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REVIEW

Interventional EUS for the Diagnosis and Treatment of Locally Advanced Pancreatic Cancer

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Summary

Endoscopic ultrasound (EUS) evolved as the diagnostic test of choice evaluating suspected pancreatic tumors. Coupled with fine needle aspiration (FNA), EUS provides high accuracy for the diagnosis and staging of pancreatic cancer. Novel EUS based techniques have emerged as a safe minimally invasive alternative to the surgical or radiological approaches. By allowing better pain control, delivering antitumor therapies or draining obstructed bile ducts, such techniques hold a big promise to improve the quality of life of patients with unresectable pancreatic cancer. In this review, we will discuss the role EUS-FNA plays in the diagnosis, staging and treatment of patients with locally advanced pancreatic cancer.

Introduction

For the last decade, endoscopic ultrasound (EUS) has been considered the procedure of choice for the diagnosis and staging of pancreatic cancer. Fine needle aspiration (FNA) is a minimally invasive sampling technique that has proved to be a safe and accurate method of tissue acquisition [1, 2]. EUS-FNA has positively influenced the diagnosis and staging of pancreatic cancer, and opened the door for numerous minimally invasive interventions to help in patient management. This review will shed some light on the role of EUS-FNA in the diagnosis and staging of pancreatic cancer. We will also review a number of EUS-guided therapeutic applications including celiac plexus neurolysis, fiducial placement to guide radiation therapy, brachtherapy, delivery of anti-tumor agents and transmural access to the biliary system.

Role of EUS-FNA in Detecting Pancreatic Cancer

EUS is the most sensitive nonoperative imaging test for the detection of benign or malignant pancreatic lesions (Video 1). When summarizing the results of 23 studies including 1,096 patients over a 21-year period, the sensitivity of EUS for detection of a pancreatic mass was in the range of 85-100% [3, 4, 5, 6]. Staging of pancreatic malignancy is done according to the American Joint Committee for Cancer (AJCC) Staging TNM classification, which describes the tumor extension (T), lymph node (N) and distant metastases (M) of tumors, respectively. Reported accuracies of T staging by EUS range from 63% to 94% and nodal (N) staging ranges from 41% to 86% [4, 7, 8, 9], which is clearly superior to computed tomography and transabdominal ultrasound [8, 9, 10]. At the same time, EUS-FNA provides tissue diagnosis particularly in

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Abbreviations CPN: celiac plexus neurolysis

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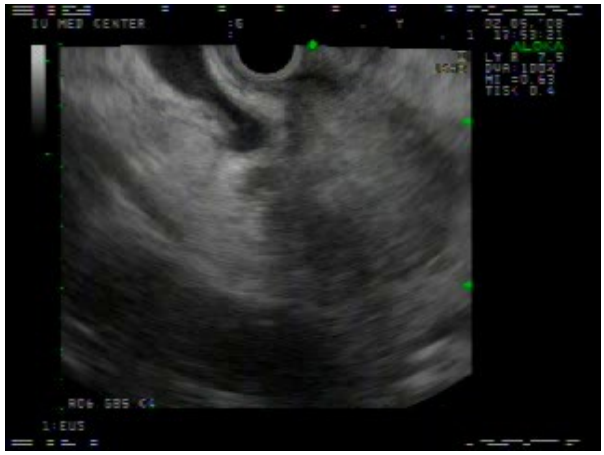


Video 1. EUS interrogation of a pancreatic head mass with portal venous encasement in a patient presenting with painless jaundice. FNA confirmed adenocarcinoma.

patients deemed unresectable and unsuitable for surgery with high accuracy. We recently reported on our cumulative data on 547 patients who underwent EUS-FNA. The operating characteristics of EUS-FNA of solid pancreatic masses were: sensitivity 95%, specificity 92%, positive predictive value 98%, and negative predictive value 80%. The overall accuracy of EUS-FNA was 94.1% [11].

