The development of endoscopic ultrasound (EUS) since its introduction in the early 1980s has added greatly to the quality of imaging of the gastrointestinal tract. EUS is probably the investigation of choice for local staging of several gastrointestinal tumors and evaluation of submucosal masses. In addition to well-established indications, newer applications of EUS are emerging. For example, EUS is proving useful in evaluation of other pathologies such as chronic pancreatitis and choledocholithiasis. However, the applications of EUS are no longer limited to the gastrointestinal system, and recent studies have suggested that it has a significant role to play in the staging of nongastrointestinal tumors, such as non–small cell lung cancer.

EUS has progressed from being a purely imaging modality to one that can provide a tissue diagnosis by fine needle aspiration (FNA) and deliver therapy (interventional EUS). Indeed, EUS-guided FNA should now be regarded as a routine extension of EUS. The ability to obtain tissue under EUS has made its acceptance more widespread. The field of interventional EUS is one that is in its relative infancy, but many potential applications are under investigation, and there is real promise with several of these applications. It is likely, as with the development of interventional endoscopic techniques, that many of these procedures will be accepted as standard in the future. There continue to be technological advances in the instrumentation used, such as mini-probes and thinner video endoscopes. Because the impact of EUS on patient care is increasingly documented in terms of both improved diagnostic accuracy and reduction in costs, the clinical applications of this tool will be difficult to ignore. After years of being limited mainly to academic centers, EUS is finally being performed more widely, but there are training issues that remain to be addressed. This review describes the established and more tentative indications for EUS (Table 1) and covers the applications of EUS in FNA and as an interventional tool. Potential future applications are also discussed.

**Instrumentation**

EUS is performed using either dedicated echoendoscopes or standard endoscopes through which mini-probes are passed. Two main types of echoendoscopes are used in clinical practice—radial and curvilinear array. Radial imaging uses a rotating 360° transducer and provides an image in a plane perpendicular to the direction of insertion of the echoendoscope. The image obtained is thus analogous to that of cross-sectional computed tomography (CT) and is more easily interpretable as a rule than the images produced by curvilinear arrays. A new echoendoscope using an electronic transverse array transducer is due to be released shortly. This gives an image in the same axis as the radial echoendoscope except that the image is about 270°. Linear devices incorporate a transducer placed at the tip of an oblique viewing endoscope and provide sector images in a plane parallel to the direction of insertion of the echoendoscope. To the novice, this latter type of imaging is less intuitive, but use of linear devices offers the significant advantage of facilitating intervention. For example, FNA and biopsy is usually performed using a linear device because one is able to view the entire length of insertion of the needle. Many linear echoendoscopes and the new electronic transverse array echoendoscopes also offer features such as pulse Doppler and color Doppler.

Standard echoendoscopes use ultrasound frequencies between 5 and 12 MHz. This allows for imaging of tissue up to 5–6 cm from the transducer but gives relatively low resolution. A significant advance in EUS came with the development of catheter ultrasound probes or miniprobes, which are passed through the operating...
channel of standard endoscopes. Frequencies between 7.5 and 20 MHz are used with these miniprobes, allowing for high resolution of structures within 1–2 cm of the transducer (Figure 1A and B). Miniprobes are particularly useful for examining the layers of the gastrointestinal wall. In addition, use of miniprobes allows the operator to use a standard endoscope, which is easier to use than the stiffer echoendoscopes. Intraductal ultrasound (IDUS) with high-frequency catheter probes is increasingly being used in imaging of the biliary tree and the pancreas. The diagnostic abilities of standard EUS, with or without FNA, is described first for all major systems. EUS as a current or potential therapeutic tool is then addressed.

**General Principles**

**The Gut Wall**

Standard EUS is able to show 5 layers of the gastrointestinal wall of alternating hyperechoic and hypoechoic layers as described in Table 2. With higher-frequency probes, 7 or more layers can be seen.

**Cancer Staging**

Cancer staging is probably the most common indication for EUS. Because it can delineate the component layers of the gut wall, EUS is very well suited to classifying gastrointestinal cancers arising from the mucosa using the widely accepted TNM classification. It is also useful for some extraluminal malignancies such as pancreatic cancer, but, in general, EUS is not useful for detecting distant metastases, other than for esophageal cancer (in which celiac nodes can be seen) and for some cancers with liver metastases. A recent abstract reported a retrospective analysis of 167 cases of EUS FNA of liver masses and found that adequate specimens were obtained in 96% of cases and that they were positive for malignancy in 86% of cases. There was a high success rate for EUS FNA in cases in which previous EUS FNA or CT FNA had failed and the overall complication rate was low at around 4%. Hence, EUS FNA may actually give important information about the M stage of a tumor.

**Lymph Nodes**

Assessment of nodes plays a critical part in the staging of gastrointestinal cancers. EUS offers a great advance in lymph node imaging because one can visualize nodes as small as 2–3 mm. The sonographic appear-

### Table 1. Indications for EUS

<table>
<thead>
<tr>
<th>Established indications for EUS</th>
<th>Debatable indications for EUS</th>
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<tbody>
<tr>
<td>Staging of gastroesophageal cancers</td>
<td>Acute pancreatitis</td>
</tr>
<tr>
<td>Staging of rectal cancer</td>
<td>Detection of pancreas divisum</td>
</tr>
<tr>
<td>Staging of pancreatic, ampullary, and biliary cancers</td>
<td>Assessment of portal hypertension</td>
</tr>
<tr>
<td>Evaluation of submucosal masses</td>
<td>Assessment of IBD</td>
</tr>
<tr>
<td>Evaluation of pancreatic cysts</td>
<td>Diagnosis of chronic pancreatitis</td>
</tr>
<tr>
<td>Detection of choledocholithiasis</td>
<td></td>
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<tr>
<td>Staging of lung cancer</td>
<td></td>
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</tbody>
</table>

![Figure 1. (A) Endoscopic image showing submucosal mass in lower esophagus. (B) EUS with a 20-MHz miniprobe shows an anechoic structure (single arrowhead) in the submucosa. This likely represents a duplication cyst. The muscularis propria is also labeled (double arrowhead).](image)
ance of nodes can suggest the likelihood of a benign or malignant nature, although there are no entirely reliable criteria. Features suggestive of malignant lymph nodes include large size (>1 cm), hypoechoic pattern, sharp borders, and rounded shape, but the reliability of EUS for determining the nature of lymph nodes has improved greatly with the use of EUS-guided FNA.

