Endoscopic ultrasound advances, part 1: Diagnosis

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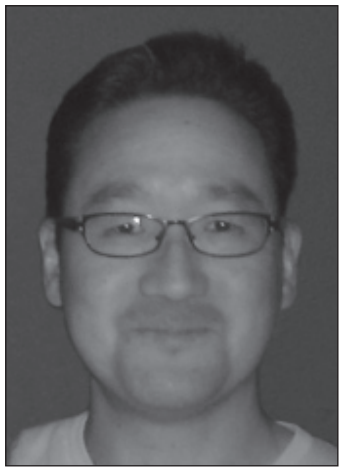
Endoscopic ultrasound (EUS) is a relatively new endoscopic technique that provides high-resolution imaging of the gastrointestinal (GI) tract by its unique ability to differentiate the histological layers of the GI tract wall as well as periluminal structures (1-4). Refinement of fine-needle aspiration (FNA) techniques have allowed for tissue and fluid sampling for diagnosis and staging, with the aid of newer techniques such as molecular analysis. Because therapeutic agents can now be delivered with EUS guidance into targeted areas by fine-needle injection, EUS-FNA has led to the development of novel therapeutic methods. The advent of larger accessory channels and needles with larger diameters has facilitated the histopathological diagnosis of biopsy specimens, and enables the endosonographer to perform therapeutic procedures such as tissue ablation and brachytherapy. The aim of the present article (and part 2 [to be published in the October 2009 issue of *The Canadian Journal of Gastroenterology*]) is to review some of the recent advances in the diagnostic and therapeutic roles of EUS.



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INTRODUCTION

Initially developed in the 1980s, interest in EUS has increased in the past decade. Introduced primarily as a diagnostic modality, it has enabled the endosonographer to visualize details of anatomy and pathology not previously attainable by most gastroenterologists or radiologists. The list of indications for EUS is growing, which has forced gastroenterologists to 'think outside the lumen'.

The introduction of linear echoendoscopes facilitated FNA by enabling the endosonographer to trace the path of the needle tip during the puncture process. FNA techniques have allowed for tissue and fluid sampling for diagnostic purposes. The most common diagnostic indications of EUS are summarized in Table 1.

EUS may not be foremost in the minds of gastroenterologists as a diagnostic and therapeutic tool. However, the combined ability to image the layers of the bowel wall and adjacent structures, and to sample these by FNA, has resulted in a powerful modality that can influence clinical decision making. A previous review in this *Journal* (5) discussed the more common indications for EUS. The present article discusses some of the recent advances in the diagnostic role of EUS.

INTRADUCTAL ULTRASOUND

Technological advances in EUS imaging has led to the development of intraductal ultrasound (IDUS) miniprobes for the evaluation of the pancreatobiliary tree and periductal structures. These radial, small-calibre (approximately 2 mm), flexible miniprobes can be passed through the working channel of a duodenoscope over a guidewire directly into the bile or pancreatic duct. IDUS operates at a high frequency (20 MHz or 30 MHz) – producing better image resolution than standard EUS – but has a decreased depth of penetration (6-8). IDUS is a safe adjunct to endoscopic retrograde cholangiopancreatography (ERCP), and its use has not led to an increase in complications and requires sphincterotomy in less than 10% of patients.

The indications for IDUS are summarized in Table 2. IDUS can demonstrate common duct stones in patients suspected of having choledocholithiasis in whom stones are not visualized with other imaging techniques, including ERCP. The combination of IDUS and ERCP is more accurate than ERCP alone to diagnose choledocholithiasis. IDUS is more sensitive for detecting small stones (smaller than 5 mm in size) and determining the number of stones, and reliably distinguishes stones from sludge and air bubbles (9-11). One study of 65 patients (12) reported that the overall sensitivity, specificity and accuracy of IDUS were 100%, 67% and 97%, respectively.