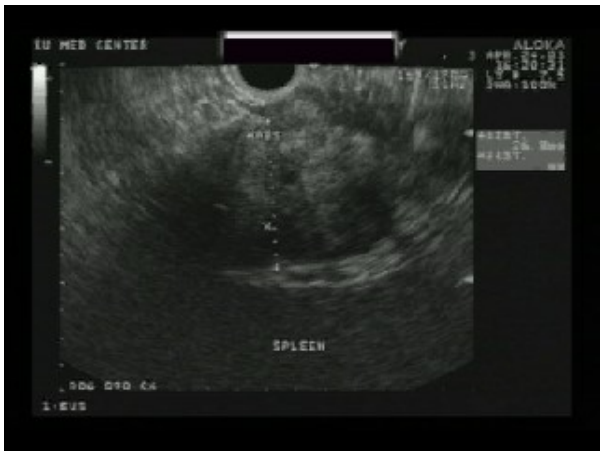
This makes EUS-FNA one of the first choice options for tissue acquisition in patients with unresectable pancreatic cancer throughout major centers. In patients with resectable tumors, the role of FNA is less clear but this remains widely practiced. At our and most large referral institutions, EUS-FNA completely replaced percutaneous approaches for this indication. It is still debatable whether preoperative tissue diagnosis is needed in patients with resectable disease, although this remains widely practiced at our centers. We and others reported that EUS-FNA carries an acceptable rate of complications, mostly pancreatitis when sampling solid pancreatic lesions. The risk of pancreatitis varies between 0.5% and 2% [2, 12].

During EUS, evaluating for metastatic disease should be undertaken due to the significant impact this has on the patients' management. Evaluating a portion of the liver is possible at the time of EUS and EUS-FNA of any suspected metastatic liver lesions should be attempted. Occasionally, EUS-FNA of liver lesions is the easiest way of providing tissue diagnosis particularly in patients with metastatic pancreatic malignancy and when the primary mass is not accessible. We also recommend biopsying celiac lymph nodes suspicious for metastasis as well as ascites; the latter possibly indicating peritoneal metastasis.

FNA Technique and Devices for Tissue Sampling

EUS-FNA is performed using the linear array echoendoscope under conscious sedation and appropriate cardiovascular and respiratory monitoring. The ultrasound transducer on the distal tip of the echoendoscope permits needle advancement into the lesion under real-time guidance. Once the mass is identified, EUS-FNA is performed with a curvilinear echoendoscope. It is recommended that Doppler is used to examine the projected path of the needle to avoid puncturing intervening blood vessels, while trying to minimize the amount of normal pancreatic tissue that has to be traversed. A variety of commercially available FNA needles is available and range in size between 19 and 25 gauge. The most widely used are 22 gauge needles, although a recent report indicated a similar tissue sampling adequacy using 25 gauge needles [13]. It is recommended that Doppler is used to examine the projected path of the needle to avoid puncturing intervening blood vessels, while trying to minimize the amount of normal pancreatic tissue that has to be traversed. Once the gut wall is punctured and the needle enters the pancreas, the stylet is withdrawn. The question of whether or not to apply suction during FNA remains controversial but should be tailored to specimen's volume and presence of blood. The needle is then moved back and forth for 10 cycles or until deemed adequate by the endosonographer (Video 2). The needle is then withdrawn back into the sheath and assembly is removed. The material retrieved from aspiration is then expressed on two glass slide sets; one set of slides is air-dried for immediate staining and on-site review while the other slide set is alcohol-fixed for later comprehensive pathologic exam. In most referral institutions, rapid onsite evaluation of specimens is available and has been shown to improve the diagnostic yield [14]. Our group has previously shown that there is excellent correlation between on site interpretation and final reports. We also believe that this practice decreases the work load of the practicing endosonographer by decreasing the amount of unsatisfactory specimen [15]. This practice also allows for immediate feedback to the patients and their families and the referring physicians and reduces the workload of the endoscopist. Obtaining additional passes for cell block is recommended when a metastatic lesion to the pancreas is suspected. Cell block is fixed in formalin and embedded in paraffin. Hematoxylin-eosin (H&E) stains and possible immunocytochemistry on the cell block may aid in the diagnosis of the suspected metastatic lesion [16].

When EUS-FNA with or without immunocytochemistry is non-diagnostic then histology on core biopsy may be required to confirm a suspected diagnosis. The Trucut biopsy device (Quick-Core®, Wilson Cook Inc., Winston-Salem, NC, USA) is a 19 gauge needle equipped with a springloaded cutting sheath and a tissue tray to capture the larger specimen appropriate for histopathological evaluation [17, 18]. The initial human experience with Trucut biopsy *versus* FNA showed superior diagnostic accuracy for submucosal lesions, lymphoma, and autoimmune pancreatitis [19]. The same studies suggested that the use of Trucut biopsy in solid lesions of the pancreas may provide a diagnosis in fewer passes. In general, we recommend using the 19 gauge Trucut needle to obtain



Video 2. FNA of a 3 cm pancreatic tail mass presenting with abdominal pain and weight loss in a 66-year-old male.

a core tissue as a rescue method when FNA results are inconclusive or when an alternative diagnosis (such as lymphoma and autoimmune pancreatitis) is suspected.

