INTRODUCTION

Endoscopic ultrasound (EUS) was introduced in 1980, specifically for the purpose of imaging the pancreas. The indications for its use have since broadened, and EUS has now become an important tool for not only diagnostic purposes, but also to obtain tissue samples for histologic diagnoses in a variety of gastrointestinal disorders. Indeed, EUS has revolutionized the approach to pancreatic diseases.

EUS offers a significant technical advantage over other imaging modalities such as trans-abdominal ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) in the evaluation of the pancreatic disorders, because the close proximity of the pancreas to the gastric and duodenal lumen allows EUS to obtain high-resolution images that are unobstructed by overlying bowel gas. In fact, EUS has been shown to be more sensitive in visualizing solid pancreatic tumors <3 cm as compared to a CT scan as well as in identifying small pancreatic lesions as compared to both a CT scan and MRI. Additionally, EUS is associated with fewer complications than endoscopic retrograde cholangiopancreatography (ERCP). Further, it can detect features of chronic pancreatitis in the pancreatic parenchyma and ducts that are not adequately visible in any other imaging modality.

Another added benefit of EUS is its ability to biopsy pancreatic lesions in real time for tissue diagnosis. A review of the literature suggests that the overall diagnostic accuracy of EUS-FNA is 76%–90% for pancreatic diseases, 82%–100% for lymph node and mediastinal diseases, and 38%–100% for gastrointestinal diseases such as submucosal tumors.

Currently, the two dedicated instruments used for EUS examination are radial- and linear-array ultrasound. The radial system uses a high-frequency (7–12 MHZ) scanner that produces a 360° image that is perpendicular to the long axis of the endoscope. Radial imaging is useful in staging disease processes in hollow visceral organs. However, a major limitation of this system is that FNA cannot be performed. Additionally, radial imaging has limited scanning depth secondary to its high frequency. Linear imaging, on the other hand, uses a lower frequency (5 to 7.5 MHZ) transducer. The linear scope obtains images parallel to the long axis of the endoscope. The benefits of the linear system include the use of a Doppler system and the ability to obtain FNA for tissue diagnosis. This system permits passage of a 19- to 25-gauge FNA needle under real-time EUS guidance for tissue diagnosis.

EUS of the Pancreas

The transgastric and transduodenal stations are used to visualize the pancreas. The transgastric approach is used to visualize the pancreatic neck, body and tail,
splenic vessels, celiac axis, left liver lobe, left kidney, left adrenal gland and spleen (Figure 1). The transduodenal approach can easily depict the pancreatic head, common bile duct, portal vein and its confluence (Figure 2). The uncinate process and mesenteric vessels are seen from the second and third portion of the duodenum.²

On EUS, a normal pancreas is homogeneous, slightly echodense as compared to the liver, and is often described as ‘salt and pepper’ in appearance. Some conditions, such as chronic and acute pancreatitis and fatty infiltration of the pancreas, can alter the homogeneous appearance of pancreas. The pancreatic duct is seen as an anechoic structure running through the pancreatic parenchyma. Side branches are not generally seen during normal examination.³ The diameter of the pancreatic duct follows the so called “rule of 1-2-3,” meaning that the diameter of pancreatic duct should not be greater than 3mm in the head, 2mm in the body, and 1mm in the tail.

Benign Pancreatic Disease

Chronic pancreatitis, as the name suggests, is a chronic inflammatory disease of the pancreas characterized by irreversible morphologic changes often associated with pain and loss of exocrine or endocrine function. The diagnosis is based on ductal and parenchymal findings and can be detected by many imaging modalities. Although ERP is considered the gold standard for the diagnosis of chronic pancreatitis, it only evaluates the ductal system. CT can evaluate the parenchyma but is limited in evaluation of small ductal disease.³ On the other hand, EUS with high frequency transducers has the combined the advantage of ERP and CT, and thus, can detect small parenchymal and ductal changes.

