Current Management of Low-Grade Dysplasia in Barrett Esophagus

Gary W. Falk, MD, MS

Dr Falk is a professor of medicine in the Division of Gastroenterology at the University of Pennsylvania Perelman School of Medicine in Philadelphia, Pennsylvania.

Address correspondence to:
Dr Gary W. Falk
Division of Gastroenterology
University of Pennsylvania Perelman School of Medicine
PCAM South Pavilion, 7th Floor
3400 Civic Center Boulevard
Philadelphia, Pennsylvania 19104-4311
Tel: 215-615-4951
Fax: 215-349-5915
E-mail: gary.falk@uphs.upenn.edu

Keywords
Barrett esophagus, radiofrequency ablation, endoscopic mucosal resection, low-grade dysplasia

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

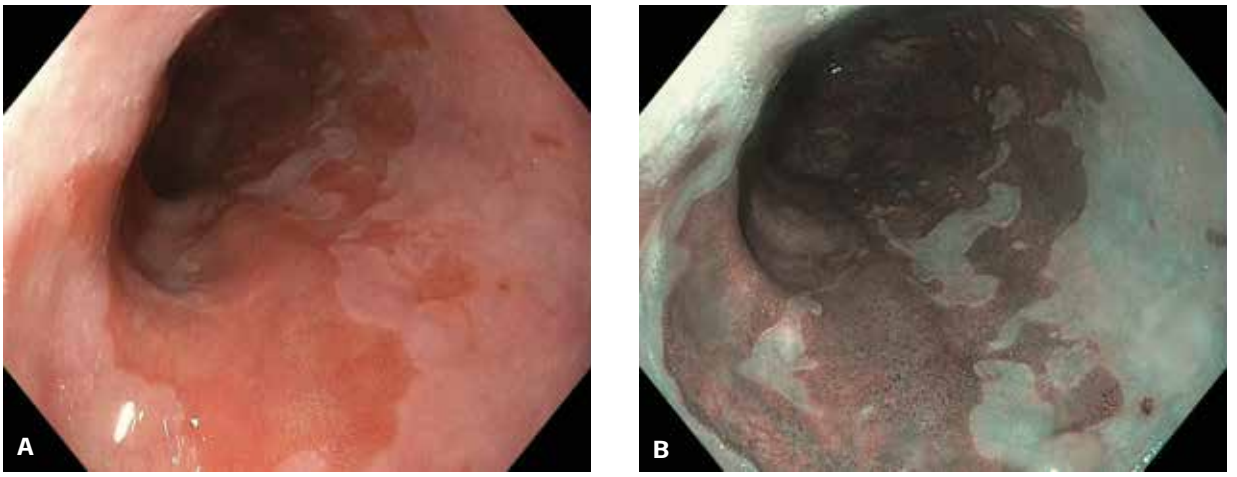

Figure 1. Endoscopic images of a patient with multifocal low-grade dysplasia using high-definition white-light endoscopy (**A**) and narrow-band imaging (**B**).

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).[2] 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.[3] 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 non-dysplastic 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

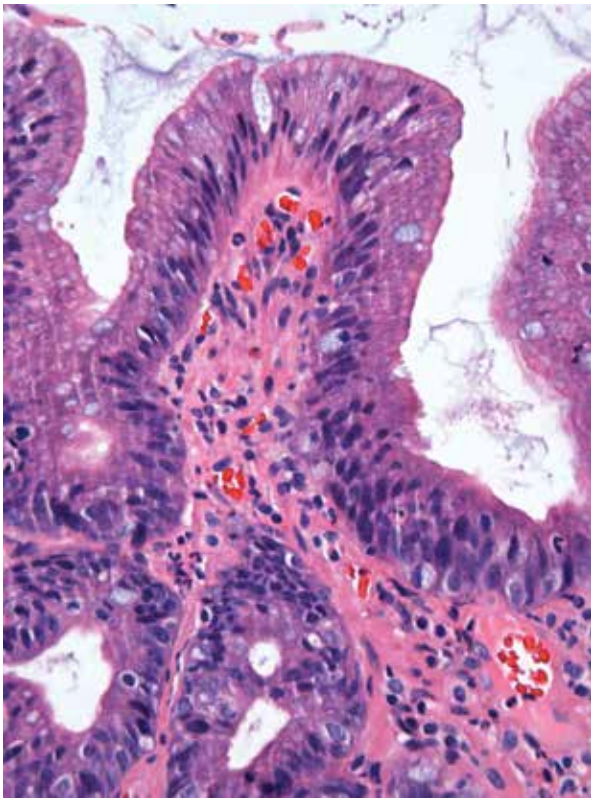

Figure 2. A biopsy specimen revealing low-grade dysplasia (hematoxylin and eosin stain, magnification 40×). Features include irregularity of nuclei such as their placement, elongation, and hyperchromasia, all of which continue to be present in the surface epithelial cells.

Image courtesy of Emma Furth, MD.

