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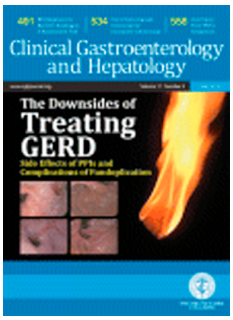

AGA White Paper: Interventional Endoscopic Ultrasound – Current Status and Future Directions

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Abstract:

The evolution of endoscopic ultrasound (EUS) from a diagnostic to a therapeutic procedure has resulted in a paradigm shift towards endoscopic management of disease states that have previously required percutaneous or surgical approaches. The last few years have seen additional techniques and devices that have enabled endoscopists to expand its diagnostic and therapeutic capabilities. Some of these techniques were initially reported over a decade ago; however, with further device development and refinement in techniques there is potential for expanding the application of these techniques and new technologies to a broader group of interventional gastroenterologists.

Lack of formalized training, devices and prospective data regarding their use in addition to a scarcity of guidelines on implementation of these technologies into clinical practice are contributing factors impeding the growth of the field of interventional EUS. In April 2019, the American Gastroenterological Association's Center for GI Innovation and Technology (CGIT) conducted its annual Tech Summit and a key session focused on interventional EUS. This article represents a white paper generated from the conference and discusses the published literature pertaining to the topic of interventional EUS and outlines a proposed framework for the implementation of interventional EUS techniques into clinical practice. Three primary areas of interventional EUS are addressed: (1) EUS-guided access; (2) EUS-guided tumor ablation; and (3) Endo-Hepatology.

There was general agreement among participants on several key components. The introduction of these novel interventions requires better tools, more data on safety/outcomes and improved training for endoscopists. Participants also agreed that widespread implementation and use of these techniques will require support from GI societies and other key stakeholders including payers. Continued work by the GI societies and manufacturers to provide training programs, appropriate equipment/work environments and policies that motivate endoscopists to adopt new techniques is essential for growing the field of interventional EUS.

Key words: EUS; interventional; EUS-guided access; EUS-guided ablation; endo-hepatology

In April 2019 during the annual Tech Summit meeting, the American Gastroenterological Association's CGIT conducted a session to discuss the current status of interventional endoscopic ultrasound (I-EUS). The discussion focused on new technologies and devices that have evolved EUS from a diagnostic tool to a therapeutic procedure. The participants constituted a range of specialists in the fields of therapeutic endoscopy, which represented the spectrum of opportunities and options within I-EUS.

The session and this paper are designed to foster detailed discussions on I-EUS, including a review of published evidence and acknowledgement of differences of opinion or inadequate evidence. Select key speakers were invited to spearhead a working group to summarize these discussion points and better define topics requiring further exploration. The authors forming this working group, which include the summit participants, select CGIT members and other invited experts have written this summary for the main purposes of: (1) exploring the different modalities of interventional EUS, (2) summarizing the evidence behind each technique and; (3) discussing knowledge gaps, research and equipment required and future directions of this technique.

Any specific recommendations within this summary are based on expert opinion, and are not intended to serve as "practice guidelines" for the American Gastroenterological Association. Instead, they reflect a level of confidence among this expert working group that, after reviewing available literature and after group consensus, the desirable effects of any particular recommendation would outweigh any undesirable effects, and that the recommendation would likely be followed by most informed stakeholders.

This white paper outlines a proposed framework for the implementation of interventional endoscopic ultrasound technologies into routine clinical practice. The paper covers three main topics: access (biliary, extralumenal, and lumen bypass), tumor ablation and endo-hepatology. We hope this paper guides those interested in adoption of these technologies into clinical practice and serves as a foundation for future research and innovation in the field.

EUS-guided access

EUS-guided biliary access and drainage

The proximity of the common bile duct and liver to the duodenum and stomach respectively, allows easy access to the biliary system for EUS guided biliary access and drainage (EUS-BD) when conventional ERCP is either unsuccessful or anatomically not feasible. Approaches for EUS-BD either facilitate ERCP by placement of a wire using EUS (rendezvous techniques) when standard ERCP is unsuccessful, or provide direct transluminal drainage of the biliary tree.[1-7]

Rendezvous techniques are multi-step procedures in which the EUS scope is used to first introduce a wire into the biliary tree. The wire may be passed either through the duodenum, *i.e.* transduodenal biliary rendezvous (TD-BR) or through the stomach, *i.e.* transgastric transhepatic biliary rendezvous (TGTH-BR). After successful wire passage, the EUS scope is exchanged for a duodenoscope. Using the rendezvous wire, ERCP is completed. Both are multi-step procedures and can be associated with challenges at different steps during the procedure (Table 1). A third technique is an extension of the TGTH technique and completed entirely with the EUS scope. During EUS guided transgastric transhepatic antegrade drainage (TGTH-AGD), a wire is first inserted into a left intrahepatic duct branch and across either the papilla or a surgical biliary anastomosis. A stent is then then placed antegrade across the appropriate location. Direct EUS-BD techniques involve creating an anastomosis between the gastrointestinal tract and the biliary tree. The two primary approaches are creation of an anastomosis between the duodenum and the common bile duct, i.e. choledocho-duodenostomy (EUS-CD), and between the stomach and the left lobe of the liver, i.e. hepaticogastrostomy (EUS-HG).

The choice of technique used for EUS biliary access and drainage is determined by the clinical scenario and long-term management strategy for the patient. EUS rendezvous techniques are preferred for benign conditions such as failed biliary cannulation during ERCP for treatment of a stricture or common bile duct stone.

Transluminal drainage of the biliary tree using metal stents is most commonly performed in malignant biliary obstruction (MBO) and the technique chosen is determined by the surgical candidacy of the patient.

The conventional approach for EUS-BD and EUS-HG has been to place self-expanding metal biliary stents (SEMS) designed for ERCP, which may be uncovered, partially covered or fully covered. More recently, partially covered metal stents designed particularly for EUS-HG have been developed and used successfully.[8, 9] However, the most significant development in this field has been the development of lumen apposing metal stents (LAMS) for EUS-CD.[10] These stents have wide flanges to oppose the walls of adjacent structures **(Figure 1).** During EUS-CD, the duodenal and common bile duct (CBD) walls are stented to create an anastomosis. The development of a cautery-assisted LAMS has further enhanced the EUS-CD procedure.[11, 12] The electrocautery tip of the catheter permits application of a cutting current during catheter advancement into the CBD. Insertion of the catheter may be done either with or without wire guidance. The stent is deployed once the catheter has been advanced into the CBD. Deployment with one catheter system eliminates the need to exchange multiple devices thus reducing the time between access and stent deployment. The combination of a single device and the lumen apposing design of the stents reduces the risk of pneumoperitoneum and bile leakage during EUS-CD. Figure 2 demonstrates a case of EUS-CD.

EUS guided biliary access and drainage involves accessing the biliary tree using an EUS fine needle aspiration (FNA) needle. EUS-FNA needles do not allow easy reorientation of the wire if it cannot be advanced in the desired direction and have a beveled sharp tip which can lead to ‘shearing’ of the hydrophilic coating of the wire even with minimal movements of the wire. A recent advancement in EUS-BD has been the development of a dedicated needle with a rotatable tip which can be used to steer the access wire in the desired direction and eliminates the risk of wire shearing (**Figure 3**).[13]

All EUS-BD techniques have been shown in several randomized controlled trials, multiple systematic reviews, and meta-analyses to have relatively high technical and clinical success rates (85% or higher for both) and a low, though not insignificant, risk of

adverse events of up to 15%.[14-19] Potential adverse events include bowel perforation, bleeding, bile leakage and peritonitis. However, the risk of pancreatitis is averted by performing EUS-BD. Bile leakage and mild peritonitis may occur despite successful completion of the procedure in some patients and this can typically be managed conservatively. Most problematic adverse events, however, occur due to failure to successfully complete drainage following initial EUS guided biliary access in an obstructed biliary system. Unlike ERCP, failure to complete the procedure has significant consequences such as bile leak and bowel perforation from an unsuccessful EUS-guided BD procedureand contrast injection into an obstructed biliary system resulting in infection, potentially requiring emergent percutaneous or surgical intervention.

EUS guided biliary drainage procedures require technical expertise in diagnostic and therapeutic EUS. Given the various approaches involved, it is important to be familiar with the various options and the associated unique technical aspects of the procedures. These procedures should therefore only be performed in centers with appropriate expertise and backup in case of adverse events. [20-22]

In patients with malignant biliary obstruction and failed ERCP, the major advantage of EUS-guided drainage is internalization of the stent thus minimizing the morbidity associated with long-term percutaneous drainage tubes and avoiding surgery in high-risk patients.[15, 16, 23]

EUS Gallbladder Drainage

EUS-guided gallbladder drainage (EUS-GBD) in patients with cholecystitis may be considered in those unable to undergo definitive management with cholecystectomy. The procedure involves EUS-guided access to the gallbladder through the duodenal (most commonly) or gastric wall and placement of a plastic, FCSEMS or LAMS.[24-26] EUS-GBD is associated with a higher technical and clinical success rate compared to percutaneous GBD (90-98% and 89-97% respectively). LAMSs have become the preferred stents for EUS-GBD due their ease of deployment, lumen apposition

configuration and wide diameter. A recent international, randomized controlled trial compared EUS-GBD to percutaneous cholecystostomy and demonstrated high technical success rates (97.4% vs 100%, p=0.494) for both procedures but significantly lower adverse event rates for the EUS-GBD group.[27] Procedure related adverse events in the EUS-GBD group included stent blockage and perforation whereas the primary adverse event related to percutaneous drainage was tube dislodgement. The optimal duration for leaving LAMS in place is not clear with some advocating removal of LAMS and replacing the stent with plastic double pigtail stents after 3-6 weeks in order to minimize stent related complications such as bleeding. The EUS guided approach offers an alternative to ERCP assisted transpapillary drainage with a relatively small caliber plastic stent or percutaneous cholecystostomy and its drain-related comorbidities.[28-30]

