

# 21. Interventional Endoscopic Ultrasound

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## Introduction

Endoscopic ultrasound (EUS) was developed as an adjunctive diagnostic modality to supplement cross-sectional imaging. EUS applications have expanded due to evolution in echoendoscope design, improved image resolution, and the development of fine needle aspiration (FNA) needles. This chapter will review current interventional EUS applications, including FNA, pseudocyst drainage, pancreatic necrosectomy, pancreaticobiliary access, celiac plexus interventions, cyst ablation, tumor injection, and vascular interventions.

## Equipment

The two major types of echoendoscopes in common use are radial and linear (Fig. 21.1). The radial echoendoscope provides a circumferential image of structures in the plane perpendicular to the shaft of the scope. The advantage of the radial scope is that the images are similar to those obtained by computed tomography (CT), which may ease interpretation. The radial scope is not a therapeutic instrument because it does not have a working channel for passage of a needle or other devices. The linear echoendoscope is the therapeutic EUS “workhorse” and provides images of structures in the plane parallel to the shaft of the scope. The linear scope has a working channel, which allows the passage of needles in the plane of the endosonographic images for high precision tissue sampling and directed interventions. Additional specialized probes are available (e.g., catheter-based mini-probes, rigid

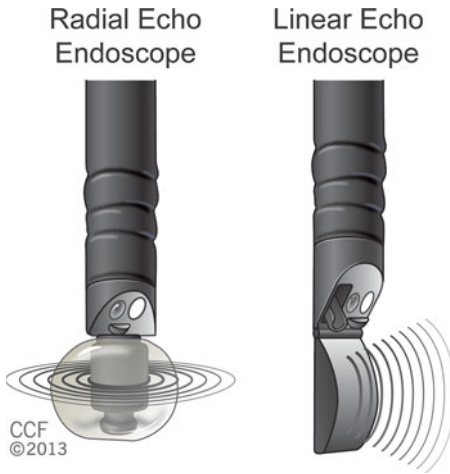


Fig. 21.1. Radial and linear echoendoscope depictions with plane of imaging. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2015.

anal probe, transpapillary intraductal ultrasound). These radial probes have higher frequency capability allowing very fine mucosal detail, and specific diagnostic applications, such as assessing subepithelial lesions and superficial cancers, evaluating the colon proximal to rectum, assessing the anal sphincter, staging anal cancer, and assessing pancreaticobiliary ductal pathology. Because they are radial instruments without a working channel, these specialized probes cannot be used for therapeutic interventions.

## EUS-Guided Fine Needle Aspiration (FNA)

EUS-guided FNA is the most commonly performed intervention and has almost completely replaced CT- and US-guided transcutaneous biopsy of pancreatic masses and other lesions in proximity to the upper GI tract. Common indications include upper GI mucosal and intramural lesions, solid and cystic pancreatic masses, and diagnosis of pathologic lymph nodes. Immunohistochemical stains and flow cytometry can be added to standard cytological interpretation to enhance the diagnosis of certain diseases like lymphoma and stromal tumors.

One limitation of EUS-FNA has been imperfect sensitivity for detecting cancer and other diseases resulting in false negative results and need for repeat procedures. A second limitation is that cytologic specimens (individual or aggregates of cells without preserved tissue architecture) are usually acquired, rather than core biopsies amenable to comprehensive histological analysis.

In recent years, clinical studies have attempted to define optimal FNA techniques and needle types that maximize cytological yield, or even achieve a core biopsy. Needle size may affect the sample, since smaller needles cause less bloody contamination and more easily actuate in torqued scope positions, whereas larger needles may obtain more cells. Studies comparing needle sizes (22 gauge versus 25 gauge) have shown varying results. Retrospective studies and a meta-analysis suggested a benefit of the 25 gauge (G) needle for detecting cancer [1, 2]. However, other studies showed no difference between these needle sizes in overall accuracy [3–8]. Twenty-five gauge needles may be more accurate for pancreatic head and uncinate lesions [4, 9]. The 19-G needle may enhance the diagnosis of cystic lesions since it drains material quickly and is less likely to become blocked with mucinous fluid.

The use of a stylet within the needle during puncture has not been shown to be beneficial [10–12]. The application of suction on the needle improved the diagnostic yield in pancreatic lesions [13, 14], but not in lymph nodes [15]. If a 25 G needle is used for FNA, then a “slow pull” of the stylet has been shown to be superior to suction [16].

The availability of an onsite cytopathologist or technician allows passes to be analyzed in real time to ensure cellular adequacy and minimize the number of passes. The optimal number of passes in the absence of onsite cytopathology is variable. Initially seven passes were recommended for pancreatic mass lesions and five passes for lymph nodes [17]. More recent studies have shown that three to four passes may be adequate [18, 19]. In some cases, core biopsies (with preserved cellular architecture) can be acquired using 19 G and “coring” needles (e.g., Cook Procure® and Trucut®) but the successful acquisition of tissue with these devices is variable.

EUS-FNA is generally safe and serious complications are rare. The overall complication rate reported is 2.5–3.4 % including bleeding (0.3 %), pain (0.85–1.2 %), infection (0.56 %), and pancreatitis (0.85–1.8 %) [20, 21].

## EUS-Guided Drainage Procedures

### *Pancreatic Fluid Collection Drainage*

Pancreatic fluid collections (PFCs) may occur as a result of acute or chronic pancreatitis, surgery, or trauma. Many of these collections are closely opposed to the stomach or duodenum, and may undergo drainage. Endoscopic drainage was previously done without the benefit of ultrasound guidance, by blindly puncturing the luminal bulge seen endoscopically using a needle knife cautery device. EUS has enhanced the safety and efficacy of endoscopic drainage because it visualizes intervening blood vessels that are common in patients with left-sided portal hypertension from prior pancreatitis, and because it allows drainage of PFCs that do not have an obvious luminal bulge. Studies of EUS-guided drainage have shown a higher technical success rate and lower complication rate than standard endoscopic drainage [22]. EUS-guided drainage has also mostly replaced surgical cystogastrostomy. A randomized control study has shown that EUS-guided drainage of pseudocysts is non-inferior to surgical drainage and associated with a shorter length of stay and lower cost [23]. Enlarging PFCs and those causing pain, obstruction (gastric or biliary), or infection require drainage. Endoscopic drainage should be timed based on the maturity of the PFC, since those with a thick, fibrous wall adhered to the gastrointestinal lumen are most safely drained.

