MINIREVIEWS

191  Endoscopic ultrasound guided interventions in the management of pancreatic cancer
     Kerdsirichairat T, Shin EJ

205  Role of endoscopic ultrasound in esophageal cancer
     Radlinski M, Shami VM

ORIGINAL ARTICLE

Retrospective Cohort Study

215  Endoscopic retrograde cholangiopancreatography for bile duct stones in patients with a performance
     status score of 3 or 4
     Saito H, Kadono Y, Shono T, Kamikawa K, Urata A, Nasu J, Imamura H, Matsushita I, Kakuma T, Tada S

Retrospective Study

226  Improving sessile serrated adenoma detection rates with high definition colonoscopy: A retrospective
     study
     Sehgal A, Aggarwal S, Mandalaya R, Loughney T, Mattar MC

Observational Study

235  Endoscopic resection of superficial bowel neoplasia: The unmet needs in the Egyptian practice
     Emara MH, Zaghloul M, Ramadan HKA, Mohamed SY, Tag-Adeen M, Alzamzamy A, Alborae M, Madkour A, Altonbary
     AY, Zaher TI, Elhassan AA, Abdeen N, Ahmed MH
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Endoscopic ultrasound guided interventions in the management of pancreatic cancer

Tossapol Kerdsirichairat, Eun Ji Shin

**Abstract**

There has been a growing interest in developing endoscopic ultrasound (EUS)-guided interventions for pancreatic cancer, some of which have become standard of care. There are two main factors that drive these advancements to facilitate treatment of patients with pancreatic cancer, ranging from direct locoregional therapy to palliation of symptoms related to inoperable pancreatic cancer. Firstly, an upper EUS has the capability to access the entire pancreas—lesions in the pancreatic head and uncinate process can be accessed from the duodenum, and lesions in the pancreatic body and tail can be accessed from the stomach. Secondly, there has been a robust development of devices that allow through-the-needle interventions, such as placement of fiducial markers, brachytherapy, intratumoral injection, gastroenterostomy creation, and ablation. While these techniques are rapidly emerging, data from a multicenter randomized controlled trial for some procedures are awaited prior to their adoption in clinical settings.

**Key Words:** Endoscopic ultrasound-guided intervention; Pancreatic cancer; Fiducials; Ablation; Intratumoral therapy

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Core Tip: Intervendental endoscopic ultrasound in pancreatic cancer has been developed via a through-the-needle fashion, using 2 techniques: Injection and/or placement. Examples of through-the-needle injection techniques include intratumoral therapy, injection of alcohol and bupivacaine for celiac plexus neurolysis, and hydrogel for bleb formation to create space in the pancreaticoduodenal groove for dose-escalation stereotactic body radiation therapy. Examples of through-the-needle placement techniques include placement of fiducial markers, placement of ablative probes for non-thermal and thermal therapies, placement of radioactive seeds for brachytherapy, and placement of a lumen-apposing metal stent to create a gastrojejunostomy in patients with gastric outlet obstruction. The vast majority of these techniques have shown comparable or superior outcomes when compared to conventional interventions and therapies.

INTRODUCTION

Pancreatic ductal adenocarcinoma has increased in incidence by 0.3% annually since 2006 and is expected to become the second cause of cancer-related death in the year 2030. It has the lowest 5-year relative survival of 11% compared to other solid organ malignancies, with an estimated death toll of 49,830 which closely reflects its incidence of 62,210 in 2021[1]. Approximately more than half of the patients presented at the metastatic stage, the highest proportion compared to other solid malignancies, while 13% and 29% presented at localized and regional stages, respectively. For those who present without overt evidence of metastasis, surgical resection is the ultimate goal to hopefully provide curative treatment. With the advancement of endoscopic ultrasound (EUS) in both diagnostic and therapeutic aspects of pancreatic cancer management, it has provided treatment options not only by tissue acquisition to get the definitive diagnosis of pancreatic cancer but also by more accurate local disease control in regional or locally advanced stages while awaiting definitive curative surgical resection and through palliative treatments in those with metastasis or advanced disease[2,3]. This review does not include EUS-guided intervention for malignant biliary obstruction.