Pseudocysts and Walled off Necrosis

Localized complications associated with pancreatitis include acute fluid and necrotic collections which over time can become encapsulated to form pseudocysts (PCs) and walled off necrosis (WON), respectively.[31] These collections are primarily in the peripancreatic retroperitoneal space adjacent to the stomach and duodenum though collections can extend deep into the pelvis retroperitoneally and/or intraperitoneally around the mesentery. Pseudocysts contain simple fluid, whereas necrotic collections contain both fluid and necrotic tissue, which may be pancreatic parenchyma or peri-pancreatic fat. Management of these collections requires a multidisciplinary approach.[32] Pseudocysts can be managed with endoscopic cystgastrostomy (CG) surgical CG or transpapillary stent placement via ERCP. [33, 34] Several randomized controlled trials over the last decade have demonstrated that in the minimally invasive treatment of acute necrotic collections and WON yield better outcomes, shorter length of stay and overall lower cost of care than open surgical necrosectomy.[34-37]

LAMS ranging from 10 to 20 mm in diameter are currently available in the USA. In recent years, LAMSs (**Figure 1**) have gained popularity in the management of pseudocysts and walled off necrotic collections. While data for their superiority over plastic stents are conflicting, potential advantages of LAMS include a wider lumen to

allow passage of necrotic tissue and the ease of performing endoscopic necrosectomy through the stent lumen. [38-41] However, LAMS have been associated with increased bleeding in the necrotic cavity possibly due to mechanical trauma of the necrotic cavity wall by the stent and infection due to occlusion of the stent lumen by indwelling necrotic material.[42] Placement of coaxial plastic stents through the lumen of LAMS has been advocated to try to minimize the risk of complications related to LAMS.[43] The use of LAMS may allow endoscopic drainage of collections without clearly definable walls, which in the past may have been considered unsafe to treat endoscopically. In a recent study, early endoscopic intervention of pancreatic necrosis (defined as less than 4 weeks from onset of pancreatitis), primarily using LAMS, was found to be safe.[44] Patients with WON in the setting of disconnected pancreatic duct syndrome may require long-term transluminal plastic stents after LAMS removal to allow drainage of the disconnected portion and decrease the risk of recurrent collections[45]. Removal of the LAMS prior to complete drainage of the necrotic collection should be considered to ensure that adequate space in the collapsed cavity is available to place plastic stents and ensure ongoing cavity drainage.

Pancreatic Duct Access

Patients with recurrent pancreatitis or pancreatic pain with pancreatic duct obstruction in whom pancreatic duct access is not possible present a major management challenge due to limited options. Surgery can be considered; however, it may offer uncertain benefit, may be technically difficult or not possible, and may be associated with a high risk of morbidity (*e.g.* diabetes or pancreatic insufficiency). EUS guided pancreatic duct access has been described in patients in whom retrograde pancreatic duct access is not successful at ERCP, not possible due to altered anatomy (i.e. inability to reach or visualize the pancreatic duct orifice after surgery) and in the setting of disconnected pancreatic duct syndrome.[46] It is achieved technically by one or two methods. The first method, EUS guided pancreatic rendezvous (EUS-PR) begins with transenteric passage of a wire into the pancreatic duct and into the intestinal lumen, followed by endoscope exchange and subsequent ERCP. The second

technique, direct drainage of the pancreas into the stomach, is known as a pancreatico-gastrostomy (EUS-PG). [47, 48] Both EUS-PR and EUS-PG are difficult procedures **(Table 1)** with a technical failure rate of up to 40% and can be associated with adverse events such as pancreatitis, perforation, bleeding or a peripancreatic fluid collection occurring in up to 35%.[49, 50] Unlike other EUS-guided drainage and access procedures, there has been limited improvement in technology to make EUS-guided pancreatic access easier or safer. In a comparative study of a small diathermic sheath (6 Fr) and an ultra-tapered mechanical dilator (2.5 Fr) from Japan, both devices have been shown to have a success rate of over 80% for EUS guided pancreatic duct access with a low risk of complications.[51] The same group has also reported on the successful use of a dedicated EUS guided plastic stent for EUS-PG.[52] None of the three devices discussed above are currently available in the USA. The role of using smaller caliber devices utilized in the fields of interventional radiology and cardiology has recently been shown to help achieve successful transgastric pancreatic drainage in a recent study from the USA.[53] There remains a significant need for the development of EUS guided devices that enable easy access and drainage of the pancreatic duct in a safe and reliable manner.

Enteral anastomosis

EUS-guided enteral anastomoses have become possible with the introduction of LAMS, especially cautery assisted LAMS **(Figure 1)**, as these stents allow for a single step procedure for stent deployment and anastomosis creation.[54] These stents permit creation of new entero-enteric anastomoses in malignant and benign gastric outlet obstruction (EUS gastrojejunostomy, EUS-GJ), drainage of obstructed small bowel limbs after surgery (e.g. post pancreatico-duodenectomy) and creation of gastro-gastric or entero-gastric fistulae after Roux-en-Y gastric bypass to facilitate ERCP.[55-59] EUS-GJ for malignant and benign gastric outlet obstruction (GOO)[60-62] first requires distension of the duodenal or jejunal lumen distal to the obstruction using various techniques. After identifying an appropriate EUS window for the anastomosis, a cutting electrosurgical current is applied via the tip of the LAMS deployment catheter to the

gastric wall and the adjacent bowel wall. The catheter is then advanced into the bowel lumen and the stent is deployed. Intravenous glucagon can be administered to reduce intestinal motility and it is important to ensure that the jejunum is adequately distended in order to provide tension against the LAMS catheter. At present there is no mechanism to anchor the jejunum prior to attempting EUS-GJ or other enteric anastomoses. EUS-GJ is a technically demanding procedure with a potential to result in bowel perforation and peritonitis due to spillage of gastro-enteric contents into the peritoneum. The technical and clinical success rate of EUS-GJ has improved with time (>90% for both) and the procedure may lower the need for re-intervention compared to intraluminal metal stents for gastric outlet obstruction.[62] Potential advantages of this technique include immediate post-procedure reintroduction of oral intake and administration of chemotherapy in patients with malignant obstruction. Although, prospective comparative data are lacking, EUS-GJ has been shown to have similar efficacy and safety compared to surgical GJ in a small retrospective study.[61]

Future directions

There has been an exponential growth in EUS guided biliary (including gallbladder) access and drainage procedures, as well as entero-enteric anastomotic procedures in recent years. This change can be attributed to the availability of LAMS. However, it should be noted that there are no prospective, randomized trials for these specific stents and although they offer several advantages for access and deployment, high quality data for their superiority are lacking. Similarly, even though there has been a shift towards the use of LAMS in the management of pancreatitis associated necrotic collections, the studies demonstrating their benefit are often case series with a mixed patient population ranging from stable ambulatory patients to critically ill patients.

LAMS are expensive with prices ranging from $4000 to $6000. Prospective data on the efficacy, safety and cost-effectiveness of LAMS as well as other EUS-guided access and drainage approaches are needed. Given the complex nature of these procedures and the potentially serious adverse events associated with failure to successfully complete the procedure (perforation, leakage, peritonitis, bleeding), it is recommended that these procedures be performed at centers with expertise in

therapeutic EUS with the availability of appropriate supporting specialties to manage any potential complications. Patients requiring these procedures typically have complex disease and should be managed by a multidisciplinary team. Finally, there continues to be a need for improvements in technology related to all aspects of EUS access and drainage including safe access to minimize the risk of complications, the ability to maneuver wires and devices once access has been obtained, and dedicated stents for EUS-guided interventions (**Table 2**).

EUS-guided tumor ablation

Because of the close proximity of the gastrointestinal tract to organs such as the esophagus, liver and pancreas, EUS would appear to be an ideal tool to provide imaging and potentially ablation of benign and malignant lesions in these locations. Using a linear echoendoscope, either an aspiration needle or a device may be passed through the working channel of the endoscope into a target organ. A needle may be used for injection of a chemical or synthetic compound. Limitations of injection include the viscosity of the injectate, the lesion targeted (*i.e.* solid versus cystic) and its proximity to the gastrointestinal tract. For example, a more viscous solution would require either dilution to thin the fluid or a larger caliber needle to facilitate injection. After stylet removal, ablation fibers may be passed through a 19-gauge needle into a target organ. However needles are not required to perform ablation as stand-alone devices may also be passed through the working channel to simultaneously target a site to provide treatment.

For patients, ablation of tumors may potentially decrease cancer risk, decrease costs over time, avoid more invasive procedures, provide psychological benefit and possibly improve outcomes and survival. However, the use of EUS for these indications may have some potential problems. First, the endoscope length and the relatively narrow caliber of the working channel must be overcome. Second, the tortuosity of the gastrointestinal lumen and its location relative to some target organs make some areas of the liver and head or uncinate process of the pancreas difficult to

treat. Third, the size, tumor characteristics and type of neoplasia (i.e. benign vs. malignant) limit which lesions can or should be approached by this technique. Finally, the high initial costs of ablation of tumors must be considered against limited healthcare resources.

Esophageal tumors

Some of these difficulties with EUS-guided tumor ablation were illustrated in a recently published trial.[63] In this multicenter, prospective study, patients with esophageal cancer were randomized to chemoradiation alone or chemoradiation plus EUS-guided injection of paclitaxel into the tumor. The principal endpoint of the trial was local tumor response as determined by CT scan following treatment. One difficulty the trial encountered was how to administer chemotherapy by EUS. A solid tumor does not readily retain a thin liquid that is directly injected into it. On the other hand, paclitaxel at full concentration (6 mg/mL) is viscous and required the assistance of a pressurized device to inject the compound with a 19-gauge needle. A second hurdle to overcome with this trial was whether local injection of chemotherapy would improve overall survival of a systemic malignancy compared to standard of care chemotherapy. Unfortunately, the study found that intratumoral injection did not improve local tumor response or overall survival.

Solid Pancreatic Tumors

For solid pancreatic masses, there have been multiple studies evaluating the use of chemical/chemotherapy injection or ablation devices in a porcine model. These have included injection of paclitaxel[64] or ethanol[65] and use of devices for radiofrequency ablation,[66] photodynamic therapy,[67] high-intensity focused ultrasound[68] or an Nd-YAG laser.[69] These studies illustrate that ablation is feasible, generally safe, and produces a well-circumscribed region of necrosis within the porcine pancreas.

