

Endoscopic Ultrasound: Indications and Applications

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Abstract

Since its development in the 1980s, endoscopic ultrasound (EUS) has dramatically expanded the breadth of gastrointestinal endoscopy and the approach to gastrointestinal and non-small-cell lung cancer staging. Combining an ultrasound transducer with a standard video endoscope, EUS produces detailed images of the gastrointestinal wall and structures surrounding the gastrointestinal tract. It is a safe and accurate method of diagnosing and staging a variety of benign and malignant lesions. Additionally, EUS-guided fine-needle aspiration can be performed on areas surrounding the gastrointestinal tract, including adjacent organs (pancreas, liver, etc.) and the mediastinum. The development of large channel scopes and new needles has led to numerous therapeutic applications for EUS, such as EUS-guided pseudocyst drainage. While the potential applications are many, availability of the technology continues to be a problem worldwide.

Key Words: Endoscopic ultrasound, esophageal cancer, Barrett's esophagus, lung cancer, pancreatic neoplasm, gastrointestinal endoscopy.

Introduction

DEVELOPED IN THE 1980s as a more accurate method of imaging pancreatic lesions, endoscopic ultrasound (EUS) has dramatically expanded the breadth of gastrointestinal endoscopy and revolutionized the staging of cancers within and surrounding the gastrointestinal (GI) tract. Over 2,000 publications have shown EUS to be a safe and accurate method of diagnosing, staging, and sampling a variety of benign and malignant lesions, including:

- Barrett's esophagus
- Esophageal cancer
- Non-small-cell lung cancer (NSCLC)
- Gastric cancer and lymphoma
- Submucosal lesions
- Pancreatic cancer
- Pancreatic cysts
- Choledocholithiasis and extrahepatic biliary disease
- Rectal cancer

The many applications of EUS rely upon its ability to visualize the various layers of the GI wall as well as surrounding organs. As its name suggests, EUS merges ultrasonography with endoscopy, allowing imaging of endoluminal structures (polyps, varices, etc.) as well as adjacent structures (liver, pancreas, mediastinum, etc.). While the endoscope permits visualization of the lumen of the GI tract, the ultrasound transducer images deep layers of the gastrointestinal wall and surrounding organs (Fig. 1). With the development of EUS-guided fine-needle aspiration (FNA), tissue diagnosis of most visualized lesions can be obtained. The following review examines some of the most frequent and validated indications for this novel technology, as well as some emerging therapeutic applications.

Indications for Endoscopic Ultrasound

Barrett's Esophagus and Esophageal Adenocarcinoma

The incidence of esophageal adenocarcinoma has increased steeply over the last several decades; it is estimated that there will be more than 13,000 new cases of esophageal adenocarcinoma diagnosed in the United States this year alone (1). Because prognosis is directly correlated with stage of diagnosis, early detection and accurate staging are critical. The development of esophageal adenocar-

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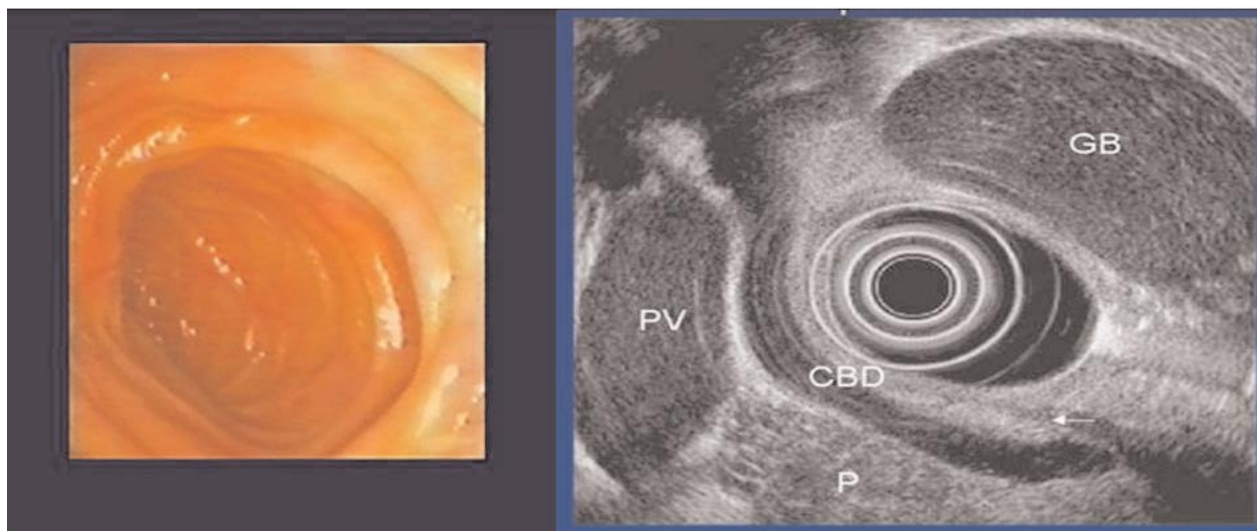


