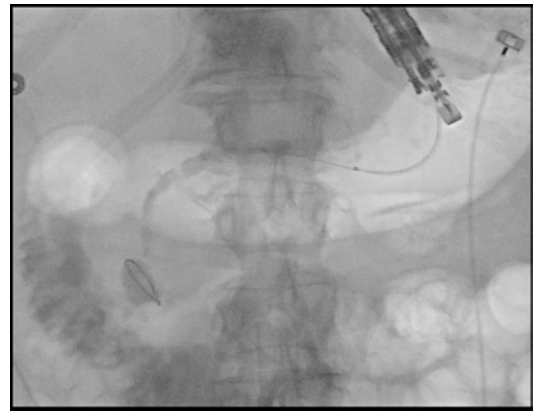

Fig. 5.7 Fluoroscopic image of a needle-knife catheter being advanced over the wire using cautery

Post-Procedure Management

Patients undergoing EUS-PD are typically hospitalized for observation post-procedure, and provided with analgesics and anti-emetics as needed as well as a short course of oral antibiotics. However, given the overall small number of studies, there remains no standardized approach to aftercare for patients having undergone EUS-PD and it is unclear if all patients undergoing this procedure warrant hospital admission. While some experts recommend revising stents contingent on patient symptoms, others use cross-sectional imaging to determine the need for revision.

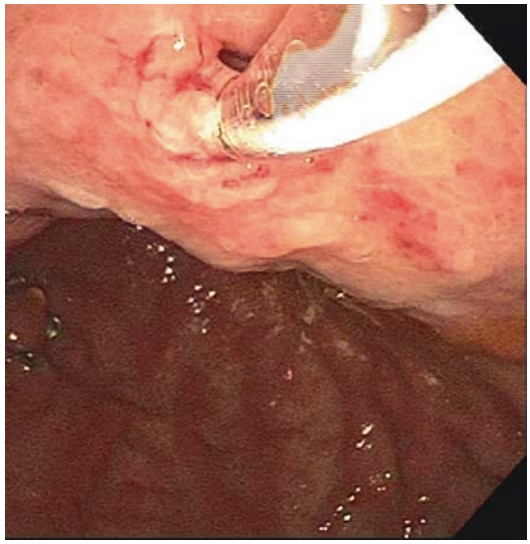

Fig. 5.8 Endoscopic image of the fistulous tract being dilated using a dilating balloon

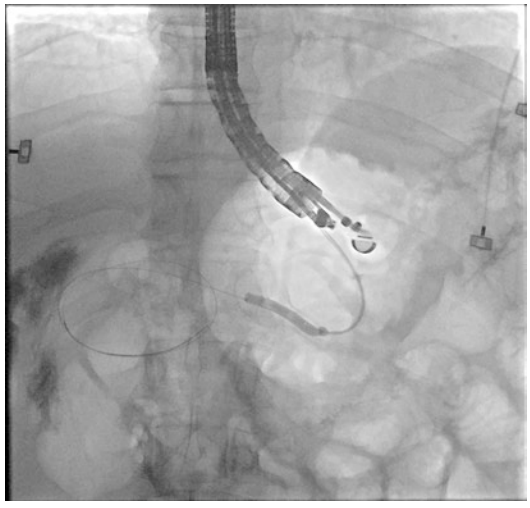

Fig. 5.9 Fluoroscopic image of the fistulous tract being dilated using a dilating balloon

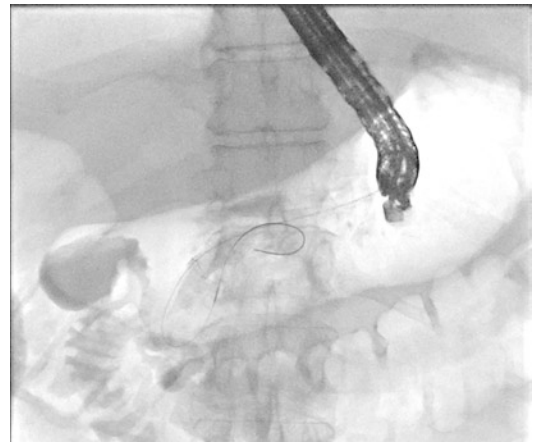

Fig. 5.10 Fluoroscopic image of a metal pancreaticogastrostomy stent, antegrade orientation, with the distal end in the pancreatic duct and proximal end in the gastric lumen

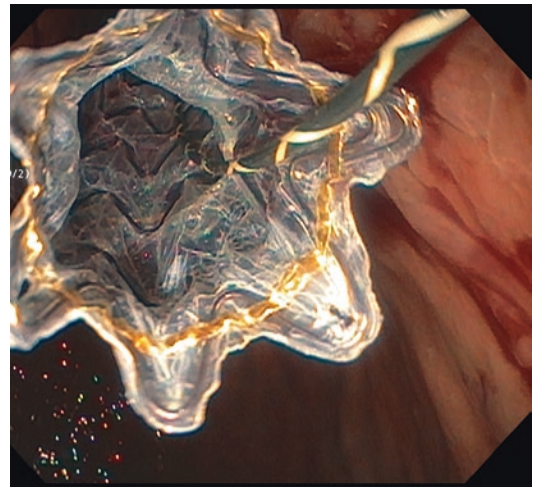

Fig. 5.11 Endoscopic image of a metal pancreaticogastrostomy stent, antegrade orientation, with the distal end in the pancreatic duct and proximal end in the gastric lumen

Analysis of Available Literature on EUS-PD

While there have been numerous publications describing EUS-PD outcomes, the overall data is limited with no prospective studies to date (Table 5.1). In 2014, Fujii-Lau et al. published a review of EUS-PD studies excluding case reports and EUS-guided pancreatograms [2]. The authors included 14 retrospective studies with a total of 222 patients with both native and surgically altered anatomy, and reported an encouraging overall technical success rate of 76.6% ($n = 170$) and a clinical success rate of 70% [7, 10, 12, 14–24]. However, technical success ranged from as low as 36% to as high as 100%.

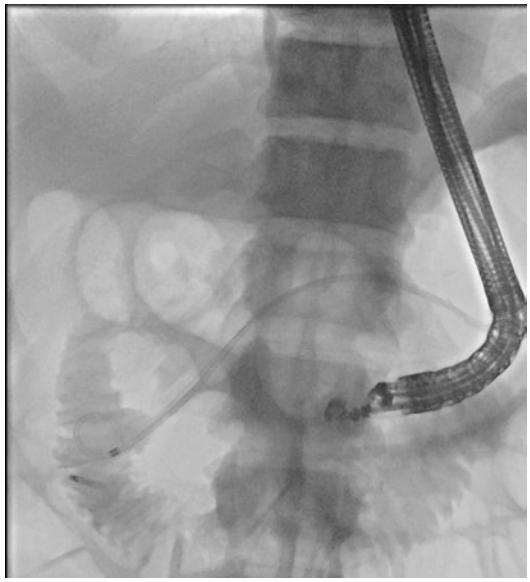

Fig. 5.12 Fluoroscopic image of a plastic pancreaticoduodenostomy stent, retrograde orientation, with the distal end in pancreatic duct and the proximal end in the duodenum

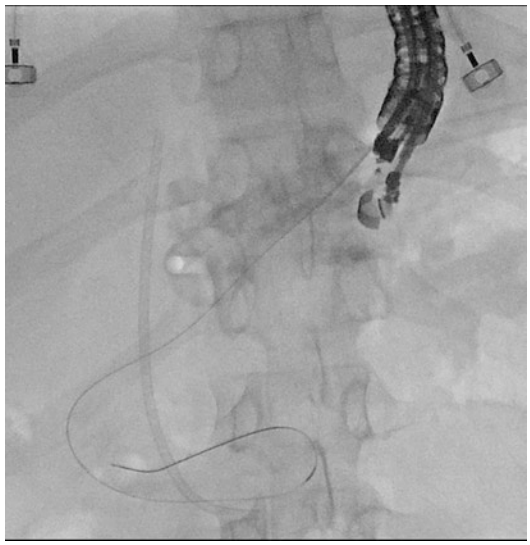

Fig. 5.13 Fluoroscopic image of wire advanced transgastrically into the pancreatic duct, antegrade orientation, and across the ampulla into the small bowel

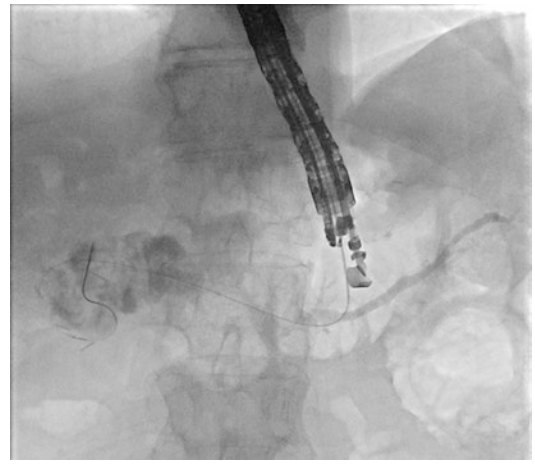

Fig. 5.14 Fluoroscopic image of wire advanced transgastrically into the pancreatic duct, antegrade orientation, and across the ampulla into the small bowel

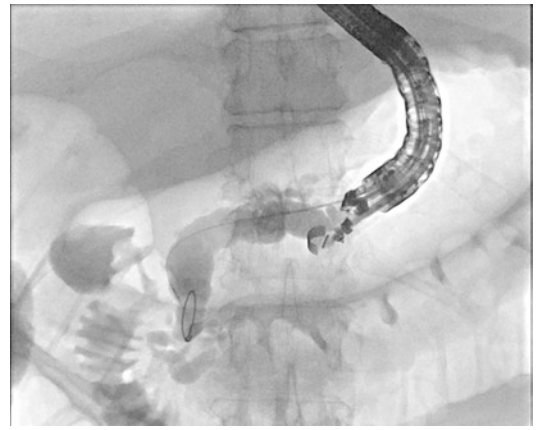

Fig. 5.15 Fluoroscopic image of wire advanced transgastrically into the pancreatic duct, antegrade orientation, and coiled in the proximal portion of the duct

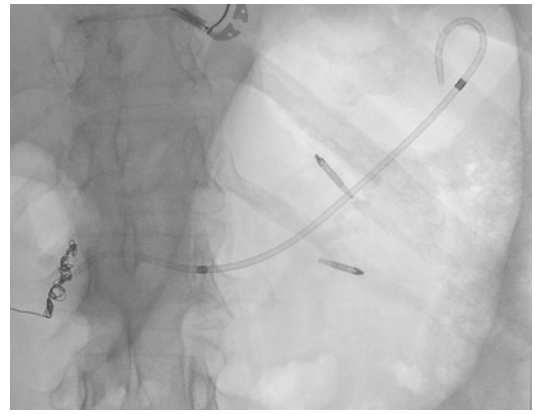

Fig. 5.16 Fluoroscopic image of a plastic pancreaticogastrostomy stent, antegrade orientation, with the distal end in the pancreatic duct and the proximal end in the gastric lumen

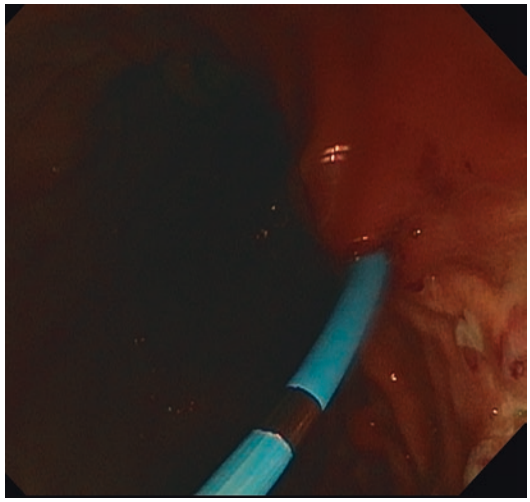

Fig. 5.17 Endoscopic image of a plastic pancreaticogastrostomy stent, antegrade orientation, with the distal end in the pancreatic duct and the proximal end in the gastric lumen

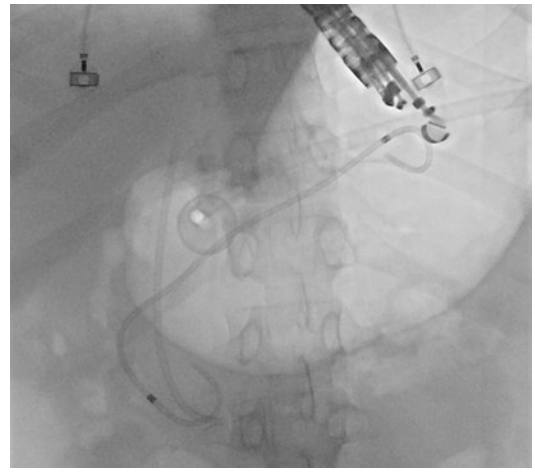

Fig. 5.18 Fluoroscopic image of a plastic pancreaticogastrostomy stent, antegrade orientation, with the distal end in the small bowel, the middle portion in the pancreatic duct, and the proximal end in the gastric lumen

Table 5.1 Outcomes of EUS-guided pancreatic duct drainage (studies with 30 or more patients)

Author, year	Number of patients	Technical success (%)	Clinical success (%)	Complications
Tessier et al., 2007 [22]	36	33/36 (91.7%)	25/36 (69.4%)	5/36 (13.9%)
Fujii-Lau et al., 2013 [16]	43	32/43 (74.4%)	20/29[a] (69.0%)	16/43 (37.2%)
Will et al., 2015 [23]	94	94/94 (100%)	68/83[b] (81.9%)	24/111[c] (21.6%)
Tyberg et al., 2017 [12]	80	71/80 (88.8%)	65/80 (81.3%)	16/80 (20%)
Total	253	230/253 (90.9%)	178/253 (70.4%)	61/253 (24.1%)

[a]Patients who followed up to death or at least 12 months
[b]83 patients required drainage
[c]111 procedures performed on 94 patients; EUS endoscopic ultrasound

In 2013, Fujii-Lau and his colleagues at the Mayo Clinic published the then largest single center Unites States experience of EUS-PD in 43 patients who failed a conventional ERCP or had surgically altered anatomy [17]. The overall technical success rate was 74% (n = 32) with symptom resolution in 68.9% of patients seen in follow-up beyond 1 year. Of the technical successes, stent insertion was antegrade in 18 patients and retrograde in 14 patients. In those with failed stent placement, reasons included inability to advance the guidewire through the papilla/anastomosis (n = 8) or main PD (n = 1), difficulty dilating the tract (n = 1), and loss of the guidewire (n = 1). This emphasizes the need to decompress the MPD regardless of crossing the papilla or anastomosis. Furthermore, 5 of the 11 patients with failed EUS-PD required pancreatic surgery while 2 patients remained asymptomatic, 2 had recurrent pancreatitis, and 2 were lost to follow-up. Interestingly, the authors reported a statistically greater chance of an unsuccessful EUS-PD when the procedure was performed on the same day as a failed ERCP. Shorter stent length and an indication other than benign anastomotic structure were associated with greater clinical success on univariate analysis; prior pancreatic surgery trended towards a lower likelihood of clinical success, possibly due to a larger pancreatic ductal diameter. Limitations similar to other prior studies included its retrospective nature, small sample size, and lack of a standardized EUS-PD technique.

In 2015, Will and his colleagues from Germany published the largest international series of patients who underwent EUS-PD after a failed ERCP over a 12-year period [25]. The authors performed 111 procedures on 94 patients, and reported a 100% rate of achieving a successful pancreatogram. The overall technical success rate was 56.6% ($n = 47$) with a clinical success rate of 81.9% ($n = 68$). Of those with successful stent deployment, 26 patients underwent transgastric or transenteric stent insertion while 21 patients underwent transpapillary stent insertion using the rendezvous technique. On follow-up, 3 patients underwent a total of 6 reinterventions as a result of stent migration ($n = 2$), stent occlusion ($n = 2$), and unsuccessful positioning of the PD drain ($n = 2$). Interestingly, 12 patients of the 36 with failed EUS-PD experienced clinical improvement after additional manipulation at the access site with use of an endoscopic knife and/or balloon dilator. Additionally, 15 patients of the 36 had continued complaints after EUS-PD failure with 1 patient requiring urgent surgical intervention from resultant perforation and 4 requiring surgery on follow-up. The authors reported that the most frequent cause for failed PD was because of difficulty obtaining PD access. However, after introduction of the Will's high-frequency ring knife to create access to the PD (used in 48 cases), the endoscopist's rate of clinical success rose from 71.4% to 89.6%, while the rate of reinterventions dropped from 31.4% to 12.5%. Additionally, the total number of adverse events decreased from 14 to 11. The authors reported no intervention-related deaths. Limitations of the study included a single experienced endoscopist performing all of the procedures and use of an endoscopic tool not widely available, raising concern about the limited applicability of this data.

In 2017, Tyberg et al. published the largest multicenter experience to date on EUS-PD. [13] The authors evaluated 80 patients who failed conventional ERCP at 4 academic centers in 3 countries. Endoscopic retrograde cholangiopancreatography failure was attributed primarily to either an anastomotic or benign main PD stricture. Overall technical success was achieved in 89% of patients ($n = 71$) with improvement in clinical symptoms or imaging in 92% of these patients. Of the 71 technical successes, stents were deployed in an antegrade approach in 51 patients and retrograde in 20 patients. The method of approach, even when controlling for indication, altered anatomy and prior failed ERCP, did not predict technical success ($p = 0.23$). That said, there appeared to be a trend towards greater clinical success in patients who underwent retrograde stent placement (95% vs. 76%, $p = 0.67$). Mean follow-up post-EUS-PD was 24 months with only 1 patient ultimately requiring surgical intervention. Limitations included the lack of a standardized approach and an adverse event rate of 20%.

There were no comparative studies evaluating ERCP and EUS-PD until recently when Chen et al. retrospectively compared the two modalities in patients with prior pancreaticoduodenectomies [26]. The authors evaluated 66 patients who underwent 75 procedures (40 EUS-PD and 35 enteroscopy-assisted ERCP [e-ERCP]) at 7 tertiary care centers across the world. The overall technical success rate of EUS-PD was 92.5% as compared to 20% in the e-ERCP cohort (odds ratio [OR] 49.3, $p < 0.001$). Transluminal stenting occurred in 52.5% of cases, followed by antegrade stenting in 40% and rendezvous stenting in the remaining 7.5% of cases. Clinical success was achieved in 87.5% of procedures in the EUS-PD cohort as compared to 23.1% in the e-ERCP group (OR 23.3, $p < 0.001$). The authors reported no severe adverse events in the EUS-PD group as well as no significant difference in procedure time or length of stay. While this is the first study to compare EUS-PD and e-ERCP directly, limitations included lack of randomization and likely selection bias. Furthermore, it is somewhat difficult to compare these two procedures directly as e-ERCP is heavily contingent on *even reaching* the pancreaticojejunostomy, let alone accessing it.

Adverse Events

One of the most significant barriers to widespread adoption of EUS-PD is the high rate of adverse events in published studies. Even when performed by experienced endoscopists, adverse events occur in a significant number of patients. In Fujii-Lau

et al.'s review of 222 EUS-PD cases, the authors reported 42 adverse events (18.9%) including pancreatitis ($n = 7$), bleeding ($n = 4$), perforation ($n = 2$), peripancreatic abscess ($n = 2$), shearing of the guidewire ($n = 2$), perigastric fluid collection ($n = 1$), pneumoperitoneum ($n = 1$), pancreatic pseudocyst ($n = 1$), and pancreatic aneurysm ($n = 1$) [2]. In Fujii-Lau's large single center study of 43 patients, moderate or severe complications occurred in 3 patients (5.8%) including acute pancreatitis, peripancreatic abscess requiring EUS-guided transmural drainage, and shearing of the guidewire into the retroperitoneum [17]. Of note, 13 patients (31.0%) required hospitalization post-procedure for abdominal pain (median hospitalization of 2 days).

Similarly, in the largest EUS-PD study to date with 80 patients by Tyberg et al., there were 12 serious immediate adverse events (15%) [13]. This included 6 patients with post-ERCP pancreatitis, 4 with pancreatic fluid collections, 1 with a main PD leak, and 1 with a luminal perforation. In addition, the authors reported delayed adverse events in 10% of patients ($n = 8$) with 4 patients developing pancreatic abscesses requiring antibiotics, 2 with pancreatitis, 1 with a luminal perforation requiring surgical repair, and 1 with a main PD leak. No deaths were reported from any of the abovementioned complications. Still, it must be recognized that EUS-PD is a complex and relatively high risk pancreatic intervention. This needs to be looked at in light of the invasive nature of alternative treatments, including pancreatic surgery, recognizing that those interventions are at least as high risk, if not higher.

Discussion

Recent advances in therapeutic EUS have allowed endoscopists to provide patients with efficacious and minimally invasive options. Whereas in the past, patients who failed conventional ERCP were limited only to percutaneous or surgical intervention, EUS-PD now offers therapeutic endoscopists a feasible alternative for PD intervention. Currently, EUS-PD is performed only at highly specialized centers. Certainly, efforts at better understanding the long-term outcomes of EUS-PD and improved standardization of the technique still need to be cultivated and evaluated in prospective studies. With improved technology both in accessories and endoscopic instruments, an overall reduction in the rate of adverse events will hopefully be achieved with increased success rate. At this stage, patients who fail ERCP for PD intervention should be considered for EUS-PD at an experienced center prior to referral to interventional radiology or surgical intervention.

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6 EUS-Guided Treatment of Gastrointestinal Bleeding

Larissa L. Fujii-Lau, Louis M. Wong Kee Song, and Michael J. Levy

Introduction

Acute gastrointestinal (GI) bleeding is one of the most common indications for inpatient GI consultation. Although most causes of GI bleeding can be successfully treated with standard endoscopic techniques, refractory or recurrent bleeding is encountered in up to 25% of patients [1]. In this situation, patients typically undergo salvage surgery or interventional radiology (IR)-guided angiotherapy. Often, it is the location and size of the bleeding lesion that complicates source identification and delivery of effective hemostasis. The efficacy and safety of endoscopic ultrasound (EUS)-guided angiotherapy has recently been demonstrated, and is a valuable alternative technique to IR or surgery in select cases presenting with challenging GI hemorrhage.

Rationale for and Limitations of EUS-Guided Angiotherapy

There are several potential advantages to EUS-guided angiotherapy over standard therapy. EUS imaging can enhance detection of the culprit vessel or vessels and allows for precise vascular targeting. The use of Doppler before and during therapy allows immediate monitoring of treatment response and guides the need for additional therapy. EUS can also be used for surveillance of the lesion to determine the long-term efficacy of treatment.

EUS-guided angiotherapy has several limitations. First, its performance is generally limited to tertiary centers with skilled interventional endoscopists. Second, the echoendoscope has a smaller caliber working channel relative to therapeutic upper endoscopes that can limit its ability to suction blood and clots (which impair visualization), as well as limited capability to perform retroflexion and circumferential torque that can be useful when delivering therapy in some locations, such as the gastric fundus and second portion of the duodenum or colon. Third, EUS is more time consuming than standard endoscopic therapy and may require the use of fluoroscopy, which makes it difficult to perform in the intensive care unit where portable fluoroscopy must be employed. Fourth, the cost of repairing an echoendoscope must be considered given the risk of damage to the channel, elevator or transducer

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when cyanoacrylate (glue) compounds are used. The risk of instrument damage secondary to glue is minimized by careful technique and vigilance when cleaning the echoendoscope immediately following therapy.

Given the complexity and limitations of EUS-guided angiotherapy, it is often reserved for patients in whom bleeding lesions are unsuitable or refractory to conventional therapy, including standard endoscopic and interventional radiologic treatment. Most published data on EUS-guided angiotherapy pertain to its use in treating gastric varices (GV). Herein, current techniques and clinical applications for EUS-guided angiotherapy for treating variceal as well as nonvariceal bleeding lesions are highlighted.

Technique of EUS-Guided Angiotherapy

The technique of EUS-guided vascular access is the same irrespective of the injectate used. After identification of the target lesion by curvilinear echoendoscopy and Doppler imaging, the vascular network should be thoroughly mapped to identify not only the specific site of bleeding, but also the network of communicating and feeding vessels when possible. In the case of varices, the goal is to target either the feeding vessel for a localized network of varices or the largest varix when varices are extensive. The hemostatic agent of choice (e.g., coil, cyanoacrylate, thrombin, or sclerosant) should be preloaded into a fine needle aspiration (FNA) needle. In general, we prefer using a 22-gauge FNA needle over a larger 19-gauge needle due to ease of use and decreased likelihood of bleeding at the needle puncture site. Larger FNA needles, typically 19 gauge, are warranted if EUS-guided intravascular coil placement is to be performed. During the actual injection, both EUS and fluoroscopy are used to ensure proper placement and therapy. Although fluoroscopy is not mandatory, we favor its use when available, especially for complex lesions and during the operator's initial experience with EUS-guided angiotherapy. After each hemostatic injection, Doppler may be used to monitor the immediate response with the understanding that the full extent of hemostasis or complete vascular obliteration may not be readily apparent. Nevertheless, this initial assessment of the treatment response is often used to determine the extent of therapy for that particular procedure.

Patients should be informed and consented to the fact that EUS-guided angiotherapy is not a Food and Drug Administration (FDA)-approved indication regarding use of various injectates, such as coils or glue. Moreover, the use of glues and coils is investigational and associated with specific risks that should be fully conveyed to the patient during the consent process. Due to the duration and complexity of the procedure, we recommend the use of general anesthesia. Preprocedure prophylactic intravenous antibiotics should be administered. The use of postprocedure oral antibiotics is individualized.

EUS-Guided Angiotherapy of Varices

EUS-Guided Coil Injection

Technical Considerations

The microcoils (Tornado or Nester Embolization Coils, Cook Medical Inc., Bloomington, IN) used during EUS-guided angiotherapy are the same as those deployed during IR angiotherapy. The selected coil diameter depends on which needle is used, with 0.035-in. coils requiring the use of 19-gauge needles while 0.018-in. coils may be deployed via 22-gauge needles. To minimize the risk of the coil itself embolizing, we typically select a coil diameter that is 1.2–1.6 times the diameter of the target vessel. The FNA needle is preloaded with the appropriate coil by removing the needle stylet, which is then used to push the coil from its original angiocatheter assembly and then advanced through the FNA needle until it lies just short of the needle tip. Although some employ a guidewire to advance the coil, we recommend using the stiffer stylet which has easier "pushability" and foregoes the need for additional equipment. To decrease the risk of coil migration, we often intentionally advance the needle through the

entire vessel and deposit the distal aspect of the coil into the deeper tissues to provide an anchor for the coil. The stylet is then advanced as the needle is slowly withdrawn to deposit the majority of the coil within the vessel lumen, while leaving the most proximal portion of the coil within proximal structures, thereby providing an additional point of anchor (Figs. 6.1 and 6.2)

Clinical Applications

Romero-Castro et al. first reported on EUS-guided coil injection in four patients with cirrhosis-related GV, leading to eradication in three (75%) patients [2]. Per the authors, the first patient had 13 coils inserted throughout the GV complex to theoretically reduce the risk of migration, followed by 9 coils placed into a 13 mm perforating vessel. The subsequent three patients had 2–7 coils placed only within the 6–12 mm perforating vessels. There was no migration of coils over a 5-month follow-up period.

The same group published a multicenter, retrospective study comparing the use of coils to cyanoacrylate injection in managing GV [3]. In the coil only group, complete GV obliteration by injection into the perforating vein occurred in 10 of 11 patients (91%) with a mean of 5.8 ± 1.2 coils placed per patient. The majority of patient (n = 9; 82%) had complete obliteration of the perforating vessel in one treatment session. Although more patients in the cyanoacrylate group required subsequent therapy as compared to the coil group, endosonographers in the study perceived coil injection to be more technically demanding. Due to the retrospective and non-randomized design of the study, the two groups should be cautiously compared.

Our reported experience with EUS-guided coil injection encompassed both esophago-gastric and ectopic varices [4]. Of the fourteen patients included in the study, 10 underwent coil injection only for esophago-gastric (n = 1), gastric (n = 2), duodenal (n = 2), and choledochal (n = 5) varices for a total of 18 procedures. The median size of the targeted varix was 6.5 mm (range 4.4–16 mm) and a mean of 4.6 ± 1.8 coils were placed during the index procedure. During a median follow-up of 18 months (range 0–104 months), three patients died and four patients did not experience recurrent bleeding up to 8 years following their index procedures. One patient had successful coil injection of GV, but re-bled 6 months later from esophageal varices which were treated with band ligation and sclerotherapy. The remaining two patients had improvement in bleeding from choledochal varices after the initial EUS therapy, but required additional EUS-guided coil placement or endoscopic retrograde cholangiopancreatography

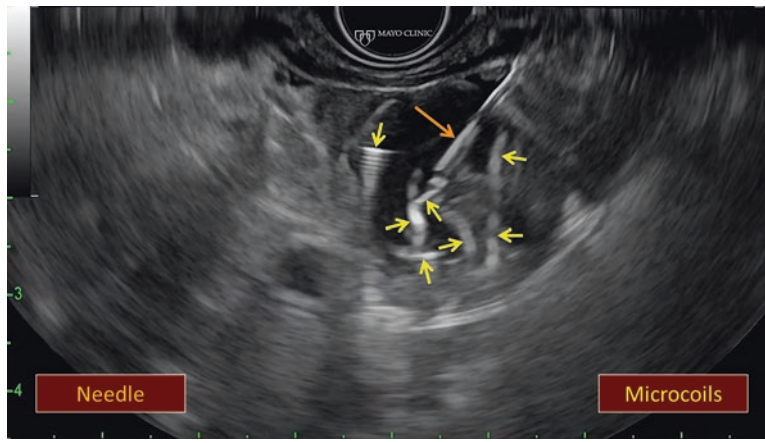

Fig. 6.1 In a patient with multiple prior episodes of gastric variceal bleeding, EUS demonstrates a network of varices with power Doppler imaging. Image demonstrate EUS-guided angiotherapy in a patient with multiple episodes of clinically significant gastric variceal bleeding resulting from alcohol and hepatitis C induced cirrhosis (Courtesy of the Mayo Clinic)

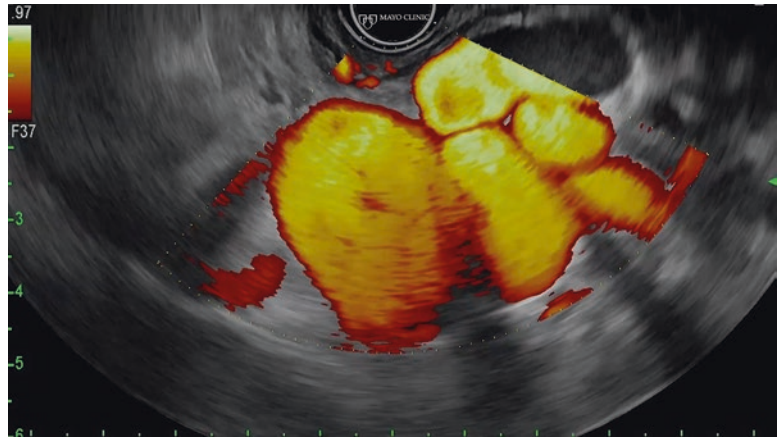

Fig. 6.2 A needle (orange arrow) is advanced into the varices and microcoils (yellow arrow) are inserted. Image demonstrate EUS-guided angiotherapy in a patient with multiple episodes of clinically significant gastric variceal bleeding resulting from alcohol and hepatitis C induced cirrhosis (Courtesy of the Mayo Clinic)

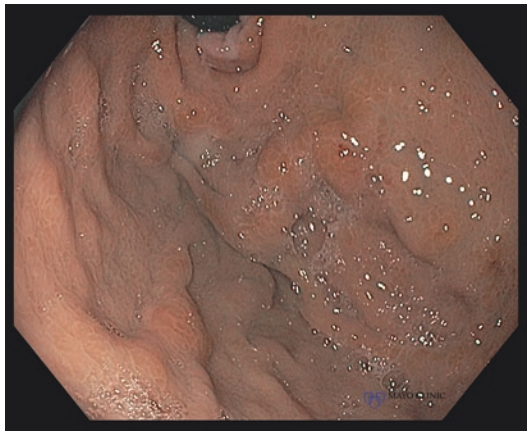

Fig. 6.3 Despite having experienced multiple clinically significant bleeds, including a recent episode when blood was seen emanating from gastric varices, there was difficulty on routine endoscopy identifying the gastric varices. Image demonstrate EUS-guided angiotherapy in a patient with multiple episodes of clinically significant gastric variceal bleeding resulting from alcohol and hepatitis C induced cirrhosis (Courtesy of the Mayo Clinic)

(ERCP) with the placement of a fully covered metal stent (to treat bile duct related bleeding) to obtain long-term hemostasis.

EUS-Guided Cyanoacrylate Injection (Figs. 6.3, 6.4, 6.5, 6.6, 6.7, and 6.8 and Video 6.1)

Technical Considerations

Cyanoacrylate polymerizes upon contact with blood, resulting in hemostasis and vascular occlusion. We recommend preloading the needle with cyanoacrylate once the target vessel has been identified. Preloading the needle avoids the need to remove the stylet after needle puncture, resulting in vacuum suction of blood into the needle that could be reinserted along with air during glue injection. If an oil-based contrast agent (e.g., Lipiodol, Guerbet LLC, Bloomington, IN) is employed to allow for fluoroscopic guidance, we typically use a 2:1 mixture of 2-octyl-cyanoacrylate (Dermabond; Ethicon Inc., Somerville, NJ) to lipiodol in 3 ml syringes when using a 22-gauge needle versus a 2.5:0.5 mixture when using a 19-gauge needle. To decrease the risk of glue embolization, the least amount of glue needed to adequately occlude the vessel is used and the mixture is injected at a rate approximating 1 ml per 15 s.

Clinical Applications

The first study on EUS-guided cyanoacrylate injection compared a historical group of patients who underwent conventional endoscopic glue injection during an acute episode of GV hemorrhage with a group who underwent endoscopic glue injection for initial hemostasis followed by EUS surveillance and further glue injection until eradication [5]. Primary hemostasis during the index procedure occurred in >95% of patients in both groups. In 43 of 54 patients (80%) in the EUS group, complete GV obliteration occurred after 2.2 ± 1.7 procedures. No adverse events were reported during the EUS-guided injection. Patients in the EUS surveillance group had significantly fewer episodes of recurrent GV bleeding compared to those who only received conventional

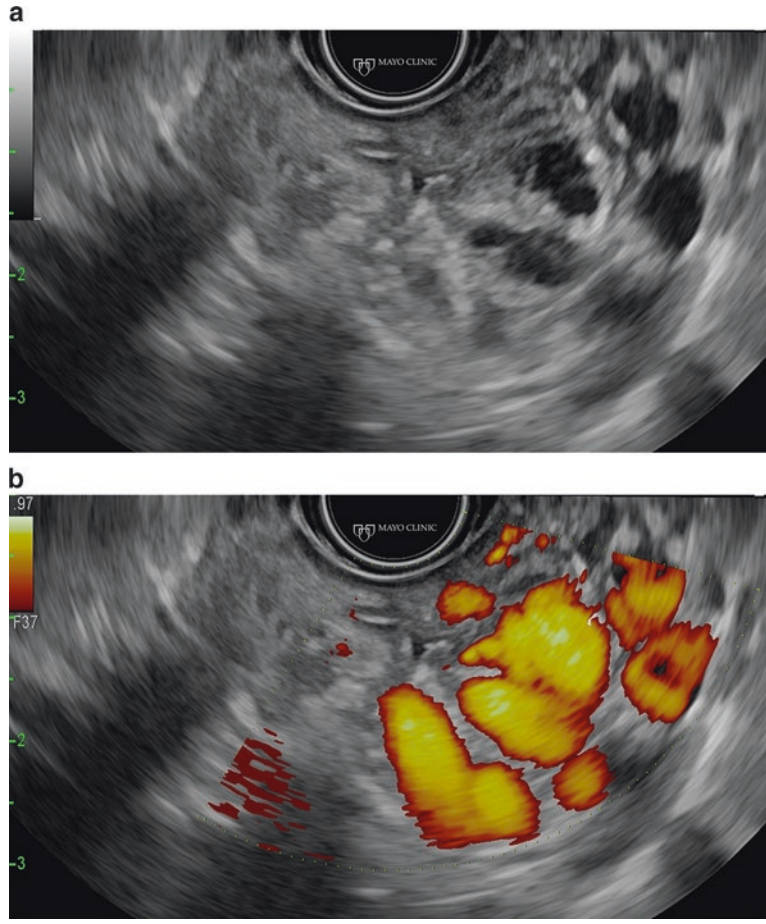

Fig. 6.4 (**a**, **b**) At EUS, grey scale (Fig. 6.2) and power Doppler (Fig. 6.3) imaging demonstrated a network of gastric varices. Image demonstrate EUS-guided angiotherapy in a patient with multiple episodes of clinically significant gastric variceal bleeding resulting from alcohol and hepatitis C induced cirrhosis (Courtesy of the Mayo Clinic)

endoscopic glue injection (26% vs 57%, respectively, $p = 0.002$). Although the use of a historical cohort is subject to bias, this study introduced the concept that patients with active GV hemorrhage may benefit from EUS surveillance with secondary prophylaxis until eradication to decrease the risk of re-bleeding.

A case series of patients with cirrhosis-related GV who underwent EUS-guided cyanoacrylate injection into perforating vessels showed complete obliteration in all five patients [6]. A mean of 1.6 ml of glue was injected. During a mean follow-up of 10 months, no adverse events or recurrent bleeding was observed. When the same group focused on patients who underwent only EUS-guided glue injection, all 19 patients had complete obliteration of the feeding gastric vessels [3]. The five patients reported in the initial case series were not included in the subsequent study. Only 42% of patients had successful treatment after one session of EUS-guided glue injection. A mean of 1.5 ± 0.1 ml of cyanoacrylate was injected per patient. Although 12 adverse events occurred in 11 patients in the cyanoacrylate group, only two patients were symptomatic, including fever ($n = 1$) and chest pain ($n = 1$). There were 9 pulmonary glue embolisms (47%) detected on routine chest CT performed in all patients in the EUS-guided glue injection group, which significantly lengthened their hospital stay.

EUS-Guided Combination Therapy

The injection of coils prior to glue theoretically provides a scaffold to help anchor the glue, thereby decreasing the amount of glue required for obliteration and minimizing the risk of embolization,

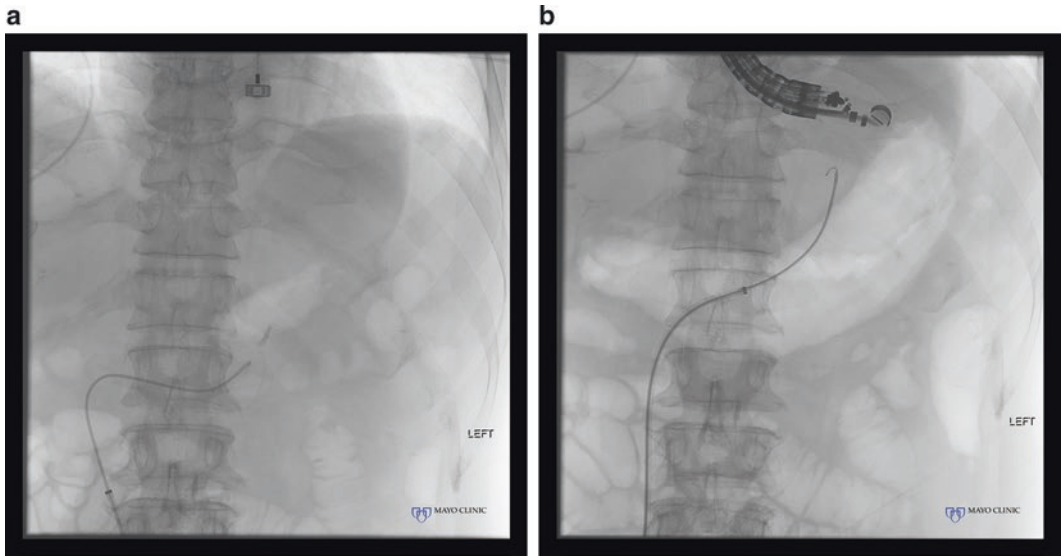

Fig. 6.5 (**a**, **b**) As the patient had a large splenorenal shunt, balloon-occluded retrograde transvenous obliteration (BRTO) was performed to minimize the risk of glue embolization. The left inferior phrenic vein was selectively catheterized and satisfactory position confirmed with venography. This catheter was exchanged for a temporary balloon occlusion catheter, positioned in the inferior phrenic vein above the confluence with the left adrenal vein. A fluoroscopic run was obtained with the balloon inflated to confirm that it does occlude flow. The balloon was left inflated while the gastric varices were treated with endoscopic glue injection. Image demonstrate EUS-guided angiotherapy in a patient with multiple episodes of clinically significant gastric variceal bleeding resulting from alcohol and hepatitis C induced cirrhosis (Courtesy of the Mayo Clinic)

the most concerning adverse event during EUS-guided angiotherapy [7]. Binmoeller et al. described an ex-vivo experiment where 1 ml of cyanoacrylate was injected into heparinized blood that contained a previously placed coil. The glue adhered to the coil fibers, allowing all of the glue to be removed with the coil in a single piece. They hypothesized that EUS-guided coil insertion followed by cyanoacrylate injection improves variceal obliteration while decreasing the risk of glue embolization. Prospective trials are needed to confirm the theoretical benefit of using coils to anchor the glue.

The same group retrospectively analyzed 30 patients with acute (n = 2), recent (defined as <1 week, n = 18), or remote (n = 10) bleeding from GV who underwent EUS-guided coil and glue embolization of feeding vessels [8]. Technical success of coil and glue injection occurred in all patients, while immediate hemostasis was achieved in both patients with overt bleeding at the time of the endoscopy. The majority of cases (93%) only had 1 coil placed and a mean of 1.4 ml of 2-octyl-cyanoacrylate was injected. No immediate adverse events occurred, particularly regarding glue embolization. In patients who underwent subsequent surveillance endoscopy (n = 24), 96% had complete obliteration of the feeding vessels and no evidence of flow on color Doppler within the variceal complex. One patient had recurrent GV bleeding 21 days after the initial procedure, which was treated with repeat EUS-guided combined coil and glue injection. At follow-up endoscopy, the glue and coils had spontaneously extruded into the stomach and eventually formed a scar.

In the largest study to date, the same group reported on 152 patients with GV treated with a mean of 1.4 coils and a mean of 2 ml cyanoacrylate for active hemorrhage (n = 7), stigmata of recent bleeding (n = 105), and primary prophylaxis (n = 40) [9]. In one patient, technical failure occurred with the inability to control the bleed despite injection of a coil and 6 ml of glue, requiring urgent transjugular intrahepatic

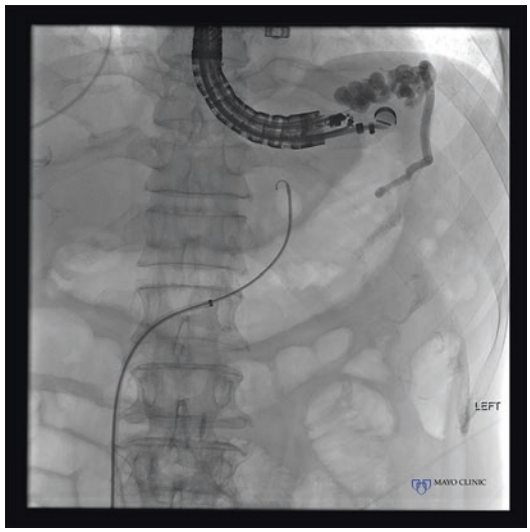

Fig. 6.6 Glue and lipiodol were injected under EUS guidance, resulting in complete filling of the variceal network. The glue migrated into the feeding vessel with protection provided by the occlusion balloon to prohibit shunt embolization. Image demonstrate EUS-guided angiotherapy in a patient with multiple episodes of clinically significant gastric variceal bleeding resulting from alcohol and hepatitis C induced cirrhosis (Courtesy of the Mayo Clinic)

portosystemic shunt (TIPS). Of the 100 patients with follow-up EUS, 93% had complete obliteration of the GV by Doppler evaluation after one (n = 79), two (n = 10), three (n = 2), or four (n = 2) procedures. Of these 93 patients, three had recurrent bleeding after a median of 324 days and were treated with additional coil and glue therapy. There were nine procedure-related adverse events, including self-limited pain (n = 4), embolization (n = 1), and minor bleeding from coil/glue extrusion (n = 4). The one patient with embolization presented 1 week after discharge with shortness of breath, hemoptysis, and fever. CT identified an acute pulmonary embolism and associated pneumonia. Although this study included patients who underwent primary prophylaxis, additional studies are required in this patient population before advocating routine EUS-guided angiotherapy.

In our experience, four patients (3 with gastric and 1 with duodenal varices) underwent a combination of coil and glue injection [4]. In these patients, the varices were deemed to be

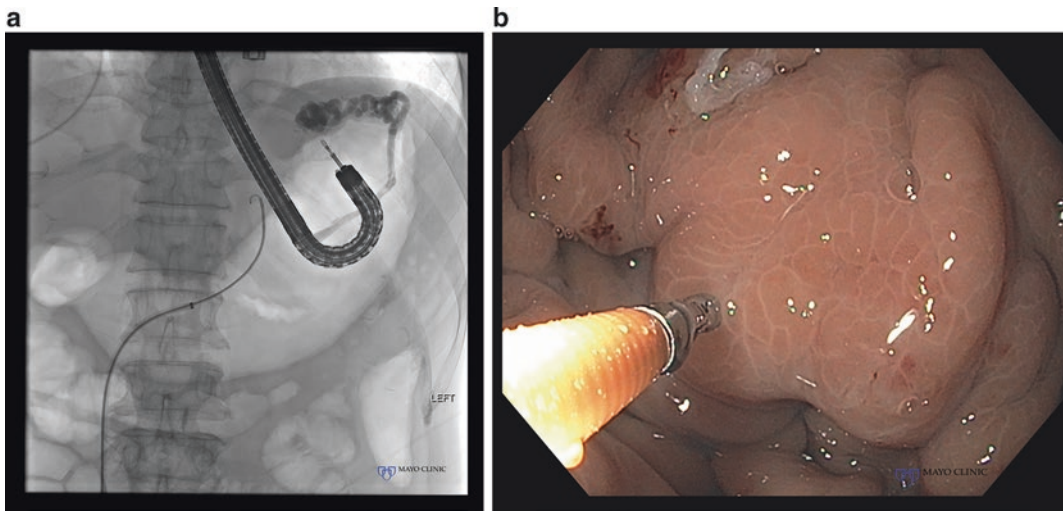

Fig. 6.7 (**a**, **b**) Standard endoscopy was then performed. A closed biopsy forceps was placed at the site of preciously identified bleeding demonstrated the site of glue injection. When applying gentle pressure, firmness was appreciated as a result of the injected glue and thrombus. Image demonstrate EUS-guided angiotherapy in a patient with multiple episodes of clinically significant gastric variceal bleeding resulting from alcohol and hepatitis C induced cirrhosis (Courtesy of the Mayo Clinic)

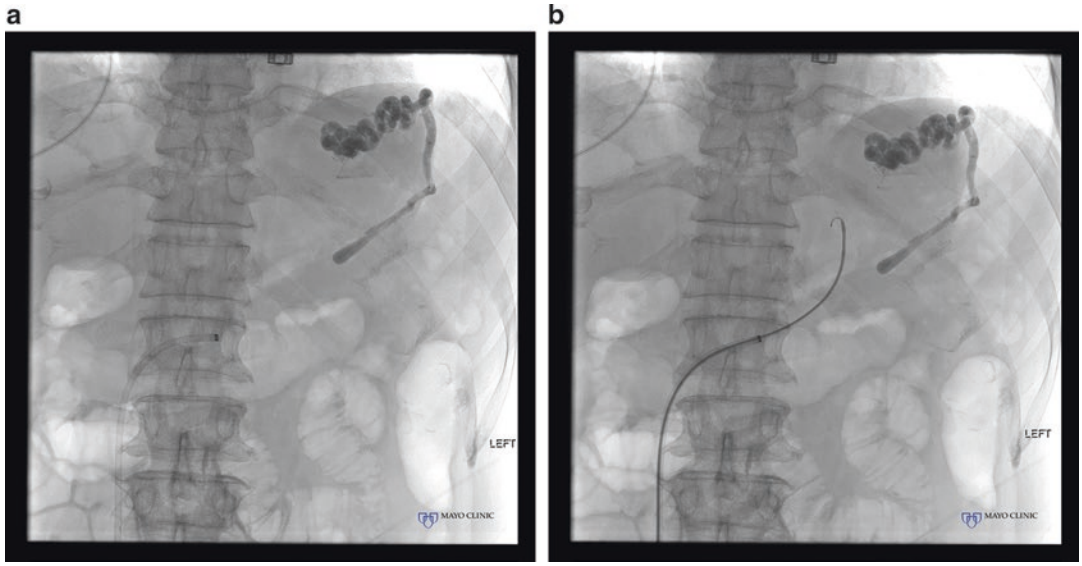

Fig. 6.8 (**a**, **b**) Following therapy, the IR-inserted balloon was deflated demonstrating no further spread or embolization of glue. Image demonstrate EUS-guided angiotherapy in a patient with multiple episodes of clinically significant gastric variceal bleeding resulting from alcohol and hepatitis C induced cirrhosis (Courtesy of the Mayo Clinic)

too large to be treated either with standard glue injection or with EUS-guided coil injection only. A mean of 7.5 coils and 3 ml of glue were injected in these patients. There was no further evidence of bleeding at a mean follow-up of 4 months.

EUS-Guided Angiotherapy of Rectal Varices

EUS can more accurately characterize the extent of rectal varices, define the hemodynamics, and target the perforating veins with therapeutic intent [10, 11]. Coil and glue injection has been reported in the treatment of recurrent bleeding rectal varices. One patient underwent 4 punctures along a large >30 mm varix with deployment of either 1 or 2 coils and 1 ml of cyanoacrylate into each puncture site and no recurrent bleeding after 12 months of follow-up [12]. These authors postulated the advantages of EUS over standard endoscopic treatment of these large varices, including its ability to deliver precise treatment without being obscured by luminal contents, visualize deeper collaterals, and confirm the absence of flow by Doppler after therapy. Another case report described placement of 1 coil and 1 ml of cyanoacrylate into a large rectal varix, with repeat sigmoidoscopy confirming the lack of large feeding vessels and collapse of the rectal varix [13]. One case report described the successful use of sclerotherapy for the treatment of recurrent bleeding from rectal varices with 2 ml of sodium tetradecyl sulfate [14].

EUS-Guided Angiotherapy of Nonvariceal Bleeding

Since most studies on EUS-guided angiotherapy are limited to the treatment of esophagogastric varices, data pertaining to the use of EUS for treating nonvariceal bleeding are scant. One of the first applications of EUS-guided angiotherapy was in eight patients with suspected Dieulafoy lesions [15]. In these patients, the stomach was filled with 200–400 ml of water and radial echoendoscopy identified potential culprit 2–3 mm vessels penetrating the muscularis propria and coursing through the submucosa for 2–4 cm. Four patients underwent sclerotherapy, 3 of which were EUS-guided. During a median follow-up of 10 months, two patients re-bled at 3

and 5 months post-therapy. One patient who was receiving nonsteroidal anti-inflammatory medications re-bled from a duodenal ulcer that contained a visible vessel, while the other patient had a lesion located at 1.5 cm from the prior sclerotherapy scar; both patients had repeat sclerotherapy performed. In three patients, surgical pathology confirmed the presence of a submucosal vessel consistent with Dieulafoy lesions. Similarly, Ribeiro et al. described a case of EUS-guided bipolar coagulation followed by sclerotherapy of a Dieulafoy lesion located 4 cm distal to the gastroesophageal junction [16].

EUS-guided thrombin injection has been described in the treatment of pseudoaneurysms [17–20]. Thrombin promotes the conversion of fibrinogen to fibrin, resulting in clot production [21]. In one study of four cases of patients who developed pseudoaneurysm formation secondary to pancreatitis, a 22-gauge needle was used to inject the thrombin solution. Within a minute, blood flow to the aneurysm ceased in each case and a thrombus had formed within the aneurysmal sac. This thrombus persisted at 6- to 42-week follow-up. Partial aneurysmal recanalization was noted on CT angiography at 12 weeks post-thrombin injection with associated reports of melena; however, this did not persist and the aneurysm had spontaneously thrombosed on follow-up CT scans at 28 and 42 weeks [17].