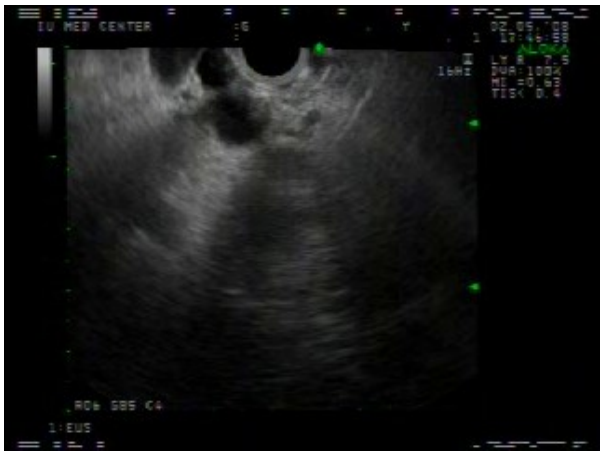
EUS Based Therapeutic Applications in Pancreas Cancer

Celiac Plexus Neurolysis (CPN)

The ability to identify the celiac axis bifurcation at the time of EUS is crucial to deliver palliative pain management in patients with locally advanced and unresectable pancreatic cancer. Celiac plexus neurolysis (CPN) is a chemical splanchnicectomy of the celiac plexus, which ablates the afferent nerve fibers that transmit pain from intra-abdominal viscera. EUS-CPN performed for the palliation of pancreatic cancer pain appears to be as safe and effective as CPN performed by other routes such as CT guided and surgical approaches [20]. An added advantage of the EUS approach is that it can be performed during staging and biopsy of the tumor.

EUS guidance offers the most direct access to the celiac plexus of all the CPN techniques short of surgical intervention. The celiac ganglia are located at the origin of the celiac artery, which is easily identified at endosonography**.** The relative proximity of the celiac ganglia to the posterior gastric wall ensures an accurate passage of the injecting needle into the ganglia, thereby minimizing the risk of complications and potentially increasing the effectiveness of the block.

Technically, we identify the take off of the celiac artery from the aortic trunk, and 19 or 22 gauge FNA needles can be used to inject 20 mL (0.25%) of bupivacaine and 10 mL of 98% ethanol (Video 3). Alternatively, a recently developed fenestrated 20 gauge CPN needle has been released that makes injection at the time of CPN much smoother and easier to administer a solution. In a pilot study, pain relief lasting for a median of 10 weeks was achieved in 88% of 25 patients undergoing EUS-CPN [21]. Similar results were observed in a later prospective study involving 58 patients; pain scores were significantly lower than baseline in 78% of patients two weeks after the procedure and were sustained for 24 weeks. On multivariate analysis, the benefit of EUS-CPN was independent of morphine use, chemotherapy, and radiation [22]. The neurolysis can be delivered on either one or both sides of the aorta, although a recent study demonstrated the superiority of the bilateral injection compared to the central single injection approach (mean pain score reduction of 70% *vs*. 46%; P=0.0016) [23].



Video 3. Intra-ganglion celiac plexus neurolysis in a patient with intractable pain from a locally advanced unresectable pancreatic head cancer. The video shows the initial part of the neurolysis while injecting bupivicaine.

Celiac plexus ganglia are relatively easy to visualize during EUS procedure [24]. Direct injection in the ganglia has been shown to be highly effective in one study of 33 patients with pancreatic cancer and chronic pancreatitis [25]. Pain relief was reported by 94% of the 17 cancer patients undergoing direct ganglia injection in this study.

EUS-Guided Fiducial Placement to Guide Radiation Therapy

The success of radiation therapy in advanced pancreatic cancer depends on the accurate localization of the tumor. Placement of fiducials into the tumor bed allows easy identification of the target lesion during radiation treatment. Therapy can be delivered and modulated in a much focused manner even during respiratory movements. Although percutaneous placement of fiducials may be possible under CT guidance [26], the procedure is technically cumbersome, demanding and carries the risk of tumor seeding.