In chronic pancreatitis, changes are seen in the parenchyma and duct on EUS. A landmark study by Wiresema et al⁶ described the features observed in chronic pancreatitis. In this study, 20 asymptomatic subjects (paid volunteers) underwent EUS. These results were compared with 69 patients with chronic abdominal pain of suspected pancreaticobiliary origin who were evaluated with EUS followed by ERCP; in 16 patients, secretin-stimulated intraductal pure pancreatic juice (PPJ) was collected. Of the 69 patients, 30 were found to have chronic pancreatitis. For all patients, the sensitivity, specificity, and accuracy of EUS in diagnosing chronic pancreatitis were 80%, 86% and 84%, respectively. In a subgroup of 22 patients with early pancreatitis, the sensitivity of EUS (86%) was significantly greater than that of ERCP (50%). This study identified eight EUS features to be indicative of chronic pancreatitis including changes in both the parenchyma and the main pancreatic duct. Parenchymal changes included hyperechoic foci (distinct 1- to 2-mm hyperechogenic points), hyperechoic strands (hyperechogenic irregular lines of varied length), lobularity (2mm to 5mm lobules), cysts (thin-walled round anechoic structures >2mm in diameter within the confines of the pancreatic parenchyma), and shadowing calcifications. Ductal changes included dilation (>3mm in the head, >2mm in the body, >1mm in the tail), irregularity, hyperechoic duct margins (duct wall visible as a hyperechogenic, distinct structure), and visible side-branches (anechoic structures budding from the
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main pancreatic duct). The sensitivity and specificity of EUS in making the diagnosis for chronic pancreatitis were optimal when ≥3 abnormal parenchymal and/or ductular features were found. The authors concluded that EUS can play an adjunctive role to ERCP and PPJ in the diagnosis of early chronic pancreatitis.

Additional criteria for the diagnosis chronic pancreatitis were developed by a group of expert endosonographers from North America and Japan at an international consensus meeting in Rosemont, IL in 2007. The major criteria were hyperechoic foci with shadowing, main pancreatic duct calculi, and lobularity with honeycombing. Minor criteria were cysts, dilated ducts ≥3.5mm, irregular pancreatic duct contour, dilated side branches ≥1mm, hyperechoic duct wall, strands, nonshadowing hyperechoic foci, and lobularity with noncontiguous lobules. EUS findings were separated into major and minor criteria based on the stronger positive predictive value of major criteria, which were thereby given more weight. These new Rosemont criteria, using a combination of major and/or minor criteria, categorize the patient as having EUS features that are either consistent or suggestive of indeterminate or chronic pancreatitis.

A study by Sahai et al was conducted in 126 patients to verify the accuracy of EUS in diagnosing, ruling out, and establishing the severity of chronic pancreatitis found by ERCP. Chronic pancreatitis was defined using the Cambridge classification defined as 0-1 = normal, 2 to 4 = all chronic pancreatitis, and 3 to 4 = moderate to severe pancreatitis. EUS was highly sensitive and specific (> 85%) depending on the number of 8 classic criteria that were present. Chronic pancreatitis was likely when >2 criteria were found. Moderate to severe chronic pancreatitis was likely when >6 criteria were present, and unlikely when <3 criteria were present. Independent predictors of chronic pancreatitis were calcification, history of alcohol abuse, and the total number of EUS criteria. The authors concluded that EUS can accurately diagnose, rule out, and establish the severity of chronic pancreatitis found by ERCP.

EUS is very sensitive in identifying the features of chronic pancreatitis. Various degrees of pancreatic abnormalities can be found in asymptomatic individuals and particularly in the elderly population and heavy alcohol users. However, caution should be used when using EUS to diagnose chronic pancreatitis in the absence of corresponding clinical data. ERCP, EUS, and pancreatic function tests are all complementary, and information obtained from these test should be carefully interpreted and analyzed before making the diagnosis of chronic pancreatitis.

