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Management of low-grade dysplasia in Barrett's esophagus: Ablate or survey?

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ABSTRACT

There are several issues that continue to make the management of Barrett's esophagus and low-grade dysplasia challenging especially in terms of determining the optimal management strategy—surveillance vs endoscopic eradication therapy (EET). Some of these include a highly variable rate of neoplastic progression to high-grade dysplasia or cancer and significant interobserver variability among pathologists (including expert gastrointestinal pathologists). The efficacy and effectiveness of EET, predominantly using radiofrequency ablation, in reducing the risk of progression has been well described. However, there are limited data that define the ideal candidates most likely to benefit from EET compared with surveillance. This review discusses the challenges in the diagnosis and management of Barrett's esophagus with low-grade dysplasia, provides practice advice for this patient population and the need for physicians to incorporate quality indicators in clinical practice.

1. Introduction

Barrett's esophagus (BE) represents the replacement of the normal squamous epithelial lining of the lower esophagus with columnar-lined intestinal metaplasia. Associated with gastroesophageal reflux disease, BE is the only identifiable precursor lesion to esophageal adenocarcinoma (EAC) [1]. EAC continues to rise in incidence, especially in the Western world, and is a highly lethal cancer associated with a dismal 5-year survival rate ranging from 15%-20% [2-4]. BE is thought to progress to EAC in a stepwise manner progressing from nondysplastic BE (NDBE) to low-grade dysplasia (LGD) to high-grade dysplasia (HGD) to invasive EAC. Despite all the advances in the field of biomarkers, the degree of dysplasia remains the best predictor for risk of progression and determining the management strategy, specifically for pursuing surveillance or endoscopic eradication therapy (EET) [5-8].

The decision to pursue surveillance or EET is particularly critical and challenging with regard to LGD given the poor intraobserver and interobserver agreement among pathologists and heterogeneous rates of progression from various cohorts [5,9-11]. Determining the ideal management strategy in this patient population becomes even more important given that 15%-40% of patients with BE are diagnosed with LGD at some point during follow-up [12]. This review will address the current controversies in diagnosis and management of patients with BE with LGD. The focus of this review will be to provide evidence-based best practice advice based on recent systematic reviews and guidelines regarding the ideal management strategy—surveillance vs ablation. This review also provides a framework for future research in this field and highlights the importance of quality indicators to optimize patient outcomes.

2. Histopathologic diagnosis of LGD and interobserver agreement among pathologists

A discussion on the histopathologic diagnosis of LGD is critical component as without an accurate diagnosis, it is difficult to make any decisions regarding management. As defined by Vienna classification, LGD is characterized by the presence of crypts with relative preservation of glandular architecture with elongated epithelial cell nuclei and nuclear stratification [13]. Other features of LGD include a reduction in goblet cells and mucin and a higher number of mitotic figures with extension of cytologic atypia from the deeper glands to the surface epithelium [13,14].

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The classification of LGD remains challenging, however, due to a variety of reasons including poor interobserver agreement, differences in criteria for dysplasia, and regional practice differences. Numerous studies have demonstrated the poor interobserver agreement between pathologists (community and expert) in the diagnosis of LGD, with κ statistics ranging from −0.17 to 0.32 [5,9,10,15,16]. A recent study compared European pathologists with pathologists from the United States using consensus histopathologic criteria and confirmed the low interobserver agreement ($\kappa = 0.11$) for LGD, with significant differences between United States and European pathologists [17]. Strikingly, there were even differences between United States and European pathologists in the number of criteria needed to diagnose LGD and HGD. Furthermore, even within the same geographic areas, significant differences in interobserver and intraobserver agreement exist between community and expert pathologists in the delineation of dysplasia levels [5,9-11].

Overdiagnosis of LGD remains a significant problem as it not only affects reported rates of progression in LGD, but ultimately influences management of these patients. A study by Curvers et al [11] demonstrates this effect in showing that after expert review of pathology slides from the community setting, 75% of LGD diagnoses were downgraded to NDBE, which is reflected in the higher rate of progression to HGD and EAC in patients with confirmed LGD compared to those downgraded to NDBE. Conversely, a recent meta-analysis of Rubenstein et al including 8 studies found a higher rate of progression to HGD or EAC in patients with LGD during the first year of follow-up (8.8/100 patient-years) compared to the annual rate of progression from LGD (4.6/100 patient-years), which likely reflects a misclassification of HGD or EAC as LGD, whether it be due to sampling error or pathologist interpretation [18]. Lastly, Duits et al [19] analyzed data from 255 patients in the SURF trial and found that the number of pathologists agreeing on a diagnosis of LGD was strongly associated with risk of progression to neoplasia. When 3 pathologists agreed on LGD, the risk of progression was significantly greater (odds ratio = 47.1).