The technical success rate of EUS-guided drainage in one of the largest single center series was 100 %, with a 5 % complication rate [24]. In a recent systematic analysis the technical and clinical success rates were reported as 97 % and 90 % respectively, with a complication rate of 17 % [25]. Reported complications include bleeding, infection, stent migration, and perforation. Most complications were managed conservatively or surgically with a mortality rate of 0.2 %. The success and complication rates of endoscopic drainage are influenced by the type of PFC. Pseudocysts arising in chronic pancreatitis respond better than those arising in acute pancreatitis. The newly revised Atlanta Classification defines different types of PFCs arising from acute pancreatitis based on location, timing following symptom onset, and the presence of solid necrotic debris. Most PFCs occurring more than 4 weeks after the onset of acute pancreatitis are actually walled off pancreatic necrosis (WOPN) rather than true acute pseudocysts. This distinction is vital for endoscopic management, since multiple sessions of aggressive

endoscopic debridement may be necessary for WOPN, whereas simple drainage may be sufficient for acute and chronic pseudocysts. EUS is advantageous because it is superior to CT scan for detecting solid material within a PFC, differentiating WOPN from acute pseudocyst.

Contraindications to endoscopic drainage include concern that the collection is a cystic neoplasm and the presence of uncorrected coagulopathy. If a cystic neoplasm is a possibility, initial EUS-FNA for diagnosis may be prudent prior to embarking on drainage. Techniques for EUS-guided drainage vary slightly between practitioners. The standard approach is the graded dilation technique. The PFC is first identified using a linear echoendoscope, and a suitable site chosen based on proximity from the lumen (preferably <1 cm) and absence of intervening blood vessels. Under fluoroscopy, the PFC is punctured using a 19-G FNA or access needle, contrast is injected to opacify the collection, and a guidewire passed through the needle and coiled within the cyst cavity. The tract is serially dilated over the guidewire using tapered and balloon dilating catheters, with or without electrocautery. After the initial intervention, the endoscopic cystogastrostomy should be maintained by placing stents. There is no consensus as to the type or number of stents. Plastic stents have lower migration rates but higher occlusion rates. Self-expandable metal stents have shown increased success rates in small case series but may increase the risk of stent migration, fluid leakage, and tissue injury from exposed metallic edges [26–29]. Newer lumen-apposing stents have been developed exclusively for drainage of pancreatic fluid collections (AXIOS™, Xlumena Inc., Mountain view, California, USA) with dedicated delivery systems (NAVIX™, Xlumena Inc., Mountain view, California, USA) [30–32].

In WOPNs and other debris filled collections that are symptomatic, endoscopic debridement should be considered. Infected WOPNs require intervention as they are associated with sepsis, multiorgan failure, and death. The recent guidelines advocate for a step-up approach starting with minimally invasive procedures such as percutaneous drainage and working up to surgical necrosectomy [33]. Delay in timing of surgical intervention improved mortality. A small randomized control trial has shown that death and major complications are lower in patients undergoing endoscopic transluminal necrosectomy compared to surgical necrosectomy [34]. Larger trials are underway to evaluate step-up endoscopic therapy versus step-up surgical therapy [35].

Endoscopic necrosectomy starts with standard EUS-guided cyst access, but involves more aggressive dilation (up to 18 or 20 mm) with subsequent passage of a standard upper scope through the endoscopic

cystogastrostomy into the cyst cavity for removal of necrotic debris using a variety of devices such as baskets, nets, and graspers. A covered self-expanding metal stent is deployed to secure the access to the cavity. Direct endoscopic necrosectomy is performed either in the same session or in the next session. The clinical success rate in a large US series was 91 % with a median of three procedures per patient and complications in 14 % of patients [36]. Complications included bleeding, perforation, pneumoperitoneum, sepsis, and failure of resolution.

### *Non-peripancreatic and Pelvic Fluid Collection Drainage*

EUS-guided drainage of abscesses, inflammatory fluid collections, and hematomas in the subphrenic space, perihepatic space, paracolic gutters, perirectal spaces, and pelvis have been described. Endoscopic luminal drainage of such collections may be quite useful when percutaneous drainage is not technically feasible. The technical and clinical success rates reported in a systematic analysis of observational case series were 99 and 92 % [25]. The EUS-guided drainage technique is similar to that described above for PFCs. The reported complications are pneumoperitoneum, pneumomediastinum, stent migration, bleeding, and fluid leakage.

### *EUS-Guided Biliary Drainage*

Percutaneous transhepatic cholangiography (PTHC) and surgical bypass have traditionally been offered when biliary cannulation fails during endoscopic retrograde cholangiopancreatography (ERCP). However, recent studies have shown that EUS-guided biliary drainage is as effective as PTHC and avoids the need for an external drainage catheter [37]. EUS-guided biliary drainage procedures encompass direct transluminal drainage (creation of a fistula maintained by a stent) and duct puncture with subsequent antegrade passage of a guidewire through the ampulla to achieve “rendezvous” access. Each technique is further subdivided into transgastric (via intrahepatic ducts) and transduodenal approaches (via common duct) as shown in Fig. 21.2. EUS-guided rendezvous procedures have fewer complications (e.g., bleeding, bile leak, pneumoperitoneum) compared with direct drainage and are usually attempted first, but are not always possible particularly if there

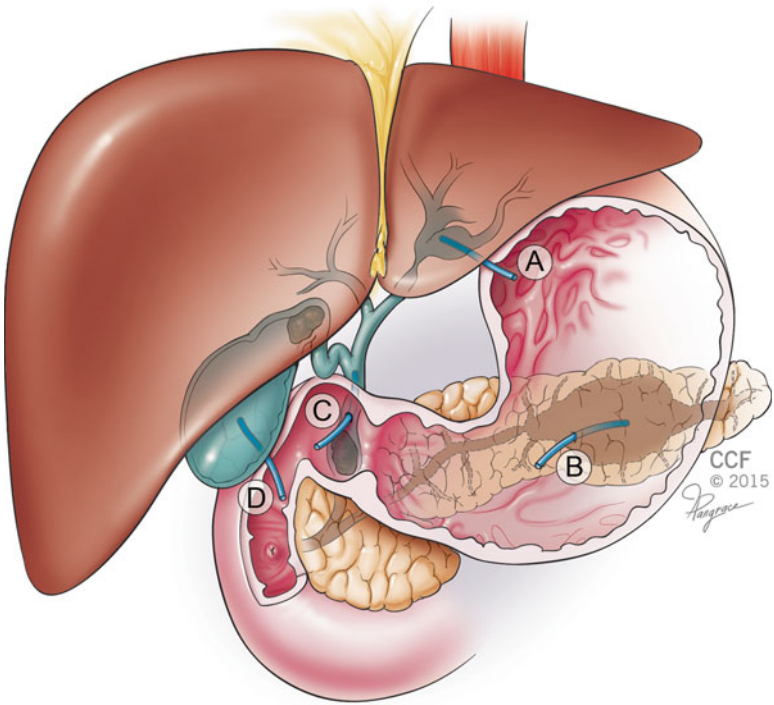


Fig. 21.2. Approaches for EUS-guided pancreatobiliary access. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2015.

is concomitant duodenal obstruction preventing access to the ampulla. Studies have shown that the complication rate for direct transluminal stenting is 20 %, and the use of needle knife for tract dilation is an independent risk factor for complications [38].