FNA

Although EUS has undoubtedly improved the accuracy of local staging of tumors, reliable differentiation of benign from malignant lesions remained difficult, a problem that has been overcome somewhat with the use of EUS-guided FNA. This practice has added greatly to the diagnostic power of EUS and has led to a great increase in the number of indications for EUS. The use of FNA is highlighted in the various systems described in this review.

EUS-guided FNA is usually performed using linear-array echoendoscopes because the whole length of the needle can be seen in real time (Figure 2). In addition, linear-array systems have pulse and color Doppler, the use of which improves the safety of FNA because one can confirm blood flow and avoid vessels. FNA is possible using radial array systems but is technically more difficult, carries a higher complication rate, and is not recommended. Needles ranging in size from 22–25 gauge are routinely used for FNA, with a 19-gauge needle available for select indications.

EUS-guided FNA using linear array has a complication rate less than 1%. A recent study described a low complication rate (0.5%) for FNA of solid lesions but a higher rate of 14% for FNA of cystic lesions, predominantly because of infectious or hemorrhagic events after puncturing cystic lesions. The theoretic risk of tumor seeding has not yet been reported. As with every technique, the success of EUS FNA is somewhat operator dependent, but the overall diagnostic rate for EUS-guided FNA is probably over 80%. In a series of 327 lesions, EUS FNA had an overall accuracy for the diagnosis of malignancy of 86%. It appears to be most sensitive for lymph nodes and mediastinal masses (up to 95% sensitivity) and less so for pancreatic cancers. In a separate study of 457 patients, the investigators concluded that EUS FNA accurately evaluates peri-intestinal lesions and improves lymph node staging accuracy. One key factor in diagnostic yield is the presence of an experienced cytopathologist at the time of the procedure. This is our practice and undoubtedly adds greatly to the success rate of FNA.

Despite the invaluable contribution of FNA to diagnosis of lesions, this modality still has limitations. For pancreatic cancer, for example, there continue to be false negatives, but development of core biopsy needles may improve this situation. However, it is interesting to note that getting larger samples using suction during FNA may not necessarily help in diagnosis because samples may be quite bloody (something which hinders detection of malignant cells). In fact, lymph node sampling may actually be more diagnostic if done without suctioning.

### Table 2. Layers of Gastrointestinal Wall Seen at EUS

<table>
<thead>
<tr>
<th>EUS layers</th>
<th>Standard EUS (5–7.5 MHz)</th>
<th>High frequency EUS (12–20 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Superficial mucosa</td>
<td>Superficial mucosa</td>
</tr>
<tr>
<td>2</td>
<td>Deep mucosa</td>
<td>Remainder of lamina propria</td>
</tr>
<tr>
<td>3</td>
<td>Submucosa</td>
<td>Interface of layer 2 and muscularis mucosae</td>
</tr>
<tr>
<td>4</td>
<td>Muscularis propria</td>
<td>Remainder of muscularis mucosae</td>
</tr>
<tr>
<td>5</td>
<td>Serosa or adventitia</td>
<td>Submucosa</td>
</tr>
<tr>
<td>6</td>
<td>Circular muscularis propria</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Septum between layers 6 and 8</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Longitudinal muscularis propria</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Serosa or adventitia</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.** EUS image of a mass (single arrowhead) in the head of pancreas. EUS FNA was performed and confirmed pancreatic adenocarcinoma. The tip of the needle (double arrowhead) is seen in the mass. A bile duct stent previously placed is also visualized (triple arrowhead).

**Gastroesophageal Masses**

**Esophageal Cancer**

There are a variety of therapeutic options for esophageal cancer including surgery, radiotherapy, chemotherapy, photodynamic therapy, palliation, and multimodal combination therapy. The appropriate treatment for esophageal carcinoma is particularly dependent...
on accurate staging, and EUS plays an increasingly pivotal role in this staging, which uses the TNM classification. Superiority of EUS over CT for local staging of esophageal cancer has been shown in several studies, and the usefulness of EUS is emphasized by the close correlation between survival rates and EUS staging. In a recent study, the authors were able to predict intrathoracic or extraesophageal extension of tumor with a high degree of accuracy based on EUS measurements of the maximal thickness of the esophageal mass. The sensitivity of T staging for esophageal cancer by EUS is between 85% and 95%. Using EUS, it is possible to assess whether esophageal tumors are limited to the mucosa or submucosa (stage T1 lesions) (Figure 3A and B) or have invaded into (T2) or through (T3) the muscularis propria. Extraesophageal invasion (stage T4) of adjacent organs can also be assessed by EUS. However, the sensitivity for N staging is lower but still high at 70%–80%. This compares with sensitivities of around 50% for both T and N staging by standard CT. If the nodal appearance is equivocal, EUS FNA can be used, increasing the accuracy of N staging to around 90%. However, if the needle passes through the primary tumor en route to the lymph node, sampling error may occur with a false-positive lymph node.

