

EUS in the Management of the Patient With Dysplasia in Barrett's Esophagus

Alan D. Savoy, MD and Michael B. Wallace, MD, MPH

Abstract: Barrett's esophagus is the most important risk factor in the development of adenocarcinoma of the esophagus. Barrett's esophagus is generally regarded as the most significant complication of gastroesophageal reflux disease. Adenocarcinoma occurs more frequently in the setting of high-grade dysplasia. The prognosis of adenocarcinoma of the esophagus is strongly correlated with the stage of disease. The prognosis of late stage disease is extremely poor. Cure may be achieved when disease is found at an early stage. Esophagectomy has been the definitive treatment of limited stage adenocarcinoma of the esophagus. The morbidity and mortality rate for esophagectomy is high. Therefore, alternative endoscopic methods for curative treatments have gained popularity. The two main endoscopic therapies, photodynamic therapy and endoscopic mucosal resection, are both effective when applied to early-stage disease. Traditional evaluation of the patient with Barrett's esophagus with high-grade dysplasia includes esophago-gastro-duodenoscopy (EGD) with biopsy and computed tomography of the chest. Endoscopic ultrasound (EUS) has gained popularity in the evaluation of the patient with Barrett's esophagus and high-grade dysplasia because it is the only imaging technique capable of delineating the separate histologic layers of the gastrointestinal tract. The principal role of EUS in evaluating patients with Barrett's-associated dysplasia is to identify patients who may be candidates for endoscopic ablative (endoscopic mucosal resection, photodynamic therapy) therapies. EUS has been shown to be superior to computed tomography (including high resolution spiral CT) or magnetic resonance imaging for preoperative staging in patients with high-grade dysplasia and carcinoma. This review of the literature summarizes the ability of EUS to evaluate patients with Barrett's esophagus and high-grade dysplasia.

Key Words: endosonography, Barrett's esophagus, esophageal neoplasms

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Barrett's esophagus is the most important risk factor in the development of adenocarcinoma of the esophagus and gastric cardia.¹ It is generally considered the most important consequence of gastroesophageal reflux disease. Adenocarcinoma of the esophagus is thought to develop within Barrett's mucosa and occurs much more commonly in the setting of

high-grade dysplasia (HGD). The incidence of adenocarcinoma of the esophagus has been increasing over the last several decades.^{2–4} It accounts for 50% of all esophageal cancers in white American men.⁵ There are 13,100 new cases and 12,600 deaths per year from esophageal cancer in the United States.⁶

The prognosis of patients diagnosed with esophageal cancer is strongly correlated with the stage of disease. Cure can be achieved if the diagnosis and definitive treatment are offered at an early stage. Screening and surveillance programs are intended to diagnose patients in the early stages of disease. The development of adenocarcinoma of the esophagus and gastric cardia occurs through the progressive changes of cellular dysplasia.⁷ The progression occurs from the development of intestinal metaplasia and cellular proliferation to low-grade dysplasia, HGD, and finally adenocarcinoma. Carcinoma frequently occurs concurrently with HGD and has been found in roughly 30% of resected specimens from esophagectomy in patients with HGD.⁸ Thus, esophagectomy has been recommended in the setting of HGD or superficial carcinoma. Esophagectomy offers the greatest chance for cure; however, it is associated with a 3% to 5% mortality and significant morbidity.⁹ As a result, interest in nonoperative alternatives to esophagectomy have become more appealing. Endoscopic therapies for HGD or superficial carcinomas have significantly less morbidity and mortality and have comparable results with esophagectomy.^{10,11} The two main endoscopic therapies, photodynamic therapy (PTD) and endoscopic mucosal resection (EMR), are both effective when applied to early-stage disease. The U.S. Food and Drug Administration has recently approved PTD for treatment of esophageal neoplasia, including Barrett's esophagus-associated HGD. FDA-approved devices for EMR have also made this procedure more convenient and accessible. Use of these modalities is increasing with further expansion anticipated. Both methods, however, cannot effectively treat tumor invading into the muscularis propria or metastatic to lymph nodes. This increasing use of endoscopic treatments has made accurate staging critical.

Historically, the staging of dysplasia in Barrett's esophagus has been performed with esophago-gastro-duodenoscopy (EGD) and mucosal biopsy. Sampling errors can occur with random biopsy protocols and targeted biopsies. Cross-sectional imaging with CT or barium is inadequate at evaluating intramucosal neoplasms. As a result, higher resolution imaging techniques are needed. Endoscopic ultrasound (EUS) is the only imaging technique capable of delineating the separate histologic layers of the gastrointestinal tract. EUS is invaluable in the evaluation of suspected cancers of the esophagus for

From the Division of Gastroenterology and Hepatology, Mayo Clinic Jacksonville, Jacksonville, FL.

