Editorial

Low risk of prevalent submucosal invasive cancer among patients undergoing esophagectomy for treatment of Barrett's esophagus with high grade dysplasia

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Barrett's esophagus (BE), a precursor for esophageal adenocarcinoma, is the transformation of the esophageal lining from the normal squamous epithelium to specialized intestinal metaplasia. Barrett's esophagus with high grade dysplasia (HGD) is the best marker that we have to identify which patients are at risk of developing adenocarcinoma. The traditional treatment for BE with HGD was an esophagectomy. The rationale for an esophagectomy for HGD was based on the suspected risk of harboring occult invasive cancer. Estimations of occult cancer were often quoted as high as 40% based on the surgical literature that reported the prevalence of cancer in those patients undergoing a prophylactic esophagectomy for the treatment of HGD (1,2). Yet, several studies suggested rigorous surveillance and biopsy protocols could effectively monitor patients for adenocarcinoma and therefore patients with HGD may be managed conservatively with surveillance (3,4). The debate regarding the appropriate treatment of patients with HGD raged on in the endoscopy and surgery worlds (5,6). Then, the entrance of endoscopic resection and photo-dynamic therapy fired up the already heated stage with centers reported high rates of early neoplasia free outcomes (7,8). The initial success from centers with endoscopic methods had to be reconciled with the high rates of occult cancer that were reported in the esophagectomy literature. Therefore, understanding of the prevalent risk of invasive cancer became a critical issue in the management of Barrett's esophagus associated neoplasia as therapeutic options ranged across the spectrum from esophagectomy to surveillance and is now centering on endoscopic management.

In order establish the true prevalence of occult cancer in patients who undergo esophagectomy for the treatment of their HGD, attention must be properly given to the issue of definitions. Dysplasia is defined as neoplastic cytologic and architectural atypia without evidence of invasion past the basement membrane. The diagnosis of low-grade dysplasia (LGD) or HGD is based on the severity of cytologic criteria that suggest neoplastic transformation of the columnar epithelium as previously described (9,10). High grade dysplasia and carcinoma in situ are regarded equivalently in terms of pathologic significance and are limited to the basement membrane. Intramucosal carcinoma (IMC) is tumor limited to the lamina propria and is limited to the mucosal lining of the esophageal wall. IMC carries only a minimal nodal metastasis risk (10,11,12), and thus, may be locally treatable with endoscopic means (13,14). Submucosal carcinoma (SMC) is tumor invading past the muscularis mucosa into the submucosa, but not into the muscularis propria. The presence of cancer with invasion into the submucosa carries a higher nodal metastasis risk and thus generally requires surgery and/or systemic therapy (10,15-18).

This issue features an article by John Nasr and Robert Schoen that seeks to clarify the prevalence of occult cancer among patients who underwent esophagectomy for the treatment of Barrett's esophagus with high grade dysplasia at their institution, University of Pittsburgh Medical Center (19).

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Patients who underwent esophagectomy for BE with HGD were identified through their medical archival record system from 1993 until 2007. Inclusion criteria included a preoperative diagnosis of HGD confirmed by the pathologists at their institution. Patients were excluded if they had a preoperative diagnosis of low grade dysplasia or invasive adenocarcinoma or if they had other indications for esophagectomy. All available preoperative endoscopy, surgical and radiology reports for each case was reviewed. Sixty-eight patients who underwent esophagectomy with the preoperative diagnosis by endoscopic biopsy of HGD were identified in the time period. The post-operative surgical specimens revealed diagnosis of LGD in 2 patients (2.9%), HGD in 54 (79.4%), and esophageal adenocarcinoma in 12 (17.6%). Of the 12 patients who had cancer in the esophagectomy specimens, 4 patients had IMC (T1a), which was 5.9% of the total cohort. The remaining 8 patients had invasive cancer (T1b or higher), which composed 11.7% of the total group. Four of the eight patients with invasive cancer had preoperative endoscopic or radiographic testing highly suggestive of advanced disease. The remaining four patients did not any reported endoscopic or radiographic findings that were suspicious of invasive disease and were considered occult. The authors also performed a time-based analysis to determine if there was a difference in prevalent disease in earlier versus later groups and did not find a significant difference.