EUS FNA may also be able to offer information in relation to the M stage of an esophageal cancer. In a study of 198 patients with esophageal cancer, enlarged distant lymph nodes (mediastinal or celiac) were detected and biopsies were performed by EUS FNA in 40 cases with 97% sensitivity and 100% specificity. EUS FNA of liver masses may also give information in relation to the M stage of an esophageal tumor. The usefulness of EUS FNA in determining the M stage of esophageal cancer remains to be proven in further studies, but early results are encouraging. However, EUS will not usually detect pretreatment adenopathy, and thus the current recommendation is that combination with CT allows completion of the TNM classification of an esophageal tumor.

Although EUS is undoubtedly useful in pretreatment staging of esophageal cancer, it is not clear if EUS staging before treatment predicts response to neoadjuvant therapy, and it would appear that it is much less reliable for staging after neoadjuvant therapy. One group found that neither the pretreatment T or N stage correlated with a complete pathologic response. In another study in which 59 patients with esophageal cancer had EUS before and after neoadjuvant therapy, EUS was only 37% and 38% accurate for T and N staging, respectively, after therapy. Reduction in tumor size may be of some help prognostically, but a difficult problem with EUS is that it cannot reliably distinguish inflammatory tissue from cancer.

Another problem with EUS and staging of esophageal cancers arises with advanced and stenotic lesions. It may prove impossible to advance the EUS probe through the stenosis, and in this situation some authors have suggested dilatation to allow for EUS evaluation. Although an increased incidence of perforation has been reported, study results vary, and it now seems to be safe if general principles of esophageal dilatation are applied. Because resectability rates are very low for these advanced tumors, it is debatable whether EUS staging is beneficial or not. Use of blind probes, which can often be passed...
Gastric Cancer

EUS has also added greatly to the staging of gastric cancers, but there are some limitations not encountered with esophageal cancer. As with esophageal cancer, superiority of EUS over standard CT in assessing both T and N stage has been shown, and EUS also compares favorably with intraoperative assessment. However, a relative inability to distinguish the muscularis propria from the serosa using EUS presents a problem when trying to define a gastric lesion as T2 or T3. Inflammation and/or fibrosis associated with a cancer can lead to overstaging of a gastric tumor. In addition, an inability to distinguish malignant infiltration from edema surrounding benign tumors or ulcers is also a problem with EUS in the stomach and can make it very difficult to distinguish a benign from a malignant gastric ulcer.

However, for cancers limited to the mucosa, EUS confers significant advantages over CT and, with the advent of mucosal resection for early gastric cancers, appropriate staging of a gastric cancer limited to the mucosa or invading the muscularis mucosa is very important. This detail is best provided with the use of high-frequency miniprobes, which can delineate the gastric wall as a 9- or 11-layer structure as opposed to the 5 layers seen with lower frequency EUS (Table 2). A very close correlation between EUS for early gastric cancers and the histology of resected specimens has been described. Combination of EUS and endoscopic mucosal resection for early gastric cancers looks like a very promising strategy.

For infiltrative gastric malignancies, EUS is also helpful in assigning a diagnosis and assessing extent of disease. Linitis plastica and lymphoma infiltrate and destroy the gastric wall, and this can be assessed by EUS, thus guiding therapy. Response to treatment can also be assessed by EUS. Special mention of mucosa-associated lymphoid tissue lymphoma is warranted because it has been shown that the response to Helicobacter pylori eradication can be predicted by EUS determination of infiltration beyond the submucosa. In a small but revealing study, 12 of 14 patients with tumor limited to the mucosa or submucosa were in complete remission after H. pylori eradication treatment compared with none of 8 patients with invasion of the muscularis propria who received the same treatment.

EUS has been studied for the evaluation of the gastric wall after treatment for gastric cancer. It is suggested that the presence of a thickened gastric wall on follow-up probably equates to presence of persistent tumor, even in the setting of negative endoscopic biopsy specimens. Using large or jumbo biopsy forceps may help but if EUS shows abnormalities in deeper layers beyond the second layer, FNA should be considered. However, the assessment of tumor recurrence after gastric surgery or chemotherapy remains a very difficult problem.

Occasionally, large gastric folds are noted at endoscopy, but EUS can aid diagnosis if there is concern about an infiltrative neoplasm causing this appearance. Involvement of the third or fourth layers of the gastric wall is much more suggestive of malignancy, but FNA under EUS increases the specificity of EUS in this situation; the sensitivity of EUS FNA for tumors of the gastric wall is about 60%.

Submucosal Tumors

Until the advent of EUS, it was difficult to know how best to image submucosal tumors found at endoscopy. EUS is able to distinguish intramural lesions from extraluminal compression and can also determine whether a lesion is solid, cystic, or vascular. It has also aided the decision regarding the suitability of a submucosal tumor for endoscopic mucosal resection. By determining which of the EUS-visible gastrointestinal tract wall layers are involved by the lesion and knowing if a lesion is hypo- or hyperechoic, the nature of a lesion can be more confidently determined (Figure 4). For example, in the upper gastrointestinal tract, stromal tumors such as leiomyomas are usually homogeneously echopoor and originate in the fourth (or occasionally second) wall layer, whereas fibromas and lipomas are more echrich and originate in the submucosa. However, differentiation of benign from malignant submucosal tumors is more difficult using EUS alone. Certain features are suggestive, but not confirmatory, of a benign nature. For example, in a series of 56 histologically confirmed stromal tumors, it was found that small tumors (<3 cm) with regular margins and homogeneous echo texture were predictive of benign lesions, whereas inhomogeneous lesions with irregular margins and lymph nodes with malignant patterns suggested malignancy. In fact, it was suggested that the presence of 2 of these 3 features gave a positive predictive value of 100%. The problem occurs when these tumors do not have most or all of these features suggestive of a benign or malignant lesion, and this would account for the great variability in the literature in the accuracy of predicted malignancy.