In humans, the initial pilot studies using EUS-guided injection in pancreatic cancer utilized Cytoimplant[8] and ONYX–015.[70] In these two studies, the minority of patients had a reduction in tumor volume on imaging following treatment and most had either stable or progressive disease after treatment. Treatment with ONYX–015 in 21 patients caused perforation and sepsis in two patients each and further studies with this compound were not performed. In a phase 1 study, Hecht et al.[71] reported that five weekly percutaneous or EUS-guided injections of TNFerade (an adenovirus vector for the TNF-alpha gene) into pancreatic cancer can be given concomitantly with chemotherapy and radiation. The authors reported that at a dose of $4x10^{11}$ particles, median overall survival appeared to be longer relative to other TNFerade doses. However, when patients in a subsequent study with locally advanced pancreatic cancer were randomized to chemoradiation alone versus chemoradiation plus injection of TNFerade, no difference in overall survival was seen.[72] Thus, EUS-guided injection of chemotherapy or a genetically engineered compound into solid cancers is feasible. However, the addition of the endoscopic therapy to standard of care chemotherapy or chemoradiation for a systemic malignancy may not improve overall survival.

The greatest experience with EUS-guided device ablation is radiofrequency ablation (RFA) of pancreatic endocrine tumors (PETs). These benign but premalignant tumors are either functional (F-PETs) or nonfunctional (NF-PETs) depending on whether or not a clinical syndrome of excess hormone secretion is present. Reported studies have largely included case reports and small case series using one of two commercially available devices (Habib RF DUO 13, Boston Scientific, Inc., Marlborough, MA or EUSRA RF Electrode; STARmed, Koyang, Korea).[73-79] Patients treated in these studies with EUS-RFA are generally averse to surgery or have significant comorbidities that preclude operative management. The studies have shown that EUS-RFA of F-PETs (generally insulinomas) is very effective at ameliorating the effects of hormone excess (i.e. hypoglycemia). Treatment of NF-PETs is more controversial as these are usually asymptomatic, indolent and therefore are managed operatively when over 2 cm in size or with surveillance when smaller. EUS-RFA of NF-PETs may produce tumor necrosis; however, it is unknown whether treatment is durable or may decrease the risk of malignant potential.

EUS-guided device ablation of pancreatic cancer has also been evaluated with multiple different techniques. Arcidicono et al.[80] reported treatment of 22 patients with pancreatic cancer with a cryotherm probe, which is a flexible bipolar device that combines radiofrequency with cryogenic cooling. These authors found that treatment in 16/22 patients was possible yet the stiffness of the tumor and gastrointestinal tract precluded therapy in 6 patients. Imaging in 10/16 patients after ablation found that tumor margins were difficult to evaluate on CT scan. Other devices that have been evaluated by EUS for pancreatic cancer include an Nd-YAG laser[81] and RFA.[82, 83] Recently, a phase 1 study evaluating the safety and efficacy of EUS guided photodynamic therapy (PDT) for locally advanced pancreatic cancer was reported.[84] The study found that 6 of 12 patients treated had tumor necrosis present by follow-up CT scan without any serious adverse events related to EUS-PDT. These studies show that EUS-guided ablation of solid pancreatic cancer can produce focal necrosis using a wide variety of devices and methods.

Pancreatic cysts

Perhaps the greatest experience with EUS-guided ablation is for pancreatic cystic tumors. These tumors include those with essentially no malignant potential (serous cysts) or mucinous cysts, which are associated with a risk of cancer. Mucinous pancreatic cysts, which include intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) have been the principal lesions that investigators have evaluated with EUS guided ablation. The initial pilot study utilized incrementally increasing doses of alcohol and found that one-third of tumors treated resolved by follow-up imaging.[85] A randomized study subsequently reported that ethanol lavage increases rates of pancreatic cyst ablation compared to treatment with saline.[86] The addition of paclitaxel injection to ethanol lavage increases ablation rates compared to ethanol alone.[87, 88] However, this technique has been reported to cause pancreatitis in up to 10% of treated patients.[89] Therefore, interest in an alcohol-free treatment has been evaluated. Moyer et al. reported that patients with mucinous pancreatic cysts randomized to saline lavage followed by injection of a gemcitabine and paclitaxel

mixture had ablation rates (67%) similar to those treated with ethanol lavage followed by the same chemotherapy mixture (61%).[90] Serious adverse events occurred in 6% of patients in the control group vs none of the patients in the alcohol-free group. The currently enrolling NIH-sponsored CHARM II study (Chemotherapy for Ablation and Resolution of Mucinous Pancreatic Cysts) randomizes 2-5 cm mucinous pancreatic cysts to saline or ethanol lavage followed by injection of a gemcitabine and paclitaxel mixture after which patients are followed for both complications and cyst resolution.[91] Figure 4 demonstrates an example of a pancreatic cyst ablation.

Future directions

While multiple devices have been used to treat pancreatic tumors, it remains unclear which device will produce safe ablation without damage to surrounding organs. Currently available EUS-FNA needles are adequate for injection of chemicals into neoplasms however future research is required for both ablation fibers passed through FNA needles (i.e. PDT diffuse fibers) and all-in-one devices passed through the working channel of the echoendoscope. Due to the challenges of using a 19-gauge needle to target lesions, development of ablation fibers measuring 0.018- to 0.021-inches in diameter (and thus capable of passing through a 22-gauge needle) or 22-gauge stand-alone ablation devices could facilitate treatment of lesions in challenging locations such as the pancreatic head, uncinate process and portions of the right hepatic lobe (Table 2).

Further studies evaluating the safety and treatment response to ablation of solid neoplasms is required. These should include dose-ranging studies, involve tumors of various morphology (i.e. solid vs. cystic) and malignant potential, and situated in multiple anatomic locations. Finally, surveillance of treated lesions remains difficult, as routine histology is not possible from treated pancreatic tissue. Investigation of non-invasive methods such as elastography and contrast-enhanced ultrasound for monitoring treatment response are needed.

EUS-guided liver applications

The landscape of liver disease is changing with the alarming increased incidence of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) and new approaches to patients with suspected liver disease are needed. The ability to clinically distinguish NASH from NAFLD is a real unmet need. Confirmation of the diagnosis of NASH, NAFLD and assessment of disease severity (i.e. degree of liver fibrosis) are traditionally performed by liver biopsy. In addition, since treatment for NASH may include either substantial weight loss (5-10% of total body weight) or new and costly therapeutic agents, the indication for liver biopsy will likely increase and be necessary to make clinical decisions.

Fortunately, indications for EUS have expanded into the liver and the application of EUS for liver indications is now termed "Endo-hepatology."[92, 93] The initial indication for Endo-hepatology was EUS-guided liver biopsy (EUS-LB). This will likely be followed by EUS-guided portal pressure gradient (PPG) measurement and EUS-guided shear wave elastography (SWE).

EUS-guided Liver Biopsy

Numerous studies have shown that EUS-LB can achieve satisfactory results with lower adverse events than traditional percutaneous approaches.[94-113] A recent meta-analysis showed that the pooled rate of successful histologic diagnosis was 93.9%.[95] Most of the studies on EUS-LB have utilized 19-g FNA or fine needle biopsy (FNB) needles. This has been further advanced by the recent introduction of two new iterations of fine needle biopsy needles utilizing a Franseen tip configuration (Acquire; Boston Scientific, Marlborough, MA, USA) and a fork-tip configuration (SharkCore; Medtronic Inc, Sunnyvale, CA, USA). A recent meta-analysis showed these second generation FNB needles could generally give more adequate specimen compared to FNA needles.[114] A prospective study also indicated that FNB needles could get longer specimen with more complete portal tracts on EUS-LB than FNA needles **(Figure 5)**.[98]

The arguments in favor of EUS-LB over conventional percutaneous approaches include: 1) real-time ultrasound guidance of the needle into the liver, with Doppler

confirmation of no blood flow within the needle track prior to removing the needle from the liver, 2) the ability to make several needle actuations within the liver with a single puncture through the liver capsule, 3) rapid recovery time (no need to have the patient lie over their right side for long periods), 4) the ability to sample both lobes of the liver and 5) potential for simultaneous endoscopy, EUS-guided shear wave elastography, and EUS-guided portal pressure gradient measurement (see below). Cost analyses also suggest a lower over-all cost of the EUS strategy when factors such as recovery time, non-diagnostic yield, and complications are factored in.[115]

EUS-guided paracentesis

Ascites is easily visualized on EUS imaging and can easily be accessed by EUS-FNA. It is particularly useful for diagnosing malignant ascites.[116] The method is similar to aspirating a pancreatic cyst. The primary concern for EUS-guided paracentesis is the risk of infection resulting in bacterial peritonitis since this is a non-sterile procedure. There is limited data regarding the risk of bacterial peritonitis after EUS-guided paracentesis with one case series demonstrating that 1/25 patients developing bacterial peritonitis.[116]

EUS-guided portal pressure gradient (PPG)

Portal hypertension (PH), resulting from increased resistance of hepatic sinusoids to blood flow, is a severe complication of liver cirrhosis increasing the risk of esophageal varices, gastric varices, portal hypertensive gastropathy, ascites, and hepatorenal syndrome. Measurement of PH has been useful in determining the stage, progression, and prognosis of cirrhosis in individual patients.

