

Endoscopic Ultrasound of the Pancreas

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ABSTRACT

Endoscopic Ultrasound (**EUS**) appeared as a promising imaging method for the study of pancreatobiliary disorders, because it allows the placement of a high-frequency ultrasound transducer near the targeted organ, thus providing detailed high-resolution images. The role of EUS in pancreatic disease initially involved visualization of parenchymal and ductal abnormalities associated with pancreatitis and malignancy. This endeavor gained great credibility and utility with the advent of EUS-guided Fine Needle Aspiration (**FNA**) for sampling of pancreatic abnormalities. Now the field is concentrating on the development of therapeutic techniques for the treatment of pancreatic disease.

EUS is currently a valuable investigative tool for endoscopists. The widespread use of EUS in the last decade has significantly impacted on the management of pancreatic disease, as it simultaneously provides primary diagnostic, biopsy and staging information. The clinical interest of EUS is now enhanced by interventional procedures. Therapeutic EUS includes techniques such as the celiac block and transmural pseudocyst drainage. Newer techniques include EUS-guided fine-needle injection therapy in which a variety of agents are being investigated for the treatment of pancreatic cancer. Novel EUS-guided techniques are being devised to drain and alleviate pancreaticobiliary and gastroduodenal obstruction.

INTRODUCTION

During recent years, Endoscopic Ultrasound (**EUS**) has become an important imaging technique for diagnosis and management of pancreatic diseases. EUS was first introduced by Dr. Eugene DiMagna in the mid-1980s for better visualization of the pancreas, and overcame many of the limitations (abdominal gas and fat) of transabdominal ultrasonography when evaluating patients for possible pancreatic diseases. It is a combination of a small, high frequency ultrasound transducer on the tip of a video endoscope, which allows close contact with the target organ so that high-resolution images can be obtained [1-3].

The technology of EUS progressed with the introduction of new electronic radial and linear EUS transducers with digital image processing, enhanced resolution, and color Doppler capability. The radial echo endoscope produces a 360° cross-sectional image that is perpendicular to the long axis of the scope, whereas the linear echo endoscope produces a view that is parallel to the long axis [1,4]. With the introduction of the curved linear array echo endoscope in the 1990s, the indications for EUS have expanded. The curved linear array echo endoscope enables the visualization of a needle as it exits from the biopsy channel in the same plane of ultrasound imaging in real time. This allows the endoscopist to perform a whole range of interventional applications ranging from Fine Needle Aspiration (**FNA**) of lesions surrounding the gastrointestinal tract [5,6].

Overall, EUS has been shown to be a cost-effective technique for evaluating pancreatobiliary disorders. It allows to clearly visualize pancreatic gland and common bile duct as well as adjacent anatomic structures. Today, the foremost clinical situations that can benefit from the high performance of EUS are the diagnosis and/or staging of pancreatic cystic or solid tumors and the diagnosis of extra hepatic cholestasis and chronic pancreatitis, particularly where others diagnostic methods have failed, and EUS has a higher diagnostic yield than Positron Emission Tomography (**PET**), Computed Tomography (**CT**) and US for recognizing early pancreatic tumors [7-9]] In parallel to the widespread importance of diagnostic endoscopic ultrasound, the therapeutic and interventional applications of this procedure are expanding and may become a major breakthrough in the management of pancreaticobiliary diseases. Including EUS-guided fine-needle injection therapy in which a variety of agents are being investigated for the treatment of pancreatic cancer, and EUS-guided drainage to celiac plexus block and drainage of pancreatic pseudocyst (10, 11).

DIAGNOSTIC ROLE OF EUS IN PANCREATICOBILIARY DISORDERS

EUS is a semi-invasive investigation technique with a low morbidity rate (the rate of complications is less than 1 in 2000) that has demonstrated its efficacy in the diagnosis of diseases of the pancreas. The intragastric and intraduodenal position of the EUS probe in close proximity to the pancreas and the extra hepatic biliary system permits the obtainment of high resolution images and the visualisation of local anatomic details not detected by other imaging techniques. This peculiarity, coupled with the ability to perform EUS-FNA to acquire tissue samples has rapidly made EUS one of the most important and accurate tools for the evaluation of both benign and malignant pancreaticobiliary disorders [11,12].

Benign pancreaticobiliary disorders

Cholelithiasis

Cholelithiasis is a common complication of gallbladder stones, occurring among 15% to 20% of patients. Among patients who have undergone cholecystectomy, 1% to 5% have retained or recurrent bile duct stones. Clinical and biochemical abnormalities associated with this condition are neither accurate nor specific enough for diagnosis. The diagnosis of cholelithiasis has remained a challenge for many years. EUS, developed in the past 15 years, has been evaluated and appears to be one of the best techniques because of its excellent spatial resolution [12,13].