TABLE 1
Diagnostic indications for endoscopic ultrasound

Diagnostic evaluation
Subepithelial lesions
Choledocholithiaisis
Bile duct strictures
Pancreatic cystic and mass lesions
Pancreatic duct strictures
Localization of neuroendocrine tumours
Mediastinal lesions
Cancer staging
Esophageal
Gastric
Rectal
Cholangiocarcinoma
Pancreatic
Lung

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TABLE 2
Indications for intraductal ultrasound

Biliary indications
Distinguish malignant biliary strictures
Perioperative staging of cholangiocarcinoma
Diagnosis of choledocholithiasis
Pancreatic indications
Distinguish malignant pancreatic strictures
Detect (small) pancreatic adenocarcinomas
Localize pancreatic neuroendocrine tumours
Determine disease extent in intraductal papillary mucinous neoplasia
Determine malignant transformation in intraductal papillary mucinous neoplasia

IDUS can assist in distinguishing malignant biliary strictures. The etiology of bile duct strictures can be determined with high sensitivity and specificity, and can significantly increase diagnostic accuracy over other imaging studies and/or tissue sampling (13-15). In patients with cholangiocarcinoma, IDUS compares favourably with other imaging modalities with respect to tumour visualization, diagnosis, staging and predicting resectability (16-18). IDUS is more accurate than ERCP in determining the longitudinal extent of a tumour (19). The limitations of IDUS stem from a reduced depth of penetration and lack of FNA capabilities, which affect the accuracy of N staging and the inability to assess for metastases. In addition, stent therapy results in bile duct wall thickening, which can lead to a overestimation of tumour length (20).

In the evaluation of patients with pancreatic duct stenosis, IDUS can be used to distinguish malignant disease, allow for the early detection of small pancreatic tumours, assist in local staging and to determine resectability (21,22). IDUS may also be useful for the localization of pancreatic neuroendocrine tumours not visualized by other imaging modalities (21,23). In the evaluation of intraductal papillary mucinous neoplasia (IPMN), IDUS is used to determine malignant disease and disease extent before surgery. IDUS and pancreatoscopy had a reported combined sensitivity, specificity and accuracy of 91%, 82% and 88%, respectively (24).

PANCREATIC CYSTIC NEOPLASMS

Cystic neoplasms of the pancreas often pose a diagnostic dilemma. Pancreatic cysts are frequently discovered incidentally, given the widespread use of cross-sectional abdominal imaging, and can represent an inflammatory mass, benign process or malignancy (25). The most common pancreatic cysts are pseudocysts (80% to 90%), with cystic neoplasms accounting for only 10% to 20% (26,27). The classification of cystic neoplasms is based on the type of epithelium, categorized as mucinous or nonmucinous, with a significant difference in the natural history and survival between the two groups (28). Mucinous lesions (mucinous cystic neoplasms and IPMN) are considered premalignant or malignant, and have traditionally been managed by surgical resection (29). However, it is becoming increasingly recognized that branch duct IPMN has a low rate of malignant degeneration and may not require resection (30) (Figure 1). Nonmucinous lesions and serous cystadenomas have much lower malignant potential, with resection being performed only in the setting of troubling symptoms (30,31).