EUS GUIDED TISSUE ACQUISITION

An initial randomized trial comparing the 22-gauge aspiration and 22-gauge biopsy needles for EUS-guided sampling of solid pancreatic mass lesions showed comparable diagnostic efficacy, technical performance, and safety profile without a significant difference in yield or quality of the histologic core between the two needle types[4]. Subsequent randomized trials with larger sample sizes were able to demonstrate that fewer passes were required to establish a diagnosis of pancreatic malignancy with improved histopathological quality using a fine needle biopsy (FNB) needle[5-7]. The use of the 25 gauge FNB needle was technically feasible, safe, efficient and was comparable to the standard 22 gauge fine needle aspiration (FNA) needle in patients with solid pancreatic masses in the absence of an on-site cytopathologist. The cytological sample quality in the liquid-based preparation and the histological diagnostic yield for specific tumor discrimination of EUS-guided sampling using a 25 gauge FNB needle were significantly higher than those using a 22 gauge FNA needle[8]. In terms of designs of FNB needle, an opposing bevel design provided significantly superior tissue yield and diagnostic performance when compared to a reverse bevel needle[9]. For second generation FNB needles, the diagnostic yield when used primarily without rapid on-site evaluation, was higher when a fork-tip needle, in comparison to a Franseen needle or FNA needle, was used[10,11]. However, a subsequent larger trial revealed that samples with the highest degree of cellularity in a single biopsy, resulting in a diagnostic accuracy of 90% or higher, were collected by FNB needles using the Franseen or fork-tip needle[12]. Another study showed that a 22-gauge Franseen needle provided more tissue for histologic evaluation and better diagnostic accuracy than a 20-gauge lateral bevel needle. These studies led to the technical guideline from the European Society of Gastrointestinal Endoscopy in 2017 suggesting performance of 3-4 needle passes with an FNA needle or 2-3 passes with an FNB needle when on-site cytologic evaluation is unavailable[13]. There may be some theoretical concern that the high yield of FNB needles might come with the cost of possibly higher risk of tract seeding, especially in patients with a resectable solid pancreatic mass, unless the tract itself is planned to be resected[14]. In terms of technique, the stylet slow pullback technique might enable better acquisition of tissue and increased cellularity for the diagnosis of pancreatic tumors suspected to be malignant, compared to the conventional negative suction after stylet removal technique or the non-suction after stylet removal technique, in the absence...
of an on-site cytopathologist.

In the era of personalized medicine, next-generation sequencing (NGS) can serve as a complementary diagnostic test and unveil potentially predictive genomic biomarkers for treatment response[15,16]. An initial experience revealed that NGS can be performed on EUS-FNA-derived samples to provide information on KRAS mutation status and 160 other cancer genes such as TP53, SMAD4, KMT2D, NOTCH2, MSH2, RB1, SMARCA4, PPP2R1A, PIK3R1, SCL7A8, ATM and FANC D2, to supplement cytological evaluation[17-21]. Similar to the efficacy of FNB over FNA for cellularity, FNB should be considered when tumor genotyping is requested, as it was associated with a higher yield of sufficient sampling for genomic testing, especially in tumors of 3 cm or smaller, and tumors located in the head/neck of the pancreas[22]. Moreover, recent data indicated that studying the expression of a selected gene set could inform the selection of the most appropriate treatment for patients, moving towards an individualized medicine approach. To accomplish this, adequate EUS tissue acquisition will allow providers to build organoids platform that can allow determination of the transcription level of informative genes[23]. Early studies were able to demonstrate the successful isolation of organoids using samples obtained from a 22-gauge FNB needle at the time of the initial diagnosis, which may be helpful in patients with pancreatic cancer that are not surgically resectable[24,25].