Reprints: Michael B. Wallace, MD, MPH, Endoscopic Research, Mayo Clinic Jacksonville, 4500 San Pablo Road, Jacksonville, FL 32224 (e-mail: wallace.michael@mayo.edu).

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submucosal invasion and malignant lymph nodes. EUS has been shown to be superior to computed tomography (including high resolution spiral CT) or magnetic resonance imaging for preoperative staging in patients with HGD and carcinoma.¹²⁻¹⁵

ANATOMY OF THE NORMAL ESOPHAGUS

The GI tract wall is comprised of four distinct histologic layers, the mucosa, submucosa, muscularis propria, and adventitia. Endosonographically, this is represented by five alternating bands of hyperechoic and hypoechoic layers (Fig. 1). The innermost layer is the superficial mucosa and endosonographically is represented as a hyperechoic band. In reality, this layer represents the initial echo-interface between the ultrasound waves, the GI tract mucosa, and the surrounding fluid. The second hypoechoic layer represents the deep mucosa. The third hyperechoic layer corresponds with the submucosa histologically. The fourth hypoechoic layer represents the muscularis propria. In the esophagus, the fifth hyperechoic layer represents the adventitial layer. The normal esophageal wall measures 3 to 4 mm in the distal esophagus and slightly less in the more proximal esophagus. Areas of focal thickening are concerning for the presence of carcinoma.

EUS examination of the esophagus provides highly accurate images of the esophageal wall and local structures. The examination is straightforward as the examination is essentially performed by a pull-through method. An understanding of the mediastinal anatomy as it relates to the esophagus is essential for understanding the ultrasound images. Periesophageal, celiac, and posterior mediastinal lymphadenopathy is easily seen with EUS and can be sampled with fine-needle aspiration (FNA). Lymph nodes generally appear darker ("hypoechoic") than surrounding fat or soft tissues (Fig. 2). Ultrasonographic features suggestive of malignancy include round (vs. any other) shape, sharply demarcated borders, hypoechogenicity, and enlarged size (>5-10 mm).¹⁶

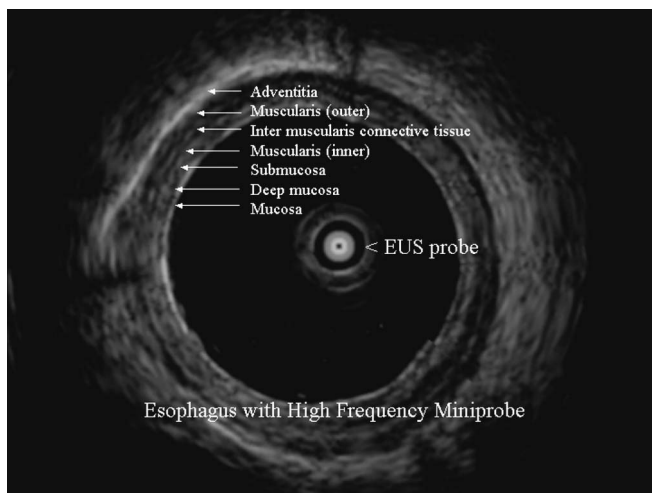


FIGURE 1. Representative layers of the normal esophageal wall seen with a high-frequency miniprobe.

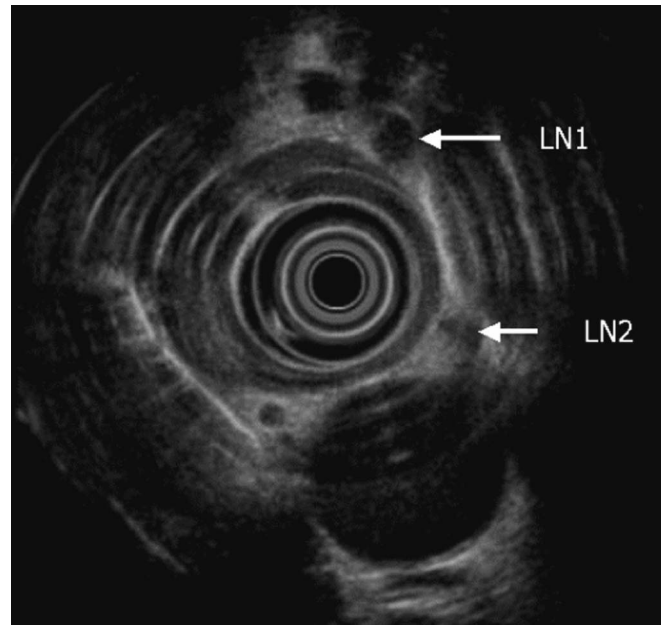


FIGURE 2. Periesophageal lymphadenopathy. The probe is centered in the esophagus, and the aorta is seen at the 5 o'clock position. Lymph node 1 is round, hypoechoic, and has distinct borders. It has a more malignant appearance than lymph node 2.