In the EUS-guided rendezvous procedure, the dilated bile duct is punctured with a 19-gauge FNA needle, followed by passage of a guidewire. The wire is manipulated antegrade through the papilla. The echoendoscope is then removed over the guidewire. A duodenoscope is advanced alongside the guidewire to the second portion of the duodenum. The guidewire is grasped using a forceps or snare and pulled into the working channel of the endoscope, allowing subsequent transpapillary biliary access to complete the drainage. The initial site of EUS-guided puncture may be the intrahepatic ducts through the lesser curve

of the stomach or the common duct through the medial wall of the duodenal bulb. Though the transgastric route into the intrahepatic ducts was initially preferred because of the presumed decreased chance of bile leak, studies have shown that the intrahepatic route is associated with a higher complication rate (20 %), and the extrahepatic approach is preferred if both routes are accessible [39, 40].

In patients with tight biliary strictures that do not permit passage of the guidewire through the papilla or with altered anatomy or duodenal strictures that hinder access to the papilla, direct transluminal stenting may be considered. In this procedure, access to the bile duct is obtained using an FNA needle. The tract is dilated and a transmural stent is placed into the duct to facilitate direct enteric drainage of bile. The potential adverse events of direct transluminal drainage are similar to those of the rendezvous technique when a needle knife is not used for dilation [41]. The transgastric route has a higher complication rate than the transduodenal route [39, 40].

### *EUS-Guided Pancreatic Duct Drainage*

In case of failed pancreatic duct cannulation during ERCP, EUS-guided pancreatic duct drainage has been used in a similar fashion as biliary duct drainage. The majority of pancreatic interventions have been for benign indications such as ductal stones or strictures from chronic pancreatitis, or in those with obstructed pancreaticojejunostomy after Whipple surgery.

The technique is similar as for biliary duct drainage and the possible access points are shown in Fig. 21.2. The pancreatic duct is visualized using a linear echoendoscope, accessed using an FNA needle, and a guidewire is advanced through the needle and if possible through the papilla for a rendezvous procedure. If the guidewire cannot be advanced past the papilla, then it is used for dilation and transmural stent placement. Pancreatic duct access is most commonly achieved via the transgastric route. Pancreatic duct drainage is more technically challenging than biliary duct drainage due to acute angulations between the scope and the pancreatic duct and fibrosis in the pancreas. The technical success rate reported in systematic analysis was 78 %, with a 20 % complication rate [25]. The complications described are pancreatitis, pancreatic leakage, bleeding, and perforation. A single large tertiary center experience concluded that EUS-guided pancreatic duct drainage may be done with good technical (74 %) and clinical (83 %) success rates and low complications (5.8 %) in large centers with experienced endoscopists [42].



## *EUS-Guided Gallbladder Drainage*

EUS-guided gallbladder drainage may be considered for patients with acute cholecystitis that requires intervention but who are poor surgical candidates. Percutaneous gallbladder drainage has been traditionally offered to such patients as a bridge to surgery or as definitive treatment. EUS-guided drainage may have similar efficacy and complications as the percutaneous approach, and does not require an external drainage catheter [43]. Complications include bleeding, bile peritonitis, and stent migration. Newer lumen-apposing stents have been used for EUS-guided gallbladder drainage with good success to minimize stent migration and bile peritonitis [32, 44].

## **EUS-Guided Celiac Plexus Intervention**

Celiac plexus blocks (CPB) and celiac plexus neurolysis (CPN) have long been performed for pain relief in patients with pancreatic cancer or chronic pancreatitis. EUS-guided celiac plexus interventions (Fig. 21.3) have been shown to be more effective than fluoroscopy or computed tomography directed percutaneous celiac plexus neurolysis in two small comparative trials [45, 46]. EUS-CPN is usually reserved for those with pancreatic or biliary cancer pain and involves injection of a neurolytic agent (most commonly 98 % dehydrated alcohol). EUS-CPB involves the injection of anesthetic agents with or without corticosteroids, has fewer complications, and is generally done for those with benign causes of pain like chronic pancreatitis. Meta-analyses suggest that EUS-CPN is durably effective in controlling cancer-related pain in 80 %, while EUS-CPB is only 50–60 % effective in temporarily controlling pain from chronic pancreatitis [47]. Early EUS-guided celiac plexus neurolysis in patients with inoperable pancreatic cancer had significantly lower pain scores with a trend towards lower narcotic usage. There was no effect on the survival or quality of life [48].

The linear echoendoscope is used to perform celiac plexus interventions. The origin of the celiac trunk from the aorta is identified along the lesser curve of the stomach. A 19 or 22 G FNA needle is advanced into the region cephalad of the celiac trunk. When the needle is in the target area 2 cc of saline is injected, and then aspirated to confirm that the needle is not within a blood vessel. After this “saline aspiration test,” the anesthetic agent/neurolytic agent is injected into the celiac plexus.

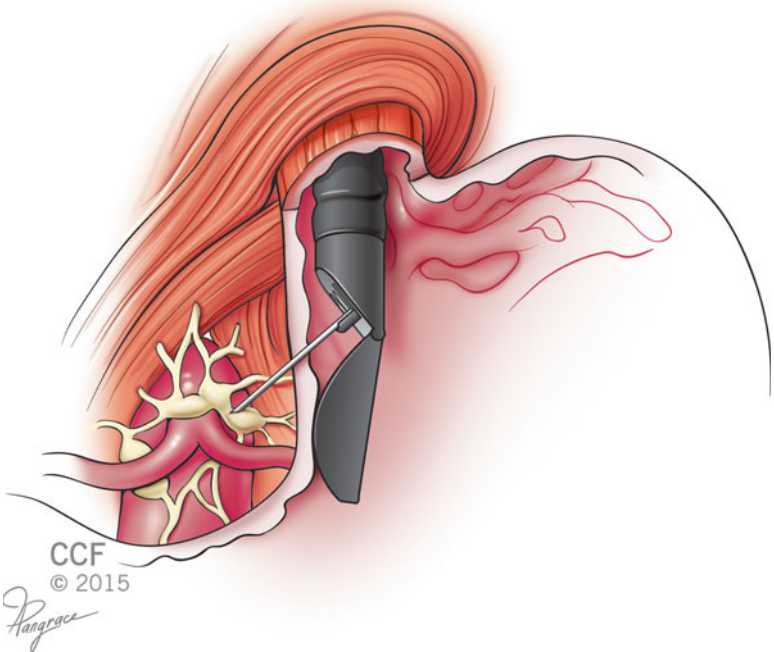


Fig. 21.3. EUS-guided Celiac plexus intervention. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2015.

