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Review Article

Novel diagnostic and therapeutic modalities using endoscopic ultrasound in pancreatic disease

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A B S T R A C T

Endoscopic ultrasound is a rapidly evolving technology with an expanding list of diagnostic and therapeutic capabilities. Innovative uses of endoscopic ultrasound in pancreatic malignancy may serve to improve survivability with earlier detection and groundbreaking interventions. This article aims to review these novel techniques.

Keywords: Cholangiography biliary drainage; Elastography; Endomicroscopy; Fiducial placement

Introduction

Endoscopic ultrasound (EUS) has evolved exponentially over the last 30 years from a superior imaging modality of the pancreas and other abdominal organs to a technology that encompass a multitude of clinical applications within and beyond the gastrointestinal (GI) tract, revolutionizing the field of gastroenterology.[1,2] Its earlier diagnostic limitations have now heralded a new era of superb and near microscopic level of imaging, thus being able to distinguish malignant and nonmalignant pancreatic lesions.[3–6] The advent of accessories and needles used in conjunction with EUS has now allowed visualization of pancreatic lesions and moreover, endoscopic therapy, allowing minimally invasive alternatives to surgical interventions involving pancreatic lesions. In this article, we will review the wide array of current innovative techniques for EUS in the diagnosis and intervention of pancreatic diseases.

Adjunctive EUS Techniques to Improve Pancreatic Cancer Detection

Contrast-enhanced harmonic EUS

Of all the solid pancreatic lesions (SPL), unfortunately, pancreatic ductal adenocarcinoma remains the most common. Implicit is the need for prompt diagnosis given its predilection for rapid progression.[7,8] Intravenous contrast agents with ultrasonography were initially used in echocardiography and transabdominal ultrasonography as a noninvasive method to improve imaging.[7] Application of this modality has yielded superior ability of EUS to distinguish pancreatic pathology. Dietrich et al[8] demonstrated increased diagnostic accuracy in tumor characterization by using contrast-enhanced EUS (CEH-EUS) with color Doppler to compare vascularity patterns in solid pancreatic masses less than 40 mm.[7,8] Contrast-enhanced Doppler EUS, however, remains limited in use secondary to blooming artifacts and lower sensitivity in vessels with low blood flow.[7,9,10] To overcome these limitations, a new generation of intravenous contrast agents, such as SonoVue® and Echogen®, which use gas-containing micro bubbles encapsulated by albumin or a phospholipid that oscillate in response to sound pressure, have been developed.[7] Given the lengthier perfusion duration, CEH-EUS performs real-time vessel imaging of pancreatic lesions without Doppler-related artifacts.[10,11] Napoleon et al[12] performed a pilot study in 35 patients with SPL using SonoVue® with a novel Olympus echoendoscope able to detect extended harmonics (XGF-UCT 180; Olympus America, Melville, NY, USA).[12,13] Of the 18 fine-needle aspiration (FNA)-confirmed ductal adenocarcinomas, 16 resulted in a hypointense signal on CEH-EUS. Hypointensity alone on CEH-EUS had excellent operating characteristics of identifying pancreatic adenocarcinoma with a sensitivity, specificity, negative predictive value (NPV), positive predictive

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value (PPV), and diagnostic accuracy of 89%, 88%, 88%, 89%, and 88.5%, respectively, as compared to EUS-FNA with values of 72%, 100%, 77%, 100%, and 86%.[12,13] Several other studies have recapitulated these findings. Gong et al[14] performed a large meta-analysis which also showed lesion hypoenhancement using CEH-EUS as a reliable means of differentiating pancreatic adenocarcinoma with a pooled sensitivity of 93% and specificity of 93%.[14–16] Most notably, Fusaroli et al[17] showed that hyperenhancement essentially excludes pancreatic adenocarcinoma with a specificity of 98%. CEH-EUS has also proven to be complementary to EUS-FNA, particularly if FNA is inconclusive; CEH-EUS has correctly diagnosed pancreatic adenocarcinoma in these instances to guide appropriate management.[18–20]

As CEH-EUS exhibits superior visualization of detecting small lesions compared to traditional EUS, it may assist in pinpointing an appropriate target to increase tissue yield for EUS-FNA.[20,21] Sugimoto et al[22] reported that CEH-EUS-guided FNA was significantly superior to conventional EUS-FNA in obtaining an adequate sample on a single needle pass (60% compared to 25%; $P = 0.027$). This was attributable to improved visualization of SPL such that samples obtained via CEH-EUS-guided FNA were obtained from areas without fibrosis and necrosis.[22] Although exceedingly rare, reports of tumor seeding following EUS-FNA with multiple needles passes have been reported; thus, CEH-EUS-guided FNA may further diminish this risk by minimizing the number of passes.

EUS with elastography

Unfortunately despite advances in needle design and increased endosonographer experience, EUS-FNA yields false-negative results in 20%–40% of pancreatic malignancy cases deemed technically challenging or with concomitant chronic pancreatitis.[13,23] The development of EUS elastography (EUS-E) aims to differentiate benign from malignant solid pancreatic masses without the need for biopsy.[6,11,13] EUS-E works by applying a compressive force to a mass during real-time EUS to assess the relative stiffness of a lesion compared to the adjacent normal tissue, with tumors or inflammatory lesions appearing less compressible.[3,6,11,13,24] The degree of tissue strain from compression produces a color-coded elastography image that is then superimposed on conventional B-mode imaging, such that red reflects soft tissue, blue represents hard tissue, and tissue with intermediate stiffness appears yellow/green (Fig. 1). Given the subjectivity of this qualitative EUS-E, second-generation EUS-E technology analyzes lesions using a strain ratio, which is the ratio of tissue elasticity to neighboring soft tissue.[3,6,11,13,25] Iglesias-Garcia et al[26] demonstrated a 100% sensitivity and 93% specificity of quantitative EUS-E in 86 consecutive patients undergoing EUS evaluation for solid pancreatic masses for differentiating malignancies from benign pancreatic lesions.[13,26] This data was replicated by Opačić et al[27] in a prospective study involving 105 patients with pancreatic masses and 44 controls, with a sensitivity of 98% using the strain ratio. There are however, conflicting results from other studies leading to several high-quality meta-analyses. Pei et al[28] reviewed 13 studies for a total of 1,042 patients and found a pooled sensitivity of 95% with a sensitivity of 69%, while Li et al[29] reported a pooled sensitivity and specificity of 92% and 68%, respectively, in 781 cases.[11,13] This data suggests EUS-E is a valuable adjunct to conventional EUS, but is not currently a reliable alternative to obtaining pancreatic tissue samples. Rather, EUS-E may help support a negative cytology by EUS-FNA. There may be an additive role of combining EUS-FNA with EUS-E. A promising prospective study by Kongkam et al[25] in 38 patients with solitary pancreatic lesions found a sensitivity of 90% vs 95.2% and NPV of 80% vs 83.3% in EUS-FNA alone compared with cytology in combination with elastography strain ratio.