ENDOSCOPIC ULTRASOUND FINDINGS IN BARRETT'S ESOPHAGUS

The differences between EUS images of Barrett's esophagus compared with the normal esophagus have been previously described.¹⁷⁻¹⁹ A thickened mucosa (second hypoechoic layer) and a thickened submucosa (third hyperechoic layer) are consistent with Barrett's esophagus, independent of the presence of dysplasia seen on mucosal biopsy. However, in patients with esophagitis without Barrett's esophagus, there is also a thickening of the muscularis mucosa and the submucosa.²⁰ These findings have been documented with standard EUS as well as with high-resolution endoluminal sonography (HRES), using a 12- to 20-MHz mini probe. Srivastava et al¹⁷ and Gangarosa et al,¹⁸ using a 12-MHz echoendoscope using HRES, compared patients with Barrett's esophagus to normal controls. The esophagus was measured proximally every 2 to 3 cm from the gastroesophageal junction. Endoscopically acquired biopsies were obtained to evaluate for the presence of dysplasia using standard criteria. The mean thickness of the entire esophagus in normal controls was 2.6 mm. Conversely, wall thickness in Barrett's esophagus patients without dysplasia was 3.3 mm. Patients with Barrett's esophagus and biopsy-proven dysplasia had a wall thickness of 4.0 mm, which was not statistically different from the nondysplastic esophagus. Additionally, 2 patients in the Srivastava et al study¹⁷ with HGD on biopsy had focal submucosal masses seen on EUS. Both patients underwent esophagectomy-revealing carcinoma invading into the submucosa. They concluded that a thickened esophageal wall was consistent with Barrett's esophagus, and dysplasia could not be identified

using EUS. EUS was effective at identifying more advanced disease in 2 patients.

Current guidelines recommend esophagectomy and lymph node dissection for patients with HGD or superficial carcinoma.²¹ However, endoscopic therapy such as EMR, PDT, laser photoablation, and contact thermal coagulation may be offered with intent to cure in selected patients for superficial lesions, as the risk of lymph node invasion in this group of patients is low. It should be noted that the risk of lymph node metastases rises rapidly with tumors that invade into the submucosa (T1sm).²² Even T1m tumors have approximately a 5% rate, whereas T1sm have a 25% rate of lymph node metastases. EMR may be an attractive alternative to esophagectomy, as the morbidity and mortality are lower. Mortality for esophagectomy ranges from 3% to 5%, with significant morbidity.²³ Additionally, the natural history of HGD is unpredictable. High-grade dysplasia may remain stable and not progress on to carcinoma, or it may regress. Alternatively, cancer may develop shortly after the diagnosis of HGD or concurrent carcinoma may be present at the time of diagnosis of HGD.

ENDOSCOPIC ULTRASOUND IN HIGH-GRADE DYSPLASIA AND CARCINOMA IN BARRETT'S ESOPHAGUS

The principal role of EUS in evaluating patients with Barrett's-associated dysplasia is to identify patients who may be candidates for endoscopic ablative (EMR, PDT) therapies. The endoscopist should diligently evaluate for tumors with invasion beyond the mucosa, or metastases to lymph nodes (Fig. 2) such patients should be considered for surgery and/or chemoradiotherapy.

There is no conclusive evidence that EUS is effective at diagnosing or grading dysplasia in Barrett's esophagus. EUS provides detailed images of the esophageal wall with effective resolution of up to 200 nm. Despite these high-resolution capabilities, the nuclear and cellular changes that occur with dysplasia are not visible with EUS. EUS studies on patients with HGD have focused on the ability to detect occult carcinoma. Most of the reported literature is limited by small patient populations and use of various low- and high-resolution instruments. Early studies using lower frequency (7.5–12 MHz) instruments have shown EUS to be inadequate. More recent studies using high frequency probes (12–20 MHz) are more promising.