Using a trans-jugular approach, the hepatic vein pressure may be measured directly (called the free hepatic venous pressure, or FHVP). However, the portal vein pressure is usually determined indirectly from the wedged hepatic venous pressure (WHVP). The gradient between the FHVP and the WHVP is termed the hepatic venous pressure gradient (HVPG) which accurately reflects the degree of PH in all forms of sinusoidal and post-sinusoidal causes of portal hypertension. HVPG has been shown to predict the likelihood of clinical decompensation in patients with compensated

cirrhosis,[117] as well as predicting the development of hepatocellular carcinoma (HCC) independently of severity of cirrhosis,[118] and to be the single best prognostic factor in liver disease.[119]

In clinical practice, portal hypertension is most often diagnosed by percutaneous transjugular pressure measurements. This method is relatively invasive, requires ionizing radiation, intravenous contrast, and provides only indirect measurements. The procedure is performed by placing a radiopaque catheter into the right jugular vein and advancing it into the hepatic vein tributaries under fluoroscopic guidance. A free and a wedged hepatic vein pressure are then obtained. The HVPG, an indirect measurement of the portal vein pressure, is estimated by subtracting the FHVP former from WHVP. This estimation can be inaccurate in cases of pre-hepatic portal hypertension, such as portal vein thrombosis, and duplex ultrasonography is often also required. In addition, patients with hepatic, pre-sinusoidal portal hypertension, such as in myeloproliferative disorders, can have an inaccurate HVPG.[120, 121]

EUS-guided PPG measurement was initially developed using a 25-gauge needle and a novel compact manometer in an animal model[122] demonstrating excellent accuracy and strong correlation with pressure values obtained by the gold standard transjugular wedged and free hepatic venous pressure measurements by interventional radiology. The initial pilot study in humans demonstrated safe and accurate direct portal pressure gradient measurements **(Figure 6c).** A total of 28 patients underwent EUS-guided portal pressure manometry in this study and pressure measurements were successfully achieved in all 28 patients. EUS-PPG values ranged from 1.5-19mmHg with a mean of 8.2mmHg. In total, 15/28 (57.1%) had evidence of PH based on EUS-PPG, of which 10/15 (66.7%) had clinically significant portal hypertension (CSPH). Eleven of 28 subjects had endoscopic evidence of either esophageal or gastric varices with all 11 (100%) having PH and 10 (90.9%) patients having CSPH based on EUS-PPG measurement.[123, 124] This study showed that EUS-guided portal pressure measurement using a 25-g needle and compact manometer was feasible and appeared to be safe in humans. An updated abstract was published with 51 patients undergoing EUS-PPG, with 100% technical success, no adverse events, and a PPG range of 0-27 mmHg with strong correlation with clinical markers of portal hypertension.[125] A study in

a cohort of patients who underwent both EUS-PPG as well as EUS-guided liver biopsy demonstrated that the two procedures could be conveniently combined in one setting.[126] EUS-PPG can also overcome the issue of accurately diagnosing hepatic, pre-sinusoidal portal hypertension – by directly measuring the pressure in the portal vein. This technique represents a promising breakthrough for procuring indispensable information in the management of patients with liver disease.

EUS-guided Shear Wave Elastography (SWE)

Non-invasive imaging modalities can evaluate for liver fibrosis by way of quantifying parenchymal stiffness. Transient elastography (TE) is a non-imaging elastographic technique, while point shear wave (p-SWE) and 2D-SWE combine imaging with shear wave elastography (SWE). SWE uses measurement of acoustically generated shear wave propagation speeds in tissue to derive estimates of liver stiffness, with the advantage of simultaneous anatomic B-mode US imaging. Percutaneous elastography is most readily performed over the right liver, typically in between the costal spaces. Studies have shown substantial variability between the left and right lobes of the liver, which may affect the correlation to liver fibrosis.[127] Most recently, the newest EUS processors have the capability of 2D-SWE during simultaneous B-mode imaging (Arietta 850 EUS System, Olympus). This allows the assessment of parenchymal stiffness in both lobes of the liver (**Figure 6E**).

Future Directions

With the increasing prevalence of NAFLD and NASH, there is an unmet clinical need to establish efficient and accurate information regarding liver inflammation, fibrosis, and overall function. With the expansion of EUS to the liver and the emergence of the field of “Endo-Hepatology,” there is now potential for “one-stop-shop” diagnosis and staging of liver disease. Potential aspects of endo-hepatology are demonstrated in Figure 4. The true advantage of Endo-hepatology is that these treatments and diagnostics can be performed all during a single procedure. Future device iterations for liver biopsy would include needles designed specifically to acquire pristine benign liver core specimen (Table 2). This would incorporate the largest possible caliber needle

(while remaining flexible), with an extremely sharp front tip, and being able to trust the needle forward at high speed. For EUS-guided portal pressure gradient measurement, future iterations should include a better display interface with recording capabilities and ability to incorporate directly into the endoscopy report. EUS-guided shear wave elastography has just recently emerged and will require continuous tweaking of the software and hardware to obtain quick and reliable measurements. Obtaining a CPT code specifically for EUS-PPG is a necessary next step, and will require larger prospective studies (some are already in progress) as well as registry studies.

EUS guided vascular therapy

In recent years EUS-guided interventions have been applied to both acute and elective management of vascular therapy, delivering therapy in the form of glue injection, endovascular coil placement or a combination of the two. The most common vascular application of EUS is in the diagnosis and treatment of gastric varices (GV), which can be associated with high morbidity and mortality.[128] EUS through the use of Doppler can differentiate varices from gastric folds or other lesions, thereby offering a clear advantage in the diagnosis of gastric varices.[129] Furthermore access to the varix can be achieved from the esophagus, thereby mitigating the need for direct injection into the varix.

EUS-guided glue injection

Cyanoacrylate (CYA) glue injection has become the standard treatment for both acute bleeding and secondary prophylaxis. Hemostasis is achieved in 80%–90% of cases, although rebleeding is a risk.[130] EUS offers several advantages over standard needle injection. It accurately targets the varix, and enables the endosonographer to watch obliteration of the varix in real time using color Doppler. This theoretically, minimizes the risk of embolization.[131]

Endoscopic ultrasound-guided coil embolization

The second method for treating gastric varices is through the placement of micro coils which leads to embolization by obliteration of the varices. The coils have a

synthetic fiber covering that promotes clot formation.[132] This technique was initially described as a case series and has been increasingly used both as monotherapy and in combination with CYA.[133] The purpose of combination therapy is that the coils would act as a scaffold for the glue, minimizing the amount of glue used and the risk of glue embolization.

A cohort study by Romero-Castro et al. compared EUS-guided CYA application with EUS-guided coiling.[134] After six months follow up there was no significant difference in the rate of obliteration of gastric varices (95% of the CYA group versus 91% of the coil group). Although the CYA group required a higher number of sessions to achieve varix obliteration; however, this did not reach statistical significance, likely due to the small sample size. A larger study by Bhat et al. using a combination of EUS-guided CYA injection and coiling demonstrated that the initial procedure was successful in achieving hemostasis in 151 out of 152 cases.[135] There was a 7% adverse event rate, the most serious was a single patient with a pulmonary embolism who recovered completely. There was an 8% risk of rebleeding.

Is combination therapy better than either treatment alone?

A randomized trial of 60 participants with GV compared combination versus embolization alone.[136] Both treatment groups had technical success rate of 100%, although single session obliteration was higher in the combination group (86.7 %) vs (13.3 %) in the coil alone group ($P < 0.001$). A recent meta-analysis aimed to evaluated the comparative effectiveness of CYA, coil embolization, and/or combination for the treatment of GV.[137] Eleven studies ($n = 536$ patients; 62.20% of males) were included. Overall technical success, clinical success, and adverse events for EUS treatments was 100% ([95% confidence interval [CI] 98–100]; $I^2 = 30.54\%$), 97% ([95% CI 92–100]; $I^2 = 59.99\%$), and 14% ([95% CI 6–23]; $I^2 = 82.23\%$), respectively. EUS-guided CYA + coil embolization in subgroup analysis demonstrated better technical and clinical success compared to CYA alone (100% *vs.* 97%; $P < 0.001$ and 98% *vs.* 96%; $P < 0.001$) and coil embolization alone (99% *vs.* 97%; $P < 0.001$ and 96% *vs.* 90%; $P < 0.001$). CYA + coil embolization also resulted in lower adverse event rates compared to CYA alone (10% *vs.* 21%; $P < 0.001$), and comparable rates to coil embolization alone (10% *vs*. 3%; $P = 0.057$).

Future Directions

EUS-guided coil embolization with cyanoacrylate injection has been demonstrated to be effective for both primary and secondary prophylaxis for GV, with lower rates of re-bleeding and re-intervention than the EUS based monotherapy. This represents the feasibility of using EUS as a platform for vascular interventions such as additional vascular embolization for treatment of bleeding or tumors. In addition, a pre-clinical study has been performed to demonstrate the possibility of performing EUS-guided creation of intrahepatic portosystemic shunts for treatment of portal hypertension.[138] Further development of EUS specific devices for vascular access, stents to create shunts, and injectable agents will be necessary to advance EUS-guided vascular therapy.

Summary and Conclusions

Interventional EUS is a rapidly evolving field moving EUS from a procedure that was primarily diagnostic to an interventional platform for treatment of gastrointestinal malignancies and other hepatopancreaticobiliary diseases and disorders. This paper is a summary of the current knowledge regarding interventional EUS focusing on three primary topics: access, ablation, and endo-hepatology. Within each topic the existing evidence behind each technique was discussed, followed by a discussion on future directions that are needed to establish these techniques for broader adoption. We believe that this serves as a guide for those interested in adopting these technologies in their current practice and as a foundation for future progress in the field. The field will continue to evolve and grow as specific equipment and devices are developed and tested for these applications. Furthermore, widespread implementation of interventional EUS is likely to require support from GI societies and buy-in from other key stakeholders including payors. Continued work by the GI societies and manufacturers in providing training programs, and creating instruments, environments and policies that motivate endoscopists to adopt new practices is essential for growing the field of interventional EUS.

