EUS and EMR/ESD:
Is EUS in patients with Barrett's esophagus with high-grade dysplasia or intramucosal adenocarcinoma necessary prior to endoscopic mucosal resection?

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The management of patients with HGD in BE remains controversial, largely because the natural history of this condition is poorly defined. For example, Reid et al. reported a 59% 5-yr cumulative cancer incidence among 76 patients with HGD in BE [1], whereas Schnell et al. found that only 12 (16%) of their 75 patients with HGD developed adenocarcinoma during a mean follow-up period of 7.3 yr [2]. Four management options have been proposed for patients with HGD in BE: (1) esophagectomy, (2) endoscopic ablative therapies, (3) EMR, and (4) intensive endoscopic surveillance, in which invasive therapy is withheld until biopsy specimens show evidence of invasion [3]. Clearly, there are risks associated with all of these approaches, and all would benefit from accurate staging of the neoplasia.

Estimation of the depth of tumor penetration

The less than perfect reliability of endoscopic staging with the adjunct of chromo endoscopy and magnification endoscopy for the estimation of cancer depth before EMR can be improved by the use of endoscopic ultrasonography (EUS), in particular high-frequency US probe sonography (HFUPS). HFUPS may 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 and in differentiating cancers limited to the mucosa from those with submucosal penetration. The main limitation of HFUPS is its tendency to overstage early lesions. The diagnostic accuracy of HFUPS in assessing depth of tumor invasion in the esophagus, stomach and colon ranges from 67% to 94% among the published studies [4–9]. This high variability in HFUPS accuracy may reflect the use of probes with different penetration (15MHz versus 20MHz) and differences in the patient populations studied. Accuracy of HFUPS, in fact, is significantly better for elevated type lesions than for depressed ones [7].

When different techniques are used in combination to select lesions suitable for EMR, the overall accuracy is high [10]. Because of the limitations of these staging techniques, however, it has been suggested that when a lesion meets the generally accepted criteria of size, and appearance is encountered, EMR can be performed without prior HFUPS, as long as the lesion can safely be removed in its entirety [11–12]. Submucosal injection used to facilitate EMR can also help to decide whether or not to continue with the procedure [13]. The observation of a bleb formation with elevation of the overlying mucosa indicates the absence of deep submucosal involvement and the feasibility of EMR [30]. On the other hand, the dense fibrosis associated with deep submucosal invasion prevents fluid infiltration through the submucosal connective tissue, decreasing bleb formation and elevation of the lesion [14]. This so-called “non-lifting sign” has been found to have 100% sensitivity, 99% specificity, and 83% positive predictive value for invasive carcinoma in patients with early cancer of the colon [15]. Ultimately, depth of tumor invasion can be precisely established by histological analysis of EMR specimens, which in fact, is part of the diagnostic algorithm for the evaluation of early gastric cancer [16], and as recently suggested for high-grade dysplasia (HGD) and early adenocarcinoma arising in Barrett’s esophagus (BE) [17].

EUS in BE with HGD, ICA and early adenocarcinoma

Falk et al. studied the utility of EUS in nine patients with BE and HGD or ICA using the conventional echo-endoscope (7.5 and 12 MHz) [18]. In the six patients with HGD, EUS correctly predicted the absence of tumor in four, but incorrectly predicted the presence of tumor in two. EUS correctly predicted that there was tumor in one of the three patients with ICA, but EUS overstaged that lesion. Indeed, EUS correctly staged only one of the three patients with ICA. The tendency of EUS to overstage was attributed primarily to inflammation in the wall of the esophagus. The authors also proposed that over staging could have been caused by artifacts, such as overlapping folds pulled up by the balloon, or tangential imaging of the esophageal wall that makes it appear thicker on one side. Such artifacts appeared to occur most frequently around the gastroesophageal junction. Based on the above data, the authors concluded that conventional EUS was unable to distinguish ICA from HGD reliably in BE, and unable to stage early neoplasia accurately. The authors suggested that better delineation of the esophageal wall with HFUPS might provide more accurate information. Srivastava and colleagues reported their prospective experience with conventional EUS (12 MHz) in the evaluation of 17 patients with BE (6 with dysplasia) and 13 controls [19]. Patients with BE in general had greater esophageal wall thickness than controls. In two of the six patients with HGD, focal submucosal thickening was identified, and invasive T1b adenocarcinomas were identified in esophagectomy specimens.