Table. Guideline Recommendations for the Management of Low-Grade Dysplasia

American Gastroenterological Association 2011[10]	American Society for Gastrointestinal Endoscopy 2012[11]	British Society of Gastroenterology 2014[12]	American College of Gastroenterology 2016[13]
Confirmation needed by 1 additional pathologist with expertise in esophageal pathology	Confirmation needed by expert gastrointestinal pathologist	Confirmation needed by 2 independent pathologists	Confirmation needed by 1 additional pathologist with expertise in Barrett esophagus
Perform surveillance every 6-12 months.	Repeat EGD within 6 months to confirm the diagnosis.	Perform EGD every 6 months until 2 in a row have negative findings.	Repeat EGD after optimizing proton pump inhibitor therapy.
Radiofrequency ablation is an option if low-grade dysplasia is confirmed.	Consider ablation in select patients or perform annual surveillance.	Radiofrequency ablation may be used in patients with low-grade dysplasia.	For confirmed low-grade dysplasia without life-limiting comorbidity, the preferred treatment modality is endoscopic therapy. However, an acceptable alternative is endoscopic surveillance every 12 months.

EGD, esophagogastroduodenoscopy.

the 22 sham-treated subjects, while no patients developed adenocarcinoma.[4] In the recently completed SURF (A Randomized Trial Comparing Surveillance With Radiofrequency Ablation of Barrett Esophagus With Low-Grade Dysplasia) study, which compared radiofrequency ablation to continued surveillance, the risk of progression to high-grade dysplasia or adenocarcinoma was 11.8% at 1 year in the surveillance group.[5] Similar results were found in a multicenter observational study that compared endoscopic therapy to surveillance: the annual risk of progression to high-grade dysplasia or adenocarcinoma was 6.6% in the surveillance arm.[6]

In a series of landmark observational studies from Amsterdam, the risk of progression of low-grade dysplasia was very much related to the expertise of the pathologist. Initial work from Curvers and colleagues found that in 147 patients with a diagnosis of low-grade dysplasia made by community pathologists, the diagnosis was downgraded in 85% to no dysplasia or indefinite for dysplasia after expert pathology review.[7] Furthermore, the risk of progression to high-grade dysplasia or adenocarcinoma was 13.4% per year in patients with a diagnosis that was confirmed compared to 0.49% per year in patients with a diagnosis that was downstaged to no dysplasia. Subsequently, Duits and colleagues found that of 293 patients referred to central pathology review with a diagnosis of low-grade dysplasia, 73% were downstaged to no dysplasia or indefinite for dysplasia, and the diagnosis of low-grade dysplasia was confirmed in only 27%.[8] The risk for developing high-grade dysplasia and/or esophageal adenocarcinoma was 9.1% per year in the confirmed low-grade dysplasia group and only 0.6% per year in patients downstaged to no dysplasia.

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.[9] 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).[10-13] 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.[13] 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.[12] 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 radiofrequency ablation or sham ablation and followed for 1 year.[4] 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.[5] 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.[6] 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.[5] Similarly, in the AIM-Dysplasia study, 22% of patients experienced spontaneous resolution of dysplasia during follow-up endoscopy.[4] 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%.[5] 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.[14] 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.[14]

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

1. Goldblum JR. Controversies in the diagnosis of Barrett esophagus and Barrett-related dysplasia: one pathologist's perspective. *Arch Pathol Lab Med.* 2010;134(10):1479-1484.
2. Hvid-Jensen F, Pedersen L, Drewes AM, Sørensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med.* 2011;365(15):1375-1383.
3. Singh S, Manickam P, Amin AV, et al. Incidence of esophageal adenocarcinoma in Barrett's esophagus with low-grade dysplasia: a systematic review and meta-analysis. *Gastrointest Endosc*. 2014;79(6):897-909.e4.
4. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med*. 2009;360(22):2277-2288.
5. Phoa KN, van Vilsteren FG, Weusten BL, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. *JAMA*. 2014;311(12):1209-1217.
6. Small AJ, Araujo JL, Leggett CL, et al. Radiofrequency ablation is associated with decreased neoplastic progression in patients with Barrett's esophagus and confirmed low-grade dysplasia. *Gastroenterology.* 2015;149(3):567-576.e3.
7. Curvers WL, ten Kate FJ, Krishnadath KK, et al. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. *Am J Gastroenterol.* 2010;105(7):1523-1530.
8. Duits LC, Phoa KN, Curvers WL, et al. Barrett's oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel. *Gut*. 2015;64(5):700-706.
9. Wani S, Falk GW, Post J, et al. Risk factors for progression of low-grade dysplasia in patients with Barrett's esophagus. *Gastroenterology.* 2011;141(4):1179-1186, 1186.e1.
10. Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ; American Gastroenterological Association. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology.* 2011;140(3):1084-1091.
11. Evans JA, Early DS, Fukami N, et al; ASGE Standards of Practice Committee; Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. *Gastrointest Endosc.* 2012;76(6):1087-1094.
12. Fitzgerald RC, di Pietro M, Ragunath K, et al; British Society of Gastroenterology. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut.* 2014;63(1):7-42.
13. Shaheen NJ, Falk GW, Iyer PG, Gerson LB; American College of Gastroenterology. ACG Clinical Guideline: diagnosis and management of Barrett's esophagus. *Am J Gastroenterol.* 2016;111(1):30-50.
14. Kastelein F, Biermann K, Steyerberg EW, et al; ProBar-study group. Aberrant p53 protein expression is associated with an increased risk of neoplastic progression in patients with Barrett's oesophagus. *Gut*. 2013;62(12):1676-1683.