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Table 1: Technical Difficulties Associated with EUS Access, Drainage and Anastomosis

Biliary Rendezvous

- Appropriate positioning of the EUS scope in the duodenum so that the orientation of the needle puncture is caudally, towards the major papilla, rather than cranially, towards the hilum of the liver
- Difficulty in passage of the rendezvous wire across a stricture, the papilla or an anastomosis
- Removal of the EUS scope without losing wire access
- Advancement of the ERCP scope without dislodging the rendezvous wire and achieving biliary cannulation alongside the wire
- Retrieval of the end of the rendezvous wire either through the channel of the scope or by grasping it and removing the scope from the patient's mouth in order to have both ends of the wire outside the patient
- Subsequent advancement of a cannulation device over the wire and reinsertion of the scope into the patient without twisting (typically in the stomach) the two intraluminal portions of the wire while advancing the ERCP scope to the papilla
- Achieving successful biliary cannulation after reaching the papillary orifice

Transgastric Transhepatic Access

- Advancing the wire in the direction of the distal bile duct
- Access to the intrahepatic duct across the gastric wall and liver, risk of leakage and bleeding
- Deployment of stent

Choledochoduodenostomy/Gallbladder Drainage

- Orientation of the wire towards the hilum of the liver
- In LAMS, maintaining EUS visualization of the duct/gallbladder during advancement of LAMS i.e. not pushing the CBD/gallbladder wall away with the LAMS catheter
- Risk of leakage and perforation related to cautery if stent deployment is not successful

Pancreatic Rendezvous/Pancreatico-gastrostomy

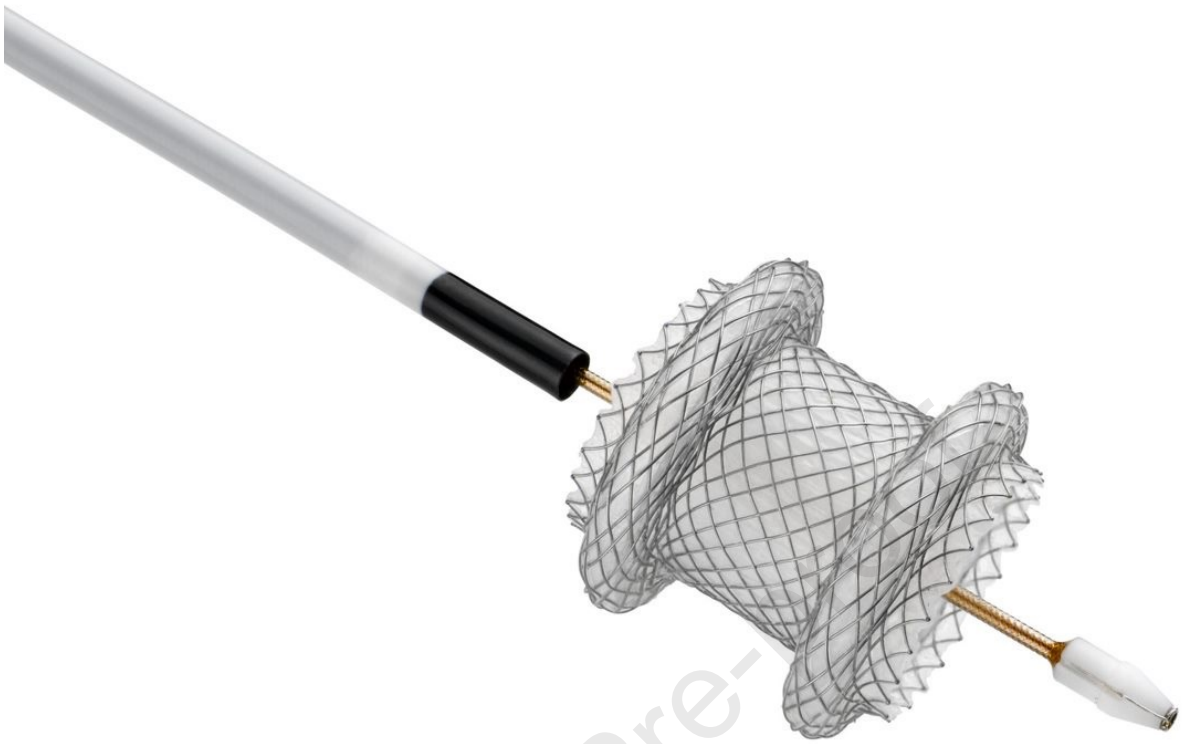
- Pancreatic duct access across the gastric wall in an often diseased or fibrotic pancreas in the setting of chronic pancreatitis
- Small size of the pancreatic duct making needle access and wire placement inside the duct difficult
- Unstable EUS scope position while exchanging the needle for other devices
- Difficulty in advancing devices across the gastric wall and pancreatic parenchyma after wire access
- Difficulty in stent deployment and a lack of dedicated stents that can be placed reliably.

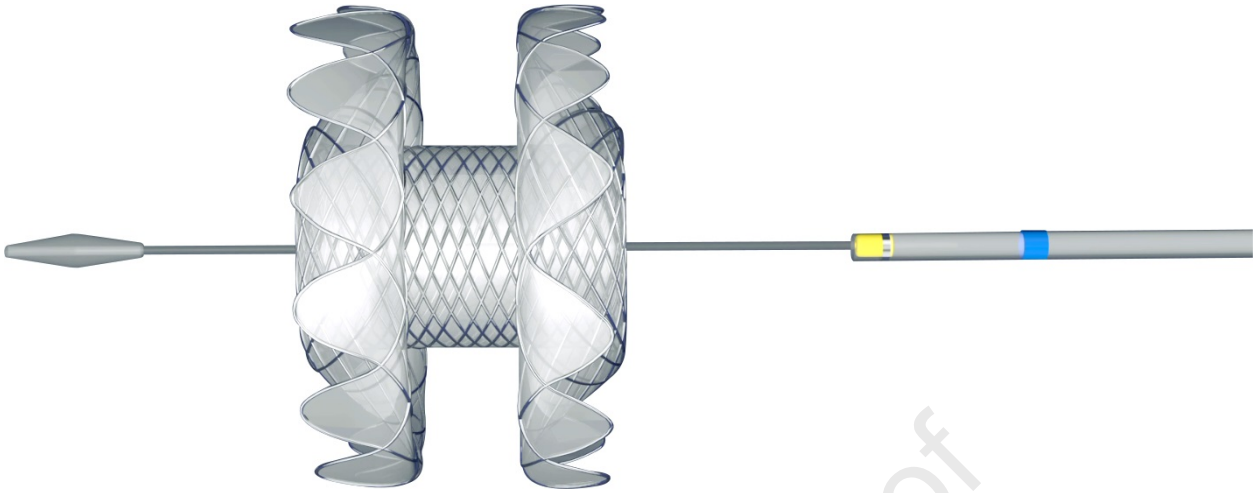
Enteric Anastomosis

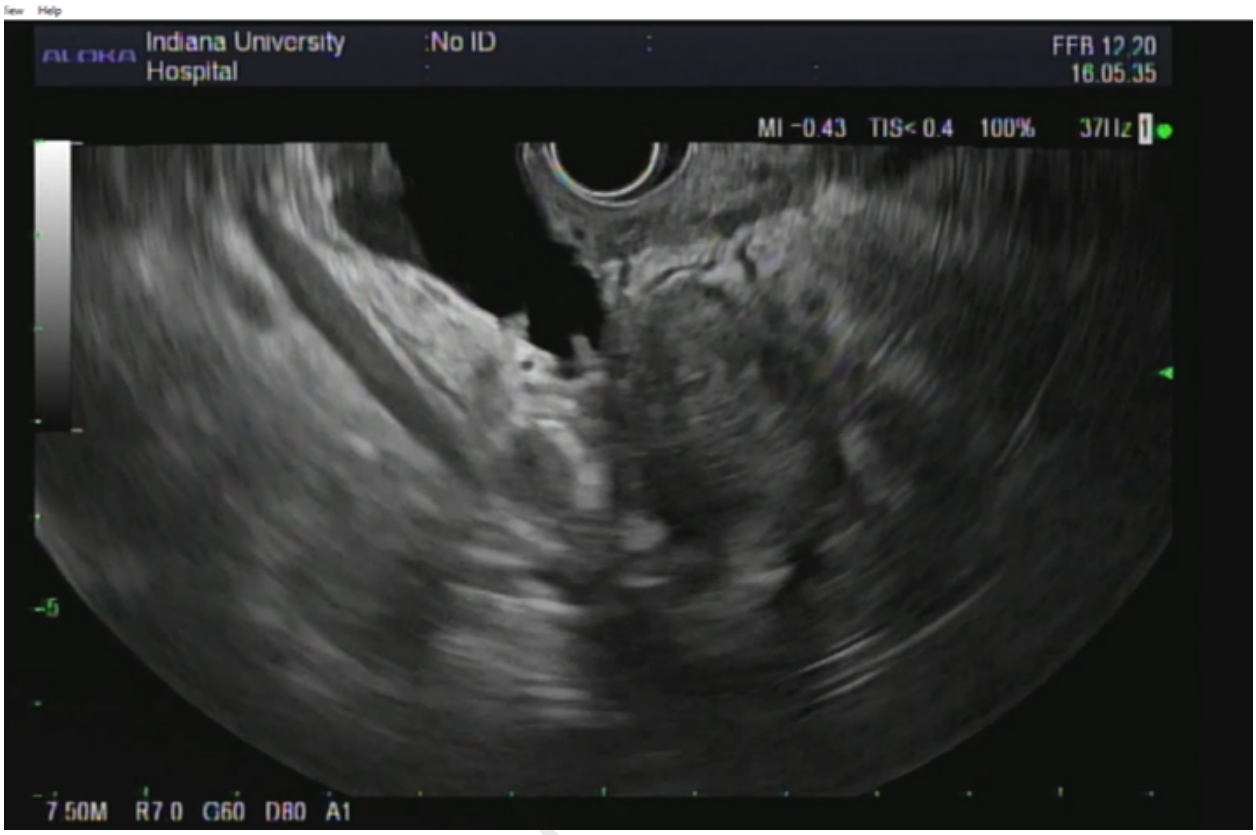
- Distension of the distal bowel lumen prior to anastomosis
- LAMS advancement across the two luminal walls without losing endosonographic visualization of the distal loop of bowel by pushing it away during LAMS advancement
- Misdeployment of LAMS in the peritoneum if the distal bowel lumen is inadvertently pushed away or due inadvertently under the impression that the stent is in the distal bowel lumen
- Familiarity with approaches to salvage stent misdeployment e.g. deployment of LAMS through misdeployed stent
- Management of pneumoperitoneum in case of misdeployment

Table 2: Summary of needed research and innovation to advance the field of interventional EUS.