EUS is ideally suited for placement of fiducial markers in pancreatic tumors. EUS provides high quality views of the different parts of the pancreas with exceedingly accurate localization of the tumor [27]. Moreover, access to the pancreas for tissue sampling has been shown to be very safe [2]. After identification of the tumor using the linear-array echoendoscope, and after excluding the presence of intervening vasculature, EUS-guided fiducial placement is undertaken. Nineteen gauge FNA needles are best suited for this task and are usually able to accommodate fiducials up to 3 mm in length and 0.8 mm in diameter. Fiducials are preloaded into the needle by retracting the stylet and manually back-loading the fiducials into the tip of the needle. The tip of the needle is then sealed with bone wax to prevent accidental dislodgement of the fiducials. After identifying a target lesion, the tumor is punctured and the needle is appropriately positioned within the tumor. The fiducials are deployed into the tumor by simply advancing the stylet forward. To achieve best results, 4-6 fiducials should be deployed evenly around the periphery and the center of the tumor under real time EUS, and ideally, under fluoroscopic visualization as well (Figure 1).

The efficacy of such approach has been recently demonstrated in few studies. Pashvaian *et al.* demonstrated technical success in placing fiducial markers under EUS guidance in 11 out of 13 patients

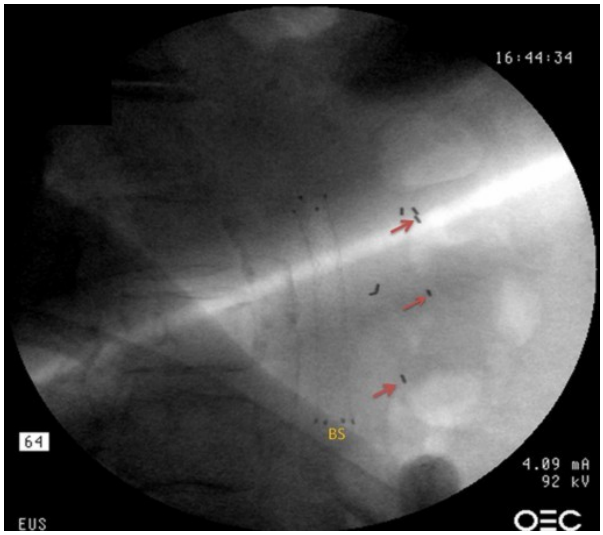


Figure 1. EUS-guided fiducial placement in a patient with locally advanced pancreatic cancer. Several fiducials were successfully placed in the center and periphery of the tumor. A biliary stent (BS) is also seen on this fluoroscopic image.

with pancreatic tumors among other mediastinal or intra-abdominal malignancies scheduled for radiation therapy. Technical failures resulted from the inability to advance the echoendoscope into the duodenum in a patient with gastric outlet obstruction and from the presence of an intervening vasculature in another. The use of the 5 mm fiducials was associated with deployment difficulty, thus the authors recommended maintaining a straight scope and using the 3 mm fiducials instead. There were no major complications related to the placement of fiducials, however, the effect of fiducial placement on radiation therapy success was not assessed.

Another study evaluated fiducial placement in 34 patients with pancreatic cancer prior to their planning CT scan [28]. EUS-guided fiducial placement was successful in 31 cases (91%) including tumors in the head and uncinate process. There were 3 technical failures related to needle stylet malfunction, loss of fiducials during deployment and a fibrotic tumor precluding puncture. All 31 patients in whom fiducials were placed underwent successful planning sessions for radiation therapy. No immediate or late complications were encountered in any patient.

From those two studies there appear to be no major limitations for the EUS-based approach. It can sometimes be technically challenging to deploy a fiducial within a pancreatic head tumor from the duodenum due to the angulation of the echoendoscope. Nevertheless, the majority of cases involving placing fiducials in head tumors were successful. Straightening the tip of the echoendoscope, use of fluoroscopic guidance and using smaller fiducials can improve the technical success rates. Until the procedure becomes standardized and definite benefit from radiation therapy is demonstrated, such intervention should be performed under closely monitored research protocols. Currently, the availability of EUS and stereotactic radiosurgery remains limited and confined to major referral centers.

