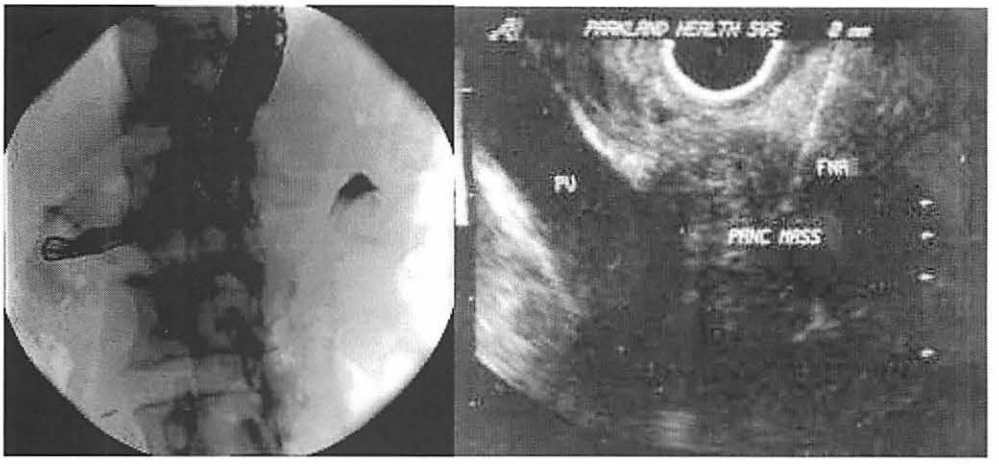
INTERVENTIONAL ENDOSCOPIC ULTRASOUND: THE NEXT FRONTEIR IN GASTROINTESTINAL ENDOSCOPY



Jayaprakash Sreenarasimhaiah, MD
Assistant Professor of Medicine
Division of Digestive and Liver Diseases
University of Texas Southwestern Medical Center
Internal Medicine Grand Rounds
January 30th, 2009

This is to acknowledge that Jayaprakash Sreenarasimhaiah, M.D. has disclosed that there are no financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Jayaprakash Sreenarasimhaiah will not be discussing off-label uses in his presentation.

Brief descriptive biography:

My interests in clinical gastroenterology lie mostly with advanced endoscopic procedures. My main focus is with all aspects of endoscopic ultrasound including diagnostic and therapeutic applications. I am also interested in endoscopic therapy such as intestinal or esophageal stricture and stenting for benign and malignant disease. Another focus is therapy of dysplastic Barrett esophagus for which I perform endoscopic mucosal resection and cryospray ablation therapy. Research interests focus on the outcomes of these patients as well as pancreatic cyst fluid analysis, tumor markers on tissue specimens of pancreatic disease, fine-needle injection therapy for locally advanced pancreatic cancer, and outcomes of Barrett's ablative therapy.

INTRODUCTION

Over several decades, the evolution of radiographic imaging has resulted in significant advancement of medical diagnostics. Physical findings can be confirmed by noninvasive or minimally invasive modalities. Moreover, high resolution characteristics and abnormalities of organs, blood vessels, and other vital structures can be detected beyond the scope of external physical examination. Therapy based on diagnostic findings is the subsequent step to radiographic imaging. In an ideal setting, both diagnostics and therapy can be combined with one procedure. One imaging modality, endoscopic ultrasound (EUS) offers this combination in a unique fashion.

EUS made its debut in 1985 as a diagnostic tool for pancreatic disease. Over the last two decades, this technology has undergone considerable evolution with imaging of almost all aspects of the gastrointestinal tract. Staging of cancers of the esophagus, stomach, small intestine, pancreas, biliary tract and rectum have been well established. Moreover, imaging outside of the gastrointestinal tract has also been effective including the mediastinum, pelvis, and perigastric organs such as the adrenal glands, kidneys, spleen, and liver. High resolution images of one millimeter have become available with current technology which exceeds several other radiographic modalities in depicting details. One of the biggest advances to EUS came in the early 1990s with the introduction of the curvilinear array echoendoscopes. Not only was imaging of high quality but the ability to perform fine-needle aspiration (FNA) biopsy became possible.

Given the ease of targeting small lesions accurately with fine-needle aspiration (FNA) biopsy, the natural evolution of this technology has led to interventions delivered through this same approach. EUS has rapidly evolved into becoming a primary modality in many interventional endoscopic techniques. This review will discuss several of the current therapeutic applications such as celiac plexus neurolysis, pseudocyst drainage, and cyst aspiration. Other evolving techniques such as fine-needle injection of therapeutic agents into tumors or angiographic interventions will also be discussed. This unique technology of combined optical and sonographic imaging is rapidly evolving into both a diagnostic and therapeutic modality.