The largest case series to date from our institution included 13 patients who had either failed prior therapy or were deemed unsuitable candidates for other endoscopic, interventional radiologic or surgical procedures [22]. Indications for EUS-guided angiotherapy included gastric gastrointestinal stromal tumors (n = 4), Dieulafoy lesions (n = 2), duodenal metastases (n = 2), esophageal cancer (n = 1), intractable marginal ulcer after gastric bypass (n = 1), duodenal ulcer (n = 1), duodenal Brunner's gland hamartoma (n = 1), and pancreatic pseudoaneurysm (n = 1). All but one patient failed prior endoscopic and/or IR-guided therapy. Fifteen EUS-guided procedures were performed in total, including cyanoacrylate injection (n = 5), hyaluronate injection (n = 3), alcohol ablation (n = 3), band ligation (n = 2), combined band ligation with alcohol injection (n = 1), and combined epinephrine injection, endoloop ligature and polypectomy (n = 1). Doppler ultrasound at the conclusion of the EUS confirmed complete cessation of flow in 11 patients (84.6%) and marked decrease in 1 patient. Only 1 patient (7.7%) had recurrent bleeding attributed to the treated lesion. This patient had a gastric Dieulafoy lesion that was managed with EUS-guided India ink marking and band ligation. This patient experienced re-bleeding 38 months later, which was again treated with EUS-guided India ink marking and band ligation using multiple bands. This patient subsequently experienced complete cessation of Doppler flow to the lesion and had no further evidence of re-bleeding at 5 months follow-up. No adverse events were encountered from these procedures.

Summary

Difficult-to-treat GI bleeding remains a common clinical challenge for gastroenterologists. EUS detection and EUS-guided angiotherapy using a variety of agents, including coils, glue, sclerosant, or a combination thereof, has increasingly been used in this situation. However, additional studies are needed to determine the optimal use of EUS-guided angiotherapy, including the ideal target lesions, injectate(s), dose, and follow-up in these complex patients. In the interim, management decisions should be based on local expertise and in a multidisciplinary manner that incorporates standard endoscopy, EUS, interventional radiology, and surgery.

Disclosures None.

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EUS-Guided Celiac Plexus Block and Celiac Plexus Neurolysis

7

Truptesh H. Kothari, Shivangi Kothari, and Vivek Kaul

Introduction

Abdominal pain can be a very common debilitating symptom in patients with upper abdominal malignancy or a benign disease process such as chronic pancreatitis. Cancer related pain could dramatically affect the quality of life of these patients [1–3]. The pain originating from upper abdominal viscera is carried by special visceral afferent fibers that relay through the splanchnic nerves and the celiac plexus [4, 5]. The celiac plexus is a network of nerve fibers located in the retroperitoneum, adjacent to the anterolateral wall of the aorta [6]. The principle of relieving the pain associated with upper abdominal malignancy is to disrupt nociceptive impulses at the level of the celiac plexus or splanchnic nerves [6].

The terms celiac plexus block and neurolysis are sometimes used interchangeably, but they differ in terms of duration of action and the agents used for treatment and indications [7]. Celiac plexus block (CPB) refers to a temporary disruption of pain transmission from the afferent nerves to the spinal cord via the celiac plexus and is accomplished by injecting corticosteroids (e.g., triamcinolone) and local anesthetics. CPB is generally used for pain relief in benign disease processes such as chronic pancreatitis [7]. In contrast, celiac plexus neurolysis (CPN) refers to the permanent destruction of the celiac plexus with a neurolytic agent along with local anesthetics. Ethanol is generally used as a neurolytic with bupivacaine as a local anesthetic for CPN. CPN is indicated for alleviating pain from abdominal malignancy [7].

The CPN technique was initially reported in 1914 and was performed as an intraoperative procedure [8]. CPN has been carried out under radiographic, fluoroscopic, computed tomography (CT), or ultrasonographic imaging guidance. Faigel et al. [9] and Wiersema and Wiersema [10] introduced endoscopic ultrasound (EUS)-guided CPN in 1996. This technique is considered safer, precise, and more convenient than other previously used techniques since EUS-guided CPN is carried out under real time ultrasound imaging and color Doppler assessment, which helps avoid injury to interposing vessels. In a randomized controlled trail (RCT), Gress et al. showed that the EUS-guided CPB technique provided more long-term pain relief than the CT-guided approach [11].

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Indications

EUS-guided CPN is often used for persistent and intractable abdominal pain due to gastric, pancreatic, esophageal, and biliary malignancy as well as retroperitoneal lymph node metastasis or pain due to metastatic liver cancer [12]. CPB is usually performed for abdominal pain associated with chronic pancreatitis [12]. It has been reported to also be beneficial in cases of nausea and vomiting due to pancreatic cancer. CPB results in unopposed parasympathetic activity, which helps with increased peristalsis relieving nausea and vomiting symptoms. The unopposed parasympathetic activity is due to the sympathetic denervation of the gastrointestinal tract.

Contraindications to CPN/CPB

1. Supratherapeutic INR (International normalized ratio >1.5).
2. Thrombocytopenia (platelets <50,000).
3. Gastric and/or esophageal varices.
4. Use of anticoagulation—medication hold required prior to procedure.
5. Severe alcohol intolerance.

Techniques of EUS-CPN/CPB

Central CPN

This technique is also known as the single injection technique. The abdominal aorta is located through the posterior gastric wall using the linear echoendoscope, at the level just below the gastroesophageal junction. Once the abdominal aorta is visualized, the celiac artery (CA) is identified as the first vessel originating from the aorta (Fig. 7.1). In this technique for CPN, an FNA needle (19 or 22 gauge) is advanced to the level just above the origination of the CA from the abdominal aorta (Figs. 7.2 and 7.3). A normal saline syringe is attached to the needle and negative suction is applied by aspirating the syringe to ensure a ves-

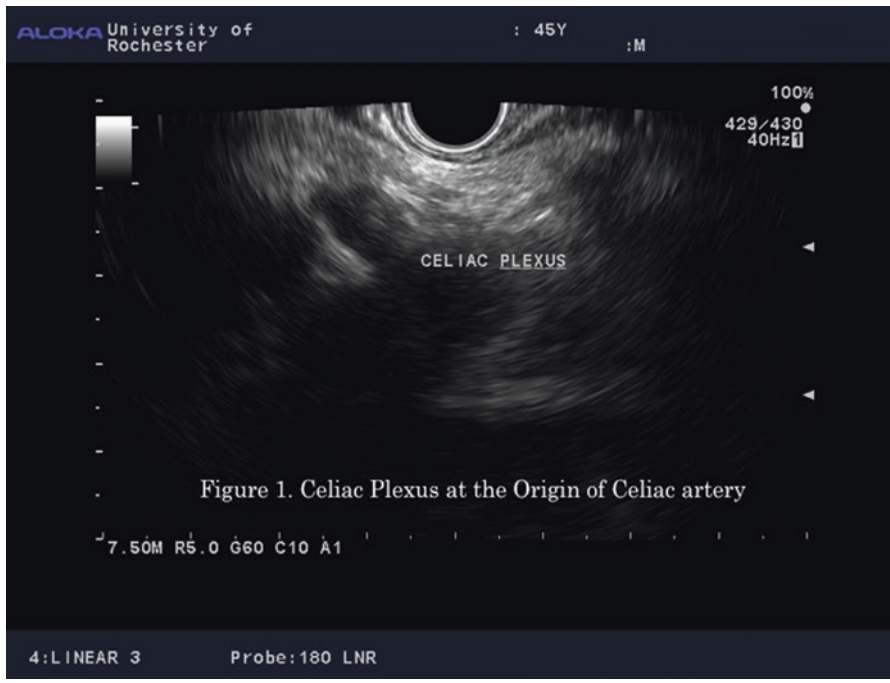

Fig. 7.1 EUS image showing the origin of the celiac artery and the expected location of the celiac plexus in most patients

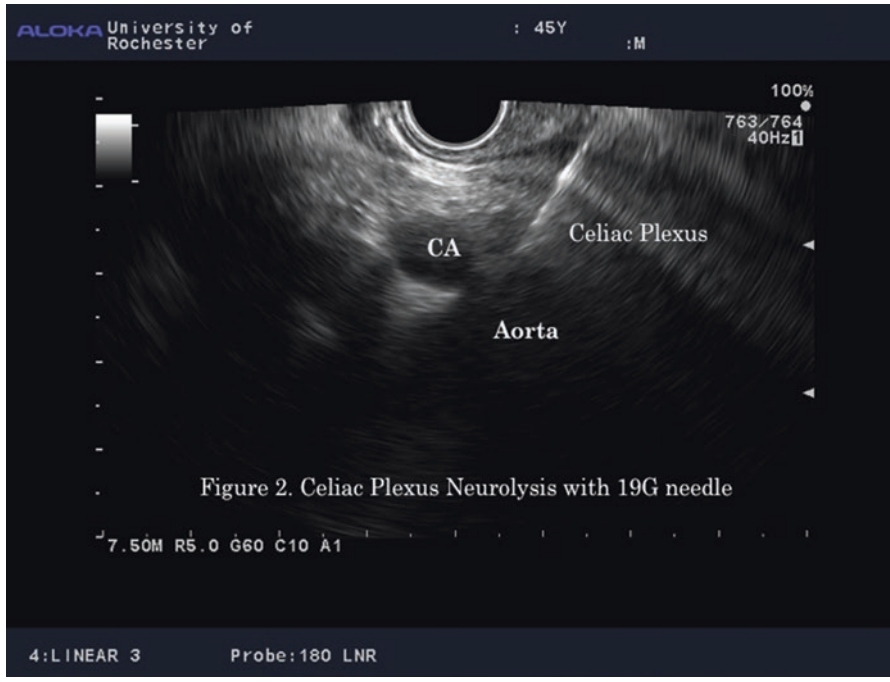

Fig. 7.2 EUS image of a central celiac plexus injection (in this case a neurolysis) into the celiac ganglia just anterior to the origin of the celiac artery

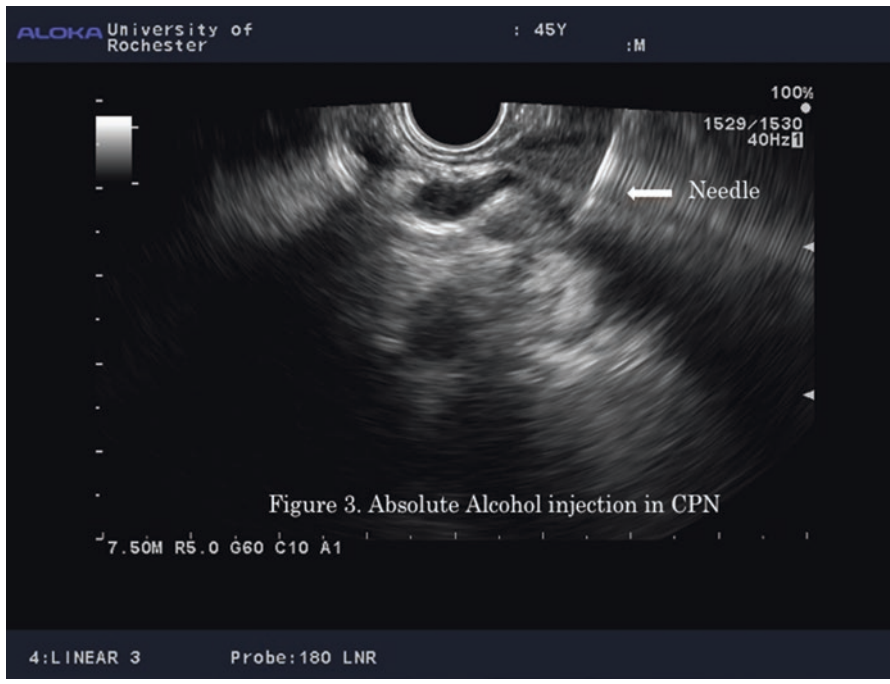

Fig. 7.3 EUS image during a celiac plexus neurolysis showing the cloudy distortion that accompanies ethanol injection

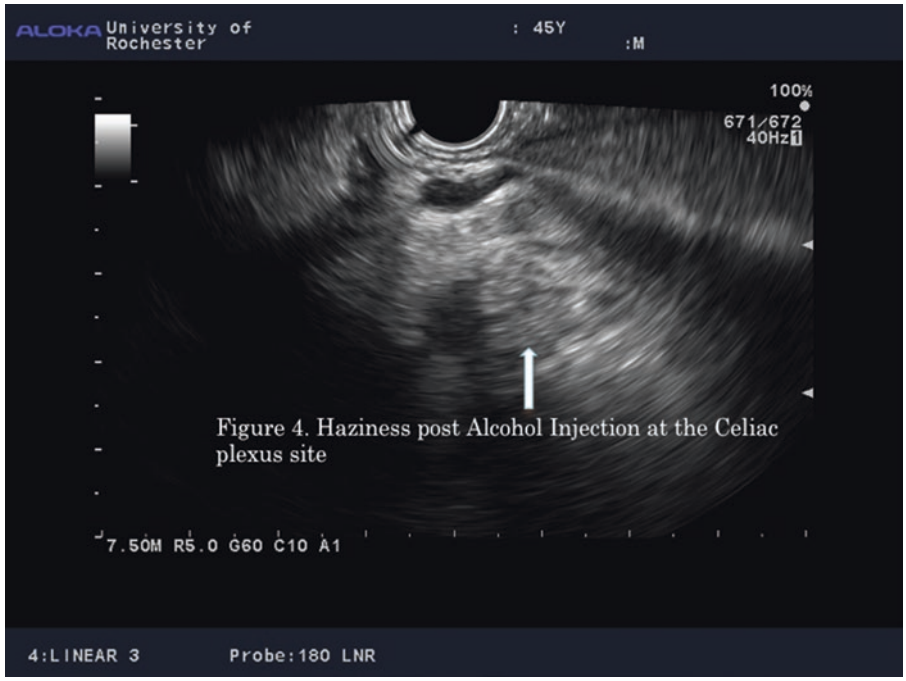

Fig. 7.4 EUS image showing persistent haziness following removal of the needle after ethanol injection

sel has not been inadvertently entered. Once the absence of blood in the syringe is confirmed, 0.25% × 20 ml bupivacaine is administered through the needle, followed by 10 ml absolute alcohol. An echogenic cloud is evident at the site of injection (Figs. 7.4 and 7.5). The needle is flushed with normal saline at the injection site followed by withdrawal of the needle (Video 7.1). In CPB, bupivacaine is administered followed by 3 ml (40 mg) triamcinolone [7].

Bilateral

After the identification of the CA origin from the abdominal aorta (Fig. 7.1), the echoendoscope is rotated clockwise until the CA and superior mesenteric artery (SMA) are not in the field of vision. The FNA needle is then advanced via the trans-gastric approach up to the point of origin of the SMA from the aorta. The injection agents are administered into this region. The needle is then withdrawn and the echoendoscope is rotated counterclockwise until the CA and SMA are no longer visible (Fig. 7.6). Now the needle is advanced again up to the level of the SMA origin from the aorta and the injection agents are administered. The steps and the volume of agents injected for bilateral technique remain the same as in central technique [13, 14].

Central Versus Bilateral Technique

Several studies have been published comparing the two CPN techniques (central vs bilateral) in terms of pain relief but it is still a matter of debate as to which technique is superior to the other. Puli et al. compared both the techniques in terms of pain relief in the pancreatic cancer group [7], concluding that the bilateral technique (84.54%) was a superior modality compared to the central technique (45.99%) (95% CI = 37.33–54.78).

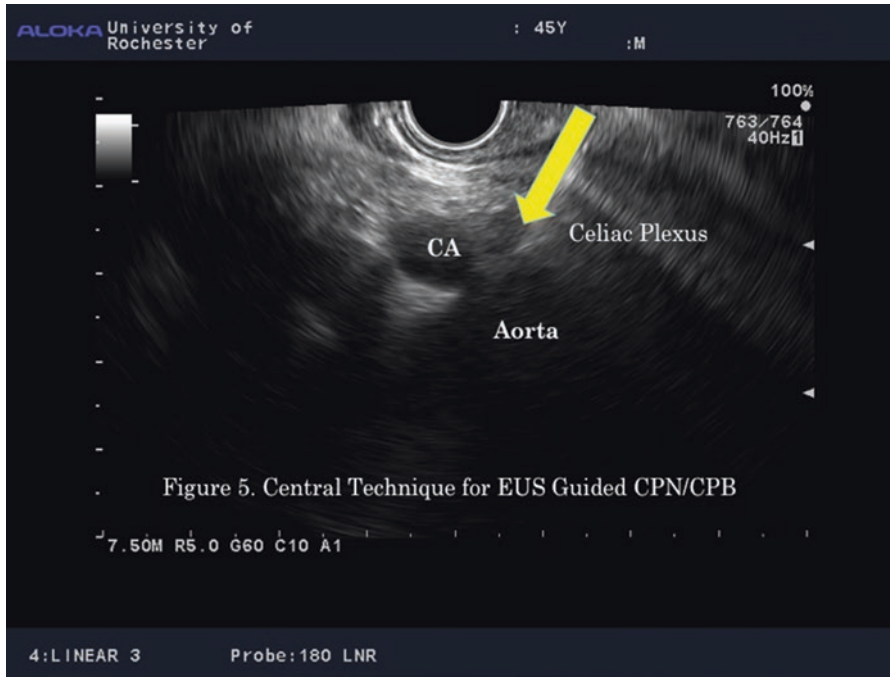

Fig. 7.5 EUS with schematic arrow showing needle path for a central celiac plexus injection

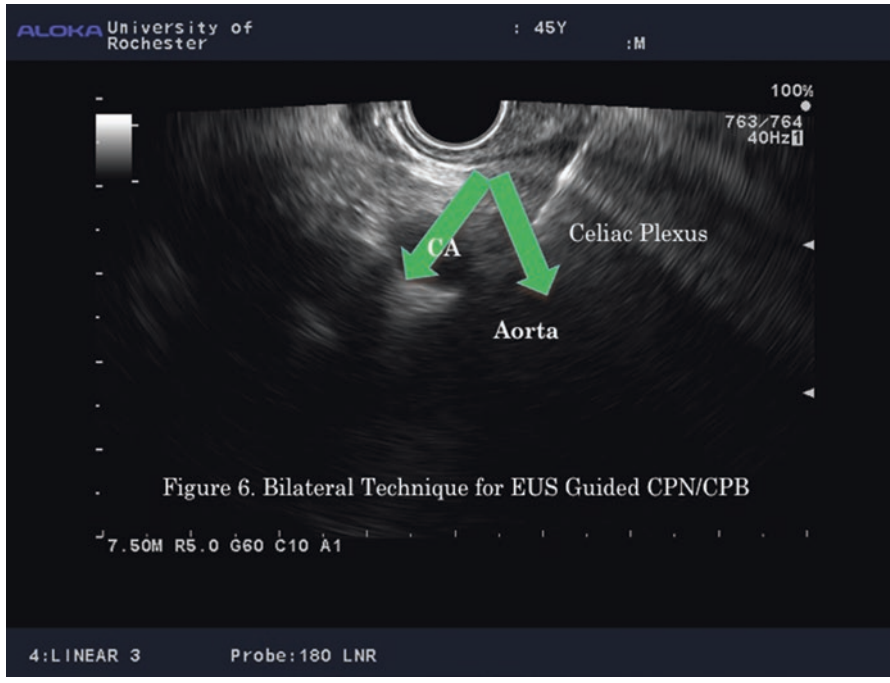

Fig. 7.6 EUS image with schematic arrows showing the needle path for bilateral celiac plexus injections

In 2009, Sahai et al. compared the short-term efficacy of pain relief (pain score reduction) with both techniques in EUS-guided CPN/CPB in 160 patients [15]. Bilateral technique was found to be more effective than the central CPB/CPN technique with a mean pain reduction of 70.4% vs. 45.9% (P = 0.0016). Bilateral CPB/CPN was reported to be the only predictor of a >50% pain reduction (OR 3.55, 1.72–7.34).

However, LeBlanc et al. [16] performed a randomized controlled trial of 50 patients, which concluded no significant difference between the two groups in terms of pain relief. It is to be noted though that for the bilateral technique in the Leblanc study, the needle was advanced laterally to the CA with injection performed on both sides of the CA without any distal advancement of the needle towards the base of the CA, whereas in the study by Sahai et al. the needle was advanced lateral to the CA and further advanced to the region lateral to the base of SMA. However, self-limited bleeding in an anticoagulated patient has been reported due to laceration of the adrenal artery with the bilateral technique and thus caution should be taken while performing this technique [15, 17].

EUS-Guided Direct Celiac Ganglion Neurolysis (CGN) and Celiac Ganglion Block (CGB)

In 2006, Levy et al. demonstrated that the celiac ganglia can be visualized with the aid of EUS. Levy et al. suggested that EUS-guided direct CGN was highly effective in pancreatic cancer pain relief with a 94% success rate when alcohol was injected (16/17 patients) and 0% success rate (0/1 patient) when steroid was injected [18, 19]. In patients with chronic pancreatitis, 80% (4/5 patients) pain relief was reported with alcohol injection versus 38% (5/13 patients) who received steroids. Initial experience by Levy et al. in 2008 suggested that EUS-guided CGN or CGB was safe. It was also noted that alcohol injection directly into the ganglia appeared to be effective in patients with cancer and chronic pancreatitis [19]. During this retrospective trial, the volume of injection and number of celiac ganglia injected were not consistently reported, perhaps since it was a new technique then. However, in general the mean number of ganglia injected were 2.7 and 2.3 in patients with pancreatic cancer and chronic pancreatitis, respectively. Depending on the size of ganglion—if smaller than 1.0 cm as measured within the axis of the needle plane, the needle tip was positioned within the central point of the ganglia. If the ganglion was 1.0 cm or greater in the needle plane axis, the needle tip was inserted to the deepest point within the ganglion and intraganglion injection was performed on slow withdrawal [19].

CPN Versus CGN

EUS-guided CPN is a well-established intervention for the relief of cancer pain. With CPN, neurolytic agents are injected around the celiac trunk where the ganglion is thought to reside. However, injection directly into the ganglion (if visualized on EUS) may provide more effective response in the treatment of pain. In 2013 Doi et al. reported a multicenter, randomized study of 68 patients comparing EUS CPN vs. EUS CGN for pain relief in patients with upper abdominal malignancy. In this study, CPN was performed using the "central method" with injection performed just above the origin of the celiac artery. EUS CGN was performed in 30 of 34 patients (88%); the celiac ganglia could not be visualized in 4 patients. In patients with ganglia <1 cm in size the injection was performed in the center whereas in patients with ganglia >1 cm in size the needle was advanced deep into the ganglion and injection performed as the needle was slowly withdrawn so as to distribute the injection throughout the ganglion. Significantly higher pain response rate (decrease in pain score to ≤3) was seen in the EUS-CGN group (73.5%) compared to the EUS- CPN group (45.4%, p = 0.026). Also 50% of patients in the EUS-CGN group had complete response to treatment,

compared to 18.2% in the EUS-CPN group ($p = 0.010$). No difference was seen in the duration of pain relief or in the complications between the two groups [20].

EUS-Guided CPB Versus CT-Guided CPB

Gress et al. [21] conducted a prospective randomized comparison of EUS-guided CPB and CT-guided CPB for management of chronic pancreatitis pain. Twenty-two consecutive patients were enrolled in the study from 7/1/1995 to 12/30/1995. Ten patients underwent EUS-guided CPB and 8 patients underwent CT-guided CPB. Four patients were excluded due to protocol violations. EUS-guided CPB was performed with a 22-gauge FNA needle. Ten milliliter of bupivacaine (0.75%) and 3 ml (40 mg) of triamcinolone was injected on both sides of the celiac artery under real time imaging with linear array endosonography.

CT-guided CPB was performed in the radiology department using a trans posterior approach with a 22-gauge, 15 cm spinal needle. The needle was inserted anterior to the aorta under CT guidance and a similar volume of bupivacaine and triamcinolone was injected.

In the group receiving EUS-guided CPB, 50% (5/10) of patients experienced decreased pain with a mean post procedure follow-up of 15 weeks.

In the group who received CT-guided CPB, 25% (2/8) experienced reduction in pain score with a mean post procedure follow-up of 4 weeks. Only 12% patients had some pain relief at 12 weeks follow-up. In summary, 75% (6/8) returned to baseline or pretreatment pain score within 6 weeks after the CT block.

Complications

EUS-CPN related common complications are due to the unopposed parasympathetic activity that develops as a result of the sympathetic blockage of the celiac plexus. Transient diarrhea, pain exacerbation, hypotension, and inebriation are the commonly reported adverse symptoms [7, 10–12]. Alvarez-Sanchez et al. reported a review of 1142 patients, which showed complications in 7% of 481 EUS CPB procedures and 21% of 661 EUS-CPN procedures [22]. Most frequent complications experienced were transient diarrhea (7% of patients) which spontaneously resolved and hypotension (4% of patients). Transient increase in pain occurred in 2% of EUS-CPB and in 4% of EUS-CPN cases.

Several major adverse events have also been reported which include infectious complications in patients with chronic pancreatitis. Therefore, antibiotic prophylaxis is recommended before EUS-CPB when steroids are used [23]. Irreversible paraparesis is one of the major adverse events reported with EUS-guided CPB with posterior approach [24]. In an RCT of EUS-CPN and EUS-CGN, the overall complication rates were similar in both groups but the overall volume of ethanol injected was significantly less in EUS-CGN [24]. Also the target was clearly visualized in EUS-CGN reducing the ischemic complication rates in that group.

Discussion/Conclusion

Abdominal pain is the most frequent presenting symptom among patients with chronic pancreatitis and/or pancreatic malignancy, often leading to a significant impairment of quality of life. Standard management of these patients involves the use of opioid analgesic medications, though its long-term efficacy is limited. CPN (ethanol) and CPB (steroid) serve as an alternative intervention for pain management in pancreatic cancer and chronic pancreatitis patients respectively, by disrupting nociceptive impulses at the level of the celiac plexus. CPN has been carried out under radiographic, fluoroscopic, CT, or EUS guidance. There is increasing evidence that EUS-guided CPN and CPB are more effective than other methods in providing persistent pain relief (for cancer and CP patients, respectively), with a similar safety profile to the other procedures (namely, CT-guided CPB). Durability of effective pain relief has been demonstrated for up to a year fol-

lowing EUS-guided CPB, although typically lasts only 2–3 months [11]. The majority of reported complications are mild (diarrhea, postural hypotension, and pain exacerbation), although severe complications can occur rarely. A preferred injection technique (single vs. bilateral) is still widely debated, as some studies have suggested higher pain relief for patients receiving a bilateral injection, while others indicate there is no difference in the outcomes between the two techniques. In conclusion, EUS-guided CPN and CPB offer a safe and effective technique to control abdominal pain in patients with pancreatic/upper abdominal malignancy and chronic pancreatitis, respectively.

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EUS-Guided Core Biopsy

8

Ali Siddiqui

Introduction

While endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has been for many years the procedure of choice to obtain samples from lesions of the gastrointestinal (GI) tract and of adjacent organs, its sensitivity is highly influenced upon the availability of rapid on-site cytopathology, which significantly influences the overall diagnostic accuracy [1–4]. However, access to on-site cytopathology and an expert cytopathologist is limited, thus [5] creating a barrier to the widespread use of EUS-FNA [6].

The ability of a tissue biopsy specimen for histologic examination by EUS-guided fine needle biopsy (EUS-FNB) in many ways overcomes the limitations of EUS-FNA. The primary advantages of a histological core specimen are:

1. Improved tissue architecture interpretation and improves diagnosis of both malignant and benign lesions.
2. Improved diagnostic accuracy.
3. Enhanced ability to perform immunostaining or advanced molecular diagnostic testing, thus allowing for targeted therapies for individualized treatment of patients with malignancies [7–9].
4. Lack of clear need for on-site cytology if core tissue is simply placed into formalin.

Fine Needle Biopsy Needles

The first needle used to perform EUS-guided biopsies was the Quick-Core (Cook Medical Inc., Bloomington, in, United States), a 19-gauge Tru-Cut biopsy needle (TCB) with a spring-loaded firing mechanism that collected an 18-mm tissue specimen for histologic analysis [10, 11]. Unfortunately, performance of EUS-TCB was disappointing with a significant variation in diagnostic accuracy (52–100%) [12, 13] and tissue yield (50–100%) [14, 15]. There was also no obvious advantage for EUS-TCB over EUS-FNA [16]. The Tru-Cut needle was also challenging to operate and cumbersome to use, thus making its widespread use limited. An additional drawback to this device was difficulty in operation when the echoendoscope was in a flexed position, making biopsies of the pancreatic head and uncinated process difficult and, in some cases, unworkable.

The newer EchoTip Procore FNB (Cook Medical) needles are available in a wide range of sizes (19, 20, 22, 25-G) and have a unique lateral opening in the distal needle shaft, presenting

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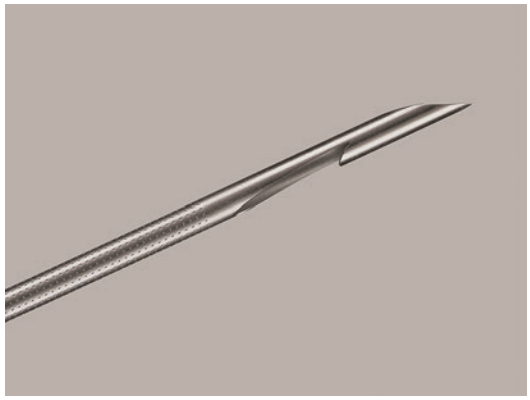

Fig. 8.1 ProCore needle tip (Permission for use granted by Cook Medical, Bloomington, Indiana)

a reverse bevel to hook and cut a core tissue (Fig. 8.1). Other FNB needles use the novel needle tip design (Sharkcore; Medtronic, Minneapolis, MN) with multiple parallel cutting surfaces at the tip and a Franseen needle tip design (Acquire, Boston Scientific, Natick, MA) (Fig. 8.2).

EUS-Guided Fine Needle Biopsy of Solid Pancreatic Lesions

Solid pancreatic lesions are the most common target for EUS-FNB, so much research has been performed to evaluate these devices in this context (Fig. 8.3).

Standard 19 Gauge Needle Aspiration Devices

In 2005 Itoi et al. reported using the standard 19-gauge needle to obtain histologic biopsy specimens in patients with solid pancreatic lesions [17]. They reported overall diagnostic accuracy of only 69%. The reason for the low diagnostic accuracy was because transduodenal biopsy of pancreatic head and uncinate process masses was unsuccessful as a result of stiffness of the 19-G needle. If the study from Itoi et al. [17] was excluded, the overall technical success and diagnostic yield to obtain histologic core tissue is above 90% in other studies [18, 19]. In a study [18] looking at patients with a pancreatic mass suspicious for autoimmune pancreatitis (AIP), adequate specimens for histologic analysis were succesfully obtained in 93% of patients. However, the diagnostic accuracy to diagnose AIP was only 43%; this was probably accounted for by the patchy distribution of histologic changes of AIP, making tissue obtained with EUS-FNB insufficient due to sample variability. There were no patients in this subset in whom a malignant etiology was not accurately excluded, making the 19-G needle 100% specific to exclude a cancer [19]. Varadarajulu et al. [20] recently looked at the new flexible 19-gauge needle (Expect™ 19 Flex, Boston Scientific) which is made of nitinol, giving it more flexibility for transduodenal puncture. The procedure was successful in all 32 patients with pancreatic lesions approached from the duodenum. Histologic core tissue to make an accurate diagnosis of cancer was obtained in 94% patients.

ProCore™ Needle

There are now multiple high quality clinical studies that have evaluated the role of the Procore needle to obtain EUS-FNB from solid pancreatic lesions. Iglesias-Garcia et al. used the 19-gauge ProCore™ needle to perform EUS-FNB of solid lesions in a large multicenter study, majority of which were pancreatic masses [21]. EUS-FNB using the ProCore™ needle was technically successful in 98% with no adverse events. Tissue deemed to be adequate for histologic examination was obtained in 90% of cases with a diagnostic accuracy was 86% for all lesions and 93% for malignant lesions. In another study evaluating the 22-gauge ProCore™ needle in 61 patients with pancreatic masses, [22] adequate tissue for histologic diagnosis (diagnostic accuracy) was obtained in 88.5%. Interestingly, a randomized trial comparing a standard 22-gauge FNA needle to the 22-gauge ProCore™ in pancreatic mass patients [23] showed no significant difference in the median number of passes required for diagnosis, rates of diagnostic accuracy, or technical failure. Histologic core to make a diagnosis was present in 66.7% of FNA specimens and 80% of FNB specimens ($P = 0.66$).

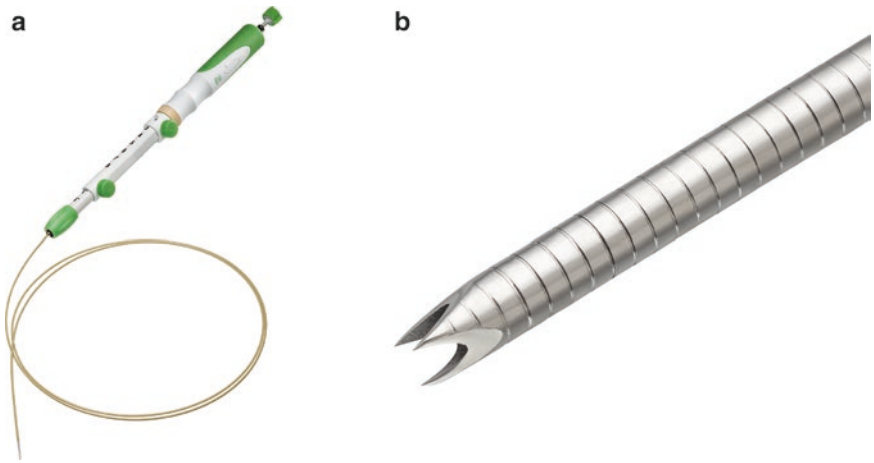

Fig. 8.2 (**a**) Handle and catheter of Acquire core biopsy needle. (**b**) Magnified image of an Acquire core biopsy needle tip (Courtesy of Boston Scientific Corporation)

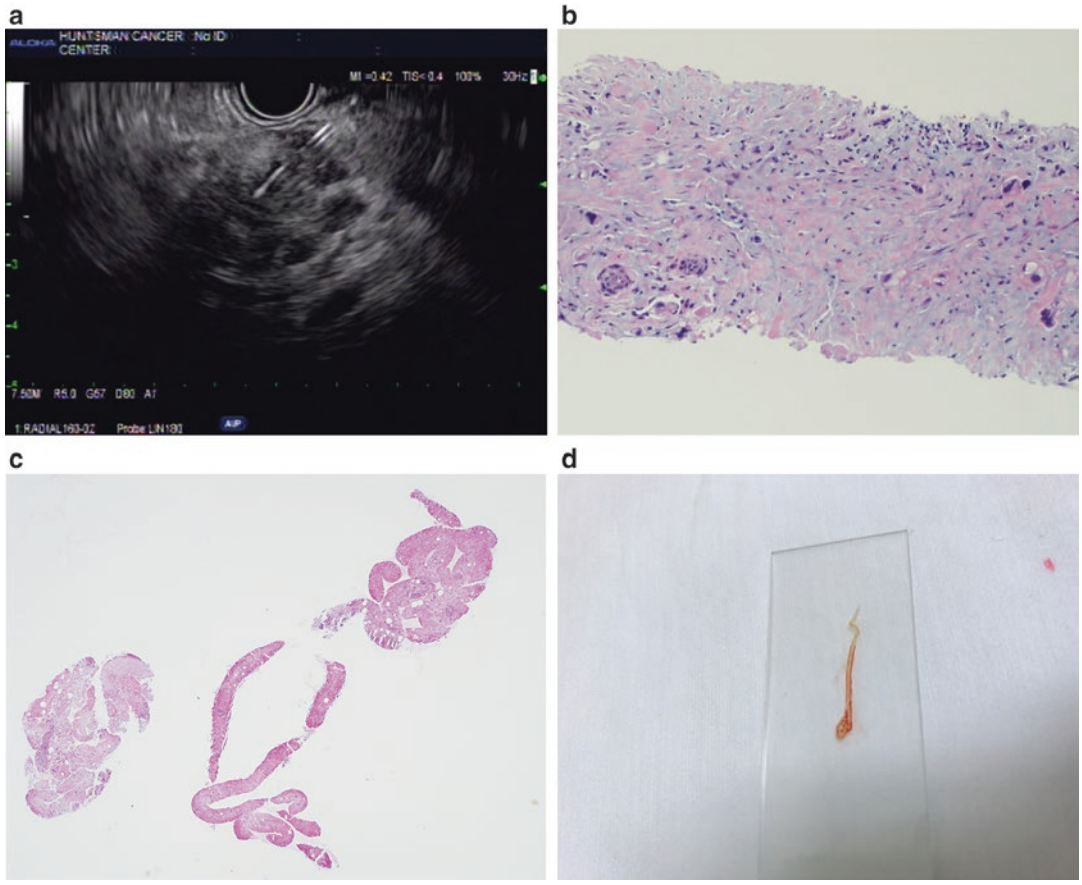

Fig. 8.3 (**a**) EUS image of a 22 gauge Acquire needle in a pancreatic mass. (**b**) Histologic specimen of a core of tissue in the patient from (**a**), showing adenocarcinoma. (**c**) Histologic specimen of a core biopsy obtained using the SharkCore needle, showing long tissue cores and malignant adenocarcinoma. (**d**) Photo of a tissue core extruded onto a glass slide from a patient with a pancreatic mass (Courtesy of Douglas G. Adler MD)

[23] Iwashita et al. [24] evaluated the use of the 25-gauge ProCore™ needle for EUS-FNB of 50 patients with solid pancreatic lesions. While the sensitivity to obtain adequate tissue for cytologic diagnosis was high (96%), the presence of a histologic core was found in only 32% of the patients. This study suggests that while the 25-gauge ProCore™ needle is excellent to diagnostic cytologic specimen, its use to obtain a tissue core biopsy specimen to make the diagnosis may be limited. Overall results with the ProCore needle are mixed with some studies showing very positive results and others with more mixed results.

SharkCore™ Needle (Video 8.1)

DiMaio et al. looked at the ability to obtain sufficient tissue for pathologic evaluation by using the 22-G and 25-G SharkCore needle in 136 solid pancreatic lesions (Fig. 8.2) [25]. The diagnostic yield to obtain adequate histological core to make a diagnosis was 85% when using the 25-G needle and 86% when using the 22-G needle. Adverse events included post-procedure pain in 5 patients, mild acute pancreatitis in 4 patients, and fever/cholangitis in one patient. 12 days after combined EUS/ERCP a pancreatic head cancer.

Kandel et al. compared the histology yield of EUS-FNB sampling using the SharkCore needle (19, 22, or 25-G) to EUS-FNA in patients who had solid pancreatic lesions. Ninety-five percent of the specimens obtained from the SharkCore needle group were of sufficient size for histologic screening, compared with only 59% from the EUS-FNA group ($P = 0.01$). The median number of passes required to achieve a sample was significantly lower in the SharkCore needle group compared with the EUS-FNA group (2 passes vs 4 passes) [26].

Another comparative study evaluating the SharkCore™ needles with the standard EUS-FNA needles by Jovani et al. showed that more histological specimens were obtained with the SharkCore™ needles compared to standard FNA needles (59 versus 5%; $P < 0.001$). However, overall diagnostic test characteristics were not significantly different (diagnostic accuracy: 92.2 versus 85.4% for SharkCore™ versus standard needles) [27].

Nayar et al. compared the diagnostic performance and yield for tissue acquisition from solid pancreatic lesions of the ProCore and SharkCore needles. In this single-center study, the SharkCore™ afforded substantially superior tissue yield and diagnostic performance compared with ProCore™ [28].

All these studies suggest that the SharkCore™ needle allows for adequate specimen collection in order to obtain a diagnosis in solid pancreatic lesions. It is also useful to obtain a tissue core biopsy specimen to make the diagnosis in 50–90% of cases.

Acquire™ Needle

Mitri et al. assessed the safety, histological sample procurement yield, and diagnostic accuracy of a newly available Acquire™ (Boston Scientific) histology needle for pancreatic lesions [29] A mean of 2.8 needle passes per lesion site were performed, without any major complication. A tissue core biopsy sample for histological evaluation was obtained in 93% cases. Considering malignant versus nonmalignant disease, sensitivity and specificity were 98.2% and 100%, respectively. EUS-FNB using the 22-gauge Acquire™ needle was able to reach a very high procurement yield and diagnostic accuracy.

EUS-Guided Fine Needle Biopsy of Gastrointestinal Subepithelial Tumors

After pancreatic masses, subepithelial lesions are among the most common targets for EUS-guided core needle biopsy (Fig. 8.4).

Lee et al. looked at the tissue acquisition and diagnostic yield of EUS-FNB for gastric subepitheal tumors greater than 2 cm in size. They used the ProCore™ 22-gauge needle in this study and performed EUS-FNB in 78 patients. The authors found that EUS-FNB was diagnostic in 82% of patients, and tissue of histologic evaluation was obtained in 97% of cases. An important observation found was that FNB specimens permitted immunostaining for the diagnosis of gastrointes-

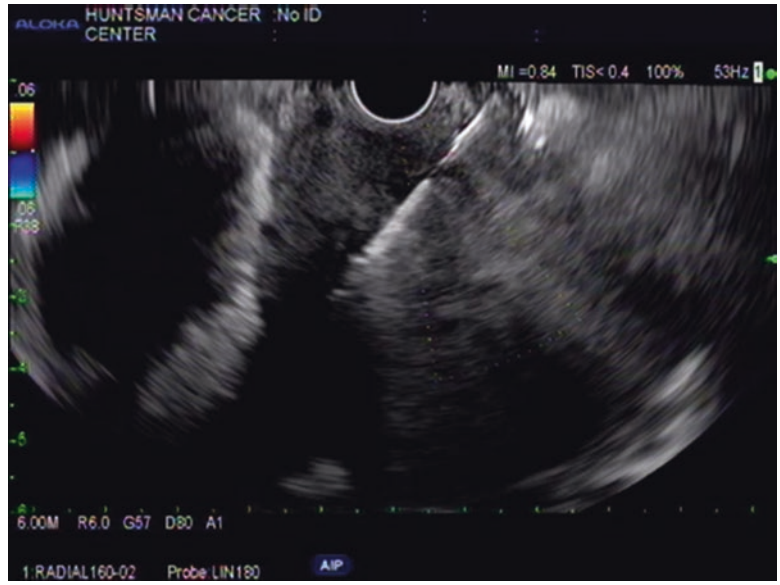

Fig. 8.4 EUS image of a 22 gauge Acquire needle being used to obtain a core of tissue from a large subepithelial lesion. The pathology revealed a gastrointestinal stromal tumor (Courtesy of Douglas G. Adler MD)

tinal stromal tumors 48%, a capability that is rarely possible when tissue is obtained using standard EUS-FNA needles. There was only a single case of self-limited post-procedural bleeding [30].

El Chafic et al. perfomed a large retrospective study [31] evaluating patients suspected GI stromal tumors greater than 2 cm that underwent EUS-FNA (n = 91) or EUS-FNB using the SharkCore needle (n = 15). The needle size at was used most often was 22 gauge in both groups. Adequate tissue was procured, allowing immunohistochemical staining in 65% patients in the FNA group and 100% patients in the SharkCore group. A diagnosis was reached by immunohistochemical staining in 53% patients in the FNA group and 87% patients in the SharkCore group. Tissue was insufficient to make a cytologic diagnosis in 24% patients in the FNA group compared with none in the FNB group. There were no reported immediate adverse events or technical difficulties in either group. The authors concluded that EUS-FNB by using a SharkCore needle for suspected GI stromal tumors is technically similar and equally safe as FNA, with better tissue acquisition, which was achieved with fewer needle passes and an improved diagnostic yield by immunohistochemical staining.

EUS-Guided Fine Needle Biopsy of Lymphadenopathy

Adequate tissue acquisition from lymph nodes using standard EUS-FNA needles can be challenging. Lymphoproliferative disorders often require histologic specimens in order to obtain architecture and allow performance of flow cytometry. Although FNA specimens have a high yield for metastatic lesions, FNA is not ideal for hematologic malignancy. Core biopsies of nodes are often preferable (Fig. 8.5). Two studies in which FNB with Tru-cut sampling was performed for enlarged lymph nodes produced diagnostic yields ranging from 69% to 73% [15, 32].

There continues to be limited data on the role of the newer EUS-FNB needles for the diagnosis of lymphadenopathy of unknown etiology. In a randomized study comparing conventional needle fine needle aspiration to ProCore biopsy needle. In patients with mediastinal lymphadenopathy [33], the diagnostic sensitivity of aspirated material obtained using EUS-FNA needle and ProCore needle were comparable (69% vs 79% respectively; $P > 0.05$). In another multicenter, randomized trial, Nagula et al. [33] compared EUS-FNA and EUS-FNB for tissue sampling of 135 solid lesions, 46 of which were enlarged lymph nodes adjacent to the GI tract. This study found that

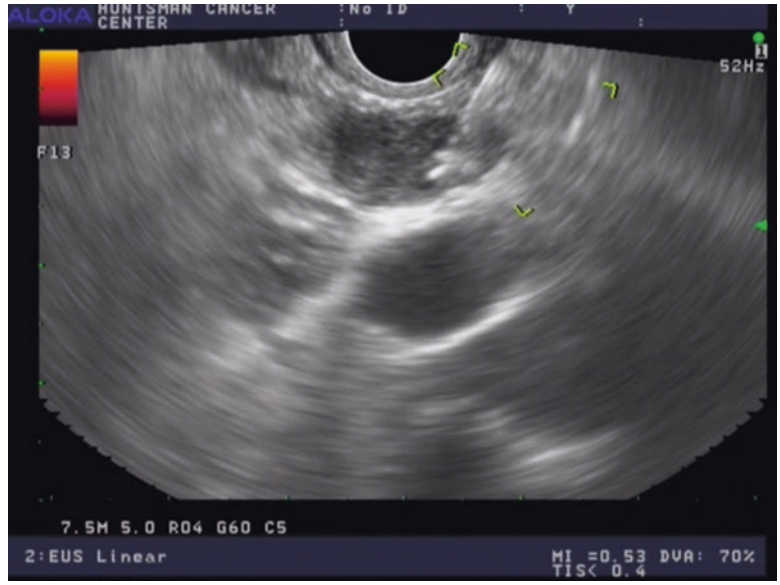

Fig. 8.5 EUS image of a 22 gauge Procore needle being used to obtain a core of tissue from a mediastinal lymph node (Courtesy of Douglas G. Adler MD)

there was no difference between FNA and FNB when stratified by the presence of on-site cytopathology or by type of lesion sampled. A median of 1 needle pass was needed to obtain a diagnostic sample for both needles. FNA and FNB obtained a similar diagnostic yield with a comparable number of needle passes. This studied argued against routine use of FNB for lymph node biopsy [34].

There continues to be controversy about when EUS-FNB is superior to EUS-FNA for the diagnosis of malignancy in patients with lymphadenopathy. In cases when a lymphoproliferative disorder is suspected, this author would recommend EUS-FNB so as to allow acquisition of tissue architecture and allow immunostaining to be performed.

EUS-Guided Fine Needle Biopsy of the Liver

Liver biopsy is not only used to determine the underlying etiology of liver disease but also to evaluate the extent of liver damage, both of which are essential in determining how such patients are treated.

There is now increasing data to demonstrate that EUS-guided liver biopsy (EUS-LB) is an alternative means for safe and accurate liver tissue acquisition for focal and parenchymal disease (Fig. 8.6). It should be noted that due to anatomy, the left lobe of the liver is easily accessible for EUS-LB from the stomach, while the right lobe needs to be assessed from the duodenum.

EUS-Guided Tru-Cut Biopsy

EUS-guided Tru-Cut biopsy uses the spring-loaded Quick-Core needle (Cook Medical, Bloomington, IN, USA) in order to obtain a tissue sample (Quick-Core, Cook Medical, Bloomington, IN, USA). This is a 19-gauge needle capable of collecting an 18-mm tissue specimen sufficient for histologic examination. Initial trails using the Quick-Core needle demonstrated its safety and efficiacy in acquiring liver tissue in a pig model [10] which then prompted its use in humans.

The initial human study evaluating the use of EUS-guided Tru-Cut biopsy in benign liver disease was performed by Dewitt et al where they adequate liver tissue to make a histologic diagnosis was obtained in 19/21 (90%) patients [35]. No adverse events occurred. While the specimen mean length was 9 mm, the size of the samples obtained was smaller than those usually consid-

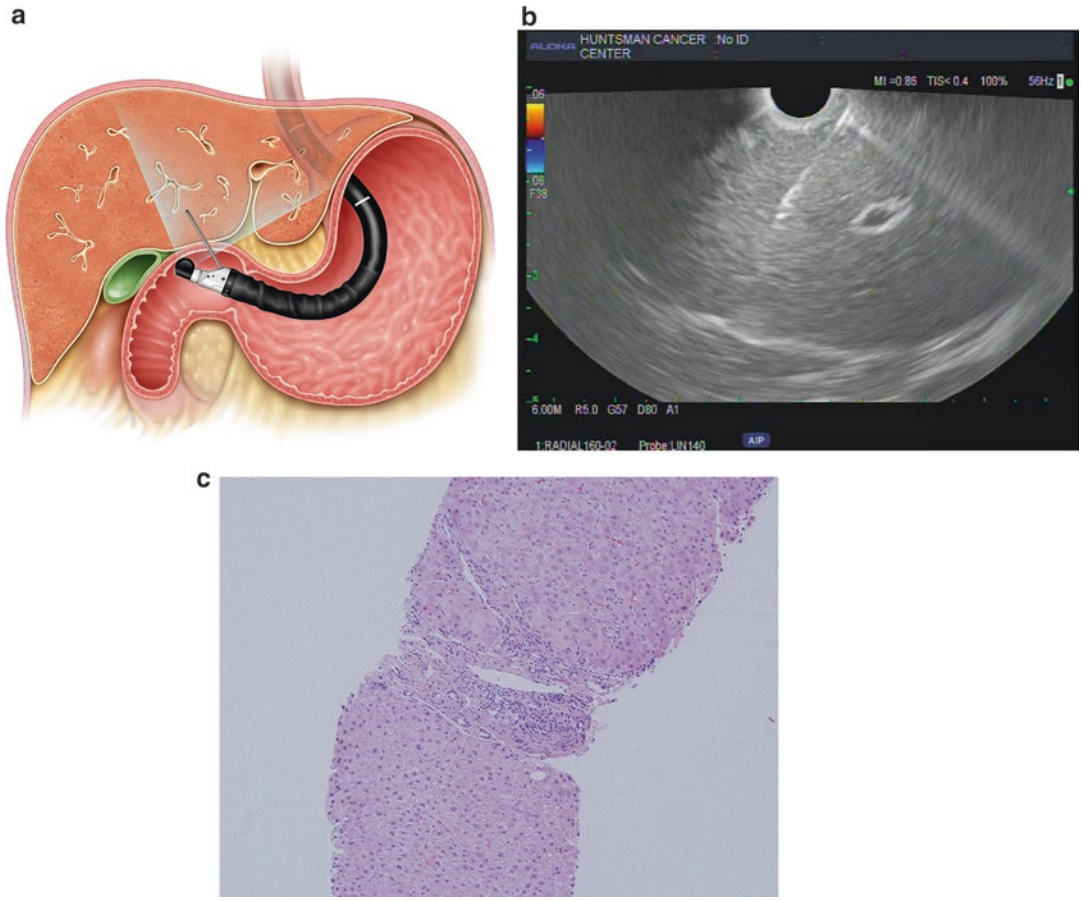

Fig. 8.6 (**a**) Diagram showing EUS-guided liver biopsy of the right lobe of the liver from the duodenal bulb. (**b**) EUS image of a 22 gauge core biopsy needle in the left lobe of liver after a transgastric passage (Courtesy of Douglas G. Adler MD) (**c**) Liver transgastric biopsy on H + E stain: High power view revealing occasional swollen/ballooned hepatocytes consistent with mild steatohepatitis. There is also mild to moderate inflammatory cell infiltrates (lymphocytes) in areas of scar. Portal tracts appear intact with surrounding inflammatory cells (Courtesy of Douglas G. Adler MD and Nicole Girard MD)

ered adequate for histologic assessment. Gleeson et al. utilized Tru-Cut EUS-LB to evaluate the number of liver portal triads obtained in 9 patients undergoing liver ibopsy [35]. This study obtained adequate diagnostic tissue in all nine cases, with a total of 63 portal triads.