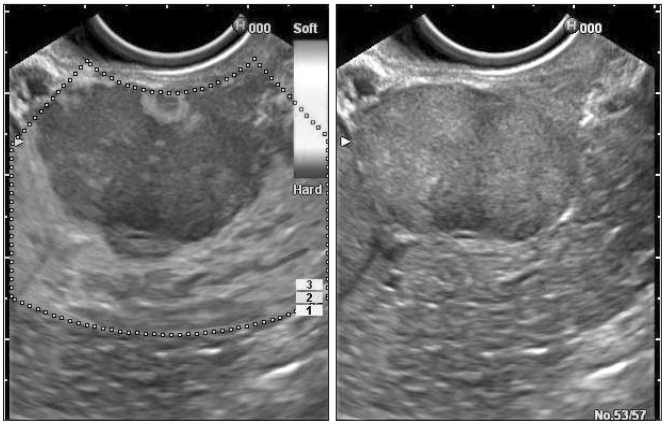

Fig. 1. Endoscopic ultrasound image of sonoelastography showing a malignant perihepatic lesion in blue (images courtesy of Pentax Medical).

Confocal laser endomicroscopy

Confocal laser endomicroscopy (CLE) is an exciting, novel technology that allows for high resolution imaging of the biliary tree and pancreatic lesions. This technology allows *in vivo* microscopic magnification of the GI tract mucosa by illuminating tissue with an external laser.[13,30] Fluorescent light is then reflected from the selected tissue through the aperture, which excludes any light reflected at angles that do not refocus into the lens.[31–34] In essence, this adjunct to EUS acts as an "optical biopsy" by providing real-time tissue histopathology.[32,35] Intravenous fluorescent agents are used to image the tissue mucosa.[33–35] Currently, two primary modalities of CLE are available: endoscope-based confocal laser endomicroscopy (eCLE) created by Pentax (Pentax America, Montvale, NJ, USA) and Optiscan (Optiscan, Notting Hill, Australia) which incorporates the confocal scanner into the distal tip of conventional endoscopes and a probe-based confocal laser endomicroscopy (pCLE) which is miniaturized to 250–300 µm, allowing it to be introduced through endoscopic accessory channels (Cellvizio; Mauna Kea Technologies, Paris, France).[13,33,34,35] This is an exciting advancement in EUS, as it can guide treatment decisions for various diseases in real-time while also preventing unnecessary biopsies. eCLE has been used to optimize endoscopic detection of colonic polyps, dysplasia in Barrett esophagus, and neoplasia in inflammatory bowel disease. One such example of its utility includes a study from Kiesslich et al[36] demonstrating diagnostic accuracy of 99.2% in detecting neoplastic mucosa of the colon.[36,37] However, the more common clinical application of CLE lies in pancreatobiliary disease. This is largely due to pCLE's size, which allows it to be passed through the EUS-FNA needle system with the CholangioFlex confocal probe (Mauna Kea Technologies) and access the bile and pancreatic ducts.[13,32–35,38]

Distinguishing malignant from benign biliary strictures remains a common diagnostic challenge despite the advent of improved computed tomography (CT), magnetic resonance, and endoscopic imaging. Despite use of brush cytology to aid in endoscopic diagnosis, sensitivity remains less than ideal, often not exceeding 70%.[33,39] Meining et al[40] reported one of the first studies

evaluating pCLE in the evaluation of pancreatobiliary duct strictures of indeterminate etiology.[33,41] In their study of 14 patients, pCLE exhibited an overall accuracy of 86% (compared to histopathology's diagnostic accuracy of 79%), based on patterns such as: large clumps of decreased fluorescent dye uptake, saccular vessels, and the loss of a reticular pattern of epithelium.[33,40] Sensitivity of histopathology alone was 50%, relative to 83% when using pCLE.[33,40] Kahaleh et al[39] also showed pCLE diagnoses aligned with that based on cytology or histopathology with a Kappa coefficient of 0.8 ($P \leq 0.0001$) in their evaluation in 18 patients. An extensive literature review by Almadi and Neumann[41] found CLE in combination with endoscopic retrograde cholangiopancreatography (ERCP) for the assessment of indeterminate ductal strictures increased the sensitivity to 98% relative to 45% with ERCP alone, but resulted in a lower specificity (67% vs 100%).

Fugazza et al[34] recently performed a meta-analysis of 8 available studies on the evaluation of biliary strictures with pCLE to find a pooled sensitivity of 90% (95% confidence interval [CI] = 0.86–0.94) and specificity of 72% (95% CI = 0.65–0.79). This data suggests that pCLE may have aid in improving earlier detection of pancreatobiliary malignancies and influencing appropriate management.