TECHNICAL ASPECTS

There are two types of echoendoscopes that are traditionally used. The radial sector scanner has an ultrasound probe attached to the tip of the echoendoscope with a water-filled balloon to facilitate imaging of the target. This provides a view of 360 degrees surrounding the probe and is useful in identifying organs and vessels and lymph nodes. It is also particularly useful in delineating significant details of the different layers of the gastrointestinal wall such as the esophagus, gastric wall, duodenum, and rectosigmoid regions. This particular endoscope serves a diagnostic purpose only. Although there is an accessory channel to pass instruments

through it, the plane at which this comes into endosonographic view is perpendicular to the cross-sectional imaging and thus prevents accurate targeting or following of the needle pathway.

The other echoendoscope is known as the curvilinear array echoendoscope. This also can use a water-filled balloon at the tip if required. It provides a limited view of 180 degrees surrounding the scope but has very high resolution. Passage of accessory instruments such as fine-needle or guidewires can easily be visualized along the entire pathway of insertion until the target as it is parallel to the sonographic plane. This particular endoscope is used for FNA biopsy and interventions as described below.

SAFETY AND COMPLICATIONS

Major complications of EUS and EUS-FNA are rare and not much increased in comparison to standard esophagogastroduodenoscopy (EGD). The risk of perforation of the gastrointestinal tract is suggested to be 1:2500. Bleeding from FNA biopsies is usually self-limited and rarely requires intervention. The risk of introducing infection into sites of targeted FNA such as pancreatic cysts is also low when a prophylactic dose of antibiotics is administered. Pancreatitis has been reported in 0.29% of cases of FNA of solid pancreas lesions. Overall, major complications from EUS-FNA have been reported at most to be 1.9% which includes acute pancreatitis, abdominal pain, bleeding, and rarely perforation (1). The risk of perforation is the same as routine upper endoscopy but may have a two- to three-fold increased risk at the site of the cervical esophagus during intubation (2).

EUS-GUIDED TRUCUT NEEDLE BIOPSY

Standard fine-needle aspiration biopsies are performed with either 22- or 25-guage needles which offer adequate specimen for most tissue sites to achieve a diagnosis. The smaller needles are particularly useful in lymph nodes and small targets. In rare cases, a larger core biopsy is required such as in the diagnosis of autoimmune pancreatitis or histologic diagnosis of gastrointestinal stromal tumors. In this setting, a trucut needle known as Quick-Core (Wilson-Cook) is available in a 19-guage size with a spring-loaded device. Studies have shown no increased yield in routine diagnosis between the trucut needle and standard 22- and 25-guage needles but have demonstrated its safety (3, 4). It has been shown to be more effective in diagnosis of autoimmune pancreatitis (5). However, the endoscopic control of such larger needles of 19-guage standard and 19-guage trucut varieties is much more difficult due to the reduced flexibility. Thus, it has a limited use in transduodenal approaches to the pancreas. Moreover, some studies suggest that the smaller needles may be as effective and have increased safety. Overall, the complications from EUS-FNA are low and self-limited. These include bleeding, hematoma, and pancreatitis in up to 1-2 % of cases and even more rarely perforation. The larger needles have been shown to result in higher risk of pancreatitis in some series (6, 7).

EUS-GUIDED CELIAC PLEXUS NEUROLYSIS

The management of pain from chronic pancreatitis or pancreatic cancer is often a challenging clinical scenario. Many of these patients depend upon narcotics for pain relief with frequent escalation of doses due to tolerance to the medications. Moreover, narcotics result in adverse effects of reduced bowel and bladder motility, respiratory effects, central nervous system effects, and rebound increases in pain. For some, intravenous dosing is the only option. Pain is mediated by a plexus of nerves that arise from the celiac ganglion. These nerves originate from the spinal cord and the ganglion is located surrounding the root of the celiac and superior mesenteric arteries. Anatomically, this is located posterior to the gastric wall and omental bursa, and lies between the adrenal glands. It is anterior to the diaphragmatic crus and the beginning of the abdominal portion of the aorta.

Given this anatomic location, the celiac plexus region can be easily imaged by EUS. In fact, the ganglion itself is sometimes visualized as a bean-shaped hypoechoic structure or chain of structures. Celiac plexus neurolysis (CPN) is achieved by advancement of a 20-guage needle into this area that is specifically designed to deliver the anesthetic medications within a wide field. In the setting of chronic pain of pancreatic malignancy, 10 – 20 mL of 98% dehydrated ethanol is injected into this area with the aim of obliterating the ganglion. It often results in scarring of the surrounding tissue. Used less commonly for chronic pancreatitis, EUS-guided celiac plexus neurolysis may be performed with injection of a combination of 40mg triamcinalone along with 0.5% bupivicaine in a volume similar to the ethanol. Prior to either type of injection, 1 – 2 mL of 1% lidocaine is often injected for immediate but temporary pain relief and to reduce the pain of the actual injections to follow. Ethanol is not used routinely in chronic pancreatitis pain as it may result in peripancreatic and perigastric scarring which could complicate potential surgical management (8).

