Pancreatic tumors being either benign or malignant can be solid or cystic. Although diverse in presentation, their imaging features share commonalities and it is often difficult to distinguish these tumors. Endoscopic ultrasonography (EUS) is the most sensitive of the imaging procedures currently available for characterizing pancreatic tumors, and is especially good in identifying the smaller sized tumors. Additional applications inclusive of EUS-guided fine needle aspiration (EUS-FNA) are useful in tissue sampling and preoperative staging of pancreatic tumors.

Although diagnostic capabilities have greatly evolved with advances in EUS and tissue processing technology (cytology, tumor markers, DNA analysis), differentiation of benign and malignant neoplasms, neoplastic and non-neoplastic (chronic pancreatitis) conditions, continues to be challenging. Recent innovative applications include contrast-enhanced EUS with Doppler mode, contrast-enhanced harmonic EUS, 3-dimensional EUS, and EUS elastography. Incorporation of these methods has improved the differential diagnosis of pancreatic tumors. Finally, a multi-disciplinary approach involving radiology, gastroenterology and surgical specialties is often necessary for accurate diagnosis and management of solid and cystic pancreatic tumors.

Introduction

Among the increasing and diverse indications for endoscopic ultrasound (EUS), evaluation for pancreatic neoplasm remains the foremost. Neoplasms of the pancreas may be solid or cystic. Chronic pancreatitis and auto-immune pancreatitis constitute benign disease processes which may mimic solid pancreatic tumors. For detection of pancreatic tumors less than 20 mm in diameter, EUS is considered superior to computed tomography (CT) and magnetic resonance imaging (MRI). It is a more sensitive test to detect lymph node metastasis and vascular infiltration compared to CT imaging. Among pancreatic tumors, EUS has better sensitivity of diagnosing pancreatic head tumors than that of body and tail of pancreas.

Endosonography provides real-time high resolution images of cystic pancreatic lesions with morphological details. The risk of progression of pancreatic cysts to neoplasms is estimated to be 15%, necessitating further evaluation and surveillance due to risk of malignancy. Estimated prevalence of pancreatic cysts in general population is 1.2% based on observational imaging and 24% based on autopsy studies.

Overall, EUS guided fine needle aspiration (FNA) is 85%-90% sensitive, 97%-100% specific and 85%-90% accurate for diagnosis of pancreatic cancer. It remains extremely accurate despite previous negative tissue sampling from endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous biopsies. Thus, EUS-FNA is preferentially utilized for detecting and staging of pancreatic lesions, obtain samples for confirming cytology and assess feasibility of resection. Over the past decade, use of EUS-FNA has evolved extensively. Numerous prospective studies have evaluated the safety of EUS-FNA. Its complication rate is estimated around 1% or less.

The potential limitations of EUS include - operator dependence, restricted visualization of right hepatic lobe and peritoneal metastasis, and difficulty in tumor detection among patients with chronic pancreatitis, especially when presenting as diffuse infiltration.

Role of EUS in the management of pancreatic adenocarcinoma

Ductal adenocarcinoma accounts for over 90% of pancreatic tumors. With a high sensitivity of 89%-100%, EUS has been successfully utilized in early detection of small pancreatic adenocarcinomas. The sensitivity of CT and MR imaging decreases for pancreatic lesions smaller than 1.5 to 2 cm. Comparatively, EUS can detect lesions with dimensions of 2 to 3 mm. During EUS, pancreatic adenocarcinomas appear as heterogeneous hypoechoic masses with irregular margins. Dilatation of the main pancreatic duct and presence of patchy hypoechoic areas adjacent to a dilated duct (periductal hypoechoic sign) are independent predictors of pancreatic cancer. However, relying on these morphological features alone only yields a diagnostic specificity of 53% since these features can
also be seen in focal pancreatitis, neuroendocrine tumors, and metastases.\textsuperscript{23} Amongst factors which decrease sensitivity of EUS for failure to detect a pancreatic lesion, presence of acute/chronic pancreatitis is foremost (Fig. 2).\textsuperscript{15} Based on a recent meta-analysis of 29 previous studies, EUS was 73% sensitive and 90.2% specific for detecting vascular invasion.\textsuperscript{24} Although EUS is highly sensitive to detect regional lymph nodes, EUS-FNA may be necessary to provide accurate nodal staging.\textsuperscript{18}