Kinjo et al²⁴ evaluated 56 patients, using a rotating, sector-scanning echoendoscope, with endoscopic biopsy-proven Barrett's esophagus. There was no statistical difference in esophageal wall thickness between Barrett's esophagus patients with no dysplasia, low-grade dysplasia, and HGD. The sensitivity and specificity for detecting cancer was 82% and 87%, respectively. The overall false-positive rate was 13%. All the false-positive patients had HGD and underwent esophagectomy.²⁴

Scotiniotis et al²⁵ studied 32 patients, with a mechanical sector-scanning echoendoscope at 7.5 MHz and 12 MHz, with Barrett's esophagus and HGD, or intramucosal neoplasm found on biopsy. EUS findings were compared with the gold standard of surgical pathology. After surgical and pathologic

evaluation, 5 of 22 had unsuspected submucosal invasion. EUS correctly identified all five. EUS was falsely positive in 1 patient for submucosal involvement. The sensitivity, specificity, and negative predictive values of preoperative EUS for submucosal invasion were 100%, 94%, and 100%. EUS was falsely positive for more advanced disease in 5 patients (1 reported to have submucosal invasion and 4 with lymph node involvement). It was concluded that EUS was very useful in detecting unsuspecting submucosal involvement and lymph node involvement. They stated that EUS should be used when nonoperative therapy is considered.²⁵

Conversely, Falk et al²⁶ studied the role of EUS in Barrett's esophagus and HGD. They prospectively evaluated 9 patients, using a rotating sector-scanning echoendoscope at 7.5 MHz and 12.0 MHz, with known HGD to determine if EUS could correctly identify high-risk patients with occult adenocarcinoma of the esophagus. All 9 patients underwent esophagectomy. EUS correctly identified only one of three cancers found at surgery. Additionally, the tumor it correctly identified was overstaged as T2N1 but found at surgery to be T1s. Furthermore, 2 patients without carcinoma on pathologic specimens were identified as having T2N0 disease by EUS. Falk et al concluded that EUS cannot consistently predict the presence of intramucosal carcinoma.²⁶

EUS has been also reported to be useful in selecting patients for endoscopic ablative therapies such as EMR or PDT,^{27–29} although the outcomes in these studies are more difficult to measure since the EUS stage cannot be directly compared with surgical stage. The fact that long-term, disease-free survival can be achieved with proper patient selection by EUS, and local endoscopic therapy is proof of principal that EUS staging can select appropriate candidates for local therapy.

An important point from all of these studies is that when EUS is inaccurate, it tends to overstage more than understage. Fortunately, such over staging would still result in curative (surgical) therapy. Since understaging rarely occurs, very few patients would receive EMR or PDT when the preferred treatment is surgery and/or chemoradiotherapy.

EUS FOR THE SELECTION OF PATIENTS FOR PDT OR EMR

Endoscopic Ultrasound Method

Conventional echoendoscopes are designed to image in a radial or linear sector pattern, at ultrasound frequencies ranging from 5 to 20 MHz. Scanning of the esophagus is generally performed with a radial echoendoscope providing a 360° image perpendicular to the axis of the endoscope. The most commonly used echoendoscope on the market is produced by Olympus Corporation (Olympus America, Melville, NY). A new near-radial echoendoscope images field of 270° with the remaining 90° images by rotating the endoscopy. This instrument has additional Doppler capabilities that may be useful for distinguishing blood vessels and lymph nodes (Pentax Precision Instrument Corporation, Orangeburg, NY). Once the endoscope is introduced into the esophagus, it is slowly advanced to the gastroesophageal junction, generally

40 to 45 cm from the incisors. For proper orientation, the aorta should be positioned at 5 to 6 o'clock. This can be performed by rotating the image on the monitor or by applying torque to the echoendoscope. Once the aorta is identified, the celiac axis is found by advancing 4 to 5 cm into the proximal stomach. The soft tissues around the celiac artery should be evaluated for the presence of lymphadenopathy (Fig. 3). Celiac lymph node involvement precludes patients from surgical excision. The esophagus is evaluated using a pull-through method with careful inspection of the esophageal wall for focal thickening of the esophageal wall, evidence of submucosal or deeper invasion, and mediastinal or peri-esophageal lymphadenopathy. If adenopathy is found, fine needle aspiration of the lymph node should be considered. It is important to recognize, though, that the needle should not be passed through malignant or even dysplastic Barrett's epithelium since this may cause contamination of the needle with malignant-appearing cells. If FNA cannot be performed, the diagnosis of malignant lymph nodes is based on the number of echo features. Most endoscopists call lymph nodes malignant if 2 or 3 or more features are present. A recent prospective study in esophageal cancer suggested 3 or more may be the best criteria.³⁰ If FNA can be performed, our threshold to perform FNA is typically 1 or 2 or more features.