However, it is fair to say that when faced with a submucosal tumor, EUS is help-
ful in distinguishing true submucosal tumors from cases of extraluminal compression. In some cases in which the EUS features suggest a benign nature and surgery is contraindicated or the patient and physician are reluctant to pursue surgical resection, monitoring any change in size of the lesion by EUS may be the most appropriate strategy.

EUS FNA has helped somewhat in the differentiation of benign from malignant submucosal lesions but has significant limitations. FNA may prove most helpful in identifying the origin (cell type) of the lesion and may diagnose malignancy in patients with metastases to the gut wall, but cytopathology cannot differentiate benign from malignant stromal tumors. The sensitivity of EUS-guided FNA cytology for submucosal tumors is only 60%–64%, but development of EUS core-biopsy needles may improve this reliability. If the lesion is small and confined to the first 3 EUS layers, snare excision after saline injection may be indicated.

**Pancreaticobiliary System**

**Pancreatic Carcinoma**

The advent of newer imaging modalities over the last decade has improved the detection rate for pancreatic cancers, but the ideal diagnostic tool should allow detection of small, potentially curable lesions. Some consider EUS to be the gold standard in imaging of tumors of the pancreas, and it appears to be superior to several other imaging modalities including endoscopic retrograde cholangiopancreatography (ERCP), angiography, and spiral CT, particularly for small masses less than 2–3 cm in diameter (Figure 5). The prognosis of pancreatic cancer remains poor, and hence early detection of small resectable masses is probably the most significant role for EUS. It has been reported in several studies that EUS has a sensitivity over 95% for imaging pancreatic tumors 2 cm or less in diameter. One study of small tumors of the pancreas (<2 cm) revealed that EUS detected all 25 tumors, CT 19 of 25, ERCP 19 of 25, magnetic resonance imaging (MRI) 10 of 25, and transabdominal ultrasound 10 of 25. However, classifying a pancreatic lesion as benign or malignant using EUS is more difficult.

Once a pancreatic tumor is identified, EUS is very accurate for local staging, and most studies confirm superiority of EUS over standard CT in this regard. EUS predicts T stage and N stage with accuracies of around 80% and 70%, respectively. Use of dual phase helical CT has improved the accuracy of CT, and some suggest it is comparable to EUS. When determining resectability of a pancreatic tumor, it is critical to know whether there is invasion of the portal and splenic veins and invasion or encasement of the celiac axis and superior mesenteric artery. Involvement of the portal system can be determined on EUS by loss of the sonographic interface between vessel and tumor and by irregularity in the lumen of venous structures and is superior compared with standard CT, angiography, and transabdominal ultrasound. However, EUS is limited in determining
arterial encasement and involvement of the superior mesenteric vein. While performing EUS for evaluation of pancreatic masses, one can obtain good views of the left lobe of the liver to look for metastatic spread (Figure 6A and B), but CT remains superior for imaging of the right hepatic lobe.

There has been recent suggestion that the staging information derived from EUS for pancreatic tumors may be biased by information available from other modalities such as CT or MRI and other clinical and laboratory data. For example, one group showed sensitivity for staging tumors (stages T1–3) of the pancreas of 72.2% for blinded EUS and 100% for unblinded EUS when the physician was aware of the patients’ CT reports. This and other studies suggest that for imaging of pancreatic tumors, a combined imaging approach is best using EUS, CT, and MRI findings together.

Specificity of EUS for pancreatic cancers has been traditionally lower than the sensitivity. However, EUS-guided FNA is being used increasingly to sample pancreatic masses, and reported accuracy rates range between 85% and 95%. No cases of tumor seeding have been reported. Having a pathologist present at the time of FNA should reduce the number of needle passes required to make a diagnosis. FNA under EUS of pancreatic masses is technically more demanding than FNA of lymph nodes because pancreatic masses can often be quite fibrotic, and it may be more difficult to advance the needle to the desired biopsy site especially if the endoscope is torqued in the duodenum. Hence, operator experience is undoubtedly a factor in success.

### Neuroendocrine Pancreatic Tumors

EUS has significantly improved the ability to localize neuroendocrine tumors (Figure 7). Other imaging modalities used to date include CT, MRI, transabdominal ultrasound, angiography, and somatostatin scintigraphy, but irrespective of imaging technique used, many neuroendocrine tumors are missed. In addition, up to 30% of patients with insulinomas or gastrinomas who undergo surgery fail to have localization of the tumor during surgery.

EUS is very well suited for detection of neuroendocrine tumors, particularly insulinomas, which are typically small, hypoechoic, often solitary lesions, with a hyperechoic rim within the pancreatic parenchyma. A series of 37 patients who had had nondiagnostic CT

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**Figure 6.** EUS appearances of liver metastases. (A) A 5-mm hypoechoic lesion and (B) a 35-mm × 30-mm hyperechoic lesion. These masses in 2 different patients were both in the left lobe of the liver and EUS FNA confirmed metastatic pancreatic adenocarcinomas.

**Figure 7.** Pancreatic neuroendocrine tumors. A 6-mm hypoechoic mass (single arrowhead) is seen immediately adjacent to the pancreatic head (double arrowhead). This was confirmed as a gastrinoma in a patient with known Zollinger-Ellison syndrome.
and transabdominal imaging proceeded to have preoperative EUS. Twenty-two of these patients also underwent selective angiography. EUS had a sensitivity for tumor detection of 82% compared with 27% for angiography, and the specificity of EUS was estimated at 95%. This superiority of EUS, particularly for insulinomas, in detection of neuroendocrine tumors has been confirmed in more recent studies. Taken alone, the sensitivity of EUS for gastrinomas is lower (around 60%) because more of these lesions lie outside of the pancreas than insulinomas. It is likely that management of neuroendocrine tumors will benefit from pretreatment EUS FNA.