**Role of EUS in the management of pancreatic neuroendocrine tumor**

Neuroendocrine tumors (NETs) comprise of less than 5% of all pancreatic tumors.\textsuperscript{25} The sensitivity, specificity and accuracy for EUS-detection of NETs is 80%, 93% and 95% respectively.\textsuperscript{20-29} Frequently, the morphological features are sufficiently distinct to differentiate from those of pancreatic adenocarcinoma.\textsuperscript{28} The EUS appearance of pancreatic NETs frequently reveals a homogeneous, hypoechoic, hypervascular mass with distinct margins (Fig. 3). The average diameter is less than 1.5 cm. Infrequently, morphological variants of NETs on EUS include isoechoic or hyperechoic lesions, where EUS-FNA can differentiate NETs from adenocarcinomas. To assess vascularity of identified NETs, EUS with doppler mode can be employed.

**Role of EUS in the management of cystic tumors of the pancreas**

The neoplastic cystic pancreatic lesions (CPLs) includes intraductal papillary mucinous neoplasms (IPMN), mucinous cystadenomas (MCN), mucinous cystadenocarcinomas, solid pseudopapillary tumors (SPT) and few other rare types. EUS has the capability of obtaining close and high resolution imaging of CPLs. Accuracy of diagnosis of malignant or premalignant lesions by EUS alone has been reported in different series as 82-96%.\textsuperscript{30-32} However, morphologic features on EUS alone are generally considered inadequate for further characterization of CPLs or predicting their malignancy potential. The overall sensitivity of EUS-FNA for diagnosis of neoplastic CPLs varies widely and is low (<50%).\textsuperscript{32-35} The reasons put forth include, patchy distribution of malignant cyst epithelium, sampling error, on-site cytology interpretation, expertise of cytopathologist, contamination of specimen, and endoscopist’s experience. On the other hand, EUS-FNA cytology is uniformly reported to have 90% specificity or more for the diagnosis of CPLs.\textsuperscript{32-34} Accuracy of EUS-FNA for diagnosis of CPLs ranges from 55% to 89%.\textsuperscript{34-36} Endosonographic appearance of microcystic serous cystadenoma (SCA) reveals well delineated lesions with multiple, small septated fluid filled cavities, usually less than 5mm in size. In about 25% of cases, a central scar is observed.\textsuperscript{33} An underlying mucinous lesion must be however suspected if there are areas of cyst wall thickening, intramural nodules, floating debris or dilatation of pancreatic duct.\textsuperscript{31} Cyst sampling is generally not needed for diagnosis of microcystic SCA since morphological features are adequate. However, EUS-FNA can be obtained, especially from the larger cystic compartments. In contrast, macrocystic variant of SCA cannot be differentiated from mucinous cystic lesions and FNA is thus required for confirmatory diagnosis. Conservative management is recommended for small asymptomatic tumors. Given the potential for malignancy, resection is advised for large serous cystadenomas.\textsuperscript{36,39} The EUS appearance of MCNs includes a visible wall, variable thickness of the septations and infrequently, peripheral calcification (Fig. 4).\textsuperscript{40} Morphological features associated with malignancy are thick, irregular cyst wall, bigger cyst size (more than 3 cm), main duct dilatation (more than 5 mm), bulging papilla, and intramural nodules or solid components (larger than 5 mm).\textsuperscript{33,41} EUS-FNA is advised for confirmation of all suspected MCN.\textsuperscript{42} The rationale for this recommendation is the relatively high risk of malignancy which is estimated around 17.5%.\textsuperscript{43} Surgical resection is hence the usual recommendation for cysts with features of malignancy.

**Role of EUS in management of intraductal papillary mucinous neoplasms of the pancreas**

Main duct intraductal papillary mucinous neoplasm (IPMN) of the pancreas is easily identified on EUS by diffuse dilation of the pancreatic duct (Fig. 5), mural tumor growth and occasionally intraductal filling defects due to mucin production.\textsuperscript{44} Branched duct IPMN morphology on EUS is indicated by visible communication of the cyst with the main pancreatic duct. However, in the absence of ductal communication, it is difficult to distinguish branched duct IPMN from MCNs. It is vital that an EUS-FNA is conducted if there is any intraductal mass, mural nodule or projections within the main duct or off a cyst wall. In the absence of visible lesions, the main or branch duct can be punctured for cytology and tumor markers. The limitations of EUS-FNA for detecting invasive malignancy includes low sensitivity coupled with unreliable carcinoembryonic antigen and CA 19-9 levels.\textsuperscript{45,46} Among IPMN lesions protruding 4mm or beyond within the pancreatic duct, application of intraductal ultrasonography (IDUS) increases sensitivity of detecting malignancy to 68%, specificity to 89% and accuracy to 78%.\textsuperscript{47} Application of contrast enhanced EUS to predict malignant IPMN and detection of either papillary (type 3) or invasive (type 4) mural nodules provides a specificity of 93%. Increased risk of malignancy in main duct IPMN necessitates surgical removal. Expectant treatment is considered appropriate for branched duct IPMNs with diameters less than 3 cm.\textsuperscript{48}

