Due to the variety of therapeutic options that are currently available for patients diagnosed with Barrett’s-related high-grade dysplasia (BE-HGD), the choice of optimal management continues to be a topic of discussion among gastroenterologists, surgeons, oncologists, pathologists, and patients. Per the current American College of Gastroenterology guidelines, HGD is considered a threshold for therapeutic intervention (1). The choice of management ranges from the most conservative approach—continued endoscopic surveillance (2,3) to the most aggressive option—esophagectomy, with endoscopic therapies such as endoscopic mucosal resection (4) and ablation therapy somewhere in the middle (5).

The potential to completely eradicate the diseased segment as well as the fact that 12.7% - 75% (mean-39.3%) of patients with a pre-operative diagnosis of HGD will harbor adenocarcinoma on esophageal resection (6) are the most compelling reasons in favor of esophagectomy. Esophagectomy, however, is associated with significant mortality and morbidity, with estimates of mortality ranging from 0% - 2% at high-volume centers to 8%-10% at low volume centers (7). On the contrary, with significant advances in endoscopic techniques, the role of esophagectomy is becoming restricted to patients diagnosed with multifocal dysplasia who have failed endoscopic therapy and patients in whom pre-operative imaging modalities such as endoscopic ultrasound staging (EUS) suggest the presence of at least submucosal disease.

Compared to that which had been found in earlier studies, where up to 40% of patients with a pre-operative diagnosis of HGD demonstrated adenocarcinoma on resection, Konda et al in a meta-analysis of 23 studies found that only 12.7% cases of HGD showed evidence of underlying invasive adenocarcinoma in esophagectomy specimens (8). In this analysis, invasive adenocarcinoma was defined as tumor invading the submucosa (submucosal adenocarcinoma, SMC) and beyond. This definition was specifically adopted for the study as the risk of lymph node metastasis is much lower with intramucosal adenocarcinoma (IMC, 0%-8%) (9) as compared to submucosal invasion (8%-33%) (10). In the study by Nasr and Schoen (11) published in this edition of the journal, using the same rationale, the authors provide compelling evidence that the rate of invasive adenocarcinoma (IMC and SMC) is 17.6%, much lower than the reported average rate of approximately 40%. In a retrospective analysis of 68 patients undergoing esophagectomy for a pre-operative diagnosis of HGD, they identified 4 cases of IMC and 8 cases of SMC on esophageal resection, with an overall rate of SMC of 11.7%. There was no statistical difference in the average size of tumors in the IMC vs invasive carcinoma categories (0.61 cm vs 1.86 cm). Of the 8 cases of invasive adenocarcinoma, the incidence rate of occult SMC was 4/68 (5.9%). A time-based analysis of two groups (1993-2000 and 2000-2007) showed no difference in the detection rate of adenocarcinoma associated with HGD.

In an attempt to predict which cases of HGD will harbor concurrent adenocarcinoma, several pre-operative factors including pre-operative biopsy protocols, endoscopic findings as well as histologic features have been the focus of attention of many recent studies. Significant variability in pre-operative sampling protocols, endoscopic evaluation techniques, histologic assessment, as well as potential
selection bias in the cohorts may have contributed to the relatively high estimated rate of occult adenocarcinoma in some of the previous studies. One of the limitations of the study by Nasr and Schoen, which according to the authors may have lead to a higher rate of occult cancer, is the lack of standardized pre-operative testing including imaging studies and presumably endoscopic evaluation. The Seattle biopsy-based endoscopic surveillance protocol, consisting of serial 4-quadrant biopsies at 1-cm intervals with jumbo biopsy forceps, along with aggressive targeting of endoscopically visible lesions has been advocated as a technique that can improve the rate of detecting carcinoma (2,12). In a recent study, Kariv et al demonstrated that even this extensive tissue sampling protocol misses a substantial percentage of cancers detected at esophagectomy (13). One needs to however bear in mind that this study was a cross-sectional study that analyzed data at one specific time point. In fact, Kariv et al have recommended that more serial endoscopies may be more important than one rigorous protocol, possibly because prevalent dysplasia, which is known to harbor higher rates of adenocarcinoma, is screened out.