The EUS-guided technique involves injection into both sides of the celiac artery origin to surround the entire celiac plexus. Alternatively, if the ganglion is visualized, the entire quantity can be injected into this area on one side of the celiac artery. This is an anterior or direct approach through the gastric wall. The alternate approach to neurolysis of the celiac plexus is the posterior approach performed by anesthesiologists. Such a procedure requires fluoroscopic guidance to inject specific nerve bundles leading to the celiac ganglion in a more indirect method. Both have been suggested to have similar efficacy. However, the safety of the anterior or EUS-guided approach has been shown to be higher than the posterior approach. Some studies have reported spinal nerve injury with paraplegia and transient motor paralysis in rare cases due to spasm of segmental lumbar arteries. Rarely permanent paraplegia has been reported due to direct neurologic or vascular injury of the injection along with retrograde spread of ethanol into the spinal cord (9, 10). This type of injury has not been reported by the anterior-crural or EUS-guided method.

Other complications of CPN include transient orthostatic hypotension which occurs in 1 to 3% of individuals for up to 5 days following injection and more commonly seen from the retrograde method. Transient diarrhea is noted up to a few weeks following neurolysis and has been reported to more common from the anterior approach. Overall the risk of serious complications (paraplegia, bowel or bladder dysfunction) is rare and was reported in a large series to be 1 in 683 procedures (11).

The efficacy of celiac plexus neurolysis has been studied extensively. In a recent meta-analysis and systemic review, EUS-guided CPN was examined in data of 8 studies of a total of 283 patients. In the pooled data, it was found that adequate pain relief was achieved in 80.12% of patients with pancreatic cancer. In patients with chronic pancreatitis, pain relief was achieved in 59.45% (12). In most of these patients, there was a reduction of opiate use. The medications used in neurolysis of chronic pancreatitis patients were most often bupivicaine and triamcinolone compared to ethanol in pancreatic cancer, which some have theorized accounts for this difference. However, many studies have demonstrated that CPN is more effective for control of pain from pancreatic cancer than pancreatitis especially in palliative care.

PANCREATIC PSEUDOCYST DRAINAGE

Pancreatic pseudocysts develop in the setting of either acute or chronic pancreatitis. These fluid-filled cavities are nonepithelial-lined cysts that usually occur from disruption of the pancreatic duct with leakage of pancreatic fluid into surrounding tissues. Some pseudocysts occur as a result of pancreatic duct obstruction or pancreatic trauma. These can be of varying sizes and can extend great distances from the pancreas itself into the abdomen and even the mediastinum. Serious complication of pain, gastric or duodenal luminal obstruction, bile duct obstruction, infection, and bleeding from internal or adjacent pseudoaneurysms may occur (13).

Management of these cysts varies considerably. Many cysts that complicate acute pancreatitis resolve spontaneously with 4 to 6 weeks and may be conservatively treated. Others that exceed 5 to 6cm in size and persist beyond 6 weeks will almost always require intervention (14). Surgical drainage has been the mainstay of therapy for decades for cysts exceeding 6cm and involves direct cyst excision or creation of drainage into a loop of jejunum. This has a 5% mortality rate but may be reduced with laparoscopic approaches or those who can be managed electively rather than semi-urgently. (15).

Percutaneous drainage is sometimes performed by interventional radiologists. However, experience has suggest that this can be fraught with complications such as skin discomfort, infection, accidental displacement or removal of catheter, and the formation of long-term cutaneous fistula after drainage removal (16).

Endoscopic drainage has been performed for more than a decade. However, more recently, the use of EUS-guided endoscopic drainage has proven to be as successful as surgical

therapy and is now considered a first-line treatment. The use of EUS helps identify the optimal site of puncture from the gastric wall into the cyst. Ideally, this distance should be less than 1cm. It also helps identify potentially intervening blood vessels. Prior to EUS, transmural endoscopic drainage of pseudocysts required the identification of a bulge. However, current techniques of EUS-guided cyst drainage can be performed across either the gastric or duodenal wall and do not require a visible bulge. Infected pseudocysts and abscess are also able to be drained by this method (17, 18).

The specific interventional techniques of EUS-guided pseudocyst drainage can be performed entirely through the therapeutic channel of the linear-array echoendoscope. The pseudocyst is identified and an optimal site of puncture is visualized as above. Once fluid is accessed and a sample sent for necessary studies such as gram stain or culture, a 0.035 inch guidewire is advanced into the cyst under fluoroscopic guidance into a coiled pattern. Over this wire, the tract is opened first with an endoscopic needle-knife and followed by dilation to approximately 8mm with a balloon dilator. Multiple double pig-tailed stents, one of which is at least 10 French size are positioned with one end in the cyst and the other secured in the gastric lumen. This is usually left intact for approximately 6 to 8 weeks and removed once the pseudocyst has collapsed completely.

The cause of pseudocyst formation is usually from pancreatic ductal disruption. Traditionally pancreatography by ERCP with stenting was performed to help with drainage. However, more recently, transmural drainage alone has been shown to be sufficient and thus pancreatography can usually be performed when the EUS-guided drainage fails. Primary pancreatic duct stenting may not improve rates of cyst resolution when compared to transmural cyst drainage with stent placement (19).

