Review Article

EUS-guided interventional management of pancreatic tumor

Pazhanivel Mohan, Dong Wan Seo*

A B S T R A C T

Pancreatic cancer is one of the most common causes of cancer-related death worldwide. Most patients have advanced disease at diagnosis, resulting in a very poor prognosis. Hence there is a need for newer therapeutic strategies and novel approaches to the management of these tumors. Advances in endoscopic ultrasound have brought a change in its role from being solely a diagnostic tool to having a therapeutic role in gastrointestinal malignancies. Interventional endoscopic ultrasound is useful in the palliation of pancreatic adenocarcinoma as well as in the treatment of cystic tumors of the pancreas. This review focuses on the present status of interventional endoscopic ultrasound for pancreatic tumor.

Keywords: Endoscopic ultrasound, Pancreatic cancer, Pancreatic cystic tumor

Introduction

Pancreatic neoplasms mostly originate from the exocrine pancreas, 90% being ductal adenocarcinomas. About 5% of cancers arise from islet cells that constitute pancreatic neuroendocrine tumors.1 Besides the solid lesions, cystic tumors also arise in the pancreas but are less frequent. However, they are being detected more due to the increased use of cross-sectional imaging modalities.2,3 Pancreatic adenocarcinoma is one of the most common causes of cancer-related deaths worldwide. Surgery offers the only chance of cure, but most patients have advanced disease at the time of diagnosis, resulting in a very poor prognosis. Systemic chemotherapy or chemoradiotherapy is an accepted standard of care in those with advanced disease. Although these treatments improve survival, these tumors are resistant to systemic therapies due to the presence of an extensive desmoplastic stroma and reduced vascularity.4,5 Hence there is a need for new and more effective therapeutic strategies for treating pancreatic cancer. The advances in the field of endoscopic ultrasound (EUS) have brought about a paradigm shift from diagnosis and staging to a therapeutic role in gastrointestinal malignancies. Interventional EUS has thus become important in the treatment of pancreatic cancer. This review will focus on the current status of interventional EUS in pancreatic adenocarcinoma and cystic tumors.

Pancreatic cyst ablation

The incidence of cystic lesions of the pancreas is increasing due to their incidental detection by current high-resolution imaging. They can be classified into benign cystic lesions and lesions with potential for malignant transformation. Such a distinction has clinical importance to decide the management approach in asymptomatic patients.

The current recommendation is surgical resection of all high-risk mucinous cystic lesions of the pancreas. However, this bears a perioperative morbidity of 20–40% and a mortality of up to 2% even in the best of the centers. Hence there is a need for alternative treatment modalities in high-risk surgical candidates and benign-looking pancreatic cystic lesions.2

EUS-guided pancreatic cyst ablation is a useful minimally invasive technique in these individuals. Pancreatic cysts that are unilocular or oligolocular (<6 locules) and greater than 2 cm in diameter, with no pancreatic duct communication, and clinical suspicion of being mucinous are amenable to ablation. The presence of septations within the cyst is not an absolute contraindication. Ablation starts from one locule and extends sequentially, piercing each septation in turn until the cyst is fully treated. The possible benefits of pancreatic cyst ablation include a decrease in the malignant potential by destroying the epithelial lining, cost-effectiveness by avoiding frequent surveillance using imaging modalities, and alleviation of anxiety, especially in patients who have a high risk for surgery or are unsuitable for resection.5,6

The most commonly used agent for cyst ablation is ethanol. Ethanol results in a rapid death of cyst epithelial cells by membrane lysis, protein denaturation, and vascular occlusion.7 Paclitaxel, a chemotherapeutic drug, is also used for endoscopic pancreatic cyst...
ablation. It binds to microtubules, stabilizes their structure, and inhibits cell processes dependent on microtubule turnover.8

EUS-guided pancreatic cyst ablation is performed by trans-gastric or transduodenal puncture of the cyst using a 22-gauge fine-needle aspiration needle. The cystic fluid is aspirated and then an equal volume of ethanol is injected. The needle stays within the cyst to prevent complete collapse of the cyst. After 20–40 minutes of retention time, the ethanol–cyst fluid mixture is drained out as completely as possible. Finally, a small amount of paclitaxel can be injected into the cystic cavity, the dose varying from 3 to 30 mg depending on the size of the cyst. When paclitaxel is used for cyst ablation, it is left in place after the ethanol lavage. Fig. 1A–D shows a possible mucinous cystic tumor in a 32-year-old woman who underwent cyst ablation with ethanol and paclitaxel along with a follow up CT scan at 1 year.