Acute Pancreatitis

There are limited data on the assessment of the pancreas when EUS is performed in the setting of acute pancreatitis. Even here, EUS can show the pancreatic parenchyma as enlarged, hypoechoic, with blurred outer margins and compression of the pancreatic duct. Further, EUS can play an important role in the diagnosis of acute pancreatitis of unclear etiology. In severe biliary pancreatitis, recognition of biliary cause can lead to early ERCP performance. The evaluation of the common bile duct for stones is the best indication for EUS. The accuracy of the results have been consistently very good over the last 15 years, more or less independent of the level of stone likelihood, stone size, and echoendoscope type. A prospective, randomized study assessed outcomes in patients with an intermediate likelihood for bile duct stones and compared an EUS-directed strategy with primary ERCP performance. The results showed that use of EUS led to significantly fewer negative outcomes (10%) as compared with the use of ERCP (40%).

Another potential indication for EUS is the evaluation of patients with idiopathic acute recurrent pancreatitis. EUS can detect cystic lesions, pancreas divisum or occult malignancy as a potential cause in such patients.

Pancreatic Cystic Lesions

Cystic lesions of the pancreas present a difficult dilemma for the clinician. Wider use of abdominal imaging may explain an increase in incidence of pancreatic cystic lesions in asymptomatic patients. Although the exact prevalence of cystic lesions of the pancreas is unknown, it is estimated to be 1% based on previous large-scale observational imaging studies and 24% based on autopsy studies. Further, these studies suggest that cystic lesions of the pancreas occur equally in both male and females, and their prevalence increases with age.

Cysts vary in malignant potential. Surgery is currently the mainstay of treatment for cysts that are malignant or have malignant potential. Other clinical factors, including existing comorbidities, patient’s age and the location of a cyst (head vs body/tail), determine feasibility and the type of surgery performed.
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There are many different types of pancreatic cystic lesions, and pathologically they can be classified by the presence or absence of epithelium lining the cyst wall. Pseudocysts lack an epithelial lining and are typically associated with inflammation of the pancreas. Neoplastic or pre-neoplastic cysts are lined by epithelium that has a potential to harbor malignancy. These pancreatic cystic lesions can include mucinous cystic neoplasm (MCN), intraductal papillary mucinous neoplasm (IPMN), serous cystadenoma (SCA), cystic neuroendocrine tumors, solid pseudopapillary tumors, and adenocarcinoma with cystic thick walls (Table 1).11,12 EUS is helpful in distinguishing different types of benign cystic lesions from malignant, mucin-producing tumors or lesions with malignant potential. Evaluation of cystic lesions in the pancreas with EUS accurately defines their location, size, number, and association with the pancreatic duct. It also defines the cystic wall thickness, extension of irregularity of the cyst wall, and presence of internal cystic polyoid lesions, internal septa, calcifications, or debris.13

EUS findings that correlate to malignant or potentially malignant lesions include: (1) associated hypoechoic mass, (2) wall thickness >3mm, (3) highly echogenic wall, (4) mural nodules, (5) internal structures or papillary projections in to the cyst lumen, (6) internal septa >2mm or multiple septa, and (7) multiple (but usually <6) cysts that are more than 2cm in diameter. The criteria for benign cysts are a thin wall, single cyst or honeycomb pattern.13

Pseudocysts account for approximately 90% of pancreatic cystic lesions.4 Pseudocysts are inflammatory fluid collections that arise in the setting of acute or chronic pancreatitis. These cysts are anechoic, thick-walled structures. Septations are rare and regional inflammatory lymph nodes may be seen. Aspiration of cyst fluid will reveal dark, thin fluid containing inflammatory cells and high levels of amylase and a low CEA level. Patients with a significant amount of debris within a pseudocyst are likely to benefit from surgical debridement and drainage rather than endoscopic transgastric or transduodenal drainage.