**EUS in other rare pancreatic tumors**

Solid pseudopapillary tumors (PST) are rare pancreatic neoplasms mainly seen in young women. On EUS, it appears as a purely solid or a mixed solid and cystic mass (Fig. 6). Preoperative diagnosis with EUS-FNA is around 75%-83% accurate.\textsuperscript{49,50} Tumor size at presentation is an important determinant about malignant transformation.\textsuperscript{51} Teratomas, choriocarcinomas, lymphoepithelial cysts, and lymphoceles should be included in rare differentials of CPLs.\textsuperscript{52,53} Primary pancreatic lymphomas are rare, constitute 0.5% of all pancreatic neoplasms. They usually are large B-cell non-Hodgkin lymphomas presenting as mass lesions and EUS-FNA with flow cytometry is helpful in differentiating from other primary pancreatic lesions.\textsuperscript{54,55} Additional special staining and need for more tissue for accurate diagnosis may require EUS-fine needle
Primary lymphoma of the pancreas is usually seen on EUS as a mass occupying the pancreas and often involves the peripancreatic lymph nodes. These tend to be intensely hypoechoic masses with multiple isoechoic peripancreatic lymph nodes. Absence of palpable superficial and mediastinal lymphadenopathy, absence of hepatic or splenic involvement and a normal white cell count are some of the clinical features that help differentiate it from nonhodgkin’s lymphoma invading the pancreas. Secondary pancreatic involvement from adjacent lymph node involvement is a common form of involvement.

**Role of EUS in management of metastatic tumors to the pancreas**

Metastatic tumors to the pancreas are rare and constitute 2%
of all pancreatic malignancies. Patients usually have advanced primary malignancies. Renal cell carcinoma, lung cancer (Fig. 7), melanoma and breast cancer are some of the most commonly metastasizing cancers to the pancreas. Since these masses are indistinguishable from adenocarcinoma of the pancreas, EUS-FNA for cytology is indispensible for diagnosis. Renal cell carcinoma has a propensity to metastasize many years after the initial diagnosis, thus necessitating long term surveillance.

**Staging**

Based on the current 2010 American Joint Committee on Cancer (AJCC) TNM Staging, the pancreatic neuroendocrine tumors, carcinoid tumors, and exocrine tumors are grouped under a
Accuracy of staging is augmented by EUS which improves management of pancreatic cancer. EUS is valuable in assessing peripancreatic vascular and lymph node involvement. Based on data from many large series, application of EUS in staging improves the T stage accuracy to 78-91% and the nodal (N) stage accuracy to 41-86%. EUS has highest accuracy for T-staging smaller lesions, whereas helical CT is more accurate in larger tumors. For nodal staging, EUS and CT scan have comparable efficacies. The four EUS features suggestive of malignant lymph node include, a hypoechoic node, round shape, well demarcated boundaries, and size > 1 cm. When present together, chances of malignancy is around 80-100%. For local and/or distant metastases (M staging), EUS has 42-91% sensitivity and 89-100% specificity in detection of vascular invasion. The splenic vein, portal vein and proximal superior mesenteric artery are better visualized on EUS than the other major peripancreatic vessels. The vascular invasion criteria include irregularity of the interface with the vessels, intravascular tumor growth, and nonvisualization of the vessel, with collateral circulation growth.

In recent pilot studies, contrast-enhanced harmonic endoscopic ultrasound (CEH-EUS) has been shown to be a useful tool for visualizing microvascular pattern in pancreatic tumors. This vital information helps distinguish adenocarcinoma from other pancreatic masses. Further, CEH-EUS can also improve diagnostic accuracy of preoperative T-staging of pancreaticobiliary malignancies.