**EUS GUIDED PLACEMENT OF FIDUCIAL MARKERS**

For patients with borderline resectable or locally advanced pancreatic cancer, neoadjuvant chemoradiation plays a vital role. While chemotherapy can potentially control systemic disease, local disease control by radiation therapy has shown additional benefit to hopefully reduce local recurrence after surgical resection[26,27]. Stereotactic body radiation therapy (SBRT) and image guided radiation therapy (IGRT) have increasingly been used in clinical practice since they can provide a higher dose of radiation with a shorter duration of treatment and acceptable rates of toxicity[28]. To be able to focally deliver radiation to the pancreas, which is an organ that moves following respiratory cycles, fiducial marker placement is recommended[29]. The markers are traditionally metallic, made of gold or platinum, or more recently, in hydrogel form, to serve as reference points for planning as well as follow-up daily image guidance over a short course of SBRT/IGRT. EUS-guided fiducial placement has evolved to become the technique of choice to place these fiducial markers, compared to conventional techniques where the markers are either placed surgically or percutaneously under cross-sectional imaging guidance such as computed tomography (CT) or transabdominal ultrasound[30]. The ideal characteristics of fiducial markers should have good visibility, minimal artifacts, and minimal migration over the course of SBRT/IGRT. Fiducials with larger diameters usually provide better visibility, at the cost of greater artifact. Furthermore, fiducial delivery systems that require a 19-gauge needle can pose challenges for EUS-guided fiducial placement when lesions are located at the pancreatic uncinate process. Therefore, the fine balance and preferred types of fiducials should be discussed in a multidisciplinary tumor board setting, especially between the endosonographers and the radiation oncologists. Generally, balanced visibility and artifacts can be achieved with a 0.35- to 0.43-mm diameter, 5- to 10- mm length, coiled or cylindrical gold fiducials[31]. A comparison study of these types of gold fiducials and the newer generations of fiducials, such as platinum or hydrogel, is still in process. A theoretical benefit of hydrogel compared to other metallic fiducials is that it can be injected via EUS in a liquid bleb formation to create additional space in the pancreaticoduodenal groove to separate the pancreatic head/neck cancer from the adjacent duodenal C loop (Figure 1) to allow for dose escalation during SBRT/IGRT while avoiding mucosal toxicity to the duodenum[32,33].

**EUS-GUIDED INTRATUMORAL THERAPY**

Given the close proximity of the probe of the therapeutic echoendoscope and several technologies that can be delivered through FNA needles, multiple modalities for local therapies of pancreatic cancer have been developed. These include placement of radiosensitive devices for brachytherapy, injections of antitumoral agents, access for passing through-the-needle probe for ablative devices, and photodynamic therapy.

**EUS-GUIDED BRACHYTHERAPY**

Intraoperative interstitial brachytherapy when used at laparotomy can improve local disease control in locally advanced pancreatic cancer. An initial animal study from China implementing EUS as a route for the implantation of radioactive seeds was proven safe and feasible. Shortly after, the group conducted a feasibility study in 15 patients who suffered from unresectable pancreatic cancer, showing 30% of patients had clinical benefit, with complications including pancreatitis and pancreatic fluid collection in
20% of patients. This was followed by a prospective cohort of 22 patients with unresectable pancreatic cancer who were treated with radioactive iodine 125 seeds, which resulted in 14% partial remission at 4 wk, 45% with stable disease, and 91% later succumbed to the disease at 2-year follow-up. Another group in China conducted a pilot study in 8 patients with T4 pancreatic cancer, using both intratumoral radioactive seeds and 5-fluorouracil, resulting in a 12% partial response at 3 mo, with overall 50% clinical benefits including a reduction in pain, without complications or hematologic toxicity[34]. Another prospective study showed that EUS-guided implantation of iodine-125 around the celiac ganglia can reduce pain visual analog scale score and analgesic drug consumption in patients with unresectable pancreatic cancer. A special EUS treatment planning system software may play a role in EUS-guided brachytherapy in patients with unresectable cancer, as it demonstrated a rate of partial remission of up to 80% in patients whose minimal peripheral dose was larger than 90 Gy, with a median survival time of 9 mo[35]. In addition to survival benefits, iodine-125 seed implantation placed percutaneously or via EUS after relief of obstructive jaundice via ERCP can improve biliary stent patency, time to development of gastric outlet obstruction, and improve quality of life by pain relief[36].