There are wide variations in the technique and agent used for celiac plexus interventions. An observational study suggested that bilateral injection in which the neurolytic agent was injected into either side of the celiac trunk was more effective than one central injection [47, 49]. Subsequent, randomized control trials in patients with pancreatic cancer and chronic pancreatitis pain comparing central injection versus bilateral injection have shown no difference in the number of patients with response, speed of onset, or duration of pain relief [50, 51]. A major advantage of EUS-guided over standard percutaneous fluoroscopy-guided or CT-guided celiac interventions is the ability of EUS to directly visualize and inject individual celiac ganglia. It has been shown that direct celiac ganglion injection is more effective than injection of the celiac plexus. Seventy-three percent of patients given direct celiac ganglion injection had pain relief compared to 45 % of those given a standard diffuse plexus injection. Complete pain relief was obtained in 50 %

with celiac ganglion injection compared to 18 % in the celiac plexus injection group [52]. The optimal type and amount of neurolytic agent has not been extensively studied. However, a common approach is to inject from 10 to 20 cc of a mixture of alcohol 98 % and 0.25 % bupivacaine. Celiac plexus blocks are performed using bupivacaine solution (0.25–0.75 %). Triamcinolone is commonly added to lengthen the duration of the block, but does not appear to add benefit [53]. The common adverse events reported with celiac plexus interventions are transient diarrhea, transient orthostatic hypotension, transient increase in pain, and abscess formation. Serious neurological complications such as lower extremity paresthesia and weakness have been reported with non-EUS-guided procedures [54], and there has been one case of permanent paralysis in a patient given EUS-guided neurolysis for pancreatic cancer pain [55]. Pooled analyses report an adverse event rate of 4.7 % for celiac plexus block and 27 % for celiac plexus neurolysis. However most of the adverse events were minor (<1 % major adverse event) and lasted less than 48 h [56].

## EUS-Guided Cyst Ablation

Cystic lesions of the pancreas are often detected incidentally during cross-sectional imaging. Most of these lesions are branch-type IPMNs, which are generally indolent and benign, but may have premalignant potential. It can be difficult to definitively diagnose pancreatic cysts, even with high resolution imaging and EUS-guided FNA. The recently revised Sendai criteria provide expert consensus guidance on evaluating and monitoring these lesions, and advocate that most be followed with periodic imaging tests. Surgery is recommended for malignant cysts or cysts with high malignant potential. However surgery carries significant morbidity and mortality.

EUS-guided cyst ablation is an emerging technique that is performed for patients with premalignant cysts who are not good surgical candidates or in whom surveillance is cumbersome. Because evidence for efficacy and safety is still limited, this intervention is currently performed at limited centers throughout the United States and Japan in the confines of a research protocol. Cyst ablation is most effective in small, unilocular cysts and is contraindicated in cysts involving the main pancreatic duct due to risk of pancreatitis and cysts with potentially malignant features such as mural nodules. An FNA needle is used to puncture the cyst and fluid is aspirated until the cyst cavity is collapsed, with care

to leave the needle tip within the cavity. The aspirated fluid is sent for analysis and a volume of absolute alcohol equal to the amount of fluid aspirated from the cyst is injected into the collapsed cavity. Lavage is performed for 5 min by aspirating the fluid into the syringe and reinjection into the cavity.

In a randomized control trial comparing saline injection to alcohol, cyst resolution occurred in three patients after just one ethanol treatment and nine additional patients had cyst resolution after the second unblended ethanol treatment in both arms resulting in an overall cyst resolution rate of 33 %. Four patients of these patients underwent subsequent surgical resection. The one patient who underwent only saline injection demonstrated no epithelial ablation, whereas the patients who had undergone one to two sessions of ethanol ablation demonstrated 50–100 % epithelial ablation [57]. The observed complications after the first treatment were abdominal pain post-procedure (23.8 %), intracystic bleeding (2.4 %), and acute pancreatitis (2.4 %). An additional study found that the addition of paclitaxel into the cyst cavity improved the cyst resolution rate to 78 % [58]. Long-term follow-up on patients undergoing cyst ablation is not available and currently surveillance with imaging or EUS is still recommended for patients undergoing this procedure.

## EUS-Guided Oncological Therapies

### *EUS-Guided Fiducial Placement*

Stereotactic body radiotherapy (SBRT) concentrates high-dose radiation precisely to tumor tissue and minimizing damage to surrounding healthy structures. Traditionally this technology involved the use of frames or bony landmarks and was used only for intracranial lesions. With recent advances and development of the frameless image-guided system, it is possible to treat extracranial lesions with the implantation of radio-opaque markers called fiducials. Fiducials are gold seeds, which measure 3–5 mm in length and 0.8–1.2 mm in diameter, and serve as radiomarkers for real-time imaging. Patients with unresectable locally advanced pancreatic cancer can be treated with image-guided radiotherapy for loco regional control or down staging. The fiducials have been implanted surgically or percutaneously under radiologic guidance, but this method was invasive and difficult due to retroperitoneal nature of pancreatic cancer. Based on these challenges, EUS-guided

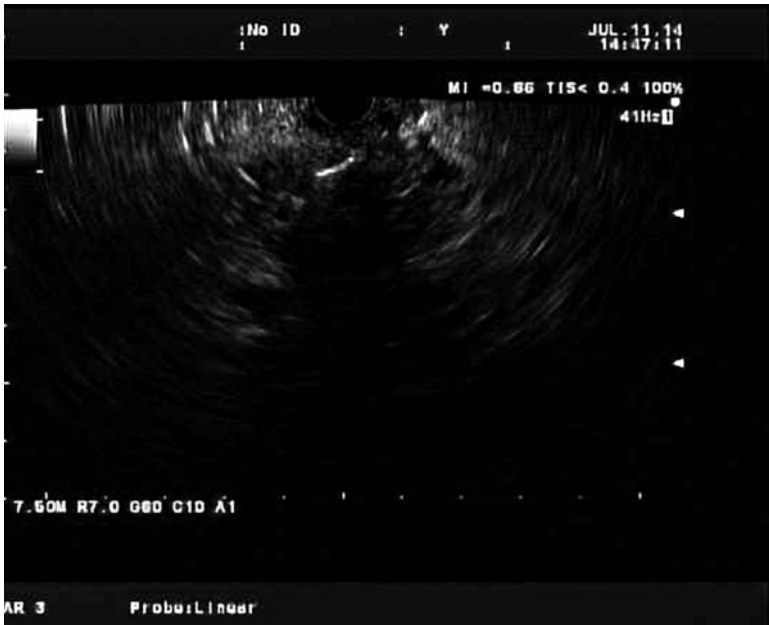


Fig. 21.4. EUS image of a pancreatic mass with a fiducial in place.

fiducial placement (Fig. 21.4) has been developed as a useful alternative [59]. Numerous studies have shown a high success rate (88–90 %) of EUS-guided placement with low migration rate and no migration related adverse events [60, 61]. Ideal fiducial geometry which is the spatial arrangement of fiducials which was believed to facilitate the best treatment planning and delivery is defined as placement of at least three fiducials, with an interfiducial angle of greater than  $15^\circ$  and a minimum interfiducial distance of 2 cm. Surgical placement of fiducials leads to more ideal geometry, but this was not clinically significant, as 90 % of patients with EUS-guided fiducial placement even if they did not have ideal geometry were able to be successfully tracked and treatment delivered [62].

