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Endoscopic Ultrasound for Evaluation of High-Grade Dysplasia in Barrett's Esophagus

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In the past decade, endoscopic ultrasound (EUS) has become an important imaging modality in the management of several gastrointestinal disorders. Given its ability to provide detailed images of the layered structure of the esophageal wall and of the surrounding structures, EUS has been proposed as a potentially sensitive method to evaluate patients with Barrett's esophagus, in particular those with high-grade dysplasia (HGD) and early adenocarcinoma. This article reviews the role of EUS for imaging Barrett's esophagus, with particular emphasis on the available studies dealing with the clinical relevance of EUS in the management of patients with Barrett's esophagus and HGD and early adenocarcinoma.

KEYWORDS **Barrett's esophagus, high-grade dysplasia, endoscopic ultrasound (EUS), high-frequency ultrasound probes sonography (HFUPS)**

The incidence of esophageal adenocarcinoma has steadily risen over the past two decades in Western countries[1] to the point that today it accounts for up to 50% of all esophageal cancers in white men.[2,3] Barrett's esophagus, a condition in which columnar-cell metaplasia replaces the native squamous-cell epithelium of the esophagus, is presently the most important risk factor for the development of adenocarcinoma.[4] Esophageal adenocarcinoma develops in approximately 0.5% of patients with Barrett's esophagus per year, a rate that is more than 30-fold higher than that of the general population, but paradoxically low in absolute terms.[5]

Similar to the colon, where several studies have provided data supporting the adenoma–adenocarcinoma sequence in colorectal cancer,[6,7] adenocarcinoma in Barrett's esophagus arises through a sequence of events in which low-grade dysplasia (LGD) progresses to high-grade dysplasia (HGD) before cancer develops.[8] Consequently, standard management for surgically fit patients with Barrett's esophagus is entry into an endoscopic surveillance program, with the primary goal of identifying patients who develop HGD.[9] The finding of dysplasia in Barrett's esophagus offers the potential to intervene before the development of invasive adenocarcinoma with an opportunity to theoretically prolong patients' survival. Although the cost effectiveness of this process has not been validated, data reporting an increased detection of cancers at an earlier stage with very high change of cure during surveillance have provided indirect evidence to support its use.[10-13]

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The advent of minimally invasive endoscopic ablative therapies, in particular endoscopic mucosal resection (EMR), able to achieve a curative effect similar to surgery[14-18] without the considerably higher rates of mortality and morbidity associated with esophagectomy,[19-21] have provided the basis to expand the role of surveillance to also include patients who are not surgical candidates. As neoplastic foci may be indistinct and not recognizable at endoscopy, the recommended surveillance protocol recommends blind four-quadrant biopsy at 1- to 2-cm intervals.[22] Even with such a rigorous biopsy protocol, however, up to 50% of patients with HGD on biopsy actually have cancer present in the surgically resected specimens.[23,24] The need for a better surrogate marker in surveillance for HGD and early cancer has prompted the search for higher-resolution imaging techniques to guide biopsies or potentially to avoid the need for biopsies altogether.[25]

Endoscopic ultrasonography (EUS) provides high-resolution imaging of the layered structure of the esophageal wall and surrounding structures.[26] For patients with cancer of the esophagus, EUS has been reported to be far superior to computer tomography or magnetic resonance imaging for preoperative locoregional staging.[27,28] Overall accuracy rates average approximately 85% for depth of tumor invasion (T stage) and 75% for nodal staging (N stage).[29] The histologic correlation of EUS images to esophageal wall layers has been well described.[30] Commonly accepted T-staging nomenclature for EUS staging to represent each layer is as follows: uT0 = normal finding, uT1a = intramucosal carcinoma, uT1b = submucosal carcinoma, uT2 = invasion of the muscolaris propria, uT3 = invasion outside the muscolaris propria, and uT4 = invasion of adjacent structures.[31] For patients with Barrett's esophagus and biopsy-proven HGD and adenocarcinoma, EUS appears to have a role in tumor staging, in

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particular evaluation for submucosal invasion and the presence of suspicious lymph nodes that are important information to determine appropriate management (Fig. 1). Some authors have also suggested that the technique may be useful in determining when to operate on patients with HGD who have no endoscopic evidence of carcinoma.[32]

This article will review the available studies dealing with the clinical role of EUS in the management of patients with Barrett's esophagus and HGD. Furthermore, the authors' personal experience on this topic will also be presented.

Endoscopic Ultrasonography Findings in Barrett's Esophagus

The endosonographic appearance of Barrett's epithelium was first described by Srivastava and colleagues.[33] Fifteen patients with Barrett's esophagus, 6 with dysplasia, and 13 controls were studied. A radial scanning echoendoscope was used for the evaluation. Esophageal wall images were taken at a frequency of 12 MHz, every 2 to 3 cm along the esophagus. Esophageal wall thickening was defined as the distance from the most innermost hyperechoic line (balloon-mucosal interface) to the outermost hyperechoic line. The authors reported greater esophageal wall thickening in both dysplastic and nondysplastic Barrett's epithelium as compared with controls (4 mm, 3.3 mm, 2.6 mm). No significant difference in wall thickness between dysplastic and nondysplastic segments was found.