Pancreatic Cysts

Pancreatic cysts can be broadly divided into non-neoplastic cysts and primary neoplastic cysts. The non-neoplastic cysts include pseudocysts (postinflammatory), simple cysts, and duplication cysts. Neoplastic cysts (approximately 10% of pancreatic cysts) include tumors with low malignant potential (serous cystadenoma) (Figure 8A and B) and those with high malignant potential (mucinous cystadenoma [Figure 9], mucinous cystadenocarcinoma [Figure 10], adenocarcinoma with cystic degeneration, and intraductal papillary mucinous tumor).

EUS is useful in differentiation of these lesions, but there are limitations. Several authors have described EUS features in keeping with benign or malignant processes. For example, it has been suggested that well-defined, simple, uniloculated cysts are probably benign and that complex cystic lesions with thick walls and septations or with solid lesion protrusion into the cyst lumen are likely malignant. Some series have suggested by using EUS findings alone that one can predict the nature of a pancreatic cyst with greater than 90% accuracy. However, as highlighted in a recent study, EUS alone cannot be considered the gold standard. In a series of 48 patients, EUS could not reliably differentiate benign from malignant cystic lesions of the pancreas. Although some limitations of this study were brought forth in an accompanying editorial (such as use of still EUS images alone and not using pancreatic duct dilation as a distinguishing feature), it nonetheless shows that further advances are required in the diagnosis and management of pancreatic cystic lesions. One advance in this regard is the use of EUS-guided FNA. In one study, pancreatic cystic lesions were aspirated under EUS and the aspirate sent for cytologic analysis and quantification of several tumor markers such as carcinoembryonic antigen and carbohydrate antigen 19-9. Positive cytology or elevated tumor markers were 86% accurate for diagnosing a cystic neoplasm. A recent multicenter study showed that combination of fluid cytology, carcinoembryonic levels, and EUS features increased the sensitivity of EUS to diagnose malignant cysts to 89%, but it should still be remembered that a negative FNA does not exclude malignancy. Prophylactic antibiotics should be given because there has been some concern that FNA of cystic lesions may lead to a higher rate of infection than FNA of solid lesions. Thus, although undoubtedly improving the imaging of pancreatic cysts, it would appear that a combined approach using history, FNA-aspirate analysis, EUS morphology, and any other imaging information will give the most reliable results.

Ampullary Tumors

The prognosis of ampullary cancers is better than for pancreatic cancers, but there have been fewer studies.
looking at EUS imaging of these lesions. One group found that EUS was very accurate for T and reasonably accurate for N staging of ampullary cancers (over 80% for T staging, 66% for N0, and 75% for N1 staging) but commented that EUS is unable to determine which of the TI tumors are limited to the sphincter of Oddi. This is an obvious disappointment because surgical ampullectomy for these lesions constitutes a cure. High-frequency (20 MHz) IDUS may allow this distinction and may lead to a reduction in the need for Whipple resection. In a prospective study comparing EUS, CT, and IDUS in the imaging of polypoid major ampullary lesions, IDUS was more sensitive (100% vs. 62.5%) and specific (75% vs. 50%) than EUS for tumor staging. Combining ERCP with catheter probe sonography offers a new diagnostic modality that has some potential advantages for local staging of small tumors of the main duodenal papilla and also conveniently can be done as one endoscopic procedure. The authors of the previously mentioned study suggest that IDUS findings should serve as the basis for minimally invasive techniques (such as endoscopic ampullectomy) for resection of seemingly benign tumors of the papilla or small carcinomas, but although this approach shows promise, it requires validation.

**Biliary Tumors**

EUS also has a useful role to play in the staging of extrahepatic bile duct carcinoma. It can determine whether there is invasion of the portal system and/or pancreas, an important determinant of resectability. IDUS may facilitate in the diagnosis and staging of this and other bile duct pathologies. A comparison of IDUS and EUS to predict resectability in patients with biliary obstruction showed that T staging was more accurate with IDUS but N staging inferior. Perhaps this is another example in which a combination approach is best using information both from IDUS and EUS. One group made recommendations that if IDUS reveals no localized intraductal lesion, no further investigation is required, but that if there is a lesion with preserved bile duct structure, tissue should be obtained by ERCP or percutaneous transhepatic cholangiography. If, however, the bile duct wall is interrupted by a protruding tumor, they suggest that the patient should undergo surgical exploration. This approach to biliary lesions is not widely accepted, and additional experience is needed with IDUS before general recommendations can be made.

**Chronic Pancreatitis**

Until recently, ERCP has been considered the gold standard investigation in the diagnosis of chronic pancreatitis, but the use of EUS in this setting is growing rapidly and may be overtaking ERCP. However, there are limitations with EUS that need to be taken into account. There is again, as with many EUS studies to date, variability in results between studies in the EUS evaluation of chronic pancreatitis. One group compared EUS, ERCP, and secretin tests in 80 consecutive patients with recurrent pancreatitis and described good correlation between ERCP and EUS for severe and moderate disease but poor correlation for mild disease. Chronic pancreatitis was diagnosed in 63 patients using EUS and
only 38 using ERCP, and it was reported that EUS had a 100% negative predictive value but a relatively low (60%) positive predictive value. However, there was no histologic correlation in this study. This and other studies suggested that EUS is more sensitive for detecting the parenchymal changes of chronic pancreatitis before the development of ductal lesions visible at ERCP and thus may be better at diagnosing early pancreatitis. EUS features compatible with chronic pancreatitis are described in Table 3.