EUS-GUIDED ACCESS TO BILIARY TRACT

EUS-guided cholangio-pancreatic drainage has been reported in the setting of failed ERCP cannulation of the papilla. This is an alternative access method to surgical or percutaneous approaches. The ampulla may be obstructed by tumor at the site of the duodenum, or distal bile duct, or ampulla itself. ERCP may also fail in certain circumstances of tight stricture, severe duct angulation, or ductal infiltration by tumor. Traditionally, drainage can be attempted percutaneously by interventional radiology. However, it may also be technically difficult to reach the distal bile duct or ampulla in certain cases. Moreover, external drainage may require internalization for long-term management. Permanent external drainage may be uncomfortable for patients requiring palliative care. ERCP has been reported to fail in 3 to 12% of such cases despite multiple attempts and thus other endoscopic options are necessary (20).

Visualization of the bile duct by EUS offers transhepatic or transduodenal access with cannulation across the papillae from an antegrade route. The left hepatic ducts are easily

visualized by EUS and thus a transgastric approach to the left biliary system can be an alternative. A guidewire can be passed into the bile duct and confirmed by fluoroscopy. Over the guidewire, catheters may be applied to inject contrast and perform a cholangiogram to define the point of obstruction. Subsequently, a rendezvous procedure from the duodenum using a guidewire that crosses the ampulla can be accomplished. This enables placement of standard ERCP instruments including plastic and metal stents into the bile duct. Similarly access to a dilated pancreatic duct can be achieved by EUS-guidance. This is accomplished from transgastric puncture and passage of a guidewire in antegrade fashion to traverse the papilla. The pancreatic duct must be dilated for access and usually is dilated proximal to the stricture or point of obstruction (21).

In a study of EUS-guided bile duct drainage, 11 patients were examined with obstructive jaundice. Malignant obstruction was noted in 8 patients (4 pancreatic carcinoma, 2 hilar cholangiocarcinoma, one duodenal cancer, and one gastric cancer). Benign obstruction was found in the remaining 3 patients with anastomotic strictures following Whipple resection. In all patients, both ERCP and percutaneous approaches failed. In these cases, a therapeutic linear echoendoscope was used to puncture the left biliary duct with a 19- or 22-guage needle and inject contrast under direct visualization with fluoroscopy. The gastro-biliary tract communication was increased to 8.5Fr with a cystotome and subsequently a metal stent was positioned between the left biliary duct and the gastric lumen. This was found to be technically successful in 10 of 11 patients. In two patients, EUS-guided wire cannulation across the obstruction into the duodenal lumen was achieved and a metallic stent was then placed across the papilla. Follow-up CT scan showed no evidence of bile leakage or pneumoperitoneum in any of the patients. Patients were followed for a mean of 213 days. Two required repeat endoscopy for stent occlusion. Five died during the study follow-up from malignancy but not related to biliary obstruction. None of the patients developed cholangitis from communication with gastric contents (22).

In another study, the feasibility of EUS-guided rendezvous drainage of biliary and pancreatic ductal obstruction was demonstrated. In 6 patients, ERCP had failed to cannulate the major papillae during multiple attempts on separate occasions. EUS-guidance was attemted to provide transgastric or transduodenal needle puncture and guidewire placement through the obstructed pancreatic duct (n=4) or bile duct (n=2). In 5 of 6 patients, the obstruction was successfully traversed and rendezvous ERCP was subsequently performed with stent placement in 3 of 6 cases (two biliary and one pancreatic). The one patient that failed had relapsing pancreatitis with pancreas divisum. No complications were noted in any of the patients. No evidence of pancreatitis or duct leakage was encountered in any of the successful or unsuccessful cases (23).

These studies show the feasibility of EUS-guided drainage of pancreatic or bile duct obstructions in the setting of failed ERCP access. The advantage of real-time imaging with

sonography combined with fluoroscopy can achieve access in these difficult circumstances. In certain cases of altered surgical anatomy of the duodenum or ampulla, EUS offers high-resolution imaging of the biliary and pancreatic ductal systems with direct access to achieve immediate internal drainage. While these circumstances are difficult in general for endoscopic or percutaneous drainage, EUS is rapidly evolving into a technique that can offer therapeutic access in circumstances that would otherwise require surgical intervention. This is particularly useful in palliative relief of ductal obstruction.

EUS - FINE NEEDLE INJECTION THERAPY

A natural evolution of EUS-FNA biopsy is the direct application or delivery of therapeutic agents or medications to a target site such as a tumor. The ease of access with high-resolution real-time images to both large and small targets offers the ability to inject medications or deliver therapeutic devices to these sites. This has been termed fine-needle injection (FNI) therapy.

Radiosensitization by TNFerade

A current multicenter phase II/III trial is being conducted in which human tumor necrosis factor-α (TNF-α) is injected into locally invasive, inoperable pancreatic adenocarcinoma. TNF-α is a cytokine which is secreted by several normal and tumor cells and is heavily responsible for anti-tumor immunity. It also plays a major influence in inflammation and tumor angiogenesis. Systemic TNF-α has been studied in human clinical trials but has been limited by significant toxicity. The mechanism of action of TNFerade (Genvec, Inc. Gaithersburg, MD) injection into the tumor by EUS-guided delivery is deemed to be enhanced sensitivity of the tumor to radiation therapy (24). In this study, five weekly injections of TNFerade are delivered into locally advanced pancreatic tumor by EUS fine needle injection (FNI). This is followed by combined chemoradiation therapy including 5-FU and gemcitabine (254). Results are still pending completion of the trial.