While initial studies with Tru-Cut needle appeared promising, this needle is technically more challenging to use compared to conventional EUS-FNA. This is especially true when EUS-LB is performed with the echoendoscope in a long position, i.e. in the duodenum. These reasons accounted for the significant variability seen in studies evaluating the Tru-Cut technique for EUS-LB and failure to obtain tissue on many occasions [35–37]. Hence, the Tru-Cut never reached widespread acceptance and use among endosonographers, leading to the use of alternative needle types to obtain EUS-LB.

EUS-Guided Fine Needle Biopsy with a 19-Gauge Needle to Obtain Histological Tissue in Patients with Benign Liver Disease

The first study to evaluate the use of EUS-LB using the standard 19-gauge FNA needle was

performed by Stavropoulos et al. [38] The 22 patients in this study underwent EUS for elevated liver function tests of unknown etiology, and EUS-LB of the left liver was done when no evidence of biliary obstruction was seen. Results of EUS-LB using the 19-gauge FNA were the following: median specimen length = 37 mm, nine complete portal triads, and diagnostic adequacy = 91%. No procedure related adverse events were seen.

In a large multi-center study, Diehl et al evaluated 110 patients with elevated liver enzymes who underwent EUS-LB [39]. These investigators used suction on the needle in most cases, and then performed up to 10 to-and-fro needle movements per pass to obtain adequate tissue. The diagnostic yield to obtain adequate tissue for diagnosis was 89% with a median core length of 38 mm a median of 14 complete portal triads. In this study, there was one bleeding adverse event that led to a subcapsular hematoma; this patient was treated conservatively and did well.

The above studies confirmed that EUS-LB using a 19-gauge FNA needle is safe, effective, and allows for a high diagnostic yield and specimen adequacy. The use of the 19-gauge FNA needle has been demonstrated to be easier to use and possibly yield better liver core tissue compared to the Tru-Cut needle.

EUS-FNB for Malignant Liver Lesions

EUS-LB allows us to obtain a histological biopsy of malignant liver lesion(s) seen on cross-sectional imaging modalities (with the exception of the right posterior segments), thus allowing confirmation of suspected malignant or metastatic lesions [40]. While several large trials have confirmed the efficacy and safety of using EUS-FNA cytological aspiration to diagnose hepatocellular carcinoma and liver metastasis, [41, 42], there is currently very limited data on the use of EUS-LB in such lesions.

Lee et al. evaluated 21 patients that underwent EUS-LB using a EUS 22-Gauge core biopsy needle in patients who failed percutaneous liver biopsy [43]. Adequate tissue to obtain a histological diagnosis of malignancy was obtained in 19 patients (91%). The overall diagnostic accuracy for malignancy and specific tumor type were 90.5% and 85.7%, respectively. No complications were seen when the EUS core biopsy needle was used. The authors concluded that EUS-FNB with core biopsy needle for solid liver masses may be helpful in the management of patients who are unable to be diagnosed using percutaneous liver biopsy.

EUS-LBs allows an effective and targeted approach for liver biospy, particularly for focal lesions. Use of the 19-G standard needle or the newer EUS core-biopsy needs may also provide a higher yield as compared to the standard EUS-FNA needles. Advantages of EUS-LB include performing bilobar liver biopsy to increase diagnostic accuracy in parenchymal disease and the ability to accurately target and biopsy focal liver masses.

Conclusion

Overall, the ability of EUS to obtain core tissue specimens from primary tumors, lymph nodes, the liver, and metastases makes these devices invaluable in the era of modern, interventional EUS. Ongoing studies will further clarify ideal needle types and sizes for different indications and target locations.

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9 Endoscopic Ultrasound-Guided Liver Biopsy

David L. Diehl

There remains an important role for liver biopsy in the current management of liver diseases despite advancements in noninvasive hepatic assessment [1, 2]. Historically, large gauge (typically 15–16 gauge, G) biopsy needles were used to obtain a biopsy after localization of a target site by percussion of the liver span [3]. Risk of inadvertent puncture of the pleural space or gallbladder led to increasing use of transcutaneous ultrasound-guided biopsy site selection. Because on-site ultrasound machines may not be widely available in the endoscopy unit or GI/Hepatology Clinic, much of the liver biopsy case load was moved to the general or interventional radiology department. With decreasing case volumes, most hepatologists and gastroenterologists got out of the business of liver biopsy. GI fellowships also dropped the requirement of training in percutaneous liver biopsy, leading to even fewer nonradiologists doing this procedure.

Other Methods for Liver Biopsy

Development of transjugular access to the hepatic venous system and liver led to a safer option for liver biopsy in patients with coagulopathy or ascites [4–6]. Using the same approach, it became possible to measure portal pressures ("portal package"), and rapidly led to the development of transjugular intrahepatic portosystemic shunt (TIPS) for the management of the complications of portal hypertension [7].

The development of endoscopic ultrasound quickly led to refinement of the technology to allow real-time fine needle biopsy of various lesions around the esophagus, stomach, and duodenum. Fine needle aspiration of focal liver lesions was found to be safe [8, 9] but the use of EUS to obtain core biopsy of liver parenchyma occurred later, with the adaptation of a Tru-Cut needle (Fig. 9.1) that could be used through the echoendoscope (QuickCore, Cook Medical, Winston Salem, NC). The first report of use of the EUS-guided Tru-Cut needle for parenchymal liver biopsy was published in 2007 [10]. Several case series were subsequently reported with this needle [11–13]. However, the device was somewhat technically difficult to use, and did not reliably deliver liver core biopsy samples. As a result, this needle never saw widespread adoption, and the use of this device was essentially abandoned.

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Fig. 9.1 This close-up view of the Tru-Cut needle shows a "tissue tray" (left); a cutting sheath cuts a core of tissue upon deployment (right) (Image used with the permission of Allan Darr, ProAct Ltd.)

The first published experience of use of a regular EUS-FNA needle for liver biopsy was described by Stavropoulos et al. [14]. In this seminal prospective case series, 22 patients underwent liver biopsy of the left hepatic lobe through a transgastric route with a regular 19G EUS needle (EchoTip, Cook Medical, Bloomington, IN). Adequate tissue yield was obtained in 20/22, with median specimen length of 36.9 mm (range 2–185 mm) and median portal triad counts of 9 (range 1–73 CPTs). Extending this pilot data, Diehl et al. conducted a multicenter study of EUS-LB in 110 patients at 8 centers. Tissue yields were excellent, with adequate specimen lengths and portal counts [15].

Comparison of tissue yields between percutaneous, transjugular, and EUS-guided routes was carried out by Pineda et al. [16]. In this study, 19G EUS-FNA needles were used by the endosonographer, and 18G or 20G needles used by interventional radiologist. Only non-cirrhotic patients were included from the transjugular liver biopsy group, as cirrhosis leads to more specimen fragmentation and could adversely affect measurements. For total aggregate specimen lengths, lengths of longest piece, and portal counts, it was found that specimen yields were comparable between the three methods, and in fact trended to higher for EUS-LB due to ease of performing multiple needle passes (Fig. 9.2).

Indications and Contraindications

Indications for EUS-LB are broadly any patient who needs a liver biopsy and does not require a transjugular approach, most commonly in patients with abnormal liver function tests of unclear etiology. If the patient requires an endoscopy (e.g., rule out varices, Barrett's surveillance or detection, and evaluation of upper GI symptoms) or an EUS (evaluation of the common bile duct, gallbladder, pancreas, or other EUS indication) in addition to a liver biopsy, then EUS-LB is the most efficient means to accomplish the testing that is required. It has previously been shown that endoscopy and percutaneous liver biopsy done on the same day is safe [17]. EUS-LB is safer for liver sampling than percutaneous biopsy due to continuous real-time imaging of the needle. Some patients require a sedated liver biopsy, for example, the patients with a great deal of anxiety regarding the procedure, or for some children undergoing liver biopsy [18], and sedated EUS-LB an excellent approach in these cases.

Situations where EUS-guided liver biopsy may not be ideal include significant coagulopathy and/or the use of anticoagulants, while ascites is a relative contraindication based on its location [1, 3]. The transjugular approach is preferred in these situations.

EUS-LB Technique (Video 9.1)

Identification of Liver Lobes

EUS-LB is performed with the curvilinear echoendoscope, which allows real-time monitoring of needle entry into the liver. A distinct advantage of EUS-LB is the ability to target spatially distinct parts of the liver (left and right lobes)

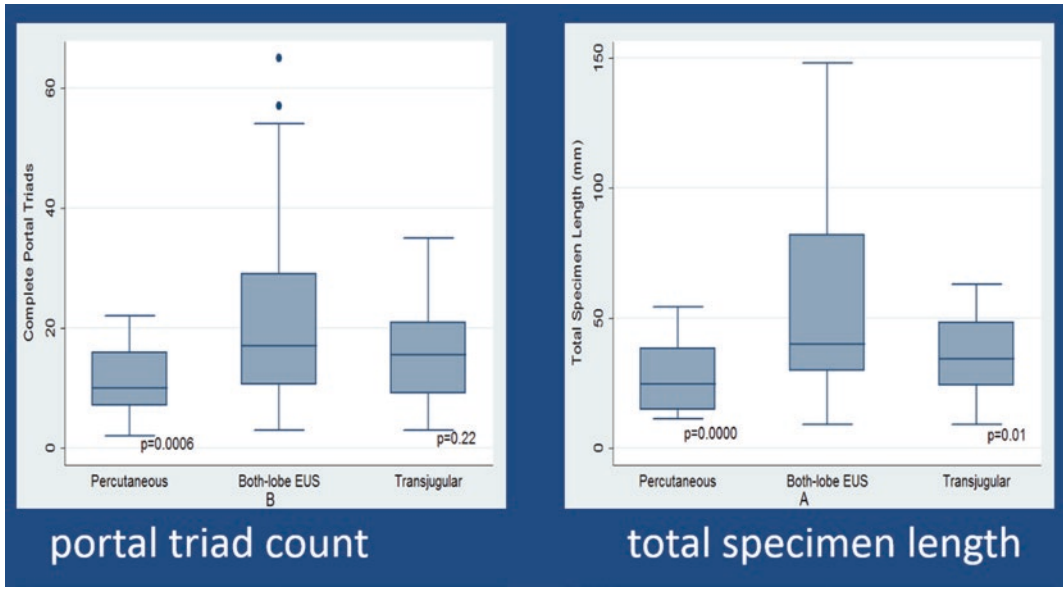

Fig. 9.2 When compared to percutaneous (left bars) and transjugular (right bars) liver biopsy, bilobar EUS-LB (center bar) gives comparable or superior samples in terms of portal triad count and total specimen length

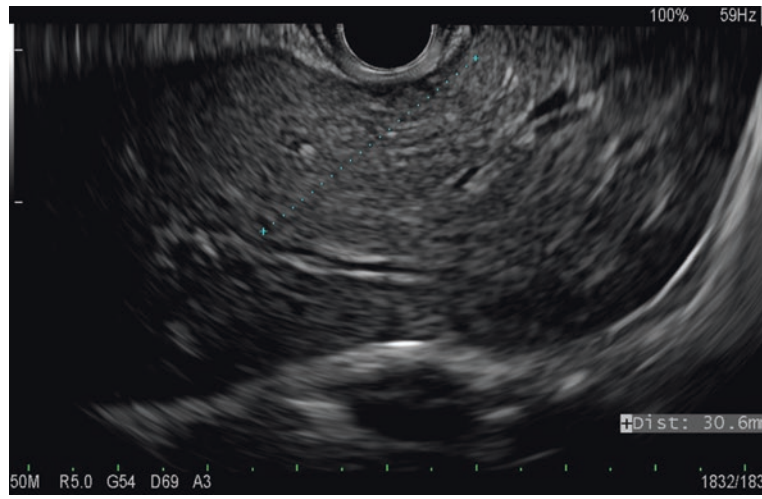

Fig. 9.3 Visualization of the left hepatic lobe from the proximal stomach; the cursor shows the expected trajectory of the biopsy needle when obtaining the core specimen

[19]. The left lobe is found by identifying the liver from the proximal stomach (Fig. 9.3). It is important to positively identify liver and distinguish it from the spleen, which is found in a similar location and may be enlarged in patients with portal hypertension. In some cases, the echotexture of the liver can be very similar to the spleen (Video 9.1) which can lead to confusion. The two organs can be distinguished by either identification of portal vein branches in the liver or tracing hepatic veins to the IVC. This confirmation will allow avoidance of inadvertent splenic puncture.

The right hepatic lobe is found by placing the tip of the EUS scope in the duodenal bulb and torqueing until the large mass of the right lobe is identified (Fig. 9.4). Gallbladder (if present) may be seen from this duodenal position.

The presence of larger vessels in the hepatic parenchyma is expected, and as a rule, direct

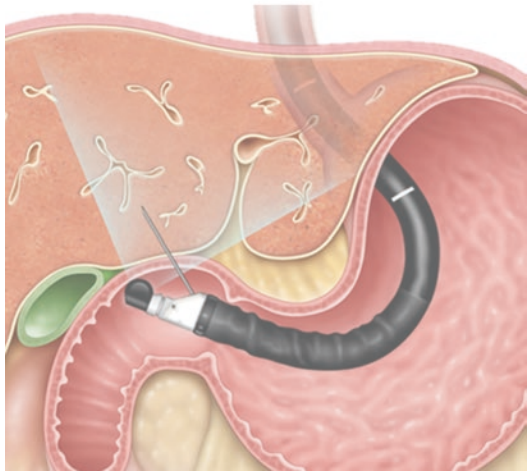

Fig. 9.4 Right lobe biopsies are obtained with the echoendoscope tip placed in the duodenal bulb (Image adapted from Boston Scientific)

puncture of these vessels should be avoided. A reasonable trajectory length without intervening vessels is identified for needle puncture. This is typically approximately 2.5–3 cm, although a slightly longer trajectory can often be found.

One of the distinct advantages of EUS-LB compared to other liver biopsy techniques is the ability to sample spatially distinct areas of liver. Some parenchymal liver diseases may have different lobar distributions [20], and bilobar biopsy can minimize sampling error. Bilobar biopsy, with 1 or 2 passes per lobe, is very safe, and does not lead to increased risk of complications.

Needle Selection

Most of the studies on EUS-LB have utilized 19G needles. A 19G spring-loaded EUS Tru-Cut needle (QuickCore, Cook) was previously used, but disappointing tissue yields and cumbersome operation led to this needle falling out of favor [21]. The seminal study of Stavropoulos [14] proved that a regular 19G needle is adequate in delivering liver cores. More recently, "core needles" with special cutting tips have become available and appear to be preferred for EUS-LB (Fig. 9.5a, b).

Ex vivo liver biopsy studies have been done to try to determine the optimal needle gauge and tip characteristics to optimize tissue yield. In one study, a core biopsy needle (SharkCore 19G, Medtronic) was found to give the highest tissue yields in terms of increased mean portal tracts [22]. Preliminary experience with a 19G core needle (Acquire 19G, Boston Scientific) has suggested that specimen lengths are longer with the core type needle than regular beveled needle [23].

We have completed a prospective randomized study of the standard 19G FNA needle that we have used for EUS-LB (19G Expect Flexible, Boston Scientific) to the 19G Acquire core biopsy needle. In a pilot group of patients randomized to either needle, there were increased tissue yields and higher portal tract counts in the core needle grout [24]. Importantly, in this group there was also an increased "length of longest piece," a critical metric for assessing quality of the liver biopsy.

A natural question is whether a 22G core needle could be used to obtain adequate liver biopsy cores. We recently conducted a prospective randomized study of the 22G SharkCore FNB needle for EUS-LB compared to a standard 19G needle [25]. We found that adequate liver biopsy specimens were obtained in 90% of cases with the 19G needle compared to only 60% with the 22G SharkCore needle. This appeared to be due to increased tissue fragmentation during histologic processing, even though before processing, liver cores of reasonable length were obtained (Fig. 9.6). We concluded that the 19G FNA needle was more reliable for EUS-LB. With the promising results from use of 19G core needles, excellent safety profile, and higher likelihood of delivering an adequate specimen, these needles are likely to become the standard needle for EUS-LB.

Needle Preparation and Amount of Suction

Full or "slow-pull" suction (wherein the stylet is slowly removed during needle actuations in the liver) can be used for EUS-LB. Most published

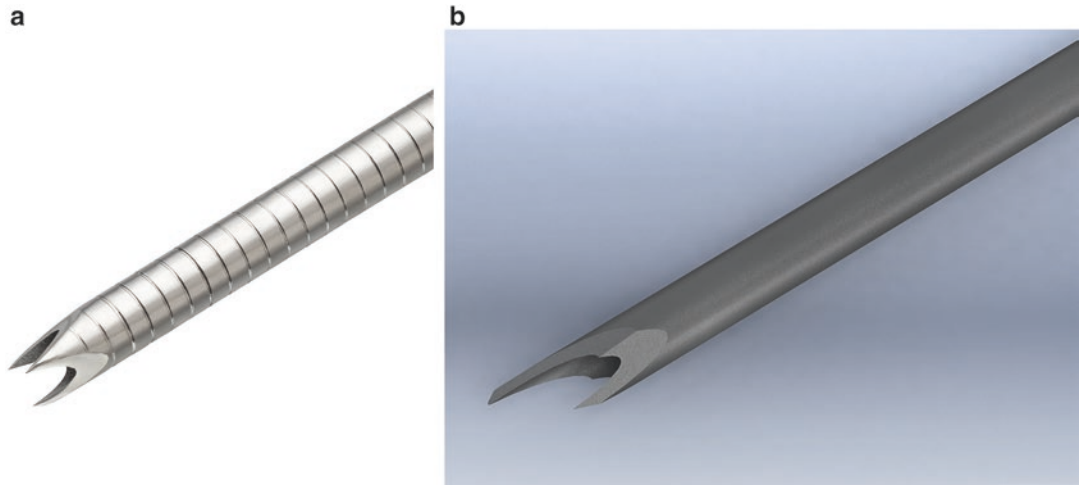

Fig. 9.5 Close-up of the tips of the core needles used for EUS-LB: (**a**) Acquire needle, Boston Scientific (used with the permission from Boston Scientific), and (**b**) SharkCore needle, Medtronic (used with the permission from Medtronic)

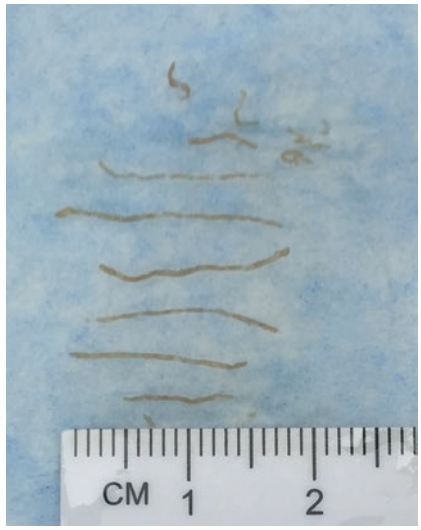

Fig. 9.6 Prefixation tissue cores obtained with a 22G SharkCore needle

cases utilize the high suction achieved with the vacuum syringe included with the EUS needles (20 cc VacLok, Merit EndoTek, Salt Lake City, UT). For slow-pull technique, the stylet is pulled slowly as the needle is advanced into the target lesion or organ. This has been demonstrated to deliver about 2–3 mL of vacuum [26].

"Dry suction" and "wet suction" have both been used for EUS-LB. For wet suction, the stylet is removed and the needle lumen primed with saline [27, 28]. In the past 2 years, we have primed the needle with a heparin flush instead of saline. This had led to good biopsy yields and no ill effect on liver histology [29]. The heparin leads to less clotting of blood in the needle, which can lead to a less bloody tissue specimen. This in turn leads to easier tissue handling by the pathology laboratory. In addition, stylet reinsertion is considerably easier for the endoscopy assistant.

Needle Technique

In the chosen lobe, a trajectory for needle passage is identified that does not include larger hepatic or portal vein branches. The longest trajectory of needle travel is sought, which is typically about 3–4 cm (Fig. 9.7). We have found advantage to having the endoscopy assistant hold the echoendoscope at the level of the bite block, which prevents "recoiling" of the echoendoscope backward during the needle throw, while still allowing torqueing of the scope to maintain needle visualization. After a suitable trajectory is defined, the luminal wall is punctured, and the needle positioned in the liver parenchyma.

At this point, the stopcock on the suction syringe is turned to "on." To-and-fro actuations of the needle are made into the liver, while "fanning" the needle trajectory in the same manner as is done

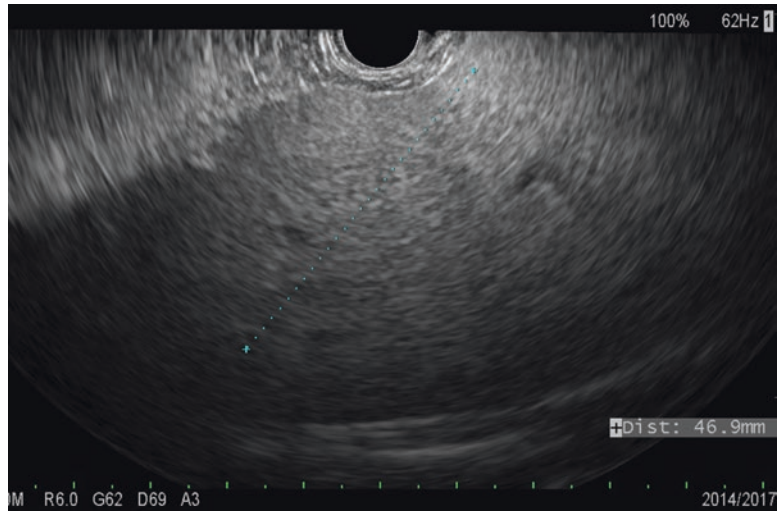

Fig. 9.7 EUS imaging of the right hepatic lobe with a long (46.9 mm) needle trajectory

for FNA of masses. The fanning is accomplished with both use of the echoendoscope elevator and the up-down wheel of the scope handle. The number of passes can be 1–10 depending on endosonographer preference; we are currently using 1–3 passes. The stopcock on the vacuum syringe is turned off prior to removing the needle from the parenchyma. The needle is then removed from the echoendoscope. A variation is the use of wet suction while making a single long pass into the liver [30]. If the slow-pull technique is being used, the assistant pulls back on the stylet as the endosonographer makes a needle pass into the liver.

Specimen Handling in the Endoscopy Suite and the Pathology Laboratory

The contents of the needle are expressed directly into a formalin cup by either stylet reinsertion, or flushing the contents with saline or the heparin flush. Most if not all the specimen will be in the needle lumen, although if blood has entered the vacuum syringe, tissue can be found there as well. It is important to avoid excessive handling of the specimen, including expressing the tissue onto gauze or a telfa pad.

For the last 2 years, we have utilized a "tissue sieve" to separate tissue from blood (Fig. 9.8). Heparinization of the needle tends to prevent formation of blood clots in the needle, which can be visualized as "blood noodles" in the formalin. When using the tissue filter, the needle contents are expressed first onto the sieve. Blood generally does not clot with the heparin priming, and the specimen is washed off using a light rinse with saline, which leaves only (or mainly) liver tissue on the sieve. This tissue is then floated off into the formalin (Fig. 9.9).

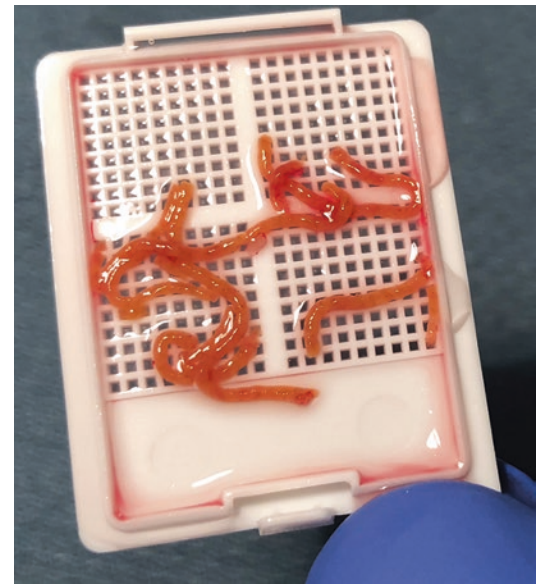

Fig. 9.8 Liver tissue is captured on a microsieve and blood is washed away

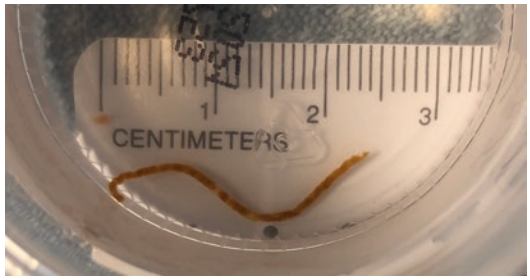

Fig. 9.9 Long liver core is floated off the microsieve into formalin jar without excessive handling

Considerations for the Pathologist

The surgical pathology receiving laboratory is typically used to handling small specimens. It is highly recommended to discuss EUS-LB with the pathologist, to ensure optimal handling. For liver cores, like other small specimens, excessive handling should be avoided to limit artifactual fragmentation of the specimen. Advances and refinements in biopsy technique and needle technology will continue to yield better (i.e., less fragmented) specimens for histological interpretation, which will make the pathologist's job easier (Figs. 9.10 and 9.11) [31–34].

The advantage of the sieve and washing step described above is the delivery to the pathology laboratory of an enriched liver specimen with little or no blood. This greatly simplifies handling of the specimen by the pathology technicians because they do not have to manually separate the blood and tissue. Blood and tissue processed together (i.e., no tissue and clot manual separation step) makes it more difficult to interpret the liver biopsy specimen (Fig. 9.12).

Standard adequacy metrics that have been used in the published literature include measures of specimen length and number of portal structures. Initially, measurement of "complete portal triads" was reported (defined as portal structures with an identifiable artery, vein, and bile duct). A recent study quantified "complete" and "incomplete" portal structures [35]. Other pathologists may describe portal triads in terms of how much liver parenchyma is visible around them (e.g., less than or more than 180°) (Fig. 9.13a, b).

The liver biopsy literature cites a wide range of "minimal number" of complete portal triads that should be obtained, typically from 6 to 10. There is no rigorously demonstrated number. However, interpretation of liver biopsies has an important *qualitative* aspect, rather than purely quantitative. A fewer number of portal structures with a lot of liver parenchyma around them are more useful for interpretation than numerically more but incomplete portal structures, which may be at the edge of the liver core.

The earlier studies on EUS-LB measured aggregate specimen length. However, the metric that we feel to be most relevant is "length of the longest piece" (LLP). Highly fragmented cores are harder to interpret, particularly for evaluation of fibrosis such as in the cases of early cirrhosis. Liver disease itself can contribute to biopsy fragmentation, of course. But, routine specimen processing contributes to fragmentation [25] which is more marked with smaller gauge biopsy needles.

Over the past 2 decades, pathologists have become more expert at rendering diagnoses with smaller and smaller amounts of tissue. However, longer cores make the job of liver biopsy interpretation significantly easier than trying to "read the tea leaves" that a highly fragmented specimen presents. Based on the early reports and trends utilizing newer needle technologies, it seems likely that the 19G core needles will be favored for EUS-LB because of their ability to deliver longer cores with less fragmentation than non-core needles. Development of a reliable Tru-Cut needle that can be used for EUS-LB may also prove useful.

Post-Procedure Recovery After EUS-LB

Self-limited pain after percutaneous large gauge liver biopsy is common, has been described in at least 80% of patients [36, 37]. More severe pain is seen in a smaller number [38]. It is possible that there is less pain after EUS-LB due to the ability of the real-time ultrasound to allow avoid-

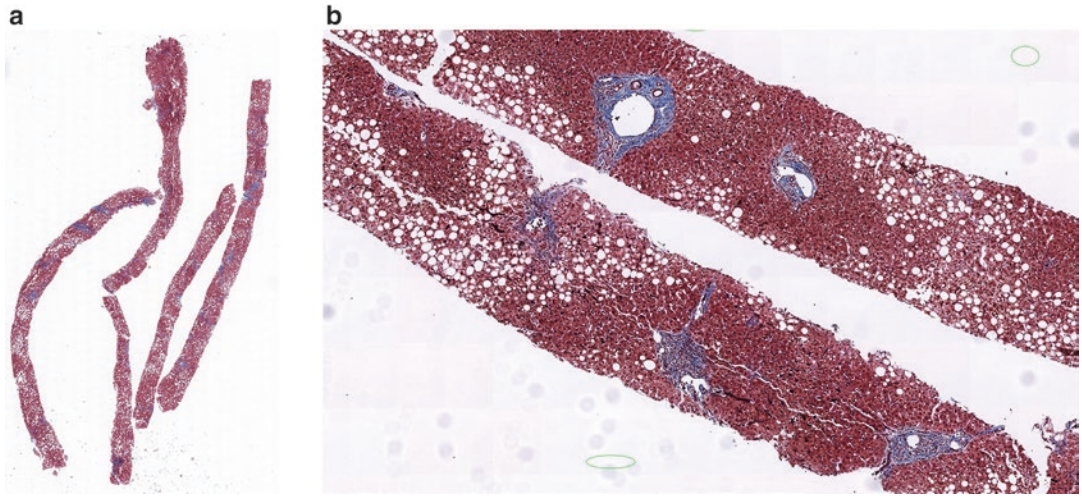

Fig. 9.10 Good liver cores demonstrated on glass slide after processing (**a**) low power and (**b**) medium power (trichrome stain)

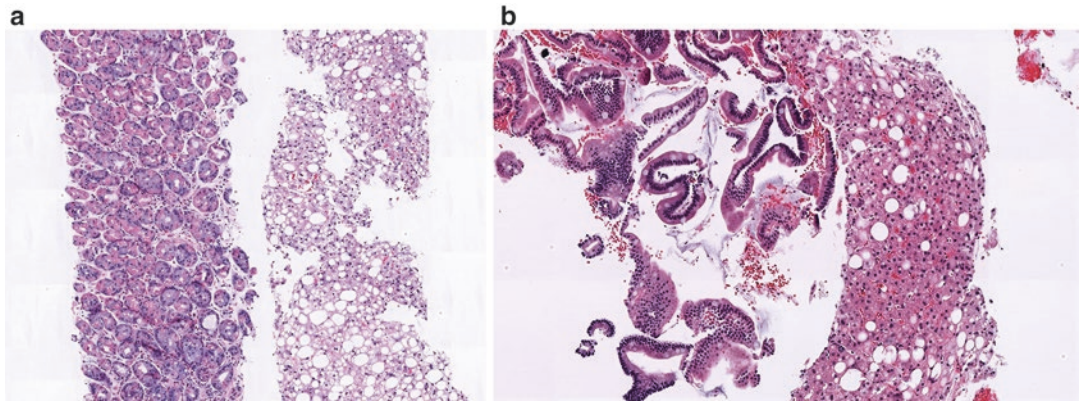

Fig. 9.11 A small fragment of gastric (**a**) or duodenal (**b**) mucosa indicates if the biopsy was transgastric or transduodenal

ance of intervening vasculature as well as the ability to use smaller gauge needles.

A common practice after percutaneous liver biopsy is to have the patient lie on their right side for 2–4 h after the biopsy, presumably because this offers "tamponade" of the peritoneal membrane to the liver capsule at the site of puncture. There is little or no available literature on the advantage of this practice. With EUS-LB, there is no opportunity to obtain "tamponade," since the point of puncture is not adjacent to the abdominal wall. In our practice, we have the patients recover in a supine position, like every other endoscopic procedure. Increased risk of bleeding after EUS-LB has not been demonstrated, even with bilobar biopsy.

We reviewed recovery data on 124 patients who underwent EUS-LB by 2 practitioners [39]. One used a 1-h recovery period and the other a 2-h recovery time. About 30% of patients experienced pain after the procedure; it was easily controlled by a small dose of IV pain medication given after they arrived in the recovery room. The vast majority (92%) were pain free by 1 h, and the other 3 (8%) had pain that resolved within 2 h. These findings would indicate that a 1-h recov-

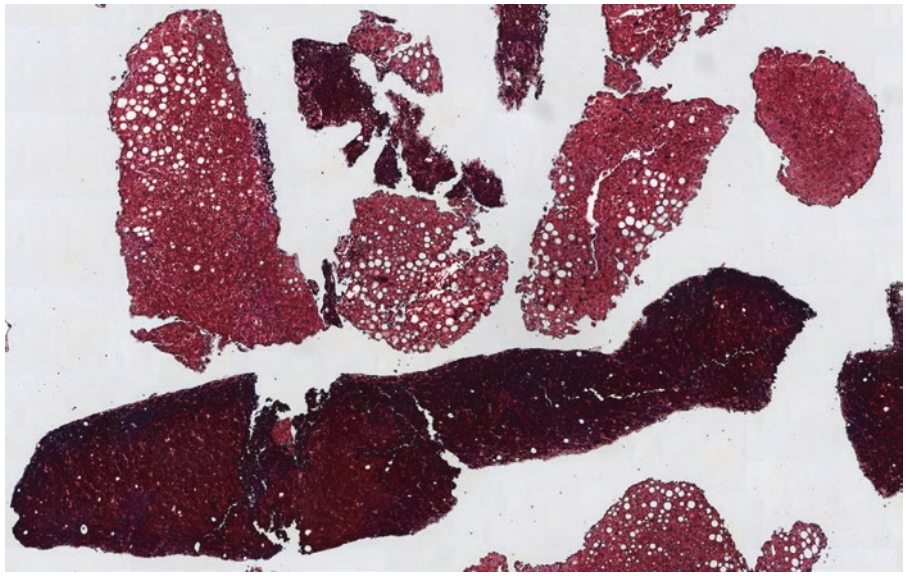

Fig. 9.12 Highly fragmented liver biopsy specimen with blood clots

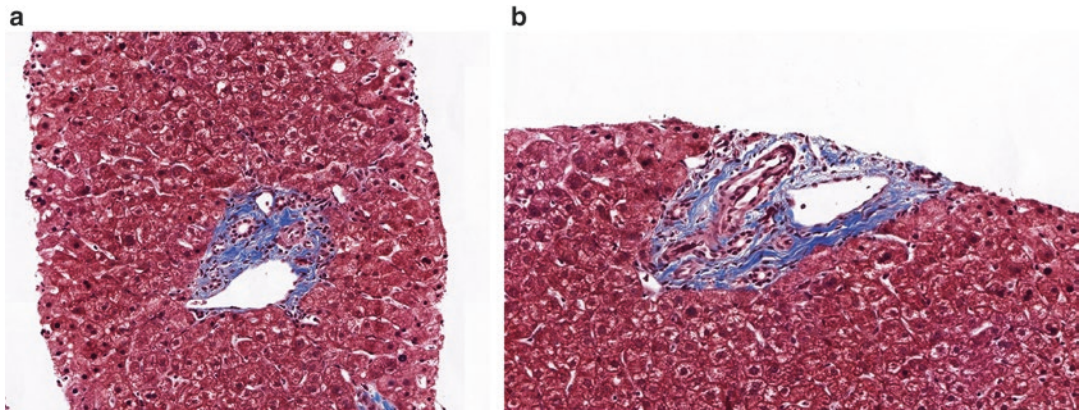

Fig. 9.13 Complete portal triads in central (**a**) or peripheral (**b**) location in the core

ery period is sufficient in almost every case, with the need for longer observation for pain control necessary in only a few.

Adverse Effects

Adverse effects (AEs) of traditional liver biopsy are infrequent but can be severe, and include life-threatening bleeding, organ perforation, and pain [40–45]. EUS-LB features "real-time" monitoring of the needle trajectory during biopsy, so a lower incidence of AEs would probably be expected compared to percutaneous approach. There are limited reports of EUS-LB-specific complications. A single case of bleeding was reported in a retrospective multicenter study of 110 patients [15]. This patient had evolving diffuse intravascular coagulation (DIC) and in retrospect should not had an EUS-LB. In a study of 75 patients comparing diagnostic yields between the Quick Core Tru-Cut needle and a regular 19G needle, 2 patients (both in the Tru-Cut group) were seen in the emergency room for

abdominal pain, but perforation and bleeding were excluded.

We have not personally encountered, but are aware of, several instances of inadvertent splenic puncture during EUS-LB. This is presumably from misidentification of the left lobe of the liver and confusing it with the spleen. Indeed, we have encountered cases where the echotexture of the spleen and left lobe of the liver are remarkably similar. Care must be taken in identifying the biopsy target; the liver has larger vessels, and they typically can be traced back to the larger venous origins of hepatic veins and main portal vein. In cases of fatty liver, the venous anatomy, particularly portal, can be obscured.

Future Directions

Standard 19G FNA needles can reproducibly produce usable core samples from liver lobes. Preliminary data suggests that 19G core needles may be able to deliver core samples with better yields than regular FNA needles, which will aid the pathologist in interpretation. Future evolution and improvement of the EUS Tru-Cut needle platform may theoretically be able to more reproducibly deliver cores with good length, due to the "automatic" nature of the cutting element of the needle, which is not dependent on operator-variable techniques.

As more endosonographers get comfortable with EUS-guided liver biopsy, a niche for this technique will continue to emerge. The ability to complete both liver biopsy and endoscopy or EUS during the same session is a step forward in convenience and comfort for the patient as well as providing more efficient use of resources. Economic analyses of these combined procedures are contemplated, and would serve to drive further use.

Development of devices and techniques for EUS-guided portal pressure measurement may also expand the role of EUS in the investigation of suspected portal hypertension [46–48]. Patients without overt cirrhosis who require both liver biopsy and portal pressure measurement currently require a transjugular approach for liver biopsy and portal pressure measurement. With further development of new devices, it is possible that EGD and EUS will be the preferred approach to provide a comprehensive evaluation of patients with chronic liver disease, being able to screen for varices, measure portal pressures, and obtain a liver biopsy. Newer research is looking into the possibility of insertion of intrahepatic portosystemic shunts by endoscopic ultrasound [49]. If this comes to pass, then a comprehensive EUS-based approach to diagnosis and treatment of portal hypertension could be realized.

There continues to be development of noninvasive methods of liver assessment and these have certainly supplanted the need for biopsy in many cases. However, there remains a clear need for liver biopsy in clinical practice as well as for clinical research [34, 50], and a method which is safe, efficient, and effective will remain important in the foreseeable future.

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EUS-Guided Fiducial Placement

10

Aamir N. Dam and Jason B. Klapman

Introduction

Image-guided radiation therapy (IGRT) uses real-time imaging to precisely localize tumors and deliver focused high-dose beams of radiotherapy [1]. Fiducials are radiopaque markers implanted at the site of a tumor or a lymph node that enhance lesion localization, and serve as reference points for targeting radiation therapy [2]. Historically, fiducial markers were placed surgically or percutaneously using ultrasound or CT guidance [3]. In the past decade, an endoscopic ultrasound (EUS)-guided approach has evolved and shown to be a safe method for fiducial marker placement.

Fiducial Types

Many types of fiducial markers have been developed and described in the literature. Table 10.1 outlines various fiducial types that have been placed using EUS. In early published studies, traditional cylindrical gold seeds were investigated. These gold seeds measured approximately 2.5–5 mm in length, ranged from 0.8 to 1.2 mm in diameter, and required a 19-gauge needle to deploy them [12, 15, 16]. Visicoil (Radio Med Corporation, Tyngsboro, MA, Core Oncology, Santa Barbara, CA) fiducials were subsequently introduced into the market and unlike traditional fiducials, they are flexible and have a coiled design to theoretically reduce risk of migration (Fig. 10.1). Visicoil fiducials are longer in length (10 mm) and produced in two different diameters (0.35 mm, 0.75 mm). The smaller diameter coiled fiducials can be used with a 22-gauge needle, providing more flexibility in anatomic areas requiring increased angulation or torque [4, 5, 8, 9]. This contrasts with the larger 0.75-mm fiducial which requires a 19-gauge needle for deployment. In addition, Visicoil fiducials utilize a specific needle-carrier delivery system to facilitate their insertion into the tip of the EUS needle (Fig. 10.2).

A retrospective study comparing traditional fiducials (0.8 mm × 5 mm) to the flexible Visicoil fiducials (0.35 mm × 10 mm) in patients with advanced pancreatic cancer demonstrated comparable technical success with no difference in migration or complication rates when fiducials were placed into tumors via EUS guidance. However, the visibility of traditional fiducials was significantly better than the Visicoil fiducials on CT scans and during subsequent IGRT, possibly related to their larger diameter [10]. In contrast, Machiels et al. reported higher rates of visibility in esophageal cancer with the newer

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Table 10.1 Summary of studies describing different gold fiducial types used with EUS

Fiducial type (Trademark)	Size (Diameter × Length)[a]	Needle gauge[a]
Visicoil flexible gold coiled fiducial (Radio Med Inc., Tyngsboro, MA) [4–7]	0.75 mm × 10 mm 0.35 mm × 10 mm	19G (Cook Endoscopy, Winston Salem, NC) 22G (Cook Endoscopy, Winston Salem, NC)
Visicoil flexible gold linear fiducial (Core Oncology, Santa Barbara, CA) [8–11]	0.35 mm × 10 mm 0.35 mm × 2–20 mm	22G (Cook Endoscopy, Winston Salem, NC)
Gold cylindrical fiducial (Best Medical International, Springfield, VA) [12–14]	0.8 mm × 3 or 5 mm	19G (MEDI-Globe, Achenmuhle, Germany, or Cook Endoscopy, Winston Salem, NC)
Gold cylindrical fiducial (Alpha Omega Services Inc, Bellflower, CA) [15, 16]	0.8 mm × 2.5 or 5 mm	19G (Cook Endoscopy, Winston Salem, NC)
Gold cylindrical fiducial (Northwest Medical Physics Equipment Inc., Lynwood, WA) [17]	0.8 mm × 3 mm	19G (Cook Endoscopy, Winston Salem, NC)
Gold cylindrical fiducial (CIVCO Medical Solutions, Orange County, IA) [18]	0.8 mm × 3 mm	19G (Cook Endoscopy, Winston Salem, NC)
Gold anchor ball shaped or line shaped fiducial (Naslund Medical AB, Huddinge, Sweden) [8]	0.28 mm × 10 mm	22G (Cook Endoscopy, Winston Salem, NC)
X-MARK gold fiducial (IZI Medical Products, Owings Mills, MA, ONC Solutions Inc., Acton, MA) [14]	0.85 mm × 1, 2, or 3 cm	19G

[a]Sizes of fiducials and needle gauge listed are limited to the ones used in the studies

Fig. 10.1 Visicoil gold fiducial marker

flexible Visicoil markers that were ≥5 mm in length when compared to the solid gold and liquid hydrogel fiducials markers. The authors suggested that length may play a critical role in improved visibility [11]. Fernandez et al. found no significant difference in visibility between the 0.35 mm × 10 mm and 0.75 mm × 10 mm diameter Visicoil fiducial markers in patients with esophageal cancer, except in patients with larger body habitus where the larger diameter fiducials were easier to see radiographically [6]. Given the limitations due to study design and sample size in many studies, firm conclusions cannot be made regarding the optimal type of fiducial to be placed by EUS guidance. Based on retrospective and limited prospective data, fiducials with increased length and diameter appear to have im proved visibility and may be preferable if the positioning of the echoendoscope allows their use.

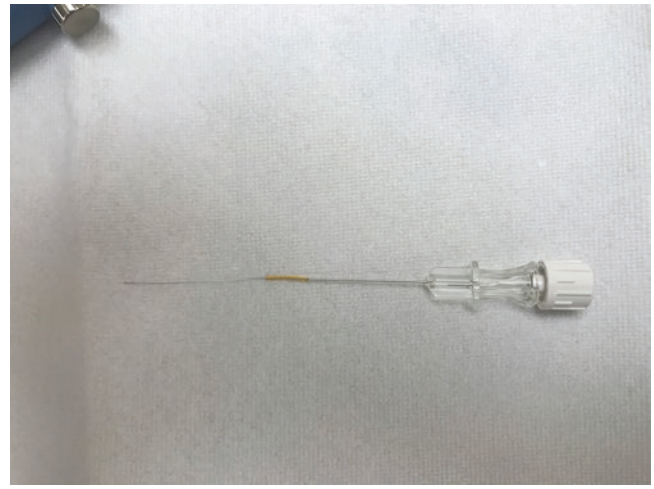

Fig. 10.2 Visicoil fiducial preloaded on a needle-carrier device

Fiducial Set Up and Deployment Techniques

Most studies have had successful outcomes with regard to delivery of fiducials into the target lesion (Table 10.2). Different techniques have been described with slight variations in technique with regard to loading of the fiducial marker into the needle and deployment into the target tissue.

An antegrade method for loading fiducials was first described in two case series [5, 12]. Ammar et al. preferred this approach because it prevented handling of the sharp end of the needle and minimized the risk of fiducial loss while accessing the lesion [4]. In this method, the needle is inserted into the target lesion and the stylet is withdrawn. Next, the fiducial is manually loaded into the needle lumen and the stylet is reinserted to push the fiducial forward into the target lesion. Another more commonly used method involves a back-loading technique using a 19- or 22-gauge EUS-FNA needle that has been described in numerous studies [6–10, 13, 15–18]. First, the stylet is withdrawn from the needle approximately 7–8 mm, and a fiducial marker is back-loaded into the needle tip in a retrograde manner using sterile forceps or using the needle-carrier delivery device (Fig. 10.3). Once the fiducial itself is within the lumen of the needle, the needle tip is sealed with sterile bone wax to prevent loss of the fiducial in the echoendoscope or in the patient before the target tissue has been reached. The needle is inserted into the operating channel of the echoendoscope and advanced into the target lesion using Doppler ultrasound to avoid intervening blood vessels. A small "track" is made in the target tissue to facilitate insertion and the fiducial is deployed by advancing the stylet completely while simultaneously retracting the needle an equal distance. The fiducial can be seen to deploy endosonographically and via fluoroscopy, if utilized. The needle is removed and reloaded with a new fiducial and the method is repeated until the desired number of fiducials have been placed. In both of these techniques, the stylet is used to deploy the fiducial. The back-loading technique and intra-tumoral deployment is demonstrated in Video 10.1.

An alternative to the stylet-push method has been developed. This technique uses a hydrostatic technique to deploy the fiducial into the target lesion. In this method, the stylet is removed, the needle is first flushed with sterile water or normal saline, and the fiducial is back-loaded into the needle. Then, the needle is inserted into the tumor and 1–2 mL of sterile water or normal saline is instilled into the needle to deploy the fiducial [13, 15]. The advantages reported include reducing air artifact and aiding delivery during difficult scope positions.

To improve efficiency, other specialists have described preloading two fiducials into the tip of the needle with the ability of placing multiple

Table 10.2 Summary of efficacy and safety of EUS-guided fiducial placement

Study	Design	Location of malignant lesion	Needle gauge (G)	Fiducial type (mm)	Technical success	Adverse events
Pishvaian et al. [12]	PS ($n = 13$)	Mediastinum Esophagus Pancreas Metastatic lesions in abdomen	19G	Gold (0.8 × 3 or 5)	11/13 (85%)	Cholangitis (1)
Sanders et al. [16]	PS ($n = 51$)	Pancreas	19G	Gold (0.8 × 5)	46/51 (90%)	Mild pancreatitis (1)
Park et al. [15]	PS ($n = 57$)	Pancreas	19G	Gold (0.8 × 2.5)	50/53 (94%)	Minor bleeding (1)
Ammar et al. [4]	RS ($n = 13$)	Pancreas Abdominal lymph node Liver lesion Adrenal gland Bile duct (CCA)	22G	VC (0.35 × 10)	13/13 (100%)	None
DiMaio et al. [9]	RS ($n = 30$)	Esophagus Pancreas Gastric Bile duct (CCA) Metastatic liver lesion	22G	VC (0.35 × 10)	29/30 (97%)	Fever (1)
Varadarajulu et al. [13]	RS ($n = 9$)	Pancreas	19G	Gold (0.8 × 3)	9/9 (100%)	None
Khashab et al. [10]	RS (n = 39)	Pancreas	19G 22G	Gold (0.8 × 5) VC (0.35 × 10)	39/39 (100%)	None
Fernandez et al. [6]	RS ($n = 60$)	Esophagus	19G 22G	VC (0.75 × 10) VC (0.5 × 10) VC (0.35 × 10)	60/60 (100%)	Abdominal pain (1)
Majumder et al. [19]	RS ($n = 77$)	Pancreas	19G	Gold (0.8 × 5)	35/39 (90%)	Abdominal pain (3) Mild pancreatitis (1)
Choi et al. [18]	RS ($n = 32$)	Pancreas Liver lesion Metastatic lymph node	19G	Gold (0.8 × 3)	32/32 (100%)	Mild pancreatitis (1)
Chandran et al. [20]	PS ($n = 8$)	Gastric	19G	VC (0.35 × 10)	7/8 (88%)	None
Davila Fajardo et al. [8]	PS ($n = 23$)	Pancreas	22G	VC (0.35 × 5–20) Gold anchor (0.28 × 10)	23/23 (100%)	Minor bleeding (1)
Moningi et al. [14]	RS ($n = 11$)	Rectum	19G	Gold (0.8 × 5) X-mark fiducial (0.85 × 10–30)	11/11 (100%)	None
Machiels et al. [11]	PS ($n = 32$)	Esophagus	22G	Gold (0.43–0.64 × 5) Visicoil (0.35 × 2–10) Hydrogel marker	30/30 (100%)	Pneumothorax (1) Mediastinitis (2)

(continued)

Table 10.2 (continued)

Study	Design	Location of malignant lesion	Needle gauge (G)	Fiducial type (mm)	Technical success	Adverse events
Dhadham et al. [7]	RS ($n = 514$)	Mediastinum Esophagus Pancreas Rectum/anal canal Metastatic lesions in abdomen and liver	19G 22G	VC (0.75 × 10) VC (0.35 × 10)	513/514 (99.8%)	Minor bleeding (9)

PS prospective study, *RS* retrospective study, *VC* Visicoil, *CCA* cholangiocarcinoma

markers at the same time [15]. Currently, preloaded needles are commercially available for use. The Beacon FNF needle (Medtronic, Minneapolis, MN) is available in two sizes and preloaded with two solid gold fiducial markers—22-gauge (0.43 mm × 5 mm) and 19-gauge (0.75 mm × 5 mm). In addition, the 22-gauge EchoTip Ultra preloaded needle (Cook Medical, Bloomington, IN) has been developed and been shown to be effective in a live porcine models [21]. The Cook needle system comes preloaded with four gold fiducials that are each 5 mm in length and 0.43 mm in diameter. A current randomized controlled trial is underway comparing overall efficiency and technical success between the 22-gauge EchoTip Ultra preloaded fiducial needle versus the traditional back-loading technique in patients with pancreatic cancer.

The optimal number of fiducials to be placed into a lesion has not been well established. In the literature, most studies have placed between 2 and 5 fiducials for each tumor/lymph node/target lesion. In our experience, we attempt to place at least three fiducials in different locations within pancreatic lesions and one fiducial marker at both the proximal and distal margins of luminal tumors if feasible, although practice in this regard varies between centers.

Technical difficulties that have been encountered include resistance while pushing the fiducial with the stylet [8, 12, 15], and the presence of intervening vasculature [7, 16] which makes safe deployment challenging. As described above, to overcome difficult anatomic positions, techniques that have been successfully reported include repositioning the scope, using a smaller size fiducial/needle or trying a different deployment technique such as the hydrostatic technique.