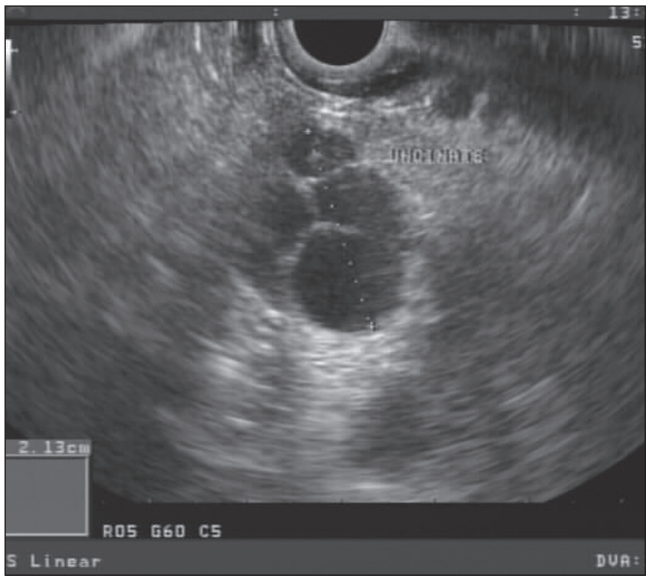

Figure 1) *Branch-type intraductal papillary mucinous neoplasia. An abdominal computed tomography scan of a 63-year-old man undergoing evaluation for right lower quadrant abdominal pain. A hypodense lesion was seen in the head of the pancreas. Endoscopic ultrasound demonstrated a cluster of cysts in the uncinate process measuring 2 cm in size. The remainder of the pancreas and the main pancreatic duct were normal. This lesion is compatible with a branch-type intraductal papillary mucinous neoplasia and will be re-evaluated one year later*

There are limitations in the extent of cross-sectional imaging with ultrasound, computed tomography (CT) and magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRCP) to determine the malignant potential of pancreatic cystic neoplasms. The most specific signs of malignancy with a pancreatic cystic neoplasm on CT include a solid mass, main pancreatic duct dilation of more than 10 mm, diffuse or multifocal involvement, and attenuating or calcified intraluminal content (32).

EUS is a very useful technique for the evaluation of pancreatic cystic morphology including the size, number of cystic components, ductal communication, cyst wall thickness, irregularity, mural nodules or papillary projections, and intracystic structures (33). EUS is able to detect IPMN, distinguish branch duct type from main duct type, and identify features associated with malignancy including main duct diameter greater than 10 mm, focal cystic lesion greater than 3 cm in size and nodule greater than 5 mm in size (32,34). However, EUS characteristics do not reliably distinguish mucinous cystic neoplasms from pseudocysts or macrocystic serous cystic neoplasms, with poor interobserver agreement even among experienced endosonographers (35).

EUS-FNA allows for the direct sampling of cyst fluid as well as the cyst wall, and has been valuable in differentiating cystic lesions of the pancreas (Figure 2). Fluid obtained during FNA may be sent for biochemical and cytological analysis, and tumour marker levels, which often determines the cyst type and the presence of malignancy (36-40). A combined analysis of 11 studies (41,42) found that cytology from cyst fluid was diagnostic in 38% to 48% of cystic pancreatic neoplasms, and the Cooperative Pancreatic Cyst Study (40) determined the diagnostic accuracy to be 59% in this setting.

When tumour markers, amylase testing and mucin staining are combined with cytological testing, the diagnostic accuracy increases