The most recent development in CLE has been a miniprobe with increased flexibility to allow introduction through either a 19-gauge or 22-gauge FNA needle, referred to as needle-based confocal laser endomicroscopy (nCLE) (Fig. 2).[13,32] Konda et al[42] published the first study of nCLE in patients with pancreatic lesions. Eighteen patients with pancreatic lesions underwent nCLE via a 19-gauge EUS-FNA needle to assess imaging feasibility.[13,32,35,42] Imaging of the pancreas was successful in 17 of 18 cases, 10 of which produced high-quality images.[42] Two patients required hospitalization for post-procedural pancreatitis, possibly related to larger EUS-FNA needle size.[32,42] Konda et al[43] followed up with a larger multicenter study in the Pancreas with Endosonography of Cystic Tumors (INSPECT) evaluating the diagnostic capability and safety of nCLE in pancreatic cystic neoplasms. They found that the presence of epithelial villous structures correlated with pancreatic cystic neoplasms with a specificity of 100%, but a low sensitivity of 59% ($P = 0.004$).[31,43] The complication rate was 9%, including two cases of pancreatitis and three with intracystic bleeding.[43] Napoléon et al[44] implemented a pilot study to ascertain diagnostic criteria for serous cystadenomas using nCLE imaging in 31 patients with single pancreatic cystic lesions. Their study demonstrated data similar to Konda and colleagues with a specificity of 100% and sensitivity of 69% for the presence of superficial vascular network pattern.[44] Interestingly, the overall complication rate was significantly lower at 3.2%, with one case of mild pancreatitis.[44] This data suggests nCLE may serve as an adjunct to EUS in order to increase the diagnostic accuracy of neoplastic pancreatic cysts, but more and larger studies are needed.[35,42–44]

EUS–FNA vs EUS–FNB in solid pancreatic lesions

EUS-FNA was developed in the early 1990s as a means to aid EUS imaging in the diagnosis of pancreatic lesions via tissue sampling.[6,11,45] It has since become standard of care to obtain EUS-FNA of SPL based on its cytological diagnostic sensitivity exceeding 80% in cases without underlying chronic pancreatitis.[3,6,11,46,47] Recently, a meta-analysis of 33 studies by Hewitt et al[48] revealed a sensitivity of 85% (95% CI = 0.84–0.86). Beyond the reliability of EUS-FNA, it also remains a safe procedure, with multiple studies demonstrating a complication rate less than 3%.[6,49] However, it is not without limitations. Multiple needle passes are often required to obtain an adequate sample for analysis, and the diagnostic accuracy of tissue has been found to be suboptimal without an on-site cytopathologist.[6,45,46,50] Additionally, a core tissue sample is often vital to the diagnosis of well-differentiated pancreatic adenocarcinomas and lymphomas, as their tissue morphology is necessary for precise histological evaluation.[45,47,50–52] These limits led to the development of the Tru-Cut biopsy needle (TCB) compatible with EUS (Quick-Core; Wilson-Cook Medical Inc., Winston-Salem, NC, USA) (Fig. 3).[53]

Levy et al[53] presented the first study comparing EUS-TCB to EUS-FNA in 19 patients with masses of varying sites, six of which were located in the pancreas. The accuracy of EUS-TCB was higher than EUS-FNA (85% vs 60%), but this difference was not statistically significant.[53] A prospective study in 18 patients by Varadarajulu et al[54] found similar results, again citing no statistical significance in the diagnostic accuracy with TCB compared with FNA. Both studies revealed challenges in obtaining pancreatic tissue with EUS-TCB due to reduced flexibility of the echoendoscope tip once the needle was secured.[53,54] Wittmann et al[55]

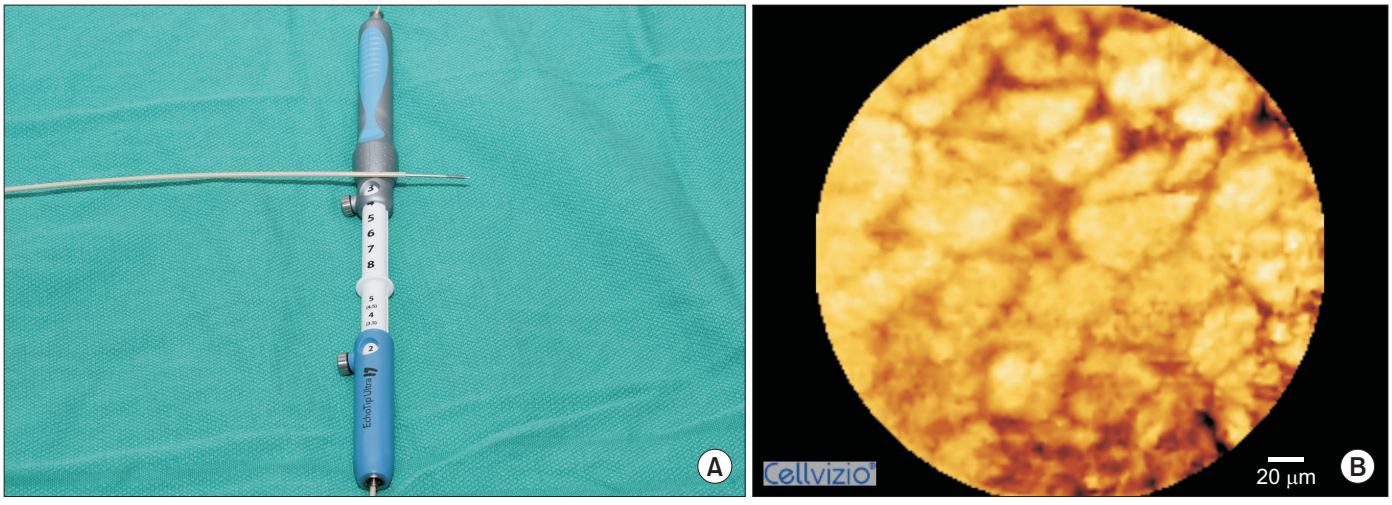

Fig. 2. Image of needle-based confocal laser endomicroscopy (A) and actual images (B) (images courtesy of Dr. Michael Wallace).