Topic	Research and Innovation Needed
EUS endoscopes	• Improved maneuverability • Larger channels for therapeutic devices • Improved imaging capabilities • Image fusion of EUS with cross-sectional imaging
EUS-guided access	• Specialized wires for biliary drainage • Target specific stents • Devices for EUS-guided pancreatic duct access and therapy • Stents specific for choledochoduodenostomy • Devices to stabilize the small bowel for enteral access (e.g., gastrojejunostomy) • Devices to facilitate necrosectomy
EUS-guided tumor ablation	• 22-gauge 'all-in-one' ablation devices to increase access to difficult to reach areas of the pancreas • EUS elastography and contrast enhanced EUS to monitor results of ablation • Chemotherapy agents for injection of pancreatic cysts • Ablation catheters that fit through 19- and 22-gauge FNA needles • Dose ranging studies for safety of ablation • Randomized trial of pancreatic cyst ablation vs. surgery • Additional agents for EUS-guided injection therapy
EUS-guided liver applications	• Improvements in shear wave elastography • Improved needles for EUS-guided liver biopsy
Interventional EUS	• CPT codes and appropriate reimbursement for EUS-guided interventions • Additional prospective studies evaluating the safety and efficacy of interventional EUS procedures • Training needs and requirements for Interventional EUS procedures



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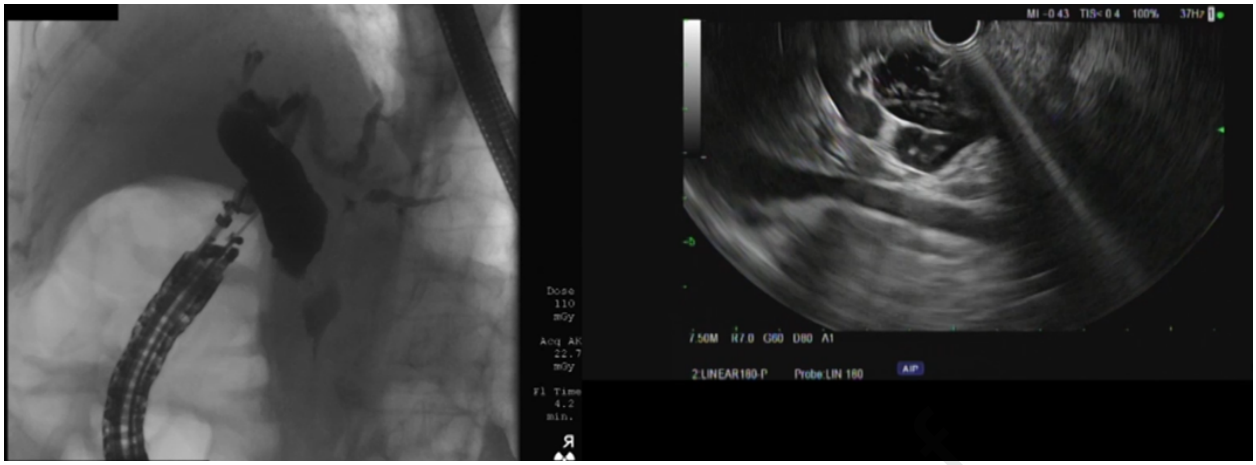