Activated T-lymphocyte therapy

EUS-FNI therapy with delivery of anti-tumoral therapy has been demonstrated previously with advanced pancreatic adenocarcinoma. In a phase I trial, 8 patients with unresectable adenocarcinoma were enrolled. The delivery of cytoimplants comprised of allogeneic mixed lymphocyte cultures was examined in a feasibility and safety evaluation. There were no procedure-related complications. Some had reversible fever and hyperbilirubinemia. Two patients had partial responses and median survival was 13.2 months. This study demonstrated the safety of cytoimplant immunotherapy by EUS-FNI guidance (26).

Pancreatic injection of modified virus

In another study of EUS-FNI for inoperable advanced pancreatic adenocarcinoma, feasibility and safety was demonstrated for ONYX-015. This is gene-deleted replication-selective adenovirus that preferentially replicates and kills within malignant cells. In this phase I/II clinical trial, this agent was easily delivered by EUS guidance into advanced or minimally metastatic pancreatic tumors in 21 patients over an 8 week period. Patients concomitantly received gemcitabine for the last half of the study period. Results indicated that two patients had partial regression of tumor, two patients had minor responses, six patients had stable disease, and 11 patients had disease progression. Despite the dismal clinical outcomes, the study did demonstrate safety and feasibility of EUS-FNI. No direct procedure-related complications were noted in any of the patients. None of the patients developed post-injection pancreatitis. This study demonstrated early on the potential to deliver anti-tumor agents via EUS injection needles (27).

EUS-guided ablation therapy in the pancreas

The use of EUS-FNI has been studied beyond the delivery of medical agents for tumor therapy. The innovation of variable devices has been tested in animal models to deliver therapies such as radiofrequency ablation or cryoablation therapy through special catheters placed by EUS guidance. The linear array echoendoscopic has evolved to have large therapeutic working channels that enable passage of a variety of devices. Clinical research has focused heavily in to oncologic applications particularly related to the pancreas. Recently, water-cooled monopolar radiofrequency ablation has been shown to be safe for application in stage III pancreatic cancer from either open or laparoscopic settings (28). Additional cooling of adjacent tissue is required to prevent complications (29). EUS offers the advantage over percutaneous applications of real-time imaging into a target deeply located in the pancreas which would be otherwise challenging to reach from external origins. The precision with which EUS can measure lesions and identify surrounding structures with a 1mm resolution may offer more controlled and directed therapies to the target and minimize damage to non-tumor tissue.

Recently, a new flexible bipolar hybrid ablation device has been developed that combines bipolar radiofrequency ablation with cyrotechnology. This results in less collateral tissue damage but also reduces the efficiency of the device. However, highly effective cooling of the tissue by cryogenic gas helps potentiate the effect of radiofrequency ablation with less required current. This has been studied in a pig model in the pancreas body and tail which are easily reached by a transgastric approach. At 1 week, 2 of 7 pigs that underwent treatment had histologic evidence of pancreatitis although only one had clinical symptoms. At 2 weeks, none of the pigs had ongoing adverse events and laboratory tests were normal. There was also a sharp demarcation between the treated and untreated areas noted. This study showed the safety of this device with a 7% major complication rate which included symptomatic necrotic pancreatitis

although the mortality was zero (30). It is theorized that the pancreatic injury is dose-dependent and may be increased with multiple treatments to the same site. This is the first report of an endoscopic ablation system using a combined radiofrequency and cryotechnology ablation under real-time guidance. This suggests great potential for future device development and applications (31).

High-intensity focused ultrasound therapy

High-intensity focused ultrasound (HIFU) has been described as having thermal, chemical, and mechanical effects in a variety of tumors. These tumor cells are more thermo-sensitive than normal cells (32). The endoscopic application of this principle has been tried in a canine rectal pseudotumor model to determine the potential of rectal tumor ablation with mixed results and is still evolving (33). In other studies using rabbits, a transducer was created that was mounted to a standard duodenoscope and used application of HIFU to the liver through a gastrostomy. This showed the potential of small transducers and their applications with an endoscope. The application of HIFU revealed well-defined lesions of coagulation necrosis that formed within target sites of the left hepatic lobe (34). As a natural progression of this technology, a pilot study was conducted with a flexible catheter and an ultrasound transducer that could be placed over a guidewire into the bile duct. Ten patients with intra- or extrahepatic bile duct or ampullary tumors were treated with intraductal HIFU. Of these, 4 patients had partial response, and one had complete regression of the cholangiocarcinoma. These applications are still preliminary and require further study and longer follow-up (35).