It can be difficult to distinguish chronic pancreatitis from pancreatic cancer using EUS, particularly in cases of severe pancreatitis, and it is here that caution is needed. With advanced inflammatory disease, widespread heterogeneous or hypoechoic areas may be mislabeled as cancers, and studies suggest that the specificity of EUS for making this distinction is no better than 75%. The increasing use of EUS FNA may improve this situation, but even FNA seems to have a lower sensitivity for diagnosing cancer in patients with underlying calcific pancreatitis compared with patients without underlying chronic pancreatitis.

Overall, it seems that EUS is good at detecting parenchymal changes in chronic pancreatitis and may be particularly useful in early cases. However, further studies in which histologic confirmation is obtained are needed to validate these suggestions.

Acute Pancreatitis

As described elsewhere in this review, EUS is very accurate for detection of common bile duct (CBD) stones and is comparable with ERCP for diagnosis of choledocholithiasis. Recent studies have examined the role of EUS in acute biliary pancreatitis, and the results suggest that EUS may play a role in determining which of these patients has choledocholithiasis and would thus benefit from early ERCP and stone extraction. Whether all patients with acute pancreatitis of presumed biliary origin should undergo early EUS to select which patients should have early therapeutic ERCP is a question still unanswered. Magnetic resonance cholangiopancreatography (MRCP) offers the advantage of being noninvasive and gives results comparable with EUS in this setting and may be the most appropriate investigation acutely. Whether EUS will prove useful in the investigation of acute pancreatitis of nonbiliary cause remains to be determined.

EUS is also able to provide information in relation to the morphology of the pancreas such as echogenicity and degree of peripancreatic fluid in the setting of acute pancreatitis. This may help in predicting prognosis; one study showed that a score based on EUS appearance of the pancreas in acute pancreatitis correlated well with number of days in hospital and number of days in intensive care.

Choledocholithiasis

Transabdominal ultrasound is not very sensitive at detection of biliary tract stones because of interference from bowel gas in the duodenum, but EUS overcomes this problem because the transducer is placed directly in the duodenal bulb. Several studies have confirmed that EUS and ERCP have very similar accuracy rates for detecting CBD stones, most describing rates for both modalities of 80% to 90%. Based on these findings and the fact that EUS is less costly than ERCP and has a lesser risk of pancreatitis, EUS may be preferable to ERCP for patients with a low and intermediate risk for choledocholithiasis, whereas ERCP is the preferred investigation for patients with a high risk. EUS has also been compared directly with MRCP in the detection of choledocholithiasis, and one study reported a sensitivity of both modalities of 100% but a specificity of 95% for EUS and only 73% for MRCP. However, MRCP does offer the advantage of being noninvasive. IDUS is also under investigation in the diagnosis of choledocholithiasis. Interestingly, in a study of patients who had had an endoscopic papillary dilation and stone extraction, IDUS detected small residual stones in 27 of the total 81 patients with normal cholangiography. The decision as to which imaging modality should be used in patients with suspected choledocholithiasis still needs to be resolved.

Gallbladder Imaging

EUS can be used in the staging of carcinoma of the gallbladder and is very sensitive for pedunculated cancers in the gallbladder and less so for flat or broad-based cancers. However, the clinical role of EUS for this indication is currently unclear. At the present time, the primary indication for EUS of the gallbladder is for evaluating the cause of biliary pancreatitis because small stones or sludge not seen on transabdominal ultrasound can often be seen using EUS.

Table 3. EUS Features Compatible With Chronic Pancreatitis

<table>
<thead>
<tr>
<th>Parenchymal</th>
<th>Ductal</th>
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<td>Heterogeneous parenchyma</td>
<td>Hyperechoic ductal walls</td>
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<td>Hyperechoic foci</td>
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<td>Small cystic cavities</td>
<td>Ductal irregularity</td>
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<td>Prominent interlobular septae</td>
<td>Side-branch ectasia</td>
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<td>Shadowing foci</td>
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Pancreas Divisum and Other Anatomic Anomalies

Although ERCP remains the gold standard for diagnosing pancreas divisum, EUS can detect pancreas divisum with a sensitivity of 66% and a specificity of 85% using the stack sign (when the main pancreatic duct lies parallel to the distal bile duct in the long endoscope position) as indicative of normal pancreatic anatomy.99 EUS can also detect anomalous pancreaticobiliary union in which the common channel is longer than normal and the junction between CBD and pancreatic duct outside the duodenal wall.100 This condition is associated with a significantly increased risk of malignancy of the biliary tree.101

Portal Hypertension

Several groups have shown that EUS can detect periesophageal collateral veins.58 It is reported that detection of these veins predicts greater recurrence of esophageal varices after oblitative therapy102 and also that EUS is better at detection of gastric varices than standard endoscopy.18 As of yet, the clinical role of EUS remains to be determined, but improved detection of gastric varices may be helpful, for example, in cirrhotic patients who have an upper gastrointestinal bleed with no evidence of esophageal varices.

Large Bowl

Rectal Carcinoma

There is a growing body of literature describing the use of EUS in staging of rectal carcinoma, but there are many conflicting results and no apparent uniform consensus. Accurate staging of rectal cancer is important to guide appropriate resection (Figure 11) because lesions that are confined to the mucosa can be resected transanally.17 Distal, invasive tumors require an abdominoperineal resection, and proximal, invasive tumors can be removed with a low anterior resection.56 Patients with rectal cancer and lymph node metastasis or invasion through the muscularis propria generally get adjuvant or neoadjuvant chemotherapy and radiotherapy.