Fig. 1. Endoscopic and ultrasonographic images of the duodenum. CBD = common bile duct, PV = portal vein, GB = gall bladder, P = pancreas.

cinoma occurs through a series of progressive changes from Barrett's esophagus (intestinal metaplasia) to low-grade dysplasia (LGD), high-grade dysplasia (HGD), and adenocarcinoma. In studies looking at surgical resection specimens from patients with an endoscopic diagnosis of HGD, carcinoma has been shown to coexist in roughly 16–30% of cases, depending upon the study (2, 3). Because of this, esophagectomy has been widely recommended for individuals diagnosed with HGD. Unfortunately, esophagectomy, despite tremendous improvements in outcomes over the last several years, remains a major operation with significant morbidity. Moreover, many individuals are poor surgical candidates. Because of this, endoscopic therapies for high-grade dysplasia have received much attention and should be considered for individuals who have high-grade dysplasia or intramucosal carcinoma. In the absence of submucosal extension, the likelihood of nodal involvement is very low, and these individuals can be safely managed with endoscopic therapy. EUS plays a critical role in ruling out submucosal involvement in patients with high-grade dysplasia under consideration for endoscopic therapy. EUS plays this role by providing detailed images of the esophageal wall; it has been shown to have a sensitivity, specificity, and negative predictive value of 100%, 94%, and 100%, respectively, for submucosal involvement (4).

For individuals who are diagnosed with esophageal adenocarcinoma itself, EUS plays a critical role in locoregional staging; EUS is usually done in conjunction with computed tomography (CT) and positron emission tomography (PET). Because the ultrasound transducer is positioned

within the lumen of the esophagus and stomach, ultrasound images can be obtained without interference from bone or air to determine depth of invasion and presence of nodal involvement (Fig. 2). For locoregional staging, EUS has been shown to be significantly more accurate than CT in identifying T stage (5). A meta-analysis demonstrated an overall T stage accuracy of 89% (6). For T3 lesions, accuracy is over 90% (7). In the evaluation of nodal involvement, EUS has been shown to be accurate when EUS-guided FNA is performed on suspicious nodes. A large prospective study reported a sensitivity, specificity, and accuracy of 92%, 93%, and 92% respectively for presence of malignant lymph nodes (8).

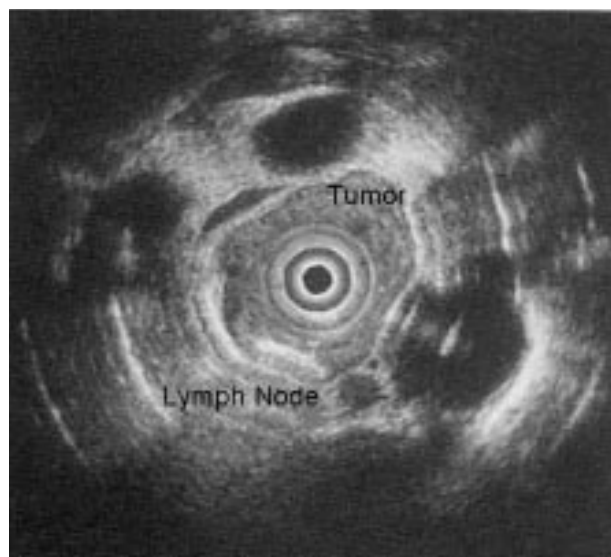


Fig. 2. Esophageal cancer with adjacent node.

After neoadjuvant chemoradiotherapy for locally advanced disease, EUS is increasingly being used to evaluate pathologic responders. Although overstaging is often an issue because of inflammatory changes and fibrosis following therapy, a reduction in tumor thickness has been shown to correlate with therapeutic response (9).