Thus, the available data suggest that individuals with confirmed LGD (defined by confirmation of diagnosis by an expert pathologist or a panel of pathologists) along with patients with LGD confirmed by multiple pathologists instead of a single pathologist diagnosis of LGD are at a higher risk of progression to HGD or EAC. The recent expert review from the Clinical Practice Updates Committee of the American Gastroenterological Association (AGA) and the American Society for Gastrointestinal Endoscopy (ASGE) guidelines recommend that for patients with LGD being considered for EET, confirmation of diagnosis is made with at least 1 expert gastrointestinal (GI) pathologist (defined as a pathologist with special interest in BE-related neoplasia who is recognized as an expert in the field by their peers) or a panel of pathologists compared with review by a single pathologist [14,20].

3. Disease progression in LGD and predictors of progression

The variability in the published rates of progression of LGD defines the major issue in the management of LGD patients. Progression rates have ranged from 0.4%-13.4%, which likely reflect small sample sizes of patients with LGD in the majority of the published studies, misdiagnosis of LGD as mentioned earlier, limited endoscopic follow-up data as well as referral and selection bias [8,10,14,21-23]. A meta-analysis examining the incidence of EAC in patients with LGD, compiling data from 24 studies involving 2694 patients with a total of 119 cases of EAC, reported a pooled annual incidence rate of EAC alone of 0.54% (95% CI: 0.32-0.76) and a pooled annual incidence rate of EAC or HGD of 1.73% (95% CI: 0.99-2.47) [21]. Substantial heterogeneity in the results was a major limitation of this study.

Identifying predictors of progression enables risk stratification for patients with BE-associated LGD, thus allowing for tailored management to individualized patient profiles. Perhaps the most important predictor of progression, persistent LGD has recently been addressed in several studies. Previous studies had demonstrated that the diagnosis of LGD was not necessarily reproduced when endoscopy was repeated after the index procedure [23-25], which may speak to both the natural course of LGD as well as interobserver variability between pathologists in the interpretation of LGD. Duits et al found a 9-fold increase in odds of neoplastic progression in patients who had LGD confirmed within 18 months of the index procedure [19]. Kestens et al [26] performed a larger retrospective study using a nationwide registry of histopathology diagnoses in the Netherlands (PALGA). After screening 4109 patients in the database, 161 cases were found to have confirmed LGD in which a second pathologist confirmed the diagnosis of LGD. During a median follow-up of 1.8 years, an annual progression rate of 5.2% was found in this confirmed LGD group. Persistent LGD was found in 49 patients (30%) within this confirmed group, and during a median follow-up period of 3.7 years, the annual progression rate was found to be 7.7%. In contrast, the progression rate was significantly lower at 2.3% in patients who were downgraded to NDBE on subsequent endoscopy. Additionally, patients who had 2 subsequent endoscopies showing NDBE after an initial confirmed LGD diagnosis had a 0% rate of progression. Persistent LGD was thus found to be an independent risk factor for development of HGD or EAC with HR of 3.5. Other predictors of progression include confirmed LGD (where the diagnosis has been confirmed by an expert GI pathologist or a panel of pathologists), number of pathologists confirming a diagnosis of LGD, presence of nodularity and multifocal dysplasia (defined as dysplasia on at least 2 specimens taken from different locations in the BE segment on the same endoscopy) [11,19,22,27,28].

Biomarkers have garnered interest in an attempt to improve risk stratification for disease progression. These biomarkers detect DNA abnormalities including methylation, mutation or loss of heterozygosity or p53 and p16 genes, as well as chromosomal abnormalities [29-35]. Unfortunately, none of these biomarkers are readily available nor used in current clinical practice. Further multicenter prospective studies will be needed to validate their use in the future. This underscores the need for improved risk stratification in this patient population to accurately identify patients with LGD at highest risk of progression who would benefit most with treatment.

4. Endoscopic assessment of patients with LGD

Once BE is detected, surveillance via repeat upper gastrointestinal endoscopy is recommended by current GI societal guidelines [1,14,36]. As mentioned above, given the significant interobserver variability among pathologists, all diagnoses of LGD should be confirmed with by an expert GI pathologist or a panel of pathologists [14]. Once LGD is confirmed, repeat upper endoscopy utilizing high-definition white light endoscopy should be performed after maximal acid suppression for 8-12 weeks. Patients with confirmed histologic diagnosis of LGD should be referred to an endoscopist with expertise in managing BE-related neoplasia at institutions with the capability to perform high-definition endoscopy, endoscopic resection, and ablation [14].

Recent studies focusing on advanced imaging modalities offer the potential to detect EAC at earlier stages. Although a detailed review of advanced imaging modalities is beyond the scope of this