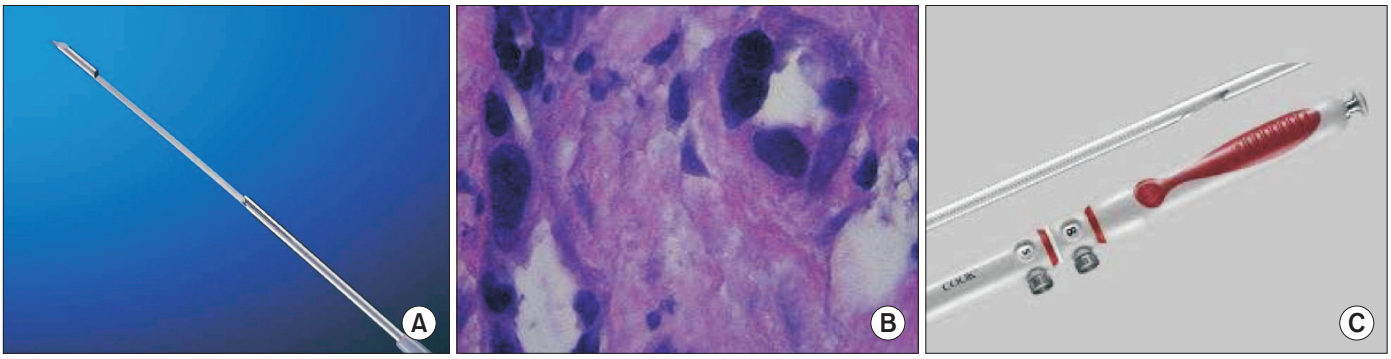

Fig. 3. (A) Endoscopic ultrasound-guided Tru-Cut biopsy needle. (B) H&E stain of a pancreatic gland showing large malignant cells. (C) Newer generation Procore™ needle (Cook Medical).

later performed a large prospective study in 159 patients, 83 of whom had pancreatic masses. All patients underwent EUS-FNA. Of the patients with lesions of the pancreas, 36 also had EUS-TCB performed. Diagnostic accuracy of TCB was reduced from that of FNA (56% vs 77%) in pancreatic sampling, as was adequacy of specimens obtained (81% to 94%, respectively).[55] The overall complication rate of EUS-TCB in this study was 0.6%, similar to the safety profile of EUS-FNA.[55]

To overcome the challenges presented by the TCB needle, new 19 G and 22 G fine needle biopsy (FNB) needles (EchoTip ProCore; Cook Medical, Bloomington, IN, USA) were developed, featuring a reverse bevel to better obtain core tissue.[45] Bang et al[47] revealed similar performance of the 22 G EUS-FNB to EUS-FNA in a prospective cohort study of 56 patients with SPL, including number of needle passes, diagnostic yield, technical success, or complications. EUS-FNB yield of core tissue was not significantly different than EUS-FNA (83.3% vs 100%; $P = 0.26$).[47] A 2015 study by Berzosa et al[56] compared the 22 G EUS-FNB needle with now-standard 25 G EUS-FNA in 61 SPL. EUS-FNB and EUS-FNA were equivocal in obtaining adequate specimens (73.8% vs 81.9%; $P = 0.37$) and diagnostic yield (68.9% vs 75.4%, respectively), but FNA required a mean of 3.5 needles passes compared with 1.7 for FNB.[56]

A smaller, 25 G core-biopsy needle (PC25, EchoTip ProCore; Cook Medical) was subsequently developed. A retrospective review of 50 patients undergoing EUS-FNB for SPL revealed cytological sensitivity of 83% and histologic diagnostic sensitivity of 63% from a single needle pass, which increased to 96% and 86%, respectively, with additional needle passes.[45] This data is similar to 25 G EUS-FNA needles. Iwashita et al[45] also found the maneuverability of the 25 G needle for accessing the pancreatic masses in diverse sites of pancreas. Recently, however, a new fork-tip needle, Shark Core® (SC; Medtronic Corp., Boston, MA, USA), has been developed to improve core tissue yield with EUS with a multifaceted bevel and differing lengths of its two sharp points.[57,58] Adler et al[57] performed a retrospective pilot study in 15 patients undergoing EUS-FNA as well as EUS-SC biopsy of SPL or peripancreatic adenopathy. Notable findings include the need for less needle passes with the SC needle (1.5 for adequacy vs 3.0 for EUS-FNA, $P < 0.001$).[57] Additionally, the SC needle attained tissue core samples in 82% cases, relative to no tissue cores with EUS-FNA ($P = 0.03$).[57] A larger case-control study by Kandel et al[58] also set to compare the ability of the SC needle to increase histologic sampling and reduce needle pass rates relative to established EUS-FNA. EUS-FNB with the SC needle required a median of two passes to acquire adequate tissue, compared with a median of four passes with FNA ($P = 0.01$).[58] Core tissue samples were obtained in 59% of FNA cases, relative to 95% of the FNB arm ($P = 0.01$) in lesions of all sites.[58] Neither study reported adverse events related to EUS-FNB with this novel core biopsy needle.[57,58] Although larger prospective studies are needed, the SC needle may allow increased core tissue yield while requiring fewer passes as opposed to standard EUS-FNA.

Innovative EUS Interventions in Pancreatic Disease

EUS-guided fiducial placement and stereotactic radiotherapy

Stereotactic body radiotherapy (SBRT) was developed as a means to better target locally invasive disease and minimize irradiation of adjacent organs.[59] SBRT achieves this via implantation of inactive radiographic markers into the target lesion.[4,6,13] These markers (cylindrical gold seeds) serve as reference points for pinpointing and tracking the tumor during SBRT. The CyberKnife radiosurgery system (Accuray, Sunnyvale, CA, USA) was approved for use with locally advanced tumors at any location in the body.[60]

Historically, fiducial placement has been with a percutaneous or intraoperative approach under CT guidance. Pishvaian et al[60] firstly used EUS-guided placement of fiducials using a 19-guage FNA needle in 13 patients, 7 of which had pancreatic adenocarcinoma. This technique was successful in 6 pancreatic cancer patients, and there were no associated complications.[6,60] Since this case series, there has been a considerable increase in the use of EUS-guided fiducial placement in nonoperable pancreatic cancer (Fig. 4). Park et al[61] successfully placed fiducials via EUS in 88% of their 57 patients with unresectable pancreatic cancer who were candidates for SBRT. Complications were infrequent and negligible.[61] Sanders et al[62] produced similar results in 51 patients with locally advanced or recurrent pancreatic cancer. Successful EUS-guided fiducial placement was achieved in 90% of their patients.[62] Fiducial migration was noted in 3 patients. One patient undergoing simultaneous fiducial placement and celiac plexus neurolysis (CPN) developed mild pancreatitis; there were no additional reported complications.[62] EUS placement of SBRT markers with a 22-gauge FNA needle has also been found to be feasible and safe in a study by Dávila Fajardo et al.[63] All 23 patients had at least two fiducials placed with a single periprocedural complication of minor bleeding.[63]