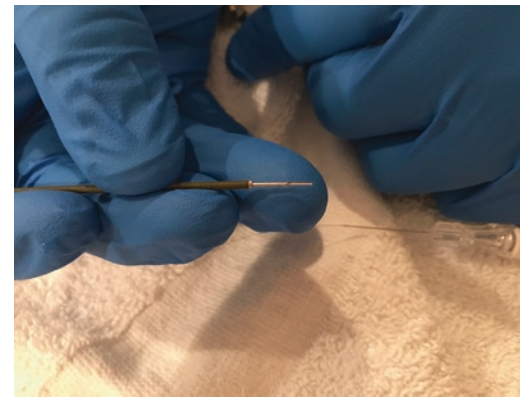

Fig. 10.3 Visicoil fiducial loaded on the distal tip of EUS needle

Fiducial Tumor Targets

Pancreatic Cancer

Pancreatic cancer has recently become the third most common cause of cancer-related deaths, and only 20% of patients are surgically resectable at the time of diagnosis [22, 23]. For patients with borderline resectable or locally advanced disease, neoadjuvant chemotherapy and radiation play an important role in controlling tumor growth and influencing overall survival [24–26]. While EUS has traditionally aided in the diagnosis and staging of pancreatic cancer, more therapeutic options have emerged including celiac plexus neurolysis, EUS-guided biliary access and drainage, fine needle injection, and fiducial placement (Fig. 10.4) [27]. In 2006, Pishvaian et al. performed the first case series evaluating EUS-guided gold fiducial placement in mediastinal and abdominal malignancies which included five patients with advanced pancreatic cancer and

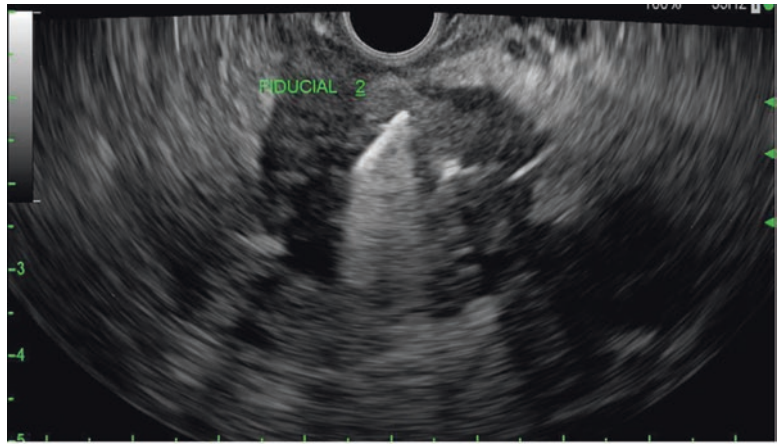

Fig. 10.4 Endosonographic image of a hyperechoic fiducial placed within the pancreatic body mass

one with recurrent cancer post-Whipple. The technique followed the same principle of EUS-guided FNA and delivered an average of 3–4 fiducials in each of the five patients using a 19-gauge needle. One failure occurred secondary to gastric outlet obstruction in a patient with a tumor in the pancreatic head. The study showed an overall technical success rate of 85% and was the first to demonstrate the safety and feasibility of EUS-guided fiducial placement for tumor marking to guide radiotherapy [12]. Since that report, multiple prospective and retrospective case series have described the feasibility of fiducial placement, specifically in pancreatic cancer, with high success rates ranging from 88 to 100% [10, 13, 15, 16, 18]. Four studies demonstrated success with the use of a 22-gauge needle to place smaller diameter Visicoil fiducial markers in patients with pancreatic cancer [4, 8–10]. There are no prospective data comparing the 19- and 22-gauge needles for fiducial placement, but experts report that the 22-gauge needle may help overcome issues of angulation in pancreatic lesions in the head and uncinate process [8, 9].

In the largest retrospective series involving 188 patients with pancreatic cancer, a 22-gauge needle was used to place 414 Visicoil fiducials (0.35 mm × 10 mm) in 80% of patients, and a 19-gauge needle was used to place 93 Visicoil fiducials (0.75 mm × 10 mm) in 20% of patients. Technical difficulty occurred in 16 patients (3.1%) mainly involving intervening blood vessels, and minor bleeding that resolved spontaneously in seven patients (1.3%) [7].

In early studies, fluoroscopy was used in conjunction with EUS to help achieve appropriate angulation and distance between fiducial markers (Fig. 10.5). More recent studies have shown successful placement of EUS-guided fiducial markers without the use of fluoroscopy, suggesting that fluoroscopy can be used if available but is not considered essential for safe and successful EUS-guided fiducial placement [6, 7, 9, 18]. In addition, a recent retrospective study by Majumder et al. found that achieving ideal fiducial geometry may be unnecessary for successful tracking and delivery of radiation in patients with pancreatic cancer [19].

Esophageal Cancer

Radiotherapy plays an important role in esophageal cancer as many patients also present with advanced stage disease [28]. Several studies have specifically evaluated EUS-guided fiducial placement in patients with esophageal cancer and have shown favorable results with high technical success [6, 7, 9, 11].

Fiducials can be placed proximal and distal to the tumor and provide accurate delineation of the extent of the lesion (Fig. 10.6) [6, 7, 11].

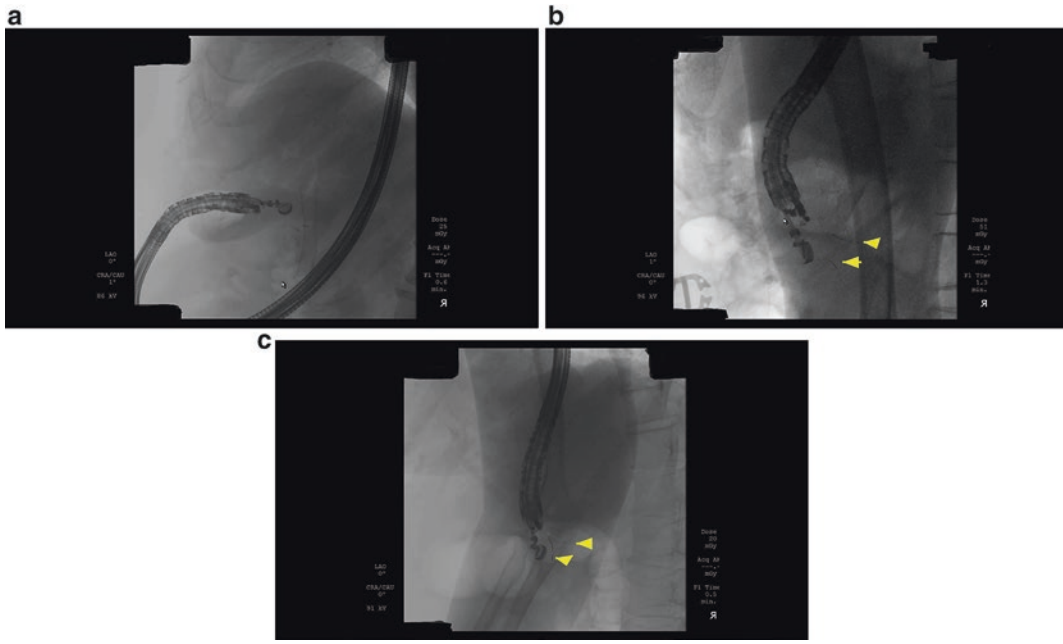

Fig. 10.5 Fluoroscopic image of fiducials placed within the: (**a**) pancreatic head, (**b**) uncinate process of the pancreas, and (**c**) pancreatic body

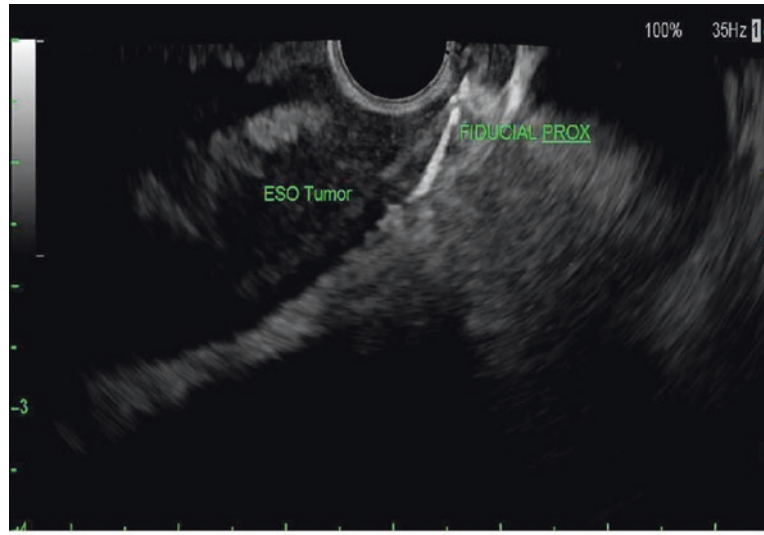

Fig. 10.6 Endosonographic imaging of a hyperechoic fiducial placed just proximal to an esophageal mass

In approximately one-third of cases, a single fiducial marker was placed given that the tumor was obstructing and prevented passage of the echoendoscope [6, 7]. Most studies have described securing the fiducial into the submucosa or muscularis propria adjacent to the tumor, instead of into the tumor itself, to theoretically reduce migration rates especially after tumor regression from treatment (Fig. 10.7) [6, 7, 11].

DiMaio et al. assessed EUS-guided fiducial placement (Visicoil 0.35 mm × 10 mm) using a 22-gauge needle in 12 patients with esophageal tumors; all were technically feasible except for one in which the lesion could not be identified

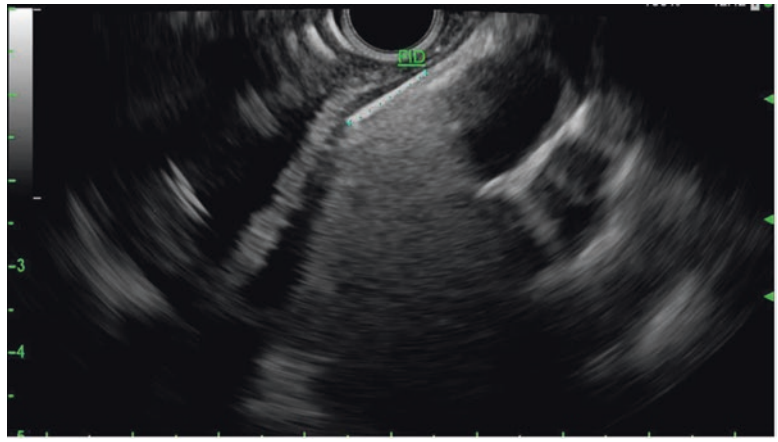

Fig. 10.7 Endosonographic image of a hyperechoic fiducial clearly placed within the muscularis propria proximal to a distal esophageal mass

[9]. Fernandez and colleagues reported a retrospective series of 60 patients with esophageal cancer who underwent EUS-guided fiducials. In the majority of patients, Visicoil fiducial markers (0.75 mm × 10 mm) were placed with a 19-gauge needle, and in a few patients, the smaller diameter (0.35 mm × 10 mm) fiducials were used. A total of 105 markers were placed, 33% had a single fiducial marker, 58% had two fiducial markers, and 8% had three fiducial markers inserted proximal and distal to the lesion if possible. The investigators concluded that implantation of fiducials for esophageal cancer was feasible, allowed for more confident target delineation, and improved assessment of respiratory tumor motion on CT simulation [6]. Another retrospective study involved 207 patients with esophageal cancer in which 348 fiducials were inserted. The 0.75 mm × 10 mm Visicoil fiducial marker was used in 91% of patients using a 19-gauge needle. In addition, there were 33 patients with gastroesophageal junction tumors, of which 64% had two fiducials placed and 36.4% of patients had one fiducial placed. These patients successfully underwent radiation therapy with no significant complications related to fiducial placement [7]. A recent retrospective analysis showed the placement of fiducial markers coupled with 3D PET/CT aided in planning tumor volume, specifically along the inferior border of the tumor, and offered more accurate radiation treatment delivery for locally advanced esophageal cancer [29].

Rectal Cancer

Two studies have evaluated the role of EUS-guided fiducial placement in rectal cancer. The first report described EUS-guided fiducial placement used in the management of rectal cancer with high-dose rate endorectal brachytherapy. In this study, 11 patients underwent EUS-guided placement of two different types of gold fiducials. All fiducials were placed at the superior and inferior extents as well as in the center of the tumor, and the mean number of fiducials placed per patient was 3.6. All fiducials, regardless of type, were clearly visible, and all 11 patients underwent IGRT with subsequent successful resection [14]. In a subsequent study, 54 patients with rectal cancer had 103 fiducials inserted, 70% fiducials were placed at both the proximal and distal margins, 16.6% at the proximal margin only, and 13.1% at the distal margin only. Minimal complications were reported with mild bleeding occurring in one patient [7]. Figure 10.8 demonstrates an endoscopic image of a rectal cancer and CT performed 1 month later with fiducials remaining visible at site of rectal tumor.

Other Sites

Several studies have described the feasibility and technical success of EUS-guided fiducial placement in a variety of other malignancies including prostate cancer [30], gastric cancer [20], anal

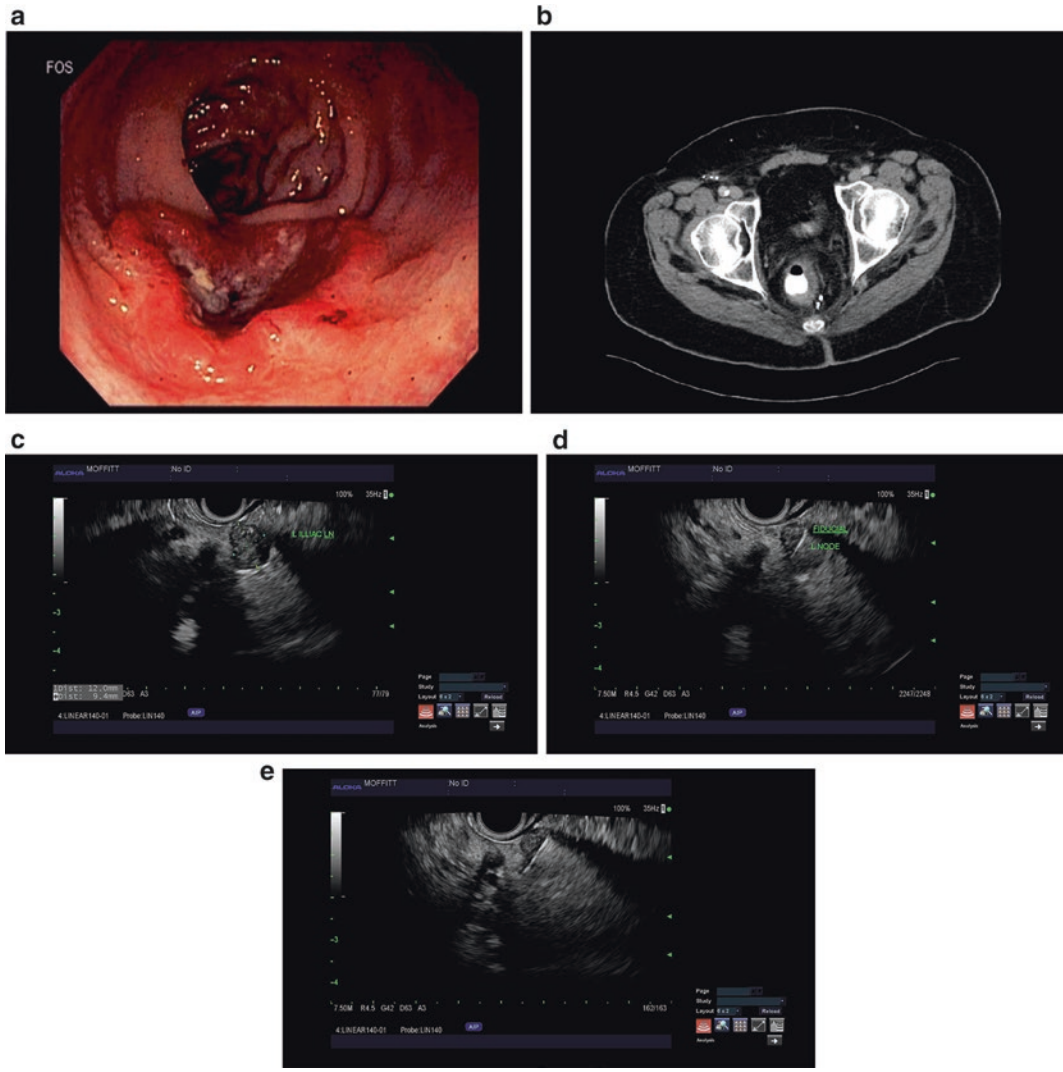

Fig. 10.8 (**a**) Endoscopic image of rectal cancer along the posterior wall of the rectum, (**b**) CT scan confirming the placement of multiple fiducial at the proximal margin of the rectal tumor. (**c**) EUS image of a peritumoral malignant left iliac lymph node near known rectal cancer. (**d**) Fiducial needle inserted in a transrectal manner into the malignant node. (**e**) Fiducials after deployment into the malignant node

cancer [7], cholangiocarcinoma [4, 9], and metastatic lesions in the abdomen, liver, or mediastinum (Fig. 10.9) [4, 7, 12, 18].

Durability of Fiducial Placement

In regard to fiducial placement and feasibility as stated above, high rates of technical success ranging from 85 to 100% have been reported. In addition, most studies have reported that over 90% of patients with successfully placed EUS-guided fiducials completed radiation therapy [6–8, 13, 16, 18]. However, data on long-term outcomes in fiducial placement are limited and have not been clearly defined. In addition, studies assessing improved overall survival with fiducials are lacking. Various endpoints that have been evaluated include the presence of markers at simulation CT scan, visibility during treatment period, and

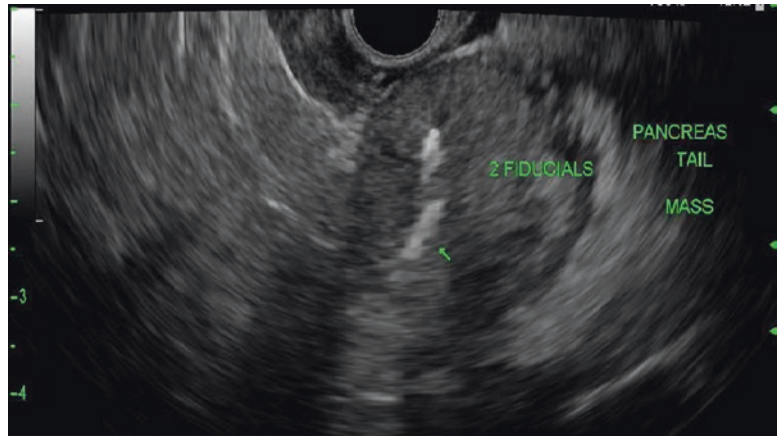

Fig. 10.9 Endosonographic image of two hyperechoic fiducials placed within a metastatic pancreatic tail mass

migration rates. Figure 10.10 demonstrates visibility of fiducials on CT scan and PET-CT.

DiMaio et al. evaluated fiducial placement in 30 patients with various GI malignancies and fiducials were identified in 83% of patients at the time of CT simulation for radiation therapy [9]. Fernandez and colleagues investigated long-term stability of fiducial placement in the setting of esophageal cancer. In their study, 105 Visicoil markers were placed; 94% of markers were still present at CT simulation, and 88% were still present in their initial position at a median time of 107 days. In patients who did not undergo surgery, 90% of fiducials were visible at a median time of 165 days following implantation [6]. Machiels et al. reported in a small prospective study that 63% of solid gold markers and 80% of Visicoil markers placed in esophageal tumors remained visible during the treatment period. In a subgroup analysis, 91% of Visicoil markers ≥5 mm in length were visible at the end of their treatment period. Most markers that lost visibility were related to detachment and small size, and rarely related to migration [11]. Dhadham et al. also reported a low fiducial migration rate of 0.4% evaluated during IGRT in 207 patients with locally advanced esophageal cancer [7].

Adverse Events

EUS-guided fiducial placement is safe with a low reported adverse event rate between 1 and 5%. Common adverse events were self-limited and include fever, cholangitis, mild acute pancreatitis, minor bleeding, and post procedure abdominal pain. Rare cases of pneumothorax, mediastinitis, and intramural duodenal hematoma have also been reported [11, 31].

Fiducial migration rates have been measured on simulation exams and during therapy and have ranged from 0.4 to 9.5%. There was one report of migration of a fiducial into the lung in a patient with esophageal cancer, although the patient remained asymptomatic [11].

The use of prophylactic antibiotics for EUS-guided fiducial placement is debatable and multiple studies have used them in their protocol [4, 10, 13, 15, 16]. Infectious complications rates were not increased in other studies that did not routinely give antibiotics [7, 8]. There are no prospective data on this topic, and based on the current literature, there is no firm evidence to support the routine use of antibiotics during EUS-guided fiducial placement.

Conclusion

EUS-guided fiducial placement is a safe, effective technique to enhance IGRT and provides precise targeted radiation while limiting dosage to normal surrounding tissue. EUS may be the preferred approach as diagnosis, staging, and therapeutic interventions can be performed in the same session and expedite treatment. Many studies have investigated EUS-guided fiducial placement in pancreatic tumors, but there is

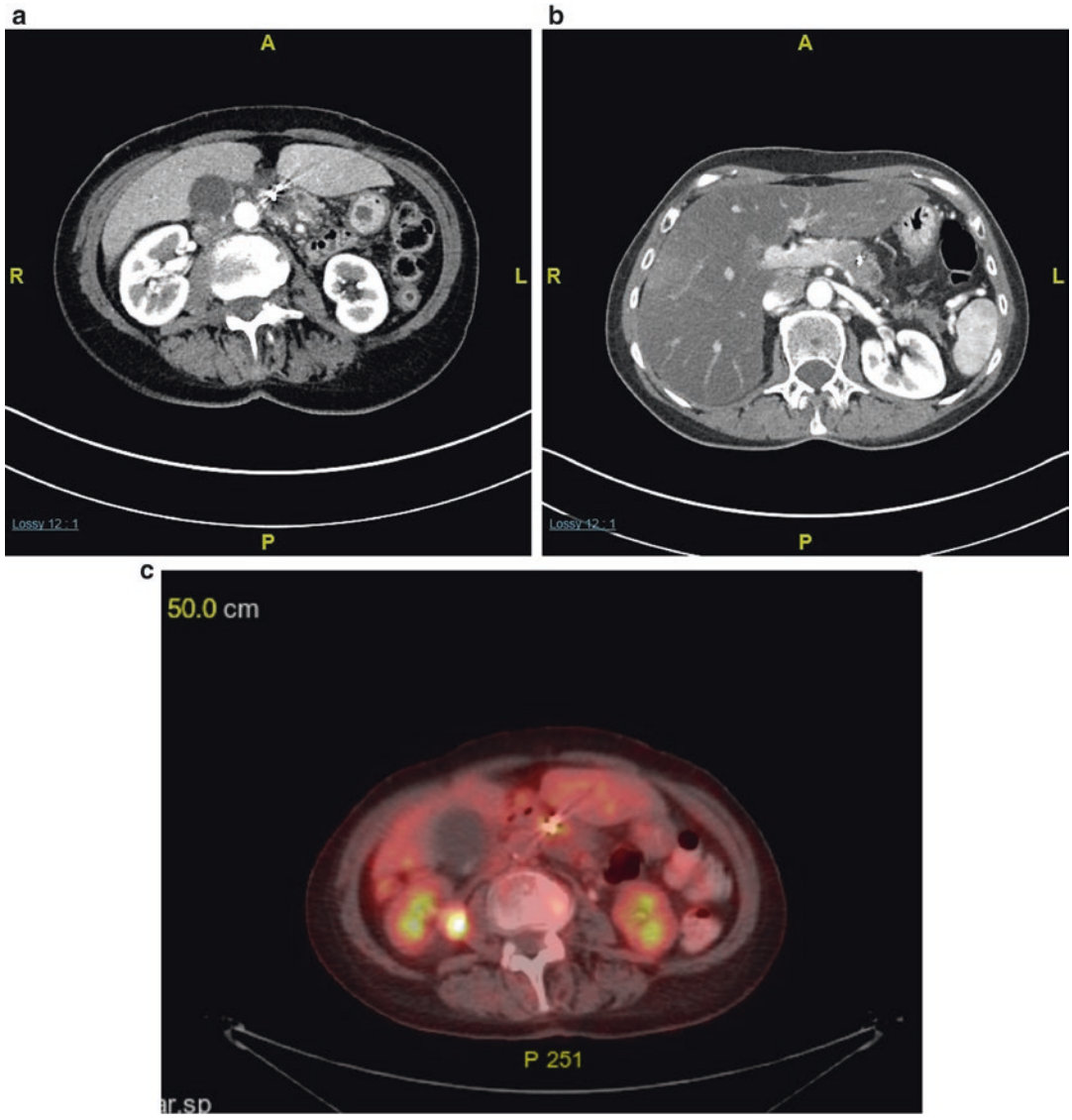

Fig. 10.10 Fiducial markers seen on: (**a**) CT scan within the pancreatic head, (**b**) CT scan within the pancreatic body, and (**c**) PET-CT within the pancreatic head

increasing evidence for its use in other GI malignancies including esophageal, gastric, rectal, anal, and hepatobiliary cancers. As described in this chapter, the technique and feasibility for EUS-guided fiducial placement has been well delineated in the current literature with high technical success. More prospective studies are needed to assess the short- and long-term clinical impact of fiducial placement on IGRT, and to help further guide the endoscopist in choosing the correct size, number, and type of fiducial/needle to use in specific malignancies.

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11 EUS-Guided Therapies for Solid Pancreatic Tumors Including Drug Delivery and Brachytherapy

Gursimran Singh Kochhar and Michael Wallace

Abbreviations

CT	Computed tomography
DC	Dendritic cells
EUS	Endoscopic ultrasound
FNA	Fine-needle aspiration
FNI	Fine-needle injection
HCC	Hepatocellular carcinoma
PDT	Photodynamic therapy
PNET	Pancreatic neuroendocrine tumor
RFA	Radio frequency ablation
US	Ultrasound

Introduction

Since its advent, endoscopic ultrasound (EUS) has quickly progressed from a diagnostic tool to a therapeutic tool adding many indications for its use over time. One such use is the management of solid pancreatic lesions and cancers in a growing variety of ways. EUS is used for diagnosis and obtaining tissue samples from lesions, but it also aids in the management of certain advanced lesions by allowing local tissue ablation or placement of fiducial markers to help our radiology colleagues.

In this chapter, we will cover the role of EUS in managing solid pancreatic lesions and local EUS-guided therapies like ethanol ablation, radiofrequency ablation (RFA), brachytherapy, and fiducial placements.

EUS-Guided Ethanol Ablation

Ethanol has long been used in the management of locally advanced cancers by radiologists, under computed tomography (CT) guidance and/or ultrasound guidance [1]. In one case, EUS was used to inject ethanol in a patient with metastatic hepatocellular carcinoma (HCC) successfully [2]. Its use in the pancreas was then widely studied in animal models [3]. Early animal studies showed that EUS-guided ethanol injection is feasible, safe, and resulted in a wide area of abalation [4]. EUS-guided ethanol injection showed a linear dose–response relationship to the concentration of ethanol used and the area of tissue ablated [4].

EUS-guided ethanol injection therapy has not been widely studied in pancreatic adenocarcinoma, although it has been reported in multiple case reports and in small series of patients with pancreatic neuroendocrine tumors (PNET). In one of the earlier case reports, EUS-guided ethanol

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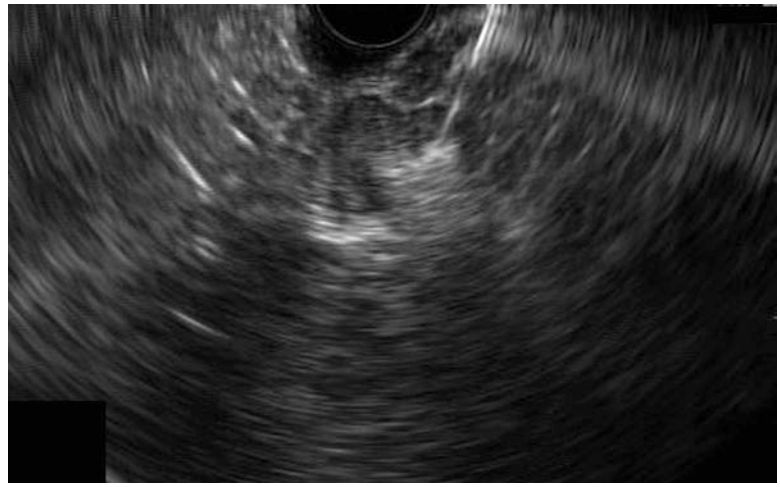

Fig. 11.1 EUS-guided ethanol ablation of a functioning insulinoma

injection was used to treat a patient with an insulinoma (Fig. 11.1) [5]. The patient had a successful response to ablation of the insulinoma, although the patient had to be hospitalized due to severe abdominal pain, likely representing some degree of pancreatitis. Subsequently, Deprez et al. reported treating an elderly patient with an insulinoma successfully via EUS-guided ethanol ablation [6]. Levy and colleagues reported a case series where eight patients with symptomatic insulinomas were treated with ethanol ablation [7]. Using 99% ethanol, five patients were injected with ethanol under EUS guidance, and three patients were injected intraoperatively. All patients achieved successful ablation after a median follow-up of 13 months. Three patients treated intraoperatively had minor complications including pancreatitis, bleeding at the tumor site, and fluid collection or pseudocyst [7]. Recently, Park et al. showed that EUS-guided ethanol ablation was successful in a larger case series of 11 patients with 14 lesions with PNET [8]. The lesions were successfully ablated in all patients, with seven lesions requiring only a single session. Three patients developed self-limiting pancreatitis.

EUS-guided ethanol injections have been successfully used to treat other malignancies including a gastrointestinal stromal tumor in one patient [9] and adrenal metastatic disease in a patient with lung cancer [10]. While this early evidence is promising, we still need large-scale clinical trials to understand its indications and complications better before it becomes more accepted as a mainstream therapy. These cases highlight the ability of EUS-guided therapy to identify and access lesions for injection-guided ablation therapy.

EUS-Guided Radio Frequency Ablation

RFA is a technique for transmitting electromagnetic energy to induce heating in the targeted tissue [11]. Based on the type of electromagnetic source, RFA can be divided into two types: monopolar and bipolar RFA. In monopolar RFA, the patient forms the part of a circuit that also includes an electrode needle, RF generator, and an electrode grounding pad [12]. The electrode delivers the RF energy to the tissue, and, depending on the time of current application and the temperature achieved in the tissue, it results in tissue necrosis. In bipolar RFA, the current oscillates between two interstitial nodes, thereby avoiding the need for a grounding pad [13].

Traditionally, RFA was done under CT or ultrasound (US) guidance, externally. With the advent of modern tools and techniques, RFA is now done under EUS guidance (Video 11.1) (Fig. 11.2).

Currently, we have four different EUS-guided RF probes for the pancreas. They can be broadly

Fig. 11.2 (**a**) Needle electrode (EUS-guided radiofrequency ablation). (**b**) Close-up of the tip of the needle electrode showing the uncovered 1-cm tip. (**c**) Needle electrode projecting from the echoendoscope tip. (**d**) Handle of the needle electrode attached to the accessory channel of the echoendoscope. (**e**) Viva Combo RFA generator, front view. (**f**) Viva Combo RFA generator, side view. (**g**) Viva pump

classified as a "through-the-needle" device and as "EUS-FNA [fine-needle aspiration] needle-type" device. The needle-type RFA devices are rigid and resemble an EUS-FNA needle. They have a variable gauge (14–19G). Through-the-needle devices include Habib™ EUS-RFA catheter (EMcision Ltd., London, UK). The remaining three probes are 19G EUS-FNA needle electrode (Radionics, Inc., Burlington, MA, USA), hybrid cryotherm probe (HybridTherm, ERBE Elektromedizin GmbH, Tübingen, Germany), and EUSRA RF electrode (STARmed, Koyang, Korea). The hybrid cryotherm probe is the only bipolar probe; the others are monopolar probes. All the RF probes are connected to their respective generators to deliver accurate energy to the target lesion.

The procedure is very similar to standard EUS procedure. The echoendoscope is inserted through the esophagus into the stomach and duodenum. After the lesion is located, a 19- or 22-G FNA needle or RFA probe is inserted through the working channel of the echoendoscope into the target lesion. The echogenic needle tip or probe is positioned at the far end inside the lesion. After confirming the exact location, energy is delivered to the target lesion. After a slight lag, one can start seeing echogenic bubbles at the target site. The wattage and exposure time for the lesions has not yet been standardized. However, in pilot studies, RF energy was applied for 90–120 s at the 5- to 25-W setting [14, 15]. The ablation was repeated two to six times in each session in prior clinical studies.

Goldberg et al. described the first experience with EUS-RFA in 1999, in porcine models [16]. In 2008, Carrara et al. used a cryotherm probe to do EUS-guided RFA of solid organs like the liver, spleen, and pancreas in pigs [17]. In 2009, Varadarajulu et al. performed EUS-RFA of the liver using an umbrella-shaped monopolar retractable electrode array in five pigs [18]. This device is similar to RFA devices used by interventional radiology. This technique was used to provide a large area of coagulative necrosis. No complications arose from the procedure. The mean zone of ablation was 2.6 cm. These early animal studies paved the way for human use.

In one such study, Arcidiacono et al. performed EUS-RFA in 22 patients with advanced metastatic pancreatic cancer [19]. They used a cryotherm probe with 18 W of energy and 650 psi. The average RFA time was 107 s. They found that 16 patients had significant volume reduction in the lesions. No major complications were observed in the study. The procedure failed in six patients due to the excessive thickness of the stomach wall and tumor. The median survival time was 6 months in the study. In another study, Pai et al. included seven patients with advanced pancreatic adenocarcinoma. The target lesions were predominantly located in the head of the pancreas (in five patients) [20]. RF was applied at 5–15 W, with a mean duration of 90 s. In follow-up examinations, the size of the lesion was reduced in two of seven patients. Again, researchers reported no significant post-procedure adverse events. Most recently, Song et al. studied six patients with advanced pancreatic cancer [21]. Song et al. used an 18-G needle electrode (STARmed), giving 20–50 W of energy for 10 s. The average number of EUS-RFA sessions in the group was 1.3, and necrosis was observed in all patients at the ablation site, with a mean ablation size of 38 mm. No major adverse events were reported in this study.

EUS-RFA has also been used to treat pancreatic cystic neoplasms. Pai et al. performed one such study in eight patients with pancreatic cysts [6]. Four patients had a mucinous cyst, two patients had pancreatic neuroendocrine tumors (one had intraductal papillary mucinous neoplasm (IPMN), and one had a microcystic adenoma). They used Habib EUS-RFA needles at 5–25 W, with exposure time ranging from 90 to 120 s. The mean number of RFA sessions was 4.5 (range, 2–7), and at the 10-week follow-up, two cysts were completely resolved, while four were reduced in size, and there was a 50% reduction in size in patients with PNET. Only two patients reported mild abdominal pain in the study. Recently, Lakhtakia et al. reported treating symptomatic insulinoma with EUS-RFA [22]. They used 19G needles (STARmed), at 50 W for 10–15 s. The average ablation size was 19 mm. Treatments were successful in all three patients; they had no more hypoglycemia symptoms during the 12-month follow-up period.

Overall, EUS-guided RFA seems to be a very promising therapy in the management of pancreatic neoplasms. Its role in PNET is even more encouraging (Figs. 11.3 and 11.4). The above data suggest that EUS-guided RFA is safe and can potentially become a mainstream therapy in the management of pancreatic cancers. Although the initial results are very encouraging, there are still a few limitations to its widespread use. Further technological advancements in needles are necessary for easy tumor penetration. Sometimes the flexible cryotherm probe poses a challenge in piercing the tumor. We also need more data on wattage setting and the number of RFA sessions required for different types of pancreatic neoplasm. Future studies will also

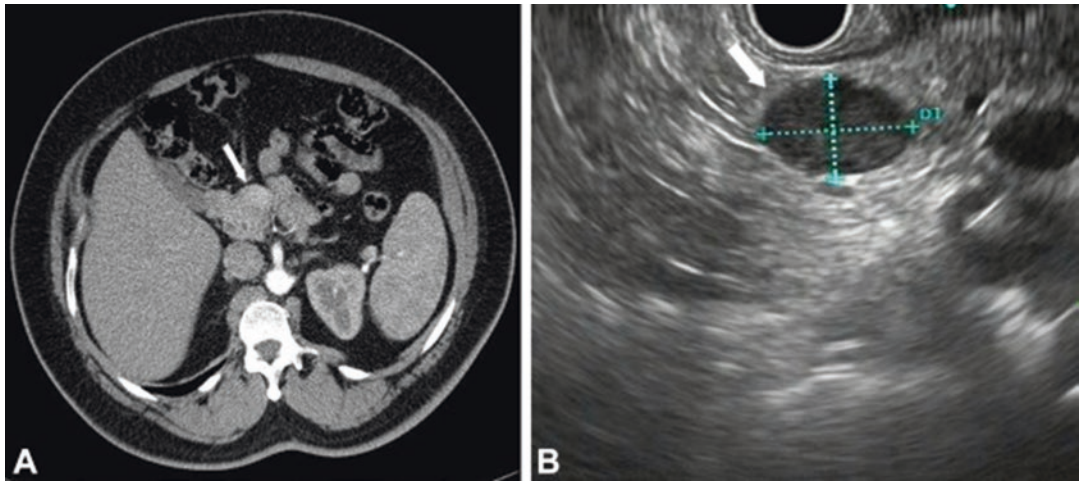

Fig. 11.3 (**a**) Abdominal contrast-enhanced CT in the arterial phase shows an enhancing lesion (insulinoma) in the pancreatic genu (arrow). (**b**) Well-defined hypoechoic oval-shaped lesion (insulinoma) in the pancreatic genu (arrow)

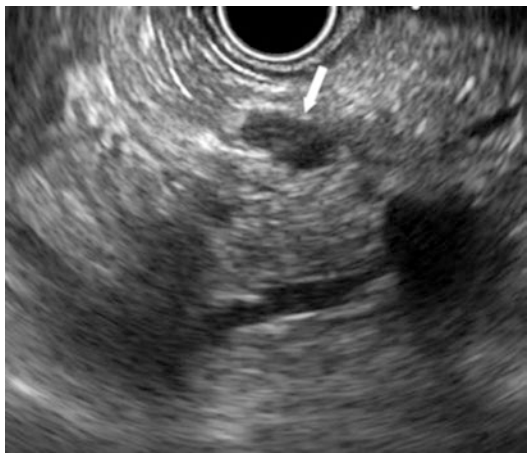

Fig. 11.4 Post-EUS-guided radiofrequency ablation at 6 weeks

hopefully better define the role of EUS in the management of pancreatic cancer. From its current use of palliation, EUS-guided therapy might become a first-line treatment strategy to downgrade and/or debulk tumors.

EUS-Guided Brachytherapy

Brachytherapy is a well-known treatment strategy for the management of various solid organ tumors like prostate cancer. Its role in the gastrointestinal tract, with the help of EUS, was first described in animal models with pancreatic cancer in 2007 [23]. It successfully achieved localized tissue necrosis and tumor destruction without major complications. Permanent seeds of iodine (I^{125}) or palladium (Pd^{103}) can be easily planted in the tumor using EUS (Figs. 11.5 and 11.6). There are several advantages to the procedure. First, the procedure can be done in an outpatient setting. Locally placed iodine or palladium beads emit low-dose radiation; hence, they do not require extensive precautions or preparations at home.

The success of the EUS-guided brachytherapy has been reported in various studies involving cancers of the head and neck and in pancreatic cancers [24, 25]. In a pilot study, patients with Stage III and IV pancreatic adenocarcinoma were selected. They underwent EUS-guided brachytherapy with iodine beads (I^{125}) [26]. A mean of 22 beads were placed per patient. Thirty-three percent of the tumors stabilized after therapy, and 30% of the patients experienced pain relief from the procedure. No major adverse outcomes were reported. In another trial, EUS-guided brachytherapy was performed in patients with unresectable pancreatic cancer [27]. A total of 85 patients were enrolled in the trial, and they received gemcitabine chemotherapy in conjunction with RFA. Patients showed longer median survival up to 7.8 months after implantation compared with patients who were not treated (median survival, 4 months). Again, no major side effects were reported from the trial.

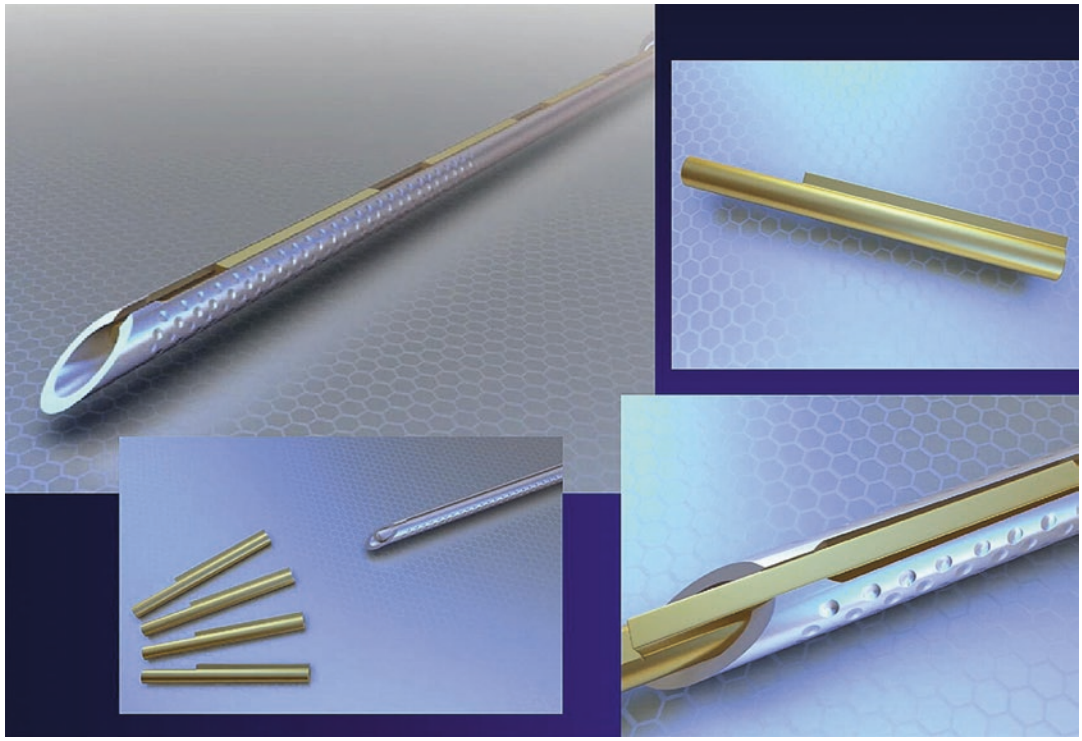

Fig. 11.5 New 22-gauge fiducial marker needle device that preloads four markers into the needle for sequential deployment (Cook Medical, Winston-Salem, NC, USA)

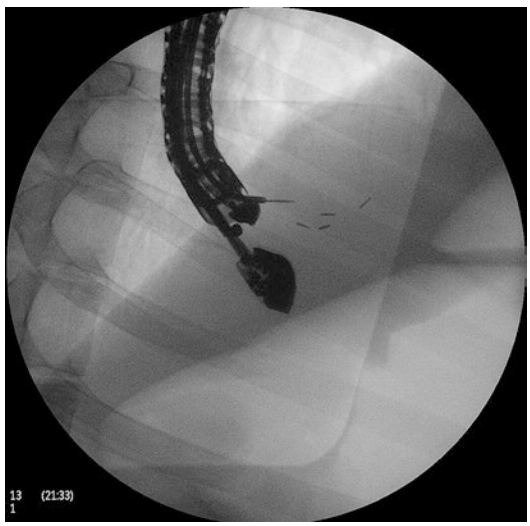

Fig. 11.6 Fluoroscopic image of four markers placed into the target tissue in the pancreas using new 22-gauge needle device (Cook Medical)

EUS-Guided Fiducial Placements

Fiducials are radiopaque markers used to direct radiation therapy. Fiducial markers have distinct advantages over traditional radiotherapy in that they allow delivery of large doses of radiation precisely at the target tissue without damaging adjacent tissues. These markers are also traceable during patient respirations, which allow health care providers to avoid damaging the surrounding tissues during radiation therapy. While CT guidance can place fiducials around pancreatic malignancy, EUS-guided placement is far more precise [28].

Currently, two types of fiducial markers are commercially available [29]. The standard fiducials are gold seeds measuring 3 or 5 mm in length and 0.8–1.2 mm in diameter, which require a 19-G EUS needle for deployment. The newer fiducials are Visicoil™ fiducials measuring

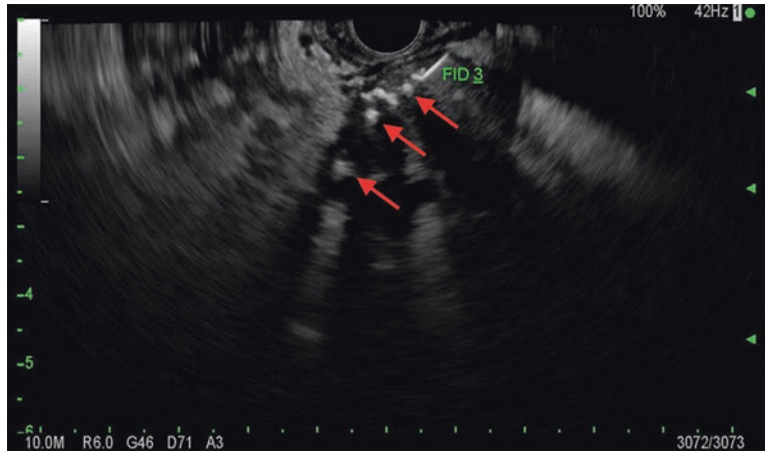

Fig. 11.7 Endosonography-guided fiducial placement. Three fiducials are seen (red arrows) within a hypoechoic mass previously determined to be pancreatic adenocarcinoma

10 mm in length and 0.35 mm in diameter (Core Oncology, Santa Barbara, CA), which can be deployed via 22-G EUS needles.

Fiducials can be deployed in two ways. In the front-loading technique, the needle tip is advanced to the tumor, then the stylet is removed, and the fiducials are loaded manually into the needle lumen. The stylet is reinserted in the needle channel, then the stylet is advanced, pushing the fiducial through the needle lumen, with ultimate deployment of fiducials in the target tissue.

In the back-loading technique, the fiducials are inserted into the needle tip with the stylet slightly withdrawn followed by insertion of bone wax at the tip to prevent premature dislodgement. The needle tip is then advanced into the tumor, and the stylet is advanced with the deployment of the markers. Recently, Park et al. described a technique using saline flushed in the needle lumen to deploy the fiducials instead of using a stylet [30]. Based on the size of the tumor, 2–6 markers are placed at the margins of the tumor.

EUS-guided placement of fiducials has been reported to be successful in 85–100% of cases (Fig. 11.7) [31]. Failures are encountered in cases where it is difficult to advance the echoendoscope, or there is a failure to maneuver the 19-G needle in especially difficult locations like the uncinate process where the scope is in a rotated position. Fiducial placement is an overall safe procedure with few side effects. Common complications include minor bleeding and fiducial migration [31].

Other EUS-Guided Therapies

Cytoimplant

Cytoimplants are an allogenic mix of lymphocytic tissue obtained from the tumor patient and a healthy donor after coincubation. Chang et al. initially described this technique in a Phase I clinical trial [32]. Eight patients with unresectable pancreatic adenocarcinoma underwent EUS-guided fine-needle injection (FNI) of cytoimplants. The median survival was 13.2 months. There were no immediate post-procedural complications. This technique has not gained much popularity due to reports of severe drug-related sepsis but has at least shown technical feasibility. A Phase II/III trail comparing gemcitabine with cytoimplant was prematurely stopped due to a better response rate and survival benefit in patients undergoing gemcitabine therapy [33].

Gene Therapy

ONYX-015 is an E1B-55kD gene-deleted replication-selective adenovirus that preferentially replicates inside malignant tumor cells and causes cell death [34]. The use of this agent was shown in one study including 21 patients with advanced pancreatic cancer with no liver metastases [35]. The study participants underwent eight EUS-guided injections; the last four of which

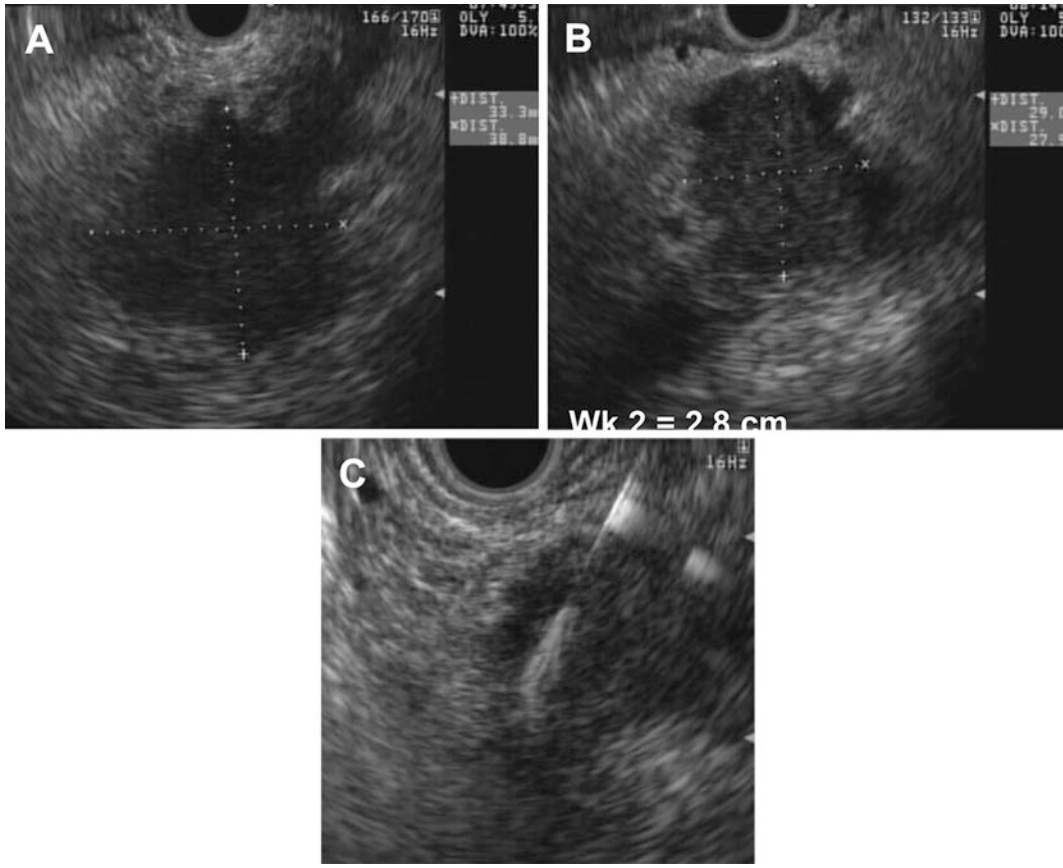

Fig. 11.8 Endosonography (EUS)-guided pancreatic tumor injection with TNFerade. (**a**) Tumor size is 3.9 cm at baseline (week 1) before treatment with EUS-guided gene therapy. (**b**) Tumor size has decreased to 2.8 cm after 1 week. (**c**) One month after completing treatment, the tumor size had decreased to 1.8 cm and a fine-needle aspiration performed at that time was negative for malignancy. No residual tumor was found at the time of surgical resection. (Reprinted with the permission from Springer: From Chang KJ, Lee JG, Holcombe RF, et al. Endoscopic ultrasound delivery of an antitumor agent to treat a case of pancreatic cancer. Nat Clin Pract Gastroenterol Hepatol 2008;5(2):107–11)

were combined with gemcitabine (1000 mg/m^2). The results of the trial were mixed. Two patients had partial regression, two had a minor response, six patients' disease stabilized while in 11 patients the disease progressed. Two patients developed sepsis, and two patients experienced duodenal perforations; this led to a change in the trial protocol, and injections were then administered using a transgastric approach rather than transduodenal. No patient developed pancreatitis, although elevations in lipase levels were observed in patients after the procedure.

TNFerade is the newest EUS-guided antitumor therapy. A local injection of TNFerade allows delivery of tumor necrosis factor-α (TNF-α) into the tumor along with standard chemoradiotherapy (Fig. 11.8) [36]. The major advantage of this approach is the potential to use anti-TNF-α locally without systemic side effects. In a recent study by Hecht et al., 50 patients with advanced pancreatic adenocarcinoma underwent TNFerade therapy via EUS-guided (n = 27) and percutaneous injection (n = 23) [36]. The study aimed to determine the maximally tolerated dose, safety, and feasibility of TNFerade with chemoradiotherapy. Over a 5-week treatment period, weekly intratumoral injections of TNFerade (4×10^9, 4×10^{10}, and 4×10^{11} particle units in 2 mL) were given in combination with intravenous 5-fluorouracil (200 mg/m^2/day, 5 days/week) and radiation (50.4 Gy). The long-

term results showed that toxicities potentially related to TNFerade were mild, and the procedure was well tolerated with only two reported cases of acute pancreatitis. The higher dose group ($n = 11$) was associated with higher locoregional control of the tumor with a longer disease-free survival. Four patients became surgically resectable and achieved pathologically negative margins, and three patients survived more than 24 months.