EUS-Guided Brachytherapy

Brachytherapy can help control locally advanced pancreatic tumors by delivering high dose radiation therapy from within the gland and with minimal toxicity to adjacent organs. A few reports demonstrated that EUS-guided brachytherapy could be a safe alternative to surgical placement or other percutaneous approaches. The technical placement of the radioactive seeds is similar to the approach described above for fiducial placement using 19 gauge needles, although the number and location of the seeds is calculated based on tumor volume evident on pre-EUS imaging. To date, two small trials evaluated EUS-guided implantation of radioactive iodine seeds (^{125}I) in patients with locally advanced pancreatic cancer [29, 30]. In the first study, 15 patients underwent such treatment and reported ‘‘partial’’ response in 27% of patients, ‘‘minimal’’ in 20% of patients, and indicative of ‘‘stable disease’’ in 33% of patients [29]. Pain reduction was reported in about one third of the patients. The overall median survival period was 10.6 months. Procedure-related pancreatitis or pseudocyst formation was encountered in 3 patients and bone marrow toxicity in 3 patients. In the second study of 22 patients, all the patients received gemcitabine-based 5-fluorouracil chemotherapy one week after undergoing EUS-guided brachytherapy [30]. Partial remission was achieved in 14% of patients, and the disease remained stable in 46% of patients. Although pain scores dropped significantly after brachytherapy, it increased again one month later. No complications were reported in any patient. Despite the initial improvement in pain, no patient survived the 2-year follow-up period. Liquid-based brachytherapy implants offers the potential of easy deployment and allows more even distribution of the treatment within the tumor. The feasibility of such approach was described in a recent study showing diffusion in up to 55% of the tumor mass on EUS cross-sectional area [31].

The limited data available so far is encouraging for brachytherapy as a potential treatment for locally advanced pancreatic cancer. Although it appears to be feasible, safe and may improve pain control temporarily; it has failed to demonstrate a survival benefit. Larger studies assessing patient safety studies as well as safety of handling and storing radioactive material in the GI endoscopy suites are needed.

EUS-Guided Delivery of Anti-Tumor Agents

The ability to approach pancreatic and GI malignancies through the GI tract alerted the EUS investigators working closely with oncologists to the abilities of EUS-guided injection of anti-cancerous agents. Two initial trials that showed proof of principal were carried out [32, 33]. The first trial used allogenic mixed lymphocyte culture (Cytoimplant) in pancreatic cancer under EUS guidance [32]. In a phase I clinical trial, 8

patients with unresectable pancreatic cancer underwent EUS-Guided FNI of Cytoimplant. The median survival of the patients was 13.2 months with two partial responders and one minor response. This study showed that local immunotherapy is feasible and safe. Another study suggested that the injection of anti-tumor viral therapy (ONYX-015) is feasible [33]. This is a gene-deleted replication-selective adenovirus that preferentially replicates in and kills malignant cells. Twenty-one patients with locally advanced cancer of the pancreas underwent eight sessions of ONYX-015 injection under EUS-guidance into the pancreatic tumor over 8 weeks. The results were not very encouraging and 4 patients experienced major complications including sepsis and perforations [33].

Another exciting recent development is the application of a novel gene transfer therapy under EUS-guidance. TNFerade® (GenVec Inc., Gaithersburg, MD, USA) is a replication-deficient adenovirus acting as a vector by containing the human tumor necrosis factor alpha gene. Once exposed to radiation, this gene is up regulated by the radiation-inducible promoter Egr-1. The combination of TNFerade® with 5 fluorouracil, a radiosensitizer itself, results in significant tumor toxicity. In a study by Chang *et al*., the long-term results from a cohort of 50 patients undergoing EUS- or CT-guided injection showed that potential toxicities related to TNFerade® were mild and well tolerated [34]. TNFerade® was combined with continuous i.v. 5 fluorouracil (200 mg/m^2/day, for 5 days/week) and radiation (50.4 Gy). In a dose escalating trial, the higher-dose group was associated with greater locoregional control of treated tumors, longer progression-free survival compared with two lower dose cohorts. In this same group, up to 45% of patients underwent surgical resection (with the majority achieving negative resection margins) and demonstrated improved median survival. Currently, there is an ongoing multicenter, randomized, controlled clinical trial that uses TNFerade® gene delivery combined with chemoradiation in patients with locally advanced pancreatic cancer. The TNFerade® is being investigated in other locally advanced tumors like esophageal cancer but the benefit in metastatic disease and its long-term efficacy remains unclear.

Gene transfer concept was recently attempted using a different vector. Oncolytic herpes simplex virus that carries the granulocyte macrophage colony-stimulating factor (GM-CSF) gene (Onco VEXGMCSF) has been tried in pancreatic cancer [35]. Such oncolytic viruses have been engineered to become highly tumor specific. They were reported to directly increase the immunosusceptibility of the tumor cells while making them increasingly susceptible to chemotherapy. The therapeutic efficacy of this agent in pancreatic cancer remains unknown.

