Review Article

Interventional endoscopy in the diagnosis and management of pancreatic adenocarcinoma

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Abstract: Pancreatic cancer accounts for approximately 3% of all cancers in US, and is the fourth leading cause of mortality in both men and women. It is a silent killer due to lack of early symptoms and the majority of patients present at advanced stage at the time of initial diagnosis. Only 15–20% of patients are candidates for curative resection and even then, the 5-year survival rates range from 10–25%. Despite recent advances in the treatment of advanced pancreatic cancer, the prognosis remains grim with 5-year overall survival (OS) of approximately 10%. Early detection is key for improving patient outcomes in this lethal disease. Contributing to the difficulty in the diagnosis and management is the anatomic location of the pancreas within the abdomen (retroperitoneal location and being adjacent to hollow viscus, solid organs and major vessels), and suboptimal response to systemic chemotherapy. Multimodality imaging (pancreatic protocol CT and MRI/MRCP) is often used for the diagnosis and staging of pancreatic adenocarcinoma. Interventional endoscopy is a relatively new field, and with Endoscopic techniques becoming more advanced, their role in diagnosis and management of pancreatic cancer is expanding rapidly. Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS) are the two main modalities used in cases of pancreatic neoplasms.

Keywords: Pancreatic cancer; pancreas cancer; interventional endoscopy; endoscopic ultrasound (EUS); endoscopic retrograde cholangiopancreatography (ERCP); biliary stent; biliary drainage; fine needle aspiration (FNA)

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Introduction

Pancreatic cancer accounts for approximately 3% of all cancers in US, and is the fourth leading cause of mortality in both men and women (1). Over 90% of the pancreatic malignancies are ductal adenocarcinomas arising from the exocrine elements. Neoplasms arising from the endocrine pancreas comprise only about 5% of the pancreatic malignancies. Pancreatic cancer is a silent killer due to lack of early symptoms and majority of patients present at advanced stage at the time of initial diagnosis. Despite recent advances in the treatment of advanced pancreatic cancer, the prognosis remains grim with a 5-year OS of approximately 10%. Only 15–20% of patients are candidates for curative resection and even then, the 5-year survival rates range from 10–25% (2,3). Early detection is key for improving patient outcomes in this lethal disease.

Contributing to the difficulty in the diagnosis and management is the anatomic location of the pancreas within the abdomen (retroperitoneal location and being adjacent to hollow viscus, solid organs and major vessels), and suboptimal response to systemic chemotherapy (4).

Multimodality imaging is often used for the diagnosis and staging of pancreatic adenocarcinoma (5). Currently,

pancreatic protocol CT scan is the preferred initial imaging tool when there is a clinical suspicion for pancreatic cancer. Seventy to eighty five percent of patients deemed to be resectable by high quality CT imaging have been able to undergo successful resection (6-8).

Magnetic resonance cholangiopancreatography (MRCP) can be used as an adjunct to CT, when a suspected mass is not seen on CT, in cases of indeterminate liver lesions, or in case of contrast allergy (9,10)

Endoscopic techniques are becoming more advanced and their role in diagnosis and management of pancreatic cancer is expanding rapidly, especially with the availability of Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS).

Endoscopic modalities

Traditional endoscopic procedures, such as upper endoscopy, flexible sigmoidoscopy, colonoscopy and small bowel enteroscopy have long been used for prevention, diagnosis and management of gastrointestinal malignancies. The development of specialized instruments and procedures, such ERCP and EUS, and the subspecialty of "interventional endoscopy" has allowed gastroenterologists to gain access to previously un-accessible areas and non-luminal organs such as the pancreas and made a significant difference in management of pancreatic diseases especially pancreatic cancer.

ERCP

ERCP is an endoscopic technique in which a specialized side viewing endoscope (duodenoscope) is advanced into the duodenum and the ampulla is cannulated for access to the biliary and pancreatic ducts for diagnostic and therapeutic purposes. The scope has a working channel for passing wires, catheters, needles or forceps, and an elevator mechanism adds to the maneuverability in addition to the traditional dials for up, down and side to side motion.

The biliary and pancreatic ducts can be injected with contrast and viewed under fluoroscopy in real time to evaluate for abnormalities including strictures or blockages. Brush cytology and forceps biopsies can also be done for diagnostic purposes. To relieve obstruction, plastic or metal stents can be placed over guidewires.

ERCP is a much older technique than EUS, but there is a constant addition of new tools and modifications to ERCP. One such technique is the cholangioscopy, in which a daughter scope (the cholangioscope) is passed through the working channel of a standard duodenoscope. The cholangioscope has its own camera and a working channel which allows tissue acquisition and some therapeutics to be performed under direct visualization within the bile duct.

ERCP is an extremely useful technique, however is does carry risks including the risk of pancreatitis (~4%), and many of its diagnostic and some therapeutic indications are now being taken over by EUS.

EUS

EUS, although conceptualized in the 1980s, is a relatively recent addition to the tools available to endoscopists for cancer diagnosis and therapeutics. EUS is complementary to CT for pancreatic cancer diagnosis and in addition to providing tissue, it can also provide information about vascular and lymph node involvement.