More recently, Adrain and colleagues[34] have reported their experience to detect mucosal changes in Barrett's esophagus using high-frequency (20 MHz) ultrasound probes sonography (HFUPS). HFUPS can distinguish nine layers within the wall of GI organs in contrast to a five-layered structure seen with conventional EUS, thus providing better images that are useful in the evaluation of transmural penetration (Fig. 2).[35] Moreover, the use of through the scope high-frequency probes may have the advantage of avoiding artifact occurring in conventional EUS by the compression exert on the esophageal wall by the water-filled balloon placed over the transducer.[36] Seventeen patients with Barrett's esophagus (3 with dysplasia) and 12 controls were first studied in an unblinded fashion to identify criteria possibly diagnostic of Barrett's. Increased thickness of the second hypoechoic layer measured using a computer was the only HFUPS feature found to correlate with the pathologic diagnosis. A subsequent blind review of all tapes by one investigator correctly identified all patients with Barrett's esophagus and 10 of the 12 controls based on the detection of a thickened second hypoechoic layer. No area of dysplasia was identified in the three patients who had it. The authors concluded that HFUPS is a sensitive method for identifying Barrett's esophagus. Nevertheless, even with the use of high-frequency probes, patients with dysplasia could not be identified.

Endoscopic Ultrasonography in the Evaluation of High-Grade Dysplasia in Barrett's Esophagus

The results of the two previously mentioned studies[33,34] showed that EUS evaluation of the thickening of the esophageal wall does not seem of value for the identification of dysplasia in patients with intestinal metaplasia. A similar conclusion has been reached in a more recent report in which patients with LGD only were evaluated.[37] All these results suggest that EUS has no role to help direct biopsies in the search for dysplasia in patients with Barrett's esophagus.

In the report by Srivastava and colleagues,[33] however, two patients are described with HGD arising in Barrett's esophagus but without visible lesions at endoscopic examination. EUS showed focal submucosal thickening. In both cases, histopathologic analysis of the resected specimens demonstrated adenocarcinoma extending into the submucosa in the area identified by EUS. Based on these findings, the authors suggested that EUS might have a role in the selection of patients with HGD in whom endoscopic surveillance is not an option and who should undergo surgical resection. Falk and coworkers,[38] who studied nine patients with Barrett's esophagus and biopsy-proven HGD who subsequently underwent esophagectomy, further evaluated the value of this observation. EUS images were obtained at frequencies of 7.5 MHz and 12.0 MHz. Four patients had mucosal nodularity, one erosions and ulceration, while the remaining four had endoscopically unremarkable Barrett's epithelium. EUS was able to identify only one out of three cancers found at surgery and overstaged it as invasive carcinoma (T2, N1 versus T1sm). In the other two patients with intramucosal carcinoma, no abnormalities were detected at EUS and they were, thus, understaged (T0 versus T1m). Furthermore, in two patients in whom the diagnosis of HGD was confirmed on surgical specimens, EUS predicted invasive carcinoma (T2, N0). All cases of overstaging occurred in patients with mucosal nodularity at endoscopy. The authors concluded that, based on their results, EUS cannot predict presence of adenocarcinoma in patients with HGD at biopsy thus preventing its use to determine the need for surgery in this patient population.

Complete opposite conclusions have been reported by the group from University of Pennsylvania,[39] which evaluated the potential of conventional EUS to discriminate superficial from more advanced stage lesions in 22 patients with Barrett's esophagus and biopsy-proven HGD or intramucosal carcinoma (ICA). Preservation of the integrity of the submucosal layer defined as absence of disruption of the hyperechoic, third sonographic layer, or the interface between the second and the third layer was used to diagnose a lesion as superficial. Lesions with these findings were accorded stage uT1a rather than uTx or uT0 because of the known HGD or ICA on biopsy. The results of EUS performed at the frequencies of 7.5 MHz and 12 MHz were compared with surgical pathologic findings. Overall, the sensitivity, specificity, and negative predictive value of preoperative EUS for submucosa invasion were 100%, 84%, and 100%, and for assessment of lymph nodes involvement were 100%, 81%, and 100%, respectively. Specifically, in the 15 patients with HGD studied, EUS correctly identified local tumor invasion in 14 cases (uT1a in 12 patients, uT1b in 1, and uT2 in 1), but suggested submucosal invasion in a patient who was found to have intramucosal carcinoma in the surgical specimen. All 15 patients had stage N0 at resection, although EUS suggested malignant lymph nodes in 3 patients. In the 6 patients with ICA on biopsy, EUS correctly identified local tumor invasion