EUS is an extremely accurate test for diagnosis of Common Bile Duct Stones (**CBDS**) and can be used to select patients who should undergo a therapeutic Endoscopic Retrograde Cholangiography (**ERCP**), thus avoiding the risk of complications associated with diagnostic ERCP. Studies have shown that EUS-based approach can reduce the number of diagnostic ERCP by 60-75% in this patient's population. In addition, this approach is more successful in the overall evaluation of CBDS, with fewer complications than using an ERCP based approach. The use of EUS instead of ERCP has been found to be cost-effective in both intermediate and high-risk patients in the context of laparoscopic cholecystectomy and in severe acute pancreatitis [11,14].

Pancreatitis

In 10-30% of patients with Acute Pancreatitis (**AP**), etiology cannot be established by history, physical examination, routine laboratory testing, and abdominal imaging (transabdominal ultrasound and/or computed tomography). After an initial episode, approximately 30% of those patients with idiopathic acute pancreatitis will experience recurrence (Acute recurrent pancreatitis) [15,16]. In patients with pancreatitis, EUS should be proposed to determine the etiology in idiopathic acute cases, especially if recurrent, to help establish the diagnosis in suspected chronic cases, and to search for cholelithiasis when a biliary etiology is suspected. Studies have shown EUS to be highly accurate in the diagnosis of gallstone disease (including microlithiasis), chronic pancreatitis, pancreatic tumors and other causes of AP which have negative or inconclusive results as assessed by other imaging methods [11,17].

Most frequent causes of Acute Recurrent Pancreatitis (**ARP**) are occult CBD and/or gallbladder microlithiasis, while other etiologies include unrecognized chronic pancreatitis, pancreas divisum, sphincter of Oddi dysfunction, and other less frequent etiological factors such as small pancreatic tumors or cysts. Given the unsurpassed capacity of EUS to visualize the biliary system, as well as its high reliability in diagnosing lesions of the pancreatic parenchyma and of the pancreatic ducts, EUS is an almost ideal minimally invasive tool for evaluation of patients with acute idiopathic pancreatitis. The diagnostic yield of EUS in idiopathic acute pancreatitis is higher when compared with Magnetic Resonance Cholangio Pancreatography (**MRCP**). Studies indicated that EUS with bile crystal analysis is of great value and substantially reduces the number of unnecessary diagnostic ERCP [11,15].

Furthermore, the diagnosis of Chronic Pancreatitis (**CP**) can be very challenging. In particular, the real dilemma in CP is to recognize and diagnose the disease in its early stages, for which there are insufficient sensitive and specific tests available. Moreover, a major limitation is the inability of clinicians to obtain a tissue or histological sample to confirm the clinical diagnosis. If EUS is demonstrated to be sensitive and specific for early CP, it would really make this procedure a major breakthrough in the evaluation of this condition. EUS detects changes of mild CP that may not be detectable with other imaging modalities or functional testing but which can be confirmed by histology. Of the EUS parenchymal and ductal criteria used to diagnose CP, parenchymal criteria including hyperechoic foci, hyperechoic strands and parenchymal lobularity can be visualized by EUS only, making it the most theoretical valuable test to diagnose early CP [3,11].

Pancreaticobiliary malignancies

Pancreatic cancer

Pancreatic cancer is the most deadly of all gastrointestinal malignancies and has a very poor prognosis. Unfortunately, most patients present late in the course of their disease and, at the time of diagnosis, only 10 to 25% of patients will be eligible for potentially curative resection. Efforts must be oriented towards an early diagnosis and towards reliably identifying patients who can really benefit from major surgery [18,19]. In recent years, diagnostic imaging techniques such as Multi-Detector-Row Computed Tomography (**MDCT**), MRI, ERCP and EUS have been developed, elevating the ability to diagnose pancreatic carcinoma, although there are still inherent limitations [20,21].

EUS has a manifold role in the evaluation of patients with clinical suspicion of a pancreatic mass, and in those in whom a solid pancreatic lesion has already been identified. This diagnostic procedure is considered a safe procedure with complication rates as low as 1.1-3% for diagnosis of pancreatic cancer. Despite recent advances in both CT and MR technologies and software, EUS is still the most accurate diagnostic test for the detection of pancreatic lesions, particularly for those smaller than 2 cm. The major advantage of EUS is its high negative predictive value, close

to 100%, indicating that the absence of a focal mass at EUS reliably excludes pancreatic cancer [11,22].