In a systematic review of the surgical literature, our group reported the rates of invasive cancer in patients undergoing esophagectomy for the prophylactic treatment of HGD among 23 studies (20). When applying strict definitions and standardized criteria, the pooled average of cases with esophageal adenocarcinoma was 39.9% in the 441 patients who underwent an esophagectomy for HGD. Of the 23 studies, fourteen studies provided adequate information to differentiate cancer cases between those patients with IMC (T1a) and those with submucosal invasive disease (T1b or higher). Among these 213 patients, only 12.7% had submucosal invasive disease, while 87.3% had HGD or IMC (20). Wang et al. performed a similar retrospective study among patients at their institution who underwent esophagectomy for the treatment of HGD or IMC over a twenty year period (21). The overall rate of submucosal invasive carcinoma among sixty patients with either a preoperative diagnosis of HGD or IMC was 6.7% and a 5% rate of submucosal invasion specifically in the 41 patients with preoperative diagnosis of HGD.

Esophagectomy may be curative, but carries a signification morbidity and mortality even in high volume centers (22,23). Therefore, esophagectomy is now reserved for more selected cases with submucosal invasion, evidence of lymph node metastasis, unsuccessful endoscopic therapy, or selected patients with high-risk features with HGD or IMC (24). Endoscopic therapy at referral centers is now an established treatment of Barrett's esophagus related neoplasia including HGD and IMC in appropriately selected patients. Therefore, it is important to appreciate the difference between IMC versus submucosal invasion as this present study has done.

One stated limitation of this study is the lack of standardized preoperative assessment. The 5.9% of cases with "occult" invasive cancer did not have any reported endoscopic or radiographic findings suspicious for advanced disease. However, it is unclear what kind of endoscopic assessment was performed or what biopsy protocol, if any, was implemented in those cases. Although the authors concluded that their time based analysis did not reveal a decrease of prevalent disease with the increase of endoscopic technology and imaging, the presence of technology is perhaps insufficient to capture subtle disease. It is a systematic protocol and ability to recognize suspicious lesions in conjunction with endoscopic imaging technology that enables endoscopists to target lesions for accurate diagnosis.

Visible lesions in the setting of HGD are at high risk of harboring cancer until proven otherwise. The cornerstone of the endoscopic assessment in Barrett's esophagus is a detailed white light examination with high resolution. The recognition of subtle lesions will enable the detection of disease. Several studies have shown that visible lesions in the setting of HGD were associated with higher risk of occult cancer (25,26). Furthermore, superficial lesions are being given more attention and a classification system is now standardized (27). Protruding or depressed lesions are at higher risk for submucosal invasion than those slightly raised or flat areas (28,29). Wang et al. described that all four cases of patient with submucosal invasive disease that was not previously diagnosed in their experience had nodular or ulcerated mucosa on endoscopy. Centers with experience with Barrett's esophagus may use tools such as digital chromoendoscopy or confocal laser endomicroscopy to find unapparent or occult neoplasia (30). However, these technologies provide only an incremental yield over a detailed white light exam. The key is not just the tool itself, but the ability to recognize the lesions.

Once a lesion is recognized as suspicious in the setting of a patient with Barrett's esophagus with high grade dysplasia, a histological specimen is required to stage the lesion. Endoscopic mucosal resection (EMR) provides an opportunity to accurately stage the depth of a lesion in areas of question. There are significant limitations with endoscopic biopsy alone. Due to limited sample size and

depth as well as potential crush artifact, pathologists may not reliably be able to distinguish between HGD, IMC, and submucosal carcinoma on a single endoscopic biopsy specimen. There is a high inter-interpreter variability in diagnosing high-grade dysplasia among pathologists (9,31-34). Therefore, it is important to confirm any neoplasia in Barrett's esophagus with an expert gastrointestinal pathologist. Endoscopic resection may provide relatively a larger and intact histological specimen from which pathologists may more reliable provides a stage of a lesion. Our center's experience in endoscopic mucosal resection of the entire segment of Barrett's esophagus in those patients with HGD or IMC illustrates the impact of the histology specimen from an endoscopic mucosal resection on final histopathological staging. Two expert gastrointestinal pathologists at our institution reviewed all of the pre-treatment biopsy specimens. The initial EMR specimen upstaged 7 of 49 (14%) and down-staged 15 of 49 (31%) the histopathological diagnosis when compared to pre-treatment biopsy results (14). EMR from four demonstrated either submucosal carcinoma or intramucosal carcinoma with lymphatic channel invasion that was not previously diagnosed (14). Thus, EMR is a critical diagnostic tool in the staging of visible lesions in the setting of Barrett's associated neoplasia.

Although esophagectomy was previously the standard treatment for patients with Barrett's esophagus with high grade dysplasia, endoscopic treatment is now an accepted treatment for Barrett's associated neoplasia. Proper patient selection, rigorous endoscopic assessment, and accurate histopathological staging of visible lesions by EMR are prerequisites for either endoscopic therapy or surgical treatment. As endoscopic technologies advance and assessment experience is fine tuned, rates of occult invasive disease in the setting of Barrett's esophagus will continue to decline.

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