Ethanol ablation of pancreatic cysts

EUS-guided injection of alcohol is another approach that has been tried for local tumor ablation. This has been shown anecdotally to have a partial response in solitary hepatic metastasis and ablation of gastric stromal cell submucosal tumors (36, 37). Alcohol has been used in many other clinical applications such as therapy of kidney, hepatic or thyroid cysts.

Recently, studies have demonstrated feasibility of alcohol injection into pancreatic mucinous cysts to slow or arrest growth and avoid surgical resection. This was initially developed by Brugge, et al. who studied 25 patients with pancreatic cysts that were presumed to be mucinous or malignant cysts based on an elevated cyst fluid CEA level with a mean of 5916 ng/ml. Cysts contents were evacuated by EUS-needle aspiration and subsequently lavaged with ethanol for 3 to 5 minutes and aspirated once again. The procedure was tolerated well without pancreatitis, symptoms or other complications in the short and long-term follow-up. It was found that 8 patients (35%) had complete resolution of their cysts. Moreover, the feasibility and safety of EUS-guided ethanol lavage of mucinous pancreatic cysts was demonstrated (38). Further studies have suggested that macrocystic pancreatic lesions between 1 to 5 cm that are known to be mucinous cystic neoplasms have a high rate of resolution after combined saline and

ethanol lavage and ablation. A randomized prospective trial is underway to determine the efficacy and indications of such therapy (39).

In another recent application of EUS-guided pancreatic cyst ablation, the combination of ethanol and paclitaxel injection has been studied. These investigators studied this therapy in 14 patients with pancreatic cystic neoplasms, presumed to be of mucinous type. One patient developed post-injection pancreatitis and another developed hyperamylasemia and abdominal pain which were self-limited. Complete resolution of the cysts was noted in 11 of 14 patients with 2 patients having reduction in volume suggesting a partial response. This is a small series that requires further follow-up in a larger group (40). These studies demonstrate potential ablation of cystic neoplasms by minimally-invasive EUS-guided therapy that may preclude surgical intervention, particularly in the head or uncinate process of the pancreas that would otherwise require a major operation such as a Whipple resection. Some small series have been performed in animal models to treat small neuroendocrine tumors with injection therapy to avoid major pancreatic surgery. The potential of EUS-guided therapy has yet to be tested in many similar circumstances in human trials.

EUS-guided brachytherapy

The delivery of radiation to specific targets of tumor tissue can be challenging to avoid damage to surrounding nontumor tissue. Delivery of radiation to specific sites has been achieved by implanting radioactive seeds into the tumor and externally activating them in a controlled manner. This form of brachytherapy has been shown to be possibly by EUS guidance as well. In a Chinese study of human patients, pancreatic adenocarcinoma was treated with placement of Iodine-125 brachytherapy seeds through a special delivery catheter under EUS visualization and access. Two patients had regression of tumor while 6 patients had stable tumor. In a follow-up study, 15 patients were similarly treated and found at a mean follow-up of 4.5 months to have a 27% rate of tumor regression, 20% minimal response, and 33% stable tumor size. However, overall survival benefit has not been demonstrated and requires further study (41). Nevertheless, the potential for brachytherapy by EUS-guidance has been shown to be feasible.

Other applications of EUS-guided therapy

Several animal studies have been used to create endoscopic gastrojejunal anastomosis under direct EUS visualization. Swain, et al. have developed a through-the-scope suturing device that can target 5cm depth from the tip of the echoendoscope to precisely located targets. Through the standard 2.8mm therapeutic channel of the EUS scope, incisions of the bowel, grasping of other bowel loops, suturing, knot-tying and cutting of suture has been accomplished. This has been shown to approximate the stomach to adjacent bowel or gallbladder. Such work demonstrates the potential for EUS-guided gastrojejunostomy in the treatment of obesity or gastric outlet obstruction.

EUS has excellent visualization of blood vessels by utilizing Doppler flow technology. Some studies have shown in a live porcine model the potential to cannulate the thoracic or abdominal aorta to use contrast angiography and clearly opacify vessels including the celiac axis, superior mesenteric artery, splenic artery, portal vein, and hepatic veins. Injection therapy of feeding vessels into peripancreatic arterial pseudoaneurysm has been successfully demonstrated in humans by EUS-guided injection of thrombin (42). Therapy with cyanoacrylate injection into vessels including gastric varices for refractory gastrointestinal bleeding has also been demonstrated. (43, 44).

SUMMARY

Interventional procedures seem to be the next logical step in the evolution of EUS. This unique technology offers direct access to a variety of sites that may not be easily reached otherwise. Once a needle can reach a target with high-resolution real-time imaging, delivery of agents and instruments to this site is often easily achieved. Guidewire placement into ducts or vessels can further improve access to these sites endoscopically. Remarkable advances have been made in the type of devices and their applications that can be used with endoscopic ultrasound. Over the past decade, the imaging of endoscopic ultrasound has become well established in its clinical impact on sampling lesions within and surrounding the gastrointestinal tract and related organs. The future of this technology is already here with many therapeutic applications. The next decade will likely show substantial progress in EUS-guided therapeutic endoscopic interventions and their application in clinical gastroenterology. EUS has yet to see its full potential in therapeutic applications and offers an exciting period to gastrointestinal endoscopy.