One study suggests that EUS staging of rectal cancer is similar in sensitivity to that of other luminal cancers.103 However, this view is not held by all, and certainly there are problems in T staging such as tumor-associated inflammation and microscopic spread and in N staging such as small malignant nodes or large benign nodes.58,104 Obviously, these problems lead to under- or overstaging of cancers and affect the accuracy of staging, but, overall, it seems that EUS is reliable preoperatively for T staging (accuracy rates between 73% and 94%) but less so for N staging (around 70% at best).105 Miniprobes may have better accuracy rates for T and N staging of rectal cancer.106

Restaging of rectal cancer by EUS after therapy has been reported to be inaccurate in one study.107 However, others report that EUS is a valuable tool for early detection of recurrence of rectal cancer.108 The role of EUS in this situation may be most useful in performing FNA of lymph nodes or soft-tissue masses in patients suspected of having recurrence.

Inflammatory Bowel Disease

Bowel wall thickening, especially small bowel, can be detected by standard ultrasound, and superior mesenteric artery flow, increased during active disease, may be measurable by Doppler studies.109,110 However, the reproducibility and clinical applicability of these parameters are not certain.110 Some studies have evaluated the use of EUS in assessment of inflammatory bowel disease111,112 and describe certain features such as increased bowel wall thickness, lymphadenopathy, and enlarged perirectal vessels. EUS may also be useful in evaluating possible abscesses and fistulae in the perirectal region. In addition, EUS may be able to distinguish ulcerative colitis from Crohn’s disease based on which bowel wall layers are involved.113

Mediastinal Masses

There is growing interest and experience in the use of EUS FNA for the evaluation of mediastinal masses
The middle and posterior mediastinum are inaccessible to percutaneous ultrasound, and, traditionally, lesions in these locations have been imaged and biopsies performed using CT, MRI, bronchoscopy and transbronchial biopsy, and mediastinoscopy/mediastinotomy. EUS staging of lung cancer has been shown to be safe and accurate in comparison to other modalities as well as being cost-effective. For patients with lung cancer, the cost per year of expected survival was $1729 with an EUS strategy and $2411 with a mediastinoscopy/mediastinotomy strategy. One study describes detection of malignant adenopathy by EUS in 84% of cases (96% with EUS FNA) compared with 49% for CT. Because the detection of contralateral or subcarinal adenopathy in cases of non–small cell carcinoma of the lung essentially precludes resectability, EUS FNA should obviate the need for unnecessary surgery. In addition, EUS FNA of nodes in the mediastinum has a role to play in the diagnosis of other conditions such as sarcoidosis or metastatic tumors. It should be noted that mediastinal EUS has not yet become widely accepted as a staging modality for lung cancer among pulmonologists and thoracic surgeons. If and when it receives this recognition, it remains to be seen who will adopt this tool as part of their service.

**Interventional EUS**

The number of therapeutic procedures being attempted under EUS is rapidly growing, and the introduction of EUS-guided FNA systems has led to many advances in the field of intervention. Following is a review of some of the procedures performed under EUS, some of which are still essentially under development (Table 4).

**Celiac Plexus Blocks**

Patients with inoperable pancreatic cancer often have significant abdominal pain that can be difficult to control. Injection of bupivicaine and alcohol into the celiac ganglia has led to a marked reduction in pain and decreased the need for narcotics in up to 88% of patients. There is also a suggestion that this technique may be safer than CT-guided celiac neurolysis, which uses a posterior approach and has very rarely been complicated by paraplegia. The role of EUS-guided celiac plexus blocks in chronic pancreatitis warrants further study, although early data are not encouraging.

**Pseudocyst Drainage**

EUS has augmented the endoscopic management of pancreatic pseudocysts. Endoscopic cystogastrostomy was often done in a blind fashion, and this may have increased the risk of complications, especially if there was not a significant intragastric bulge. EUS can locate a puncture site devoid of vessels and less than 1 cm away from the stomach wall. A study on this topic is shown in Figure 12A and B. The middle and posterior mediastinum are inaccessible to percutaneous ultrasound, and, traditionally, lesions in these locations have been imaged and biopsies performed using CT, MRI, bronchoscopy and transbronchial biopsy, and mediastinoscopy/mediastinotomy. EUS staging of lung cancer has been shown to be safe and accurate in comparison to other modalities as well as being cost-effective. For patients with lung cancer, the cost per year of expected survival was $1729 with an EUS strategy and $2411 with a mediastinoscopy/mediastinotomy strategy. One study describes detection of malignant adenopathy by EUS in 84% of cases (96% with EUS FNA) compared with 49% for CT. Because the detection of contralateral or subcarinal adenopathy in cases of non–small cell carcinoma of the lung essentially precludes resectability, EUS FNA should obviate the need for unnecessary surgery.

**Table 4. Present and Future Therapeutic Applications of EUS**

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<td>Celiac plexus blocks</td>
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<td>FNI for achalasia</td>
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<td>EUS directed endoscopic resection</td>
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<td>FNI of tumors with immunotherapeutic, chemotherapeutic, gene therapy, or radionuclide agents</td>
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<td>EUS-directed cholangiography</td>
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<td>Pancreatic pseudocyst drainage</td>
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<td>Radiofrequency ablation of tumors</td>
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<tr>
<td>Establishment of hepatico-luminal anastomoses for inoperable biliary obstruction</td>
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<td>Transrectal abscess drainage</td>
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FNI, fine needle injection.
between the gastric and cyst lumens, and one can mark this site by a double biopsy. In a series of 32 patients, preinterventional EUS provided essential information that resulted in a major change in therapeutic management in one third of patients. Some argue that endoscopic drainage should not be done without prior endosonographic examination. With the advent of larger echoendoscopes, the entire procedure, including stent placement, can be performed under EUS guidance.