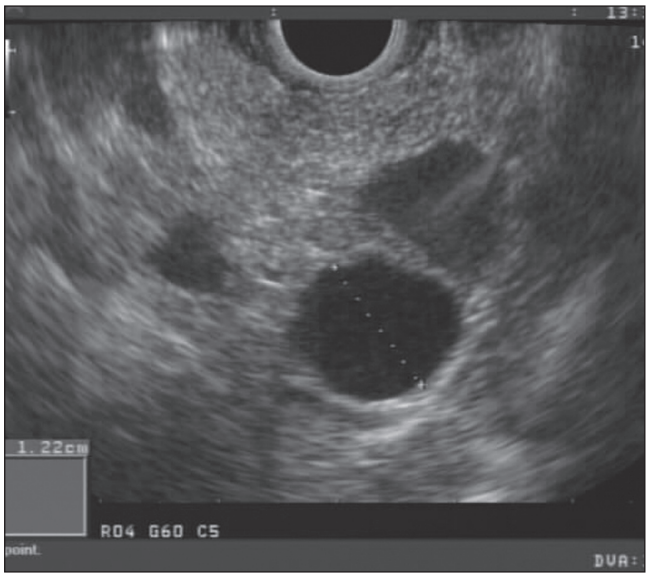

Figure 2) *Mucinous cystic neoplasm. An abdominal computed tomography scan of a 61-year-old woman undergoing evaluation for hematuria revelaed a 1 cm pancreatic cyst, discovered incidentally in the body of the pancreas. Fine-needle aspiration was performed, with benign acinar cells seen on cytological examination. Cyst fluid amylase was low and carcinoembryonic antigen was high at 760 µg/L, consistent with a mucinous cystic neoplasm. She was referred for consideration of surgical excision*

to 80% or 90% (40,43). Carcinoembryonic antigen (CEA) is a tumour marker with the greatest diagnostic value for distinguishing between mucinous and nonmucinous lesions (Table 3). A cyst fluid CEA level of less than 3.1 ng/mL is highly diagnostic of serous cystadenomas, and values higher than 480 ng/mL are suggestive of mucinous lesions (44,45). By receiver operating characteristics, a CEA level of more than 192 ng/mL had an accuracy of 79% for mucinous lesions and was superior to cytology and EUS morphology in a large multicentre study (40). This finding was further validated by a subsequent meta-analysis and cost-benefit analysis. However, CEA level is not predictive of malignancy (40,41,46,47). Other glycoprotein markers (carbohydrate antigen 19-9, 72-4 and 15-3) provided little diagnostic value. High levels of cyst fluid amylase are more often found in cysts that communicate with the pancreatic duct (pseudocysts and IPMN); a cyst fluid amylase level greater than 5000 U/L has a sensitivity and specificity of 61% and 58%, respectively, for distinguishing pseudocysts from other cystic neoplasms (42,48). Recently, molecular studies of cyst fluid DNA (49,50) have shown that mutations in *K-ras* (a tumour suppressor gene) are found more often in malignant than in benign lesions. The utility of this test has not yet been established, and further data are needed before its routine use in the evaluation of pancreatic cystic neoplasms can be adopted.

Cystic lesions of the pancreas, even when found incidentally, may represent malignant or premalignant neoplasms. EUS findings alone cannot definitively distinguish a mucinous cystic neoplasm of the pancreas or determine underlying malignancy. Cytological analysis of cyst fluid obtained by EUS-FNA lacks sensitivity but has high specificity for mucinous cystic neoplasms and malignancies (51). Together with morphological feature assessment and cytology, cyst fluid amylase and CEA often identify cystic lesions that require surgery as opposed to surveillance.

TABLE 3
Pancreatic cyst fluid levels of amylase and tumour markers

	Serous cystadenoma	Mucinous cystic neoplasm	IPMN	Pseudocyst
Amylase	Low	Low	High	High
CEA	Low	High	High	Low
CA 72-4	Low	High	High	Low
CA 19-9	Variable	Variable	Variable	High
CA 125	Low	Variable	Low	Low

CA Carbohydrate antigen; CEA Carcinoembryonic antigen; IPMN Intraductal papillary mucinous neoplasia. Data adapted from reference 40

MEDIASTINAL LESIONS

EUS-FNA can visualize and sample abnormalities in the upper retroperitoneum and posterior mediastinum, usually identified by chest CT. Mediastinal lymph nodes that can be visualized include the aortopulmonary window, the subcarina, the paraesophageal area and the area adjacent to the inferior pulmonary ligament. Abnormalities may also be detected in the paratracheal areas and adjacent to the ascending aorta if they are large enough (52-55). When lung cancer is suspected, the examination will focus on nodal stations as well as infradiaphragmatic sites of metastatic disease such as the left adrenal gland and the liver.