Serous cystadenoma are mainly benign cystic lesions of the pancreas.4 However, certain case reports have described focal malignant transformation in serous cystic lesions and the presence of atypical cells pointing to a possible malignant potential.14-16 They have a female predilection and are most commonly discovered in the 7th decade of life. These cysts are generally microcystic, but solid and macrocystic variants have been described. This leads to a honeycomb appearance in cross-section. Central or “sunburst” calcification is considered pathognomonic, but is found in <20% of cases.4,11,17

Mucinous cyst neoplasia (MCN) include mucinous adenomas and adenocarcinomas. They are generally macrocystic and composed of a small number of discrete compartments >2cm in size. The septations are thick, irregular and occasionally a peripheral area of calcification is present. It has a female predilection, mostly present in the body-tail region of the pancreas and occurs most commonly in the 5th to 7th decade of life.13 The presence of mural nodules is suggestive of invasive carcinoma. The histopathologic hallmark of MCN is the presence of ovarian stroma underlying the mucinous columnar cyst epithelium and is necessary to differentiate this lesion from IPMN. Cyst fluid is viscous and clear. Cytology will reveal mucin-rich fluid with columnar mucinous cells. The risk of malignancy in these tumors was described to be 17.5% in a case series of 163 patients.11,18

IPMN are premalignant mucinous cystic lesions that arise from the main pancreatic duct (MD-IPMN), from its side branches (SB-IPMN), or both sites (mixed-IPMN). There is an equal or a slightly higher incidence of IPMNs among males than in females. The peak incidence is in the 6th and 7th decades of life.4,13 Like mucinous cyst adenomas, the cyst fluid is viscous, clear and will contain mucinous epithelial cells.12 The reported risk of malignancy in surgical patients ranges from 57% to 92% for MD-IPMN, and is 20% for SB-IPMN.11,19,20

Cyst fluid analysis also helps in differentiating between benign, premalignant, and malignant cystic lesions. Cyst fluid can be checked for cytology, amylase, lipase, tumor markers (CEA, CA19-9, CA 72 to 4 and CA-125), and genetic makers. The cyst fluid cytology is highly specific (>90%) for the diagnosis of cystic pancreatic neoplasms; however, the sensitivity is <50%.11 The serous cyst adenoma fluid is generally thin, non-viscous, and cytology reveals cuboidal cells, which stain positive for glycogen without the presence of mucin. The fluid from IPMN and mucinous cysts is generally viscous, and cytology reveals columnar epithelial cells and thick extracellular mucin.

Multiple tumor markers are present in the cyst fluid as described above, but CEA is the most widely used
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Table 1. TNM Classification for Pancreatic Adenocarcinoma

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>NX</td>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>T0</td>
<td>N0</td>
<td>M1 Distant metastasis</td>
</tr>
<tr>
<td>Tis</td>
<td>N1</td>
<td></td>
</tr>
<tr>
<td>T1</td>
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<td>T2</td>
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<td>T4</td>
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marker. In the Cooperative Pancreatic Cyst Study, the authors compared the findings of pancreatic cyst fluid of 112 patients (obtained via EUS-FNA) to surgical histology.\(^{21}\) EUS morphology, fluid cytology and cystic fluid tumor markers were evaluated. The results demonstrated that cyst fluid CEA levels (optimal cut-off 192 ng/mL) provided a sensitivity of 73% and a specificity of 84% for differentiating mucinous versus non-mucinous pancreatic cysts. In addition, the accuracy of cyst fluid CEA was higher than that of EUS morphology, cyst fluid cytology, or any combination of the tests.\(^{21}\)

The role of pancreatic cyst fluid molecular analysis and specific genetic changes associated with various tumors in predicting the cyst pathology and their premalignant potential has also been investigated. In a multicenter, prospective study, Khalid et al\(^{22}\) analyzed pancreatic cystic fluid DNA obtained via EUS-FNA in 124 patients with confirmed surgical histopathology or malignant cytology. The authors hypothesized that polymerase chain reaction (PCR) amplification of DNA from whole or lysed cells shed into the cyst fluid may be predictive of cyst pathology. A high level of mutational damage would predict an underlying malignancy. In addition, as malignant cysts would have high cell turnover, cyst fluid DNA content may be higher in malignant cysts. This study found that the elevated concentration of cyst fluid DNA (>40 ng/mL), the high-amplitude of K-ras mutations or individual allelic loss and specific mutation acquisition sequences were indicators of malignancy.\(^{22}\)

Solid Pancreatic Masses

Solid tumors of the pancreas include adenocarcinoma,
islet cell neoplasms, and metastases. Adenocarcinoma constitutes most of the solid pancreatic tumors (90%), whereas islet cell tumors constitute only 2%–5% of the solid pancreatic lesions. These masses typically appear as hypoechoic in homogeneous lesions surrounded by the normal echogenicity of the pancreas on EUS.