Immunotherapy

Dendritic cells (DCs) are potent antigen-presenting cells that can stimulate a T-cell-dependent immune response. In a pilot study, seven patients with stage IV pancreatic cancer refractory to gemcitabine therapy received intratumor injections of immature DCs by EUS-FNI [37]. DCs were administrated every 7 days and the number of EUS-FNIs ranged from 2 to 21. All injections were well tolerated without significant complications. The median survival was 9.9 months with two patients having a mixed response, two patients had stable disease, and three patients had disease progression. While immunotherapy is an exciting prospect for managing cancer, additional studies with more effective antitumor agents are needed for pancreatic cancer.

Photodynamic Therapy

Photodynamic therapy (PDT) was initially successful in managing advanced cholangiocarcinoma, but its use in pancreatic cancer in humans is still in its infancy. In a pilot study, Choi et al. included four patients with advanced pancreaticobiliary cancer [38]. Patients underwent EUS-guided PDT with a chlorin e6 derivative (Photolon, Belmedpreparaty, Minsk, Republic of Belarus) and a flexible laser-light catheter (Photo Glow, South Yarmouth, MA, USA). The procedure was safe, feasible, and all patients showed stable disease at the end of the 5-month follow-up period. It was shown to be a feasible procedure in all patients. Additional studies and data are needed for the use of PDT in pancreatic cancer management.

Conclusion

EUS has come a long way from its first use as a tool for diagnosing pancreatic malignancies to a means to treat them now. The EUS-FNI technique is well-described and safe. With direct tumor-guided therapy with EUS FNI, many of the systemic side effects of other therapies can be avoided. Although, to date, the data are very encouraging for the management of pancreatic cancer with EUS-guided therapies, its use is still limited due to a lack of large randomized clinical trials. More studies with larger numbers of patients are needed to study exact indications and safety profiles of these interventions to define a more clear role for EUS-guided therapies in the management of pancreatic cancer.

Conflict of Interest The authors declared no conflict of interest.

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12 EUS-Guided Enhanced Imaging and Sampling of Neoplastic Pancreatic Cysts

Shivangi Kothari, Enqiang Linghu, Truptesh H. Kothari, and Vivek Kaul

Introduction

Advances in recent imaging and the high number of cross-sectional imaging studies (CT and MRI) being performed for a variety of gastrointestinal complaints has led to an increase in detection of pancreatic cystic lesions. Approximately, 2.5% of the cross-sectional imaging studies report pancreatic cysts and this can be as high as 10% in patients older than 70 [1]. Pancreatic cysts can be seen in 3% of CT scans and up to 20% of MRI [2, 3]. An autopsy study on 300 elderly patients reported a 24.3% prevalence of pancreatic cysts [4]. The rate of malignant transformation of IPMN cysts can range from 10% to >70% depending on the presence of high risk features (mural nodules, main duct involvement, multifocal cysts, etc.) [5–8]. The management of these incidentally discovered pancreatic cysts is challenging and poses a clinical dilemma in being able to distinguish neoplastic from nonneoplastic cysts. Distinguishing mucinous cystic neoplasm (MCN) from nonmucinous cysts is extremely important given the malignant potential of the mucinous lesions, including intraductal papillary mucinous neoplasm (IPMN), and to avoid unnecessary surgical interventions on benign cysts. Current guidelines recommend surgical resection for all surgically fit patients with MCNs, all patients with main duct-IPMNs and branch duct-IPMNs with worrisome features (cyst ≥3 cm, thick enhancing cyst wall, main duct 5–9 mm, mural nodules, and positive cytology) [8]. Nonmucinous cysts such as pseudocysts and serous cystadenomas are considered benign and do not require continued surveillance or intervention in asymptomatic patients.

The limitations in achieving a definitive diagnosis of these cysts and the uncertainty regarding the potential for malignant transformation of these cystic lesions leads to patient anxiety, unnecessary surveillance, and even surgical interventions (some of which will ultimately be found to have been unnecessary), posing significant management challenges to the patient and the physician. Therefore, diagnostic tools that can help differentiate these cysts are essential to the endosonographer to be able to accurately assess these cystic lesions and only refer the truly malignant and high risk cystic lesions for surgery, while avoiding surgery for the more benign lesions.

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Endoscopic ultrasound (EUS) is widely used in the evaluation of pancreatic cystic lesions (PCL) but the sensitivity, specificity, and accuracy of EUS imaging alone in PCL evaluation has been reported to be low [9]. EUS is operator dependent and has a low accuracy in differentiating mucinous from nonmucinous cysts based on imaging alone. Even among experienced endosonographers, there is a poor rate of interobserver agreement between neoplastic and nonneoplastic pancreatic cystic lesions. Other than the serous cystadenoma with a classic "*honey-comb*" microcystic appearance, differentiating premalignant cysts solely based on EUS imaging can be very difficult.

According to the 2012 guidelines, the presence of "high-risk" features such as obstructive jaundice in a patient with a cystic lesion of the head of the pancreas, enhancing solid component within cyst, main pancreatic duct >10 mm in size, or "worrisome" features such as cyst >3 cm in size, thickened/enhancing cyst walls, nonenhancing mural nodule, main duct 5–9 mm in size, abrupt change in caliber of pancreatic duct with distal pancreatic atrophy, and lymphadenopathy indicate higher risk of malignancy in a patient with a pancreatic cystic lesion [8]. Due to the poor interobserver variability and low sensitivity of EUS imaging alone in differentiating benign from malignant PCLs, many patients require cyst fine needle aspiration (FNA) for obtaining fluid for evaluation and analysis. Fluid CEA, amylase, and cytology are the most commonly performed tests on PCL fluid. However, cyst fluid cytology has limited diagnostic yield, with a recent meta-analysis showing a pooled sensitivity of 54%, but a high specificity of 93%, in differentiating mucinous from nonmucinous cysts. High CEA levels (> 192 ng/mL) are associated with mucinous cysts, with a meta-analysis reporting a 63% sensitivity and 88% specificity for a high cyst fluid CEA level in the diagnosis of a mucinous pancreatic cyst [10]. However, a high cyst fluid CEA level alone cannot help distinguish malignant from benign cysts and thus has limited overall accuracy.

New intracystic markers (mutated KRSA DNA, mutated GNAS DNA, glucose, and proteomic analysis) are being studied and developed but their widespread clinical use is yet to be established. In addition, the cost associated with these additional tests, their availability, and additive value to currently available cytology needs to be evaluated.

All these factors have led to the development of new techniques to help overcome the limitations of EUS-FNA and also better characterize pancreatic cystic lesions. In this chapter, we will discuss novel EUS- and FNA-based imaging and tissue acquisition tools that can help clinicians better distinguish benign from neoplastic pancreatic cysts.

Contrast Harmonic EUS

Recently, contrast harmonic EUS (CH-EUS) has been reported as a useful adjunct in the evaluation and differential diagnosis of pancreatic solid tumors which has led to its application in the assessment of pancreatic cysts. CH-EUS uses a microbubble-based contrast to enable evaluation of the microcirculation of lesions. A 2–5-micron gas bubble core, which is stabilized by a shell, is used as the contrast. The injection of this IV contrast is used to visualize the blood flow even in very small vessels and that in turn allows for evaluation of the vascularity of the cyst wall, mural nodules, and septa. This also helps differentiate small neoplastic solid components in the PCLs which would show signs of vascularization in comparison to the debris and mucus in a cyst which would appear avascular on the CH-EUS (Fig. 12.1).

Technique

A 16- or 18-gauge IV is placed in the patient with a 3-way stopcock to avoid breaking down the microbubbles in the contrast. The contrast is injected followed by a saline flush. The area of interest is imaged with the fundamental B mode imaging and then simultaneous imaging is performed on a split screen with the B mode imaging on one half of the screen and CH-EUS image

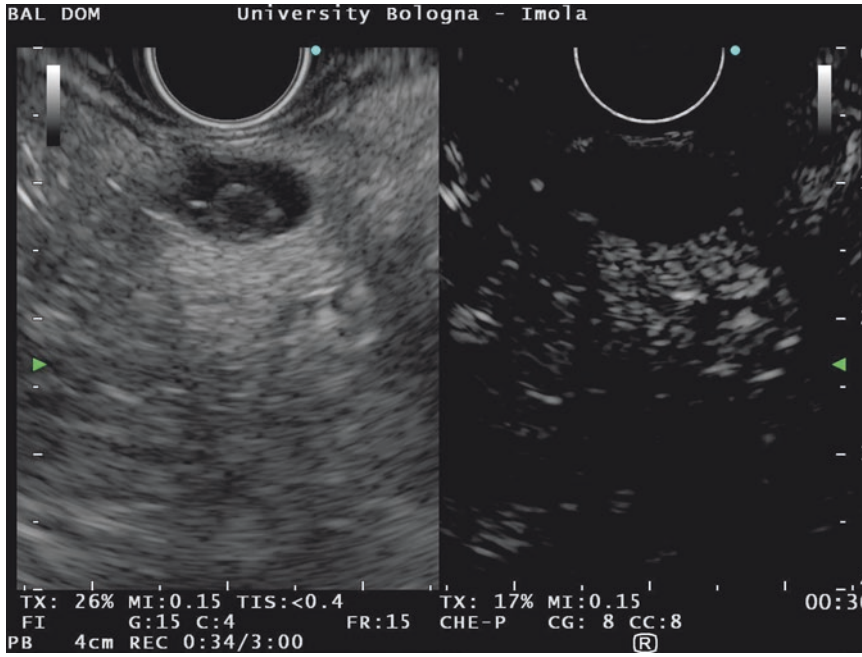

Fig. 12.1 IPMN with nodule: nonenhancement seen on CH-EUS (Courtesy of Dr. Pietro Fusaroli, Italy)

on the other side. The arterial phase starts about 10–20 s after the injection of the contrast and lasts for about 30–45 s. After the arterial phase, the venous phase persists for about 30–120 s during which there is progressive washout of the contrast [11, 12].

During CH-EUS, the vascular portions of the cyst are echogenic and the intracystic debris, mucin, and blood clots remain nonechogenic or invisible. If the cyst or IPMN has a mural nodule, it is usually difficult to distinguish the nodule (especially small nodules) based on CT and MRI; however, CH-EUS can help distinguish these nodules due to the echogenicity and microvascular perfusion of the nodule (Figs. 12.2 and 12.3 and Video 12.1).

The use of CH-EUS in evaluation of pancreatic cysts was first reported in 2009 [13]. In a study of 87 patients with IPMN with mural nodules, CH-EUS findings were compared with the pathologic findings. Mural nodules were classified into four types based on the morphology: type I: low papillary nodule, type II: polypoid nodule, type III: papillary nodule, and type IV: invasive nodule. The study reported that hyperenhanced nodules type III and IV were associated with malignancy, particularly invasive cancer, 88.9% and 91.7% of times, respectively [14]. In 2013, Yamashita et al. used CH-EUS (with Sonazoid) in 17 patients with IPMN with mural lesions. CE-EUS demonstrated vascularity in all 12 cases with pathologically confirmed mural nodules, whereas all four cases without vascularity had mucous "clots." [15] One case of a cystic septum which was interpreted as a hyperenhanced solid nodule on CH-EUS accounted for a false-positive. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CH-EUS for mural nodule detection were 100%, 80%, 92%, 100%, and 94%, respectively. Five of the 12 mural nodules (three of them larger than 10 mm) in this study were not detected by multidetector CT.

Studies of indeterminate pancreatic cysts have reported that CH-EUS could not differentiate between serous and mucinous cysts due to the similarity in enhancement of the cystic walls and septae. However, CH-EUS was helpful in targeting FNA of cysts that revealed malignant nodule enhancement in cysts and thereby helping avoid FNA of cysts containing mucus plug and debris [16, 17].

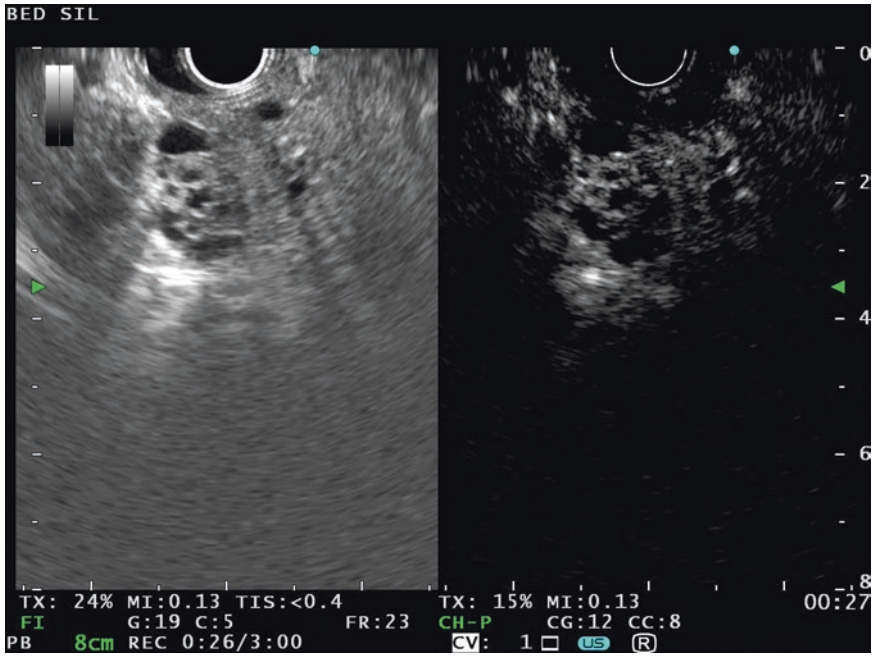

Fig. 12.2 Hyperenhancement seen on CH-EUS in serous cyst (Courtesy of Dr. Pietro Fusaroli, Italy)

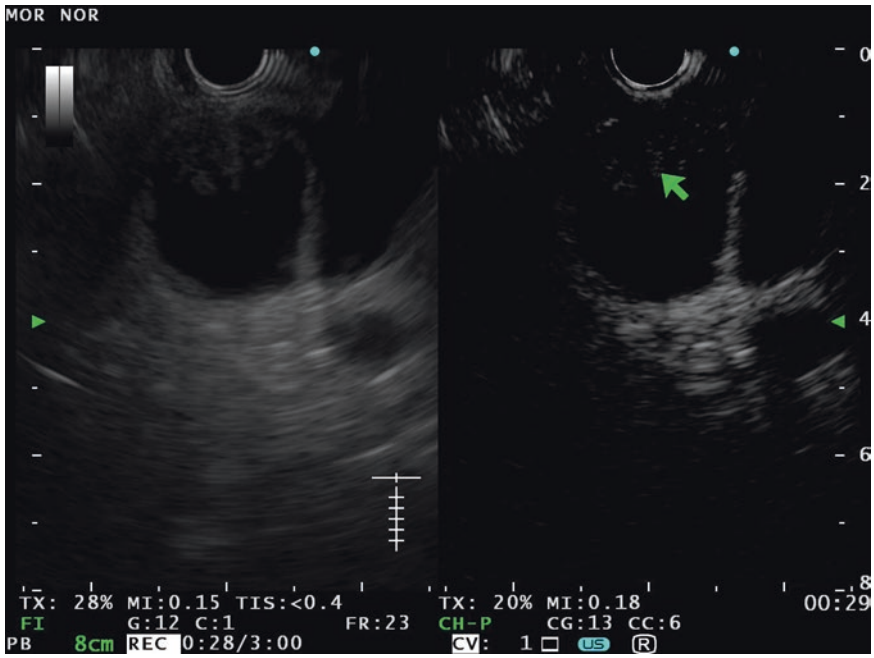

Fig. 12.3 IPMN nodule seen enhancing on CH-EUS (Courtesy of Dr. Pietro Fusaroli, Italy)

CH-EUS has been shown to have a higher accuracy than B mode EUS imaging in diagnosing a malignant cyst with a mural nodule >4 mm in height. Standard B mode imaging had a low specificity (40%) compared to CH-EUS (75%) in the evaluation of mural nodules [18].

In a study of time-intensity curve parameters and evaluation of microvessel density of mural nodules, the diagnostic accuracy of CH-EUS in differentiating the grade of dysplasia inside nodules (low-grade, intermediate grade vs. high-grade dysplasia/carcinoma) was reported [19]. In 30 patients with resected IPMNs (14 LGD/IGD, 16 HGD/invasive carcinoma), the authors observed that the nodule/pancreatic parenchyma contrast ratio was significantly higher in the HGD/invasive carcinoma group than in the LGD/IGD group ($p < 0.05$).

In summary, the preliminary experience shows that CH-EUS may not be able to universally distinguish between enhancing patterns of cystic wall and septa but can help in differentiating intracystic solid components to help detect malignant cysts and may help identify prime targets for FNA within PCLs.

New EUS-FNA-Based Technology

CT/MRCP characteristics, EUS-FNA, fluid analysis (CEA, amylase, and other markers), cytology, fluid characteristics (viscosity), serum tumor markers (CA 19-9), and changes in cyst size and/or morphology over time are currently used to help evaluate pancreatic cysts. This approach is not always diagnostic and is limited at times in allowing an accurate differentiation between the various PCLs, especially in distinguishing IPMNs from MCNs. It is for these reasons that additional diagnostic modalities and newer EUS-FNA-based platforms have been investigated for facilitating characterization between mucinous and nonmucinous cysts. These new approaches may also help differentiate branch duct IPMN and MCN. Some of the recently developed technologies that have been used in combination EUS-FNA that will be discussed in this chapter include needle-based confocal laser endomicroscopy, cystoscopy, the cytobrush, and the use of intracystic biopsy forceps.

Needle-Based Confocal Laser Endomicroscopy (nCLE)

Probe-based confocal laser endomicroscopy (Cellvizio, Mauna Kea Technologies, Paris, France) has been used for real-time imaging at the microscopic level in Barrett's esophagus and in the biliary tree to evaluate for dysplasia and carcinoma [20, 21]. Recently, its application has been extended in the evaluation of pancreatic cystic lesions, using a submillimeter probe that fits through the 19-G FNA needle [22] (Fig. 12.4).

Technique

A 19-gauge EUS-FNA needle is used in this procedure. Ex vivo, the stylet of the needle is

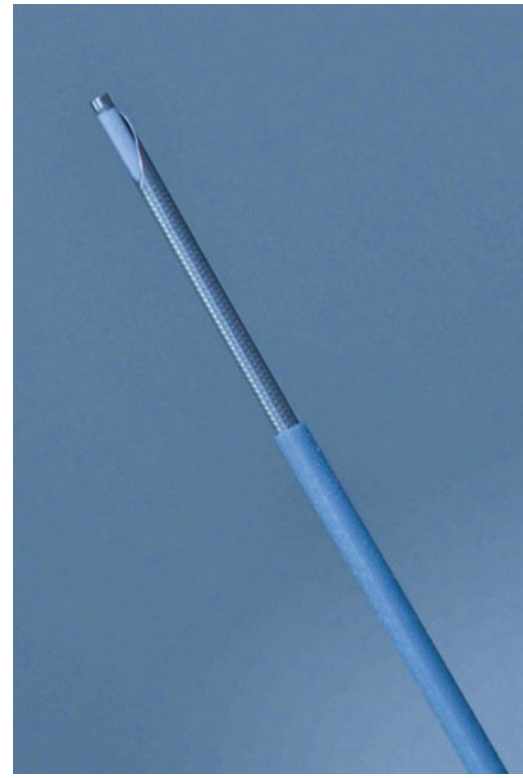

Fig. 12.4 nCLE probe at FNA needle tip (Courtesy of Mauna Kea Technologies)

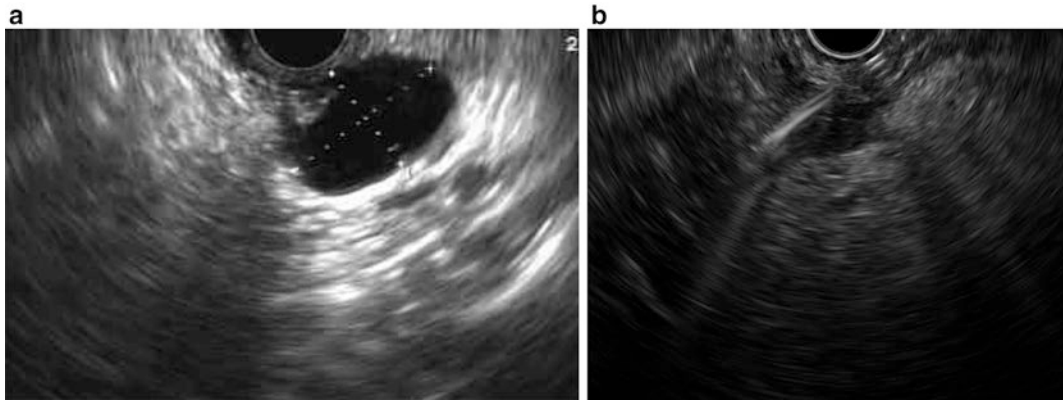

Fig. 12.5 EUS-nCLE evaluation of large pancreatic cyst with a mural nodule

removed and a proprietary locking device is attached to the needle Luer Lock. The AQ-Flex-19 nCLE probe is inserted into the needle and locked into a predetermined position, extending approximately 2 mm from the beveled edge of the FNA needle. The probe is then retracted 1 cm into the needle. Then, under real-time EUS guidance the cyst is punctured using the 19-gauge FNA needle.

Upon entering the cyst, the probe is slowly advanced into the needle, locked in place and then real-time imaging of the cyst wall is performed in vivo. Intravenous injection of fluorescein (2.5–5 mL of 10% fluorescein sodium) immediately prior to the actual imaging is required to facilitate and enhance the image. Fluorescein stains the vessels and helps delineate the tissue structures. The nuclei are not stained and appear as dark spots on the exam. The probe is placed gently against the cyst wall without pressure and various parts of the cyst wall and mural nodules if present are evaluated using a fanning approach by moving the FNA needle (Fig 12.5). The endomicroscopy images and videos are then recorded.

Diagnostic criteria for various pancreatic cysts as represented by nCLE examination: [23–25] (Table 12.1 as described by Krishna and Lee [26]).

1. Mucinous cystadenoma—Large white or gray bands with rare vessels. Vessels are deeper in the ovarian like stroma.

Table 12.1 nCLE diagnostic criteria as proposed by Krishna and Lee [26]

Cyst type	nCLE features
IPMN	• Finger-like projections • Dark rings • Parallel thick bands • Absence of "superficial vascular network" • Absence of "bright floating heterogeneous particles"
Mucinous cystadenoma	• Solitary epithelial bands • Large caliber blood vessels • Clusters of bright particles
Serous cystadenoma	• "Superficial vascular network" • Multiple blood vessels • Absence of finger-like projections
Pseudocyst	• Clusters of bright, floating, heterogeneous particles • Absence of finger-like projections

2. Serous cystadenoma—Blood vessels are superficial and closer to the cystic lumen (superficial vascular network) (Fig. 12.6 and Video 12.1).
3. Intraductal papillary mucinous neoplasm—Finger-like "papillary" projections, dark ring with white core (cross-section), which correspond to the villous changes of the intestinal-type IPMN lesion and presence of fine caliber vessels characterize benign IPMN compared to dark clumps with neovascularization and large vessels (>20 μ diameter) which represent malignant IPMN. (Fig. 12.7).

4. Pseudocysts: Three types of structures are noted with nCLE (Fig. 12.8 and Video 12.1):
   (a) Heterogeneous floating bright particles
   (b) Small black floating particles
   (c) Large, dark, round homogenous floating structures
5. Cystic neuroendocrine tumor: Black neoplastic cell clusters with white fibrous areas.

The use of nCLE to evaluate pancreatic cysts was first assessed in a porcine model in 2010. The first human experience was reported by Konda et al. in 2011 to evaluate the feasibility of nCLE in evaluation of PCLs [22]. Eighteen patients were enrolled in the study (16 cysts and two solid masses). Patients received intravenous injection of 2.5 mL of 10% fluorescein immediately prior to the procedure. Technical feasibility to perform nCLE with good imaging was noted in 17 out of 18 cases. Two patients (11.1%) developed post-procedure pancreatitis—the first patient developed mild pancreatitis requiring a short hospital stay and the second patient developed moderate pancreatitis requiring a 5-day hospitalization. Out of the 17 patients, ten patients had very good images, five had "moderate" quality images, and two had "poor" images. Overall, there were few technical difficulties with loading of the nCLE probe and performing nCLE via the transduodenal approach.

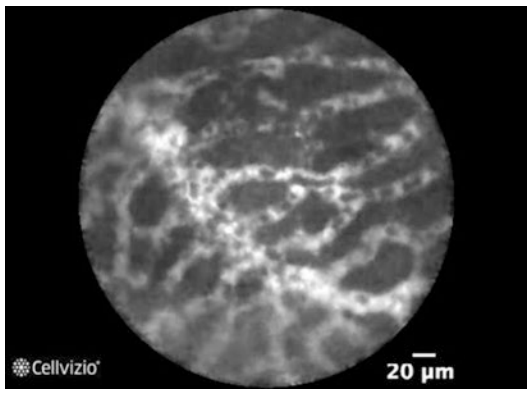

Fig. 12.6 Superficial vascular network (seen in serous cystadenoma) (Courtesy of Mauna Kea Technologies)

In 2013, Konda et al. conducted an international multicenter pilot study (INSPECT trial) to develop descriptive criteria for the image interpretation of nCLE findings in various PCLs and also to assess both safety and diagnostic potential of nCLE in differentiating PCLs [23]. Sixty-six patients at eight referral centers underwent nCLE imaging of which 14 (21.2%) had confirmation by surgical histopathology. Images from eight patients were excluded due to insufficient information for consensus reference diagnosis. Villous structures could be identified in IPMNs as demonstrated by INSPECT trial, which confirmed the preliminary findings of the feasibility trial [22]. The presence of epithelial villous-like structures on nCLE was strongly associated with neoplastic cystic lesions (IPMNs, MCN, or adenocarcinoma). Patients who were identified with villous- or finger-like structures via nCLE were felt to be

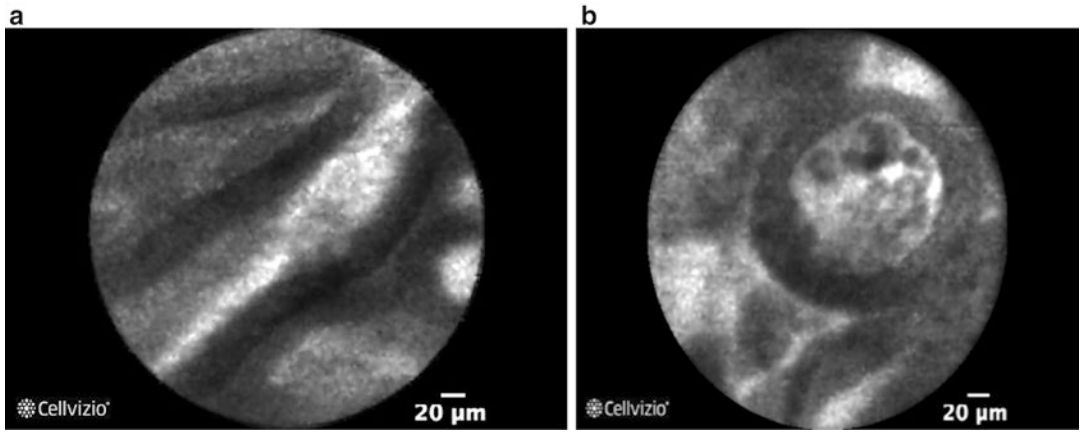

Fig. 12.7 Finger-like projections and dark ring with white core seen in IPMN (Courtesy of Mauna Kea Technologies)

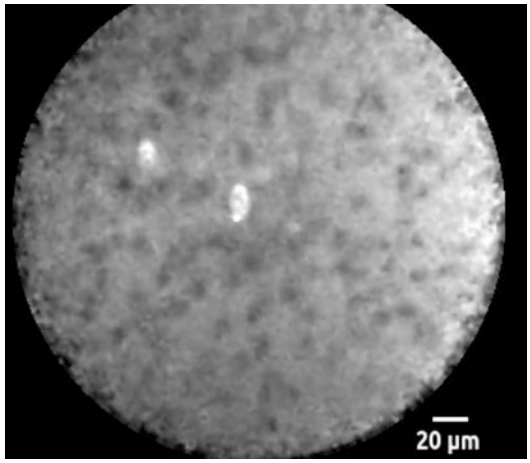

Fig. 12.8 Bright floating particles and lack of blood vessels seen in a pseudocyst

likely to have IPMN despite equivocal fluid analysis and nondiagnostic cytology. This trial demonstrated a sensitivity of 59%, specificity of 100%, positive predictive value of 100%, and a negative predictive value of 50% in differentiating the different PCLs. Overall complication rate was 9%, which included pancreatitis (3%, $n = 2$) (one patient developed mild and other patient developed moderate pancreatitis), intracystic bleeding ($n = 3$), and transient abdominal pain ($n = 1$). The lower rate of pancreatitis in this study was attributed to the investigators limiting the cyst imaging time to <10 min.

Apart from the potential for complications (although typically mild and self-limited), one major limitation of this technology is the ability to only evaluate a very small portion of the cyst wall, i.e., a small area on the contralateral side of the cyst relative to the access point through the cyst wall. In addition, there is a complete inability to image the cyst wall adjacent to the entry point of the FNA needle in the cyst. Also, the ultrathin straight gray bands seen in serous cystadenoma are also seen in adenocarcinoma, representing the desmoplastic fibrous reaction. Other limitations include limited data, lack of datasets on large numbers of patients, and an unknown inter-reader reliability.

In 2015, Nakai et al. assessed the feasibility, safety, and diagnostic yield of the combination of cystoscopy (using the spyglass probe) and nCLE in the clinical diagnosis of pancreatic cystic lesions—DETECT trial (Diagnosis of Pancreatic Cysts: EUS, Through-the-Needle Confocal Laser Endomicroscopy, and Cystoscopy Trial) [24]. This was a single center study with 30 patients with PCLs (only two had surgical histopathology) who underwent dual modality evaluation; cystoscopy performed with the spyglass probe followed by nCLE. The main outcome evaluated was achieving a firm clinical diagnosis of the PCL, using a combination of cystoscopy and nCLE. Clinical diagnoses were established with high probability in 18 patients. Mucin seen during cystoscopy and papillary projections seen via nCLE were characteristic findings for mucinous cystic lesions. The sensitivity of cystoscopy was 90% (9/10) and that of nCLE was 80% (8/10), and the combination yielded 100% sensitivity for diagnosis of pancreatic cystic neoplasm. The procedures were technically successful with the exception of one probe exchange failure. nCLE had a specificity of 100%, PPV of 100%, NPV of 80%, and accuracy of 89% for diagnosis of mucinous cysts. Two patients developed post-procedure pancreatitis (6.6%) requiring 4–5 days of hospitalization without intensive care unit admission or intervention (7%).

A recent multicenter study on the Clinical evaluation of nCLE in cystic lesions of the pancreas (CONTACT) was published in 2015. This study was performed in two phases. Phase 1 involved retrospective validation of specific nCLE diagnostic criteria of pancreatic cysts and Phase 2 was the prospective validation of the specific criteria. A superficial vascular network was found to be a unique feature of serous cystadenomas in this study, of note. In the multicenter evaluation of 31 patients with PCLs, six nonblinded investigators reviewed the nCLE sequences and identified the superficial vascular network as a single feature that was only present in serous cystadenoma (SCN). For nCLE-based diagnosis of SCN, the sensitivity, specificity, PPV, and NPV were 69%, 100%, 100%, 82%, and 87%, respectively. The interobserver agreement for the nCLE SCN findings was high ($k = 0.77$) [27].

Thus, the specificity of nCLE in identifying branch duct IPMN (finger-like papillae) and SCN (superficial vascular network) is high (nearing 100%); however, in the absence of these "classic"

findings, the accuracy of nCLE evaluation remains low. Also, for MCN and pseudocysts, the validation of the nCLE findings in large clinical trials is lacking.

In conclusion, nCLE is a novel FNA-based tool that can help classify certain PCLs with high accuracy and represents a recent advance in this realm. There are some limitations and there is a learning curve for image interpretation, as well as cost associated with the technology. Pancreatitis, although mild to moderate, remains a potential risk. Future studies with higher volume of patients and long-term outcomes will help further clarify and validate the role of nCLE in pancreatic cyst evaluation.

EUS-Guided Cystoscopy

The Spyglass Direct Visualization System (Boston Scientific, Natick MA) has been used widely for various applications in the bile and pancreatic ducts for visualization, stone management, stricture evaluation, etc. [28–30]. It allows for direct visualization and targeted biopsies and/or therapy and ability to assess epithelial abnormalities. The first generation of this device utilized a 0.035″ wide fiber optic probe that can be advanced through the lumen of a 19-gauge FNA needle into a target structure for endoscopic evaluation. Of note, the second generation of the spyglass device utilizes a digital imaging system and no longer uses this fiber optic probe.

This platform has been used to visualize the contents of pancreatic cysts and also direct biopsies. This platform allows for direct visualization of the cyst wall and contents to help distinguish between various PCLs. Its successful use in evaluation of pancreatic cysts has been reported in single case reports, case series, and also more recently in larger prospective studies [24, 31–33].

Technique (as Described by Chai et al.) [33]

The cyst of interest is evaluated with EUS and punctured using a 19-gauge FNA needle and the cyst fluid is aspirated. The color and turbidity of the fluid is assessed. The authors graded the cyst fluid from A to C based on clarity (A—clear background, B—blurred background, C—background not visible). If the cyst fluid is turbid, then saline injection is performed to replace the turbid cyst fluid and facilitate the intracystic visualization with the fiber optic probe. Following this, the fiber optic probe is advanced through the needle into the cyst to directly image and visualize the cystic contents and the cyst wall.

Intracystic imaging characteristics that have been evaluated include:

1. Blood vessels:

   Blood vessels have been characterized as the thick main blood vessel and the branch vessels (Fig. 12.9 and Video 12.1) which are then subcategorized as:

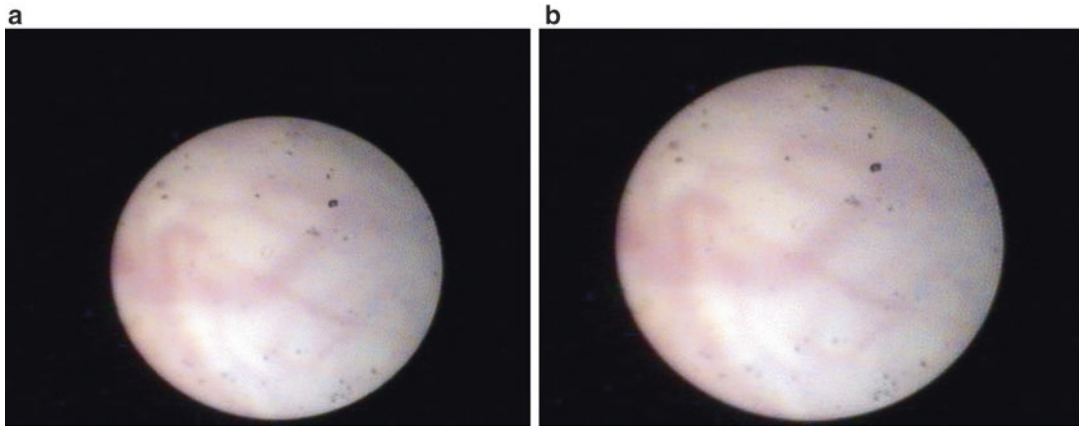

Fig. 12.9 Blood vessels in wall of cyst on cystoscopy (Courtesy of Dr. Enqiang Linghu, China)

(a) Type I: Sparse tree-like branching pattern, seen in SCN (61.5%)
(b) Type II: Dense grid-like pattern, seen in MCN (66.7%)
(c) Type III: Vine-like pattern, seen surrounding papilla like protrusions or partitions (19.4%)

2. Papillary protrusions:
   Papillary structures can be seen on cystoscopy and have been classified into two types:
   (a) Yellow-white: Seen in MCN or IPMN (Fig. 12.10).
   (b) Red: Seen mostly in IPMN due to a richer blood supply.
3. Imaging characteristics of various PCL:
   (a) SCN: Smooth cyst walls, mainly type I like vessel distribution. Also, partitions frequently seen within the cyst with type II blood vessel distribution next to the partitions.
   (b) MCN: Type II blood vessels distribution, opaque cyst fluid. White-yellow deposits on cyst wall.
   (c) IPMN: White roe-shaped or red papilla-like structures can be seen. Fluid can sometimes be white mucus or jelly like.
   (d) Pseudocyst: Yellow or back necrosis/necrotic deposit can be seen in the cyst wall with scant blood vessels. Flocculent particles can be seen in the cyst.

Cystoscopy has been combined with nCLE for evaluation of PCLs and the results reported in the DETECT trial [24]. In this study, cystoscopy had a sensitivity of 90% with an accuracy of 83% in diagnosing mucinous cysts. If surgical pathology is used as a gold standard for mucinous cyst diagnosis on cystoscopy, the criteria of finger-like projections has a low sensitivity of 22%, accuracy of 42% but a 100% specificity [34]. Biopsy proven mucinous cystadenomas have also been reported to have smooth cyst walls on cystoscopy evaluations [32].

In a preliminary study of 43 patients with PCLs using the single operator cholangioscopy fiber optic probe for visualizing the cyst contents, no complications were seen with the platform [33]. The study was performed in cysts >1 cm in size and it provided the image interpretations of the cystoscopy findings of various PCL that were definitively diagnosed with histopathology. Cyst fluid clarity is very important for visualizing the cyst wall and contents and thus this platform requires removal of the turbid cyst fluid and replacing it with saline to be able to visualize the cyst wall. In this study, the tree-like branching pattern of blood vessel distribution was found to be a common characteristic of a serous cystic neoplasm. Intracystic papillary structures were an important characteristic for diagnosing mucinous cystic neoplasms in this study.

Widespread application of cystoscopy is still limited due to the cost of the cholangioscopy probe, limited availability of the probe, need for saline/clear fluid in the cyst to facilitate visualization, and lack of large prospective studies validat-

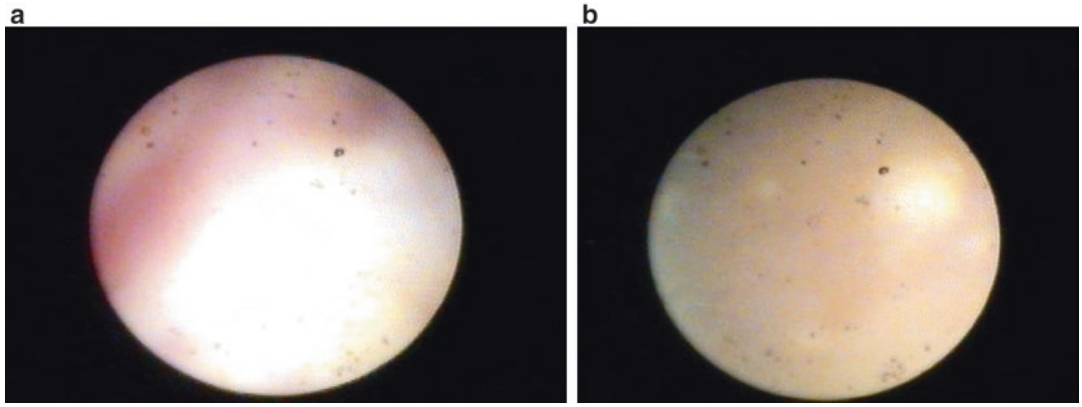

Fig. 12.10 White yellow deposits seen in mucinous cyst (Courtesy of Dr. Enqiang Linghu, China)

ing the cystoscopy findings with the gold standard of surgical pathology. In addition, given the advancement of this technology to a digital platform, it is unknown for how much longer the vendor will continue to manufacture the fiber optic probe.

EUS-Guided Cytobrushing

Another EUS-based platform to improve the yield of FNA in the pancreatic cyst evaluation described in the literature is the cytology brush. A "through-the-needle" cytology brush system (EchoBrush; Cook Endoscopy, Winston-Salem, NC) that was FDA approved for cytology sampling during EUS evaluation of cystic lesions of the pancreas was developed (Fig. 12.11).

Technique

After aspirating 50% of the cyst volume using a standard 19-gauge needle FNA, the EchoBrush is introduced into the needle and advanced into the cyst under EUS guidance. After ensuring that the needle is in the cyst, the brush is moved back and forth repeatedly for 30 s ensuring adequate tangential contact with the cyst wall. The brush can also be rotated on its axis to gain maximal contact with the cystic wall and obtaining the cytology specimen. The brush is then removed and final aspirate of the cyst with the needle is performed to collapse the cyst and the cyst is completely aspirated.

Studies have reported a higher yield of epithelial cells using the cytobrush compared with standard EUS-FNA for cystic lesions of the pancreas (mean size >2 cm). Complication including GI bleeding and pancreatitis has been reported with the cytobrush [35, 36].

In another study of 30 patients with cysts >15 mm, the technique failed in eight patients (27%). A cellular diagnosis was obtained using the brush in 20/22 cases (91%) and the EUS cytology brushing was superior to the aspirated fluid for detecting diagnostic cells (73% vs. 36%, $p = 0.08$) and mucinous cells (50% vs. 18%, $p = 0.016$). However, the procedure had a 10% complication rate with 13.6% morbidity and 4.5% mortality [37].

In 2011, Lozano et al. published their cytobrush data with a total of 127 cystic lesions of the pancreas from 120 patients. Mean size of the cystic lesions was 23.43 ± 21.67 mm. Diagnostic material was obtained in 85.1% (40 of 47) cases using the cytobrush compared to the 66.3% (53 of 80) with conventional EUS-FNA ($p < 0.05$). Three patients had self-limited intracystic bleeding and were observed in recovery room post-procedure, and then discharged home. One

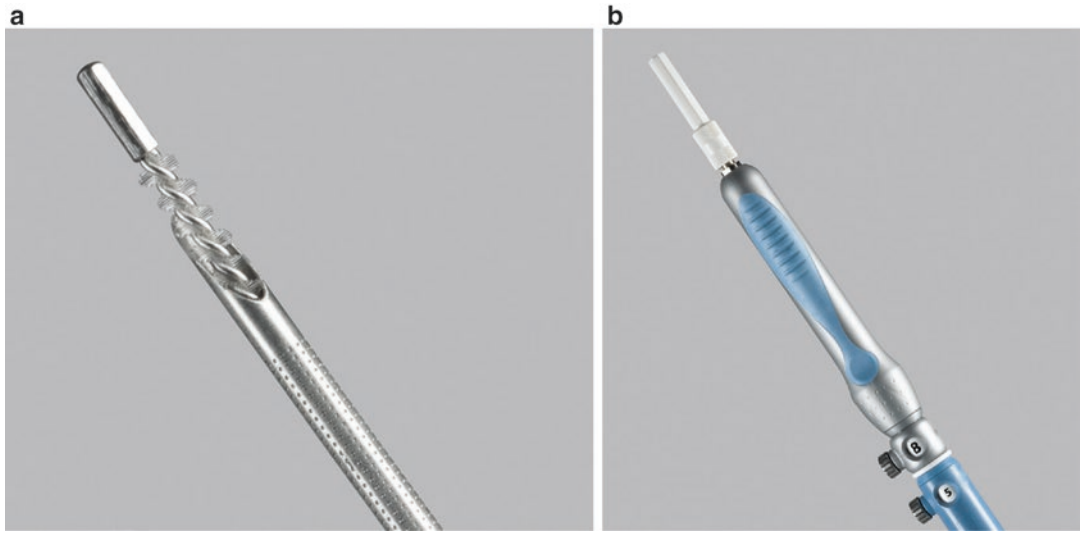

Fig. 12.11 EUS cytology brush at tip of FNA needle and at the FNA needle handle (Courtesy of Cook Medical)

patient developed perigastric abscess, which required hospitalization [38].

Despite encouraging results, the studies have had mixed results due to the complications and technical failure rates. Development of a new and improved commercially available cytobrushing platform is required for clinical use in the future.

EUS-Guided Cyst Biopsy

EUS-FNA-guided intracystic biopsy using a 220 cm × 0.8 mm biopsy forceps has been reported in 2010 in a pilot study of two patients with PCLs. Mucinous cystic neoplasm was diagnosed in both the patients; however, one patient developed severe acute pancreatitis 1 month after the procedure which was possibly thought to be a late complication of the procedure [32]. The latest FDA approved EUS-FNA-based pancreas cyst tissue sampling device is the disposable Moray microforceps (US Endoscopy, Ohio, USA). The device is 230 cm in length, with an open jaw width of 4.3 mm. The jaws are serrated and attached to a flexible 0.8-mm stainless steel spring sheath for easy passage through a 19-gauge FNA needle and allowing its use in tortuous positions (Fig. 12.12).

Technique

The cyst of interest is imaged with EUS. The cyst is then punctured using a 19-gauge FNA needle and the stylet is withdrawn. Then, keeping the grasping jaws of the forceps in the closed position, the microforceps is advanced slowly through the FNA needle to avoid kinking of the sheath. Then, maintaining EUS visualization at all times the forceps is slowly advanced through the needle and the jaws are then opened to capture the desired tissue (Fig. 12.13 and Video 12.1). The tissue grabbed with the forceps can dislodge the needle tip and thus it is very important for the endosonographer to maintain control of the needle handle at all times and to keep the needle tip and forceps under constant EUS vision. An extraction pick may be used to assist in specimen removal from the forceps if necessary.

The microforceps has been used in many case reports and series of indeterminate pancreatic cysts and confirmatory diagnosis was established in these cases revealing IPMN, mucinous cyst, and lymphoepithelial cyst [39–41]. In a case of a 68-year-old male with an 8-cm pancreas cyst with mixed solid/liquid components with inconclusive CEA, amylase, and cytology, the microforceps was successful in obtaining adequate tissue samples from the cyst wall and a

Fig. 12.12 EUS microforceps open and at tip of FNA needle (Courtesy of US Endoscopy)

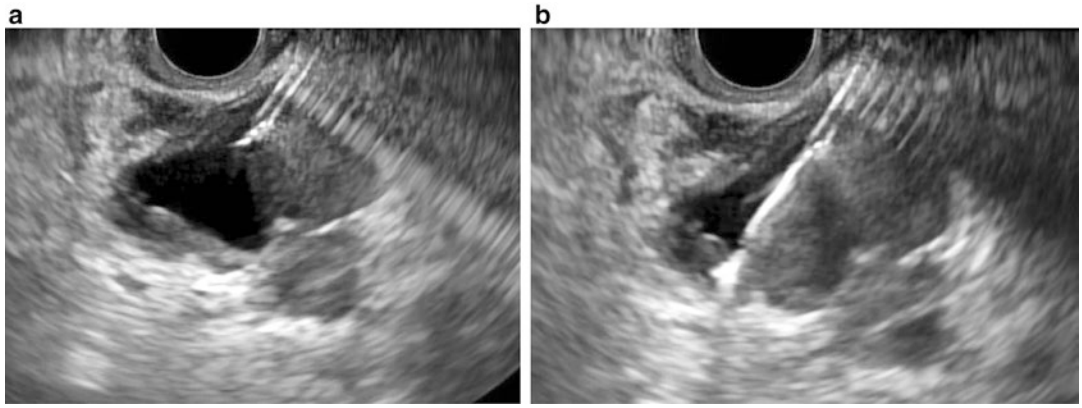

Fig. 12.13 Biopsy of pancreatic cyst wall using EUS microforceps (Courtesy of Dr. Harshit Khara, USA)

diagnosis of lymphoepithelial cyst was established and surgery was avoided [42].

The preliminary limited data on the EUS microforceps with the case reports and case series is promising; however, large prospective trials are needed to evaluate the safety and efficacy of the forceps and also to assess its diagnostic accuracy when compared to the gold standard with surgical histopathology of the lesions.

Summary

With the rising frequency of incidental pancreatic cyst detection, accurate diagnosis and differentiation of malignant from nonmalignant cysts continues to remain a challenge. There are many new promising technologies and techniques to enhance image quality and improve the diagnostic yield of EUS-FNA, thereby facilitating a more definitive and accurate evaluation of pancreatic cystic lesions. Although promising, all these platforms need large prospective trials to determine their safety, efficacy, reproducibility, and accuracy. At this time, all these techniques are only adjuncts to EUS-FNA and the role of the abovementioned technologies from a cost–benefit standpoint and applicability to everyday practice is yet to be established.

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EUS-Guided Pancreatic Cyst Ablation

13

Kristopher Philogene and William R. Brugge

Introduction

With the increasing use of cross-sectional imaging over recent years, there have also been an increasing number of incidental pancreatic cysts discovered. The prevalence of incidental pancreatic cysts based on screening computed tomography (CT) is 2.6% and magnetic resonance imaging (MRI) is 13.5%, respectively [1, 2]. Although pancreatic cysts are usually found incidentally, there is a wide variety of histopathology, with some pancreatic cysts that are inherently neoplastic. Some cystic lesions that have been historically classified by pathologists as neoplastic include mucinous cystic neoplasms (MCN) and intraductal papillary mucinous neoplasms (IPMN). What is essential when it comes to knowing what histological cystic lesions have malignancy potential is being able to differentiate between a benign and malignant cyst [1]. Cyst fluid analysis for certain tumor markers like carcinoembryonic antigen (CEA) and CA 19-9 have been used to differentiate a malignant versus benign mucinous lesion with variable results. Cyst fluid analysis remains in widespread use despite its clear limitations. A significant proportion of cystic lesions are found to be indeterminate with regard to perceived risk of malignancy or potential malignant transformation even after rigorous investigation, including cystic fluid aspiration and analysis [3].

Chiaro et al. released a study of patients who were diagnosed with pancreatic cysts and who had underwent surgical resection found that 8.5% of the patients who underwent surgery had experienced an error in their preoperative diagnosis, showing that these patients may not have required surgical intervention at all based off of the histology of their lesions [4]. Although surgical resection has a mortality rate of <1% (with the most commonly resected lesion being IPMN) complications developed in up to 18% of patients, with pancreatic fistula being the most common complication, underscoring the relatively high-risk nature of pancreatic surgery (even in the modern era). The 90-day mortality rate in patients who required a total pancreatectomy was also as high as 7% [5, 6]. Therefore, a clinical decision often needs to be made on whether to observe the cyst or go through with surgical resection of an indeterminate incidental pancreatic cyst, which can be a difficult decision to make.

Because of the unclear management strategy for these patient populations, there was an

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important need to find a safe and effective treatment modality for pancreatic cysts. Endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA) of cystic fluid has been a widely used diagnostic tool for pancreatic cyst analysis and identification. With EUS-FNA, pancreatic cyst evaluation then turned towards management and treatment through pancreatic cyst ablation by EUS-guided ethanol injections along with injections of other potentially ablative agents. There are several accounts and studies that have shown that ethanol ablation through EUS-guided injections can be performed safely with few complications, particularly evidenced by the successful ablation attempts on insulinomas, thyroid nodules, splenic, liver, and renal cysts [7–10]. The use of antitumor agents during these injections has also been found to be safe and feasible in treating pancreatic cancer [11–13]. EUS-guided pancreatic cyst ablation has been studied as a possible alternative to surgical resection by several clinical trials with special attention on ethanol injections and the use of Paclitaxel injections in conjunction with ethanol injections. The purpose of this review is to examine the procedural basics, safety, and efficacy of cyst ablation along with the treatment response and future application that derives from this treatment modality.

How to Perform an EUS-Guided Cyst Ablation

The equipment that is required to assess the internal structure of the pancreatic cyst must be able to determine the number of septations within the cyst, the presence of a mass or nodule, and the overall wall thickness of the cyst. To determine the structure of the cyst, traditional EUS imaging utilized a radial scanning echoendoscope. The curvilinear-array echoendoscope with 7.5-MHz transducer is also an instrument that can be used to image pancreatic cysts, and is favored by many operators. Both have high-resolution imaging capabilities. Curvilinear-array echoendoscopes are used to puncture the cyst through a transgastric or transduodenal route using an EUS aspiration needle (Fig. 13.1). Cyst fluid should be evacuated from the cyst prior to injection and sent for cyst fluid analysis. Subtotal evacuation of the cyst is followed by injection with the volume of fluid removed equaling the volume of fluid being replaced. The cyst is then allowed to undergo lavage with ethanol for 3–5 min. The ethanol is typically aspirated as much as possible from the cyst after lavage (Fig. 13.2 and Video 13.1). If a chemotherapeutic agent is being injected following an ethanol injection into the cyst, the chemotherapeutic agent should be injected and left within the cyst, with the total volume of injection not exceeding the amount of fluid that was aspirated. To avoid leakage within the cyst wall or parenchymal injury, the needle tip must be maintained in the cyst cavity. After lavage and aspiration is complete, the needle is then removed from the cyst cavity.