Non-Small-Cell Lung Cancer

Non-small-cell lung cancer remains the number one cause of cancer deaths in the United States. As with esophageal cancer, the stage of the disease determines the therapy, and mediastinal node involvement determines the stage. Correct assessment of direct mediastinal invasion is crucial, since it represents a clear contraindication to surgery. While CT, mediastinoscopy and bronchoscopy are typically used for staging, they have certain limitations. Mediastinoscopy is limited in its ability to reach the posterior mediastinum and bronchoscopy is often unable to access the inferior mediastinum and aortopulmonary (AP) window. EUS has been shown to have up to a 90% sensitivity in detecting lymph nodes in the superior mediastinum, AP window, subcarinal, and peri-esophageal regions. With EUS-guided FNA, specificity is nearly 100% (10, 11). This EUS-based approach has been shown to be cost-effective. For patients with CT-positive lymph nodes in locations accessible to EUS, the cost per year of expected survival was \$1,729 with an EUS-based strategy, and \$2,411 with a traditional mediastinoscopy/mediastinotomy approach (12).

Gastric Neoplasms

Though less accurate than it is when staging for esophageal cancer, EUS has been used to stage gastric carcinoma. Surgical resectability can be predicted with a sensitivity and specificity of 87.5% and 100%, respectively (13). Preoperative EUS for advanced gastric carcinoma has been shown to alter therapy in 30% of cases, usually leading to more limited resections for earlier stage tumors (T1–T3) (14). For early (T1) gastric cancers, accurate staging is critical, as endoscopic therapy can be safely performed on tumors limited to the mucosa, thus sparing the patient a gastrectomy.

For mucosa-associated lymphoid tissue (MALT) lymphomas, EUS has been shown to be very accurate both in diagnosis and staging, and in predicting outcome. Low-grade MALT with involvement of only the mucosa and/or submucosa can be treated with *Helicobacter pylori* eradication therapy, with up to an 80% response rate (15).

With this strategy, chemotherapy and/or surgery can be avoided in a large number of patients. After eradication therapy, EUS can be used to monitor treatment response and to detect early relapse.

Subepithelial (“Submucosal”) Lesions

During routine endoscopy, lesions arising from the deep layers (submucosa, muscularis propria) of the gastrointestinal wall are often identified as a nonspecific “lump or bump,” invariably with an unremarkable overlying mucosa. These subepithelial lesions encompass a broad differential (Table), from benign to neoplastic conditions, and a definitive diagnosis may be impossible with standard endoscopic and radiologic imaging. EUS, by visualizing the deep wall layers and extrinsic organs, can distinguish extrinsic compression from genuine intramural lesions. By better characterizing the lesion (solid vs. cystic) and identifying which wall layer the lesion is arising from, EUS can better define the nature of the lesion (e.g., stromal tumor vs. lipoma, etc.). Additionally, FNA of deep lesions can be performed for pathologic confirmation and in instances where nonoperative treatment is under consideration (e.g., GI stromal tumor [GIST]). Small lesions (< 2 cm) arising from the mucosa or muscularis mucosa can be removed endoscopically.

Pancreatic Cancer

Currently the fourth leading cause of cancer deaths in the United States, pancreatic cancer is

TABLE
Subepithelial Lesions of the Gastrointestinal Tract

Wall Layer	Differential
Submucosa	Lipoma Carcinoid Granular cell tumor Varices Pancreatic rests Histiocytoma, fibroma Duplication cysts
Muscularis Propria	Gastrointestinal stromal tumors (GIST) Leiomyoma, leiomyosarcoma (can also arise from muscularis mucosa)
Extrinsic Compression	Spleen Liver Heart Pancreatic masses/cysts Lymph nodes

usually diagnosed at an advanced stage in which surgical resection is no longer an option. Despite advances in surgical techniques and chemotherapeutic options, five-year survival rates remain < 5% (16). Because radical surgical resections are possible only in a minority of cases and carry a significant morbidity and mortality, accurate preoperative staging is critical to avoid unnecessary operations. EUS is currently the most accurate method of locoregional staging and is superior to helical CT for determining vascular invasion and lymph node involvement (17). EUS allows close-up, detailed images of the pancreatic parenchyma, including ductal changes and dilatation, fibrosis, and calcifications. Tumor can be easily differentiated from normal parenchyma, and extension of tumor into the portal and mesenteric vasculature can be assessed to evaluate for resectability (Fig. 3). Accuracy for tumor and nodal staging is approximately 80% and 72%, respectively (18). EUS-guided FNA of pancreatic lesions can be performed with a sensitivity of 92% (19).