Most studies demonstrate a dismal overall 5-year survival rate of between 3%–5% for advanced pancreatic cancer. Staging of pancreatic cancer is done according to the American Joint Committee for Cancer (AJCC) Tumor Node Metastasis (TNM) classification (Table 2).

As therapies have improved, it is imperative that patients diagnosed with pancreatic adenocarcinoma undergo appropriate staging to most effectively direct their management. Pancreatic cancer is considered to be non-resectable whenever there is direct tumor involvement of the superior mesenteric artery or other

### Table 2. Classification of Pancreatic Cystic Lesions

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Demographics</th>
<th>Location</th>
<th>Fluid Characteristics</th>
<th>Cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous cystadenoma</td>
<td>Seventh decade, F &gt; M</td>
<td>Body/tail &gt; head</td>
<td>Colorless, may be blood stained, low CEA, low amylase</td>
<td>Usually acellular or Cuboidal cells</td>
</tr>
<tr>
<td>Mucinous cystic neoplasm</td>
<td>Fifth and sixth decade, F &gt; M</td>
<td>Body/ tail &gt; head</td>
<td>Highly viscous, moderate to high CEA, low to variable amylase</td>
<td>May be acellular with background of mucin, mucinous epithelial cells may be seen.</td>
</tr>
<tr>
<td>Intraductal papillary mucinous neoplasm</td>
<td>M = F</td>
<td>Head &gt; body/tail</td>
<td>High viscosity, moderate to high CEA, high amylase</td>
<td>May be acellular with background of mucin, mucinous epithelial cells may be seen.</td>
</tr>
<tr>
<td>Pseudocyst</td>
<td>In setting of acute or chronic pancreatitis</td>
<td>Not specific</td>
<td>Brow clear fluid, low to undetectable CEA, high amylase</td>
<td>Acellular</td>
</tr>
<tr>
<td>Solid pseudopapillary tumors</td>
<td>Second and third decade, F &gt; M</td>
<td>Body/ tail &gt; head</td>
<td>Colorless, low viscosity</td>
<td>Branching papillae with myxoid stroma that reacts to vimentin on cell block</td>
</tr>
<tr>
<td>Pancreatic neuroendocrine tumor</td>
<td>Third to sixth decade, M &gt; F</td>
<td>Body/ tail &gt; head</td>
<td>Colorless, low viscosity</td>
<td>Small homogenous small- cells associated with round nuclei that stain positive for chromogranin and synaptophysin on cell block</td>
</tr>
</tbody>
</table>
major arteries of the upper abdomen. There is debate among clinicians about the resectability of neoplasms that involve the superior mesenteric vein or portal vein and its confluence. Multiple studies and EUS reports have demonstrated superior accuracy for preoperative staging of pancreas cancer (85% to 100%) when compared with dynamic CT (64% to 66%) or transcutaneous ultrasound (61% to 64%).

EUS is clearly the most sensitive technique for detection of pancreatic masses, particularly when they are <3cm. Accuracy of EUS for tumor staging is similar from one series to another, ranging from 80% to 90%, whereas helical CT results range from 56% to 90%. The visualization of vascular structures may be difficult with EUS in patients with large tumors or altered anatomy. Accuracy of EUS staging in pancreatic cancer is also dependent on other factors influencing good visualization. The logical recommendation that optimal EUS-based T- and N-staging of pancreatic head neoplasms should be performed prior to biliary stent placement was recently supported by a study performed in a consecutive series of 65 patients who underwent preoperative EUS for diagnosis and staging of suspected pancreatic cancer (some of whom had biliary stents in situ and some of whom did not). According to the multivariate analysis, patients with stents were 6.55 times more likely to be incorrectly T-staged and 3.71 times more likely to be incorrectly N-staged than patients without stents.