Ablative Agents

Ethanol has been the most frequently used ablative agent for cyst ablations because of its low cost compared to other agents. Ethanol has an extremely low cost and it has a low viscosity that makes it easy to inject when using a small gauge needle. In hepatic cyst injections, ethanol can lead to cell membrane lysis, protein denaturation, and vascular occlusion [14, 15]. It is felt that similar benefits can be seen in pancreatic cyst injections.

Paclitaxel is a widely used chemotherapeutic agent whose mechanism of action is to bind to the β-subunit of the tubulin protein leading to stabilization of microtubules ultimately inhibiting normal mitotic spindle formation [16]. Paclitaxel is hydrophobic and viscous, which reduces the risk of leakage within the cystic cavity when used as an ablative agent. However, given the high viscosity of paclitaxel and its cosolvent, castor oil, paclitaxel has to be diluted 1:1 with 0.9% normal saline solution for injection. There is another formula of the paclitaxel solution that uses a polymeric micelle that is a less viscous delivery mechanism and can be administered without dilution [17]. Paclitaxel injection is less common than ethanol injection, of note.

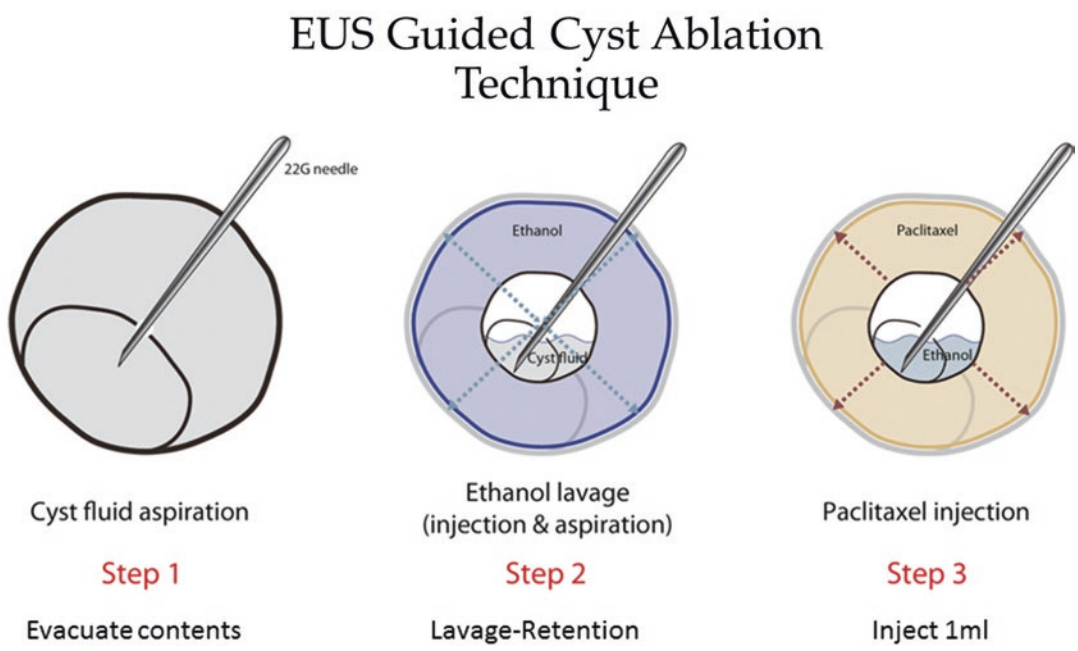

Fig. 13.1 Technique summary of EUS-guided injection and lavage of a pancreatic cyst

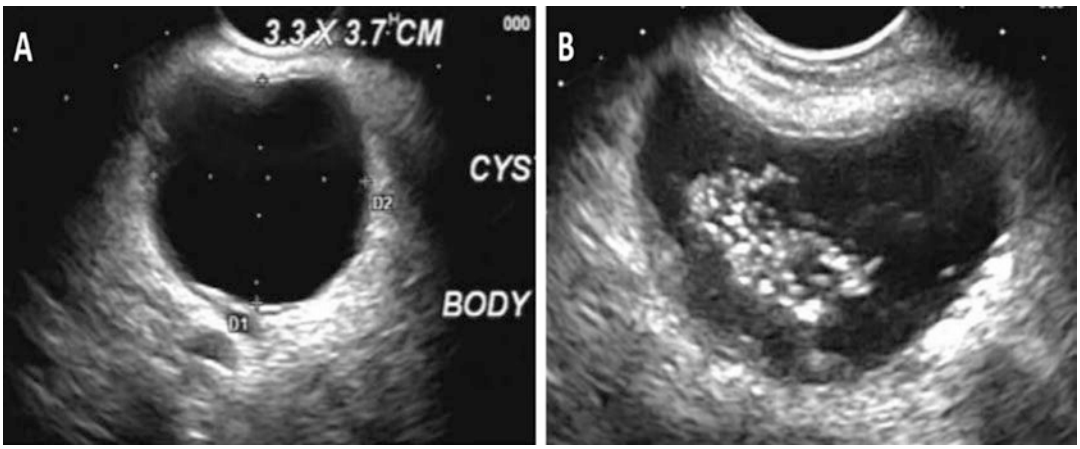

Fig. 13.2 Linear EUS image of ethanol lavage before (**a**) and after injection (**b**): note the presence of injected bubbles of ethanol in the cyst fluid

Special Considerations for EUS-Guided Cyst Ablation

The morphologic characteristics of a pancreatic cyst will guide the approach of how to best manage these cysts through injection and ablation while also giving a better sense of efficacy and resolution of a cyst. An initial cyst size of <35 mm was predictive of complete resolution of pancreatic cysts that underwent ablation. Cyst injection therapy and its overall efficacy are also affected by the number of loculations that the cyst may have as well as the number of septations. A unilocular or oligolocular cyst with 2–3 locules has the greatest chance of having a successful ablation with first needle pass as the entire cyst

can be accessed via a single injection (especially if septations are perforate in nature). A second needle pass may be required in cysts that have more than 2–3 locules [18]. When all locules cannot be visualized through endoscopic imaging, needle passage through a septation may be indicated. To determine good distribution of the ablative agents within the cyst after needle passage through a septation, there will be formation of echogenic bubbles across the septation along with collapse of the locules. Sometimes, if a locule is missed, there may be regrowth of the cyst, indicating inadequate treatment or treatment failure. It is important to determine the optimal needle angle in order to maximize the number of targeted locules with the fewest passes as there are associated risks with injection therapy. Pancreatitis related to the ablative agent, particularly if there is a communication between the main pancreatic duct and the cyst (although relatively uncommon), is one of those complications [17]. Repeated lavage and injection can lead to an outflow tract to form and thus diminish the ablative effect as well due to reduced time of contact with the cyst. Because of this inherent risk, multiple injections and lavages should be avoided when possible.

Near-complete evacuation of the cyst prior to injection therapy also leads to increasing the surface area that is directly exposed to the ablative agent, which increases the effectiveness of the ablation. Ethanol lavage before using other ablative/chemotherapeutic agents may reduce the viscosity of the thick mucin and improve the delivery of the ablation agent within the cyst locules.

Safety and Controversy of Cyst Ablation

With any budding treatment, modality, safety, and efficacy must be considered when it comes to investigating and, eventually, implementing management. Therefore, the complications related to cyst ablation can be described in several clinical trials. Most complications were self-limited and mild. Abdominal pain is the most common complication after cyst ablation. Pancreatitis is also a possible complication. However, several studies have shown that pancreatitis is a relatively rare adverse effect of cyst ablation ranging from 2% to 10% of patients [19].

Portal vein thrombosis has also been seen as a complication, evidenced by a case report of a 68-year-old woman who underwent her second pancreatic cyst ablation and was found to have portal vein thrombosis on CT imaging. Portal vein thrombosis can be precipitated by local inflammation seen in pancreatitis and diverticulitis. EUS-guided pancreatic cyst ablation induces inflammation locally within the cyst leading to atrophy of the epithelial lining of the cyst (Fig. 13.3). With that, however, cyst ablation can lead to extensive inflammation around the cyst and within the cyst. Splenic vein thrombosis/obliteration is also another rare complication of cyst ablation, seen in a prospective double-blind randomized control trial where one patient developed splenic vein obliteration [19]. Any leakage of the ablative agent from the cyst can also induce inflammation that could spread to nearby vessels which can lead to portal vein thrombosis [20]. Similar outcomes were observed in another study of 52 patients who underwent EUS-guided ablation where one patient developed splenic vein thrombosis/obliteration with collateral formation [17].

When it comes to the concern of using chemotherapeutic agents as a means for cyst ablation, it raises the question of possible systemic effects after chemotherapy injection. In a case series of ten patients who underwent cyst ablation with alcohol followed by paclitaxel, the plasma paclitaxel concentrations were nearly undetectable and rarely caused any adverse effect [21].

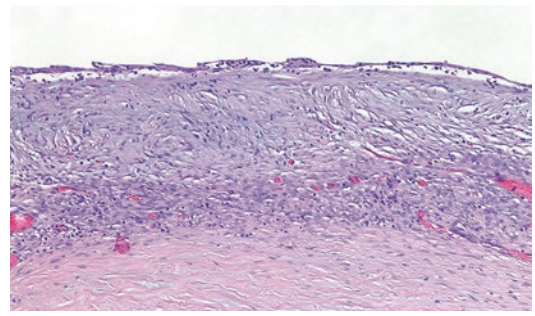

Fig. 13.3 Histology of ethanol ablated cyst epithelium: note the thin attenuated epithelium

In recent years, there has been the question of how to minimize adverse effects of EUS-guided cyst ablation while maintaining the efficacy of the procedure. It has been thought that the use of alcohol as an ablative agent is what leads to the serious complications of ablation (pancreatitis, splenic vein obliteration, etc.) due to alcohol extravasation or due to the known inflammatory effects of alcohol on the pancreatic parenchyma and its surrounding tissue [22]. Ablation of benign cysts should also be considered. These procedures and interventions do have their own risk of complications. Using cystic fluid analysis can help guide the management strategy that can be pursued but despite cystic fluid analysis, there are still a cohort of patients who will be have an indeterminate pancreatic cyst.

It is widely accepted to continue to monitor pancreatic cysts in asymptomatic patients who are not good surgical candidates. However, lifelong surveillance is time consuming, economically challenging, and a burden on the patients, particularly the elderly patients who are most commonly diagnosed with pancreatic cystic lesions. Cyst ablation could be an alternative for patients who are not surgical candidates and used to promote early management of possible premalignant lesions. With the proposed eradication of premalignant lesions through EUS-guided cyst ablation, it may be a reasonable treatment modality especially because of its low risk and relatively high efficacy.

Clinical Trials for EUS-Guided Cyst Ablation

Several studies have been published on EUS-guided cyst ablation since the initial pilot study in 2005, focusing both on ethanol injection alone and ethanol followed by paclitaxel injection. In the initial pilot study, ethanol lavage was administered alone during EUS-guided cyst ablation and the patients were followed up in a 6–12-month period. Thirty-five percent of 23 patients had complete resolution. All septated cysts persisted. Five patients from this same study underwent surgical resection, all of which were MCN with a variable degree of epithelial ablation [23]. A retrospective study done at two tertiary care centers had 13 patients undergo ethanol lavage through EUS-guided ablation and 11 of the 13 (85%) patients had complete resolution with a mean follow-up of 26 months [24] (Fig. 13.4). One study that included the longest follow-up and largest number of patients within a clinical trial for EUS-guided cyst ablation had 91 patients who were categorized as having indeterminate pancreatic cystic lesions undergo the procedure. The resolution rate for MCN was 50% as compared to IPMN where the resolution rate was a disappointing 11%, suggesting that communication with the pancreatic duct may reduce the efficacy of ethanol [4].

To increase the ablative effect, Paclitaxel, a chemotherapeutic agent used for treatment of

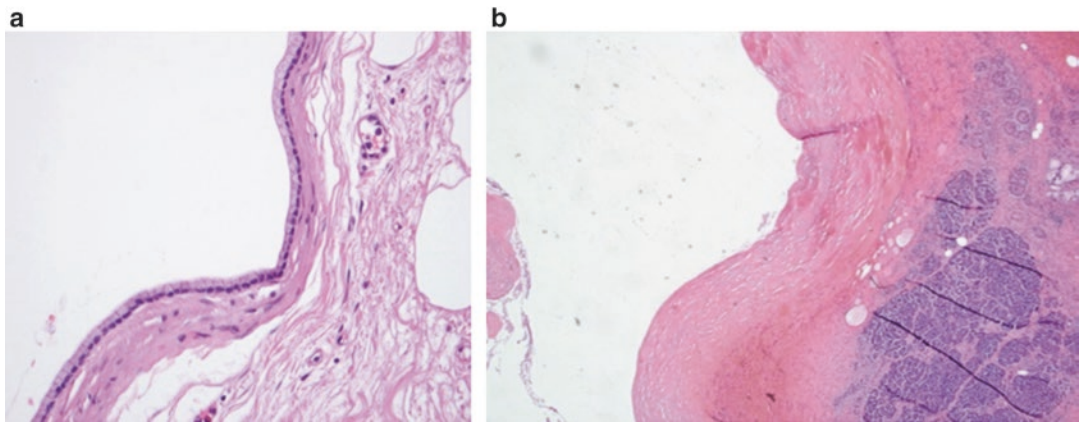

Fig. 13.4 Histology of cyst epithelium after saline lavage (**a**) and after ethanol (**b**): note the intact epithelium after saline lavage and the attenuated epithelium after ethanol lavage

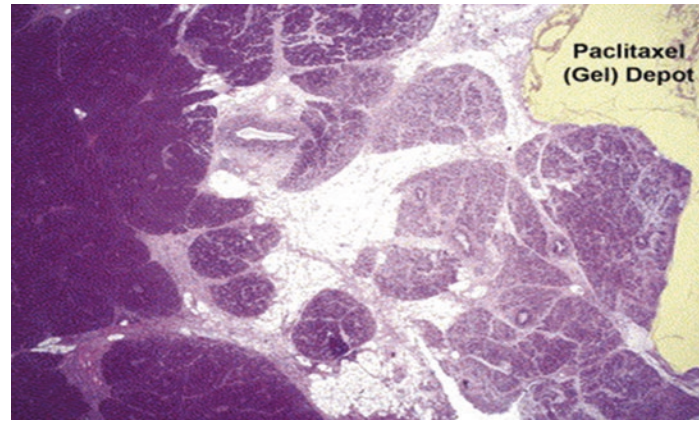

Fig. 13.5 Histology of injected Paclitaxel gel into the pancreas: note the lack of inflammatory response to the gel

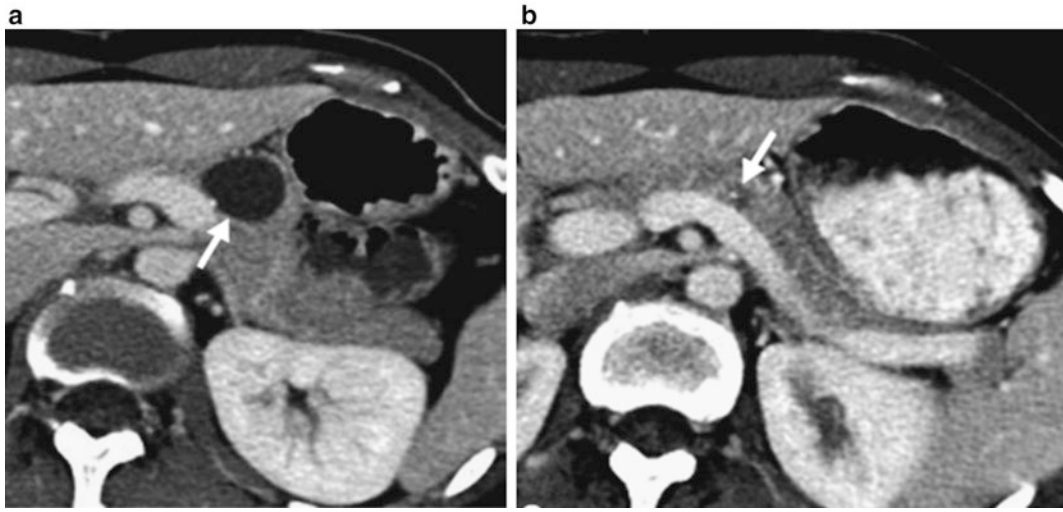

Fig. 13.6 CT scan of pancreatic body cyst before (**a**) and after (**b**) ablation therapy

several malignancies, has been combined with ethanol injection (Fig. 13.5). It was proposed that ethanol can be used to distort the epithelial lining of the cyst, which would allow for paclitaxel or any other ablative agent to diffuse through the damaged epithelium leading to additional inhibitory effects through apoptosis. In a pilot study of 14 patients who underwent ablation therapy using ethanol injection followed by paclitaxel injection, 11 of the 14 patients saw complete resolution at 6-month follow-up (Fig. 13.6). This could represent a synergistic effect given that ethanol alone had a resolution rate of 33% in the previous investigations [25]. Another study of 52 patients who underwent ethanol and paclitaxel lavage, 62% of patients had complete resolution, with smaller cystic lesions having a higher likelihood of resolution [17].

There has also been increased interest in eliminating ethanol injections from cyst ablation altogether given that it is thought that the complications that arise with cyst ablation come from the ethanol injections (Fig. 13.7). The CHARM trial, a prospective, randomized double-blinded pilot study of ten patients with mucinous cysts, had patients divided into two groups: those undergoing ablation using ethanol injections followed by a combination of paclitaxel and gemcitabine and those getting normal saline injections followed by the chemotherapeutic agents

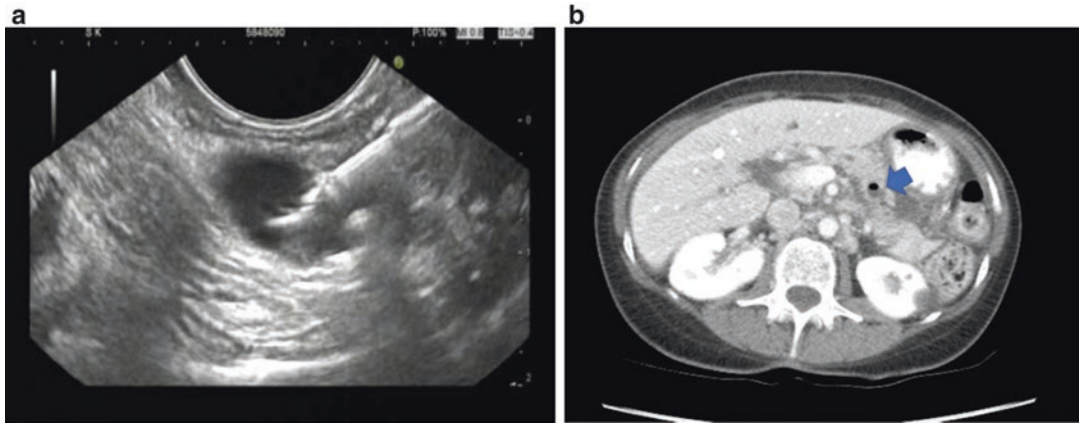

Fig. 13.7 EUS-guided cyst injection into a 2-cm unilocular cyst (**a**) complicated by acute pancreatitis as seen on a CT scan with an air-fluid level in the cyst (**b**). The patient made a quick recovery

described. At 6 months and 12 months, the alcohol-free group had a resolution rate of 67% while the alcohol group had a resolution rate of 50% and 75%, respectively. This study suggests that alcohol use may not be required for effective cyst ablation [26]. In a single-center, prospective, double-blind clinical trial, 39 patients with mucinous pancreatic cysts also were divided into two groups both receiving paclitaxel and gemcitabine with one group receiving prior normal saline injection and the other group receiving ethanol injection to determine the efficacy of an alcohol-free ablation as well as assess its effect on the complication rates. Sixty-seven percent of the alcohol-free group had complete resolution of cysts compared to 61% for the alcohol group. Six percent of patients within the alcohol group had serious adverse effects (e.g. pancreatitis) and 22% developed minor side effects (e.g. mild abdominal pain). The alcohol-free group had no reports of any complications, minor or serious [27]. Therefore, it is worth noting that removing alcohol from the treatment modality for cyst ablations may be a safer technique, but with very good efficacy.

Septations in a pancreatic cyst is an important morphological factor when it comes to the effectiveness and efficacy of cyst ablation. In a case series of ten patients who had septated pancreatic cysts, complete resolution occurred in six of the ten patients. Two patients had an initial response to ethanol and paclitaxel ablation but by 12 months had regrowth of the cyst thought to be due to the presence of, and subsequent proliferation of, remnant mucinous epithelium in missed locules, confirmed by histopathology [28]. Therefore, careful selection and review of the patients and the morphology of the cystic lesion is important to consider for improving the efficacy of using cystic ablation as an effective treatment method.

The short-term outcomes of EUS-guided cyst ablation appear to be promising. However, there had been concern for the overall efficacy in the long term when it comes to complete resolution with no recurrence. In a single-center, prospective study of 164 patients with pancreatic cysts undergoing EUS ablation using ethanol and paclitaxel, complete resolution of the cyst occurred in 114 (72.2%) patients with only two patients (1.7%) showing cyst recurrence at a median follow-up of 72 months. This study may indicate that EUS-guided cyst ablation is an effective and durable alternative therapy to surgery [29].

To improve the ablative effect and resolution of pancreatic cysts using this treatment modality, a second needle passed at different angles along with booster ablation have been proposed and trialed. Cysts that have six or fewer locules are usually preferred when evaluating which cysts are amenable to ablation because the presence of septa may prevent the delivery of the ablative agents to all locules. To minimize the risk of

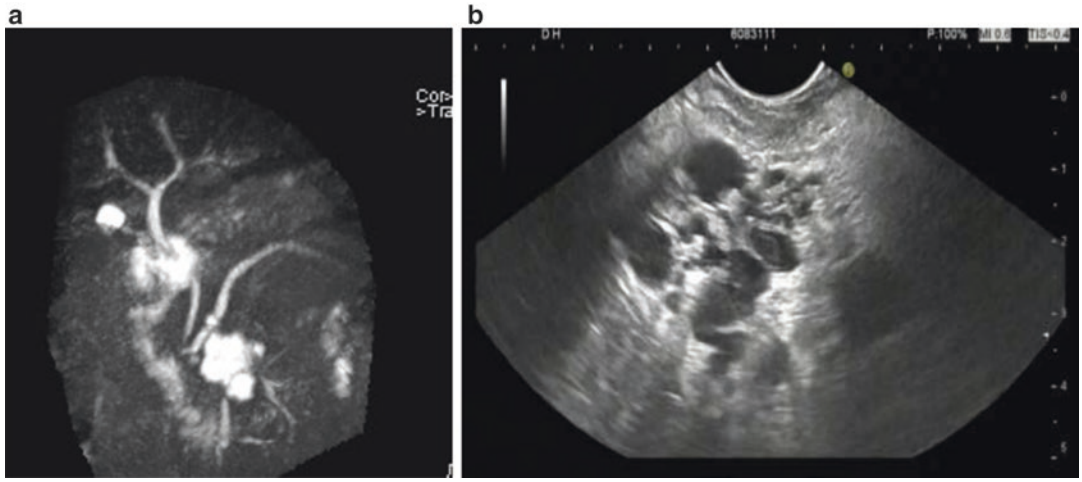

Fig. 13.8 MRCP of a side branch IPMN located deep in the uncinate with multiple septations (**a**) making the EUS-guided injection technically difficult (**b**). A 19-gauge needle was required because of the viscosity of the fluid

missing locules, multiple needle passes at different angles may be warranted. In a case series of 13 patients with suspected IPMN, complete resolution seen on computed tomography (CT) or magnetic resonance imaging (MRI) occurred in five (38%) patients after two EUS-guided ethanol lavages compared to no patients showing resolution with a single needle pass, measured by the decrease in size of the cyst and its surface area. The results of this study demonstrate that there may be a need for multiple ethanol lavage sessions in the presence of viscous fluid and/or septa to allow for more epithelial surfaces to encounter the ablative agent, resulting in higher cyst ablation rates [18]. (Fig. 13.8) However, multiple needle passes may increase the complications associated with cyst ablation and, therefore, a second needle pass should be performed during the same session with caution [30].

Indications for EUS-Guided Cyst Ablation

EUS-guided pancreatic cyst ablation is still being investigated and should be used only for a select group of patients based on the overall efficacy of this treatment modality while also keeping the procedure-related risks/complications low. The ideal candidates for ablation are (1) 2–3.5-cm unilocular or oligolocular cysts without any obvious communication between the cyst and the main pancreatic duct on imaging, (2) cysts that have increased in size at follow-up, (3) when FNA is required for characterization, and (4) patients who have a high surgical risk or decline surgery [29]. Physicians should also have a multidisciplinary approach to discussing the patient's case prior to making the decision to manage the cyst using cyst ablation.

The ideal cyst for treatment with cyst ablation appears to be mucinous cystic neoplasms. These lesions, however, can often be removed easily with laparoscopic distal pancreatectomy with minimal mortality and no risk of recurrence after resection [31]. It is still too early to suggest that surgery or cyst ablation alone would be the only treatment modality that should be offered for pancreatic cysts and would require further study.

Future Use and Modifications to Therapy of EUS-Guided Cyst Ablation

EUS-guided cyst ablation has been studied and has the potential to be an acceptable alternative to surgical resection of cysts without the associated risks of surgery. However, the acceptance of ablation by surgeons as an alternative to surgery and

for oncologists, institutions, and institutional review boards to permit gastroenterologists to use chemotherapy to treat pancreatic cysts would have to be addressed before EUS-guided ablation can become more commonplace [31].

Some procedural modifications that can be made to improve the efficacy of ablation include a second needle pass technique for septated cysts, booster ablation for larger cyst that are unresponsive to treatment, maintenance of ethanol concentrations during lavage, and developing slow release ablative agents [32]. Long-term follow-up in patients who undergo cyst ablation will also need to be established, particularly because there are no conventional imaging techniques available that could accurately ensure effective identification of resolution. Oh et al. determined that some patients who underwent ethanol/paclitaxel injection and, eventually, surgical resection had at least 50% of the epithelial lining intact. These patients continue to be at risk for tumorigenesis and this risk should be kept in mind in selecting patients for EUS-guided ablation [33].

There are several other treatment modalities that are currently being studied in place of EUS-guided ablation that have been emerging in recent years. Radiofrequency ablation (RFA) is a well-studied antitumor treatment for dysplastic Barret's esophagus and hepatocellular carcinoma that utilizes local thermal-induced coagulative necrosis. This technique has been applied to pancreatic cancers. However, the postprocedural morbidities were high and most likely due to the local effects of heat damage. Unlike hepatic tumors, which have a surrounding parenchyma that is protective, pancreatic tumors are usually wrapped around blood vessels or the distal bile duct, which can sustain thermal injury during the procedure. However, multiple studies have demonstrated that radiofrequency ablation is a feasible, safe treatment modality. RFA does require further investigation in larger study populations [34–36]. A new EUS needle prototype is being developed that would be able to connect to standard electrosurgical units found in many endoscopy laboratories. This would help reduce costs in purchasing new equipment and decrease the need for additional training [37].

Photodynamic therapy (PDT) has also been shown to be an effective means of inducing coagulation with the photosensitizing agent Porfimer sodium and has been shown in the previous studies to be effective in tissue ablation within porcine liver, pancreas, kidney, and spleen. Brachytherapy is a type of radiation therapy where the radiation source is inserted within or adjacent to known cancer tissue. Brachytherapy has been utilized in the management of several localized cancers. However, it is still under investigation for pancreatic cancer. One clinical trial of 15 patients with pancreatic adenocarcinoma who underwent brachytherapy showed some improvement in pain for a limited period. However, there was no survival benefit and three patients had complications of pancreatitis and pseudocyst formation. High-intensity focused ultrasound (HIFU) is another rapidly developing treatment modality that is being used more often for noninvasive and minimally invasive ablation of benign and malignant tumors. HIFU works by delivering ultrasound energy to the tumor which ultimately leads to heating of the tumor tissue and tissue denaturation. HIFU may be both curative and palliative for patients with pancreatic cancer. Studies have shown pain reduction in patients with unresectable pancreatic cancer [38].

Conclusions

A large number of trials have now demonstrated the technical ease and safety of EUS-guided injection and ablation therapy of pancreatic cystic neoplasms. Morphologically, the ideal candidate for ablation is a 2–4-cm unilocular cyst in the body or tail of the pancreas. Mucinous cystic neoplasms appear to have a better response rate as compared to side branch IPMN lesions. Macrocystic serous cystadenomas have not been well studied, but will probably respond well to injection therapy. Malignant cysts and neuroendocrine cystic neoplasms should not be treated with ablation therapy. In order to achieve complete elimination of the cyst, it is ideal to provide injection therapy every 3 months until eradication has been achieved. MRCP should be used as

the imaging guide that can provide highly accurate measurements of the cysts. This type of therapy is still considered "investigational" and should be performed under the guidance of a formal protocol approved by an institutional review board. In the future, EUS-guided radiofrequency ablation therapy might be used in conjunction with injection therapy to provide long-term resolution of cystic neoplasms.

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14 Endoscopic Ultrasound-Guided Access to the Stomach in Patients with Prior Gastric Bypass to Facilitate Endoscopic Retrograde Cholangiopancreatography

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Background

Over the last four decades the prevalence of obesity among adults in the United States (US) has increased significantly. According to the 2013–2014 national health and nutrition examination survey the estimated percentage of US adults with obesity is 37.7 that means more than 1 in 3 adults were considered to be obese [1, 2]. Surgical treatment of obesity is an effective method of achieving weight loss and the most commonly performed bariatric surgery worldwide is Roux-en-Y gastric bypass (RYGB) [3]. RYGB patients are predisposed to develop cholelithiasis and other pancreatobiliary pathologies that pose a different challenge to the gastroenterologist. Performing conventional endoscopic retrograde cholangiopancreatography (ERCP) in these patients has its own obstacles since the normal anatomy to reach the papilla has been altered. Multiple endoscopes and techniques have been described to gain access into the excluded pancreatobiliary system with varying success rates and limitations (Table 14.1). Enteroscopy-assisted ERCP using double-balloon enteroscopy, single-balloon enteroscopy, or spiral enteroscopy has been used in patients with Roux-en-Y reconstruction. However, these scopes do not have elevators and thus the manipulation of the accessories may be challenging, if not impossible. The overall success rate using enteroscopy-assisted ERCP has been evaluated in retrospective analysis and multicenter clinical trial and was found to be around 63% [4–6]. This is significantly lower compared to when ERCP is performed through a gastrostomy tract into the excluded stomach [4]. Gastrostomy-assisted ERCP is another approach in this patient population. It consists of accessing the gastric remnant by placing a gastrostomy tube and then proceeding with conventional ERCP. This often requires aggressive dilation of the gastrostomy tract, which can be painful for patients. This procedure has a higher success rate; however, the rates of adverse events are more common when compared to double balloon-assisted ERCP and mostly related to the gastrostomy creation (14.5% vs 3% $p = 0.022$) [4]. Access into the excluded stomach can be

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Table 14.1 Success rate and adverse events of device-assisted enteroscopy facilitated ERCP versus transgastric ERCP

Route of access	Overall success rate (%)	Adverse events	Limitations
Device-assisted enteroscopy facilitated ERCP	63 [4, 5]	3–12.4% [4, 5]	– Length of Roux-en-Y limb – Limited manipulations of accessories due to lack of elevator – Forward vision enteroscope
Transgastric ERCP techniques 1. Laparoscopic-assisted ERCP 2. Open surgery 3. Antecedent gastrostomy tube placement 4. EUS directed transgastric ERCP	98.5 [7] 98.9 100 96.4 93.8	14% complication rate [7] • 83% gastrostomy related • 17% ERCP related	– Need for staged procedure with antecedent G tube placement – Increased cost of the procedure – Need for multidisciplinary collaboration

obtained laparoscopically, by open surgery, via previous gastrostomy tube placement by interventional radiology and staged ERCP or with endoscopic ultrasound (EUS) guidance.

The overall success rate of transgastric ERCP has been evaluated in a recent systematic review by Banerjee et al. and was found to be 98.5% regardless of the technique used to gain access into the excluded stomach with a 14% complication rate (Table 14.1) [7]. In this chapter, we will focus on an innovative approach of endoscopic ultrasound-guided access into the gastric remnant in patients with RYGB for assisted ERCP. The use of endoscopic ultrasound to facilitate creation of a gastrostomy in patients with RYGB has been described as early as 2011 [8]. Multiple approaches have been used and are noteworthy such as EUS-guided sutured gastropexy for transgastric ERCP (ESTER) [9], external EUS-directed transgastric ERCP (EDGE) [10], and internal EDGE [11]. Percutaneous assisted transprosthetic endoscopic therapy (PATENT) is another minimally invasive endoscopic approach to access the gastric remnant and create a gastrostomy; however, it does not involve endoscopic ultrasound and access into the excluded stomach is obtained via deep balloon enteroscopy [12]. The same group has reported recently a modified PATENT using endoscopic ultrasound [13].

Overview of the EDGE Procedure

Equipment Needed for Internal EDGE

a. Linear echoendoscope (GF-UCT180; Olympus, Central Valley, PA
b. Nineteen-gauge EUS needle (ECHO-19; Cook Medical, Winston-Salem, NC), or similar
c. Diluted contrast with 120 mL water
d. 0.025- or 0.035-inch guidewire
e. Four to six millimeter dilation balloon (Hurricane RX; Boston Scientific, Natick MA)
f. Lumen apposing metal stent (LAMS) 15 mm (Axios; Boston Scientific, Natick MA)
g. Dilation balloon: 15- to 18-mm balloon (controlled radial expansion balloon dilator [CRE]; Boston Scientific, Natick MA)
h. Duodenoscope and other equipment needed for conventional ERCP
i. Optional plastic double-pigtail stents (10 F × 10-cm) for anchoring LAMS if concerns for migration
j. Endoscopic snare or grasping forceps for LAMS removal
k. Endoscopic suturing for gastrogastric fistula created (Overstitch; Apollo Endosurgery, Austin, Tex) or over-the-scope clip (diameter 12 mm; Ovesco, Los Gatos, California, USA)

Procedure Techniques

The external EDGE and ESTER procedures are similar in principals with some minor changes in techniques and instruments used. The first step consists of accessing the gastric remnant. This is achieved by advancing a linear echoendoscope to the gastric pouch or Roux limb, identifying the gastric remnant and puncturing it with a 19-Gauge fine needle aspiration needle under sonographic guidance (Fig. 14.1). A small amount of contrast (5–10 mL) is then injected to confirm placement in the gastric remnant. The gastric remnant is then inflated to obtain apposition with the gastric wall for a gastrostomy placement. Inflation has been described with air (400–500 mL) (ESTER technique) or with 120 mL sterile water and 120 mL of air (EDGE technique): both are effective. A guidewire is subsequently advanced through the needle and coiled into the stomach. The second step consists of creating a gastrostomy that will be used as an access route for ERCP. Again, different instruments and approaches can be used.

The external EDGE describes using an 18-gauge needle for creating the gastrostomy. In this procedure, once adequate position in the gastric remnant is confirmed, a stiff guidewire is advanced through the needle and coiled into the stomach followed by dilation of the tract using 8- Fr to 16-Fr dilating catheters. A 16-Fr gastrostomy tube is then sutured in place (Fig. 14.2). The second stage of the procedure consists of dilating the tract and placing a metallic stent across the tract itself. This is achieved by passing a guidewire through the PEG tube and coiling it into the stomach then the PEG tube is removed and the extra thin scope (GIF-XP 180; Olympus) is advanced over the wire into the excluded stomach. Three T fasteners are then placed under fluoroscopic and endoscopic guidance to maintain apposition of the gastric and ventral walls. The fistula tract is then progressively dilated using Maloney dilators up to 54-Fr followed by over the wire deployment of a fully covered metal esophageal stent (Fig. 14.3). The metal stent is sutured to the surrounding skin and ERCP is then performed using the antegrade approach.

In the ESTER approach, once the inflation of the excluded stomach is achieved, an 18-gauge needle is used to percutaneously access the remnant. Once position confirmed fluoroscopically two 0.018 inch guidewires are passed though the needle and coiled into the stomach. One guidewire is used to pass a 20 mm stone extraction balloon that will be used to provide counter traction while a sequential dilation up to 24-Fr is performed through the second wire. This is followed

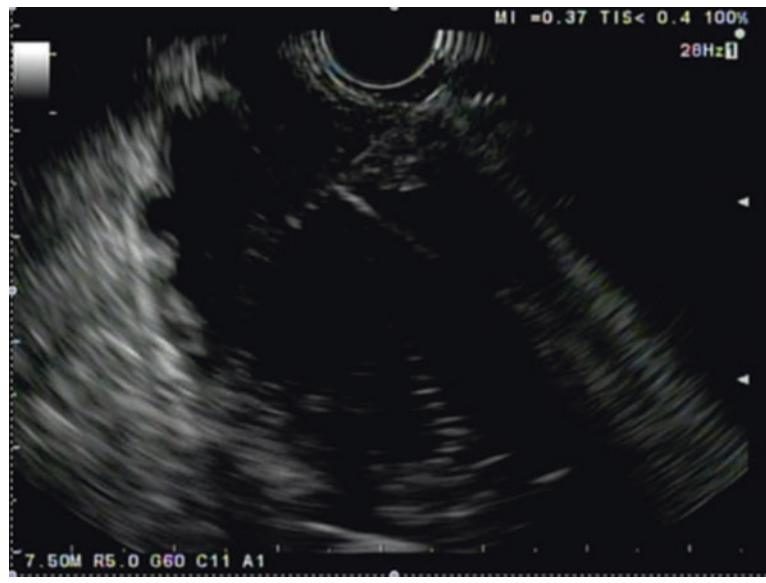

Fig. 14.1 EUS-guided puncture of the excluded stomach before insufflation with air

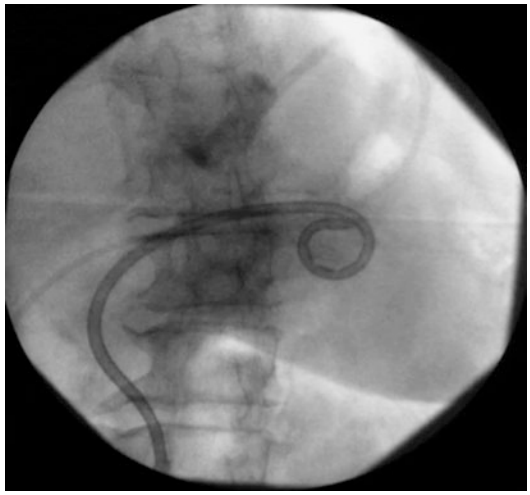

Fig. 14.2 Placement of a percutaneous gastrostomy

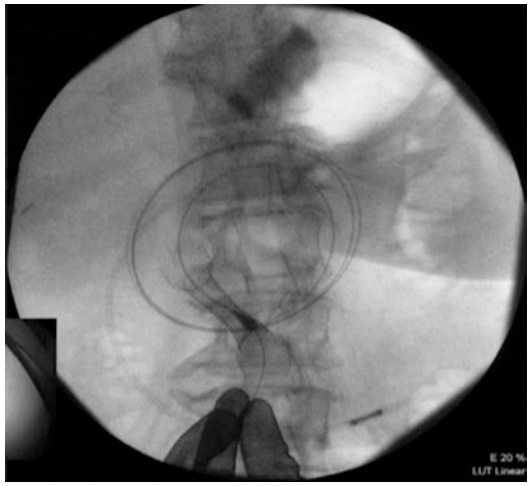

Fig. 14.3 Placement of a transcutaneous fully covered esophageal stent

by the insertion of 20-Fr "peel away" sheath (Cook endoscopy) instead of the 16-Fr gastrostomy tube used in the external EDGE technique. The ultrathin scope (GIF-XP 180; Olympus) is then advanced through the sheath into the excluded stomach and endoscopic sutured gastropexy is performed using a 2 mm laparoscopic suture passing needle under endoscopic visualization. Once the apposition of the gastric and ventral wall is obtained the "peel away" sheath is replaced by a laparoscopic trocar system through which the duodenoscope is inserted to proceed with the conventional antegrade ERCP. These two procedures were described in 2014 and both studies included a small number of patients.

These novel and minimally invasive approaches were just the introduction to another innovative approach, the internal EDGE procedure, that bypasses the need to create a percutaneous gastrostomy with sutured gastropexy. The procedure was first described by Kedia et al. in 2014 (Video 14.1). The initial steps of the internal EDGE procedure are similar to the external EDGE where a linear echoendoscope is advanced into the gastric pouch and the excluded stomach is identified and then punctured using a 19-gauge needle (Fig. 14.4). The access into the remnant can be obtained from the pouch or via the afferent limb. Contrast mixed with water is then injected through the needle to distend the gastric remnant followed by advancing a 0.035 inch guidewire through the needle and coiling it within the lumen of the stomach (Figs. 14.5 and 14.6). This creates a gastrogastric fistula between the pouch and excluded stomach which is subsequently dilated over the wire using 4 mm balloon (Hurricane RX, Boston Scientific). The next step is to deploy a transluminal stent to provide apposition of the gastric pouch and remnant through which ERCP will be performed. The delivery system of the lumen apposing metal stent (LAMS) is then advanced into the fistula (Fig. 14.7) and the distal flange deployed into the excluded stomach (Fig. 14.8) and proximal flange into the gastric pouch using both fluoroscopic and sonographic guidance (Figs. 14.9 and 14.10). The lumen of the stent is then dilated using a 15–18 mm dilating balloon (CRE; Boston Scientific) (Figs. 14.11 and 14.12). The duodenoscope is then advanced through the stent and conventional antegrade ERCP is performed (Figs. 14.13 and 14.14). Once further access into the pancreatobiliary tree is no longer needed the LAMS is removed using a 25 mm snare and the fistula tract is closed using over-the-scope clip (OTSC; OVESCO, Los Gatos, CA, USA) or endoscopic suturing device (Overstitch; Apollo Endosurgery, Austin, TX, USA). In some cases, the stent can be left in place if repeated ERCPs are needed. The tract can also

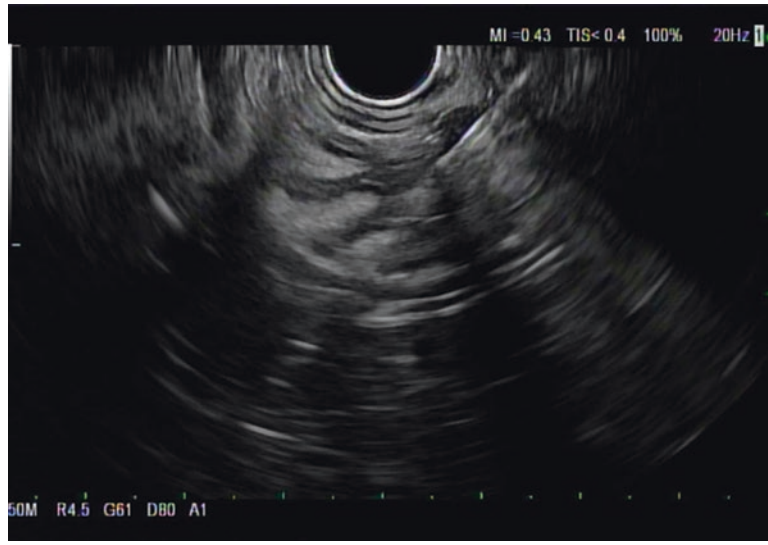

Fig. 14.4 EUS-guided puncture of the excluded stomach

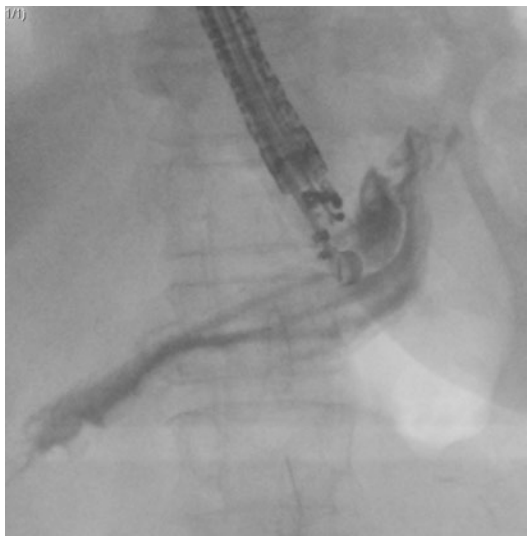

Fig. 14.5 Injection of contrast into the excluded stomach under fluoroscopy

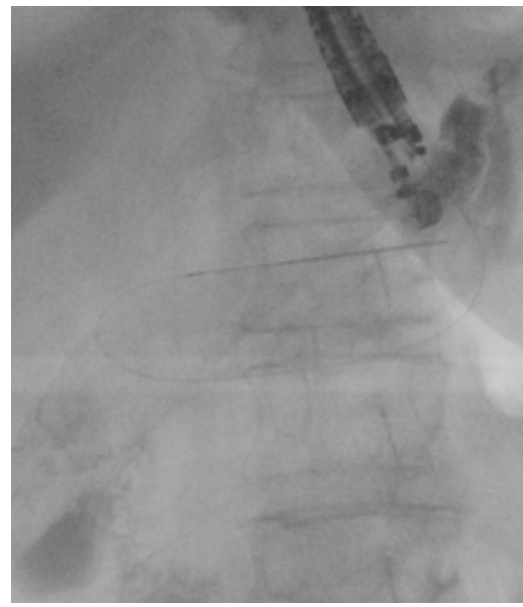

Fig. 14.6 Placement of a guidewire in the excluded stomach under fluoroscopy

be left to close secondarily after transluminal stent removal. Also, the use of argon plasma coagulation (APC) to de-epithelialize the fistula tract and enhance transgastric fistula closure has been described.

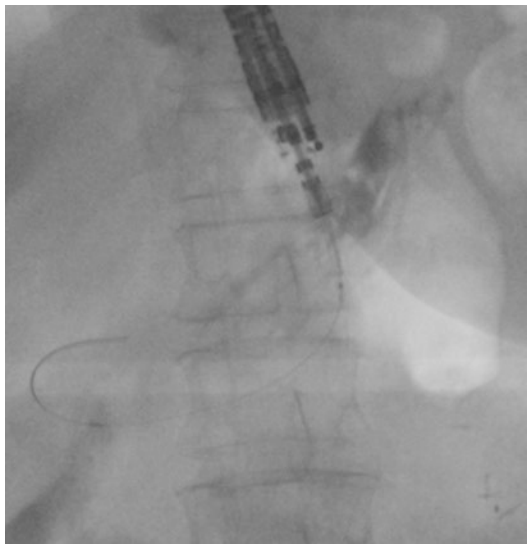

Fig. 14.7 Advancement of a cautery enhanced lumen apposing metal stent in the excluded stomach under fluoroscopy

Outcomes

Success Rate

The use of endoscopic ultrasound to assist transgastric ERCP in patients with gastric bypass is of no doubt a new technique and innovation with limited overall experience. The outcomes discussed here are mostly based on results from different case series reported in the literature. Most case series report a technical and clinical success rates (Table 14.2).

The reported success rate of the ESTER technique is 90% [9]. In a case series of six patients Kedia et al. reported an 83% success rate of EUS-guided gastrostomy tube placement with 100% success rate of ERCP [10]. The percutaneous access using the standard percutaneous endoscopic gastrostomy (PEG) tube needle kit could not be obtained in one patient and subsequently patient required PEG placement by interventional radiology.

In a midterm analysis of internal EDGE, Tyberg et al. reported a 100% technical success rate and 91% clinical success rate in sixteen patients undergoing EDGE at two academic centers [14]. Technical success rate was defined by successful creation of gastrogastric fistula

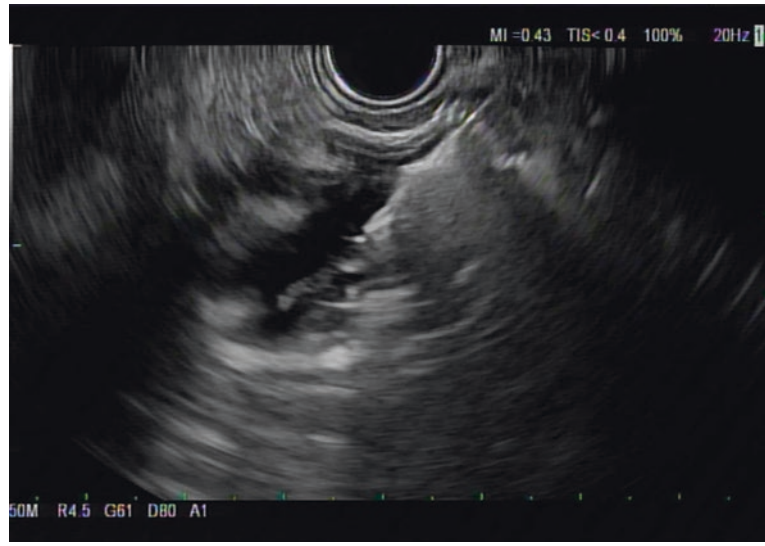

Fig. 14.8 Deployment of inner flange of the lumen apposing metal stent under ultrasonography

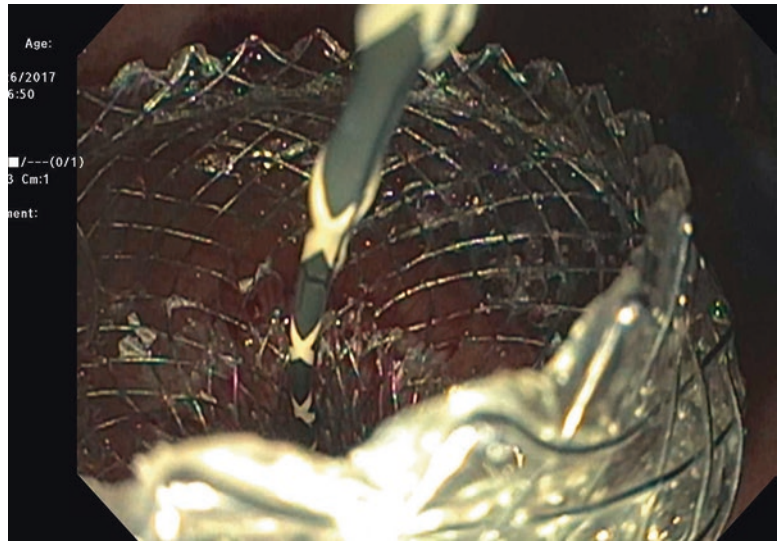

Fig. 14.9 Deployment of the outer flange in the pouch under endoscopic visualization

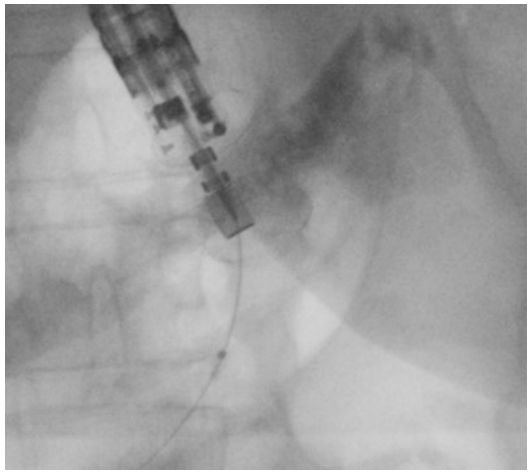

Fig. 14.10 Fluoroscopic vision of complete deployment of the lumen apposing metal stent

(37.5%) or jejunogastric fistulas (62.5%). Clinical success rate was defined by successful ERCP or EUS through LAMS which was performed in only 11 of the 16 patients since 5 patients were awaiting fistula tract maturation. Four patients had ERCP at the same index procedure.

Another multicenter experience with EDGE has been published by Ngamruengphong et al. [15]. The study included a total of 13 patients with RYGB with different indications for ERCP. The group reported a technical and clinical success rate of 100% [15]. In summary, the overall success rate of EUS-guided transgastric ERCP from the reported case series ranges between 83% and 100%. This depends on the local expertise and approach used.