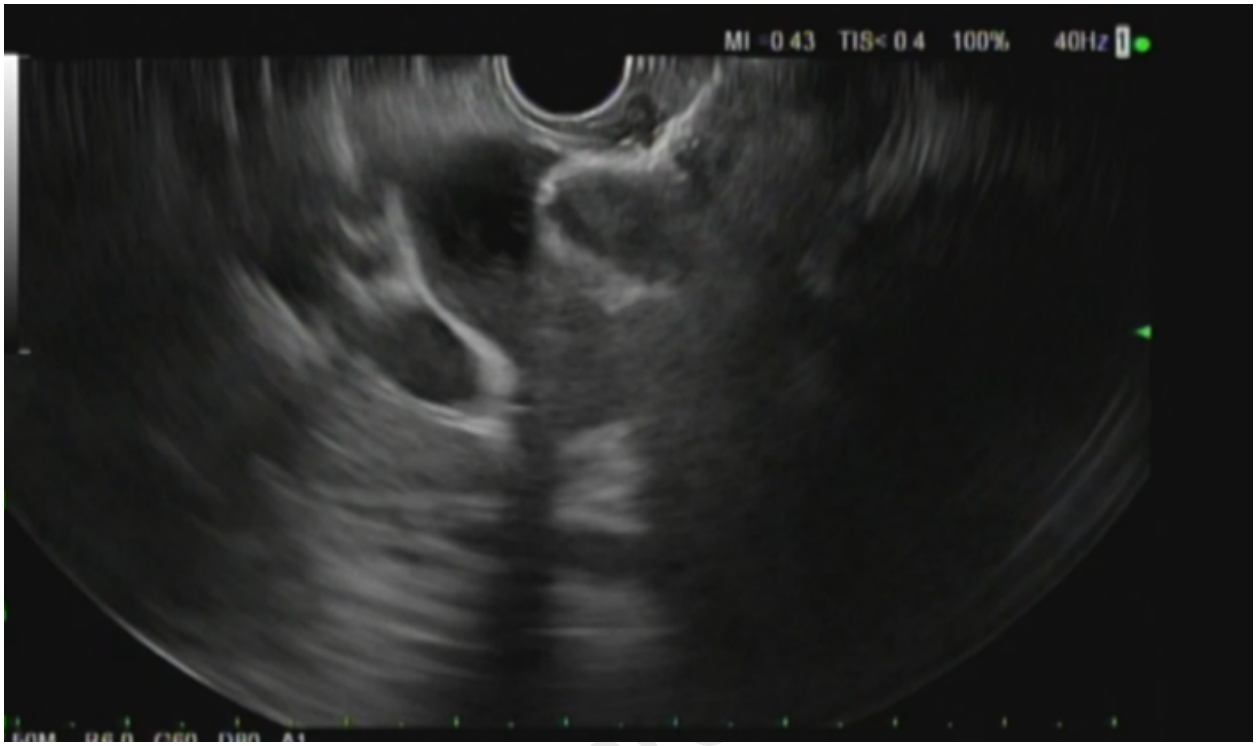

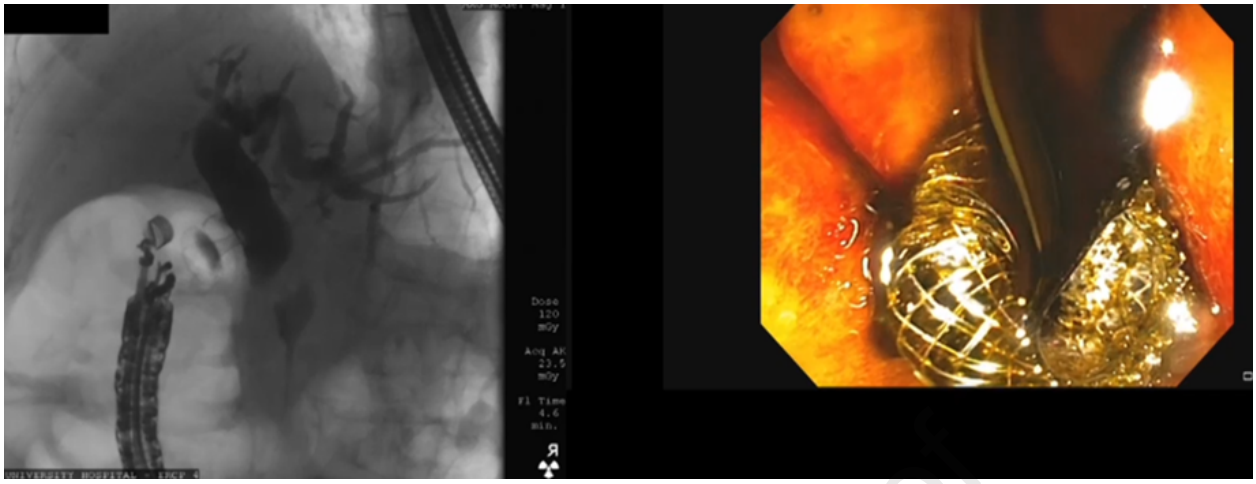

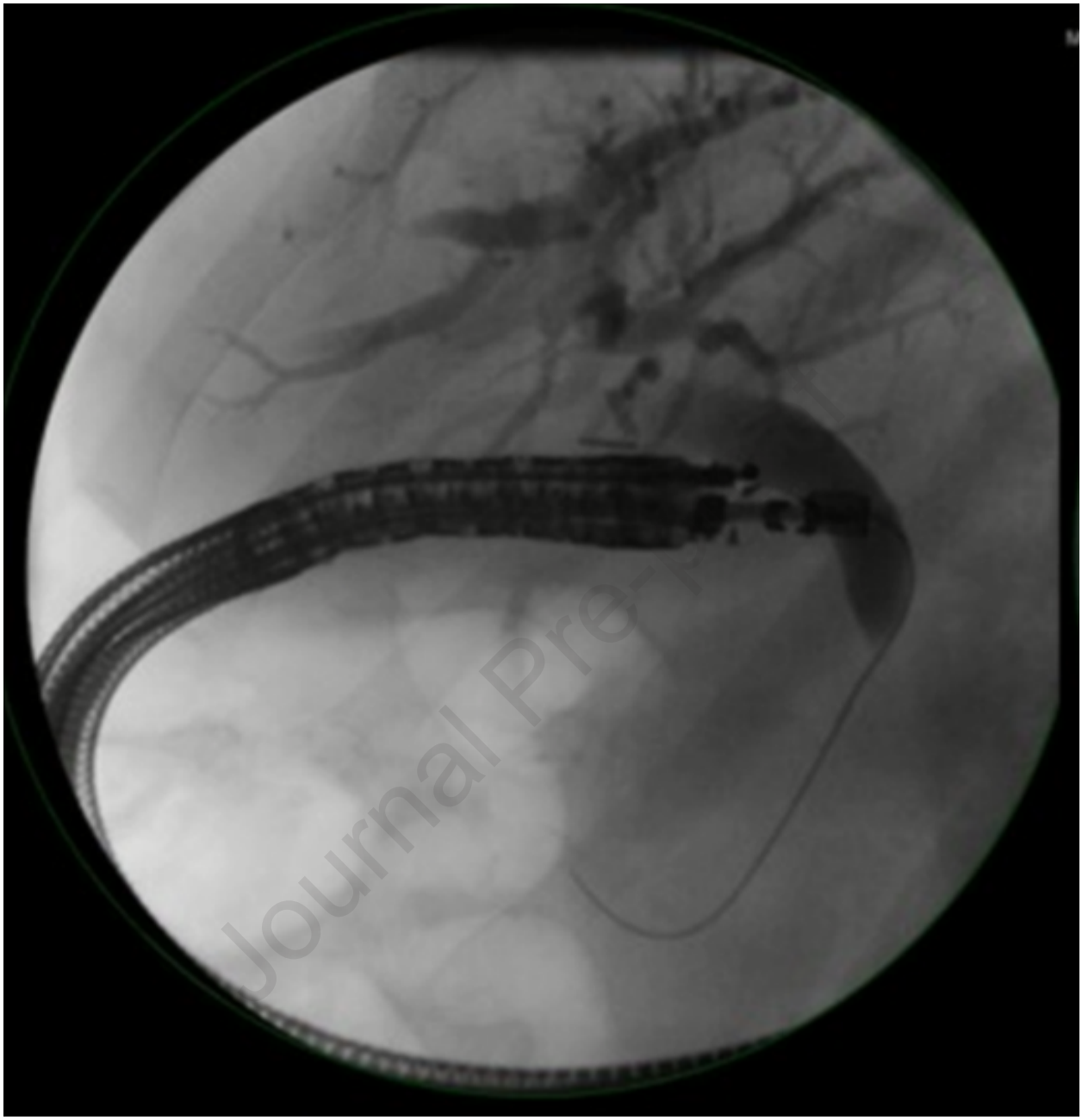

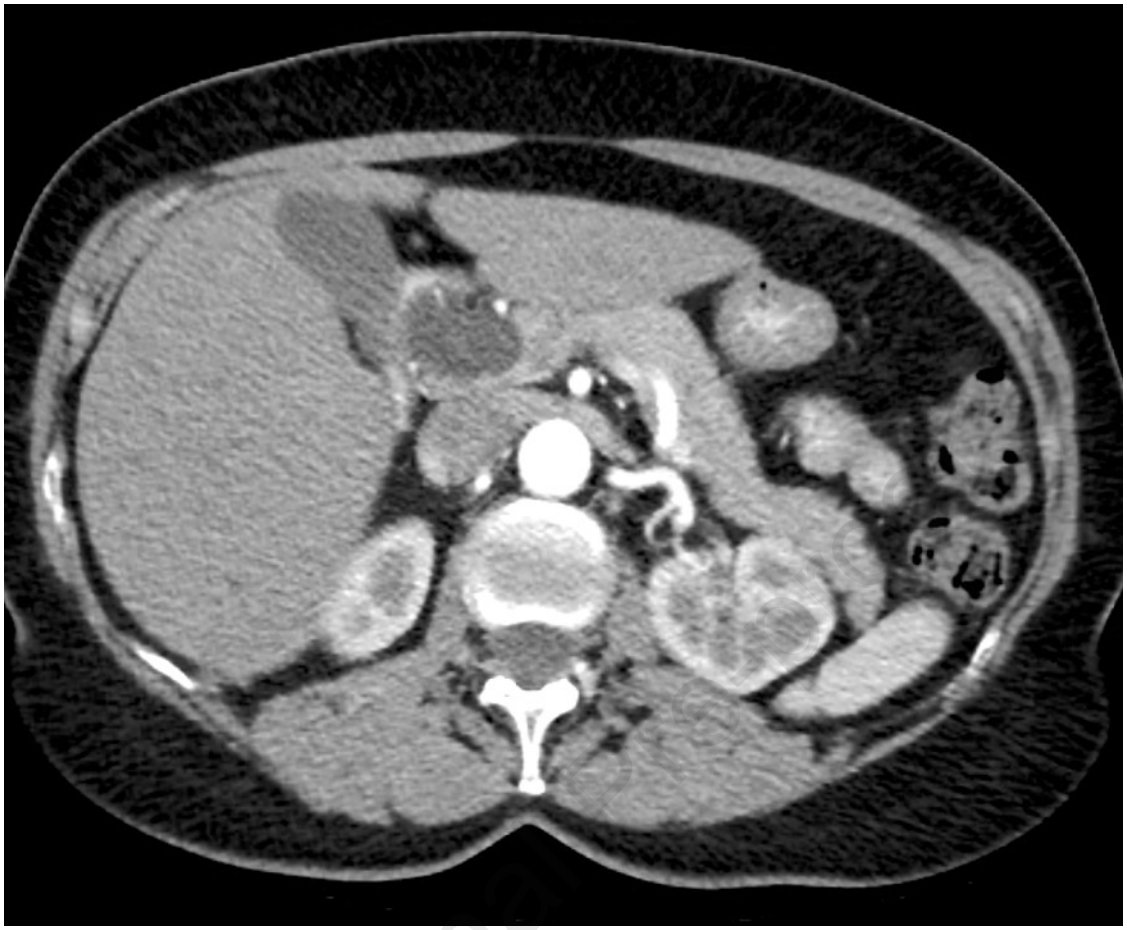

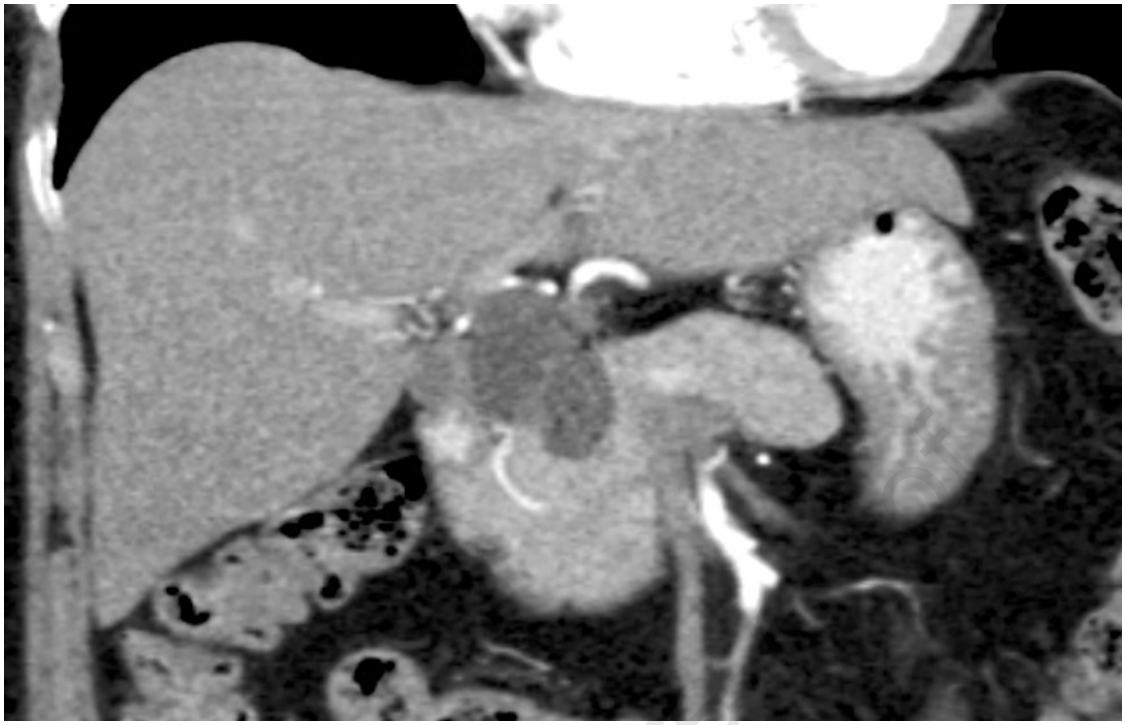

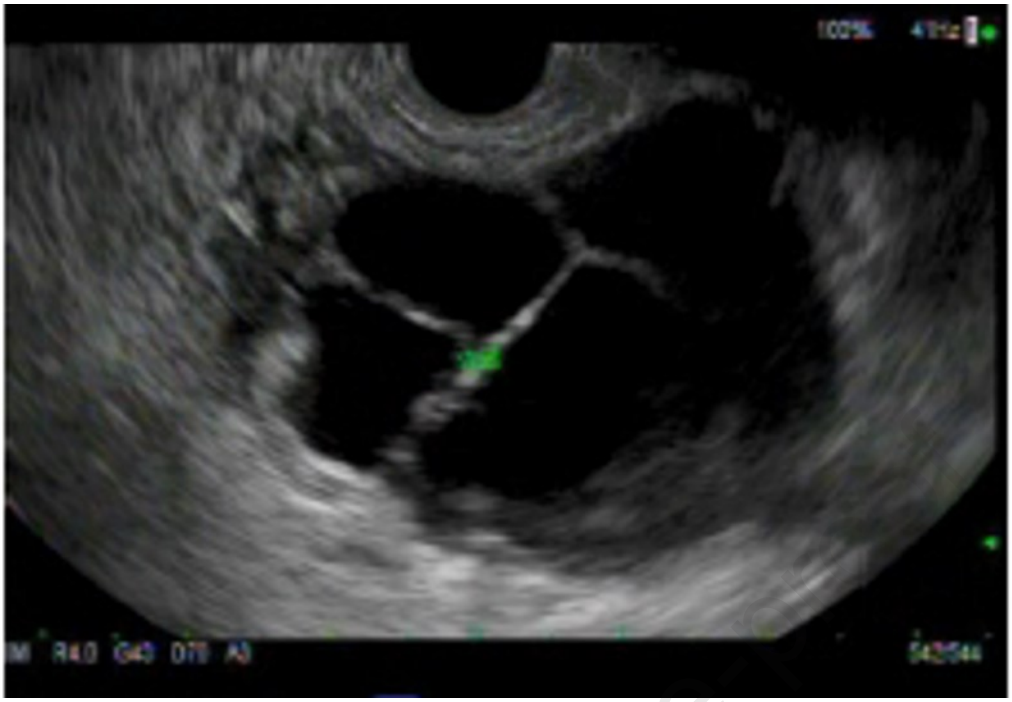