In everyday clinical practice, the role of CT and EUS in the diagnosis and staging of pancreatic cancer is complementary. EUS-FNA has been shown to be a highly accurate method for distinguishing benign from malignant pancreatic masses, rather than relying on ultrasound images alone. The reported accuracy of EUS-FNA, ranging from 83% to 95%, is better than that of CT or MRI.

Several investigators have reported the usefulness of EUS-FNA samples obtained from pancreatic masses for genetic analysis. Genetic analysis of p53 and K-ras, which are frequently seen in pancreatic cancers, appears to be useful as an adjunct in the diagnosis of malignancy in combination with the standard technique of hematoxylin-eosin stained section. Moreover, the risk of complications in EUS-FNA is relatively low with no reported severe adverse events.

Therefore, EUS-FNA appears to be the gold standard for the diagnosis of pancreatic masses although several issues affecting yield (eg, choice of needle, presence of on-site pathologist, operator skill, tumor size, etc) still remain. Of the various factors that affect tissue acquisition or diagnostic ability, the choice of needle is one of the more important variables. A 22- or 25-gauge needle is recommended when sampling a pancreatic mass because these flexible needles handle acceptably even in difficult puncture locations like the pancreatic uncinate. In contrast, when standard EUS-FNA has failed using a 22- or 25-gauge needle to sample a mass at the pancreatic body or tail, a 19-gauge needle or Trucut needle can be used, especially if there is no on-site pathologist.

EUS elastography
Recent advances in EUS, such as EUS elastography and contrast-enhanced EUS, have opened new doors for diagnosis and management of pancreatic masses. Tissue elastography enables the expression of tissue hardness by differences in color, namely blue, green, and red, suggesting hard, moderate, and soft tissue, respectively. EUS elastography is useful in determining the ‘hardness’ of the tumor, leading to possible differentiation within a pancreatic mass as ‘virtual biopsy’ or to aid in directing the EUS-FNA needle for yield optimization. Saitou et al showed that combined contrast-enhanced EUS and EUS elastography appear to be useful in the differential diagnosis of focal pancreatic masses (sensitivity 75.8%, specificity 95.2%, accuracy 83.3%, positive predictive value 96.2% and negative predictive value 71.4%).

Limitations of EUS
EUS in its current state of advancement has become the gold standard for the evaluation of pancreatic masses. Nevertheless, it has some limitations because technical success still depends on operator skill and other variables.

EUS is a highly operator-dependent procedure with interobserver variability and several potential limitations. There is a considerable learning curve for performing EUS. Also, patients need to be appropriate medical candidates for intravenous sedation. Prior surgery (eg, Billroth II or gastrectomy) or the presence of splenic artery calcifications may preclude visualization of the entire pancreas. In addition, the presence of varices or collaterals may limit FNA of pancreatic masses.

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Interventional EUS for Pancreatobiliary Disease

In recent times, advances in EUS and ERCP have converged that has allowed expert interventional gastroenterologists, alone or in tandem, to perform EUS-guided therapeutic interventions. Accessories, such as guide wires can be advanced through a needle into a target structure to carry out interventions. EUS-guided drainage of pancreatic fluid collections including pseudocysts and wall-off pancreatic necrosis with endoscopic necrosectomy are routine procedures in expert centers with good outcomes. EUS-guided drainage procedures also provide an alternative in patients in whom ERCP fails to drain the obstructed biliary or pancreatic ducts. FNA offers not only the ability to acquire tissue samples for diagnostic purposes, but also to introduce, for example, drugs by fine-needle injection (FNI). EUS–FNI allows intratumoral cancer therapy. Currently, EUS–FNI involves injection of antitumoral agents, immunotherapy, and use of ablative techniques. A number of studies have been published with different agents injected by EUS–FNI in pancreatic tumors.

CONCLUSION

EUS has proved to be a valuable tool in the diagnosis and treatment of pancreatic diseases. With the ongoing developments in cross-sectional imaging, including multidetector CT scans and MRI, diagnostic indications for EUS may decline, although its ability to acquire instant tissue samples remains appealing and of great clinical use. Undoubtedly, applications of interventional EUS will further evolve and develop to aid in the management of patients with complex pancreatic diseases.

References