EUS-guided biopsy of lesions (Figure 3) in the mediastinum is a minimally invasive diagnostic method that spares patients from more aggressive methods such as mediastinoscopy or thoracoscopy. Histological confirmation of malignant or benign mediastinal disease by EUS-FNA can impact patient management, because surgery and other invasive sampling methods may be avoided if small cell lung cancer, lymphoma or benign disease such as sarcoidosis are confirmed (56-59). EUS-FNA should be considered if the lesion is in the posterior or inferior mediastinum and appears accessible from the esophagus. EUS-FNA has a high yield, and accurately identifies benign and malignant – both primary and metastatic – mediastinal disease (56,60-64). Approximately 50% of mediastinal nodes or mass lesions in patients without a known diagnosis of cancer were found to be malignant on EUS-FNA (54,56,64,65). The overall accuracy for diagnosing posterior mediastinal malignancy with EUS-FNA is greater than 90% (56,63,66). Complications are uncommon, occurring in less than 1% of patients (67,68).

Endobronchial ultrasound (EBUS) has become more widely available, and provides unique access to lymph nodes and masses adjacent to the trachea in the anterior and superior mediastinal areas, not easily accessible by EUS. EBUS-guided transbronchial fine-needle aspiration (TBNA) and EUS-FNA are often combined to provide near complete evaluation of the mediastinum. This strategy improves the diagnostic yield when compared with either procedure alone (69,70).

EUS-FNA is well-suited for diagnostic sampling of mediastinal abnormalities, has a high accuracy for diagnosis of benign and malignant conditions, is associated with a low complication rate, and can allow patients to avoid more invasive procedures or surgery.

LUNG CANCER STAGING

Accurate staging of nonsmall cell lung cancer (NSCLC) is critical for determining a patient's prognosis and guiding initial management. The current staging system for NSCLC uses the American Joint Committee on Cancer TNM system that

incorporates pathological evaluation of the primary tumour, regional lymph nodes and distant metastases. Up to 50% of patients with lung cancer present with malignant involvement of mediastinal lymph nodes, and up to 16% have metastases to the left adrenal gland (71-73). One retrospective study (74) found that up to 36% of thoracotomies performed for NSCLC were futile due to the discovery of benign lesions or locally advanced, unresectable cancer, despite standard staging methods.

Both noninvasive and invasive staging modalities are available to assess nodal involvement and distant metastatic disease in patients with lung cancer. However, CT has a sensitivity and specificity of only 70% in determining the size and location of mediastinal lymph nodes. When compared with surgical pathology, staging by CT misses mediastinal lymph node metastases in 13% of patients and is falsely positive in approximately 50% (55,73,75). Positron emission tomography scanning is significantly more accurate than CT, and has a high negative predictive value but a 30% false-positive rate, because benign lesions with a high metabolic rate such as granulomatous disease or inflammation can mimic malignancy (76,77). TBNA performed with a flexible bronchoscope can be used for FNA of enlarged subcarinal and paratracheal lymph nodes, but does not allow for imaging of the lymph node or needle tip during sampling. The sensitivity of 'blind' TBNA for staging NSCLC has been reported to range from 25% to 81% (78).

Mediastinoscopy has traditionally been accepted as the 'gold standard' for mediastinal staging, and was especially useful in patients who required sampling of multiple lymph nodes for accurate staging. It allows direct visualization and sampling of pretracheal, paratracheal and anterior subcarinal lymph nodes, and is reported to be accurate in 83% to 89% of patients with NSCLC (78-80). However, this staging surgery does not access the aortopulmonary, retrotracheal, posterior carinal or inferior mediastinal lymph nodes. Mediastinoscopy requires general anesthesia and is associated with complications in 1% to 3% of cases. In addition, 10% to 15% of patients who undergo thoracotomy for NSCLC after a negative mediastinoscopy have evidence of N2-N3 disease (80,81).