The echoendoscope is a specialized scope which combines traditional optical endoscopy with ultrasound technology. The transducer on the tip of the echoendoscope makes the sound waves, and also receives the echoes. There are two types of echoendoscopes, radial and linear (also called curvilinear or linear-array), based on their field of ultrasound imaging. Both types have the ultrasound transducer at the distal end of the scope. The optical camera gives an oblique field of vision similar to the ERCP scopes. The radial scopes are used for diagnostic purposes, whereas the linear scopes can be used for both diagnostic and therapeutic purposes since they have a working channel and an elevator mechanism (similar to ERCP scopes), which helps in performing therapeutic procedures.

EUS-guided interventional procedures include EUS-fine needle aspiration (FNA), EUS-fine needle biopsy (FNB), EUS-guided drainage of pancreatic fluid collection, EUS-guided celiac plexus neurolysis and block (EUS-CPN, EUS-CPB), EUS-guided biliary drainage, EUS-guided gallbladder drainage, EUS-guided pancreatic duct drainage, pancreatic fiducial placement, and EUS-guided drainage for abdominal and pelvic abscesses (4). Emerging interventional procedures are EUS-guided tumor ablation, EUS-guided vascular intervention, EUS-guided delivery of antitumor agents, and brachytherapy, EUS-guided creation of anastomosis, and EUS-guided liver biopsy and portal pressure measurement (4).

EUS in screening

Early detection is key to increasing survival in pancreatic

cancer. Delayed diagnosis is responsible for poor survival, since treatments for metastatic pancreatic cancer are not very effective.

However, given the relatively low incidence of pancreatic cancer, screening programs for general population are neither feasible nor cost effective. Therefore, screening targeted towards high risk populations or high-risk individuals (HRI) is more practical.

Populations at a higher risk of pancreatic cancer include patients with hereditary pancreatitis, Peutz-Jeghers syndrome, Lynch syndrome, familial breast-ovarian cancer syndrome, familial atypical multiple mole melanoma, and familial pancreatic cancer (FPC) syndrome (11-13).

Magnetic resonance imaging (MRI)and EUS are the two most useful screening modalities, with EUS having an advantage of allowing tissue sampling (14).

Ludwig *et al.* (15), in a study, looked at whether screening at-risk relatives of FPC patients was safe and had significant yield. They enrolled asymptomatic at-risk relatives into a Familial Pancreatic Tumor Registry (FPTR) and offered them screening with MRCP followed by EUS-FNA if indicated. Relatives with findings were referred for surgical evaluation. Out of the 109 relatives evaluated, abnormal radiographic findings were present on initial screening in 18 patients (16.5%), 15 of whom underwent EUS. A significant abnormality was confirmed in 9 of 15 patients, 6 of whom ultimately had surgery for an overall diagnostic yield of 8.3% (9/109). Yield was greatest in relatives >65 years old (35%, 6/17) when compared with relatives 55–65 years (3%, 1/31) and relatives <55 years (3%, 2/61). The study concluded that, screening at-risk relatives from FPC families has a significant diagnostic yield, particularly in relatives >65 years of age, confirming prior studies. MRCP as initial screening modality is safe and effective (15).

In another recent multicenter prospective study, Harinck *et al.* (12) aimed to compare the efficacy of EUS and MRI in their ability to detect clinically relevant lesions in HRI.

The results of 139 asymptomatic HRI (>10-fold increased risk) undergoing first time screening by EUS and MRI were described. Clinically relevant lesions were defined as solid lesions, main duct intraductal papillary mucinous neoplasms and cysts ≥10 mm.

Two solid lesions and nine cysts ≥10 mm were detected in nine HRI (6%). Both solid lesions were detected by EUS only and proved to be a stage I pancreatic ductal adenocarcinoma and a multifocal pancreatic intraepithelial neoplasia, whereas of the nine cysts ≥10 mm, six were detected by both imaging techniques and three were detected by MRI only. The agreement between EUS and MRI for the detection of clinically relevant lesions was 55%. Of these clinically relevant lesions detected by both techniques, there was a good agreement for location and size. The study concluded that, EUS and/or MRI detected clinically relevant pancreatic lesions in 6% of HRI. Both imaging techniques were complementary rather than interchangeable (12).

Hence, EUS is a useful tool to complement imaging modalities for screening in pancreatic cancer and if implemented in the right setting/targeted population has the potential to impact the overall management of pancreatic cancer.

Diagnosis and tumor staging

Patients with adenocarcinoma of the pancreas, especially involving body or tail of the pancreas, do not develop symptoms until they are at an advanced stage. Those with the carcinoma of the head of the pancreas can present with obstructive jaundice at earlier stages. The initial workup and diagnosis is usually accomplished by imaging modalities.

The role of endoscopy in pancreatic cancer diagnosis is mainly detection, staging and obtaining accurate tissue diagnosis in patients not going immediately to surgery (11). Although there is some data to suggest that preoperative EUS-FNA is not associated with adverse perioperative or long-term outcomes in patients undergoing surgery, such as distal pancreatectomy for pancreatic cancer (16), however for patients going straight to surgery, an additional procedure (such as EUS) is usually not necessary and can cause delays and potential adverse effects.