A distinct advantage of EUS is its ability to obtain tissue via FNA. EUS-FNA was first reported in 1992, and it was developed to enhance the diagnostic capability of EUS by providing diagnostic material. With the addition of tissue sampling via FNA, some limitations exist in the differentiation of benign from malignant solid pancreatic lesions. EUS-guided biopsy is superior to percutaneous biopsy for the investigation of many intra-abdominal malignancies, as it has a lower risk of tumor seeding both along the needle tract and intraperitoneally. EUS-FNA is technically successful in 90-95% of procedures, with high sensitivity and specificity for malignancy. However, EUS-FNA may be technically demanding and multiple punctures may be needed to obtain adequate cytological samples, which may be associated with few but not insignificant complications such as acute iatrogenic pancreatitis, bleeding, and infection. In addition, EUS-FNA provides false-negative results up to 20-40% for malignancy, especially in patients with underlying chronic pancreatitis [1,23].

EUS-guided core needle biopsy (EUS-CNB) was designed to overcome the limitations of EUS-FNA by providing a histologic specimen that increases the accuracy of diagnosis. The overall diagnostic accuracy of EUS-CNB with fewer passes was initially reported to be higher than that of EUS-FNA (85% versus 62%), although the difference was not statistically significant. Moreover, recent innovations in EUS that intended to address these limitations include contrast-enhanced EUS (CE-EUS) and EUS elastography (EUS-E). Contrast-enhanced EUS to better assess the perfusion inside the pancreatic mass has been evaluated in one study using Levovist and more recently using the second generation contrast agent SonoVue [1,4,11].

Finally, EUS plays a key role in the staging and assessment of resectability of pancreatic cancer. Treatment of pancreatic cancer is an evolving field and an accurate staging becomes increasingly important. The staging of pancreatic cancer is based on the Tumor-Nodemetastasis (**TNM**) system. Owing to the close proximity of the ultrasound probe to the pancreas, EUS is highly accurate in the assessment of the pancreas itself (T-staging) and structures adjacent to the pancreas (N-staging and local resectability); however, it performs less well in assessing distant disease (M-staging), owing to the limited distance of ultrasound penetration [1,23].

Bile duct cancer

The accurate diagnosis of extra hepatic bile duct carcinoma is difficult, even now. Most patients with bile duct cancer are diagnosed in an advanced stage. Malignant bile duct tumors, i.e. cholangiocarcinomas, present as biliary strictures that need to be differentiated from strictures of benign origin, which in the proximal biliary tree corresponding to the hepatic hilum can be responsible for up to 20% of all cases. In the presence of jaundice, ERCP with brush cytology and/or endobiliary forceps biopsy is usually first performed to reach a definitive diagnosis, while EUS-

FNA has been used in some centers as the second [11,24].

Pancreatic cysts

Pancreatic cysts represent a wide spectrum of pathology, including inflammatory pseudocysts, benign serous cystadenoma, and premalignant or malignant lesions, such as intraductal Papillary Mucinous Neoplasms (**IPMN**), mucinous cystadenoma and cystadenocarcinoma, and other rare forms. An increased number of pancreatic cysts are being diagnosed due to the increased usage of cross-sectional imaging. Pancreatic cysts can be diagnosed and assessed by using CT and MR, but these imaging modalities have been inconsistent in differentiating them. EUS is now being used to investigate cystic pancreatic lesions, particularly as a means of EUS-guided cyst aspiration [11,25].

The use of EUS in this setting plays a pivotal role, both diagnostic (appearance and tissue sampling) and therapeutic (aspiration, ablation). Based on the information obtained at EUS and FNA a decision can be reached to cease further work up, follow-up with repeat imaging, or to resect the cyst. An important distinction is that of mucinous from nonmucinous cysts, and this mainly relies on analysis of the cystic fluid that can be safely and efficiently sampled by EUS-FNA. The diagnostic accuracy of EUS alone for detection of malignant or premalignant cysts reaches 95%, although it has important limitations for the differential diagnosis of benign and malignant cysts with overall accuracy rates of 40 to 93% [11,25].

THERAPEUTIC AND INTERVENTIONAL ROLE OF EUS IN PANCREATICOBILIARY DISORDERS

With the advancement of technology in the echo endoscopes and the various accompanying instruments, EUS is now playing a role in therapeutic and interventional endoscopy. During the last 15 years, EUS has become an important imaging procedure for management of pancreatic diseases. The clinical interest of EUS is now enhanced by interventional procedures. Noteworthy, fine-needle aspiration biopsy is one of the most important contributions of EUS, in particular for the investigation of patients with pancreatic cancer and cystic tumors [1,7].