EUS is a safe procedure to accurately assess mediastinal lymph nodes in the staging of NSCLC, and can allow for FNA of tissue for cytopathology and molecular analysis (55,82,83). In the detection of metastases, EUS-FNA with cytology has been shown to improve the accuracy of detecting mediastinal metastases compared with CT and positron emission tomography (55,76,82-84). Several prospective studies have demonstrated the sensitivity and specificity of EUS-FNA in detecting metastases of posterior mediastinal lymph nodes to be 88% to 96%, and 80% to 100%, respectively (55,78,85). The management of up to 95% of patients with NSCLC may be impacted when EUS is used for staging (56,82,86-88). Several studies demonstrated that EUS-FNA was able to confirm advanced disease (stage 3 or 4) by pathology, thus avoiding surgical staging or futile thoracotomies (57,89,90). Moreover, EUS-FNA is more cost-effective than surgical methods of lymph node sampling such as mediastinoscopy (91).

Analysis of molecular biomarkers in NSCLC is an emerging field of study, and has the potential to provide further prognostic information and optimize therapy for better outcomes. Early 'micrometastases' in lymph nodes often cannot be detected with current cytology or histopathology, but techniques such as

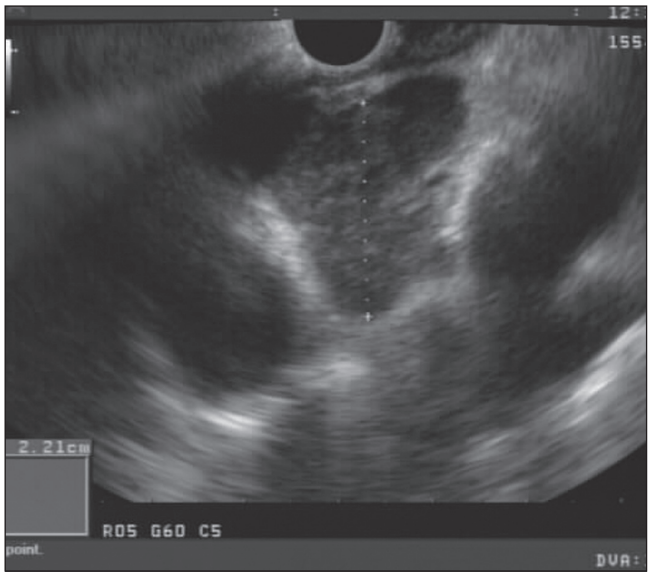

Figure 3) *Mediastinal lymphadenopathy. A 39-year-old African man with a history of treated pulmonary tuberculosis presented with odynophagia and supraclavicular lymphadenopathy. A computed tomography scan of the chest revealed mediastinal lymphadenopathy. Endoscopic ultrasound was undertaken and fine-needle aspiration performed on a mediastinal lymph node. Cytology demonstrated caseating granulomatous disease. Staining for acid-fast bacilli was negative but a DNA probe for tuberculosis was positive. His symptoms improved with tuberculosis treatment. Courtesy of Dr Eric Lam*

polymerase chain reaction and immunohistochemistry have been used to detect minute numbers of cancer cells obtained by minimally invasive methods. These molecular assays have been shown to improve the detection of metastatic cells in the lymph nodes and bone marrow of patients with lung cancer (92). Several markers have been identified, such as telomerase, which can accurately detect metastatic disease in approximately 19% of lymph nodes with negative cytopathology. Up to 50% of histologically normal lymph nodes have micrometastases detected by these molecular biomarkers, which can have a significant impact on long-term survival (93,94). Analysis of molecular markers can also be used to predict response to lung cancer therapies. The presence of epidermal growth factor receptor (EGFR) expression in NSCLC has been found to be predictive of a response to erlotinib and gefitinib (inhibitors of tyrosine kinase of EGFR). Tsao et al (95) found that the presence of this molecular marker was associated with a better response to erlotinib, but was not associated with a significant survival benefit. Recent advances in genomics and gene expression profiling has facilitated the development of assays involving groups of genes ('metagenes') that are abnormally expressed in disease states. Potti et al (96) determined that metagene analysis can predict the relapse of lung cancer more accurately than standard methods.