EUS and cytology

Although EUS is more operator dependent, as compared to CT and MRI, it is the most sensitive test in expert hands to detect pancreatic mass lesions or pancreatic adenocarcinoma, particularly when lesions are equivocal by CT or <2 cm in size (11). EUS has the advantage of providing not only imaging but also tissue sample. EUS guided tissue sampling can be performed by two methods, FNA or FNB.

EUS-FNA has a very high sensitivity and specificity, a meta-analysis of 41 studies showed a sensitivity of 86.8% and a specificity of 95.8% (17), whereas sensitivity and specificity as high as 95% and 100% have been shown in other studies and referenced in the ASGE (America Society of Gastrointestinal Endoscopy) guidelines (11). This is the preferred method for making a pathologic diagnosis of a pancreatic mass. In addition to that, the presence of

an onsite cytopathologist during sampling for immediate assessment of adequacy improves the diagnostic yield by 10–15%, and reduces the number of passes required to get adequate sample (18-21).

In general, EUS-FNB is not superior to EUS-FNA of pancreatic masses but can be considered if EUS-FNA is non-diagnostic and a histologic diagnosis is required. However, EUS-FNB is preferred if autoimmune pancreatitis is in the differential as there is an increased risk of false positive cytology in this population (11).

Historically, FNB has been technically difficult for sampling of pancreatic head masses because of the stiffness of the needle and the acute angulation of the endoscope required to biopsy this location. However recent development of more flexible needles has largely solved this problem and core biopsies of masses in the head of the pancreas can routinely be obtained (22).

EUS-guided sampling of pancreatic masses has potential adverse effects, including a 0.5% to 2% risk of pancreatitis or bleeding. Tumor seeding with EUS-FNA is rare, with isolated cases being reported. Moreover, for pancreatic head masses, the small risk of tumor seeding, may not be relevant, since any potential site of seeding would likely be included in the resection specimen (11).

Historically, EUS has been performed before ERCP with stent placement because of the potential negative impact of the biliary stent on the accuracy of EUS staging. However, recent data suggests otherwise (23-25). Performing an EUS before ERCP also may identify unresectable pancreatic adenocarcinoma and help decide if biliary self-expandable metal stent (SEMS) need to be placed at subsequent ERCP.

ERCP

With the advent of EUS, the role of ERCP in pancreatic cancer diagnosis has decreased. There is still a potential role of ERCP following a non-diagnostic EUS or evaluation of suspicious pancreatic duct strictures. Pancreatic duct and common bile duct brush cytology and biopsies can be done, with a specificity of almost 100% but sensitivities of only 15–50% for cytology and 33–50% for biopsy (11,26,27). ERCP also has more potential adverse effects than EUS, and thus EUS is the preferred diagnostic procedure, and the role of ERCP is largely reserved for relieving biliary obstruction.

Relief of obstruction

Pancreatic cancer can lead to two types of obstruction, biliary or intestinal [usually gastric outlet obstruction (GOO)]. They can occur independently or concomitantly.

Biliary obstruction

Interventional endoscopists are frequently asked to consult on jaundiced patients with pancreatic cancer and a request to perform ERCP with biliary drainage. A few considerations should be kept in mind prior to proceeding, since ERCP carries significant risks. The points to consider are: is the indication appropriate? Is effective drainage technically possible? And does percutaneous drainage offer any advantages over endoscopic drainage?

Types of stents used for endoscopic biliary drainage

Biliary or pancreatic stents are usually placed using an ERCP scope, under fluoroscopic guidance over a guidewire. The stents can be plastic or metal.

Plastic stents are made of polyethylene, polyurethane, and Teflon, come in various shapes including straight (which have flaps at each end to help anchor the stents), single-pigtail, and double-pigtail. A variety of diameters and lengths are available and chosen based on the size of the stricture.

SEMS are called as such since they are made in a cylindrical mesh shape, made of metal alloy materials and come tightly wound up to facilitate their placement through the working channel of the scope over a guidewire. They start expanding immediately after deployment, and embed into the tumor or normal tissue by expansile, radial pressure. This helps to keep the stent from migrating. Like the plastic stents, the metal stents also come in various diameters and lengths to suit the size of the stricture. SEMS can be uncovered, partially covered, or fully covered. The advantage of using an uncovered metal stents is a low rate of stent migration. A study of 101 patients who received uncovered stents did not have any cases of stent migration (28), whereas another study of 241 patients receiving uncovered metal stents for unresectable malignant biliary strictures had only three cases of stent migration (29). They are however more difficult to remove and are more prone to tumor or tissue ingrowth. The covered metal stents on the other hand are easier to remove and less prone to tumor or tissue ingrowth. However, head to head studies have not shown any advantage of covered stents in terms of maintaining patency. The covered stents are more prone to migration and cannot be used at the hilum because of

possibility of "walling" off one side of the ductal system.