Complications and Limitations

The complications that can occur with EUS-guided transgastric ERCP can be related to the EUS-guided gastrogastric or jejunogastric fistula creation in the case of EDGE procedure, to the percutaneous gastrostomy creation in case of external EDGE and ESTER, or to the ERCP procedure itself. Attam et al. reported no immediate complication related to the ESTER procedure, however there was no mention of how long patients were followed and whether there were any delayed complications [9]. With the external EDGE, the reported ERCP complication rate was 0% and 33% of cases had complications related to gastrostomy tube placement (localized PEG site infection). Internal EDGE reported complications included lumen apposing metal stent dislodgement requiring repositioning or bridging with a fully cover metal stent at a rate 19% [14]. Ngamruengphong et al. reported 16% rate of LAMS dislodgment during ERCP requiring stent repositioning [15]. In their report, patients who underwent ERCP using the therapeutic duodenoscope had a higher stent migration rate when

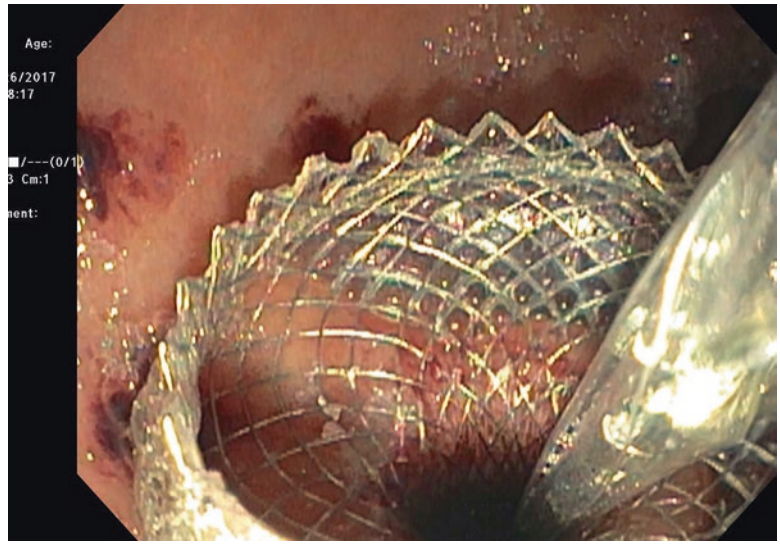

Fig. 14.11 Endoscopic placement of a 15 mm wire guided balloon into the lumen apposing stent

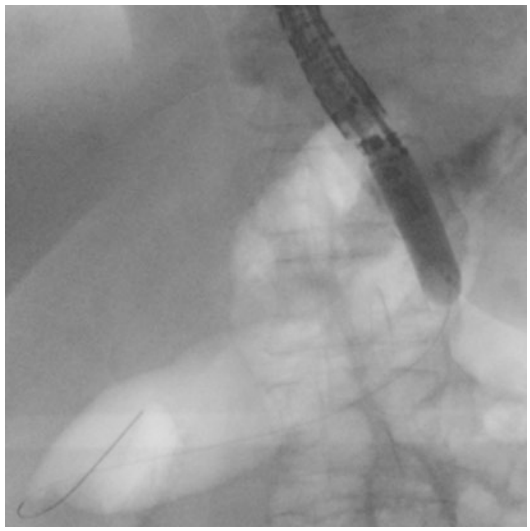

Fig. 14.12 Balloon dilation of the lumen apposing metal stent up to 15 mm under fluoroscopy

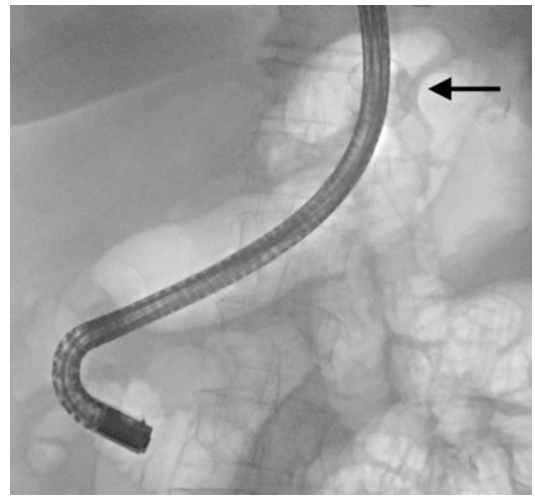

Fig. 14.13 Advancement of the duodenoscope until the second portion of the duodenum though the lumen apposing metal stent (indicated by arrow)

compared to no cases of migration when the slim duodenoscope was used (33% vs 0%) [15]. The risk of stent migration can therefore be mitigated by using a diagnostic duodenoscope (if one is available), avoiding excessive stent dilation and allowing the fistula tract to mature by performing ERCP at a later stage if possible in non-urgent cases.

Another concern with the creation of a gastrogastric or jejunogastric fistula is persistent fistula despite attempted closure which is reported to range between 8 and 12.5% [14, 15]. The persistence of a fistula (failed closure or staged procedures) between the pouch or afferent limb and the gastric remnant is a concern for weight gain. This did not appear to be a major concern in the reported series, however the number of cases and the duration of follow-up in these reports are not enough to make a final conclusion about the risks of weight gain. Another observed complication is

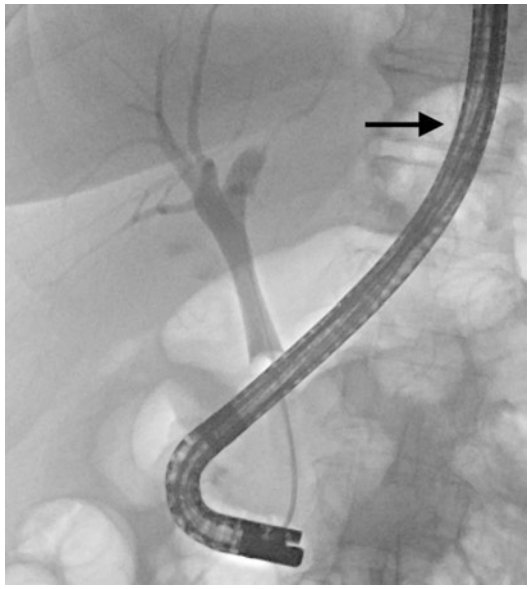

Fig. 14.14 Cholangiogram performed with the duodenoscope advanced though the lumen apposing metal stent (indicated by arrow)

bowel perforation which can typically be closed endoscopically when diagnosed in a timely fashion.

Although the introduction of these novel techniques of EUS-guided transgastric ERCP in patients with RYGB offers many advantages with a significant success rate, each above described technique has its own limitations. In addition, all case series reported in the literature are retrospective, included a small number of patients and some series included a multicenter experience which entails different endoscopist technique with possible variation in instruments used.

Conclusion and Future Directions

Despite the trend over the last 10 years to perform fewer RYGB and the rise of sleeve gastrectomy (which is currently the most commonly performed surgery for obesity in the USA), RYGB remains the most common surgery worldwide. These patients have an altered anatomy which limits access to their pancreatobiliary tree. While enteroscopy-assisted ERCP has a success rate of 63%, the rate increases to 98% when a transgastric approach used. When a surgical approach is used to create the gastrostomy access this entails a multidisciplinary approach and an increase in the cost, time, and complications. There is no doubt that the indication for ERCP, the urgency, and the existence of other surgical indications to explore the abdomen play an important decisive role for the endoscopist with regard to which route to use (surgical, enteroscopy assisted, or ultrasound guided). With the advances of therapeutic endoscopic ultrasound, we learned that access into the gastric remnant is possible using endoscopic ultrasound without the need for a surgical/interventional radiology approach. The introduction of lumen apposing metal stent has revolutionized the word of therapeutic interventions and proves its utility in creating a gastrogastric or jejunogastric fistula in patients with RYGB for ERCP. This procedure offers the benefit of avoiding a percutaneous gastrostomy and its complications, doing ERCP during the same index procedure or doing a staged procedure which allows the fistula tract to mature and perform non-urgent ERCP as well as repetitive procedure as needed (i.e., benign biliary strictures, etc.). The experience is still limited and larger randomized trials are needed to prove the long-term outcomes of this procedure and the risk of weight gain in this population. Cost-benefit analysis of these innovative approaches compared to laparoscopy-assisted ERCP or enteroscopy-assisted ERCP will certainly shape the future of endoscopic ultrasound-guided access to the stomach in patients with RYGB to facilitate ERCP.

Table 14.2 Characteristics of studies that used endoscopic ultrasound-guided access to the stomach in patients with prior gastric bypass to facilitate endoscopic retrograde cholangiopancreatography

Study	Number of patients	Success rate	Complication rate	Procedure time	Median follow-up	Weight gain in kg
Attam et al. [9] (ESTER approach)	10	90% (9/10)	Immediate procedure related adverse events: 0%	88 min (median)	Not reported	Not reported
Kedia et al. [10] (external EDGE, two stages)	6	EUS access into remnant success rate: 100% Gastrostomy tube placement success rate: 83% ERCP success rate: 100%	Gastrostomy tube related adverse events 33% ERCP related adverse events 0%	EUS-guided gastrostomy tube placement: 81 ± 26 (median ± SD, minutes) ERCP: 98 ± 24 (mean ± SD, minutes)	Not reported	Not reported
Tyberg et al. [14] (internal EDGE)	16	Technical success rate: 100% Clinical success rate in 10 patients: 91%	LAMS dislodgement: 19% Jejunal perforation: 6.25% Persistent fistula after attempted closure 12.5% (1/8)	Not reported	Not reported	Mean −2.85
Ngamruengphong et al. [15] (internal EDGE)	13	Technical success rate: 100% Clinical success rate: 100%	Procedure related 0% Post-procedure 1. LAMS migration 16% (2/12) 2. Persistent fistula after attempted closure 8% (1/12)	30 ± 17 (mean ± SD, minutes)	68 days	Mean −3.6 ± 4.8 (SD)

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Endoscopic Ultrasound-Guided Gastroenterostomy (EUS-GE)

15

Steven P. Shamah and Uzma D. Siddiqui

Background

Gastric outlet obstruction (GOO) is a term used to define any mechanical obstruction, typically in the distal stomach or proximal duodenum, impeding gastric emptying. Presenting signs and symptoms include nausea, vomiting, early satiety, and abdominal distention. Workup can include upper endoscopy and cross-sectional imaging, such as computerized tomography (CT). These allow for better delineation of the location, severity, and etiology of the obstruction. Currently, the most common etiology of GOO has become pancreatic cancer, but in some cases may be from benign disease such as chronic pancreatitis or peptic ulcer disease, among other causes. Other malignancies that can cause GOO include cholangiocarcinoma, ampullary cancer, or gallbladder cancer [1]. Unfortunately, many patients with GOO may not be candidates for primary tumor resection and are therefore managed with palliative measures such as surgical gastrojejunostomy (open or laparoscopic) or, more commonly, endoscopic enteral stent placement.

Enteral stents that are currently available have been used in malignant obstruction for over 15 years with high success rates (>90%) when compared to surgical gastrojejunostomy [2]. Although surgical gastrojejunostomy offers better long-term clinical outcomes, it is associated with higher rates of morbidity and mortality when compared to endoscopic stenting in some studies, although many surgeons prefer not to operate on patients with advanced unresectable malignancy. Retrospective data comparing enteral stenting to surgery showed stenting had significantly less complications and shorter hospital stays as well as decreased costs, but there was a higher re-intervention rate [3]. Enteral stents are designed for patients with malignancy who have short life expectancies and may not be ideal for use in benign conditions [4–6].

Endoscopic ultrasound (EUS)-guided creation of a gastroenterostomy has recently been described and studied as a viable alternative treatment for gastric outlet obstruction (GOO) arising from benign and malignant conditions. EUS-guided gastroenterostomy (EUS-GE), also referred to as EUS-gastrojejunostomy (EUS-GJ), was made possible with the advent of lumen apposing metal stents (LAMS) used to create luminal anastomoses. In 2012, Binmoeller and Shah first described this technique using a porcine model [7]. The procedure was performed using an anchor wire to appose the lumen of the small

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bowel to the stomach and a LAMS was deployed under EUS guidance to create the gastroenteric anastomosis. The procedure was technically successful in all animals without complications. Another animal study by Itoi et al showed similar results with a successful gastroenterostomy creation and no adverse events [8]. In this study, the authors utilized a novel double balloon enteric tube to access and stabilize the small bowel. Since then, there have been multiple studies in patients and these have utilized various EUS-GE techniques and types of LAMS.

In the USA, a cautery-enhanced (CE) LAMS system (Hot Axios, Boston Scientific, Natick, MA) allows for direct puncture through the stomach and into the small bowel and obviates the need for tract dilation or fluoroscopy with stent deployment. Furthermore, the single-step access to the small bowel may minimize the chance for separation between the stomach and small bowel. However, the use of LAMS and CE-LAMS for gastroenterostomy is an off-label indication.

The following chapter will review the different EUS-GE techniques that have been described in the literature, as well as the data on safety and efficacy.

Endoscopic Technique

EUS-GE using LAMS was developed as a way to bypass the obstructed portion of the GI tract in GOO with direct placement of a stent between the stomach and more distal duodenum or proximal jejunum. This new endoscopic technique continues to evolve as endosonographers gain more clinical experience and as more devices are developed for the creation of endoscopic enteroenteric anastomosis. There is no "ideal method" for how to perform this procedure and the technique itself has multiple steps that require an expert operator and a multidisciplinary plan of care. EUS-GE indications include both malignant and benign obstruction; while contraindications include multi-focal obstruction or blockage distal to small bowel puncture site, coagulopathy precluding safe creation of a gastrojejunostomy, a distance of >1 cm between stomach and small bowel walls, and large volume ascites.

Pre-procedure Care

Regardless of the technique, all patients undergoing EUS-GE should receive IV antibiotics. Some suggest the patient be positioned in the supine position, and be intubated prior to initiating the procedure as well, but these recommendations are not standardized. IV glucagon can be administered to decrease small bowel contractions during the procedure, however minimal data currently exists to support its routine use.

The main procedural steps in EUS-GE include filling the target small bowel with water or contrast to distend it for better identification and apposition with the gastric wall, creation of a gastroenterostomy, and finally stent deployment across the gastroenterostomy with the distal flange in the small bowel and the proximal flange in the stomach. In the USA, LAMS come in 10 mm, 15 mm, and 20 mm diameters (our preference is 15 mm). We will henceforth describe the four EUS-GE techniques that have been described in the literature.

EUS GJ Techniques

Water Immersion Method [9]

A large volume of isotonic saline with or without a readily identifiable dye such as methylene blue is infused through the working channel of the linear echoendoscope, via a puncture of the distal small bowel with a 22-gauge (G) fine needle aspiration (FNA) needle, or via a nasojejunal tube. This infusion of fluid distends the target small bowel, allowing for better visualization under EUS. A 19 G FNA needle is then used to puncture the gastric wall and through the small bowel wall into the distended loop of small bowel. Aspiration of fluid (with or without dye) to confirm proper placement in the small bowel is helpful. A 0.035-inch or 0.025-inch guidewire is

passed through the FNA needle into the small bowel and then the 19 G needle is exchanged over the wire, leaving the wire connecting the gastric cavity and the small bowel. A 10-French cautery-enhanced LAMS catheter system is passed over the guidewire and deployed under endosonographic guidance with the distal phalange in the small bowel and the proximal end in the gastric cavity. The lumen of the LAMS is then dilated to the diameter of the stent diameter using a through the scope (TTS) dilation balloon, although dilation of the LAMS is not considered a mandatory step as the stent may be left to fully efface on its own.

Balloon Assisted Method [10]

A standard endoscope is advanced to the level of the obstruction. A stiff guidewire is passed across the obstruction into the small bowel, under fluoroscopic guidance. The gastroscope is withdrawn leaving the wire in the small bowel distal to the obstruction. Under fluoroscopic guidance, a large caliber (18–20 mm) TTS dilation balloon is passed over the wire into the small bowel and inflated with a contrast agent. The echoendoscope is then passed into the gastric cavity and is used to locate the dilation balloon using EUS imaging. Once located, a 19 G FNA needle is used to puncture across the gastric wall, the small bowel wall, and the balloon itself across the small bowel to ensure proper access. A second guidewire is passed downstream into the small bowel through the 19 G needle. A CE-LAMS is then deployed over the guidewire creating the LAMS assisted gastroenterostomy. The LAMS is then balloon dilated to the maximal stent diameter (either 10 mm or 15 mm) if so desired (Figs. 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, 15.8, and 15.9 and Video 15.1 demonstrate balloon assisted technique).

EUS-guided Double-Balloon-Occluded Gastrojejunostomy Bypass: EPASS Method [11]

A standard endoscope is advanced to the level of the obstruction. A guidewire is passed under fluoroscopic guidance across the obstruction. The endoscope is exchanged leaving the wire in place across the obstruction. Over the guidewire a specialized double balloon enteric tube (Tokyo Medical University, Japan) is passed in combination with a guidewire that allows for better maneuverability. Once the enteric tube is in across the obstruction the distal and proximal balloons are filled with saline. The lumen between the balloons is filled with saline and contrast, thereby distending a focal area of small bowel and limiting the amount of fluids infused. A linear echoendoscope is advanced into the gastric cavity and the lumen between the balloons is identified endosonographically. A 19 G FNA needle is used to puncture the small bowel in the space between the balloons and fluid is aspirated confirming location. If a non-cautery-enhanced LAMS is used, then a dilation balloon and fluoroscopy is needed prior to stent deployment. If the CE-LAMS is used, then the delivery system is placed over the guidewire and deployed using cautery under EUS guidance. The distal phalange is deployed into the distal small bowel and the proximal end into the gastric cavity. The stent lumen is balloon dilated to LAMS maximal diameter if so desired.

Direct ("Freehand") Method

The small bowel lumen is first distended with copious amounts of isotonic saline, a contrast agent, and dye (usually methylene blue) [12]. An echoendoscope is advanced to the distal stomach and the closest loop of small bowel is identified. Once the small bowel site is confirmed, the CE-LAMS catheter system is used to puncture through the stomach and into the small bowel and the LAMS is deployed creating the gastroenterostomy without the use of a wire, dilation balloon, or fluoroscopy [12]. This technique mirrors the common "wire free" techniques used to drain pancreatic fluid collections via CE-LAMS.

The above techniques described do not represent an exhaustive description of the procedures available to perform EUS-GE; however, they are the most commonly used techniques for the establishment of an EUS-guided gastroenterostomy. As expertise with currently available tools grows and/or new technology is created, these techniques will continue to evolve.

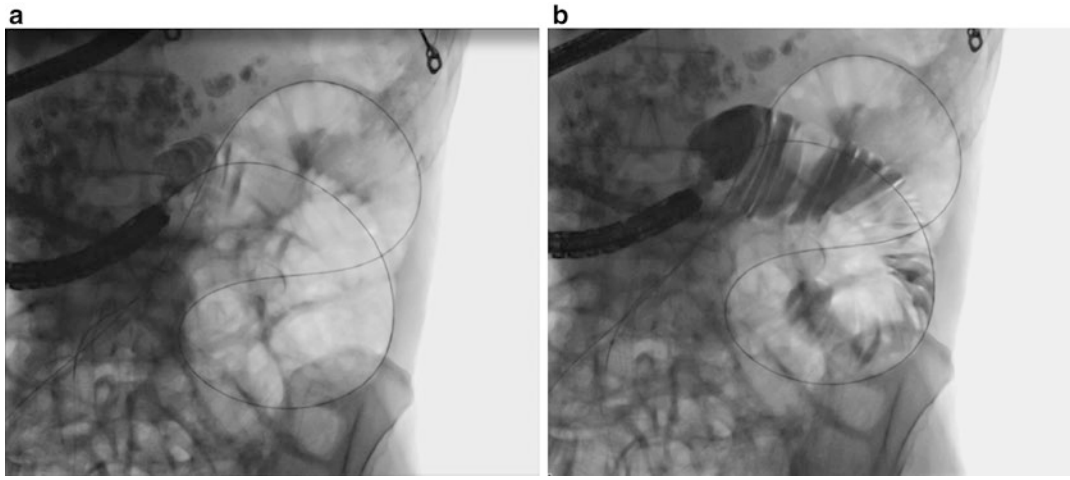

Fig. 15.1 (**a**) Passage of a guidewire across the gastric outlet obstruction. (**b**) Contrast injection confirms guidewire passage into the small bowel distal to the level of the obstruction

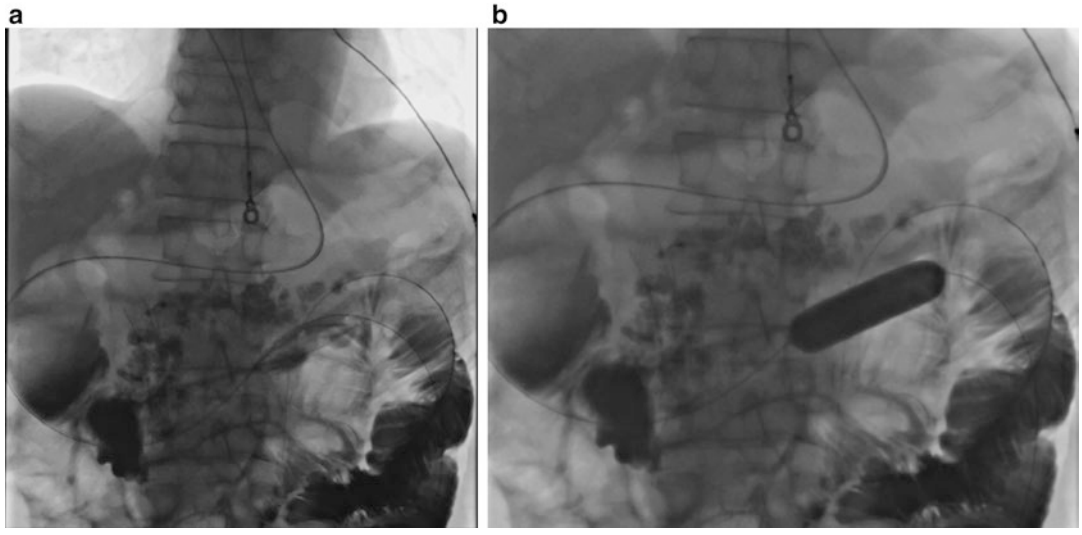

Fig. 15.2 (**a**) Dilation balloon passed over the guidewire into the small bowel under fluoroscopy. (**b**) The dilation balloon is inflated via filling it with contrast dye

Post-procedure and Follow-up Care

There is no consensus on the post-procedural management of patients undergoing EUS-GE. Patients will generally be admitted for close observation; will be kept NPO for the first 24 h and then advanced to clear liquids for 2–3 days. Antibiotic regimens vary from anywhere from 3 days to 7 days post-procedure [9, 13]. Patients are discharged home when they demonstrate adequate tolerance to oral diet, at least to the level of liquids in most cases [14]. In terms of long-term management, there are no available data on (a) optimal duration of LAMS placement or (b) whether or not the LAMS should be removed at some time in the future when the anastomosis becomes chronic and stable. Closure of the anastomosis after LAMS removal is a possibility, but the frequency of this remains unknown.

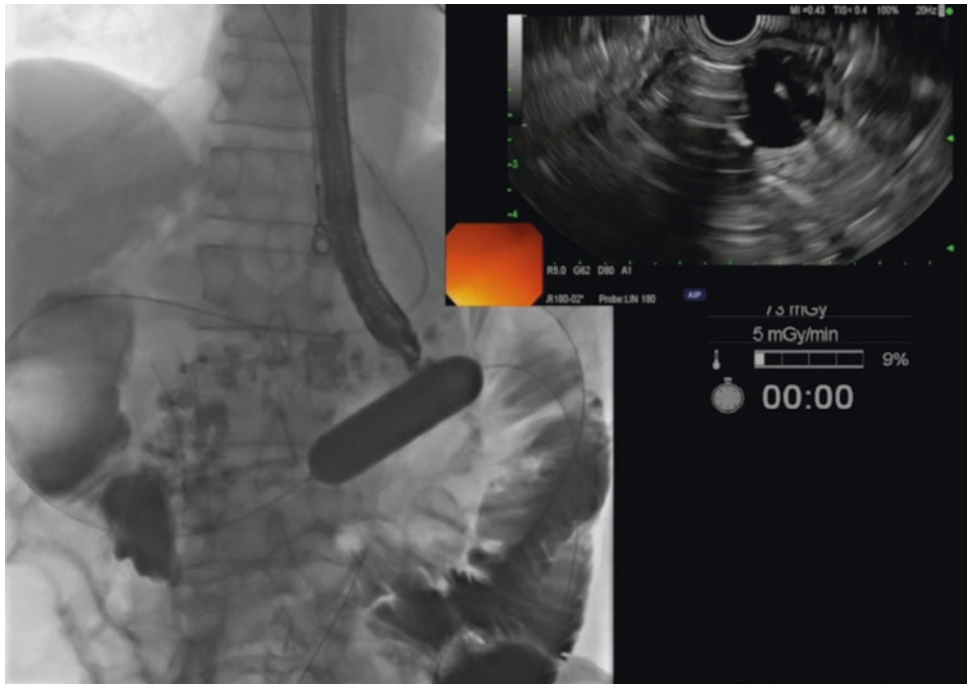

Fig. 15.3 Linear echoendoscope passed into the stomach and used to locate the dilation balloon in the adjacent small bowel

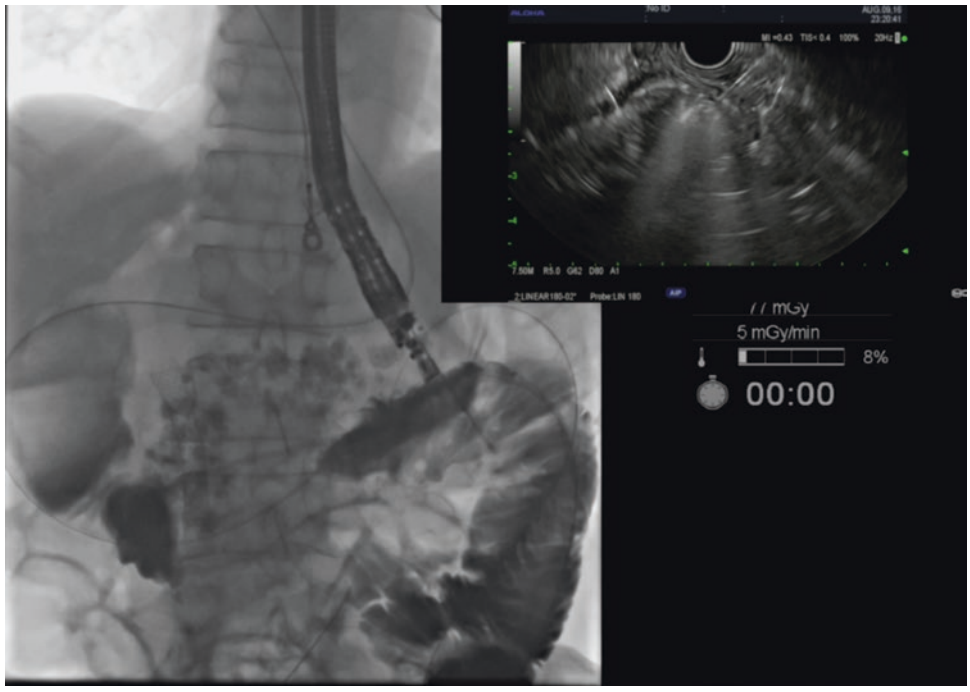

Fig. 15.4 19 G needle used to puncture the balloon in the small bowel under EUS guidance

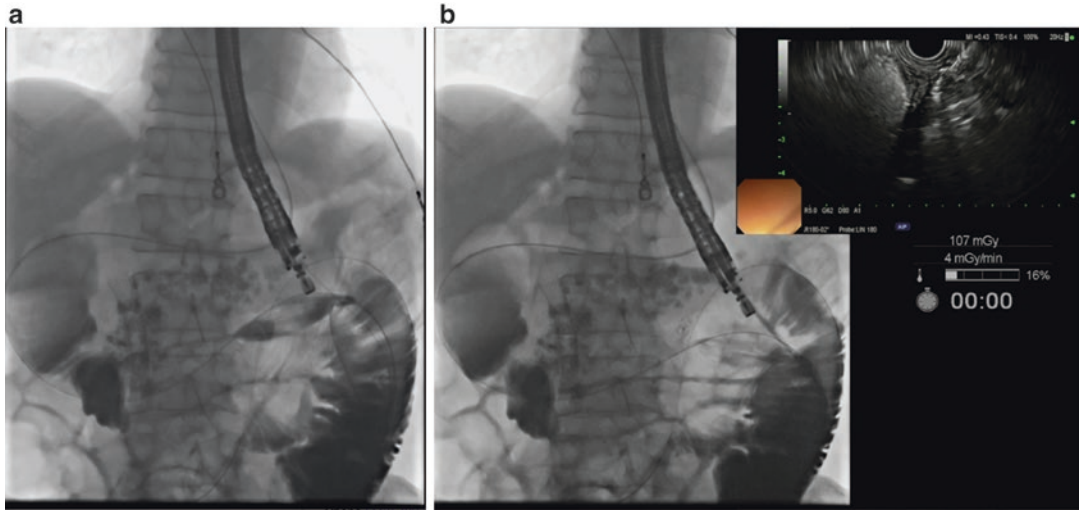

Fig. 15.5 (**a**) Second guidewire passed through the EUS needle from the stomach and into the small bowel. (**b**) Electrocautery-enhanced LAMS is passed over the wire and into the small bowel beyond the obstruction

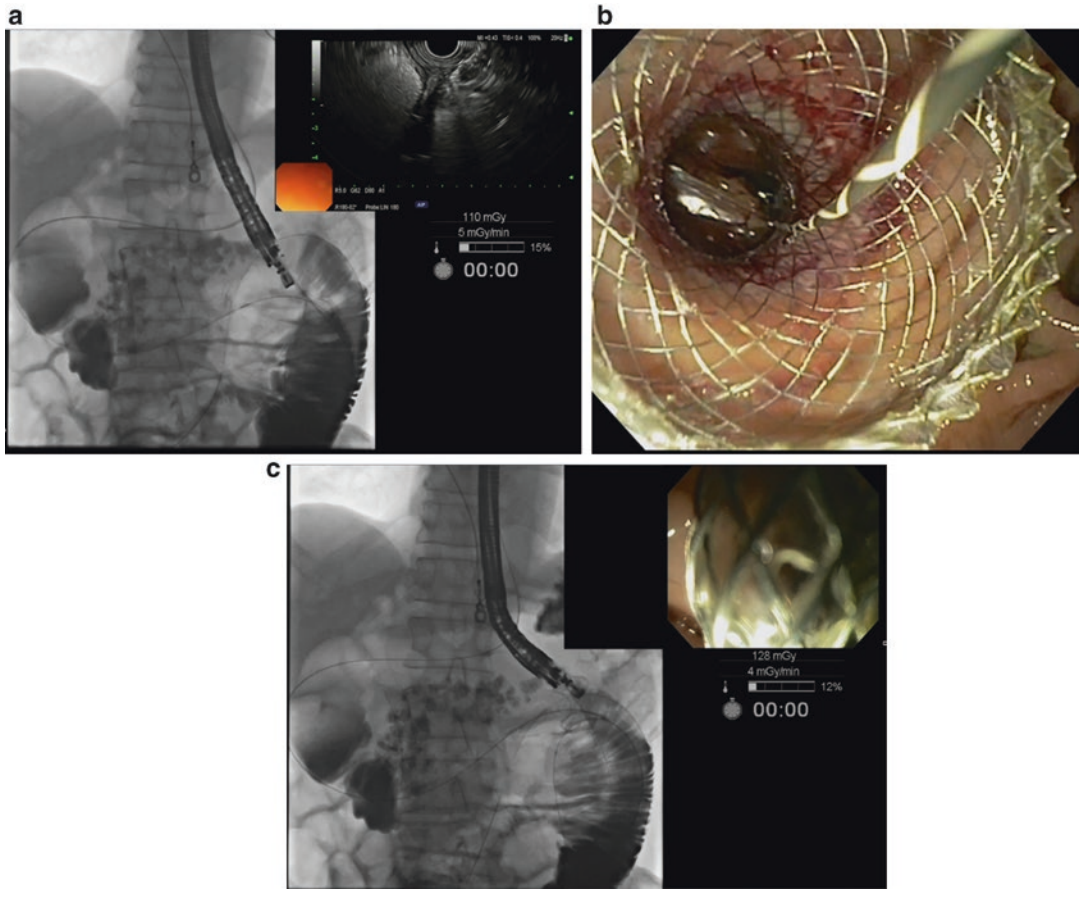

Fig. 15.6 (**a**) Distal flange of LAMS deployed into the small bowel. (**b**) Endoscopic view of the proximal flange of the lumen apposing metal stent (LAMS) after deployment. (**c**) Fluoroscopic view of fully deployed LAMS before dilation

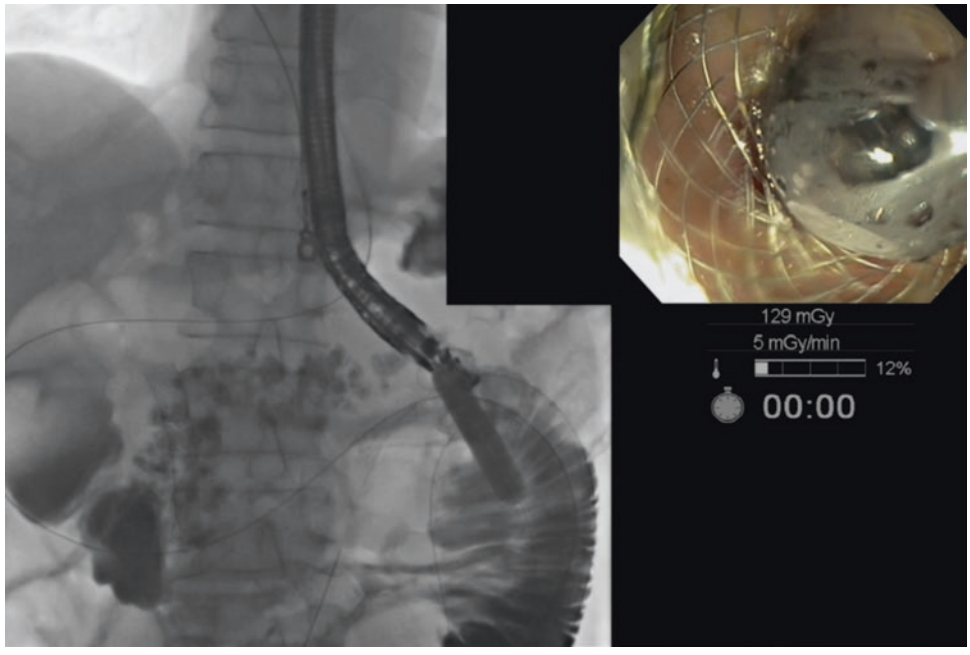

Fig. 15.7 Balloon dilation of the LAMS to ensure maximal opening diameter

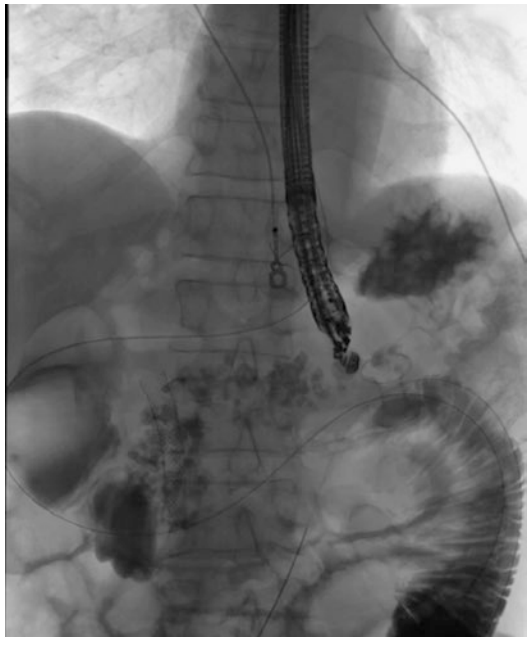

Fig. 15.8 Fluoroscopic view of the fully deployed LAMS between the stomach and small bowel creating the gastroenterostomy

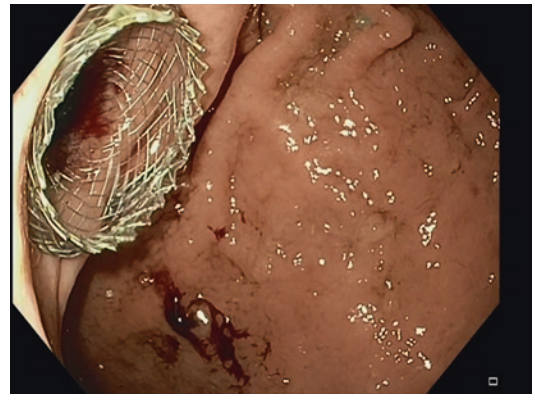

Fig. 15.9 Final endoscopic view of LAMS when viewed from the gastric side

Review of Data

Technical and Clinical Success

Most of the data for EUS-GE can be found in case reports and case series, it is only recently that comparative studies have emerged from the literature. The largest retrospective case series, published by Tyberg et al., was a multicenter international collaboration encompassing 26 patients with GOO (17 malignant, 9 benign) [13]. Technical success was 92%, defined as a successful creation of an EUS-GE. Clinical success, defined as the ability to tolerate PO diet was slightly lower at 85%. In a case series of 20 patients; Itoi and his colleagues in Japan published their experience with a double balloon enteric tube that they used to facilitate gastroenterostomy formation [14]. In their experience, similar technical success rate of 90% was obtained.

Safety and Adverse Events Related to EUS-GE

Since EUS-GE is still in its investigational stages with comparative studies just beginning to be published, most of the data regarding safety and adverse events is derived from a limited number of patients. The studies include patients with benign and malignant gastric outlet obstruction and reported an overall adverse event rate of less than 12% [11–16].

Tyberg and colleagues reported three adverse events in their patient series (11.5%) described as bleeding, worsening abdominal pain and, notably, one death caused by peritonitis [13]. The patient with peritonitis had ascites and carcinomatosis and experienced a LAMS misdeployment. Khashab in 2015 published a case series of ten patients and reported no procedure related adverse events [12]. The case series by Itoi et al. reported one adverse event (5%) out of twenty patients, which resulted in pneumoperitoneum [14].

In a recently published comparative study with surgical gastrojejunostomy by Khashab et. al., 93 patients were studied: 30 undergoing EUS-GE and 63 undergoing surgical gastrojejunostomy. There were five reported adverse events in the EUS-GE group, which included three patients with stent misdeployments into the peritoneum and two patients with severe abdominal pain requiring hospitalization [15]. All five patients were managed conservatively and there were no fatalities. In this study, surgical gastrojejunostomy had a higher technical success rate but a similar clinical success rate when compared to EUS-GE.

Misdeployment rates of LAMS range from 4 to 6% across the multiple case series emphasizing the difficulty in maintaining lumen apposition between the small bowel and the gastric cavity, even in expert hands [11–16]. Adverse events can be potentially severe or life threatening and therefore close collaboration with surgical colleagues, review of the technique, and careful patient selection are keys to ensure success and safety during this intervention.

EUS-GE vs Enteral Stenting

Enteral stenting (ES) has historically offered a less invasive palliative approach to relieve malignant gastric outlet obstruction in comparison to its counterpart surgical gastrojejunostomy. However, with recent technical advances in therapeutic endoscopic ultrasound and stent technology EUS-GE has emerged as another palliative option. Chen and colleagues conducted the largest retrospective analysis to date comparing EUS-GE vs enteral stenting (ES). Primary outcomes included symptom recurrence rates and rates of re-intervention, while secondary outcomes included technical and clinical success rates between these two endoscopic techniques [17].

Fifty-two patients were included into the ES group and thirty in the EUS-GE group. Other than age, with the ES group being significantly younger, both groups had similar baseline characteristics. Similar rates of technical (86.7% EUS-GE vs 94.2% ES; $P = 0.20$) and clinical success (83.3% EUS-GE vs 67.3% ES; $P = 0.12$) were identified between the two groups. Enteral stenting had a higher rate of re-intervention and symptom recurrence (28.6%) in comparison to

EUS-GE (4%). Enteral stenting is still in widespread practice and is often technically simple, whereas EUS-GE is still a relatively uncommon procedure

EUS-GE vs Surgical Gastrojejunostomy (SGJ)

Two recent studies have been published comparing surgical gastrojejunostomy (SGJ) and EUS-GE by evaluating the difference in clinical success, technical success, adverse events, length of hospital stay (LOHS), and symptom recurrence.

Khashab and colleagues conducted a non-randomized, retrospective multicenter study that compared open surgical gastrojejunostomy vs EUS-GE [15]. A total of 93 patients (63 SGJ and 30 EUS-GE) were included in the analysis. There was no standardization in the technique of EUS-GE. All EUS-GE used LAMS to create the gastroenteric anastomosis. The EUS-GE group had a higher rate of peritoneal carcinomatosis.

While technical success rates significantly favored open SGJ vs EUS-GE (100% vs 87% $p = 0.009$), the clinical success rates (defined as the ability to tolerate oral intake without vomiting) were similar (90% SGJ vs 87% EUS-GE $p = 0.18$). Rate of adverse events was lower in the EUS-GE group but was not statistically significant (16% vs 25% $p = 0.3$). The mean length of hospital stay, time to re-intervention, and rate of GOO recurrence were similar between the two groups, concluding that EUS-GE is a less invasive and comparable palliative intervention [14].

In a similar study Perez-Miranda et al. compared EUS-GE to laparoscopic surgical gastrojejunostomy and demonstrated similar clinical and technical success rates [16]. However, this study demonstrated lower adverse events in the EUS-GE group (EUS-GE 12% vs laparoscopic GJ 41%, $p = 0.03$) and a significant healthcare cost benefit of approximately $10,000 per procedure in favor of EUS-GE.[18]

In the era of cost-effective medicine, the lower cost of EUS-GE compared to SGJ should be considered. The expected cost of a laparoscopic SGJ is $14,778.80 (95% confidence interval, $14,807–$16,541) compared to the cost of an EUS-GE at $4515 (95% confidence interval, $4079–$4905.5) ($P < 0.00001$) [16].

Conclusion and Future Direction

Several case series and comparative studies have confirmed that EUS-GE can be performed with high technical and clinical success rates. Recent data has suggested that this approach for the treatment of GOO may also be a more cost-effective option compared to surgical gastrojejunostomy and more durable than enteral stenting.

Several challenges and unanswered questions still exist. Further comparative studies need to be conducted to establish which EUS-GE technique can offer the highest rates of success and limit adverse events. There also needs to be development of better tools and devices to reproducibly maintain close apposition of the small bowel with the stomach to prevent misdeployment of LAMS. With advancements in scope technology, stent design, and device development we look forward to EUS-GE, a procedure currently in its infancy, developing into a weathered alternative to SGJ and enteral stenting for the treatment of GOO.

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Endoscopic Ultrasound-Guided Portal Pressure Measurement

16

Jason B. Samarasena, Allen R. Yu, and Kenneth J. Chang

Introduction

A growing number of studies have explored endoscopic ultrasound (EUS)-guided vascular catheterization due to the relative proximity of the gastrointestinal tract to the major blood vessels of the mediastinum and abdomen and the use of Doppler during EUS to ensure the absence of hemorrhage with needle puncture and withdrawal without additional administration of ionizing radiation. In particular, EUS-guided access to the portal vein (PV) may be favorable given the relative difficulty of PV access via standard percutaneous routes. Two major diagnostic applications of EUS-guided vascular access include angiography and assessment of intravascular pressure. This review will outline the different devices and techniques employed to obtain angiographic visualization and/or direct pressure measurements of the portal circulation. Ease of access, safety, and important lessons learned from each approach will be highlighted.

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EUS-Guided Portal Venous Angiography

The portal vein is well seen from both the stomach and the duodenum during EUS. The vessel itself is usually in very close proximity to the tip of the echoendoscope, making this an ideal target for vascular access. Portal venous angiography is a modality to assess the anatomy of the hepatic vasculature. Initial cases of successful in vivo EUS-guided PV catheterization were performed in porcine models. In 2004, Lai and colleagues reported an EUS-guided transduodenal approach to access the extrahepatic portal vein in 21 swine with a 22 G fine needle aspiration (FNA) needle. A small amount of contrast was injected through the needle for fluoroscopic confirmation of proper placement [1]. This study proved the feasibilty on a technical level of EUS-guided portal vein access.

The first study solely assessing PV angiography was a porcine study reported in 2007 by Magno and colleagues [2]. 19 G, 22 G, and 25 G needles were inserted under EUS guidance into the celiac, splenic, superior mesenteric artery, the thoracic and abdominal aorta, and the splenic, portal, and hepatic veins. All vessels were successfully identified and punctured in 5 of 5 pigs. No signs of intraprocedural hemodynamic instability were observed. Immediate post-procedure necropsy showed no signs of injury with the 25 G needle. The 22 G needle left puncture marks

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without bleeding, and the 19 G needle caused a vascular hematoma in large-caliber vessels with intraabdominal bleeding in 1 of the 5 pigs. Injection of contrast provided good opacification of smaller vessels—the celiac trunk, splenic artery, and hepatic veins—with only transient opacification in larger caliber vessels. As would be expected, the amount of resistance associated with instilling the iodinated contrast was inversely correlated with needle caliber.

Giday and colleagues attempted EUS-guided PV access in 2007 using a transgastric, transhepatic approach with a 25 G needle and a modified endoscopic retrograde cholangiopancreatography (ERCP) catheter [3]. This protocol was again performed in 2008 as part of another PV catheterization study [4]. Angiography was achieved using both standard iodinated contrast and medical grade carbon dioxide (CO2). PV catheterization was achieved in 6 of 6 swine in 2007 and 6 of 6 swine in 2008, and no complications were noted in either study. Necropsy showed no evidence of bleeding, hematoma formation, or liver injury. The transgastric, transhepatic approach is postulated to be safer than the transduodenal approach by allowing for natural tamponade of the needle track by liver parenchyma during withdrawal [3, 5]. The use of CO_2 as a contrast medium allowed for better visualization of the PV as well as easier intravascular administration through the small-caliber FNA needle when compared to the viscous iodine-based contrast. These studies as a whole suggested that needle puncture of these vessels would not necessarily lead to intraabdominal hemorrhage or vascular injury.

The safety of CO_2 use has been evaluated in both animals and humans. It is highly soluble and easily cleared by the lungs [6] and, unlike iodinated contrast, is not associated with nephrotoxicity or increased risk for hepatorenal syndrome [7]. The current data suggest that combining CO_2 with a 25 G needle may allow for easier injection of contrast, adequate visualization of the portal circulation, and possibly decreased risk of needle- and contrast-related complications.

EUS-Guided Portal Pressure Gradient Measurement

Portal hypertension (PH), resulting from increased resistance of hepatic sinusoids to blood flow, is most commonly a complication of liver cirrhosis. The pathogenesis involves alteration of the liver vasculature due to fibrosis as well as increased production of vasoconstrictive mediators relative to endogenous vasodilators. Complications of PH include esophageal varices, portal hypertensive gastropathy, ascites, and hepatorenal syndrome. Measurement of portal hypertension has been useful in determining the stage, progression, and prognosis of cirrhosis in individual patients. Portal pressure gradient measurement (PPG) of $\geq$10 mmHg is associated with development of esophageal varices [8] and PPG of $\geq$12 mmHg with variceal hemorrhage [9]. Reduction of PPG by 20% or to below 12 mmHg with pharmacotherapy has been found to decrease risk of future bleeding or rebleeding episodes [10, 11].

Previously, PPG values were obtained directly via either a percutaneous approach or using a transjugular intrahepatic portosystemic shunt (TIPS). The current standard for evaluation of PH is indirect measurement of the hepatic venous pressure gradient (HVPG). In this technique, a catheter is inserted into the hepatic vein percutaneously via either the jugular or femoral vein. The free hepatic venous pressure is recorded and subtracted from the wedged hepatic venous pressure to determine the HVPG. Both percutaneous PV catheterization and HVPG measurement are invasive procedures and require a high level of technical expertise. Direct PV catheterization has been associated with a high complication rate [12, 13] and is not commonly performed. Despite the overall safety profile of HVPG measurement, it is only routinely performed at tertiary medical centers [14, 15]. Furthermore, HVPG has been shown to correlate poorly with directly measured portal pressure in cases of presinusoidal PH, which may be seen in cases of non-cirrhotic portal fibrosis and presinusoidal PH, including portal vein thrombosis and schistosomiasis [4, 16, 17].

Animal Studies

Lai and colleagues were the first to report EUS-guided PVP measurement in a porcine model [1]. In a cohort of 21 pigs, a PH model was generated in 14 animals using polyvinyl alcohol injection and a coagulopathy model generated in 7 animals with heparin administration. A transduodenal EUS approach was used to access the portal vein in 21 pigs with a 22 G FNA needle and a transabdominal ultrasound (TAUS)-guided transhepatic approach in 14 of 21 pigs via a 22-gauge needle. PVP measurements were obtained in 18 of 21 swine. Minor complications found at necropsy included small subserosal hematomas at the EUS puncture site in all 21 pigs and a 25 mL blood collection between the liver and duodenum in 1 of 7 anticoagulated pigs. Failure to measure pressures in 3 subjects may have occurred due to thrombosis within the FNA needle. There was a strong correlation between EUS- and transhepatic-measured PVP (r = 0.91). The development of hematomas in this study suggests that a transduodenal approach that does not traverse the liver may increase risk of bleeding and therefore an approach traversing through liver parenchyma may be favorable.

In 2007, Giday and colleagues used the transgastric approach with a 19 G needle and modified ERCP catheter to obtain continuous PVP measurement without an echoendoscope in place [3]. Five of 5 pigs were successfully catheterized, and no hemorrhage or liver injury was noted on necropsy in all subjects despite the use of a significantly larger caliber needle. Two of 5 pigs were survived for two weeks and exhibited no signs of adverse events prior to and after necropsy. In a later study, the same group used the same methods to measure fluctuations in PVP and inferior vena cava (IVC) pressures in pigs that underwent common endoscopic procedures: esophagogastroduodenoscopy (EGD), colonoscopy, and ERCP [18]. PV and IVC were accessed using a 19 G needle and modified ERCP catheter. Access and pressure measurements of both vessels were achieved in 5 of 5 pigs. Necropsy showed no evidence of injury in all subjects. A threefold increase in PVP was noted between baseline and during ERCP. Values of IVC pressure, as well as of PVP for EGD and colonoscopy, were similar between baseline and procedure time.

Schulman and colleagues demonstrated a novel method of measuring PVP in 2016 using an EUS-guided 22 G needle through which a wire with a digital pressure sensor was passed [19]. Conventional transjugular catheterization was performed as a control. Successful device placement and PVP measurement were achieved in 5 of 5 pigs with no hemorrhage or thrombosis noted on both EUS and post-procedural necropsy. Comparison of EUS-measured PVP with transjugular HVPG measurements showed a difference of within 1 mmHg for all pigs. The study endoscopists rated the procedure as having overall low subjective workload. The authors used the same device to perform PVP measurement in 5 other pigs that were then survived for 14 days before necropsy [20]. PVP was again measured on day 14. No signs of complications were observed during the 2-week survival period, and necropsy again showed no abnormalities. PVP values on day 0 and day 14 were similar for all 5 pigs.

Our group developed a method of EUS-guided portal pressure measurement using a 25 G needle and simple transducer setup. The apparatus for PPG measurement included a linear echoendoscope, a 25 G FNA needle, and a compact manometer (Fig. 16.1) with non-compressible tubing [21]. Prior to echoendoscope insertion, the manometer was zeroed at the mid-axillary line. Measurements were conducted in the portal vein (PV) and hepatic vein (HV) and the inferior vena cava (IVC). When the PV was targeted, manometry was performed via a transgastric, and less often a transduodenal, transhepatic approach and only the intrahepatic portion near the PV bifurcation was accessed (Fig. 16.1). When evaluating the HV, the needle tip was placed 2 cm distal to the ostia where possible. Needle placement was meticulous to ensure consistency. One milliliter of heparinized saline was flushed through the needle before pressure measurement to clear the needle lumen and confirm intravascular placement. We also measured pressures in a swine model of portal hypertension induced by Dextran-40 administration. Percutaneous measurements in

Fig. 16.1 Compact manometer used for EUS-guided portal pressure measurement (Cook Medical, Bloomington, IN). Reprinted from Gastrointestinal Endoscopy, 85(5), EUS-guided portal pressure gradient measurement with a simple novel device: a human pilot study, May 1, 2017, with permission from Elsevier

the same vessels were obtained for comparison. All vessels were successfully accessed and pressures measured via EUS in all 3 pigs. Necropsy was not performed, but intraprocedural monitoring showed no signs of cardiorespiratory instability. Correlations between EUS-guided and percutaneous pressure measurements were very strong, with R values in all vessels greater than or equal to 0.985.

Human Studies

The first human single case of EUS-guided PVP measurement was reported by Fujii-Lau and colleagues in 2014, in which a 22 G FNA needle connected to an arterial pressure catheter was used to rule out portal hypertension in a 27-year-old man with arteriovenous malformations secondary to Noonan syndrome. The measured portal pressure gradient was 1 mmHg and correlated with the gradient obtained by interventional radiology at a prior procedure. There was no evidence of bleeding or hemodynamic instability after this procedure [22].