More recently, a large retrospective review sought to assess the safety and technical feasibility of fiducial placement via EUS guidance.[64] Of 514 patients undergoing EUS fiducial placement of

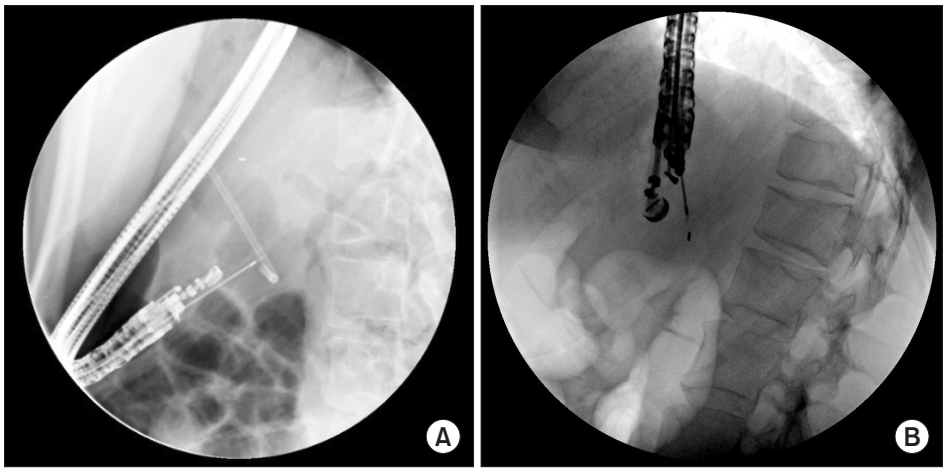

Fig. 4. (A, B) Fluoroscopy image of endoscopic ultrasound-guided fiducial placement (images courtesy of Dr. Shyam Varadarajulu).

various sites, 188 had undergone fiducial placement for pancreatic cancer. Technical success was achieved in 99.5%, with interfering blood vessels preventing marker placement in one patient. Complications remained rare at 1.3% and were minor, primarily consisting of bleeding at site that quickly resolved.[64] This data may lead to more widespread use of this technique, which allows further accessibility to pancreatic tumors.

EUS-guided needle delivery of anti-tumor agents

EUS-guided fine-needle injection (FNI) has emerged as novel technique to treat pancreatic adenocarcinoma. This procedure involves injection under EUS guidance of anti-tumor agents directly into the pancreatic tumor.[4,6,13,65,66] The theoretical advantage of EUS-FNI is direct delivery of high-concentration agents to the lesion of interest along with minimization of adverse effects associated with systemic chemotherapy. Various agents have been utilized in clinical trials.

Cytoimplant

Chang et al[67] was the first study using EUS-FNI of an anti-tumor agent, consisting of allogeneic mixed lymphocyte culture (cytoimplant). In this Phase I trial of 8 patients with unresectable pancreatic adenocarcinoma, median survival was 13.2 months with two partial responders and one minor response; no substantial toxicities were reported.[67] This was followed by a randomized multicenter study of EUS-FNI of cytoimplant vs standard chemotherapy, but was halted early due to superior survival in the chemotherapy arm.[68]

Dendritic cell immunotherapy

Dendritic cells (DC), antigen-presenting cells, induce a T-cell response against tumor antigens.[66,69] Irisawa et al[69] conducted a trial with EUS-guided DC injection of 7 patients with unresectable pancreatic cancer who had failed gemcitabine. One patient exhibited a complete response, with 3 partial responders and a median survival of 9.9 months without associated complications.[69] In a study by Hirooka et al,[70] five patients with locally advanced pancreatic cancer were treated with systemic gemcitabine and biweekly EUS-FNI of DC, followed by intravenous lymphokine-activated killer cells. One patient partially responded and two patients exhibited stable disease beyond 6 months.[70] A Phase I trial evaluating patients with nonmetastatic and resectable pancreatic adenocarcinoma compared EUS-FNI of DC plus OK-432 (an immune-potentiating agent) to 9 patients with a control group of 15 patients receiving standard chemotherapy.[71] There was no significant difference in median survival times, but FNI of DC with OK-432 was fairly well tolerated; however, two patients in the DC arm developed pancreatic fistula relative to one of 15 patients in control arm. This was not statistically significant.[71]

ONYX-015

ONYX-015 is an adenovirus modified with deletion of E1B gene that targets and replicates in malignant cells, resulting in apoptosis.[4,66,68] A Phase I/II trial conducted EUS-FNI of ONYX-015 in 21 patients with locally advanced cancer of the pancreas.[72] Half of the FNI treatments were administered in combination with systemic gemcitabine. Over 50% of the patients had disease progression or could not complete the study due to treatment toxicity. Overall median survival was 7.5 months. Four patients experience serious complications of duodenal perforation or sepsis.[72] More recent studies have used ONYX-015 in pancreatic models, but to date there are no randomized clinical trials evaluating this agent's efficacy.[73]

Tumor necrosis factor erade

Tumor necrosis factor (TNF) erade (GenVec, Gaithersburg, MD, USA) is a second-generation replication-deficient adenovector that expresses the TNF-alpha gene, which is regulated by a chemotherapy and radiation-inducible promoter. Injection of TNFerade directly into tumor cells allows delivery of TNF-alpha via gene transfer.[4,66,74] A Phase I/II trial injected TNFerade via EUS-guidance or percutaneous approach in 50 patients with unresectable locally advanced pancreatic cancer.[74] Anti-tumor FNI was performed in conjunction with systemic 5-fluorouracil and radiotherapy. One patient had complete response, three were partial responders, and 12 patients were progression-free for a median survival of 297 days. Additionally, 7 patients underwent surgical resection with increased median survival.[74] Herman et al[75] performed a randomized multicenter trial comprising 90 patients receiving conventional treatment and 187 undergoing percutaneous- or EUS-FNI of TNFerade along with standard of care. Although TNFerade was well tolerated, there was no survival benefit relative to the control arm. Furthermore, TNFerade administered under EUS resulted in inferior progression-free survival.[75]