Indications for biliary drainage

Common indications for ERCP and biliary stenting in patients with pancreatic cancer include cholangitis, biliary drainage prior to surgery or chemotherapy, and pruritis. Having jaundice alone, without other accompanying symptoms may not be enough to justify a potentially risky procedure.

Cholangitis

Acute inflammation and infection of the bile duct constitutes acute cholangitis. The classic presentation is fever, abdominal pain, and jaundice (also known as Charcot's triad). Though only 50–75% of patients with acute cholangitis present with all three findings. Reynold's pentad is when these three are accompanied by lethargy and mental confusion. Cholangitis usually occurs in the setting of biliary obstruction and bacterial contamination, and organisms can also potentially ascend from the duodenum.

Protective factors against development of cholangitis are; an intact sphincter of Oddi, continuous flushing action of the bile, bacteriostatic activity of bile salts and secretory IgA and biliary mucous. Whereas, factors promoting cholangitis are; biliary obstruction (which raises intrabiliary pressure, thus increasing permeability of ductules and bacterial translocation, decreased bile flow and IgA production), disruption of the natural protective barrier, i.e., sphincter of Oddi from a stent, or a nidus of infection (such as a stone).

It is extremely rare for cholangitis to develop in a patient with a native (or non-instrumented) papilla. The biliary tree is sterile and patients with malignant obstruction who have never had a biliary intervention generally present with jaundice and/or pruritis only. Cholangitis almost always occurs in the setting of prior instrumentation such as sphincterotomy or stent placement. Therefore, when considering biliary drainage, possibility of cholangitis developing in future should be considered when weighing risks and benefits.

On the other hand, if cholangitis develops (as commonly occurs in the setting of an occluded biliary stent) then biliary drainage is an appropriate indication, and along with antibiotics, provides definitive and rapid relief from symptoms.

Pre-operative biliary drainage

Preoperative biliary drainage was introduced with the hope of improving the postoperative outcome in patients with carcinoma of the head of the pancreas and obstructive jaundice.

However, there are substantial arguments against performing routine pre-operative biliary drainage, the most important being an increase in the rate of complications. Others, which are less substantiated, include stents interfering in surgery or tumor dissemination.

Several retrospective studies and analysis of prospective databases (30-33) have associated preoperative biliary drainage with increased postoperative complications, including higher rates of infectious complications, such as postoperative wound infections. In a multicenter, randomized trial, preoperative biliary drainage was compared with surgery alone, for patients with cancer of the head of pancreas. In the study 202 patients with obstructive jaundice were randomly assigned to undergo either preoperative biliary drainage for 4 to 6 weeks (n=106), followed by surgery, or surgery alone (n=96) within 1 week after diagnosis. Preoperative biliary drainage was attempted primarily with ERCP and placement of biliary plastic stents. The primary outcome was the rate of serious complications within 120 days after randomization. The rates of serious complications were 39% in the early-surgery group and 74% in the biliary-drainage group [relative risk in the early surgery group, 0.54; 95% confidence interval (CI): 0.41–0.71]. The higher incidence of complications was mainly stent related and cholangitis. The study concluded that routine preoperative biliary drainage in patients undergoing surgery for cancer of the pancreatic head increases the rate of complications. However, the study has several limitations, including exclusion of patients with bilirubin >14mg/dL, low technical success rate for ERCP, and the use of plastic stents (since metal stents have a higher patency rate) (34).

In a recent meta-analysis, Scheufele *et al.* (35), looked at the impact of preoperative biliary drainage in malignant pancreatic head tumors on postoperative morbidity and mortality. They pooled the incidence of overall complications, wound infection, pancreatic fistula, intra-abdominal abscess, and death within the perioperative time period. In the final analysis, 22 retrospective studies and 3 randomized controlled trials were included with a total number of 6,214 patients. They showed an increased incidence of overall complications (odds ratio: 1.40; 95% CI: 1.14–1.72; P=0.002) and wound infections (odds ratio: 1.94; 95% CI: 1.48–2.53; P<0.00001) in patients receiving preoperative biliary drainage compared to surgery first. Mortality, incidence of pancreatic fistula, or intra-abdominal

abscess formation were not affected by preoperative biliary drainage. Their conclusion was also that, preoperative biliary drainage does not have a beneficial effect on postoperative outcome, and the increase of postoperative overall complications and wound infections urges for precise indications for preoperative biliary drainage and against routine preoperative biliary decompression.

Although it has now become generally accepted that routine biliary stenting prior to pancreatoduodenectomy (PD) is not indicated, many patients still require biliary drainage while awaiting surgical resection, including those needing to delay surgery to correct comorbidities, those symptomatic from hyperbilirubinemia, patients requiring vascular reconstruction, patients with severe hyperbilirubinemia (>20 mg/dL) or those receiving neoadjuvant therapy. However, it is important that the stent chosen has the best patency profile and not interfere with resection.