Based on these results, the authors suggested that EUS may help in selecting patient’s with HGD who may benefit from surgical resection. However, the conclusions that can be drawn from that study are limited because the authors did not specify the grade of dysplasia in four of the six patients in the dysplastic group, and surgical results are not provided in another four cases. Hence, the accuracy of EUS in this small number of patients cannot be ascertained.
Scotiniotis et al. studied the accuracy of conventional EUS (7.5–12 MHz) in the evaluation of BE with HGD or ICA in 22 patients [20]. The sensitivity and specificity of EUS for detecting submucosal tumor invasion were 100% and 94%, respectively. However, 55% of their patients had endoscopically apparent mucosal lesions or strictures. Similar to our results, EUS resulted in one false-positive diagnosis. Like Falk et al. [18], these authors also speculated that HPFUS might provide more accurate information. HPFUS with 20-MHz probes provides finer resolution of the esophageal wall than conventional EUS. In contrast to the five-layered gastrointestinal wall structure seen with conventional EUS, HPFUS reveals 7–9 layers. There is better definition of the mucosa with clearer visualization of the muscularis mucosae, features that conceivably might result in better staging of neoplasia in BE [21,22]. Drain et al. used HPFUS to evaluate 17 patients with BE (3 with dysplasia) and 12 control subjects [22]. BE was diagnosed when the second hyperechoic layer was thicker than the first hyperechoic layer of the mucosa and, using these criteria, HPFUS was 100% accurate in distinguishing patients with BE from normal. However, the investigators identified no specific sonographic finding for dysplasia. They concluded that HPFUS is a sensitive tool for identifying Barrett’s epithelium but not for detecting dysplasia. In a study by Waxman et al. HPFUS was not highly accurate for detecting invasive esophageal cancer in patients with BE and HGD or ICA (23). As in the study by Drain et al. [22], the authors found that HPFUS showed thickening of the mucosal sonographic layers of the esophagus in all nine of our patients. Although there was some correlation between the HPFUS and surgical pathology findings in six patients (67%), HPFUS mistakenly diagnosed cancer in one patient (11%) and missed cancers in two (22%). In one of the two patients with a missed cancer by HPFUS, the error might have been due to the location (gastroesophageal junction) and small size (2 mm) of the cancer [23]. This suggests that, even at 20 MHz, HPFUS does not have the resolution needed to identify superficial cancers reliably. Similar experience was reported in abstract form by Parent et al. in 13 patients with HGD [24]. Thickening of layer two was noted in all patients studied, but HPFUS could not detect adenocarcinomas in the absence of endoscopically visible lesions.

Furthermore, in patients with biopsy-proven ICA, a normal sonographic examination could not exclude the presence of submucosal carcinoma [24]. Finally, in one of the largest recent studies dealing with the question of HPFUS in early cancer in BE by May et al. [25], only two of 14 patients with submucosal tumor invasion diagnosed after EMR had been correctly identified beforehand. Furthermore, endoscopic assessment of tumor penetration was as good as HPFUS.

Two recent published studies dealing with malignant adenopathy in the presence of ICA and early adenocarcinoma support revisiting the role of EUS in the evaluation on patients who are being considered for endoscopic therapy [26,27]. Although the studies have many limitations, further research into the role EUS may play in the management algorithm of patients being considered for endoscopic therapy is warranted [28].

In summary, based on available data, HPFUS appears to have limited value in accurately predicting depth of penetration of early adenocarcinoma in BE and hence cannot be the sole factor in deciding a therapeutic conduct. A detailed endoscopic assessment provides invaluable information and should be undertaken prior to EMR in patients with BE with ICA or early adenocarcinoma. The role of EUS in excluding malignant adenopathy remains to be determined.

References

17. Lightdale CJ, Laghi A, Rotterdam H, Okpara N. Endoscopic ultrasonography (EUS) and endoscopic mucosal resection (EMR) for staging and treatment of high-grade dysplasia (HGD) and early adenocarcinoma (EAC) in Barrett’s esophagus (BE). Gastrointest Endosc (abstract AB90), 2004; 59 (5)

Waxman I. EUS and EMR/ESD. Endoscopy 2006; 38 (51): S12–S53
22 Adrian AL, Ter HC, Cassidy MJ et al. High-resolution endoluminal sonography is a sensitive modality for the identification of Barrett’s metaplasia. Gastrointest Endosc 1997; 46: 147 – 151
24 Parent J, Levine DS, Haggitt RC et al. Role of endoscopic ultrasound in patients with Barrett’s esophagus and high grade dysplasia. Gastrointest Endosc 1997; 45: A76