BC-819

BC-819 (also known as DTA-H19) is a DNA plasmid that carries the diphtheria toxin-A chain regulated by the H19 promoter. In pancreatic cells overexpressing H19, toxin expression is initi-

ated and results in selective destruction of the malignant cells.[4,76] A Phase I/IIa trial in 6 patients with locally advanced and unresectable pancreatic cancer administered BC-819 via EUS-guided FNI.[76] Several patients had concurrent chemotherapy or radiation. Notably, a partial response was met in three patients; two patients achieved progression-free disease with one down staged to undergo surgical resection.[76]

EUS–guided radiofrequency ablation

Radiofrequency ablation (RFA) has been studied and applied to malignancies of the esophagus, rectum, and liver.[77,78] RFA has traditionally been used in percutaneous and intraoperative management of the aforementioned malignancies. By delivering heat at the site of contact, RFA induces local coagulative tumor necrosis.[77,79] Only recently has this technique been explored to manage advanced, unresectable pancreatic adenocarcinoma via endoscopic application, as many patients presenting with advanced pancreatic cancer are not surgical candidates. Steel et al[79] performed the pilot study of endobiliary RFA in patients with unresectable pancreatic cancer or cholangiocarcinoma causing malignant biliary obstruction. The RFA catheter (Habib EndoHPB; EMcision, London, UK) was applied directly to the biliary stricture under fluoroscopy guidance. Following RFA treatment, self-expandable metal stents (SEMSs) were placed. This procedure was successful in 21 of 22 patients with adverse effects including cholecystitis requiring percutaneous drainage in two patients, sepsis, and mild pancreatitis.[79] RFA was subsequently applied under EUS in several animal studies, leading to the development of a novel monopolar RFA probe placed through a 19 or 22 gauge FNA needle (Habib EUS-RFA catheter; EMcision) (Fig. 5).[80] Pai et al[80] performed the first human study treating pancreatic cancer directly with EUS-RFA in eight patients, six of whom had cystic neoplasms. EUS-RFA was completed in all patients. Of the six patients with pancreatic cystic neoplasm, two patients had total resolution of cysts on 6-month imaging; another three patients had a nearly 50% reduction in cyst size. The only reported complications were limited abdominal pain.[80] More recently, Pai et al[81] went on to assess EUS-RFA with Habib catheter in 7 patients with inoperable adenocarcinoma of the pancreas. Two patients had neoplasms in the pancreatic body. All patients were able to undergo EUS-RFA successfully with a single patient developing mild pancreatitis. At six-month follow-up, two patients had decrease in neoplastic size on imaging; lesions were stable in the remaining patients.[81] Additional and larger studies are warranted, but these early findings demonstrating the cytoreductive potential of RFA may lead to additional patients becoming candidates for surgical resection, as less than 20% are diagnosed with resectable pancreatic cancer.[82]

The latest data suggest EUS-RFA may represent an innovative method of treating pancreatic cancer while also providing a survival advantage. Kallis et al[82] discovered significant survival benefit in 23 patients who underwent Habib RFA with SEMS compared with 46 cases of SEMS only (226 days vs 124 days, respectively; $P = 0.010$).[82] Hu et al[83] performed a multicenter randomized control trial (RCT) in 63 patients with advanced cholangiocarcinoma. Thirty-two patients received RFA with SEMS while the remaining underwent stenting only. Patients in the RFA group survived a median of 311 days, while the stent only arm exhibited a median survival of 172 ($P = 0.012$).[83] It is hypothesized that the pathophysiology behind increased survivability with RFA lies in the inflammatory response it induces within the neoplastic tissue.[84] While RFA may only achieve necrosis of 10% of the total malignant lesion, this limited area of cell death releases tumor antigens with subsequent development of local inflammation. CD8+ T cells are then activated. Heat shock protein 70 transports antigenic peptides to antigen-presenting cells, which stimulate a tumor-specific immune response. This leads to eradication of tumor cells and thus, limits micro-metastasis.[84] While neither study evaluated EUS-RFA in pancreatic cancer, one may surmise a similar immune reaction may be induced in pancreatic adenocarcinoma with RFA, but further trials are needed.

EUS–guided cholangiography biliary drainage

ERCP is the first-line intervention for palliation of biliary obstruction secondary to pancreatic malignancy, as it is minimally invasive with symptom resolution in up to 95% of patients.[4,13,85–87] The subset of cases not achieving technical success in accessing the papilla are primarily due to anatomical variation, ampullary pathology, or malignant duodenal or biliary obstruction.[85,86] Traditionally, patients failing biliary drainage via ERCP were managed with percutaneous transhepatic biliary drainage (PTBD) or a surgical approach. Both procedures are associated with serious potential complications; their use of external drainage also leads to a less-desired outcome for patients.[85–87] A unique aspect of EUS guided biliary drainage (EGBD) is it can be performed immediately following failed ERCP.[88] Wiersema et al[89] first described EUS-guided cholangiopancreatography in 1996, leading to a multitude of case studies establishing EGBD as a safe, successful, and minimally invasive technique for failed transpapillary biliary cannulation. One key RCT from Artifon et al[90] revealed 100% technical success rate in both transluminal EGBD and PTBD arms with no