Therapeutic EUS has thus far revolved around three themes. The first is fine-needle injection therapy. Using this technique, a needle is advanced into a target tissue, and a therapeutic agent is deposited locally under EUS guidance. Celiac plexus block involves the delivery of ablative or analgesic compounds into the celiac ganglion through EUS-guided fine needle injection. Pancreatic cancer injection therapies are under active investigation using a variety of therapeutic agents. Second, EUS-guided drainage and anastomosis allows the establishment and maintenance of drainage tracts between the gastrointestinal tract and adjacent cavities or visceral lumens. Third, EUS is used to identify patients who are appropriate candidates for standard endoscopic interventions [10,11].

Fine-Needle Injection Therapy

Celiac Plexus Block

The celiac plexus is a horseshoe-shaped series of neural ganglions that are draped over the origin of the celiac artery. The splanchnic nerves descend through the diaphragm, innervating this ganglionic plexus. The celiac plexus acts as the center for transmitting both visceral and efferent pain sensation to the majority of the abdominal viscera including the pancreas. Consequently, celiac plexus block has been used for pain relief in patients with unresectable pancreatic cancer or chronic pancreatitis [5,10].

Pancreatic cancer and chronic pancreatitis commonly produce pain that is difficult to control. When the pharmacological therapies are inadequate, infiltration of the splanchnic nerves or celiac plexus neurolysis may improve pain control and quality of life, while reducing the risk of drug-related side effects. Celiac plexus block can be administered percutaneously or under EUS guidance [7,10]. EUS-guided Celiac Plexus Block (EUS-CPB) for pain control in chronic pancreatitis and EUS-guided celiac plexus neurolysis (EUS-CPN) for cancer related pain control are the most well established interventional procedures performed under EUS guidance. Celiac plexus block involves injection of a steroid (triamcinolone) and an anesthetic agent (bupivacaine) into the celiac plexus. Celiac plexus neurolysis is the injection of a neurolytic agent (absolute alcohol) into the celiac plexus in order to ablate or destroy the ganglia, thereby interrupting pain transmission. Major complications are rare with EUS-guided celiac block. Minor complications associated with celiac block have included diarrhea (38%) and orthostatic hypotension (44%). These effects are a consequence of sympathetic blockade and for the most part are transient [5,10,11].

Pancreatic Cancer Injection Therapy

Locally advanced pancreatic cancer remains a major clinical challenge with limited treatment options and a very poor prognosis. Because systemic chemotherapy and radiotherapy have limited efficacy, a major effort is underway to develop locally administered therapeutic agents. This approach capitalizes on the ability of EUS to place needles precisely within focal masses. Proposed therapeutic agents include activated lymphocytes, viral vectors, gene therapy, and physical ablation [10,11].

EUS-guided injection of antitumor agents is an attractive treatment option in pancreatic cancer. Antitumor agents for treatment of pancreatic cancer including allogeneic mixed lymphocyte culture (Cytoimplants), ONYX-015, and TNFerade. The most recent advance in the area of PC is the use of TNFerade. TNFerade is a replication-deficient adenovector containing human TNF- α cDNA that is regulated by a radiation-inducible promoter, Egr-1 (Early growth response). It was found that TNFerade was generally well tolerated, with encouraging indications of activity using both routes except for injection site pain. Cytoimplants lead to activation of immune effector cells and release cytokines, causing tumor regression. Furthermore, ONYX-015 is an E1B 55-kDa gene-deleted replication-selective adenovirus that preferentially replicates in malignant cells, leading to cell death [1,26,27].

Another application of EUS is in the EUS-guided placement of fiducial markers for image-guided radiation therapy in the treatment of unresectable PC. The advantages of imaging-guided radiation therapy include accurate localization of the tumor with precise delineation of its local extent, the use of escalating doses of radiation with minimal toxicity to surrounding normal tissues. The markers were traditionally being placed percutaneously, which has a similar complication profile to percutaneous organ biopsy. However, placement of the fiducial markers under EUS guidance is now feasible, safe and effective [1,28].

EUS-Guided Drainage

Pancreatic Pseudocyst Drainage

A pancreatic pseudocyst is the most common cystic lesion of the pancreas. A pseudocyst is a fluid collection, rich in amylase, which is enclosed by a nonepithelialized wall and localized within or adjacent to the pancreas after acute or chronic pancreatitis, pancreatic trauma or obstruction of the pancreatic duct. Pseudocysts should be drained when symptomatic, progressively enlarging, or infected. Drainage can be achieved through endoscopic, radiologic, or surgical techniques. Pseudocysts have been drained through stenting of the pancreatic duct (Transpapillary drainage) or stenting of a drainage tract created between the pseudocyst and the gastroduodenal lumen (Transmural drainage). Endoscopic drainage of pancreatic pseudocysts is less invasive than surgery, but is not possible in all cases [7,10].