Evaluation of the esophagus with high-resolution ultrasound probes provides even higher resolution images. These probes are 2 to 3 mm in diameter and can be passed through the working channel of a standard or therapeutic gastroscope. Several methods are used to obtain good acoustic coupling with the esophagus. The probe manufacturers also produce a water-balloon sheath that fits over the probe, and provide a water balloon distensible to 1 to 2 cm in diameter. This method is convenient, however; the balloons are fragile, somewhat cumbersome, and disposable. An alternative



FIGURE 3. Celiac lymphadenopathy. Real-time EUS-guided FNA with needle visualized within the target node.

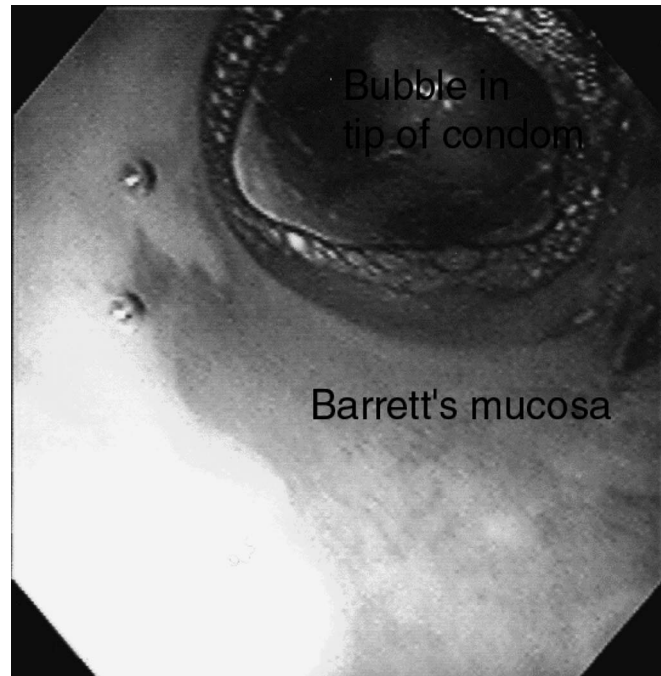


FIGURE 4. Endoscopic evidence of Barrett's esophagus. There is no evidence of erosion, ulceration, or nodule.

method uses a commercial latex condom placed over the end of a 2-channel endoscope.³¹ The condom is collapsed by suction during passage of the endoscope through the mouth, then filled with water in the distal esophagus. This provides a long, water-filled column, into which the ultrasound probe is passed. The view of the esophagus through the water-filled condom is remarkably clear (Fig. 4). The entire esophagus and mediastinum can be visualized with this method; however, the celiac axis is poorly seen. The water-filled condom method

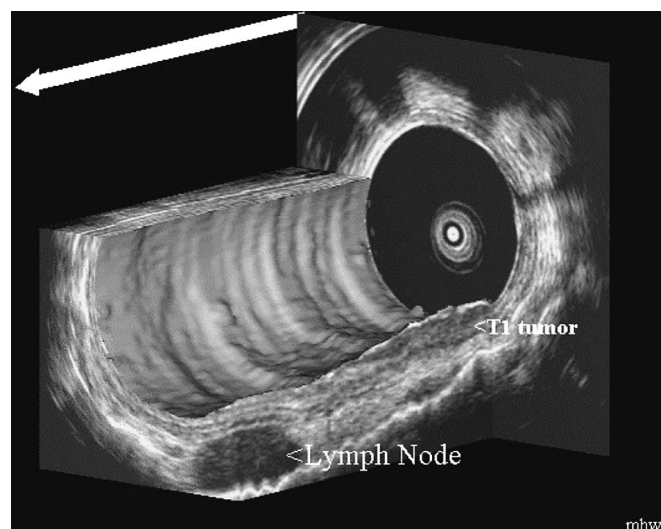


FIGURE 5. Helical images with three-dimensional reconstruction of the esophageal wall with a high-frequency miniprobe. Evident is a peritumoral lymph node.

also allows continue “helical” images to be obtained, which can provide dramatic evidence of early tumors with lymph node metastases (Fig. 5).

In summary, current EUS technology limits its ability to detect and discriminate Barrett’s esophagus and dysplasia. As a result, its routine use in patients with Barrett’s esophagus without dysplasia or focal lesions cannot be endorsed. As a diagnostic tool for detecting dysplasia, EUS is not effective and should not be used for this purpose.

Its main use in Barrett’s esophagus appears to be in the detection of more deeply invading tumors, and metastatic lymph nodes, which would preclude the appropriate use of endoscopic ablative therapies. Ablative, intent-to-cure therapy can be offered if disease is limited only to the mucosa (intramucosal neoplasm) and selected submucosal tumors without malignant-appearing lymph nodes.

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