**Therapeutic role of EUS**

Recent years have seen emergence of newer techniques involving EUS for therapeutic benefits. EUS-guided therapy for palliation is a new and exciting area of research. Although, larger studies are needed, some of these techniques are mentioned below.

**EUS-guided Celiac plexus block**

This procedure uses EUS guided fine needle injection (FNI) of the celiac ganglion with a steroid and an analgesic (triamcinolone+bupivacaine) or alcohol and an analgesic (98% alcohol+bupivacaine). This blocks the afferent pain stimulus from the pancreas. It has been shown in prospective studies that there is significant reduction in pain scores and reduction in oral analgesic requirement.

**EUS-guided Injection of Biological and Chemotherapy Agents**

The principles of therapeutic EUS are based on critical ability to guide fine-needle injection in close proximity to the target lesion. Therapies that have been investigated include: allogenic
mixed lymphocyte culture,\textsuperscript{73} anti-tumor agent TNFerade,\textsuperscript{76,77} and systemic chemotherapy with EUS-FNI of ONYX-015 (replication-selective adenovirus).\textsuperscript{78} TNFerade\textsuperscript{TM} (GenVec, Inc., Gaithersburg, MD) is a replication-deficient adenovirus. It contains the human TNFα gene that is activated by a radiation-induced promoter.\textsuperscript{79} The treatment principle involves weekly EUS guided injection of TNFerade coupled with chemotherapy, followed by standard radiation therapy, the combination of which induces the production of tumor necrosis factor-α with resulting tumor destruction.\textsuperscript{77}

**EUS-Assisted Radiotherapy**

Placement of gold fiducials under EUS guidance is being used to assist stereotactic radiosurgery for pancreatic cancer.\textsuperscript{80,81} EUS guided implantation of iodine 125-seeds in combination with chemotherapy has been attempted in unresectable pancreatic cancers.\textsuperscript{82} EUS-guided ablation of pancreatic tissue with photodynamic therapy or radiofrequency ablation has been attempted, but more human trials are required.\textsuperscript{83} A non-randomized study demonstrated effective placement of gold fiducials for image-guided radiation therapy in unresectable pancreatic cancer with a success rate of 88% (50 of 57 patients).\textsuperscript{84}

**Ablation of pancreatic cysts and tumors.**

In a novel technique, EUS-guided pancreatic cyst ablation with ethanol and/or paclitaxel has been shown to achieve CT-defined cyst resolution rates of 33% to 79%.\textsuperscript{85-87} A recent study evaluated long-term follow up after EUS-guided ethanol ablation of pancreatic cysts. Durable resolution for up to 12 months was shown.\textsuperscript{88} There is new research involving alcohol ablation of isolated pancreatic insulinomas. In a recent pilot study involving six patients, EUS-guided FNI of ethanol was performed in patients with insulinomas who were not candidates for surgical resection due to comorbidities. The procedure was safe and effective during immediate follow-up.\textsuperscript{89}

**Newer devices and techniques used in conjunction with EUS**

**EUS Elastography**

Elastography, is a novel technology that estimates tissue elasticity by comparing images before and after application of minimal tissue-compression. The foundation of the procedure is based on the fact that malignant tumors are generally harder than surrounding tissue. Hence, elastography may provide improved ultrasound characterization of the lesion and thereby better direction for targeted FNA. Elastography might be particularly more helpful in diagnosing challenging cases of suspicious lesions where FNA cytology is negative. A recent European multicenter study compared EUS elastography and standard EUS for diagnosis of pancreatic malignancy. While the sensitivities of both the techniques were comparable at 92%, EUS elastography was significantly more specific (80%) compared to standard EUS (62%) in diagnosis of pancreatic malignancy.\textsuperscript{90} Similarly, for detection of peripancreatic lymph nodes, EUS elastography was significantly more sensitive and specific (92% and 83%, respectively) compared with standard EUS (79% and 50% respectively).\textsuperscript{90} In another recent study, 258 patients diagnosed with chronic pseudotumoral pancreatitis and pancreatic cancer focal masses were included from 13 participating centers. The EUS elastography recordings were converted into a hue histogram form (quantitative data). The sensitivity, specificity, and accuracy for the differential diagnosis of benign and malignant pancreatic lesions were 96.7%, 63.8% and 90.7%, respectively.\textsuperscript{91}