EUS-FNA is a safe and accurate diagnostic procedure that can contribute to each component of TNM staging by characterizing the primary tumour, assessing the mediastinal lymph nodes for evidence of metastatic disease, and evaluating sites of distant metastasis such as the left lobe of the liver and adrenal glands.

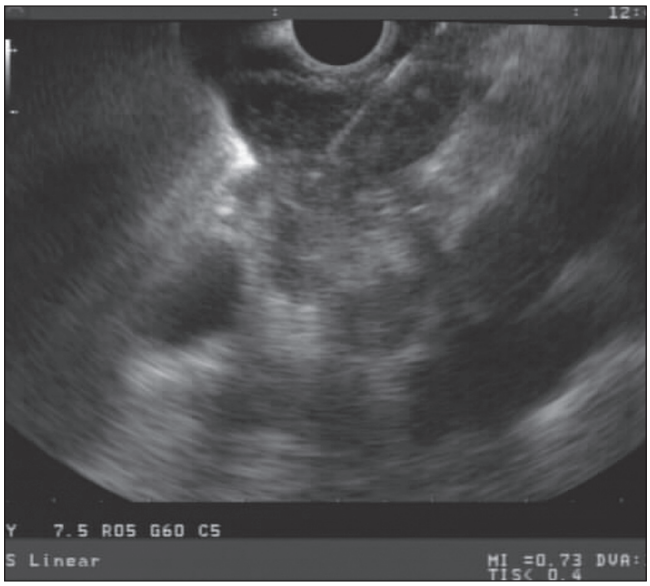

Figure 4) *Trucut biopsy of a 2 cm subcarinal lymph node. A previously well, 46-year-old man presented with third-degree heart block. Cardiac magnetic resonance imaging demonstrated features compatible with sarcoidosis. Transbronchial biopsy of subcarinal lymphadenopathy was not diagnostic. Endoscopic ultrasound Trucut biopsy revealed noncaseating granulomatous disease and negative fungal staining consistent with sarcoidosis. Courtesy of Dr Eric Lam*

TRUCUT BIOPSY

EUS-FNA of mass lesions has a reported diagnostic accuracy of 70% to 90%, depending on the site being sampled (68,78,97-99). However, EUS-FNA has several limitations because accuracy relies, in part, on the immediate review of the specimen for sampling adequacy by an onsite cytopathologist. The diagnostic yield drops 10% to 15% when a cytopathologist is not immediately present (100-102). In addition, EUS-FNA may not be ideal in the setting of lesions such as GI stromal tumours and lymphomas, which can be difficult to diagnose by cytology alone (103-106).

Larger calibre cutting needles were designed to acquire larger tissue specimens, preserve tissue architecture and allow for histological evaluation (107-110). The 19 gauge Trucut biopsy (TCB) needle was developed to be used with linear echoendoscopes (Figure 4). Initial studies suggest greater diagnostic accuracy of EUS-TCB compared with EUS-FNA for subepithelial lesions and lymphomas because of the opportunity for histological review (111,112). EUS-TCB may also have a role in the diagnosis of cystic pancreatic lesions and autoimmune pancreatitis (113). However, other reports have not confirmed the superior diagnostic accuracy of EUS-TCB compared with EUS-FNA in a variety of other diagnostic settings (114-116). Although several recent studies (117,118) have shown that the diagnostic accuracy of combined EUS-FNA with a TCB is greater than either alone, one study (119) showed no difference in the sensitivity of FNA/TCB for sampling pancreatic masses compared with FNA alone.

A recent prospective study of 24 patients with pancreatic masses who underwent biopsies with both EUS-FNA and EUS-TCB has been published (120). Three Trucut needle sizes were evaluated (25 gauge, 22 gauge and 19 gauge), with an overall accuracy of 91.7%, 79.7% and 54.1%, respectively. The 25 gauge needle was found to be technically easier to use and obtained greater overall diagnostic accuracy than the others, especially in lesions of the pancreatic head and uncinate process. However, the accuracy of histological diagnosis using the 25 gauge needle was significantly inferior to the the others. The authors concluded that the 25 gauge needle should be considered "the best choice needle for cytological diagnosis" of solid pancreatic lesions, except when histological diagnosis is needed.