Fiducials are backloaded into a 19-G FNA needle plugged with sterile bone wax and a stylet is used to push the fiducial into the tumor under direct sonographic visualization [61]. Reported complications include migration, bleeding, and acute pancreatitis. EUS-guided fiducial placement has also been used to aid in intraoperative localization of small pancreatic neuroendocrine tumors [63] and therapy of prostate cancer [64].

## *EUS-Guided Brachytherapy*

Implantation of radioactive seeds has been used extensively in the therapy of prostate cancer. Intraoperative implantation of radioactive seeds has also been described for locally advanced pancreatic cancer in combination with systemic chemotherapy. Pilot studies have shown that it is feasible to implant  $^{125}\text{I}$  seeds under EUS guidance. A significant improvement in survival was not observed; however, seed implantation improved pain control and stabilized disease in a few patients [65–68]. More data is needed regarding the long-term effects and benefits prior to routine use of interstitial brachytherapy.

## *EUS-Guided Cryothermal Ablation*

Cryothermal ablation is performed using a device that combines bipolar radio frequency ablation (RFA) with cryogenic cooling to limit the thermal damage caused by RFA alone. This probe can be passed through a therapeutic linear echoendoscope and therapy delivered to the target lesion under real-time visualization. The power of the radiofrequency current and the pressure of the cryo gas are maintained at a constant level and the duration of delivery is varied based on the tumor size. In order to prevent unintended tissue damage, an automatic stop is built into the system based on detection of increased tissue desiccation, which stops therapy irrespective of programmed time. A pilot study was performed using this device in patients who failed neoadjuvant chemoradiation therapy for pancreatic cancer, and demonstrated the technical feasibility and safety of this procedure [69]. More data is needed to determine the oncologic efficacy of this device.

## *EUS-Guided Fine Needle Injection*

EUS has been used to inject various agents into lesions in the pancreas and esophagus using the FNA technique with injection of the agent instead of aspiration of tissue. There is wide variation in the agents used and their success. The agents that have been described are allogenic mixed lymphocyte culture, TNFerade, ONYX-015, immature dendritic cells, and Onco VEX<sup>GMCSF</sup> [70]. Most studies are still preliminary and more data is still required before routine use can be recommended.

## EUS-Guided Vascular Interventions

### *EUS-Guided Treatment of Gastric Variceal Hemorrhage*

Gastric varices are difficult to treat and injection of cyanoacrylate has been advocated for treatment of bleeding gastric varices. Initial studies have shown that EUS can be used to direct the injection of gastric varices, monitor successful obliteration, and reduce the re-bleeding rate [71]. Subsequent studies have compared EUS-guided cyanoacrylate injection and EUS-guided coil embolization and found both techniques to be equally effective but a high rate of distant emboli with cyanoacrylate use [72]. Even though these emboli were asymptomatic, this is a concerning finding. The simultaneous use of coil embolization followed by cyanoacrylate injection can theoretically reduce the incidence of emboli by forming a matrix for the glue [73]. Current evidence shows that EUS-guided therapy of gastric varices is effective and safe but a clear advantage over conventional therapy has not been demonstrated. Routine use has not been advocated as EUS use adds additional cost and expertise. Also, dealing with active bleeding using an EUS scope introduces technical challenges related to its oblique endoscopic view and smaller working channel [74].

### *EUS-Guided Therapy of Pseudoaneurysms*

There are numerous case reports of managing a visceral artery pseudoaneurysm using EUS-guided therapy [75–78]. In patients who are not good operative candidates and angiography fails to reach the target vessel or the feeding stalk is unable to be demonstrated, EUS-guided therapy may be considered. There are reports of injecting cyanoacrylate and thrombin into the pseudoaneurysm until flow has been obliterated under the guidance of a linear echoendoscope. Even though EUS-guided therapy is not first-line therapy in these cases, this approach can be offered in certain instances where other options are not feasible.

## EUS-Guided Gastroenterostomy

Gastric outlet obstruction is a frequent complication of gastric, duodenal, and pancreatic malignancies. Surgical bypass is used to palliate some of these patients. However, many patients are poor surgical

candidates and have significant morbidity and mortality related to surgery. Studies have shown that enteral stenting has better short-term outcome than surgery [79]. The long-term outcomes with enteral stents are not as good due to tumor ingrowth and stent migration. Several new devices and methods for EUS-guided gastroenterostomy have been described in porcine models [80, 81]. In one method using a novel lumen-apposing stent, the small bowel is distended with large amounts of water. The linear echoendoscope is positioned in the stomach and used to identify a bowel loop close to the stomach and punctured using a 19-G needle and an anchoring wire is placed into the small bowel and used to appose the stomach and small intestine. Access is gained again into the now anchored small bowel and using a dedicated stent deployment device the lumen-apposing stent is deployed and anchoring wire is removed [80]. In another technique, the small intestine was distended using a novel double-balloon enteric tube. Access to the small intestine was obtained using a 19-G FNA needle as previously described. The tract is dilated and novel bilaterally reflected lumen-apposing stent was deployed [81]. In both procedures the stent was removed in 4–5 weeks and the animal models showed patent anastomosis even after stent removal. No major complications have been described in the animal models. However, studies in human subjects are still needed before routine use.

## Conclusions

EUS-guided therapeutic interventions are becoming increasingly popular less invasive alternatives to surgery and percutaneous therapies. There are numerous well-established interventions that are described here and more interventions that are on the horizon. This is a quickly evolving field with great potential.

## References

1. Yusuf TE, Ho S, Pavey DA, Michael H, Gress FG. Retrospective analysis of the utility of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in pancreatic masses, using a 22-gauge or 25-gauge needle system: a multicenter experience. *Endoscopy*. 2009;41(5):445–8.
2. Madhoun MF, Wani SB, Rastogi A, Early D, Gaddam S, Tierney WM, et al. The diagnostic accuracy of 22-gauge and 25-gauge needles in endoscopic ultrasound-guided fine needle aspiration of solid pancreatic lesions: a meta-analysis. *Endoscopy*. 2013;45(2):86–92.