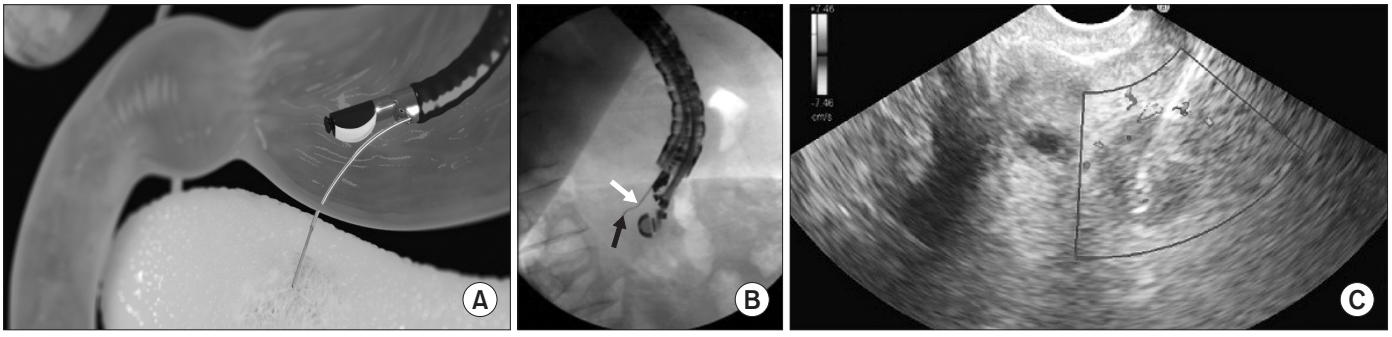

Fig. 5. (A) Schematic of endoscopic ultrasound (EUS)-guided radiofrequency ablation (RFA). (B) Fluoroscopy image of EUS-guided RFA. (C) EUS image of EUS-guided RFA of a neuroendocrine tumor (images courtesy of EMcision).

significant difference in complication rates.

EGBD is achieved by two main methodologies: EUS-guided intrahepatic (IH) duct drainage, in which the biliary system is punctured from transesophageal, transgastric, or transjejunal approach, and EUS-guided extrahepatic (EH) drainage, where the common bile duct is directly accessed from the stomach or duodenum.[4,46,85] Three current techniques are used in EGBD: (1) transmural (endoscopic choledochoduodenostomy) access involves tract dilation with stent placement, (2) rendezvous (transpapillary) comprises cannulation of the papilla via antegrade advancement of a guided wire, or less commonly, (3) antegrade placement of a biliary stent across the papilla via transduodenal approach (Fig. 6).[4,85] A recent retrospective analysis comparing transmural with rendezvous techniques in patients with malignant biliary obstruction reported 100% technical success in both groups.[91] Patients undergoing transluminal EGBD had a 95% clinical success rate relative to 100% in the rendezvous group with complication rates of 10% and 15.4%, respectively; this was not statistically significant and suggests comparable efficacy. One patient required cholecystectomy for acute cholecystitis.[91] These findings are in line with the reported adverse rate of 10%–20% with EGBD.[90,92] Gupta et al[93] recently published the retrospective analysis of IH EGBD vs EH EGBD in 240 patients. Both methods demonstrated equivalent success rates (84.3% EH vs 90.4% IH), with higher rates of success using either modality in patients with malignant obstruction (90.2%). Adverse events included pneumoperitoneum, bleeding, peritonitis, and cholangitis with similar event rates with both approaches.[93]

EUS–guided anastomosis

Gastric outlet obstruction (GOO) is common in patients with advanced pancreatic adenocarcinoma, often resulting in debilitating symptoms such as nausea, vomiting, anorexia, and weight loss.[4,94–97] Traditionally, malignant GOO is managed either by endoscopic gastroduodenal self-expanding stent placement or gastrojejunostomy anastomosis via surgical bypass. However, duodenal stents may result in recurrent obstruction due to tumor infiltration or stent migration.[95,97,98] Additionally, bypass surgery is invasive with considerable morbidity, and patients who fail endoscopic stent placement may be poor surgical candidates.[4,97] EUS-guided anastomosis may offer a minimally invasive alternative to achieve palliation in this patient population. EUS-guided double-balloon gastrojejunostomy bypass for malignant GOO was first described in two recent case reports.[99,100] Tyberg et al[99] achieved successful anastomosis by advancing an EUS needle distally in small bowel over a guide wire to dissect a fistulous tract with subsequent placement of a lumen-apposing metal stent (LAMS). A novel method of EUS-guided bypass used a cautery-tipped LAMS along with a double-balloon enteric tube. This tube can fill the small bowel luminal space between the two balloons only, after which the LAMS was deployed between the jejunum and stomach.[100] A small, multi-center retrospective study assessed feasibility of anastomotic stenting via balloon-assisted EUS-gastroenterostomy (EUS-GE) in 10 patients with GOO of varying etiologies.[98] Both technical success and resolution of symptoms were reported in 90% of patients. No complications were associated with this procedure.[98] More recently, 26 patients with GOO—17 due to malignant etiology—were included in a prospective multicenter study utilizing various approaches to EUS-GE with LAMS placement.[101] Technical success was reported in 92% of patients, with symptom resolution in 15 of the 17 patients with malignant GOO. Major post-procedural complications included one patient with severe bleeding and one report of peritonitis.[101] Itoi et al[102] performed the innovative EUS-guided double-balloon-occluded bypass using LAMS in 20 patients with GOO due to malignancy. All patients with procedural success (90%) experienced GOO-related symptom improvement. Reported adverse events included stent mal-deployment, which was recognized periprocedurally without associated complications.[102] Preliminary data from a retrospective trial com-