Pancreatic Cysts

The likelihood of a cyst in the pancreas having neoplastic potential is greater than that for cysts in other organs. Pancreatic cysts span the histologic spectrum from inflammatory lesions (pseudocyst), to benign lesions (serous cystadenoma), premalignant lesions (mucinous cystadenoma), and malignant lesions (intraductal papillary mucinous tumor, mucinous cystadenocarcinoma). EUS can provide detailed images of pancreatic cysts, but cannot, on appearance alone, reliably distinguish

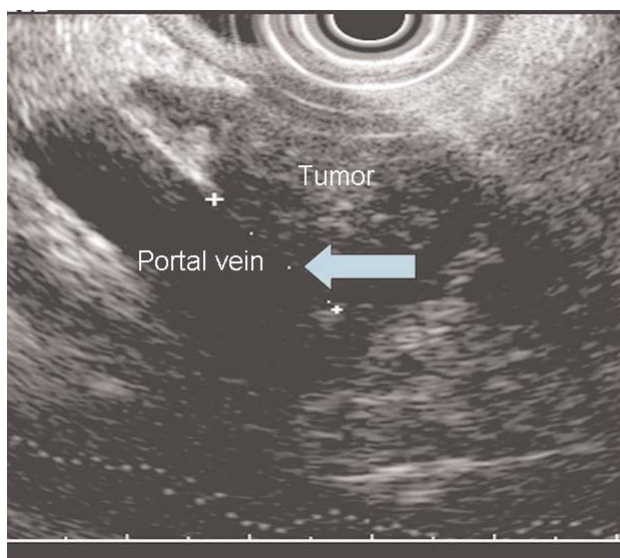


Fig. 3. Pancreatic head tumor with invasion of portal vein (arrow).

between benign and malignant ones. Interobserver agreement is low and morphologic criteria alone are nonspecific (20). With EUS-guided FNA, and analysis of cyst fluid markers, these limitations can at least partly be overcome. In a multicenter study, Brugge et al. prospectively looked at EUS imaging, cyst fluid cytology, and cyst fluid tumor markers (CEA, CA 19-9, CA 72-4, CA-125, CA 15-3) in a wide range of cystic lesions. With histology as the diagnostic standard, the accuracy of cyst fluid CEA (79%) was significantly greater than that of EUS morphology (51%), cytology (59%), and other diagnostic tests combined, in differentiating mucinous from nonmucinous cystic lesions (21).

Cholelithiasis and Extrahepatic Biliary Disease

Because of the proximity of the duodenum to the gallbladder and bile duct, EUS is an ideal method for evaluating diseases of the extrahepatic biliary tree (choledocholithiasis, unexplained dilatation of the common bile duct, etc.). The sensitivity of EUS for the diagnosis of choledocholithiasis is >95%, a rate roughly equivalent to that of endoscopic retrograde cholangiopancreatography (ERCP), and equivalent or slightly better than that of magnetic resonance cholangiopancreatography (MRCP) (22). Because the complication rate is markedly lower than for ERCP (23), EUS should be performed before ERCP in individuals with an intermediate probability of common duct stones, with ERCP reserved for those who have a high probability of harboring stones. In institutions that have EUS capabilities and can perform EUS and ERCP sequentially, an EUS-centered approach is the most cost-effective approach to the management of choledocholithiasis (24).

Rectal Cancer

Unlike colon cancer, for which locoregional staging plays no role, rectal cancer management is directly guided by local staging. EUS is used routinely in the preoperative staging of rectal cancer to determine whether neoadjuvant therapy is appropriate (25). Although EUS is often used for restaging after neoadjuvant therapy, this practice is controversial, since the accuracy of EUS after radiotherapy is markedly reduced (26).

Therapeutic EUS

The development of large channel echoendoscopes, new and larger needles, and refinements in

technique have led to numerous advances in interventional or therapeutic EUS.

Communications can be made between the GI tract and other organs under EUS guidance. Giovannini et al. described the creation of a hepaticogastrostomy under EUS guidance in a patient with inoperable hilar tumor (27). Pancreatic pseudocysts and abscesses can be drained using large channel echoendoscopes and stents to create a communication between the stomach and pancreas (28). Directed antitumor therapy using a needle advanced under real-time imaging is an evolving frontier. Additionally, EUS is being used in phase I and II clinical trials, to inject cytokine directly into pancreatic cancers. For patients with intractable pain due to pancreatic cancer or chronic pancreatitis, EUS-guided celiac plexus neurolysis has been shown to significantly reduce pain scores (29, 30).

Conclusion

Endoscopic ultrasound has dramatically extended the reach of gastroenterology, moving endoscopists beyond the lumen and into adjacent organs and the mediastinum. Additionally, EUS has radically impacted the approach to cancer staging of gastrointestinal malignancies. Despite all this, EUS is highly operator dependent and only available in a limited number of predominantly high-volume medical centers. Moreover, the results published to date have come largely from these high-volume referral centers. Thus, the above studies should be interpreted with some caution. Despite these shortcomings, the past two decades have seen tremendous improvements in the accuracy of EUS. With further improvements in technique and technology, the potential applications seem to be limitless.

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