Abdominal pain, hemorrhage into the cyst, acute pancreatitis, abscess formation, splenic vein obliteration, transient hypotension during injection, and ethanol intoxication are complications of ethanol ablation. Oh et al6 reported a case of portal vein thrombosis following EUS-guided pancreatic cyst ablation with ethanol and paclitaxel.

EUS-guided ethanol ablation of pancreatic cystic lesions caused complete resolution in over one-third of the patients in an initial pilot study.9 Subsequently, a randomized controlled study showed that EUS-guided ethanol ablation of pancreatic cystic lesions was safe, feasible, and efficacious.10 In 36 patients who underwent either one or two EUS guided ethanol lavage sessions, follow-up computed tomography (CT) imaging demonstrated complete cyst resolution in 12 cases (33.3%). Long-term follow-up after a median period of 26 months was possible in nine of these patients, with CT showing no evidence of cyst recurrence.11

Oh et al12 showed a combination of ethanol and paclitaxel to be safe and effective in ablation of pancreatic cystic lesions. The feasibility, safety, and outcome of EUS-guided ethanol lavage with paclitaxel injection in cystic tumors were evaluated in a prospective study involving 14 patients. The procedure was successfully performed in all except one. Complete resolution of the cyst was documented in 11 patients, with partial resolution in two and persistence of the cyst observed in one patient. The authors noted that smaller cystic lesions (<3 mL cyst volume) resolved completely compared to the ones with partial resolution (>5 mL cyst volume). They proposed a prerequisite minimum cyst diameter of 15 mm and a cyst volume of 1.5 mL for safe performance of the procedure. There were no serious complications except for mild pancreatitis in one patient.

The response to pancreatic cyst ablation may be influenced by factors like cyst wall thickness, presence of septations, and mural nodules. Oh et al13 studied the effectiveness of EUS-guided ethanol lavage with paclitaxel injection (EUS-EP) in the treatment of septated cystic tumors of the pancreas. Six out of 10 patients had complete resolution of the cysts with partial resolution in two patients. The authors concluded that careful patient selection, ideal angle of entry of the needle to target the maximum number of locules, use of more concentrated doses of ablating agents, and booster injections are required for a better outcome with septated cystic tumors. Booster ablation improves cyst resolution in septated cystic tumors owing to repeated contact with ablative agents. This
may be considered in large cysts that show a plateau response to
the first ablation with persistent septa or show cyst regrowth.\textsuperscript{10,14}

The factors predicting the response to EUS-EP along with the
outcome at long-term follow-up were also studied. The mean
diameter of the cystic lesion was 32 mm, and the estimated volume
was 14 mL. Out of 47 patients who were followed up for more than 12
months, 29 patients had a complete response, six had a partial
response, and cysts persisted in 12 patients. The diameter of the cysts
and estimated volume at the time of the procedure predicted the
resolution of the cysts after treatment in univariate analysis, while
only the latter was found useful in multivariate analysis. There were
no major complications observed. Long-term follow-up (median 20
months) was possible in the majority. CT scanning documented
complete resolution in 80% of patients at 1 year of follow-up.\textsuperscript{15}

The correlation between the number of ethanol lavage sessions
and cyst resolution has been retrospectively reviewed.\textsuperscript{16} Two EUS
ethanol lavage sessions resulted in a significant decrease in the size
and surface area of the pancreatic cystic lesion, and hence a
significantly higher rate of cyst resolution, compared with only one
ethanol lavage session.