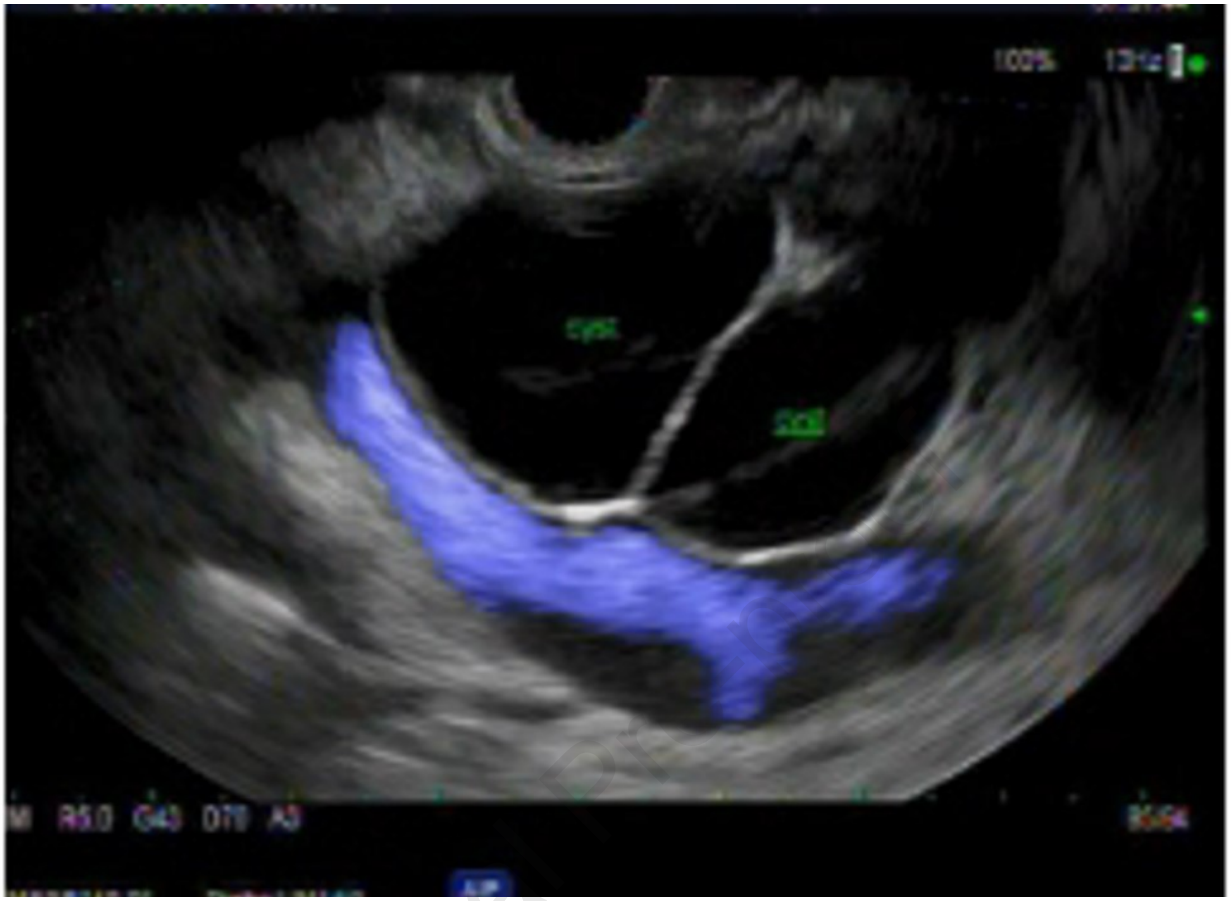

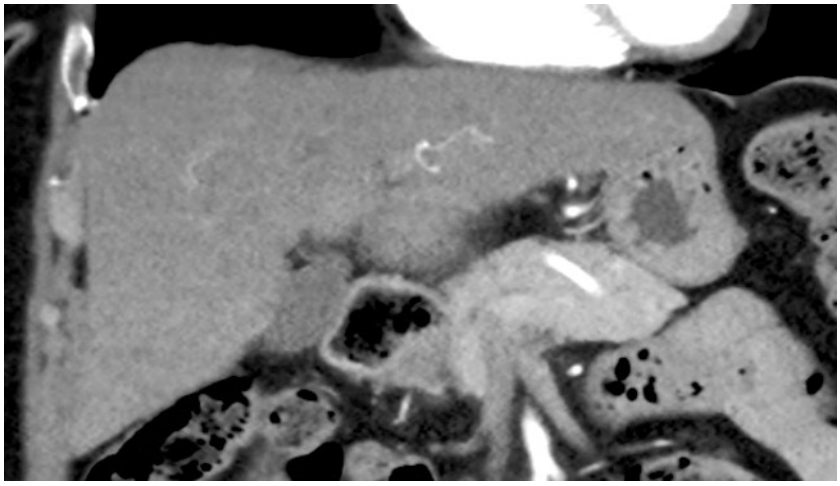

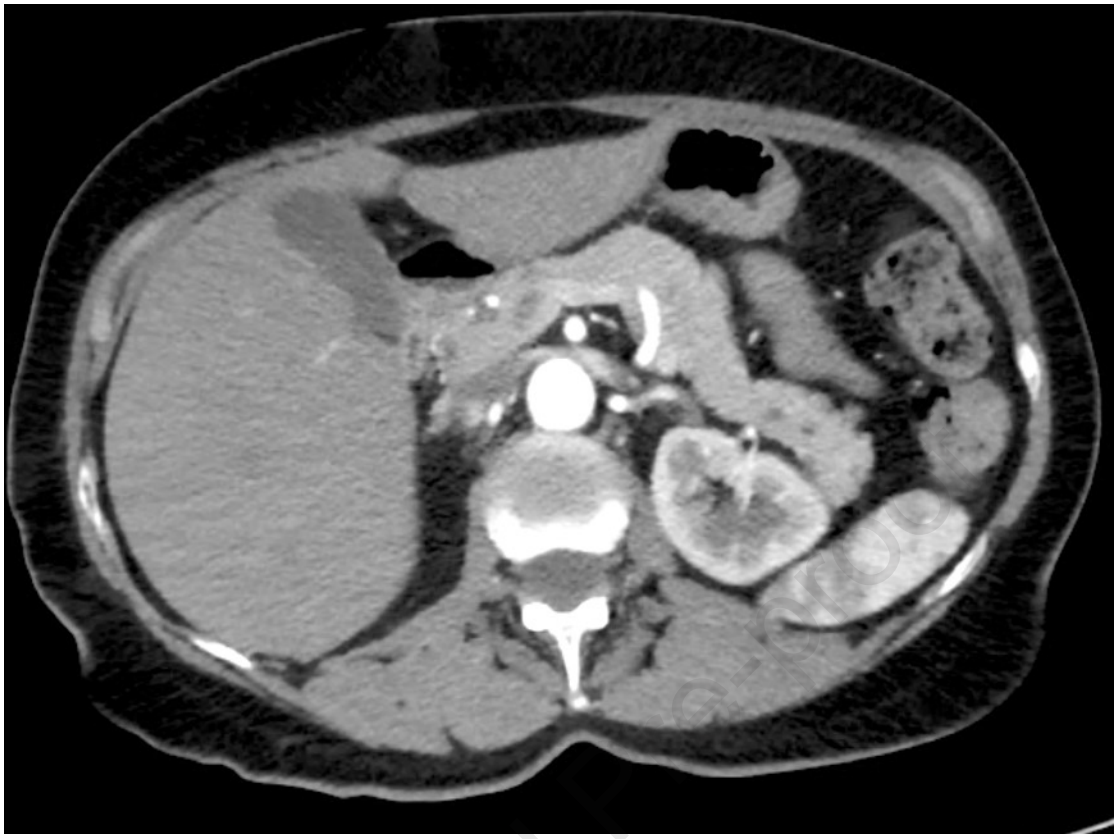

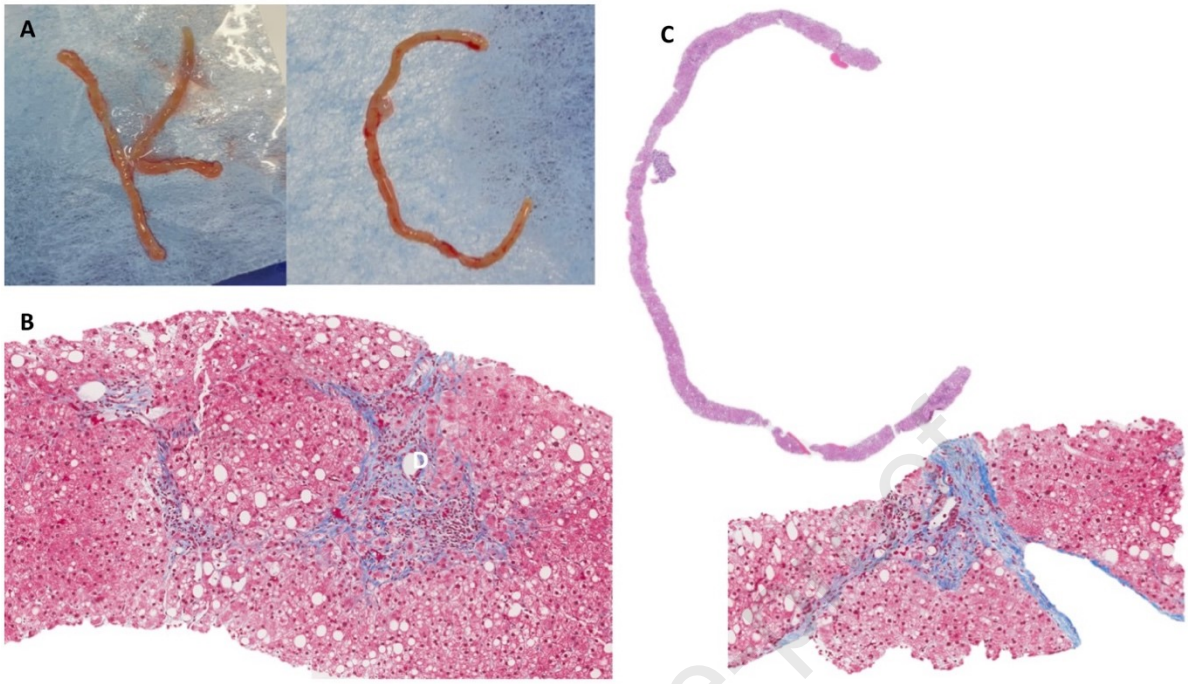

One-stop shop:

Endoscopic liver evaluation