There has been a debate, whether to place a plastic or a metal endobiliary stents. Although SEMS provide better drainage compared with plastic stents and have superior patency profile, there have been concerns that SEMS may compromise resection and increase postoperative complications. Cavell *et al.* (36) compared surgical outcomes of patients undergoing pancreaticoduodenectomy (PD) with SEMS in place *vs.* plastic endoscopic stents (PES) and no stents (NS). Perioperative complications, margin status, and the rate of intraoperative determination of unresectability were looked at. Among patients who had a preoperative stent, SEMS did not increase overall or serious postoperative complications, 30-day mortality, length of stay, biliary anastomotic leak, or positive margin, but was associated with more wound infections and longer operative times. In those with adenocarcinoma, intraoperative determination of local unresectability was similar in the SEMS group compared with other groups. The study concluded that although SEMS are associated with longer operative times and post op wound infections, the benefits outweigh the risks and once the decision is made to drain prior to PD, there is no contraindication to place SEMS (36).

In summary, any biliary drainage is associated with possible complications, the risk of which has to be weighed against benefits, based on the clinical situation. Data suggests more frequent negative outcomes with routine preoperative biliary drainage. Therefore, biliary drainage is usually performed only in surgical patients who are also candidates for neoadjuvant therapies, in patients with acute cholangitis, or in patients with intractable pruritus or in whom surgery will be delayed.

Chemotherapy

Adequate therapy with some chemotherapy agents require the bilirubin to be below a certain level and based on the advice of the patient's oncologists, biliary drainage can be performed if technically feasible to help bring the bilirubin level down.

Pruritis

Pruritis is usually seen in the setting of jaundice, but can be the only manifestation of cholestasis, and the intensity of itching does not have to correlate with the serum bilirubin level. The pathophysiology of pruritis in the setting of hyperbilirubinemia is not entirely clear but is attributed to an increase in serum levels of two mediators, namely lysophosphatidic acid (LPA, which is a potent neuronal activator) and autotaxin (an enzyme which helps form LPA). When biliary obstruction is the cause of pruritus, drainage of even a small portion of the biliary tree results in a decrease or complete resolution of pruritis (37,38). Therefore, intractable pruritis can be an independent indication for performing biliary drainage.

Palliative biliary drainage

As discussed above, biliary drainage should be reserved for certain indications only after weighing risks and benefits because of its risks and procedure related complications. However even in palliation, it can potentially have an important role. Endoscopic palliative biliary drainage has been associated with an improvement in quality of life (QOL) (39,40). Barkay *et al.* conducted a QOL survey where a total of 164 patients responded and a significant improvement in physical, emotional, functional and overall QOL scores was reported after endoscopic biliary stenting (40). As far as choosing what types of stent to use for palliative biliary stenting, in patients with short survival, there is no significant difference in the total cost per patient between plastic stents and SEMSs (39).

Obstructive jaundice can result in altered taste and decreased appetite. Padillo *et al.* (41) looked at the role of biochemical and hormonal factors in the pathogenesis of reduced food intake in 62 patients with biliary obstruction. They observed that decreased food intake in these patients correlated with serum bilirubin, alkaline phosphatase and cholecystokinin levels. After biliary drainage, the resulting decreases in serum levels of bilirubin, alkaline phosphatase and cholecystokinin lead to an increase in appetite and food

intake (41). However, due to the inherent risks of ERCP and biliary drainage, and lack of substantive data, altered taste or decreased appetite by themselves are not considered definite indications for biliary drainage.

Intestinal or GOO

Relief of GOO is an important palliative modality. Malignant mechanical GOO can result from cancer affecting the distal stomach or proximal duodenum. Pancreatic cancer is one of the most common causes of malignant GOO. The symptoms of GOO include nausea, vomiting, weight loss, abdominal bloating, early satiety, and abdominal discomfort. The symptoms may not appear until high-grade obstruction occurs because of the ability of the stomach to distend significantly to accommodate its contents (42). Management options include surgical bypass, endoscopic stenting and palliative decompressive gastrostomy, also known as venting PEG or drainage PEG (with or without a feeding tube placement). Endoscopic stenting is done with SEMS, provided there is no obstruction distal to the planned site of stenting. In patients who have multiple sites of obstruction, e.g., in case of peritoneal carcinomatosis, a drainage PEG can be placed to palliate symptoms.

Luminal SEMS are made of metallic alloys in a mesh pattern, which are expand into the proper shape after deployment. SEMS can be uncovered, which are good for anchoring in place, but can become blocked from tumor ingrowth, whereas, fully covered stents avoid the tumor ingrowth issues, but are more prone to become dislodged. Stents used in duodenal obstruction are usually deployed through the working channels of therapeutic endoscopes. A combination of direct (endoscopic) visualization and fluoroscopic guidance allow for correct deployment of endoscopic stents.

The complications and risks include stent migration, stent blockage from food, debris or tumor ingrowth, bleeding, perforation, blocking the ampulla and causing pancreatitis or cholangitis, stent degradation and rarely breakage. With advancements in therapeutic regimens for malignancies, and improvement in life expectancies, these complications are becoming more relevant. Patients need to be informed about dietary limitations to avoid stent occlusion.