EUS-GUIDED INJECTION OF ANTITUMORAL AGENTS

Immunotherapy
The hypothesis of intratumoral therapy was based on that of other malignancies where both local disease control effect and systemic response effect (i.e., metastasis) can be achieved through the immune response against the tumors, including breast cancer, renal cell carcinoma, and melanoma[39-43]. In addition, immunological responses induced by zoledronate-pulsed dendritic cell-based vaccines have been associated with therapeutic effects in clinical trials[44,45]. The first pilot study in patients with unresectable pancreatic cancer treated with EUS-guided injection of allogeneic mixed lymphocyte culture proved its feasibility and safety profile[46]. Subsequent pilot studies included an injection of immature dendritic cells in pancreatic cancer refractory to gemcitabine[47], a combination of systemic gemcitabine and intratumoral OK-432-pulsed dendritic cell therapy, followed by an intravenous infusion of lymphokine-activated killer cells stimulated with an anti-CD3 monoclonal antibody[48], and dendritic cell-based vaccination and concomitant chemotherapy in patients with advanced or recurrent pancreatic cancer[49]. The first phase 1 comparative trial of intratumoral injection of immature dendritic cells and OK-432 for resectable pancreatic cancer patients had one in nine patients with transient fever. Two out of nine patients treated with immunotherapy, one of whom had stage IV with distant lymph node metastasis, survived five years without further adjuvant therapy[50]. In a phase I/II trial of comprehensive immunotherapy combined with intratumoral injection of zoledronate-pulsed dendritic cells, intravenous adoptive activated T lymphocytes, and gemcitabine in unresectable locally advanced pancreatic cancer, a synergistic therapeutic response was shown with overall survival and progression-free survival of 12 and 5.5 mo, respectively[51]. To date, there has not been a study of EUS-guided intratumoral injection of other types of immunotherapy such as ipilimumab or nivolumab (Figure 2).

Chemotherapy
Pancreatic cancer is unfortunately insensitive to many chemotherapeutic drugs. It is thought that
inefficient delivery of chemotherapy into the tumor plays an important role in chemoresistance in pancreatic cancer. A combination therapy that can increase intratumoral vascular density and intramural concentration of gemcitabine was shown to lead to a transient stabilization of disease[52]. The initial experience using OncoGel (Regel/paclitaxel) for local tumor management via EUS guided 22-gauge needle in a pig model provided high and sustained localized concentrations of paclitaxel. A feasibility study using EUS-guided injection of gemcitabine in 38 patients with locally advanced and metastatic pancreatic cancer confirmed the safety and efficacy of the technique. More recently, a feasibility study of EUS guided injection of a novel polymer-based microparticles for a drug delivery system in a pig model appeared promising[53]. A phase I study evaluating the role of EUS guided injection of epidermal growth factor receptor antibody cetuximab as a radiosensitizer with chemoradiation for locally advanced pancreatic cancer in 16 patients proved its feasibility and safety profile when administered with abdominal radiation and concurrent gemcitabine. The incidence of grade 1-2 adverse events was 96% and the incidence of grade 3-4 adverse events was 9%[54].

**Gene therapy**

An initial feasibility study in 21 patients with locally advanced or metastatic pancreatic cancer treated with EUS guided injection of ONYX-015 (dl1520), an E1B-55kD gene-deleted replication-selective adenovirus that preferentially replicates in and kills malignant cells, was promising and generally well-tolerated either alone or in combination with gemcitabine[55]. In a multi-center feasibility study of 50 patients, intratumor delivery of TNFerade biologic (AdGVEFR.TNF.11D), a replication-deficient adenoviral vector that expresses tumor necrosis factor-alpha under the control of the Egr-1 promotor, by EUS-guided injection or percutaneously, combined with chemoradiation in the treatment of locally advanced pancreatic cancer, appeared promising, especially at the maximal tolerated doses. Adverse events such as cholangitis and pancreatitis were observed in 6%. The rate of patients who were able to proceed with surgery and achieve negative margin resection was 12%. In a randomized trial of 304 patients, treatment with TNFerade plus standard of care was safe but not effective for prolonging survival in patients with locally advanced pancreatic cancer[56].