3. Affolter KE, Schmidt RL, Matynia AP, Adler DG, Factor RE. Needle size has only a limited effect on outcomes in EUS-guided fine needle aspiration: a systematic review and meta-analysis. *Dig Dis Sci*. 2013;58(4):1026–34.
4. Camellini L, Carlinfante G, Azzolini F, Iori V, Cavina M, Sereni G, et al. A randomized clinical trial comparing 22G and 25G needles in endoscopic ultrasound-guided fine-needle aspiration of solid lesions. *Endoscopy*. 2011;43(8):709–15.
5. Vilmann P, Saftoiu A, Hollerbach S, Skov BG, Linnemann D, Popescu CF, et al. Multicenter randomized controlled trial comparing the performance of 22 gauge versus 25 gauge EUS-FNA needles in solid masses. *Scand J Gastroenterol*. 2013; 48(7):877–83.
6. Lee JK, Lee KT, Choi ER, Jang TH, Jang KT, Lee JK, et al. A prospective, randomized trial comparing 25-gauge and 22-gauge needles for endoscopic ultrasound-guided fine needle aspiration of pancreatic masses. *Scand J Gastroenterol*. 2013;48(6): 752–7.
7. Fabbri C, Polifemo AM, Luigiano C, Cennamo V, Baccarini P, Collina G, et al. Endoscopic ultrasound-guided fine needle aspiration with 22- and 25-gauge needles in solid pancreatic masses: a prospective comparative study with randomisation of needle sequence. *Dig Liver Dis*. 2011;43(8):647–52.
8. Siddiqui UD, Rossi F, Rosenthal LS, Padda MS, Murali-Dharan V, Aslanian HR. EUS-guided FNA of solid pancreatic masses: a prospective, randomized trial comparing 22-gauge and 25-gauge needles. *Gastrointest Endosc*. 2009;70(6): 1093–7.
9. Sakamoto H, Kitano M, Komaki T, Noda K, Chikugo T, Dote K, et al. Prospective comparative study of the EUS guided 25-gauge FNA needle with the 19-gauge Trucut needle and 22-gauge FNA needle in patients with solid pancreatic masses. *J Gastroenterol Hepatol*. 2009;24(3):384–90.
10. Wani S, Early D, Kunkel J, Leathersich A, Hovis CE, Hollander TG, et al. Diagnostic yield of malignancy during EUS-guided FNA of solid lesions with and without a stylet: a prospective, single blind, randomized, controlled trial. *Gastrointest Endosc*. 2012;76(2):328–35.
11. Rastogi A, Wani S, Gupta N, Singh V, Gaddam S, Reddymasu S, et al. A prospective, single-blind, randomized, controlled trial of EUS-guided FNA with and without a stylet. *Gastrointest Endosc*. 2011;74(1):58–64.
12. Sahai AV, Paquin SC, Garipey G. A prospective comparison of endoscopic ultrasound-guided fine needle aspiration results obtained in the same lesion, with and without the needle stylet. *Endoscopy*. 2010;42(11):900–3.
13. Puri R, Vilmann P, Saftoiu A, Skov BG, Linnemann D, Hassan H, et al. Randomized controlled trial of endoscopic ultrasound-guided fine-needle sampling with or without suction for better cytological diagnosis. *Scand J Gastroenterol*. 2009;44(4):499–504.
14. Lee JK, Choi JH, Lee KH, Kim KM, Shin JU, Lee JK, et al. A prospective, comparative trial to optimize sampling techniques in EUS-guided FNA of solid pancreatic masses. *Gastrointest Endosc*. 2013;77(5):745–51.
15. Wallace MB, Kennedy T, Durkalski V, Eloubeidi MA, Etamad R, Matsuda K, et al. Randomized controlled trial of EUS-guided fine needle aspiration techniques for the detection of malignant lymphadenopathy. *Gastrointest Endosc*. 2001;54(4):441–7.

16. Nakai Y, Isayama H, Chang KJ, Yamamoto N, Hamada T, Uchino R, et al. Slow pull versus suction in endoscopic ultrasound-guided fine-needle aspiration of pancreatic solid masses. *Dig Dis Sci.* 2014;59(7):1578–85.
17. LeBlanc JK, Ciaccia D, Al-Assi MT, McGrath K, Imperiale T, Tao LC, et al. Optimal number of EUS-guided fine needle passes needed to obtain a correct diagnosis. *Gastrointest Endosc.* 2004;59(4):475–81.
18. Rong L, Kida M, Yamauchi H, Okuwaki K, Miyazawa S, Iwai T, et al. Factors affecting the diagnostic accuracy of endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) for upper gastrointestinal submucosal or extraluminal solid mass lesions. *Dig Endosc.* 2012;24(5):358–63.
19. Suzuki R, Irisawa A, Bhutani MS, Hikichi T, Takagi T, Sato A, et al. Prospective evaluation of the optimal number of 25-gauge needle passes for endoscopic ultrasound-guided fine-needle aspiration biopsy of solid pancreatic lesions in the absence of an onsite cytopathologist. *Dig Endosc.* 2012;24(6):452–6.
20. Katanuma A, Maguchi H, Yane K, Hashigo S, Kin T, Kaneko M, et al. Factors predictive of adverse events associated with endoscopic ultrasound-guided fine needle aspiration of pancreatic solid lesions. *Dig Dis Sci.* 2013;58(7):2093–9.
21. Eloubeidi MA, Tamhane A, Varadarajulu S, Wilcox CM. Frequency of major complications after EUS-guided FNA of solid pancreatic masses: a prospective evaluation. *Gastrointest Endosc.* 2006;63(4):622–9.
22. Varadarajulu S, Christein JD, Tamhane A, Drelichman ER, Wilcox CM. Prospective randomized trial comparing EUS and EGD for transmural drainage of pancreatic pseudocysts (with videos). *Gastrointest Endosc.* 2008;68(6):1102–11.
23. Varadarajulu S, Bang JY, Sutton BS, Trevino JM, Christein JD, Wilcox CM. Equal efficacy of endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in a randomized trial. *Gastroenterology.* 2013;145(3):583–90.e1.
24. Varadarajulu S, Christein JD, Wilcox CM. Frequency of complications during EUS-guided drainage of pancreatic fluid collections in 148 consecutive patients. *J Gastroenterol Hepatol.* 2011;26(10):1504–8.
25. Fabbri C, Luigiano C, Lisotti A, Cennamo V, Virgilio C, Caletti G, et al. Endoscopic ultrasound-guided treatments: are we getting evidence based—a systematic review. *World J Gastroenterol.* 2014;20(26):8424–48.
26. Penn DE, Draganov PV, Wagh MS, Forsmark CE, Gupte AR, Chauhan SS. Prospective evaluation of the use of fully covered self-expanding metal stents for EUS-guided transmural drainage of pancreatic pseudocysts. *Gastrointest Endosc.* 2012;76(3):679–84.
27. Nici AJ, Hussain SA, Kim SH, Mehta P. Unique usage of a partially covered metal stent for drainage of a pancreatic pseudocyst via endosonography-guided transcystogastrostomy. *Dig Endosc.* 2012;24(3):185–7.
28. Talreja JP, Shami VM, Ku J, Morris TD, Ellen K, Kahaleh M. Transenteric drainage of pancreatic-fluid collections with fully covered self-expanding metallic stents (with video). *Gastrointest Endosc.* 2008;68(6):1199–203.
29. Fabbri C, Luigiano C, Cennamo V, Polifemo AM, Barresi L, Jovine E, et al. Endoscopic ultrasound-guided transmural drainage of infected pancreatic fluid collec-