Quite often, patients require both biliary and duodenal stenting. Biliary stents can be placed or accessed after duodenal stent placement but this can be technically very challenging. EUS is now being used as an alternative to gain access to the biliary tract from the stomach to place biliary stents in cases of duodenal obstruction or presence of a duodenal stent.

Necrosectomy/debridement and drainage of post-surgical fluid collections

Postoperative fluid collections are a known complication of pancreatic resection and are a source of increased mortality and increased length of hospital stay. The symptoms can range from abdominal pain and infection to compressive symptoms causing gastric outlet or biliary obstruction. Traditionally, drainage has been done via surgical or interventional radiology (IR) guided percutaneous drain placement. The location of the collections can vary and sometimes drainage can be challenging, and EUS provides a viable alternative to these routes. EUS guided drainage of pancreatic pseudocyst has been well published, and similar approach is taken to drainage of postoperative fluid collections.

EUS guided transgastric drainage has the advantage of avoiding external drains, therefore preventing fluid and electrolyte losses and fistula formation (43). After accessing the fluid collection via EUS guided needle aspiration, the track is dilated and double pigtail plastic stents or lumen opposing metal stents are placed for continuous drainage. Complications include bleeding, stent migration and blockage. The access created for drainage also provides an opportunity to perform debridement and necrosectomy in case it is needed.

Tilara *et al.* (43), published a review of 31 patients, who underwent EUS-guided drainage of post pancreatic resection fluid collections, and showed a 100% technical (successful deployment of transgastric stents) and 93% clinical (resolution of symptoms and fluid collection on f/u imaging) success rate (43).

Pain control

Pain is reported by up to 90% of patients with advanced pancreatic cancer (44), making pain control a very important but at the same time a challenging aspect of pancreatic cancer management. World Health Organization (WHO) suggests a three-step approach for pain control, starting with non-opioid analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) and progressing to increasing doses of opioid analgesics (45). However, opioids often provide incomplete pain relief and are limited by their

adverse effects. This has led to exploring other options as alternatives or to supplement opioids for pain relief.

CPN

The celiac plexus is located around the site of origin of the celiac axis and the superior mesenteric artery. Consisting of ganglia and interconnecting neural rami, it transmits pain signals from the upper abdominal organs (pancreas, liver, gallbladder, stomach, ascending and transverse colon) to the spinal cord. In CPN, a neurolytic agent (ethanol) and an analgesic agent (bupivacaine) is injected into the celiac plexus to disrupt the transmission of pain signals. When this procedure is performed for benign diseases such as chronic pancreatitis, it is called celiac plexus block (CPB) and the agents used are local anesthetics or steroids (46).

EUS-CPN

Although, chemical ablation of the celiac plexus nerves (CPN) has been performed for over a century, the relatively recent introduction of EUS guidance for CPN has markedly improved its outcomes (47,48). Prior to the use of EUS, it used to be done surgically, then subsequently under radiographic, fluoroscopic, ultrasound or CT guidance. EUS-CPN, as compared to the percutaneous approaches, has the theoretical benefits of improving needle localization and spread of the injected agent, thereby minimizing complications and improving pain relief. EUS-CPN has also been shown to provide more durable pain relief than CT guided CPN (49). More over early EUS-CPN has been shown to provide better pain relief and greater reduction in morphine consumption than conventional pain management (50). Several techniques are currently used for EUS-CPN.

The classic approach (central technique), involves injection of a neurolytic agent at the base of the celiac axis. Using the EUS, the abdominal aorta is first identified through the posterior wall of the upper gastric body, and then traced to identify the celiac axis. A needle is then pierced through the gastric wall and advanced to a point just above the point of origination of the celiac axis from the aorta. The agent is then injected to produce a sufficient echogenic cloud (usually about 10–20 mL of ethanol) (46).

In the second method (bilateral technique), after identifying the origin of the celiac axis, the EUS scope is rotated clockwise and then counterclockwise to inject a total of 10-20 mL of neurolytic agent (usually ethanol) on both sides of the celiac axis (46).

In addition to these, another relatively recent technique is EUS-guided direct celiac ganglia neurolysis (EUS-CGN) (46). In this technique, which was developed by Levy *et al.* (51) in 2008, the celiac ganglion (CG) is identified with EUS guidance, and punctured with a needle, followed by absolute ethanol injection. The CG are usually identified between the aorta and the left adrenal gland in most cases and cephalad to the origin of the celiac axis in some cases. These CG are hypoechoic with hypoechoic connections, likely representing the adjoining neural rami. They can appear caterpillar-like or small and nodular. Ethanol is injected until the targeted ganglion becomes hyperechoic and difficult to visualize (46,52).

In an early study 79–88% of patients undergoing EUS-CPN experienced long-lasting improvement in pain scores, and 82–91% of patients required the same or a lower amount of pain medication (48). A meta-analysis published by Puli *et al.* in 2009 showed relief of pain in 80.12% (95% CI: 74.44–85.22) of 283 patients with pancreatic cancer and 59.45% (95% CI: 54.51–64.30) of 376 patients with chronic Pancreatitis (53). Similarly, Kaufman *et al.* in 2010 showed relief of pain in 72.54% of 221 patients with pancreatic cancer and 51.46% of 119 patients with chronic Pancreatitis (54).

