Current Management of Low-Grade Dysplasia in Barrett Esophagus

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Abstract: Low-grade dysplasia in Barrett esophagus remains an ongoing challenge in clinical management. Recent studies suggest an increased risk in progression of low-grade dysplasia to high-grade dysplasia and/or adenocarcinoma. This is especially seen when 1 or more expert gastrointestinal pathologist confirms the diagnosis and in the setting of low-grade dysplasia that persists on more than 1 endoscopy. In the setting of confirmed and persistent low-grade dysplasia, level 1 evidence supports endoscopic ablation as a treatment option for these patients, although continued surveillance remains a viable option. Current management of these patients emphasizes the importance of the following principles: (1) biopsies should not be obtained in the setting of erosive esophagitis; (2) any diagnosis of low-grade dysplasia should be confirmed by a second pathologist with extensive expertise in Barrett esophagus; (3) surveillance endoscopy should be repeated within 3 to 6 months of the initial diagnosis with rigorous visual inspection to exclude higher-level lesions; and (4) the advantages and disadvantages of both endoscopic ablation and continued surveillance should be reviewed with the patient.

The Challenges of Low-Grade Dysplasia

Low-grade dysplasia in Barrett esophagus (Figure 1) is a histologic diagnosis based upon the following pathologic abnormalities: closely packed overlapping basal nuclei with hyperchromasia and irregular contours, basal stratification of nuclei, and diminished goblet and columnar cell mucus (Figure 2).1 However, there is considerable interobserver variability in the interpretation of this finding among pathologists likely due to a number of factors, especially involving the separation of true low-grade dysplasia from regenerative inflammatory changes as well as concern regarding the underdiagnosis of actionable dysplasia. This interobserver variability has led to considerable inconsistency in natural history studies of low-grade dysplasia and, hence, confusion regarding optimal management. What is clear from a variety of studies is that overdiagnosis of low-grade dysplasia is associated with a low risk of progression. Furthermore, biopsy protocols are highly variable, and it is well known that real-world adherence to the Seattle protocol (4-quadrant biopsies every 1-2 cm of the...
Barrett esophagus segment in conjunction with separate sampling of any mucosal abnormality) is suboptimal, which may lead to the failure to detect more advanced endoscopic and histologic abnormalities. The bottom line is that the current knowledge base of low-grade dysplasia is highly variable, leading to considerable confusion regarding optimal clinical management of these patients.

The Risk of Progression of Low-Grade Dysplasia

A population-based study of progression of Barrett esophagus in Denmark found that the relative risk of progression to adenocarcinoma for patients with a baseline diagnosis of low-grade dysplasia was 0.5% annually, with a relative risk of progression of 4.8% compared to those without baseline low-grade dysplasia (95% CI, 2.6-8.8). A recent systematic review of the natural history of low-grade dysplasia found that the annual risk of progression to adenocarcinoma was 0.54% per year, and it was 1.73% per year for the combined endpoint of high-grade dysplasia and/or adenocarcinoma. However, there was substantial study heterogeneity, and only 6 of the 24 studies described expert pathologic confirmation. Interestingly, the incidence rate was higher in studies in which the diagnosis of low-grade dysplasia was made by an expert pathologist and was lower in settings in which the ratio of the diagnosis of low-grade dysplasia to nondysplastic Barrett esophagus was higher, suggesting that overdiagnosis was problematic and likely indicated poorer-quality pathologic interpretation.

What is known from randomized clinical trials with central pathology review? In the AIM-Dysplasia (Ablation of Intestinal Metaplasia Containing Dysplasia) study, the results of which were published in 2009, the risk of progression to high-grade dysplasia at 1 year was 14% in
On the other hand, a multicenter cohort study from the United States found that the risk of progression to high-grade dysplasia or adenocarcinoma was only 1.83% per year. However, this study mixed both low-grade dysplasia and indefinite for dysplasia, making interpretation somewhat problematic given the variable natural history of indefinite for dysplasia. As such, there continues to be a debate regarding the rate of progression of low-grade dysplasia in both the United States and Europe. It is safe to say that the rate of progression of low-grade dysplasia is greater than that of nondysplastic Barrett esophagus but less than that of high-grade dysplasia.