\textbf{Interventional EUS for the management of pancreatic cancer}

\textit{EUS-guided fiducial placement}

The development of imaging-guided radiation therapy has been
a major advancement in the palliation of pancreatic cancer. It
involves the placement of fiducial markers, which are radiopaque
spheres, coils, or seeds directly implanted into the tumor. The ad-
vantages include accurate localization of the tumor with precise
delineation of its local extent, the use of escalating doses of radia-
tion with minimal toxicity to surrounding normal tissues, and the
fact that it does not require target tissue immobilization as it allows
quantification of respiratory-associated tumor motion, unlike
external beam radiotherapy.\textsuperscript{17–19}

The fiducials can be placed using a percutaneous, endoscopic, or
surgical approach. EUS-guided placement of fiducial markers in
pancreatic tumors is technically easier as it provides high-quality
images of the pancreas with safer access to tissue sampling. Fiduc-
ials are preloaded into a 19-gauge 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
dislodgement. After localization of the tumor, three or four fiducials
are evenly placed demarcating the center and periphery of the
tumor.\textsuperscript{19} Fig. 2A–D shows EUS-guided fiducial placement and
image-guided radiotherapy in a patient with inoperable pancreatic
cancer.

The initial Phase I and II studies of image-guided radiotherapy
in patients with locally advanced pancreatic cancer resulted in
excellent local control, although with no survival benefit.\textsuperscript{20,21}
Park et al\textsuperscript{22} found EUS-guided gold fiducial insertion in pancre-
atic cancer to be safe and effective in 94% without the use of
fluoroscopy. They flushed the needle with sterile water instead of
pushing the stylet in a majority of their cases for deploying the

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{(A) Computed tomography (CT) scan showing a low-attenuation mass extending from the pancreatic head into the celiac trunk. This lesion was confirmed as inoperable pancreatic cancer by endoscopic ultrasound (EUS) fine-needle aspiration. (B) Placement of fiducial markers into the tumor using a 19-gauge needle (echogenic line) under EUS guidance. (C) Plain abdominal X-ray showing three fiducial markers in the head and tail of the pancreas. (D) CT scan 1 year after stereotactic radiosurgery and gemcitabine chemotherapy, showing stable disease.}
\end{figure}
fiducials, which prevented them from coiling. Sanders et al\textsuperscript{23} studied the safety and feasibility of EUS-guided fiducial placement in locally advanced and recurrent pancreatic cancer. Fiducials were successfully placed in 90\% with a technical failure rate of 8\%, attributed to surgically altered anatomy. A total of 91\% of patients successfully completed stereotactic body radiotherapy after EUS-guided fiducial delivery, with no major complications.

EUS-guided fiducial placement can be at times technically demanding, especially in tumors involving the pancreatic head due to the angulation of the scope within the duodenum. However, straightening the tip of the echoendoscope, use of fluoroscopic guidance, and use of smaller fiducials can improve the technical success rate. New delivery systems have been recently developed using a 22-gauge needle with preloaded seeds for sequential deployment.\textsuperscript{18,19}

**EUS-guided celiac plexus neurolysis**

Celiac plexus neurolysis (CPN) refers to permanent chemical ablation of the celiac plexus or celiac ganglia. It may be performed by surgical, percutaneous, or endoscopic approaches. EUS-guided CPN is theoretically safer than the percutaneous posterior approach: as the approach is anterior and coupled with Doppler scanning, it reduces the risk of vascular and neurologic complications by avoiding the diaphragm, spinal nerves, or arteries. EUS-guided CPN may be cost-effective if performed at the time of diagnosis and staging of the tumor.\textsuperscript{5,17,24}

The procedure begins with visualization of the celiac take-off from the aorta. The celiac plexus is located anterior and lateral to celiac trunk. Bupivacaine (0.25\%) 5 mL followed by 10–20 mL of ethyl alcohol (98\%) is injected onto the area cephalad to the origin of the celiac artery in the midline method, while split doses are injected on either side of the of the celiac artery in the bilateral approach.\textsuperscript{25,26} The complications following EUS-guided CPN were often mild transient diarrhea and hypotension. Retropertioneal bleeding and abscess formation were the major complications reported.\textsuperscript{27}

Demonstration of the celiac ganglia on EUS allowed for direct injection of agents into the ganglia in pancreatic cancer.\textsuperscript{28} Ascunce et al\textsuperscript{30} retrospectively analyzed the predictors of response to EUS-guided CPN in 64 patients with pancreatic malignancy, and observed that visualization of the celiac ganglia for direct injection was the best predictor of a pain response. However, the benefit of direct injection into the ganglia has to be confirmed in prospective controlled studies. Sakamoto et al\textsuperscript{30} described a new technique of broad plexus neurolysis with superior pain relief, in which the injection was made adjacent to the superior mesenteric artery.