- tions with placement of covered self-expanding metal stents: a case series. *Endoscopy*. 2012;44(4):429–33.
30. Binmoeller KF, Shah J. A novel lumen-apposing stent for transluminal drainage of nonadherent extraintestinal fluid collections. *Endoscopy*. 2011;43(4):337–42.
  31. Gornals JB, De la Serna-Higuera C, Sanchez-Yague A, Loras C, Sanchez-Cantos AM, Perez-Miranda M. Endosonography-guided drainage of pancreatic fluid collections with a novel lumen-apposing stent. *Surg Endosc*. 2013;27(4):1428–34.
  32. Itoi T, Binmoeller KF, Shah J, Sofuni A, Itokawa F, Kurihara T, et al. Clinical evaluation of a novel lumen-apposing metal stent for endosonography-guided pancreatic pseudocyst and gallbladder drainage (with videos). *Gastrointest Endosc*. 2012; 75(4):870–6.
  33. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology*. 2013;13(4 Suppl 2):e1–15.
  34. Bakker OJ, van Santvoort HC, van Brunschot S, Geskus RB, Besselink MG, Bollen TL, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. *JAMA*. 2012;307(10):1053–61.
  35. van Brunschot S, van Grinsven J, Voermans RP, Bakker OJ, Besselink MG, Boermeester MA, et al. Transluminal endoscopic step-up approach versus minimally invasive surgical step-up approach in patients with infected necrotising pancreatitis (TENSION trial): design and rationale of a randomised controlled multicenter trial [ISRCTN09186711]. *BMC Gastroenterol*. 2013;13:161.
  36. Gardner TB, Coelho-Prabhu N, Gordon SR, Gelrud A, Maple JT, Papachristou GI, et al. Direct endoscopic necrosectomy for the treatment of walled-off pancreatic necrosis: results from a multicenter U.S. series. *Gastrointest Endosc*. 2011;73(4): 718–26.
  37. Artifon EL, Aparicio D, Paione JB, Lo SK, Bordini A, Rabello C, et al. Biliary drainage in patients with unresectable, malignant obstruction where ERCP fails: endoscopic ultrasonography-guided choledochoduodenostomy versus percutaneous drainage. *J Clin Gastroenterol*. 2012;46(9):768–74.
  38. Park do H, Jang JW, Lee SS, Seo DW, Lee SK, Kim MH. EUS-guided biliary drainage with transluminal stenting after failed ERCP: predictors of adverse events and long-term results. *Gastrointest Endosc*. 2011;74(6):1276–84.
  39. Dhir V, Bhandari S, Bapat M, Joshi N, Vivekanandarajah S, Maydeo A. Comparison of transhepatic and extrahepatic routes for EUS-guided rendezvous procedure for distal CBD obstruction. *United European Gastroenterol J*. 2013;1(2):103–8.
  40. Dhir V, Artifon EL, Gupta K, Vila JJ, Maselli R, Frazao M, et al. Multicenter study on endoscopic ultrasound-guided expandable biliary metal stent placement: choice of access route, direction of stent insertion, and drainage route. *Dig Endosc*. 2014;26(3): 430–5.
  41. Khashab MA, Valeshabad AK, Modayil R, Widmer J, Saxena P, Idrees M, et al. EUS-guided biliary drainage by using a standardized approach for malignant biliary obstruction: rendezvous versus direct transluminal techniques (with videos). *Gastrointest Endosc*. 2013;78(5):734–41.

42. Fujii LL, Topazian MD, Abu Dayyeh BK, Baron TH, Chari ST, Farnell MB, et al. EUS-guided pancreatic duct intervention: outcomes of a single tertiary-care referral center experience. *Gastrointest Endosc.* 2013;78(6):854–864.e1.
43. Jang JW, Lee SS, Song TJ, Hyun YS, Park do H, Seo DW, et al. Endoscopic ultrasound-guided transmural and percutaneous transhepatic gallbladder drainage are comparable for acute cholecystitis. *Gastroenterology.* 2012;142(4):805–11.
44. de la Serna-Higuera C, Perez-Miranda M, Gil-Simon P, Ruiz-Zorrilla R, Diez-Redondo P, Alcaide N, et al. EUS-guided transenteric gallbladder drainage with a new fistula-forming, lumen-apposing metal stent. *Gastrointest Endosc.* 2013;77(2):303–8.
45. Santosh D, Lakhtakia S, Gupta R, Reddy DN, Rao GV, Tandan M, et al. Clinical trial: a randomized trial comparing fluoroscopy guided percutaneous technique vs. endoscopic ultrasound guided technique of coeliac plexus block for treatment of pain in chronic pancreatitis. *Aliment Pharmacol Ther.* 2009;29(9):979–84.
46. Gress F, Schmitt C, Sherman S, Ikenberry S, Lehman G. A prospective randomized comparison of endoscopic ultrasound- and computed tomography-guided celiac plexus block for managing chronic pancreatitis pain. *Am J Gastroenterol.* 1999;94(4):900–5.
47. Puli SR, Reddy JB, Bechtold ML, Antillon MR, Brugge WR. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review. *Dig Dis Sci.* 2009;54(11):2330–7.
48. Wyse JM, Carone M, Paquin SC, Usatii M, Sahai AV. Randomized, double-blind, controlled trial of early endoscopic ultrasound-guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable pancreatic cancer. *J Clin Oncol.* 2011;29(26):3541–6.
49. Sahai AV, Lemelin V, Lam E, Paquin SC. Central vs. bilateral endoscopic ultrasound-guided celiac plexus block or neurolysis: a comparative study of short-term effectiveness. *Am J Gastroenterol.* 2009;104(2):326–9.
50. LeBlanc JK, Al-Haddad M, McHenry L, Sherman S, Juan M, McGreevy K, et al. A prospective, randomized study of EUS-guided celiac plexus neurolysis for pancreatic cancer: one injection or two? *Gastrointest Endosc.* 2011;74(6):1300–7.
51. LeBlanc JK, DeWitt J, Johnson C, Okumu W, McGreevy K, Symms M, et al. A prospective randomized trial of 1 versus 2 injections during EUS-guided celiac plexus block for chronic pancreatitis pain. *Gastrointest Endosc.* 2009;69(4):835–42.
52. Doi S, Yasuda I, Kawakami H, Hayashi T, Hisai H, Irisawa A, et al. Endoscopic ultrasound-guided celiac ganglia neurolysis vs. celiac plexus neurolysis: a randomized multicenter trial. *Endoscopy.* 2013;45(5):362–9.
53. Stevens T, Costanzo A, Lopez R, Kapural L, Parsi MA, Vargo JJ. Adding triamcinolone to endoscopic ultrasound-guided celiac plexus blockade does not reduce pain in patients with chronic pancreatitis. *Clin Gastroenterol Hepatol.* 2012;10(2):186–91. 191.e1.
54. Eisenberg E, Carr DB, Chalmers TC. Neurolytic celiac plexus block for treatment of cancer pain: a meta-analysis. *Anesth Analg.* 1995;80(2):290–5.
55. Fujii L, Clain JE, Morris JM, Levy MJ. Anterior spinal cord infarction with permanent paralysis following endoscopic ultrasound celiac plexus neurolysis. *Endoscopy.* 2012;44(Suppl 2 UCTN):E265–6.