Endoscopic methods for pancreatic pseudocyst drainage are associated with low mortality and acceptable success rates. EUS-guided drainage is associated with a low rate of complications. Thus, this technique has the theoretical advantage of reducing the risks of bleeding, perforation, and, potentially, infection. Furthermore, EUS can provide important information in aiding pancreatic pseudocyst drainage. It allows accurate measurement of the distance between the gut lumen and the cystic cavity of the pseudocyst. Color Doppler imaging can be used to avoid major vessels and allows the diagnosis of important pseudocyst complications such as pseudoaneurysm and varices. EUS is helpful in identifying debris within a pseudocyst, which may not be drainable and which may increase the risk of infection. EUS can image the nature of the presumed pseudocyst and be helpful in differentiating it from other cystic lesions of the pancreas [5,7].

Bilioenteric Drainage

Over 50% of patients with pancreatic cancer present with jaundice and malignant biliary obstruction. ERCP is widely used in current medical practice as a biliary drainage method for biliary obstruction. Recently, EUS-guided Biliary Drainage (**EUS-BD**) has emerged as a minimally invasive alternative to percutaneous and surgical interventions for patients with biliary obstruction who had failed ERCP. EUS-guided biliary drainage has become feasible due to the development of large channel curvilinear therapeutic echo-endoscopes and the use of real-time ultrasound and fluoroscopy imaging in addition to standard ERCP devices and techniques [29,30].

EUS-guided needle insertion into the visible intrahepatic bile ducts allowed guide wire placement, balloon dilation, and plastic stent placement. EUS-guided decompressions is not only minimally invasive but it is a single step procedure that provides more physiological internal bile drainage with improved patient comfort and decreased risk for fluid and electrolyte disturbances. Furthermore, EUS-guided biliary drainage using transgastric puncture of the intrahepatic duct or the common bile duct is feasible in patients with inaccessible papillae due to duodenal obstruction, surgically altered anatomy or hilar block due to cholangiocarcinoma or gallbladder cancer. Finally, EUS-guided biliary drainage may be safer than Percutaneous Transhepatic Biliary Drainages (**PTC**) since the bile duct is accessed under real-time EUS guidance using Doppler to avoid blood vessels in the needle path [10,29].

EUS-Guided Conventional Endoscopic Intervention

Ampullary Adenoma

EUS is used to identify patients who are appropriate candidates for standard endoscopic interventions. The absence of invasive disease allows the consideration of endoscopic snare resection. Ampullary adenoma is a pre-cancerous lesion arising from the duodenal papilla that is often asymptomatic. Endoscopic snare resection is the treatment of choice in appropriately selected patients with ampullary adenoma. Ampullary adenomas can contain loci of carcinomatous change that are often undetected on standard forceps biopsy. The presence of invasive carcinoma is a contraindication to endoscopic resection. EUS is the most sensitive method for identifying invasive disease. Patients with no evidence of malignancy on forceps biopsy and no sign of invasive disease on EUS can be considered for snare resection [10,31].

Gallstone Pancreatitis

Gallstones are responsible for about half of the cases of acute pancreatitis in many countries. Although the exact mechanism of biliary pancreatitis is not understood, gallstone migration into the common bile duct is presumed to initiate pancreatitis. Endoscopic sphincterotomy and stone extraction provide significant benefits in patients with acute pancreatitis and choledocholithiasis. Due to the morbidity and mortality associated with ERCP, an effort has been made to identify common bile duct stones by less invasive means. EUS provides a safe method to examine the common bile duct and accurately identify choledocholithiasis [10,32].

CONCLUSION

The use of Endoscopic Ultrasound (**EUS**) in pancreatic disease is rapidly evolving as the field moves from a primarily diagnostic role to one of therapeutic intervention. EUS is a major advance in the evaluation of both benign and malignant conditions, and has now been incorporated into the diagnostic algorithm of pancreaticobiliary disorders worldwide. It is crucial for an accurate preoperative evaluation and staging of pancreatic cancer which is essential to choose the correct management strategy. Furthermore, EUS-guided intervention has opened a new realm of exciting clinical applications for endoscopy including FNA of lesion/lymph node, celiac plexus block/neurolysis and pancreatic pseudocyst drainage.

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