For patients with unresectable pancreatic cancer, an open-label, dose-escalation trial using BC-819, which is a DNA plasmid developed to target the expression of diphtheria-toxin gene under the control of H19 regulatory sequences, in combination with systemic chemotherapy, may provide an additional therapeutic benefit, with minimal adverse events such as asymptomatic elevation of lipase[57]. EUS-guided injection of HF10, a spontaneously mutated oncolytic virus derived from herpes simplex virus 1 that has the potential to show a strong antitumor effect against malignancies without damaging normal tissue, in combination with erlotinib and gemcitabine, was a safe treatment for unresectable locally advanced pancreatic cancer[58]. The EUS-guided injection of STNMO1, the double-stranded RNA oligonucleotide that specifically represses carbohydrate sulfotransferase-15, was safe and feasible without any adverse events. The authors also proposed that injections of STNMO1 during the start of treatment could lower carbohydrate sulfotransferase-15 level, while its overexpression was associated with worse prognosis[59,60].

An open-label phase 1/2a study in the first-line setting of patients with inoperable locally advanced pancreatic cancer using an EUS guided injection of siG12D-LODER to release a siRNA drug against KRAS (G12D), along with systemic chemotherapy, was promising in terms of potential efficacy that 70% had a reduction in tumor marker CA 19-9, and 80% of patients had either stable disease or partial response with a median overall survival of 15 mo. However, one third of patients experienced serious adverse events.
EUS-GUIDED ABLATIVE THERAPIES

Radiofrequency ablation

Radiofrequency ablation is a local ablative method that can destroy the tumor by thermal coagulation and protein denaturation[61]. A phase II pilot study using radiofrequency ablation via a laparotomy in patients with locally advanced pancreatic cancer showed its feasibility and safety profiles with a 24% complication rate, with 9% requiring a reoperation. After a feasibility study in a porcine model, a feasibility study of using EUS-guided radiofrequency ablation of unresectable pancreatic cancer showed promising safety data, with one-third of the patients only developing mild abdominal pain without pancreatitis. The safety profile of the technique was later confirmed by subsequent feasibility studies showing no evidence of early or late major adverse events[62,63]. However, it required an 18-gauge electrode, which could be challenging for the treatment of lesions located in the pancreatic head or uncinate process. A new monopolar radiofrequency probe may be technically more versatile because it can be used through a 22-gauge needle[64]. In patients with locally advanced pancreatic cancer treated with EUS-guided radiofrequency ablation, those with wild-type SMAD4 may have improved survival benefits after treatment[65]. For other solid pancreatic lesions such as pancreatic neuroendocrine tumors and pancreatic insulinoma, EUS-guided radiofrequency ablation has shown clinical benefits such as fewer episodes of hypoglycemia[66,67], regression of neuroendocrine syndromes, improved pancreatic cystic sizes, and complete radiological ablation[68]. A prospective study of 29 patients using EUS-guided radiofrequency ablation for pancreatic neuroendocrine tumors (PNET) and pancreatic cystic neoplasms revealed an overall tumor resolution of 86% in PNET and a significant response rate of 71% of patients with cystic neoplasms, with an overall complication rate of 10%.

Another application of radiofrequency ablation is to use it along with a simultaneous cryogenic cooling of carbon dioxide. An animal feasibility study was promising, given that only 14% of pigs developed histochemical pancreatitis after the procedure. The group has expanded this technique to 16 explanted pancreatic tumors from 16 patients, showing that the flexible bipolar ablation device, combining radiofrequency and cryotechnology, can create an ablation zone, defined by histological signs of coagulative necrosis, and that the extent of the ablation zone was related to the duration of application. However, data on this technique in in-vivo studies are still forthcoming.

Laser ablation

An initial animal study using a neodymium-doped:yttrium aluminum garnet (Nd:YAG) was based on the finding that the ablation resulted in a high rate of tissue necrosis and can be considered as a palliative option in patients with hepatocellular carcinoma, liver metastases in colorectal cancer, and malignant thyroid nodules[68-72]. There was no major post-procedural complication and all 8 pigs survived at 24 h after EUS-guided laser ablation of normal pancreatic tissue. The same group conducted another animal study to evaluate tissue temperature distribution, which plays a crucial role in the outcome laser-induced thermal therapy, proving that the tissue downward from the tip is mostly heated at 60 Celsius degree. The authors further conducted a human feasibility study in nine patients with unresectable pancreatic cancer who were unresponsive to previous chemoradiotherapy. Laser ablation was performed by using a 300-micrometer flexible fiber preloaded onto a 22-gauge fine needle. A 1064-nanometer wavelength Nd:YAG was used at different settings (2-4 Watts and 800-1200 Joules), resulting in an ablation area ranging from 0.4 cm² with the setting of 2 Watts and 800 Joules, to 6.4 cm² with the setting of 4 Watts and 1000 Joules, without adverse events. A comparative study using laser ablation compared to other EUS-guided techniques for patients with unresectable pancreatic cancer is awaiting.