Real-time guidance and color Doppler imaging by EUS has made the procedure easier and safer, resulting in greater pain relief. Pain relief is achieved by EUS-CPN in 70–80% of patients with pancreatic cancer and in 50–60% of those with chronic pancreatitis. The bilateral technique may be more efficient than the central technique, although the central technique is easier and possibly safer. Moreover, EUS-CGN may provide greater pain relief than conventional EUS-CPN. Procedure-related complications include transient pain exacerbation, transient hypotension, transient diarrhea, and inebriation. Although most complications are not serious, major adverse events such as retroperitoneal bleeding, abscess, and ischemic complications can occasionally occur.

EUS can be a useful tool to tackle the difficult but important issue of pain control and improve the QOL of patients with pancreatic cancer.

EUS as an aid to the actual treatment of pancreatic cancer

Placement of fiducials is a routine procedure, however the rest of the modalities in this section, including the local therapies are still investigational and not common practice at this time.

Placement of markers

Fiducials

EUS guided fiducial marker placement can be done with or without fluoroscopy. Fiducial markers are inert radiopaque spheres, coils, or cylindricals that are implanted inside or adjacent to the tumor to aid image-guided radiation therapy (IGRT) (4,55). IGRT allows precisely aimed delivery of radiation to the tumors while minimizing radiation to normal tissues, but requires presence of multiple reference points through which the tumor can be identified and tracked. Prior to the use of EUS-FNA, fiducial markers were placed either by surgery or percutaneous route under ultrasound or CT guidance (4). Adverse effects include migration of fiducials, minor bleeding and mild acute pancreatitis.

In addition to radiation therapy, fiducial markers can also potentially be used for localization of small neuroendocrine tumors to aid in parenchyma-sparing pancreatic surgery (56).

EUS-guided fine-needle tattoo (EUS-FNT) for preoperative localization of small pancreatic tumors

Small pancreatic tumors are difficult to locate during minimally invasive laparoscopic surgeries. Several case reports and case series have demonstrated the efficacy and safety of EUS-FNT for the preoperative localization of small pancreatic tumors. Once the tumor is localized with EUS, fine-needle injection is performed with various dyes [India ink, methylene blue, indocyanine green, or purified carbon particles (SPOT)] to tattoo the tumor This helps limit resection of normal pancreatic parenchyma.

Local endoscopic treatment of the tumor

EUS is an ideal platform to deliver therapy to pancreatic tumors. This field is in its infancy and reports are generally related to small case series. Various therapeutic options are being evaluated including brachytherapy, ablations, or delivery of biologics or chemotherapeutic agents either alone or as an adjuvant. However, as mentioned above, these are not standard of care at this time, and the experience with these is in the form of case report, small case series or pilot studies.

Brachytherapy

Radioactive seeds used for brachytherapy include iodine-125, iridium-192, and palladium-103. Out of these, iodine-125 is the most commonly used, since it has a long half-life (59.7 days) and is appropriate for treatment of rapidly growing tumors. As compared to the traditional approaches to brachytherapy (by open laparotomy or image guidance), EUS-guided brachytherapy has an advantage of a more precise placement in the tumor itself and the minimization of damage to the surrounding normal tissue (4,55).

Ethanol ablation

EUS-guided ethanol ablation of solid pancreatic tumors was first reported in 2006, it has been used in the management of pancreatic neuroendocrine tumors, and also used in combination with EUS-CPN for pain control. This technique requires further study and refinement.

Radiofrequency ablation (RFA)

RFA has been used for the treatment of primary and metastatic liver cancers. EUS guidance is now also being investigated to aid in RFA of pancreatic tumors (57). The potential targets are neuroendocrine tumors and insulinomas. The role of RFA in unresectable advanced pancreatic cancer is also being investigated (4,58,59).

Photodynamic therapy (PDT)

EUS-PDT of the pancreas has previously been done mostly in animal studies. The first clinical experience with EUS-PDT in pancreatic cancer was published in 2015 (60). Four patients with locally advanced pancreaticobiliary cancers were included. There was one patient with pancreatic tail cancer who had localized tumor progression despite chemoradiotherapy. The median follow-up period was five months and all the patients showed stable disease during the follow-up. For the patient with pancreatic tail cancer, the follow-up period was three months. Authors suggested utilization of EUS-PDT as a salvage treatment for patients with locally advanced pancreaticobiliary cancers who are poor surgical candidates and/or had progression despite chemoradiotherapy (4,60).

EUS-guided fine needle injection (EUS-FNI) of biologics or chemotherapeutics

One of the challenges in systemic chemotherapy for pancreatic cancer is the lack of penetration of the chemotherapy agents into the tumor secondary to its dense desmoplastic stroma. This has led the researchers to look into alternative delivery methods. A prospective study by Levy *et al.* (61), describes EUS guided injection of gemcitabine for locally advanced and metastatic pancreatic cancer. EUS-FNI was performed prior to conventional therapy in 38 patients with stage II, III and IV pancreatic

cancer. There were no significant adverse effects, and although this particular study was limited in the sense that it did not allow a determination of survival advantage, however it did suggest feasibility, safety and potential efficacy of EUS-FNI (61).