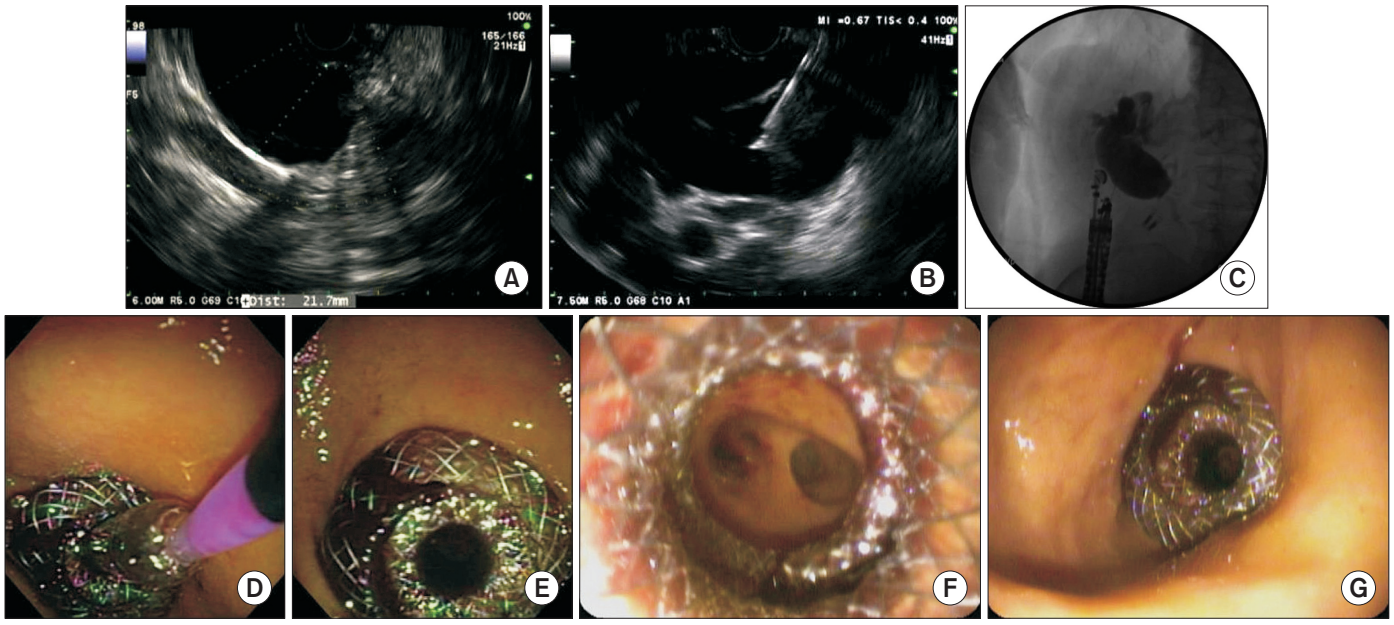

Fig. 6. (A) Dilated common bile duct (CBD) to 2.2 cm in a patient with malignant obstruction. (B) Endoscopic ultrasound (EUS) image of needle puncture directly into the CBD. (C) Endoscopic retrograde cholangiopancreatography image of EUS guided cholangiography. (D–G) EUS guided stent deployment directly into the bile duct from the duodenum with a view of the left and right intrahepatic ducts (all images courtesy of Dr. Rishi Pawa).

paring enteral stenting with EUS-GE revealed comparable clinical success, with 83.3% in the EUS-GE arm and 69.9% in the enteral stent cohort ($P = 0.2$).[103] Most notably, those undergoing EUS-GE had a lower rate of stent obstruction (3.3% EUS-GE vs 26.9%) or need for re-intervention (3.3% vs 46.2% enteral stent).[103]

Celiac plexus neurolysis and celiac ganglion neurolysis

Debilitating abdominal pain secondary to pancreatic adenocarcinoma results in significantly reduced quality of life in patients, and is frequently challenging to alleviate. CPN was developed as a means to effectively treat pancreatic cancer pain while reducing patient need for high doses of narcotic analgesics. CPN is attained via injection of alcohol or phenol into the celiac plexus, resulting in chemical ablation of the visceral afferent nociceptors.[3,4,10] Celiac plexus block (CPB) employs the injection of triamcinolone in combination with a local anesthetic to inhibit the transmission of pain.[4] CPN had primarily been performed via percutaneous approach involving blind needle puncture. Wiersema and Wiersema[104] were the first trial demonstrating EUS-CPN provided successful pain relief without serious periprocedural complications. EUS is advantageous for CPN given the ability to visualize needle injection in real-time. A multitude of randomized controlled trials and meta-analyses have established EUS-CPN as an effective and feasible treatment for pancreatic cancer pain. Notably, a large meta-analysis of 8 studies revealed EUS-CPN achieved pain reprieve in 80% of patients, equivocal to standard approaches, with no serious complications.[105] Wyse et al[106] randomized 96 patients with late stage pancreatic adenocarcinoma to early EUS-CPN or standard management. Patients receiving early EUS-CPN reported significant reduction in pain at three months relative to the conventional treatment arm. Although not statistically significant, the EUS-CPN group also reported decreased opioid use.[106] These findings were further supported by a systematic review of 6 studies involving 358 patients; pain scores were significantly lower in CPB at both four and eight weeks.[107] The CPB group also exhibited a drastic reduction in opioid analgesics ($P < 0.00001$).[107]

A more innovative approach to improve the efficacy of neurolysis involves direct celiac ganglion neurolysis (CGN). Gleeson et al[108] performed a large prospective cross-sectional study to assess how frequently celiac ganglia were visualized during EUS. The diagnosis of presumed celiac ganglia was confirmed with EUS-FNA. Successful identification of celiac ganglia during EUS occurred in 81% of patients, with more ganglia identified with linear-array EUS.[108] Levy et al[109] reported 94% complete or partial pain relief in 18 patients with unresectable pancreatic cancer undergoing CGN. Following these promising results, a recent study randomized 68 patients with upper GI cancer pain to undergo either EUS-CPN or EUS-CGN.[110] Four patients from the CGN arm crossed over to CPN when the celiac ganglia could not be visualized. EUS-CGN resulted in superior reductions in pain scores (25 of 34 cases) compared with EUS-CPN (15 of 33 patients; $P = 0.026$).[110] Furthermore, CGN achieved total pain relief in 50% patients, relative to 18.2% in CPN arm ($P = 0.01$) with number needed to treat (NNT) of 3.[110] Complications from CGN in both studies were minimal and similar to those observed with CPN, including but not limited to diarrhea, hypotension, bleeding at puncture site, and abdominal pain.[3,4,6,109,110]

Discussion

EUS with FNA remains an exceedingly accurate method in diagnosing and staging pancreatic cancer. However, this accuracy is limited in certain cases, such as chronic pancreatitis. Innovative methods such as contrast-enhanced EUS, EUS with elastography, and confocal endomicroscopy may overcome this limitation to further improve early detection of pancreatic malignancy. EUS-FNB may serve to increase accurate diagnoses of neoplasms requiring histopathologic confirmation. A multitude of therapeutic techniques to manage cancer of the pancreas may not only improve this population's quality of life, such as with pain control via EUS-CGN and management of malignant obstruction via EUS-guided anastomosis or biliary drainage, but also may increase survival. EUS-guided fiducial placement and anti-tumor injection therapy provide alternative treatments for those patients failing other modalities. While data on the efficacy of EUS-RFA is limited, this emerging technique may ultimately lead to a new algorithm in treating inoperable pancreatic adenocarcinoma.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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