**Newer fine needle aspiration needles and cytobrush devices**

The new 22-gauge (EchoTip® ProCore™; Cook Medical, Winston-Salem, NC, USA) fine needle core biopsy needle features a core trap and a reverse bevel for tissue-core procurement. Adequate tissue can be potentially acquired utilizing this core biopsy needle when compared to a FNA needle.\textsuperscript{92} A cytobrush device (Echobrush®, Cook Medical Inc., Winston-Salem, NC, USA) has been approved for use with a 19-gauge EUS-FNA needle in evaluation of pancreatic cysts. Lesions suitable for cytobrush use include cystic pancreatic lesions at least 2 cm in diameter that are located in the neck, body or tail of the pancreas.\textsuperscript{84,94} During EUS-FNA, cyst fluid can contain scant amount of epithelium for cytopathological assessment.\textsuperscript{95} In a prospective, blinded study comparing diagnostic yield of standard FNA to EUS-cytobrush, there was higher likelihood of obtaining intracellular mucin.\textsuperscript{93} Larger studies are needed before recommending this technique as routine practice.

**Contrast-enhanced endoscopic ultrasound**

The foundation of contrast-enhanced (CE) EUS involves intravenous injection of ultrasound contrast and detection of signals from micro bubbles in vessels with a very slow flow without Doppler-related artifacts. It is used to characterize tumor vascularity in the pancreas and thus distinguish pancreatic tumors from chronic pancreatitis. It can also serve as a non-invasive diagnostic technique in patients with bleeding disorders. In a study of 62 patients with ductal adenocarcinoma of the pancreas, 92% showed hypo-vasularity of the tumor using CE-EUS. Hypo-vascularity on CE-EUS was estimated to be 92% sensitive and 100% specific as a sign of malignancy.\textsuperscript{96} With adjuvant use of a second generation ultrasound contrast agent (SonoVue®), the specificity of distinguishing benign and malignant focal pancreatic lesions increased to 93.3% using power Doppler CE-EUS compared with 83.3% for conventional EUS.\textsuperscript{97} Pancreatic NETs had a strong contrast enhancement indicative of hypervascularity and metastatic lesions to the pancreas were also likely to be hypervascular.\textsuperscript{97-99} In another trial, CE-EUS was found to have significantly higher sensitivity compared to power Doppler ultrasound and contrast-enhanced helical-CT for diagnosis of < 2 cm ductal carcinoma (sensitivity of 83.3% compared to 50% and 11% for power Doppler and helical-CT respectively).\textsuperscript{100} However, it is to be noted that CE-EUS cannot replace EUS-FNA for identification of malignant lymph nodes.\textsuperscript{101} Contrast-enhanced harmonic EUS (CEH-EUS) uses a prototype electronic linear array echo endoscope (xGF-UC1T180; Olympus Medical Systems, Tokyo, Japan) which is equipped with a wideband transducer improved the accuracy of detecting vascular patterns of pancreatic tumors.\textsuperscript{102,103} CEH-EUS has been shown to successfully visualize the microvascular pattern in pancreatic solid tumors in pilot studies. Potentially, this may improve preoperative
T-staging of pancreatic malignancies. Despite above advances in technology, histology remains the gold standard. However the combination of EUS-FNA and CEH-EUS could make it the most reliable procedure for assessing solid pancreatic lesions.

**Tridimensional-EUS (3D-EUS)**

Tridimensional (3D) endoscopic ultrasound (EUS) is a novel enhanced modality for interpretation of the anatomy and vascularity of the pancreatic tumors. The 3D images are reconstructed from a digitized set of 2D images. The principal advantage is accurate localization of tumors in relation to surrounding structures. Furthermore, contrast-enhanced power Doppler 3D-EUS, performed with the 3D freestanding module, yields high quality images of the vascular structures related to the pancreatic tumor. Other advances like 3D-EUS elastography can also be performed through automated techniques. The 3D technology continues to progress, and further innovation and larger studies are necessary before conventional application. A hybrid CT-imaging and EUS study demonstrated improved localization of pancreatic lesions permitting better image interpretation.

**Conclusion**

Endosonography is an operator dependent minimally invasive procedure for diagnosis and staging of pancreatic cystic and solid tumors. While a multi-disciplinary approach is required for pancreatic tumors, recent developments in the field of endosonographic imaging contribute to better diagnostic accuracy allowing improved differentiation of pancreatic lesions.

**Disclosures**

No financial relationships with a commercial entity producing health-care related products and/or services relevant to this article.

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