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Low-Grade Dysplasia in Patients with Barrett's Esophagus — Ablate?

Note: *For debate purposes, the pro and con positions for patient management will be taken by the invited authors. However, actual decisions on patient care must involve discussion of the risks and benefits of each treatment considered.*

Case Presentation

A 73-year-old, obese white male with a history of hypertension and obstructive sleep apnea noted new onset nocturnal heartburn for six weeks. He was prescribed Ranitidine 150 mg orally at night by his primary care doctor, which initially controlled his symptoms. Three months later he noted substernal "burning" after eating spicy or high fat foods and returned to his primary care physician. Consequently, he was advised to take Omeprazole 20 mg orally once daily and continue his H2 blocker at night. Despite these medication changes, his postprandial chest discomfort continued. His physician ordered an exercise stress test, which was negative. Subsequent referral to a gastroenterologist was made and an upper endoscopy was performed. This demonstrated a 3 cm hiatal hernia, erosive esophagitis and suspected short segment Barrett's esophagus.

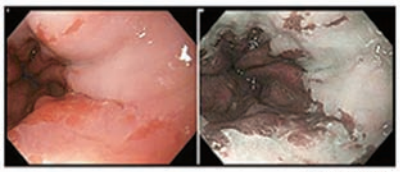
FIGURE 1.

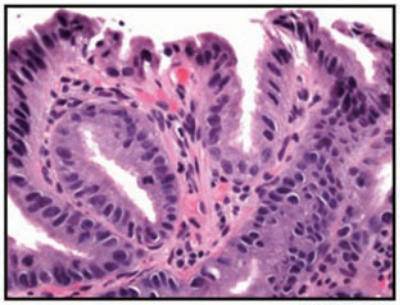
FIGURE 2.

He was treated with Omeprazole 20 mg orally twice daily (before meals) for eight weeks. The patient returned for repeat EGD, which disclosed complete healing of the esophagitis and a 3 cm segment of C0M3 (Prague Classification) Barrett's esophagus without visible nodules or ulcers. (Figure 1). Random 4 quadrant biopsies (every 1 cm from the columnar lined esophagus) found intestinal metaplasia with low-grade dysplasia (LGD) at 35 cm and 36 cm from the incisors (Figure 2). Remaining biopsies disclosed intestinal metaplasia without dysplasia. Pathology slides demonstrating LGD were confirmed by expert external review. At a follow-up office visit, the patient is informed about the diagnosis of LGD.

What would you advise him to do?

PRO

David E. Fleischer, MD
Mayo Clinic — Arizona

Pro: Low-Grade Dysplasia Should be Treated Endoscopically with Radiofrequency Ablation

There seems to be little question that this 73-year-old male with co-morbid conditions should be treated with radiofrequency ablation (RFA) for his low-grade dysplasia (LGD). My decision is based upon what is known and what is unknown about LGD regarding: (1) natural history; (2) surveillance versus endoscopic treatment as a management strategy; (3) efficacy; (4) safety; and (5) clinical experience.

There are several reasons that endoscopic treatment is indicated rather than surveillance. The patient has a premalignant lesion, and in some reports, 15 to 25% of patients with LGD progress to high-grade dysplasia (HGD)/carcinoma (Ca).[1, 2] Unfortunately, we do not have molecular/biologic markers to predict risk of histologic disease progression.

Surveillance Alone is Not a Perfect Strategy

Dr. Chak will argue that surveillance for LGD is a better strategy and if a patient prefers this option then I always respect that decision. However, I would remind the patient that surveillance alone is not a perfect strategy. Surveillance as a primary strategy has not been shown to be cost effective and there have been no randomized trials comparing it to the natural history of Barrett's esophagus. Falk and colleagues have noted "At least half the patients who develop HGD and/or Ca had two consecutive previous endoscopies that did not even show dysplasia," let alone LGD. [3] The "con" stance will also argue that he *might* be more inclined to consider endoscopic therapy if it would at least reduce or eliminate the need for subsequent endoscopic surveillance after treatment. Surveillance after endoscopic treatment for Barrett's dysplasia is performed currently; however, this is done to prove that endoscopic therapy is efficacious, safe and durable. Once safety and durability have been established, surveillance will not be part of post-RFA management. It should also be noted that patients who have had adenomatous polyps of the colon removed are similarly followed. Along with the majority of U.S. gastroenterologists, I suspect that Dr. Chak would remove diminutive polyps during colonoscopy — even though the likelihood that most will advance to cancer is far less than the chance that a patient with Barrett's esophagus with LGD will develop esophageal cancer. This point is reiterated by Drs. El-Serag and Graham in a recent editorial. [4]