REFERENCES

1. 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 Apr;63(4):622-9.

2. Eloubeidi MA, Tamhane A, Lopes TL, Morgan DE, Cerfolio RJ. Cervical esophageal perforations at the time of endoscopic ultrasound: a prospective evaluation of frequency, outcomes, and patient management. Am J Gastroenterol. 2009 Jan;104(1):53-6.

3. Levy MJ, Jondal ML, Clain J, Wiersema MJ. Preliminary experience with an EUS-guided Trucut biopsy needle compares with EUS-guided FNA. *Gastrointest. Endosc.* 2003; 57: 101-6.

4. Varadarajulu S, Fraig M, Schmulewitz N *et al.* Comparison of EUS-guided 19 gauge Trucut needle biopsy with EUS-guided fine-needle aspiration. *Endoscopy* 2004; 36: 397-401.

5. Levy MJ, Reddy RP, Wiersema MJ, Smyrk TC, Clain JE, Harewood GC, Pearson RK, Rajan E, Topazian MD, Yusuf TE, Chari ST, Petersen BT. EUS-guided trucut biopsy in establishing autoimmune pancreatitis as the cause of obstructive jaundice. Gastrointest Endosc. 2005 Mar;61(3):467-72.

6. Levy MJ, Jondal ML, Clain J, Wiersema MJ. Preliminary experience with an EUS-guided Trucut biopsy needle compares with EUS-guided FNA. *Gastrointest. Endosc.* 2003; 57: 101-6.

7. Varadarajulu S, Fraig M, Schmulewitz N *et al.* Comparison of EUS-guided 19 gauge Trucut needle biopsy with EUS-guided fine-needle aspiration. *Endoscopy* 2004; 36: 397-401.

8. Collins D, Penman I, Mishra G, Draganov P. EUS-guided celiac block and neurolysis. Endoscopy. 2006 Sep;38(9):935-9.

9. Wong GY, Brown DL. Transient paraplegia following alcohol celiac plexus block. Reg Anesth. 1995;20:352-355.

10. van Dongen RT, Crul BJ. Paraplegia following celiac plexus block. Anaesthesia. 1991;46:862-863.

11. Davis DD. Incidence of major complications of neurolytic coeliac plexus block. J Royal Soc Med. 1993;86:264-266.

12. Puli SR, Reddy JBK, Bechtold ML, Antilon MR, Brugge WR. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systemic review. Dig Dis Sci. 2009 Jan 10. [Epub ahead of print.]

13. Habashi S. Draganov PV. Pancreatic pseudocyst. World J Gastroenterol. 2009;15:38-47.

14. Pitchumoni CS, Agarwal N. Pancreatic pseudocysts. When and how should drainage be performed? Gastroenterol Clin North Am. 1999; 28:615-39.

15. Barthet M, Bugallo M, Moreira LS, Bastid C, Sastre B, Sahel J. Management of cysts and pseudocysts complicating chronic pancreatitis. A retrospective study of 143 patients. Gastroenterol Clin Biol. 1993;17:270-6.

16. Van Sonnenberg E, Wittich GR, Casola G. Percutaneous drainage of infected noninfected pancreatic pseudocysts: experience in 101 cases. Radiology. 1989;170:757-61.

17. Barthet M, Lamblin G, Gasmi M, Vitton V, Desjeux A, Grimaud JC. Clinical usefulness of a treatment algorithm for pancreatic pseudocysts. Gastrointest Endosc. 2008 Feb;67(2):245-52.

18. Aghdassi A, Mayerle J, Kraft M, Sielenkämper AW, Heidecke CD, Lerch MM. Diagnosis and treatment of pancreatic pseudocysts in chronic pancreatitis. Pancreas. 2008 Mar;36(2):105-12.

19. Curry L, Sookur P, Low D, Bhattacharya S, Fotheringham T. Percutaneous Cystgastrostomy as a Single-Step Procedure. Cardiovasc Intervent Radiol. 2008 Dec 9. [Epub ahead of print].

20. Schofl R. Diagnostic endoscopic retrograde cholangiopancreatography. Endoscopy 2001; 33:147-157.

21. Shami VM, Kahaleh M. Endoscopic ultrasonography (EUS)-guided access and therapy of pancreatico-biliary disorders: EUS-guided cholangio and pancreatic drainage. Gastrointest Clinics N Am. 2007;17:581-593.

22. Bories E, Presenti C, DCaillol F, Lopes C, Giovannini M. Transgastric endoscopic ultrasonography-guided biliary drainage: results of a pilot study. Endoscopy. 2007;39:287-291.

23. Mallery S, Matlock J, Freeman ML EUS-guided rendezvous drainage of obstructed biliary and pancreatic ducts: report of 6 cases. Gastrointest Endosc. 2004;59:100-107.

24. Mauceri HJ, Beckett MA, Liang H, Sutton HG, Pitroda S, Galka E, Efimova E, Darga T, Khodarev NN, King CR, Posner MC, Hellman S, Kufe DW, Weichselbaum RR. Translational strategies exploiting TNF-α that sensitize tumors to radiation therapy. Cancer Gene Therapy; 2008 October 31. [Epub ahead of print].