Professional Society Guidelines on Low-Grade Dysplasia

Professional society guidelines have changed over time with the evolution of the low-grade dysplasia literature (Table). All professional society guidelines agree on the critical need for confirmation of low-grade dysplasia by a second pathologist with expertise in gastrointestinal pathology. There is also a need to repeat the endoscopy within 6 months to both confirm the diagnosis and exclude a higher-level abnormality. If the diagnosis is confirmed, the most recent guidelines released by the American College of Gastroenterology recommend endoscopic ablation therapy in the absence of a mucosal abnormality. Similarly, an update of the British Society of Gastroenterology guidelines suggests that radiofrequency ablation is now an appropriate treatment option to offer patients with confirmed low-grade dysplasia. However, it is thought that continued endoscopic surveillance is a reasonable option as well for these patients, and both options should be discussed.
The Case for Ablation Therapy of Low-Grade Dysplasia

The case for ablation is supported by the results of the randomized, controlled clinical trials described above. In the first study, the AIM-Dysplasia trial, patients with low-grade dysplasia were randomized to radio-frequency ablation or sham ablation and followed for 1 year. Progression to high-grade dysplasia at 1 year was 5% in the intervention group compared to 14% in the sham-treated group. However, this secondary endpoint was not statistically significant, perhaps because the study was not designed to address this endpoint. Subsequently, the European SURF study randomized patients to radiofrequency ablation or continued endoscopic surveillance. At 3 years, 1.5% of the treated patients developed high-grade dysplasia or adenocarcinoma compared to 26.5% in the surveillance group. This led to an absolute risk difference of 25% and a number needed to treat of 4. Finally, a multicenter North American cohort study examined radiofrequency ablation compared to continued surveillance in patients with low-grade dysplasia. Here, too, the progression risk to high-grade dysplasia and/or adenocarcinoma was decreased: 0.77% in the intervention group compared to 6.6% in the observation group (number needed to treat of 3). Taken together, it appears that ablative therapy is superior to continued surveillance in carefully selected individuals with low-grade dysplasia that is confirmed by expert pathologists.

The Case Against Ablation Therapy of Low-Grade Dysplasia

Although the data presented above seemingly offer compelling reasons to proceed with ablation of low-grade dysplasia, there are equally compelling reasons not to proceed with widespread ablation. In the SURF study, 28% of patients in the surveillance arm experienced resolution of dysplasia during follow-up and would, therefore, have undergone unnecessary ablation. Similarly, in the AIM-Dysplasia study, 22% of patients experienced spontaneous resolution of dysplasia during follow-up endoscopy. Taken together, at least 1 in 4 patients would have undergone ablation unnecessarily.

Although radiofrequency ablation is typically touted as simple, safe, and easy to perform, there are several downsides to the procedure. For example, the SURF study reported adverse events in 19% of treated patients, including strictures in 11.8%. Other uncommon adverse events included abdominal pain, bleeding, chest pain, and mucosal lacerations. It is also important to remember other concerns about radiofrequency ablation, including the cost, the need for multiple endoscopies, and indirect costs (such as time away from work), as well as the need for ongoing surveillance in spite of ablation.

Future Perspectives

Moving forward, it will be important to better identify low-grade dysplasia patients who are at high risk for progression compared to those who are at low risk of progression, and tailor therapy accordingly. Conceptually, this could be accomplished by taking the subjectivity out of pathology by widespread central review using new platforms to digitize images, electronic image enhancement, computer neural networks, or biomarkers of increased risk. Another option would be to develop risk scores composed of clinical, histologic, and endoscopic variables.

Biomarkers of increased risk have long been a goal of Barrett esophagus surveillance. This area has led to few actionable results over the years thus far. However, research by Kastelein and colleagues suggests a potential role for immunohistochemical staining for p53. In their work, the researchers found that aberrant p53 expression, defined as either overexpression or complete loss of progression, led to a relative risk of progression of 12.2 when compared to patients with no dysplasia and normal p53 expression.

Lastly, a variety of clinical markers of increased risk have been identified in some but not all studies. These include confirmation by multiple pathologists, persistent low-grade dysplasia on more than 1 endoscopy, multifocal low-grade dysplasia, segment length, and nodularity within the Barrett esophagus segment.

Conclusion

Low-grade dysplasia in Barrett esophagus remains a challenging area for both patients and gastroenterologists. That being said, certain overarching principles should guide the management of these patients. First, patients should not undergo biopsy in the setting of ongoing active inflammation, such as erosive esophagitis. Second, any diagnosis of low-grade dysplasia should be confirmed by a second pathologist with extensive expertise in Barrett esophagus. Third, surveillance endoscopy should be repeated within 3 to 6 months with rigorous visual inspection and endoscopic mucosal resection of any nodularity or mucosal abnormality. Fourth, the advantages and disadvantages of both endoscopic ablation and continued surveillance should be reviewed with the patient. Factors supporting endoscopic ablation of low-grade dysplasia include confirmation by more than 1 pathologist, persistence on more than 1 endoscopy, multifocal nature, and presence in a long segment of Barrett esophagus.
Dr Falk has no relevant conflicts of interest to disclose.

References