Photodynamic therapy

EUS-guided photodynamic therapy has two steps: An injection of a photosensitizing agent, followed by the insertion of a 19-gauge needle into the targeted area to pass a small quartz optical fiber to illuminate and ablate tissue with the laser light. Initial pilot studies in porcine models using EUS-guided photodynamic therapy appeared promising. In a rabbit model, the efficacy of verteporfin delivery could be enhanced with perfusion CT, to serve as a non-invasive method of mapping photodynamic therapy, proving that the tissue downward from the tip is mostly heated at 60 Celsius degree. The authors further conducted a human feasibility study in nine patients with unresectable pancreatic cancer who were unresponsive to previous chemoradiotherapy. Laser ablation was performed by using a 300-micrometer flexible fiber preloaded onto a 22-gauge fine needle. A 1064-nanometer wavelength Nd:YAG was used at different settings (2-4 Watts and 800-1200 Joules), resulting in an ablation area ranging from 0.4 cm² with the setting of 2 Watts and 800 Joules, to 6.4 cm² with the setting of 4 Watts and 1000 Joules, without adverse events. A comparative study using laser ablation compared to other EUS-guided techniques for patients with unresectable pancreatic cancer is awaiting.
Figure 3 Endoscopic ultrasound guided celiac plexus neurolysis. A: The structures while the echoendoscope is located at the posterior proximal gastric body/gastric cardia. A star demonstrates the pre-ceeliac region. The white arrow demonstrates the celiac trunk. A orange arrow demonstrates the superior mesenteric artery. An asterisk indicates the descending abdominal aorta; B: An area of hyperchoic blush of injected dehydrated alcohol (asterisk) delivered from a 19-gauge needle (arrow) for celiac plexus neurolysis.

Figure 4 Endoscopic ultrasound guided liver biopsy. A: Liver parenchyma without major intervening intrahepatic blood vessels, which is an optimal location for endoscopic ultrasound-guided liver biopsy. An asterisk indicates a small amount of perihepatic ascites; B: An endoscopic ultrasound-guided liver biopsy using a heparin-primed wet-suction technique via a 19-gauge Franseen needle tip design. The hyperechoic tip of the needle (white arrow) and the shaft of the needle (orange arrow) must be visualized at all times during the fine needle biopsy of the liver.

post-procedural related complications.

*Alcohol*

The vast majority of studies using EUS-guided ethanol ablation for solid pancreatic tumors are focused on non-functioning pancreatic neuroendocrine tumors and insulinoma\(^74-76\). Data of EUS-guided ethanol ablation in pancreatic ductal adenocarcinoma, especially in combination with EUS-guided celiac plexus neurolysis, are still needed.

**EUS GUIDED CELIAC PLEXUS NEUROLYSIS**

EUS-guided celiac plexus intervention has gained popularity in the management of pain from pancreatic cancer due to its safety profile when compared to narcotics\(^77\). An initial meta-analysis and systematic review showed that the pooled proportion of patients with pancreatic cancer treated with EUS-guided celiac plexus neurolysis had pain relief up to 53%-80% of the time\(^78-80\). The first randomized controlled trial in 96 patients assigned to either EUS-guided celiac plexus neurolysis or conventional pain management, showed that early EUS intervention reduced pain and may have moderated morphone consumption in patients with painful, inoperable pancreatic cancer, especially at 3 mo after treatment\(^81\). While the number of injections might not improve the degree of pain relief\(^82\), the targeted celiac ganglia neurolysis was superior to celiac plexus neurolysis. EUS-guided radiofrequency ablation, using a 1 French monopolar probe passed through a 19-gauge targeting the area of celiac plexus or visualized ganglia, showed superiority in pain relief and improved quality of life when
compared to traditional EUS-guided celiac plexus neurolysis. However, a recent study raised the concern that combined celiac ganglion and plexus neurolysis may reduce median survival time without improving pain, quality of life, or adverse events when compared to traditional celiac plexus neurolysis. Furthermore, newer generations of opioids such as oxycodone and fentanyl may be comparable to EUS-guided celiac plexus neurolysis in terms of pain relief, quality of life, and opioid consumption (Figure 3).