25. Chang KJ, Lee JG, Holcombe RF, Kuo J, Muthusamy R, Wu ML. Endoscopic ultrasound delivery of an antitumor agent to treat a case of pancreatic cancer. Nat Clin Pract Gastroenterol Hepatol. 2008 Feb;5(2):107-11.

26. Chang KJ, Nguyen PT, Thompson JA, Kurosaki TT, Casey LR, Leung EC, Granger GA. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by

endoscopic ultrasound-guided fine-needle injection in patients with advanced pancreatic carcinoma. Cancer. 2000 Mar 15;88(6):1325-35.

27. Hecht JR, Bedford R, Abbruzzese JL, Lahoti S, Reid TR, Soetikno RM, Kirn DH, Freeman SM. A phase I/II trial of intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in unresectable pancreatic carcinoma. Clin Cancer Res. 2003 Feb;9(2):555-61.

28. Wu Y, Tang Z, Fang H. High operative risk of cool-tip radiofrequency ablation for unresectable pancreatic head cancer. J Surg Oncol. 2006; 392-395.

29. Spiliotis JD, Datsis AC, Michalopoulos NV. Radiofrequency ablation combined with palliative surgery may prolong survival in patients with advanced cancer of the pancreas. Langenbecks Arch Surg. 2007;392:55-60.

30. Hines-Peralta A, Hollander CY, Solazzo S. Hybrid radiofrequency and cryoablation device: preliminary results in an animal model. J Vasc Interv Radiol 2004; 15:1111-1120.

31. Carrara S, Arcidiacono PG, Albarello L, Addis A, Enderle MD, Boemo C, Campagnol M, Ambrosi A, Doglioni C, Testoni PA. Endoscopic ultrasound-guided application of a new hybrid cryotherm probe in porcine pancreas: a preliminary study. Endoscopy 2008;40:321-326.

32. Lubbe AS, Bergemann C. Ultrasound therapy for malignant tumors. A conceptual assessment. J Clin Ultrasound. 1994;22:113-117.

33. Wiersema MJ, Kochman ML, Sanghvi NT. Initial experience using intraluminal high-intensity focused ultrasound (HIFU) to ablate rectal pseudo tumors in a canine model [abstract]. Gastrointest endosc. 1993;39:260.

34. Prat F, Chapelon J-Y, Arefiev A, Cathignol D, Souchon R, Theilliere Y. High-intensity focused ultrasound transducers suitable for endoscopy: feasibility study in rabbits. Gastrointest Endosc. 1997;45:348-351.

35. Prat F, Lafon C, DeLima DM. Endoscopic treatment of cholangiocarcinoma and carcinoma of the duodenal papilla by intraductal high-intensity US: results of a pilot study. Gastrointes Endosc 2002; 56:909-915.

36. Barclay RL, Perez-Miranda M, Giovannini M. EUS-guided treatment of solid hepatic metastasis. Gastrointest Endosc. 2002; 55:266-270.

37. Gunter E, Lingenfelser T, Eitelbach F. EUS-guided ethanol injection for treatmentof a GI stromal tumor. Gastrointest Endosc 2003;47:113-115.

38. Gan SI, Thompson CC, Lauwers GY, Bounds BC, Brugge WR Ethanol lavage of pancreatic cystic lesions: initial pilot study. Gastrointest Endosc. 2005 May;61(6):746-52.

39. Brugge WR. Management and outcomes of pancreatic cystic lesions. Dig Liver Dis. 2008 Nov;40(11):854-9. Epub 2008 May 27.

40. Oh HC, Seo DW, Lee TY, Kim JY, Lee SS, Lee SK, Kim MH New treatment for cystic tumors of the pancreas: EUS-guided ethanol lavage with paclitaxel injection. Gastrointest Endosc. 2008 Apr;67(4):636-42. Epub 2008 Feb 11.

41. 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 Apr;40(4):314-20. Epub 2008 Feb 19.

42. Robinson M, Richards D, Carr N. Treatment of a splenic artery pseudoaneurysm by endoscopic ultrasound-guided thrombin injection. Cardiovasc Intervent Radiol. 2007 May-Jun;30(3):515-7.

43. Levy MJ, Wong Kee Song LM, Farnell MB, Misra S, Sarr MG, Gostout CJ. Endoscopic ultrasound (EUS)-guided angiotherapy of refractory gastrointestinal bleeding. Am J Gastroenterol. 2008 Feb;103(2):352-9. Epub 2007 Nov 6.

44. Romero-Castro R, Pellicer-Bautista FJ, Jimenez-Saenz M, Marcos-Sanchez F, Caunedo-Alvarez A, Ortiz-Moyano C, Gomez-Parra M, Herrerias-Gutierrez JM EUS-guided injection of cyanoacrylate in perforating feeding veins in gastric varices: results in 5 cases. Gastrointest Endosc. 2007 Aug;66(2):402-7.