56. O'Toole TM, Schmulewitz N. Complication rates of EUS-guided celiac plexus blockade and neurolysis: results of a large case series. *Endoscopy*. 2009;41(7):593–7.
57. DeWitt J, McGreevy K, Schmidt CM, Brugge WR. EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study. *Gastrointest Endosc*. 2009;70(4):710–23.
58. Oh HC, Seo DW, Lee TY, Kim JY, Lee SS, Lee SK, et al. New treatment for cystic tumors of the pancreas: EUS-guided ethanol lavage with paclitaxel injection. *Gastrointest Endosc*. 2008;67(4):636–42.
59. Pishvaian AC, Collins B, Gagnon G, Ahlawat S, Haddad NG. EUS-guided fiducial placement for CyberKnife radiotherapy of mediastinal and abdominal malignancies. *Gastrointest Endosc*. 2006;64(3):412–7.
60. Park WG, Yan BM, Schellenberg D, Kim J, Chang DT, Koong A, et al. EUS-guided gold fiducial insertion for image-guided radiation therapy of pancreatic cancer: 50 successful cases without fluoroscopy. *Gastrointest Endosc*. 2010;71(3):513–8.
61. Sanders MK, Moser AJ, Khalid A, Fasanella KE, Zeh HJ, Burton S, et al. EUS-guided fiducial placement for stereotactic body radiotherapy in locally advanced and recurrent pancreatic cancer. *Gastrointest Endosc*. 2010;71(7):1178–84.
62. Majumder S, Berzin TM, Mahadevan A, Pawa R, Ellsmere J, Sepe PS, et al. Endoscopic ultrasound-guided pancreatic fiducial placement: how important is ideal fiducial geometry? *Pancreas*. 2013;42(4):692–5.
63. Law JK, Singh VK, Khashab MA, Hruban RH, Canto MI, Shin EJ, et al. Endoscopic ultrasound (EUS)-guided fiducial placement allows localization of small neuroendocrine tumors during parenchymal-sparing pancreatic surgery. *Surg Endosc*. 2013;27(10):3921–6.
64. Yang J, Abdel-Wahab M, Ribeiro A. EUS-guided fiducial placement before targeted radiation therapy for prostate cancer. *Gastrointest Endosc*. 2009;70(3):579–83.
65. Sun S, Qingjie L, Qiyong G, Mengchun W, Bo Q, Hong X. EUS-guided interstitial brachytherapy of the pancreas: a feasibility study. *Gastrointest Endosc*. 2005;62(5):775–9.
66. Sun S, Xu H, Xin J, Liu J, Guo Q, Li S. Endoscopic ultrasound-guided interstitial brachytherapy of unresectable pancreatic cancer: results of a pilot trial. *Endoscopy*. 2006;38(4):399–403.
67. Jin Z, Du Y, Li Z, Jiang Y, Chen J, Liu Y. Endoscopic ultrasonography-guided interstitial implantation of iodine 125-seeds combined with chemotherapy in the treatment of unresectable pancreatic carcinoma: a prospective pilot study. *Endoscopy*. 2008;40(4):314–20.
68. Du Y, Jin Z, Meng H, Zou D, Chen J, Liu Y, et al. Long-term effect of gemcitabine-combined endoscopic ultrasonography-guided brachytherapy in pancreatic cancer. *J Interv Gastroenterol*. 2013;3(1):18–24.
69. Arcidiacono PG, Carrara S, Reni M, Petrone MC, Cappio S, Balzano G, et al. Feasibility and safety of EUS-guided cryothermal ablation in patients with locally advanced pancreatic cancer. *Gastrointest Endosc*. 2012;76(6):1142–51.
70. Chang KJ, Irisawa A. EUS 2008 Working Group. EUS 2008 Working Group document: evaluation of EUS-guided injection therapy for tumors. *Gastrointest Endosc*. 2009;69(2 Suppl):S54–8.

71. Lee YT, Chan FK, Ng EK, Leung VK, Law KB, Yung MY, et al. EUS-guided injection of cyanoacrylate for bleeding gastric varices. *Gastrointest Endosc.* 2000; 52(2):168–74.
72. Romero-Castro R, Ellrichmann M, Ortiz-Moyano C, Subtil-Inigo JC, Junquera-Florez F, Gornals JB, et al. EUS-guided coil versus cyanoacrylate therapy for the treatment of gastric varices: a multicenter study (with videos). *Gastrointest Endosc.* 2013; 78(5):711–21.
73. Binmoeller KF, Weilert F, Shah JN, Kim J. EUS-guided transesophageal treatment of gastric fundal varices with combined coiling and cyanoacrylate glue injection (with videos). *Gastrointest Endosc.* 2011;74(5):1019–25.
74. Levy MJ, Wong Kee Song LM. EUS-guided angiotherapy for gastric varices: coil, glue, and sticky issues. *Gastrointest Endosc.* 2013;78(5):722–5.
75. Gonzalez JM, Ezzedine S, Vitton V, Grimaud JC, Barthet M. Endoscopic ultrasound treatment of vascular complications in acute pancreatitis. *Endoscopy.* 2009;41(8): 721–4.
76. Roberts KJ, Jones RG, Forde C, Marudanayagam R. Endoscopic ultrasound-guided treatment of visceral artery pseudoaneurysm. *HPB (Oxford).* 2012;14(7):489–90.
77. Roach H, Roberts SA, Salter R, Williams IM, Wood AM. Endoscopic ultrasound-guided thrombin injection for the treatment of pancreatic pseudoaneurysm. *Endoscopy.* 2005;37(9):876–8.
78. Lameris R, du Plessis J, Nieuwoudt M, Scheepers A, van der Merwe SW. A visceral pseudoaneurysm: management by EUS-guided thrombin injection. *Gastrointest Endosc.* 2011;73(2):392–5.
79. Jeurink SM, Steyerberg EW, van Hooft JE, van Eijck CH, Schwartz MP, Vleggaar FP, et al. Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial. *Gastrointest Endosc.* 2010;71(3):490–9.
80. Binmoeller KF, Shah JN. Endoscopic ultrasound-guided gastroenterostomy using novel tools designed for transluminal therapy: a porcine study. *Endoscopy.* 2012; 44(5):499–503.
81. Itoi T, Itokawa F, Uraoka T, Gotoda T, Horii J, Goto O, et al. Novel EUS-guided gastrojejunostomy technique using a new double-balloon enteric tube and lumen-apposing metal stent (with videos). *Gastrointest Endosc.* 2013;78(6):934–9.