**EUS GUIDED GASTROENTEROSTOMY**
Approximately 50% of patients with pancreatic cancer develop nausea and vomiting from malignant gastric outlet obstruction[83]. In patients with an inoperable stage, this was traditionally managed by endoscopic enteral stent placement or surgical gastrojejunostomy creation, depending on life expectancy. EUS-guided gastroenterostomy creation using a lumen apposing metal stent has emerged and gained in popularity due to a higher rate of initial clinical success and/or a lower rate of stent failure requiring repeat intervention when compared to enteral stent placement[84-86]. Compared to surgical approaches for gastrojejunostomy, EUS-guided gastroenterostomy was associated with fewer adverse events[87,88], shorter time to resume oral intake and chemotherapy, shorter lengths of stay, and reduced hospital costs. The technique of EUS-guided gastroenterostomy has been developed over time. The direct technique, defined by using an electrocautery-enhanced lumen-apposing metal stent, rather than a balloon-assisted approach, resulted in shorter procedure time and comparable clinical success (> 90%). In addition, the clinical success of direct-EUS-guided gastroenterostomy is durable with a low rate of re-intervention based on a long-term cohort[89]. Randomized trials comparing these endoscopic and surgical interventions for palliation of malignant gastric outlet obstruction caused by pancreatic cancer are awaiting. It should be noted that the learning curve of the technique can be challenging as it requires up to 40 procedures to achieve competency, otherwise fatal adverse events can occur at a very high rate (> 10%).

**EUS GUIDED LIVER BIOPSY**
Immune checkpoint inhibition targeted against cytotoxic T-lymphocyte-associated antigen 4 and programmed cell death protein 1 has shown survival benefit to treat multiple types of advanced cancer, including pancreatic cancer. Hepatotoxicity from checkpoint Inhibitors is a less common type of immune related adverse events, and it is often mild[90,91]. Concurrent treatment with nivolumab and ipilimumab, which is commonly used in pancreatic cancer, increases the risk of hepatotoxicity up to 37% and the risk of high-grade toxicity by up to 15%[92,93]. In complicated or severe forms, or unclear etiologies, liver biopsy can be used to confirm the etiology of injury[93,94], and/or to clarify the diagnosis in those with elevated liver enzymes refractory to steroid or immunosuppressant treatment [95].
EUS-guided liver biopsies have increased in popularity due to their decreased invasiveness compared to surgical routes and comparable tissue acquisition compared to transjugular or percutaneous route [96]. Bilobar liver biopsies, with one needle pass with three to-and-fro needle movements to each lobe of the liver, enhanced the assessment of disease severity due to an increased number of complete portal tracts, and longer aggregate specimen length, without severe adverse events[97]. A 19-guage Fransen-tip or reverse bevel core needle outperformed FNA needles or other types of core needles, resulting in longer aggregate length, more complete portal tracts, and more adequate specimens despite fewer passes. A heparinized wet suction technique can improve tissue adequacy compared with dry needle techniques. A randomized trial using these specific techniques for EUS-guided liver biopsies, compared to other conventional approaches, is needed (Figure 4)[98].

**CONCLUSION**
EUS-guided interventions provide a broad spectrum of treatment modalities for patients with borderline resectable, locally advanced, and inoperable pancreatic cancer. These include direct treatment for locoregional stages such as ablative therapies, brachytherapy, placement of fiducial markers for SBRT/IGRT, as well as palliative treatments such as EUS-guided gastroenterostomy creation for malignant gastric outlet obstruction and EUS-guided celiac plexus neurolysis to manage pain. While many of these procedures are considered investigational with limited data, particularly those from randomized controlled trials, the vast majority of these techniques have been widely used in clinical practice. For patient safety, it is important to note that most of these procedures should be performed at a facility with a multi-disciplinary tumor board and experienced interventional endosonographers.
FOOTNOTES

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