Of the 8 cases of invasive adenocarcinoma in this study, 4 (50%) had evidence of an endoscopic abnormality (erosion, nodules or stricture). There is sufficient evidence to support the contention that endoscopically visible lesions in a Barrett’s segment are often associated with adenocarcinoma on esophagectomy and therefore must be targeted aggressively, particularly with a biopsy diagnosis of HGD (13-16).

The more conservative treatment options demand better distinction between HGD, IMC, and SMC on mucosal biopsies. This large surgical series further provides evidence that it is important to separate IMC from SMC, as it may influence the choice of therapeutic intervention. Given the clear prognostic difference between HGD, IMC, and SMC, pathologists are often expected to reliably make this distinction on small biopsy material. The approximately 40% adenocarcinoma rate in patients with a pre-operative diagnosis of HGD highlights the fact that it is not always possible for pathologists to make this distinction. The two main problems are: 1) sampling error – e.g., do more biopsies help pathologists distinguish HGD from IMC from SMC? and 2) interobserver variability – e.g., can pathologists reliably distinguish the higher end of Barrett’s neoplasia spectrum? In an attempt to assess histologic features on pre-operative biopsies that would be associated with a higher risk of concurrent adenocarcinoma on resection, two recent studies performed at the University of Michigan (UM) (17) and Cleveland Clinic (CCF) (18) identified categories of HGD suspicious for adenocarcinoma (UM) and HGD with marked glandular architectural distortion (CCF). Compared to HGD alone, both categories were significantly associated with IMC or SMC. Nevertheless, pathologists are relatively poor at separating HGD from IMC and even SMC (18). In addition, pathologists rarely find diagnostic evidence of SMC in biopsy material. In another study performed at the Cleveland Clinic, the overall rate of SMC on esophageal resections from patients diagnosed with Barrett’s-related HGD or worse was 21.4% (24/112). Of these cases, only 3 cases (2.7%) had unequivocal evidence of submucosal invasion on biopsy (19). Pathologists also struggle with the distinction between SMC and IMC because of the well-recognized split muscularis mucosae (20,21). On superficial biopsies, or even endoscopic mucosal resection (EMR) specimens, it is often difficult to decide whether neoplasm below one layer of muscularis mucosae is within the submucosa or “pseudo-submucosa.”

While all the available modalities of risk assessment including endoscopy, imaging, and histology do allow us to guide clinical intervention, none are perfect. Although EMR and ablation therapy are emerging as popular choices for management of Barrett’s-related HGD and IMC, recurrence of neoplasia at the rate of 11%-21% has been reported in these patients (22,23). The advantages of these approaches, specifically EMR, are larger tissue samples that not only allow better evaluation of histologic landmarks, but also improve diagnostic accuracy and staging (24). This approach does sound reasonable if there is an endoscopically visible lesion. In a series of 78 patients undergoing esophagectomy, Oh DS et al demonstrated that nearly a third of patients with IMC did not have any visible lesions on endoscopic evaluation, thus concluding that some cases of IMC may not be amenable to endoscopic therapies (25). The current study does, however, caution about overestimating the rate of occult adenocarcinoma, suggesting that esophagectomy is not indicated in all patients diagnosed with HGD; others may examine this same data and argue that 6% risk of unsuspected (deeply) invasive adenocarcinoma is too high to justify carte blanche conservative therapy. In fact, this series highlights the difficult decisions that patients and their doctors must make when faced with a diagnosis of HGD. Unquestionably, there is a risk of unsuspected adenocarcinoma and lymph node metastasis in patients with Barrett’s-related HGD. This risk is dependent on numerous factors including, the rigor of the sampling protocol, the endoscopic appearance, the reliability of the pathologic interpretation, the multifocality of the neoplasia, whether the patient is actively under endoscopic Barrett’s surveillance, and the results of additional staging modalities such that there is no “cookbook” answer for the treatment of HGD. In reality,
the ultimate choice of therapy must be individualized by taking into consideration all of the variables in addition to the patient’s individual profile to come to a consensus decision for therapeutic intervention.

References