Meta-analysis evaluating the usefulness of EUS-guided CPN in pancreatic cancer pain found it to be safe and effective, with pain relief in up to 80\%. Conversely, a critical review of the available evidence by Levy et al\textsuperscript{31} reported a pain response in 58\% of cases, with documentation of a complete pain response in only 22\%. They observed that the available studies were too different for useful comparison. The studies were lacking in sufficient methodology and well-defined criteria for pain response. Moreover, the assessment of the pain response was carried out very early after therapy and did not take into account the probable beneficial effect of chemoradiation.

The treatment of pain in pancreatic cancer is still very difficult and challenging. It often requires high doses of analgesics with undesirable side effects. It is important to realize that the goal of EUS-guided CPN is to optimize and reduce the dose of analgesics required in order to minimize their side effects.\textsuperscript{24}

**EUS-guided celiac ganglion radiation**

Pain relief with CPN is short-lasting and is less effective the greater the invasion of the celiac ganglia. EUS-guided brachytherapy with implantation of iodine-125 seeds beside the celiac ganglion is a new technique for pain relief in pancreatic cancer. The onset of the analgesic effect is slow when compared to CPN, but it lasts longer owing to the longer period of decay of iodine-125 seeds.\textsuperscript{18}

Wang et al\textsuperscript{32} recently conducted a pilot study to determine the feasibility and safety of EUS-guided direct celiac ganglion irradiation with iodine-125 seeds in humans following their demonstration of its safety in a porcine model. They inserted two seeds into ganglia less than 0.8 cm in diameter, and four seeds into those ganglia 0.8 cm or larger. They showed the technique to be safe, effective, and feasible for pain relief in pancreatic cancer, with a significant reduction in the pain scores and mean analgesic consumption at 2 weeks. However, further randomized and comparative clinical trials are required to confirm the safety and long-term effectiveness of this new technique.

**EUS-guided drainage for biliary obstruction**

Endoscopic retrograde cholangiopancreatography (ERCP) and bile duct stenting is the procedure of choice in obstructive jaundice resulting from advanced pancreatic cancer. It is not always possible, especially when the disease is advanced and involves the ampulla, common bile duct, or duodenum, resulting in a tight stricture or altered anatomy of the duodenum.\textsuperscript{5,19}

EUS-guided biliary drainage and stenting is a reasonable alternative in these patients. It is composed of two techniques, a rendezvous technique and a direct access technique. EUS rendezvous involves puncturing of the bile duct through the gastric or duodenal wall followed by placement of a guidewire through the papilla to allow subsequent ERCP. However, this technique works only if the ERCP scope can be negotiated into the duodenum to the papillary orifice.\textsuperscript{25} EUS-guided direct access techniques involve a direct transgastric (hepaticogastrostomy) or transduodenal approach (choledochoduodenostomy) and placement of stents to create bilioenteric anastomosis in situations where ERCP is not possible.\textsuperscript{26} Fig. 3A–E shows hepatogastrostomy in a patient with pancreas cancer with liver metastasis, duodenal obstruction, and ascites. The potential advantages of EUS-guided biliary access over percutaneous transhepatic drainage have been reported to be puncture with real-time ultrason and color Doppler scanning, lack of an external drain, and feasibility even in the presence of ascites.\textsuperscript{25}

Isayama et al\textsuperscript{33} reviewed the EUS-guided rendezvous technique for biliary access and found an overall success of 74\% with a complication rate of 11\%. The major complications included bleeding, bile leakage, peritonitis, pneumoperitoneum, and pancreatitis. The comparison of various routes of bile duct access showed good scope stability, maintenance of the guidewire in position upon withdrawal of the scope, and a low risk of bile leak with the transgastric approach. However, manipulation of the guidewire was easier with the transduodenal approach. There is a need for larger randomized studies of the use of these techniques to become standardized before widespread use in the community is adopted.