Large, prospective studies comparing EUS-TCB with EUS-FNA are needed to establish the accuracy, role, safety and cost-effectiveness of TCB for application outside of research protocols.

CONTRAST AGENTS AND NEW IMAGING TECHNIQUES

Contrast-enhanced harmonic ultrasound imaging uses microbubbles as contrast media that oscillate to acoustic waves, producing echoes, which are received at higher frequency than standard ultrasound waves. This harmonic imaging improves the spatial resolution of the EUS image and sharpens the contrast between subtle scale differences, improving resolution of fine structures. Contrast-enhanced transabdominal ultrasound has been used to determine tumour vascularity in the liver and pancreas, and can be useful in the differentiation of benign or malignant liver lesions, and in the diagnosis of pancreatic masses (121-124). The use of tumour vascularity as a method to differentiate malignant and benign pancreatic tumours has also been applied to contrast-enhanced EUS (CE-EUS) (125,126). In one study, 57 of 62 (92%) of patients with ductal adenocarcinoma of the pancreas showed tumour hypovascularity with CE-EUS. All other pancreatic lesions had a isovascular or hypervascular pattern, and included neuroendocrine tumours, serous cystic adenomas and teratomas (127). Pilot studies have evaluated the use of CE-EUS in the differentiation of focal chronic pancreatitis and adenocarcinoma, with promising results (128). Becker et al (129) found that the overall sensitivity, specificity and positive predictive value of CE-EUS for the diagnosis of pancreatic carcinoma was 94%, 100% and 100%, respectively. Preliminary studies have evaluated potential indications for CE-EUS, including investigation of biliary diseases and lymphadenopathy, staging of gallbladder cancer and gastric carcinoma, and evaluation of portal hypertension and varices. In addition, drug substances can be incorporated into microbubbles, which can then be destroyed by targeted EUS, with subsequent delivery of the drug to targeted tissue and organs (130-133).

Ultrasound elastography is based on the principle that compression of tissue produces strain, which is proportional to its consistency. Because the consistency of normal and pathological tissues differ, benign tissue can be distinguished from malignancy. EUS elastography has been studied for the assessment of submucosal tumours, pancreatic masses, adrenal tumours and differentiation of benign from malignant lymph nodes (134,135). Giovannini et al (136) found a sensitivity of 100% and specificity of 67% when using EUS elastography for the diagnosis of malignant pancreatic masses in a study of 49 patients. With further advancements, this technique may be particularly helpful in scenarios in which EUS-FNA is nondiagnostic.

Three-dimensional EUS imaging uses advanced rendering software to provide volume and shape to two-dimensional images acquired in standard EUS, allowing for easier recognition of tissue structures and more intuitive interpretation of EUS images. Preliminary studies have shown that rectal cancer staging and

lymph node assessment is more accurate with three-dimensional EUS imaging, allowing for more precise determinations of cancer infiltration and staging of rectal cancer (136,137).

CONCLUSION

EUS provides useful information to guide clinical decisions. This minimally invasive test can further characterize gastrointestinal lesions and stratify patients to additional risk-appropriate testing and treatments. Its main diagnostic indications are to evaluate subepithelial lesions, pancreatic disease and biliary pathology and to stage luminal malignancies.

Recent diagnostic advances in EUS include staging of lung cancer, IDUS for assessment of pancreaticobiliary pathology, evaluation of mediastinal structures and pancreatic cysts, contrast imaging and the use of larger cutting needles for histological diagnosis.

Although currently limited to a few Canadian centres, the future diagnostic role of EUS is promising and expanding.

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