Finally, the potential of direct cytotoxic effects using adenovirus has been recently presented in abstract form by Zhu *et al*. [36]. Repeated EUS-guided injections with adenovirus H101 were performed in 5 patients with locally advanced pancreatic cancer over the course of two months, combined with gemcitabine (1,000 mg/kg). At the end of the two months, 4 were found to have clinically and radiologically stable disease and only one progressed. Like the other antitumor agents though, its impact on survival is unclear.

EUS-Guided Bile Duct Drainage

Endoscopic retrograde cholangiopancreatography (ERCP) is the procedure of choice for bile duct stenting in obstructive jaundice resulting from advanced pancreatic cancer. Although this is successful in 90% of the times, biliary drainage cannot be achieved via ERCP in certain cases, usually in association with difficult anatomy from prior surgical interventions or due to locally advanced pancreatic, ampullary or biliary tumors obstructing the duodenum. Traditionally, such patients underwent percutaneous transhepatic cholangiography; however, this method carries a high complication rate and could be associated with fistula formation and recurrent cholangitis [37]. Since the initial report published in 2001 [38], an increasing number of case series have described successful EUS assisted bile duct drainage.

Two main approaches currently exist to access the bile duct: either from the stomach (draining the left biliary ductal system) or the duodenum (draining the extrahepatic common bile duct). A needle-knife catheter or a 19 gauge FNA needle can be used to achieve the initial puncture. After the bile is aspirated, contrast is injected to obtain a cholangiogram. Once confirmed to be in the bile duct (or its main left branches if accessed from the stomach), a 0.035 inch guidewire is inserted into the bile duct via the FNA needle or catheter. At that point, every effort should be made to advance the guidewire across the stricture into the duodenum to allow trans-papillary stenting using the standard ERCP based approach. This EUS-guided "rendez-vous" technique appears to be the safer than placing a trans-mural biliary stent. If this is not possible, then the new tract is dilated using a biliary catheter for or a papillary balloon dilator. This is followed by placement of biliary plastic stents (up to 10 F in size) or self expandable metallic stents.

Up to date, choledochoduodenostomy has been described in 24 patients in 10 case series [38, 39, 40, 41, 42, 43, 44, 45, 46, 47]. The overall technical and clinical success rates approach 100% in all series with the exception of one series of two patients [40]. Among the 24 patients, 2 developed bile peritonitis and 3 developed pneumoperitoneum. On the other hand, the transgastric approach (hepaticojejunostomy) has been demonstrated in six studies totaling 20 patients [40, 43, 48, 49, 50, 51]. The technical success rate was 100% in five studies (9 patients) and 91% in one study (11 patients) [49]. The clinical success rate was 100% in 5 out of the 6 studies. Seven out of the 20 patients sustained different complications including stent occlusion, cholangitis, stent migration and a biloma.

The success of the "rendez-vous" technique has been well demonstrated in a series by Kahaleh *et al*., describing a total of 13 cases undergoing trans-gastric puncture of the left biliary system [43]. Advancement of the wire across the papilla into the duodenum in a "rendez-vous" fashion was successful in 11 of the 13 cases. The investigators suggested that, for trans-papillary "rendez-vous" procedures, the trans-gastric route is preferred because of the lower risk of bile leak. The above summary testifies that such approach is technically feasible although can be associated with complications. Such procedures remain technically demanding, and until the procedural technique is standardized and its clinical efficacy and safety profile is better established, it should only be performed at centers of expertise. New device development including the new forward viewing curvilinear forward-viewing echoendoscope could improve safety and spread the use of such techniques. Further large studies are needed to demonstrate its feasibility in the community settings outside referral centers.

Future Developments of Ablation Techniques

Similar to its use to ablate Barrett's esophagus, photodynamic therapy has been described in a few preclinical studies. Photosensitization agent was injected first followed by EUS-guided light delivery to pancreas via FNA needle. Localized necrosis was achieved in the pancreas and other organs in all animals [52, 53]. Finally, radiofrequency ablation has been described by Goldberg *et al*. on a porcine model and successfully induced coagulation necrosis of the pancreas [54]. One pig developed post-radiofrequency ablation pancreatitis. Judging the safety and efficacy of such ablation techniques is premature as no human studies have been performed to date.

Conflict of interest The authors have no potential conflicts of interest

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