**EUS-guided experimental therapies in pancreatic cancer**

**EUS-guided injection of antitumoral agents**

EUS-guided injection of antitumor agents is an attractive treatment option in pancreatic cancer. The antitumor agents include allogeneic mixed lymphocyte culture (cytoimplants), ONYX-015, and TNFerade.
Allogeneic mixed lymphocyte culture (cytoimplants)

Cytoimplants lead to activation of immune effector cells and release cytokines, causing tumor regression. Chang et al. showed in their Phase I study that EUS-guided local immunotherapy using increasing doses of cytoimplants was feasible and safe for pancreatic tumors. There were no major complications, and the most common side effect was low-grade fever without leukocytosis. However, there are no large randomized or comparative trials available to demonstrate its clinical utility.

Fig. 3. (A) Gastric outlet obstruction in a 54-year-old man with advanced pancreatic cancer following chemoradiotherapy and biliary metal stenting. (B) Visualization of a dilated left intrahepatic duct (LIHD), which was punctured using a 19-gauge needle for endoscopic ultrasound (EUS)-guided hepaticogastrostomy. (C) Contrast injection into the LIHD and visualization of complete occlusion of the previous biliary metal stent. (D) Insertion of a fully covered metal stent into the LIHD via a transgastric approach. (E) Endoscopic view showing the fully expanded metal stent through the hepaticogastrostomy with bile flow from the LIHD.
ONYX-015

ONYX-015 is an E1B 55-kDa gene-deleted replication-selective adenovirus that preferentially replicates in malignant cells, leading to cell death. The efficacy of ONYX-015 was evaluated in a Phase I/II trial, where EUS FNI of ONYX-015 was combined with gemcitabine in 21 patients with advanced pancreatic cancer. The response was not very convincing. Four patients experienced major complications including sepsis and perforations, and no significant survival benefit could be demonstrated.35

TNFerade

TNFerade is a second-generation replication-deficient adenovector, expressing the complementary DNA for human tumor necrosis factor (TNF). The gene is upregulated by a radiation-inducible promoter Egr-1 (early growth response) that ensures maximal gene expression and subsequent TNF secretion to be constrained in space and time by radiation therapy. This approach helps to localize the antitumor effects, thereby reducing systemic toxicity.

Hecht et al46 reported the long-term results of EUS or percutaneous transabdominal delivery of TNFerade with chemoradiation in locally advanced pancreatic cancer in a Phase I/II study. Fifty patients completed a 5-week treatment of weekly injections of escalating doses. The median time to tumor progression was 184 days, and the median overall survival was 297 days. Gastrointestinal bleeding, deep vein thrombosis, pulmonary emboli, pancreatitis, and cholangitis were the major adverse events observed. Seven patients underwent surgical resection, with six of them having negative surgical margins and one a complete pathologic response. The authors concluded that intratumoral TNFerade with chemoradiation appears promising in locally advanced pancreatic cancer given the high rate of pathologically negative surgical resection after treatment.

A Phase II/III randomized controlled trial of chemoradiation with and without TNFerade initially showed an increased overall survival in the combination group. However, the authors did not observe survival benefits from the addition of TNFerade when the results of the study were analyzed. A subgroup analysis showed that the benefit of TNFerade was evident in patients with T1–T3 tumors and low (CA) 19-9 U/mL [<1000]. Hence, patients with borderline resectable, locally advanced tumors are appropriate candidates who will benefit most from TNFerade therapy.47

EUS-guided photodynamic therapy

Photodynamic therapy (PDT) involves the administration of a photosensitizing agent that is avidly taken up by tumorous tissue followed by exposure of the target to light of appropriate wavelength. This results in generation of a singlet oxygen that causes extensive tumor necrosis with minimal damage to the surrounding normal tissues. EUS-guided PDT requires insertion of a quartz optical fiber through the EUS needle to illuminate the target tissue with laser light. The mechanisms of the antitumor effects include direct cytotoxicity, vascular damage, and induction of an inflammatory response with development of systemic immunity.38,39

Chan et al42 reported their experience of EUS-guided PDT in a porcine model. Subsequent to intravenous injection of porphyrin sodium, a 19-gauge EUS needle was inserted into the pancreas, liver, spleen, and kidney. A small-diameter optical fiber was passed through the EUS needle and used to illuminate the target tissue with laser light. Localized tissue necrosis was seen in all the organs studied without any significant complication. Yusuf et al41 studied the effectiveness and safety of EUS-guided PDT with verteporfin, a photosensitizer associated with lower photosensitivity, and observed localized pancreatic tissue ablation in a dose-related fashion with no post-procedural complications. Larger studies are required to address the safety of this technique as well as determine the choice of photosensitizing agents, dose, and wavelength of the light to be used, as well as the drug–light interval.