**Fine Needle Injection for Achalasia**

One of the treatments used for symptom relief in achalasia is the injection of botulinum toxin into the lower esophageal sphincter. However, although initial results are good, there is a high relapse rate necessitating frequent repeat injections. It has been suggested that the often short-lived effect of toxin injection is because of incomplete delivery of the toxin to the muscularis propria layer of the lower esophageal sphincter. Accordingly, EUS-guided injection has been attempted to try to improve this situation. Toxin is delivered to regions of focal thickening in the muscularis propria at the gastroesophageal junction. Initial data are encouraging and suggest that the relapse rate may be lower using an EUS approach, but results of larger trials are awaited.

**EUS-Guided Sclerotherapy**

There are limited data suggesting that the rebleeding rate with EUS-guided sclerotherapy may be lower than standard band ligation, but no recommendations can be made at this time. It seems unlikely that EUS will oust standard endoscopic therapy for varices.

**EUS Fine Needle Injection of Tumors With Therapeutic Agents**

A particularly exciting area of ongoing research is the EUS-guided delivery of a variety of therapeutic agents to tumors. The development of EUS FNA allowed this possibility, and it is still a very young discipline but preliminary results are encouraging. In 1 study of pancreatic cancer, a local cytotoxim (containing activated T lymphocytes) was placed by using EUS guidance. Longer-term results are awaited with interest.

**EUS-Directed Cholangiopancreatography**

ERCP is not always successful in accessing the pancreaticobiliary tree for a variety of reasons including anatomic problems such as with Roux-en-Y reconstructions or luminal obstruction by tumor. EUS is able to visualize the pancreatic and biliary ducts in almost all situations. In some such circumstances, EUS-guided transgastrointestinal injection of contrast material into the biliary tree or pancreatic duct can be performed. Again, there are limited data in this regard, but this technique is unlikely to be used often because it does not allow for other therapeutic measures such as stone extraction and stent placement, and MRCP is improving all the time as a noninvasive modality for imaging of the biliary system.

**EUS-Directed or Assisted Resection**

Endoscopic resection (ER) of mucosal and submucosal lesions has gained a lot of publicity in recent years. However, some safety fears have been expressed, and the issue of completeness of resection of a lesion has also been called into question. Guiding the submucosal injection of saline using EUS may help but generally will probably be unnecessary. It would appear from data so far that the greatest help offered by EUS for mucosal resection is in the selection of appropriate patients for ER. One retrospective study on early gastric cancers showed a sensitivity of 93% and specificity of 86% regarding the assessment of patients for ER. The patients were classified as unsuitable for endoscopic mucosal resection of early gastric cancer if EUS showed involvement of the third layer and as suitable if such involvement was not seen. If a submucosal lesion is present, ER may be possible if EUS confirms that the lesion is superficial to the muscularis propria. EUS may also be useful after ER to assess lesion removal.

**EUS-Guided Paracentesis**

Small amounts of ascites may be missed on standard ultrasound or CT. If there is a question of underlying malignancy, EUS-guided FNA may aid in diagnosis.

**Future Developments**

There are many exciting developments in the field of interventional EUS. EUS-guided fine needle injection of tumors with immune modulators is under study as described earlier. It is likely with advances in tumor therapy and echoendoscope technology that EUS fine needle injection may also deliver chemotherapeutic agents, gene therapy, and radionuclide preparations directly into tumors. Delivery of radionuclide agents by EUS would require a shielded delivery system. Another exciting development is that of EUS-guided radiofrequency ablation of tumors using high-intensity ultrasound probes. This has been tried in a porcine pancreatic model and produced discrete areas of coagulation necrosis in the pancreas (Figure 13), but further animal and human data are needed. This may prove
especially useful in treating cystic lesions of the pancreas. Another group has investigated the use of microwave coagulation therapy during laparoscopic ultrasound for treatment of small liver tumors. This could potentially be applied to EUS systems if results proved success of the technique.

Work is ongoing looking at the use of contrast agents that may aid echoendosonography. Injection of suspensions of galactose microparticles improved color Doppler signals in assessment of malignant vascular invasion in pancreatic cancer. Others have described favorable findings with the use of IV sonicates of albumin to better demarcate gut wall tumors.

There has been recent excitement at the use of ultrasound virtual endoscopic imaging in which 3-dimensional images can be displayed in a short time during ultrasound examinations. Similar computer processing methods are used for CT and MRI multiplanar imaging and 3-dimensional reformating. In a series of patients with pancreaticobiliary disease, use of 3-dimensional IDUS allowed accurate definition of the surrounding vasculature and assessment of the relationship of tumor to other organs. Other potential invasive applications of EUS include transrectal drainage of perirectal abscesses and the establishment of anastomoses between the liver and stomach in cases of inoperable malignant obstruction of the biliary tract.

**Summary**

EUS is now firmly established as the investigation of choice in the locoregional staging of several gastrointestinal tumors and submucosal masses. In some situations, it is recommended that combination of information from other imaging modalities with EUS findings is needed to maximize accuracy. However, the increasing use of EUS-guided FNA should improve the accuracy of EUS as a stand-alone investigation.

Other advances have been made in the diagnosis of chronic pancreatitis with EUS, especially patients with early changes. EUS may also emerge as the investigation of choice in patients with biliary pancreatitis of low to moderate risk of persistent choledocholithiasis. EUS staging of lung cancer is very accurate, and undoubtedly EUS will continue to be used more and more for this indication.

With the increasing use of EUS FNA, other potential therapeutic applications of EUS were developed, and some of these show great promise. As technical advances are made with scope design, accessory devices, and probes, it is likely that many of these potential therapeutic applications will become routine procedures. The discipline of EUS intervention is a young one, and other new therapeutic advances are a certainty.

EUS has matured over the last few years as a pivotal investigation in many disorders of the gastrointestinal tract and mediastinum. Recognition of this has finally led to a wider availability of EUS in clinical practice, and undoubtedly EUS will be regarded over the next few years as a standard investigation rather than one of intellectual curiosity.

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