Similarly, carbohydrate sulfotransferase 15 (CHST15) has been known to promote tumor growth and invasion and considered to be an emergent therapeutic target for pancreatic cancer. In a recent publication, Nishimura *et al.* (62), showed successful EUS-FNI of STNM01 (the double-stranded RNA oligonucleotide that specifically represses CHST15) in 6 patients with pancreatic cancer. There were no adverse events. The mean tumor diameter changed from 30.7 to 29.3 mm 4 weeks after injection. Four patients exhibited necrosis of tumor in biopsy specimens. CHST15 was highly expressed at baseline, with 2 patients showing large reductions of CHST15 at week 4. The mean OS of these 2 patients was 15 months, whereas it was 5.7 months for the other 4 patients. They concluded that, EUS-FNI of STNM01 in pancreatic cancer is safe and feasible, and CHST15 reduction could predict tumor progression and OS. Injections of STNM01 during the beginning of treatment may reduce CHST15 and warrants further investigation (62).

EUS-guided intratumoral injection of a mixed lymphocyte culture of donor and host mononuclear cells (cytoimplant) into the tumor with EUS-guided FNI for the treatment of advanced pancreatic cancer was reported in 2000 (63). It was hypothesized that the lymphocyte reaction would result in activation of immune effector cells and release of cytokines with tumor suppressive properties. Of eight patients, two had partial responses and one a minor response with a median survival of 13.2 months (63). No further reports have been published.

OncoGel is a chemotherapeutic formulation for intralesional injection of paclitaxel for local treatment of unresectable solid tumors. A thermosensitive, biodegradable copolymer, ReGel is used to deliver paclitaxel to solid tumors, and provides continuous controlled-release for up to 6 weeks (64,65).

Role of TNF-alpha in locally advanced pancreatic cancer (LAPC)

Tumor necrosis factor alpha is a potent inflammatory cytokine with substantial anticancer activity. Despite the effectiveness, its use is limited due to severe systemic toxicity consisting of hypotension and shock-like symptoms. TNFerade biologic is a novel means of selectively delivering TNF-α to tumor cells by gene transfer through intratumoral vector injection. Pre- clinical studies have shown low systemic toxicity. Direct delivery to the pancreatic tumor can be done via percutaneous route or by EUS (weekly injections). A study by Herman *et al.* (66) showed TNFerade administration to be safe, but not effective in prolonging survival in patients with unresectable LAPC. Further studies are needed to investigate the efficacy of this interesting approach.

Future/potential roles

Novel EUS techniques

Novel EUS techniques are currently being investigated for Pancreatic cancer screening in HRI.

Contrast-enhanced harmonic EUS

This technique detects signals from microbubbles in vessels and thus can visualize parenchymal perfusion and microvasculature in the pancreas, and is not limited by the artifacts associated with Doppler ultrasound. In pancreatic cystic lesions, neoplastic solid components can be identified as hyper enhanced lesions. It has a high sensitivity and specificity in the diagnosis of pancreatic cancer (67,68).

EUS elastography

Cancerous tissue is stiffer than healthy tissue, and EUS elastography can make this distinction based on tissue elasticity. However, there are limitations, e.g., chronic pancreatitis and pancreatic cancer can appear similar on elastography. This is still a work in progress (69).

EUS guided FNA and pancreatic juice sampling:

Combining cytopathology with KRAS mutation analysis increased the sensitivity, negative predictive value and accuracy of pancreatic cancer *in situ* diagnosis. TP53 mutations in secretin stimulated pancreatic juice analysis is also indicative of high grade dysplasia and invasive pancreatic cancer (70,71).

Needle-based confocal laser endomicroscopy (nCLE)

This is an endomicroscopic technique where the mucosal layers are imaged at a subcellular level and can identify patterns corresponding to IPMNs, serous cystadenomas and pancreatic cancer (71,72).

Duodenal spectroscopy

The periampullary duodenal mucosa shares the genetic and

environmental makeup of the pancreas. Low-coherence-enhanced backscattering spectroscopy parameters and optical properties of the periampullary duodenal mucosa are being studied to predict the probability of pancreatic cancer (73).

Conclusions

Pancreatic cancer is a deadly disease, and while dealing with it is obviously not easy for the patients, it can also be particularly challenging for health care providers to provide adequate care to these patients. A multidisciplinary approach can help both the patients and providers. In addition to oncologists, oncology nurses, hepatobiliary surgeons, pain specialists, nutritionists, and social workers, now Interventional radiologists and Interventional gastroenterologists have become an integral part of the team taking care of pancreatic cancer patients. The composition of the team varies according to the available resources and expertise in each institution.

The above is meant to be just an overview of the available options, and is by no means a comprehensive review. Interventional endoscopy is a dynamic field and with each passing day, experience is being gained, research is being done and new techniques are being evolved, with the ultimate goal of enhancing patient care.

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Footnote

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