EUS-guided radiofrequency ablation

Radiofrequency ablation (RFA) uses electromagnetic energy to induce thermal injury, which produces coagulative necrosis of a predefined area. It is the safest, most studied, and most predictable of all the available techniques for thermal ablation. EUS-guided RFA may be an effective alternative to the previously existing percutaneous and surgical approaches.42–44

Goldberg et al45 studied the feasibility and effectiveness of EUS-guided RFA in the pancreas in 13 pigs. Needle electrodes (19-gauge) were used to deliver the radiofrequency current to the pancreas through a transgastric approach for 6 minutes. The subsequent pathologic examination showed discrete, well-demarcated spherical foci of coagulation necrosis. The procedure was well tolerated, with focal pancreatitis in one, transmural gastric burns in three, and a serosal small intestinal burn in one pig.

EUS-guided laser ablation

Laser ablation with an Nd:YAG laser can produce a high rate of complete tissue necrosis. The laser energy produces sustained tumorcidal temperatures within a prescribed area, leading to coagulation and irreversible cell death. It differs from other modes of energy delivery in its great precision of tissue necrosis. Another advantage of the Nd:YAG laser over RFA is the shorter application time to achieve the desired effect. Di Matteo et al46 conducted a pilot study to assess the feasibility of EUS-guided laser ablation of normal pancreatic tissue in a porcine model using an Nd:YAG laser. There were no major complications, and no signs of thermal injury to adjacent organs were observed. The authors concluded that EUS laser ablation of the pancreatic tissue was feasible, and more studies were required to determine the survival benefit and establish the relationship between the energy required and area of ablation.

EUS-guided brachytherapy

Brachytherapy consists of placing radioactive seeds directly into the tumor, and has been widely used in various malignancies, including pancreatic cancer. The radioactive seeds used in brachytherapy include iodine-125, iridium-192, and palladium-103. Iodine-125 has the longest half-life, and hence is useful in rapidly growing pancreatic cancers by delivering high-dose radiation therapy from within the gland with minimal toxicity to the adjacent organs. The unique property of a low dose rate of the radioactive seeds helps in targeted and optimal radiation dosage with minimal effects on normal tissues. The technique of placement of these seeds is similar to EUS-guided fiducial placement using 19-gauge needles. However, tumor volume is assessed by EUS to calculate the number and locations of radioactive seeds required.18,19

Sun et al47 initially showed that EUS-guided implantation of radioactive seeds was safe and effective in animal studies. Two clinical studies48,49 have evaluated EUS-guided implantation of radioactive iodine seeds (125I) in locally advanced pancreatic cancer. The first was a pilot study in 15 patients, which showed pain reduction in about one-third and a median survival of 10.6 months.48 Jin et al49 reported the effects of combined chemotherapy and EUS brachytherapy in 22 patients with inoperable pancreatic cancer. All patients received gemcitabine-based 5-fluorouracil chemotherapy a week after EUS-guided brachytherapy. There was a significant initial
improvement in pain scores in over 80% of patients, with an overall median survival of 9 months and no major complications reported.

Conclusion
In conclusion, the role of interventional EUS for pancreatic cancer has been well investigated in experimental and clinical studies. EUS-guided pancreatic cyst ablation offers a safe and effective nonoperative treatment for patients with cystic tumors. Further studies are required to evaluate the technique, choice of ablating agents with number of lavages, and optimal criteria for selection of patients for cyst ablation. EUS-guided antitumor therapy for pancreatic adenocarcinoma is continuously evolving, with many of the current approaches still investigational and not standardized for routine clinical use. Hence, further prospective and large randomized clinical trials are required to assess the feasibility and clinical applicability of these techniques.

Conflict of interest
There is no conflict of interest in publishing this article.

References