Our group performed the first prospective pilot study of PPG measurement in human patients with suspected or confirmed cirrhosis [23]. The setup employed the simple transducer setup discussed above with our animal study. The compact manometer was zeroed at the midaxillary line of each patient, and care was taken to consistently place the needle 2 cm distal to the hepatic vein ostia. Pressure readings were taken of the PV and either the HV or the IVC if anatomy was unfavorable for HV access. Needle placement was achieved and PPG measurement obtained in 28 of 28 patients, and no adverse events including bleeding, perforation, or infection were noted. The time required to obtain pressure measurements was short, under 30 min per patient. PPG measurements correlated well with clinical and endoscopic parameters with significant differences in PPG noted in patients that were high-risk versus low-risk for cirrhosis and in patients with esophageal varices, portal hypertensive gastropathy, and thrombocytopenia relative to patients without these conditions. There were no complications in any of the 28 patients. In addition, the majority of the patients in this study had EUS-guided liver biopsies performed at the same procedure suggesting that combining a PPG measurement and liver biopsy in the same session should be safe.

EUS-guided PPG Measurement Technique

The EUS manometry apparatus used in our human study is a simple setup that includes a 25 G FNA needle, non-compressible tubing, a compact digital manometer, and heparinized saline (see Video 16.1). The tubing is connected by a luer lock to the distal port of the manometer,

while the heparinized saline is connected the proximal port. The end of the tubing is connected via a luer lock to the inlet of the 25 G needle. The patient is positioned supine and during EUS-guided pressure measurement reading the manometer is placed at the patient's mid-axillary line (Fig. 16.2). We prefer monitored anesthesia care or general anesthesia for this procedure.

The hepatic vein measurement is conducted first. Of the hepatic veins, the middle hepatic vein is targeted most commonly due to its larger caliber and better alignment with the needle trajectory on linear EUS (Fig. 16.3). Doppler flow is used to confirm the typical multiphasic waveform of hepatic venous flow (Fig. 16.4). Using the 25 G FNA needle, a transgastric transhepatic approach is used to puncture the hepatic vein. Approximately 1 cm^3 of heparinized saline is used to flush the needle which is visible on EUS confirming good position within the vessel. Following the flush, the pressure reading on the manometer will immediately rise and then fall and equilibrate at a steady pressure which is recorded. This measurement should be repeated and second and third time to minimize any error or fluctuation and to give a range of pressures from which to derive a mean pressure. The mean of the three pressures is then considered the hepatic vein pressure. The FNA needle is slowly withdrawn from the vein into the liver parenchyma and then back into the needle sheath with Doppler flow on to ensure there is no flow within the needle tract.

The portal vein measurement is conducted next and the umbilical portion of the left portal vein is targeted (Fig. 16.5). Doppler flow is used to confirm the typical venous hum of portal venous flow (Fig. 16.6). Using the 25 G FNA needle, a transgastric transhepatic approach is used to puncture the portal vein. The procedure that follows is the same as what was performed for the hepatic vein. Approximately 1 cm^3 of heparinized saline is used to flush the needle which is visible on EUS confirming good position within the vessel. Following the flush, the pressure reading on the manometer will immediately rise and then fall and equilibrate at a steady pressure which is recorded. This measurement should be repeated and second and third time. The mean of the three pressures is then considered the portal

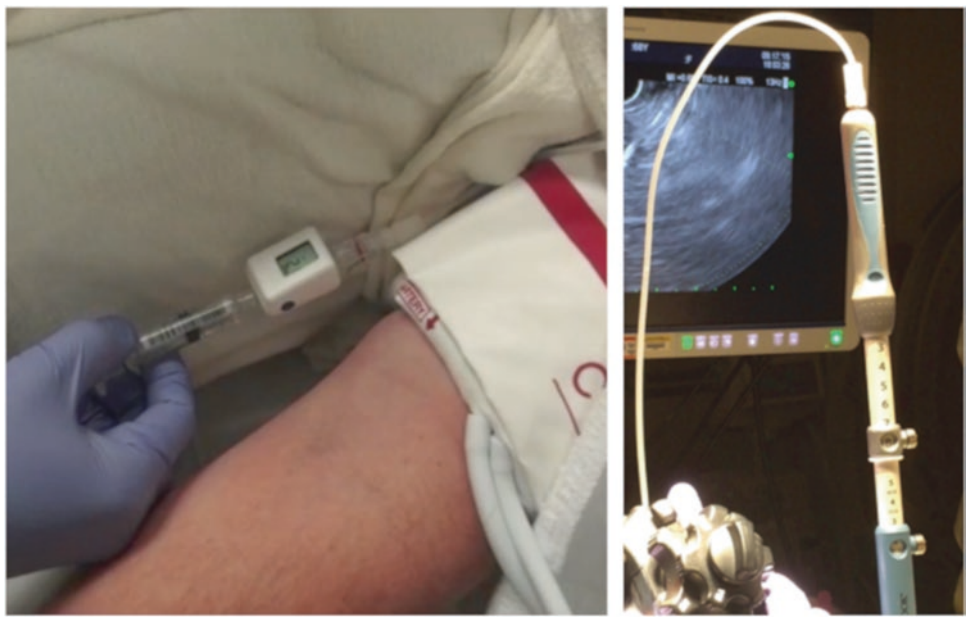

Fig. 16.2 Endoscopic ultrasound-guided portal pressure measurement apparatus showing non-compressible tubing attached to the FNA needle inlet (right panel) and compact manometer being placed at the mid-axillary line of the patient (left panel)

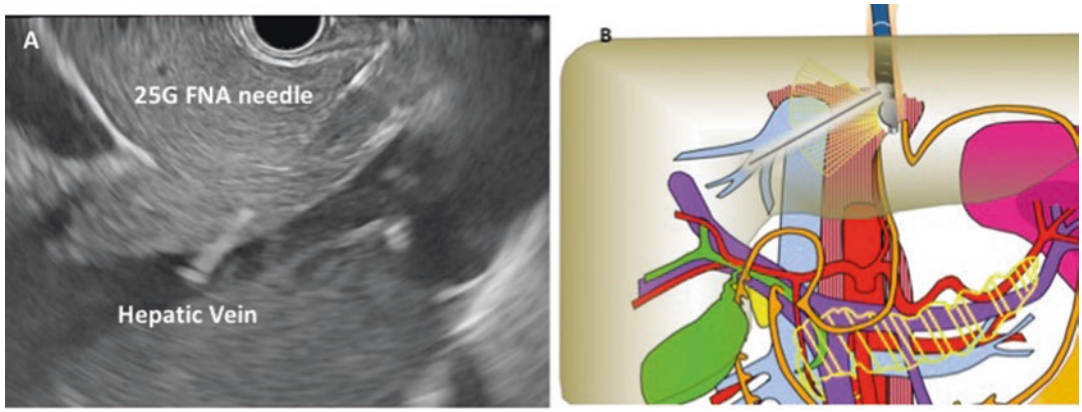

Fig. 16.3 **A**: EUS image of needle puncture of middle hepatic vein with 25 G FNA needle. Reprinted from Gastrointestinal Endoscopy, 85(5), **B**: EUS-guided portal pressure gradient measurement with a simple novel device: a human pilot study, May 1, 2017, with permission from Elsevier

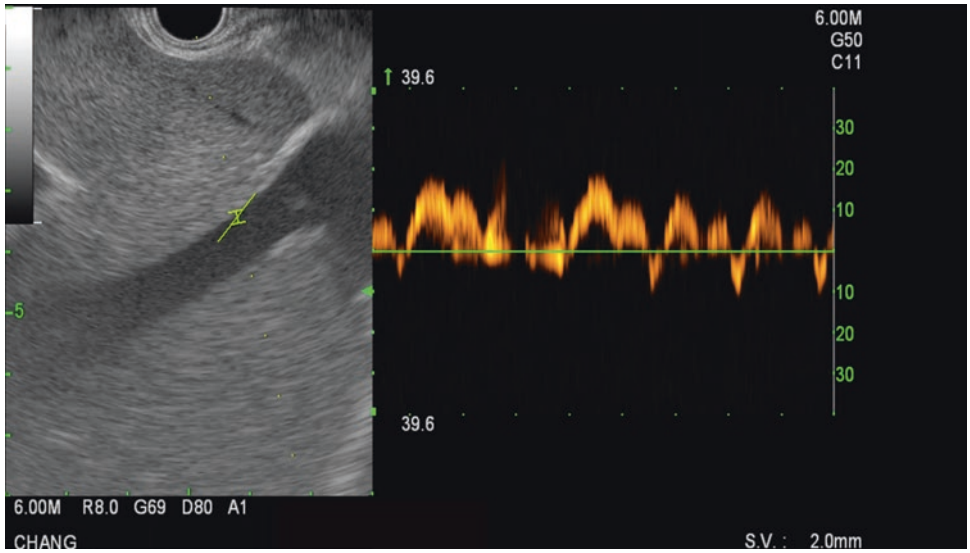

Fig. 16.4 EUS Doppler flow image of middle hepatic vein demonstrating multiphasic waveform

vein pressure. The FNA needle is slowly withdrawn from the vein into the liver parenchyma and then back into the needle sheath with Doppler flow on to ensure there is no flow within the needle tract.

The portal pressure gradient is calculated by subtracting the mean portal vein pressure from the mean hepatic vein pressure. The patient is recovered in a similar manner to a routine diagnostic EUS with FNA. Post-procedural antibiotics are usually given for 5 days post-procedure.

Conclusion

Recent advances in the field of hepatology have included new and effective treatment for viral hepatitis, with an increased need for assessment of liver function and histology. At the same time

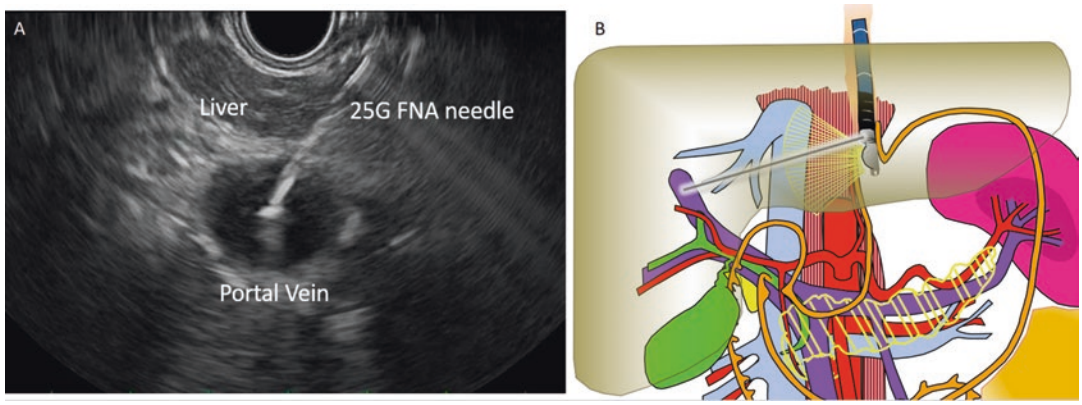

Fig. 16.5 **A**:EUS image of needle puncture of left portal vein with 25 G FNA needle. Reprinted from Gastrointestinal Endoscopy, 85(5), **B**: EUS-guided portal pressure gradient measurement with a simple novel device: a human pilot study, May 1, 2017, with permission from Elsevier

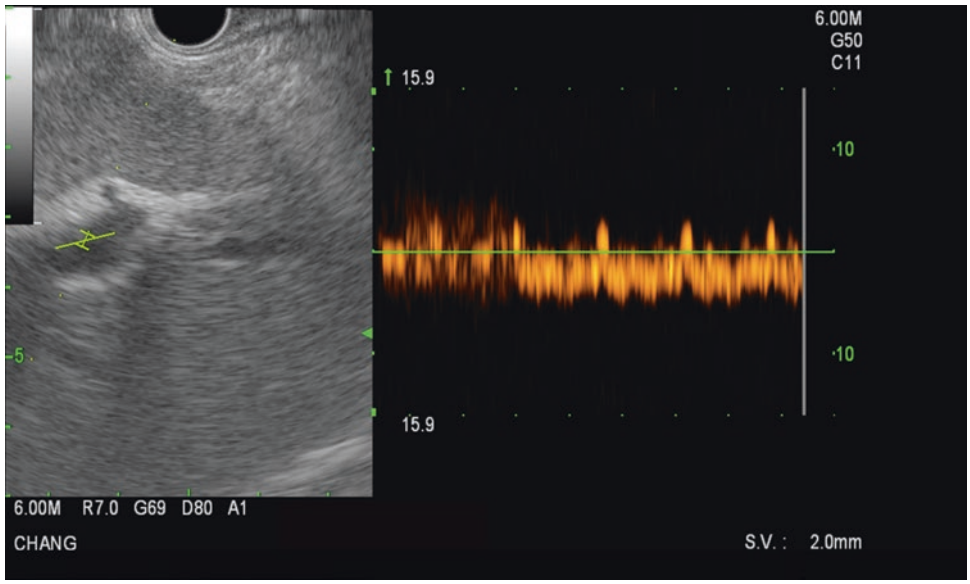

Fig. 16.6 EUS Doppler flow image of left portal vein demonstrating typical waveform

there have been a growing number of endoscopic procedures that are pertinent to liver patients. It would be ideal if the assessment and treatment of liver disease and portal hypertension could be performed and assimilated by the primary liver/GI specialist. We have termed this area of integration or overlap of endoscopic procedures within the practice of hepatology as *Endo-Hepatology*. Given the wide availability of EUS, an EUS-guided approach for the measurement of the portal pressure gradient would be a great advance in the field of Endo-Hepatology. As we have just covered, the current literature suggests EUS-guided measurement of the portal pressure gradient is becoming safe and feasible. We look forward to the results of an international multicenter human trial using our recently designed manometry apparatus to further evaluate the safety and clinical utility of this approach for patients with liver disease.

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17 Endoscopic Ultrasound-Guided Drainage of Pelvic, Intra-abdominal, and Mediastinal Abscesses

Enad Dawod and Jose M. Nieto

Introduction

Abscess formation results from pus accumulating within a tissue that has formed a cavity caused by contamination either by bacteria, injury, or foreign substances. An abscess can persist from weeks to months [1]. Abscesses can either drain naturally or through a variety of medical, radiologic, or surgical interventions. Due to the high risk of septicemia and shock due to the proximity of deeper abscesses to vital organs, intervention for these deeper abscesses is usually necessary.

Pelvic abscesses have various etiologies. Pelvic abscesses can occur as a complication to surgery (i.e., low anterior resection), Crohn's disease, ulcerative colitis, ischemic colitis, diverticulitis, and sexually transmitted diseases causing pelvic inflammatory disease [2]. Pelvic abscesses are commonly located proximal to the rectum and sigmoid [3]. The standard therapy for pelvic abscesses has traditionally involved percutaneous drainage under ultrasound guidance through the transrectal or transvaginal route or under CT guidance through the transgluteal route. This modality however has some limitations, most importantly due to the complexity of the structures surrounding the abscess, making percutaneous drainage hard to achieve [3]. Moreover, transrectal and transvaginal drainage is only possible when the abscess is proximal to the ultrasound probe. Percutaneous drainage is also associated with complications such as leakage, pneumoperitoneum, pneumomediastinum, bleeding, infection, pain at the procedural site, and limitations to ambulation make these interventions inconvenient and risky [4].

Mediastinal abscesses are mostly secondary to an infection, commonly odontogenic and peritonsillar abscess (descending necrotizing mediastinitis). These lesions could also arise as a result of an esophageal perforation, postoperative leakage, or following cardiovascular and thoracic surgeries. Other causes include trauma, tuberculosis, skin infections, and hematogenous spread [5–7]. Mediastinal abscesses require prompt action as they are potentially life threatening and are usually associated with prolonged hospital stays with the vast majority of cases requiring surgical intervention [8]. Mediastinal abscesses due to esophageal perforation or postoperative leakage nearly always require surgical intervention [9]. Alternatively, mediastinal collections could be treated with interventional radiological techniques and transcutaneous US and CT-guided

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thoracentesis with catheter drainage [10]. Endoscopic treatment for mediastinal abscess has been described in the literature the past two decades either through direct endoscopic vision or, most recently, under endoscopic ultrasound (EUS) guidance [9–11].

Abdominal abscesses have a variety of etiologies including Crohn's disease, diverticular disease, and postoperative causes [4]. Liver abscesses are usually caused by biliary obstruction, hepatic trauma, bacteremia, amebiasis, or a history of abdominal surgery [12]. Subphrenic abscesses are a complication of gastric, hepatic, and colonic disease, in addition to abdominal surgery trauma [13]. Bilomas can result from bile duct disruption or hepatic trauma [14]. Splenic abscess could occur as a complication of surgery or in patients with concurrent infections, more commonly in immunocompromised patients [15, 16]. Abdominal abscess are conventionally treated with interventional radiology-guided percutaneous drainage with concomitant use of antibiotics [17, 18]. Abdominal abscesses that are not amenable to percutaneous drainage are usually managed via surgery. Although EUS-guided drainage of pancreatic fluid collections has become the standard of care, to date there have only been limited reports of using EUS in treating intra-abdominal abscess [19, 20].

As a result, over the past 15 years, EUS-guided drainage of abscesses has been studied in relation to stenting, dilation, drainage, clipping, and cutting. This chapter will review the efficacy and safety of EUS-guided drainage of pelvic, mediastinal, and intra-abdominal abscesses. This chapter will also analyze what specific conditions and procedural modifications can lead to better results.

Background

The general technique for EUS-guided abscess drainage is as follows: EUS is used to locate the abscess via either a transrectal/transcolonic, transgastric, transintestinal, or transesophageal window. Once the abscess is identified, a 19-gauge needle is used to puncture the abscess site. Fluid from the abscess can be sampled as needed if clinically indicated-often no such sampling is performed as the abscess is assumed to be polymicrobial and the patient is already on broad-spectrum antibiotics. A guidewire is passed through the needle into the cavity and is coiled in the cavity. Once guidewire access to the abscess is obtained, drainage by the placement of one or more transluminal stents is performed, with or without balloon or passage catheter dilation of the transluminal tract. If using an electrocautery-enhanced lumen apposing metal stent (LAMS), the steps of needle access, guidewire passage, and tract dilation may be obviated.

Any other intervention involved such as dilation, clipping, or cutting were considered in this review as "other devices" used to facilitate abscess drainage. The type and number of stents used, other devices used for facilitating abscess drainage, and site of drainage were correlated with abscess resolution and adverse events/relevant clinical complications from the procedure.

Management

Pelvic Abscesses

To date, EUS-guided drainage of pelvic abscess has been reported in 105 patients (Figs. 17.1, 17.2, 17.3, 17.4, 17.5, 17.6, 17.7, 17.8, and 17.9). The total average size of all of the pelvic abscesses in these studies was 59.47 × 46.31 mm ($n = 49$) with a range of 7.50 mm to 96.00 × 7.40 mm to 83.00 mm. Seven cases had incomplete resolution of their abscess (6.67%), 98 cases had complete resolution of their abscess (93.33%), and 9 cases had adverse events (8.57%) [3, 21, 22–24, 25–28].

Transrectally drained abscesses were thought to have more complications in comparison to trans-sigmoid drained abscesses. This is due to the fact that transrectal stents can migrate or clog easily by fecal matter or pus causing complications [2]. Eighty-one out of 105 (77.1%) cases had their abscesses drained transrectally, highlighting both the frequency of pelvic abscesses and their amenability to EUS-guided drainage. 14 (13.3%) cases had their abscesses drained

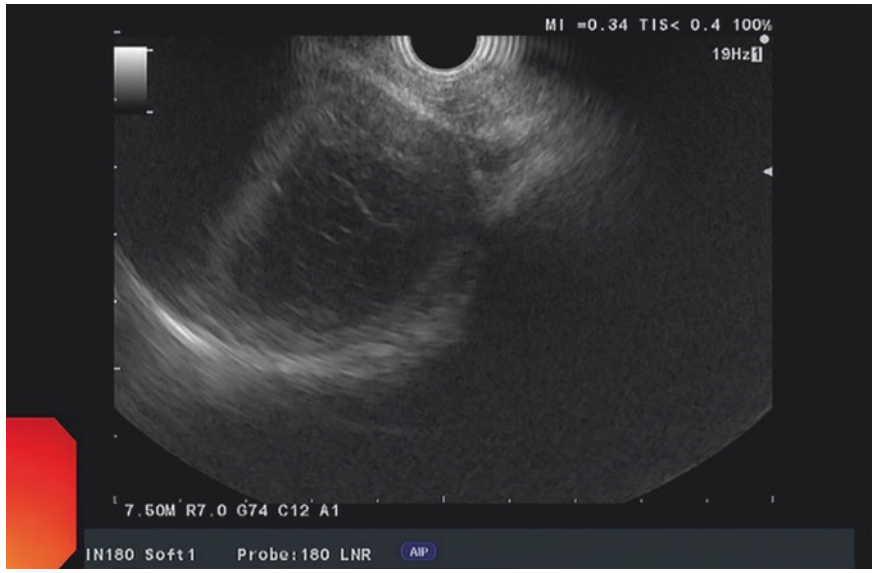

Fig. 17.1 EUS image of a pelvic abscess prior to drainage

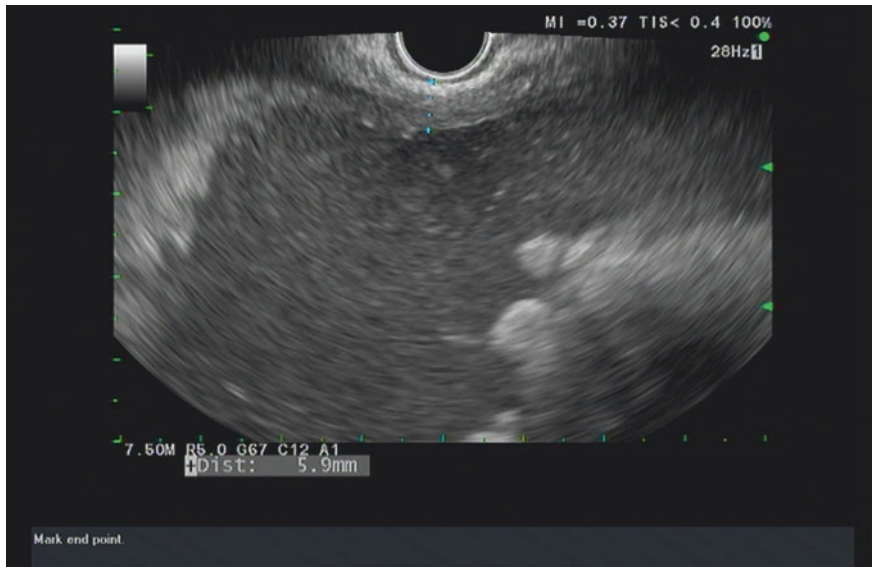

Fig. 17.2 EUS image of same abscess showing internal debris/contents

through the trans-sigmoid route. In 7 (6.67%) patients, the abscess was drained through the transcolonic route and through trans-abdominal route in 2 (1.9%) cases [3, 21, 22–24, 25–28].

Contrary to our expectations, drainage through the trans-sigmoid route led to a higher rate of incomplete abscess resolution and adverse events. Fourteen percent of patients who underwent drainage of their abscesses through the trans-sigmoid route experienced adverse events versus approximately 5% of those who underwent transrectal drainage. Due to the lower case count for patients with trans-sigmoid abscess drainage, the results are not significant. In addition, while it has been quoted that transrectal drainage can lead to a higher chance of clogging

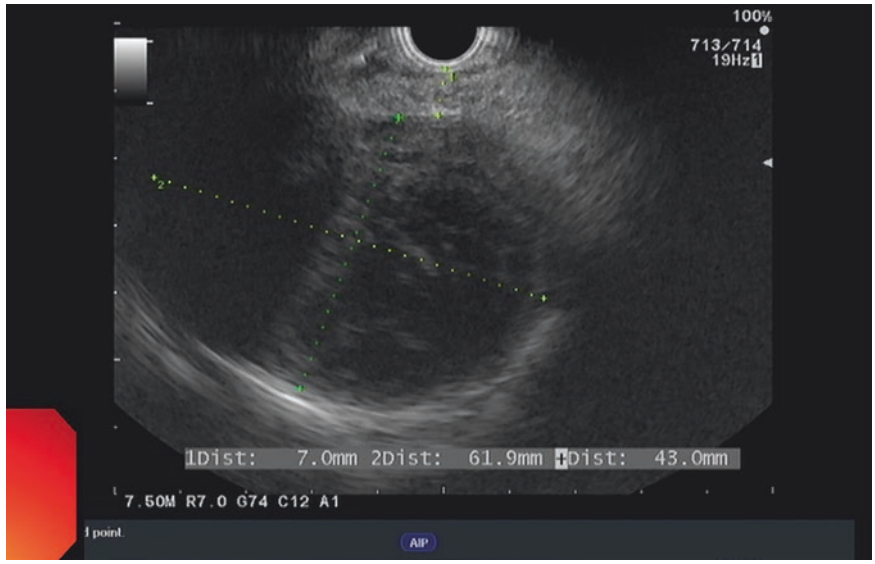

Fig. 17.3 Global view of abscess cavity on EUS

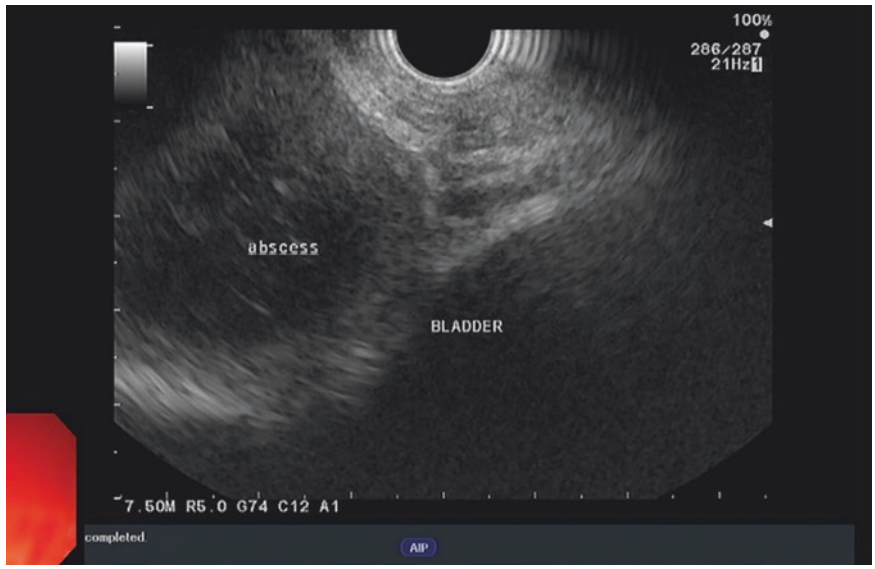

Fig. 17.4 EUS image of the abscess in proximity to the bladder

the lumen, because of the tortuosity of the sigmoid colon, a similar issue could arise and possibly be worse. Also, the drainage catheter used would have to be significantly longer due to the distance from the anus and this could also lead to more complications such as accidental closure or leakage of the catheter inside the lumen. Adverse events in both groups included fever, abdominal pain, nausea, vomiting, and left lower quadrant pain.

Historically, for biliary and pancreatic stent placement, plastic stents have been known to have a higher rate of stent migration and stent occlusion. In general, metal biliary stents develop stent occlusion at a later date and with less frequency than plastic stents. In addition, there is a

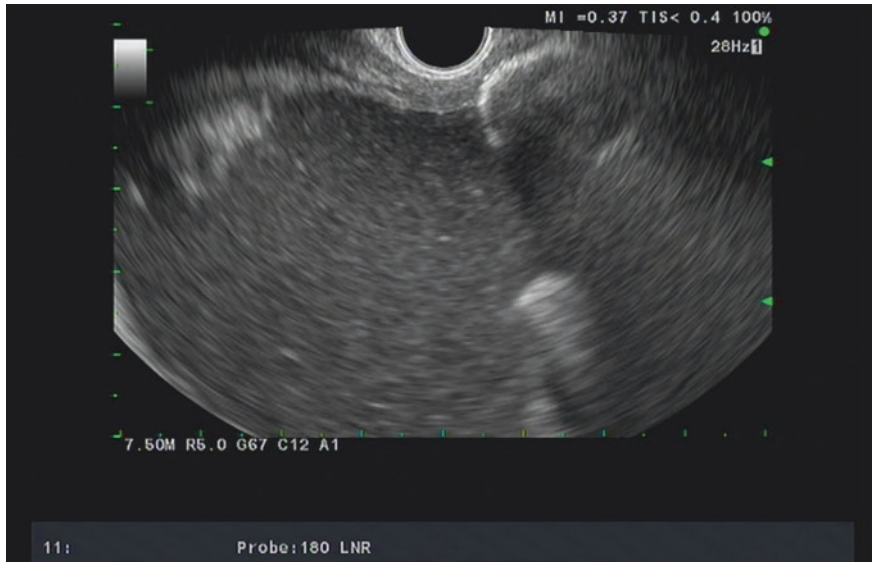

Fig. 17.5 Figure EUS view of same abscess after distal flange of the first LAMS deployed. Ultimately, two LAMS were used to drain the abscess in its entirety

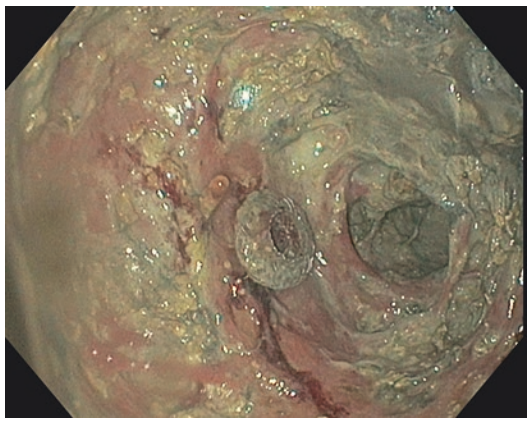

Fig. 17.6 Internal view from within the abscess showing one of the flanges of a LAMS

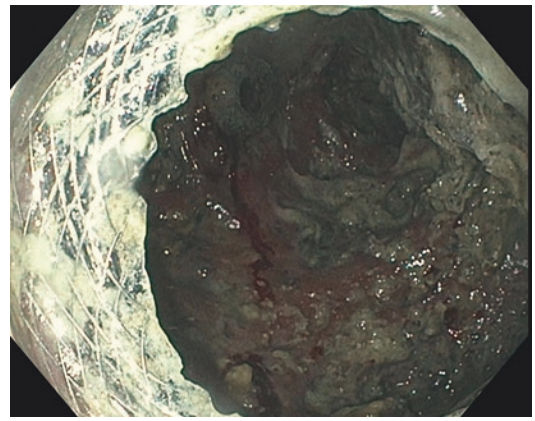

Fig. 17.7 Endoscopic view through one LAMS showing the 2nd LAMS in the abscess cavity

reduced risk of perforation due to a reduced need for prior stricture dilatation [29, 30] As a result, for pelvic abscess cases, we predicted a similar outcome, in which metal stents would have a lower rate of incomplete resolution and adverse events.

Out of 105 cases, 85 (80.95%) cases utilized transluminal stents and 20 (19.05%) cases were treated with aspiration alone. Among the 85 cases that had a stent deployed, 29 cases had one 10F double pigtail stent deployed, 16 cases had one 7F double pigtail stent deployed, 25 cases had two 7F double pigtail stents deployed, 1 case had three 7F double pigtail stents deployed, 1 case had two 10F double pigtail stents deployed, 5 cases had one 8.5F double pigtail stent deployed, 1 case had 1 lumen apposing metal stent (LAMS) deployed, and 3 cases had 1 fully covered self-expandable metal stent (FCSEMS). Within these studies, cases that had 1 full covered metal stent, 1 10F plastic stent, or 1 10F double pigtail stent and 1 8.5F double pigtail stent had a higher

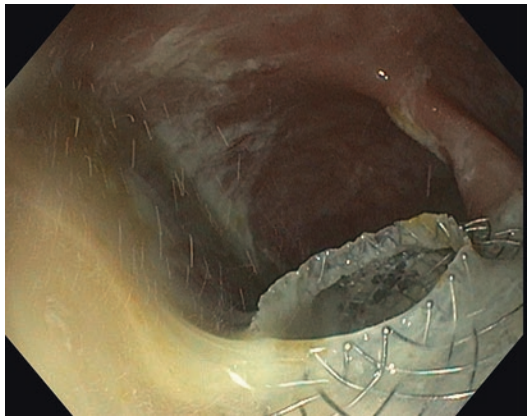

Fig. 17.8 Endoscopic view of pus draining into the colon through a LAMS after deployment in the pelvic abscess

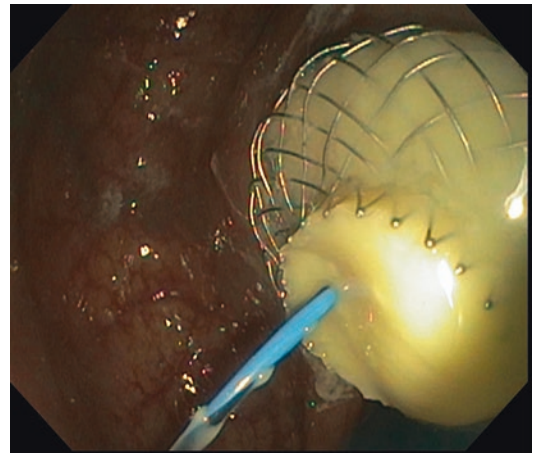

Fig. 17.9 An additional view of pus draining through the LAMS into the bowel lumen

rate of adverse events/relevant clinical complications compared to cases that had other stents placed, suggesting the multiple stents may be better than a single stent when treating abscesses. Twenty patients had their abscess aspirated and did not undergo stent placement and of those 3 had incomplete resolution of their abscess. Patients that did not have a stent placed had a higher rate of adverse events compared to cases that had one or more stents placed [3, 21, 22–24, 25–28].

The average time from stent placement to stent removal was calculated in weeks. 72 cases had usable data for average stent removal. The average number of weeks for stent removal for every case with usable data was 5.34 weeks (0.29–30.10). The average stent dwell time in weeks for cases that had incomplete abscess resolution was 16.05 weeks (2.00–30.10) as compared to 5.03 weeks (0.29–30.10) in the patients who had complete resolution of their abscesses. The average number of weeks from stent placement to stent removal for cases that had adverse events was 16.55 weeks (n = 6) with a range of 4–30.10 weeks as opposed to 3.83 (n = 66) with a range of 0.29–30.10 weeks in the patients who had no adverse events. Cases that had stents placed for a longer period of time had an overall higher incidence of having incomplete abscess resolution and adverse events. This suggests that it is possible that these were sicker patients to begin with or that longer stent dwell time may be associated with a worse outcome [3, 21, 22–24, 25–28]. These results were consistent with our prediction that plastic stents had a higher rate of incomplete resolution, but were not consistent with our hypothesis that plastic stents would have a higher rate of adverse events compared to metal stents. Due to the small sample size of patients found for cases with metal stents placed, the results for the rate of adverse events might not be representative of what was expected. As a result, more research has to be done regarding metal stents deployed for pelvic abscess drainage

Taking a look at the other instruments used to facilitate drainage in these cases, we believed dilation and catheter drainage would be superior to the other modes of drainage. This is due to the fact that after using a dilator or cystotome, the placement of a stent or catheter should be easier. Because no electrocautery is used during the dilation procedure, bleeding or perforation is generally only seen in 1% of patients. Due to the use of electrocautery with cystotomes, perforation is a frequent complication of the procedure [31]. In addition, catheter drainage poses the risk of accidental dislodgement of both the catheter and the stent due to the catheter protruding from the anus, but allows for access to the abscess cavity and for frequent irrigation to allow the drainage to complete as quickly as possible [2].We hypothesized that in this retrospective case study, there would be the fewest incomplete abscess resolutions and

adverse events in patients with both a catheter and dilator used to facilitate drainage

The total number of cases that had other devices and techniques used to facilitate abscess drainage was 86 cases. Nineteen cases had dilation and catheter drainage done along with the main intervention. Ten cases had only catheter drainage to facilitate abscess drainage along with the main intervention, but no usable data was found in the studies.

Fourteen cases had dilation done and a guiding catheter placed. Thirty-seven cases had only dilation done to facilitate abscess drainage along with the main intervention and 6 cases used cystotomes to drain the abscess. Thirty-seven had no other intervention done along with the main intervention [3, 21, 22–24, 25–28]. While these other interventions do make a difference in the efficacy and safety of the outcome of the results, stent placement is more crucial for a beneficial outcome according to the data collected in this study.

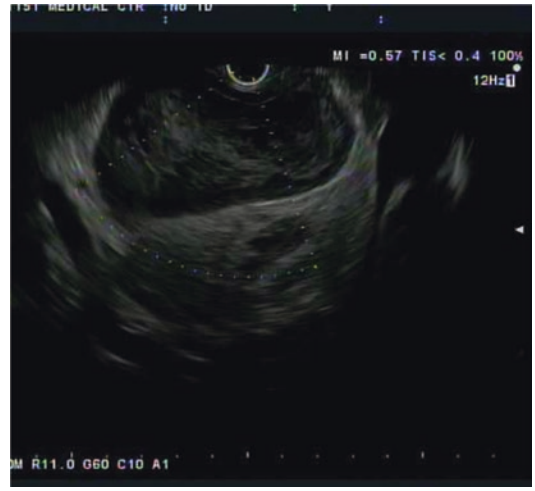

Fig. 17.10 EUS views of a hepatic abscess

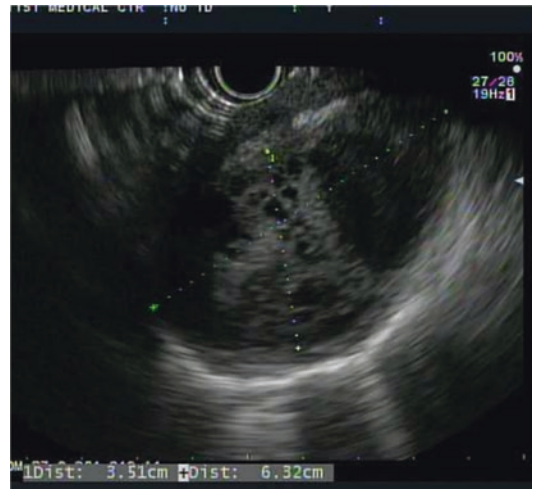

Fig. 17.11 EUS view of same abscess showing internal debris/contents

Intra-abdominal Abscess

Currently there are multiple published reports which include 37 patients that have undergone EUS-guided drainage of intra-abdominal abscesses, including hepatic abscesses (Figs. 17.10, 17.11, and 17.12) and (Video 17.1). The average size of these abscesses was 59.83 × 52.72 mm (n = 18) with a range of 25 mm to 150 × 21 mm to 170 mm. Notably, 100% of the cases had complete resolution of the abscesses and 4 cases had adverse events or relevant clinical complications (10.81%) [4, 12, 14, 16, 18, 32–37].

Procedures and cases that used the transgastric route for drainage had more adverse events in comparison to cases that had abscesses drained from the transduodenal route. Thirty-two abscesses were drained through the transgastric route, 4 via the transduodenal route, and 1 via the transjejunal route [4, 12, 14, 16, 18, 32–37].

Thirteen cases involved the use of a transluminal, fully covered self-expanding metal stent (FCSEMS) and 3 out of 13 cases had adverse events/relevant clinical complications (23.08%). Twenty-two cases had at least one double pigtail of various sizes with no adverse events being reported. Two cases had no stents deployed and one out of 2 cases had adverse events (50%). The type and number of stent had no effect on resolution of the abscess, however, cases with FCSEMS stents had more adverse event outcomes compared to cases who had other types of stents deployed [4, 12, 14, 16, 18, 32–37].

The average time from stent placement to stent removal was calculated in weeks. The average number of weeks throughout all the cases that had EUS-guided intra-abdominal abscess

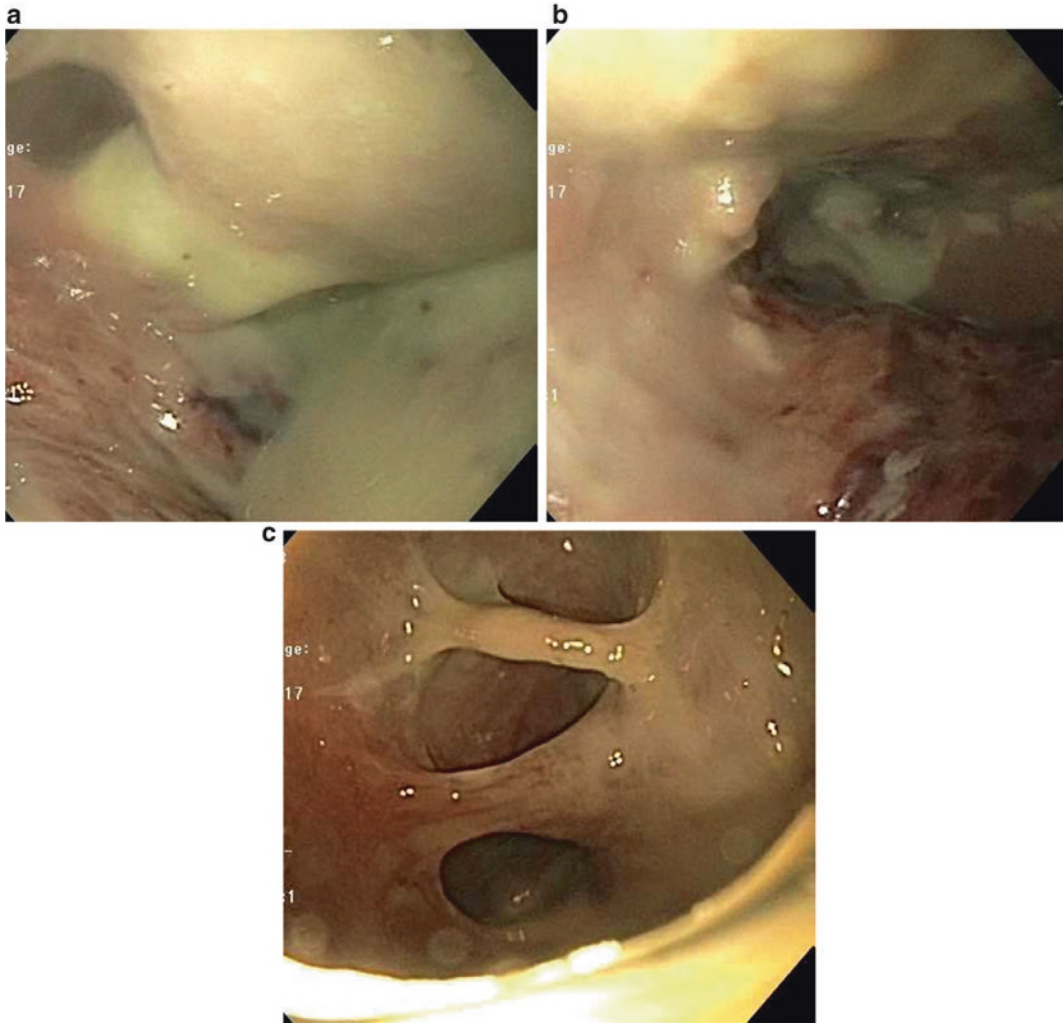

Fig. 17.12 (**a**–**c**) Endoscopic views of the interior of the hepatic abscess as seen through the LAMS with an upper endoscope

drainage stent placement was 5.55 weeks ($n = 14$) with a range of 1.57–12 weeks. In the 14 cases that provided stent removal data, 0 cases had incomplete abscess resolution or any adverse events [4, 12, 14, 16, 18, 32–37] (Figs. 17.10, 17.11, 17.12, and 17.13).

When looking at hepatic abscesses in particular, large-diameter metal stents provided effective drainage of liver abscess. Covered metal stents have been used to facilitate hepatic abscess debridement [37–39].

Fourteen cases involved the use of both dilators and drainage catheters, of which 3 cases developed adverse events (21.43%). Ten cases utilized only drainage catheters, while one case had an adverse event (10.00%). Twelve cases utilized only dilators to facilitate abscess drainage in addition to the main interventions and 1 additional case involved a hemostatic clip placed to close the fistula in addition to the main interventions. These cases did not have any adverse events [4, 12, 14, 16, 18, 32–37].

The mortality rate with the surgical method of treating hepatic abscesses has been reported to be between 17 and 32%, and the percutaneous method is associated with serious complica-

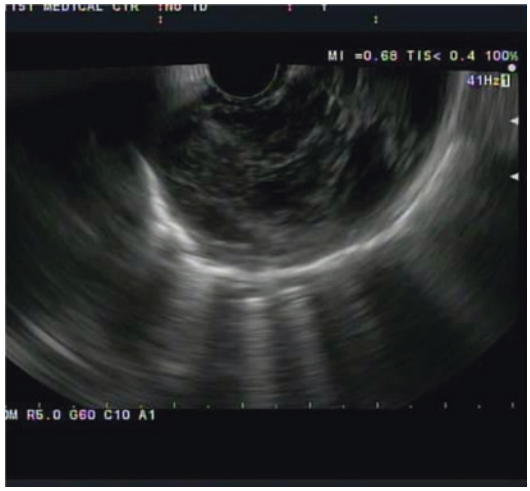

Fig. 17.13 EUS view of a mediastinal abscess

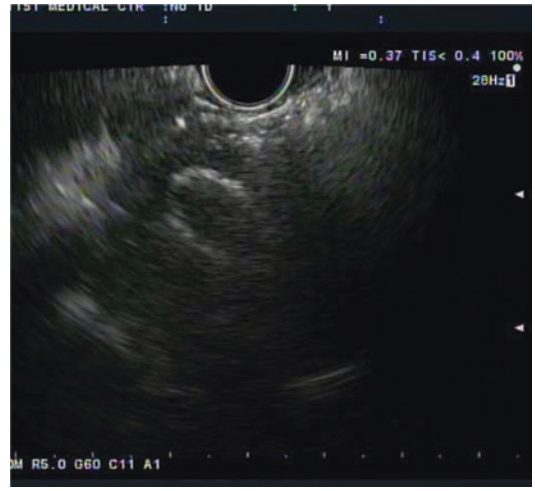

Fig. 17.14 EUS view of LAMS deployed into the mediastinal abscess

tions such as bleeding, biliary peritonitis, and fistula formation. EUS-guided drainage decreases the risk of injury to intervening vasculature, resulting in decreasing the rate of complications [12, 18, 33]. Additionally, EUS decreases the incidence of infections associated with the transcutaneous route and also allows for potential replacement of the external stent with an internal stent that could prevent recurrence [34]. EUS-guided drainage presents itself as a safe and superior modality in treating hepatic abcess [18, 36, 40]. One of the limitations of EUS is its inability to visualize and access the right lobe of the liver. However, this is not the case with left lobe, thus permitting full access and visualization [18].

Mediastinal Abscesses

The literature describes 6 patients who underwent EUS-guided drainage of mediastinal abscesses via transesophageal or transgastric approaches. The total average size of the cases' abscesses was 45.18 × 33.85 mm (n = 5) with a range of 17.70–63.00 mm in which there was 100% complete resolution of their abscess. One case had an adverse event/relevant clinical complication (16.67%) [7, 9–11, 41–43]. Mediastinal abscesses have been drained using lumen apposing metal stents (LAMS), FCSEMS, and double pigtail stents (Figs. 17.14 and 17.15).

The average number of weeks stents were placed was 5.43 weeks (n = 4) with a range of 0.71–16.00 weeks and reported adverse events in these patients included esophageal stenosis, esophageal ulceration, perforation, sepsis, fever, pain, and bleeding [7, 9–11, 41–43].

Due to the very small sample size, no significant differences could be established in terms of which specific conditions and procedural modifications can lead to better results and less adverse outcomes. EUS visualizes and accurately localizes blood vessels and other vital structures within close proximity of the abscess and identifies a clear and safe path for drainage. Furthermore, EUS has an advantage where there is no mucosal indentation of the abscess in which case blind per oral drainage might pose a high risk [7].

Summary

The results from these studies demonstrate that EUS-guided abscess drainage is an effective and safe method. Out of the 148 total cases in these studies, 95.27% of cases had complete abscess drainage, and 90.54% of cases had no adverse

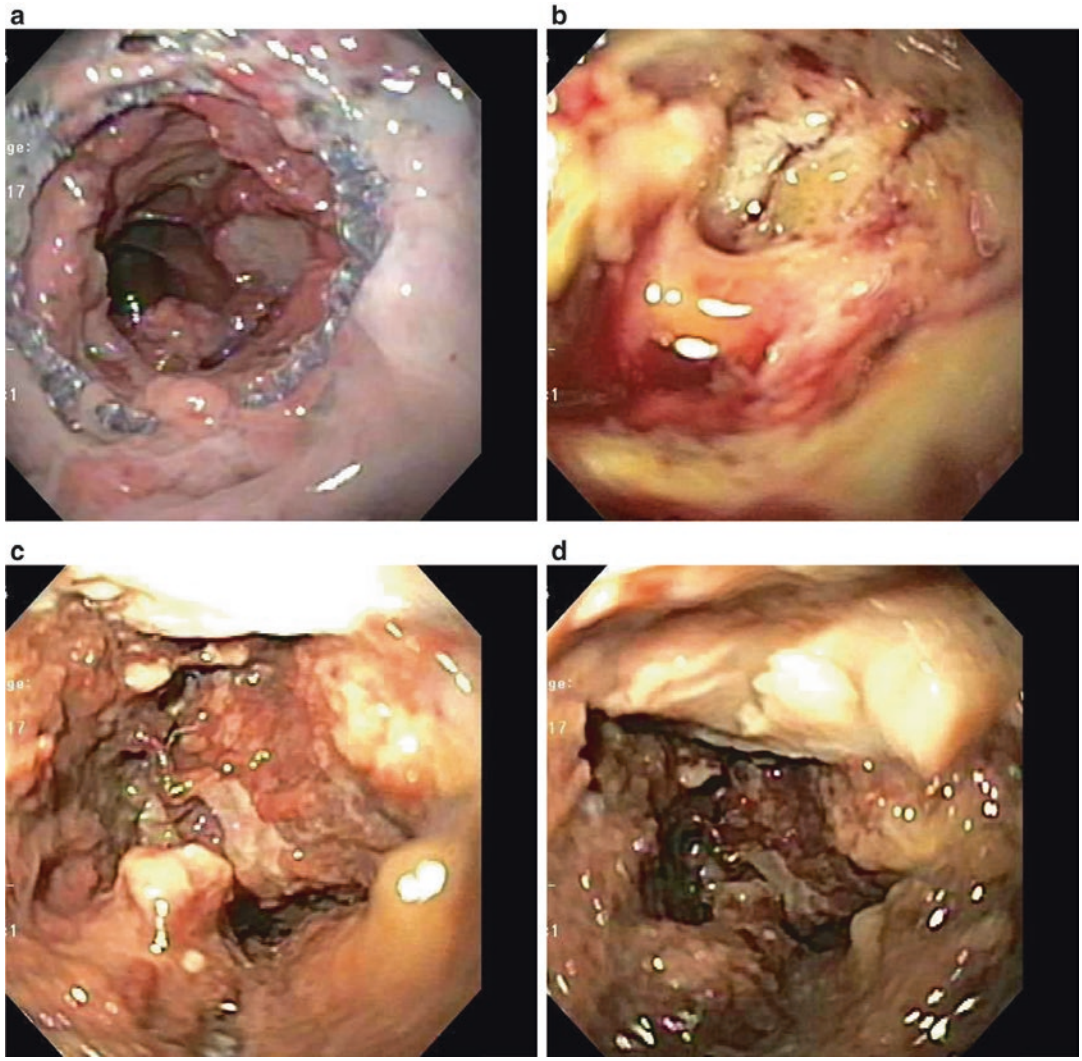

Fig. 17.15 (**a**–**d**) Endoscopic views of the interior of the mediastinal abscess as seen through the LAMS with an upper endoscope

events. While limited, the data suggests that double pigtail stents may produce better outcomes than metal stents.

The studies cited above were heterogeneous and reported their data in different ways, limiting their generalizability to some extent. As such, this leads to some degree of ambiguity when correlating data between types and number of stents, other devices used, and drainage route to clinical improvement and overall resolution of the abscess and adverse events/relevant clinical complications.

Overall, EUS-guided abscess drainage offers a safe and effective alternative option for drainage of abscesses in patients who are poor surgical candidates or in patients who prefer not to undergo surgery or percutaneous catheter drainage [2].

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