Treatment with RFA for LGD is Effective and Durable

A landmark paper randomized patients with dysplastic Barrett's esophagus to treatment with RFA versus control and analyzed data from both the intention-to-treat and the per-protocol perspective. [5] The eradication of both dysplasia and Barrett's was significantly better in the treatment group. Successful treatment of these groups was durable with 98% of patients receiving RFA for LGD being free of both intestinal metaplasia and LGD at 2 to 3 years. [6] This led to the American Gastroenterologic Association (AGA) concluding in its most recent medical position statement on the management of Barrett's esophagus that "Endoscopic eradication with RFA should be a therapeutic option for treatment of patients with confirmed LGD in Barrett's." [7] Other studies assessing RFA for LGD have demonstrated similar results.

RFA for LGD is Safe

To date, more than 30,000 patients and 70,000 procedures have been performed in the United States. The major complication of this technique is *stricturing*, which occurs in approximately 6% of patients. Initial concerns about subsquamous buried glands has not proven to be a problem.[5] Since endoscopic ablation was shown to be more cost effective than surveillance in patients with non-dysplastic Barrett's esophagus in a study (using a Markhov model), it is expected that it would be even more cost effective in patients with LGD.[8]

Conclusion of "Pro" Position

In addition to published literature, I call upon my observations as a clinical gastroenterologist who has seen patients with

Barrett's esophagus for more than 30 years. Most patients would rather be free of Barrett's esophagus than have it remain. Patients read about available endoscopic therapy for Barrett's esophagus and seek out physicians who provide endoscopic therapy for LGD. In that way, 'they vote with their feet.' Therefore, I would opine that treatment with RFA in this patient is appropriate. BE with LGD is a pre-malignant condition. RFA is an established treatment that is effective, safe, and durable; it is also endorsed as a therapeutic option in patients like this one by a major GI Society. Now, Dr. Chak is a good man and a knowledgeable "Barrett-ologist," but his views on the management of the patient in this case are simply outdated. I would refer him to one of the great poets of our time, Robert Zimmerman (a.k.a Bob Dylan), who said "Please get out of the way if you can't lend a hand...for the times, they are a-changin'."

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Con: Low-Grade Dysplasia Should Not be Treated Endoscopically with Radiofrequency Ablation

Simple answer: Reassurance, reassurance, reassurance. As a physician your responsibility is to allay a patient's fears. Explain to the patient that low-grade dysplasia (LGD) in Barrett's esophagus is completely benign, it often disappears on follow-up EGD, and you will see him back in six months to determine if he truly has LGD. Physician, *"Primum Non Nocere* — First Do No Harm."

The "con" arguments *against* ablation in this elderly patient with comorbid conditions and newly diagnosed LGD are quite straightforward:

1. LGD itself is not a well-defined diagnosis
2. LGD often regresses without intervention
3. The risk of progression from LGD to cancer is significantly low
4. Ablative therapy is not completely harmless

Always Doubt the Diagnosis of LGD

The histological features of LGD are nuclear hyperchromasia; nuclear stratification generally confined to the lower half of the epithelium; increased mitotic figures; depleted mucin; and decreased goblet cells, generally in the setting of preserved glandular architecture. These features are non-specific and are also seen with inflammation. Even expert gastrointestinal pathologists with specific interest in Barrett's esophagus have major disagreements interpreting LGD.[1] Ablative therapy for a diagnosis that may represent misinterpreted inflammation in this patient would be wrong. Physician, "*Primum Non Nocere* — "First Do No Harm."

LGD Can Regress Without Intervention

Studies on the natural history of LGD are limited because the condition is rare. To date, the best data from a multicenter prospective study show that 66% of LGD regresses without any intervention and another 21% does not progress beyond LGD on long-term follow-up.[2] So why perform intervention on a benign condition that may disappear without intervention? My recommendation is to wait to see if he develops high-grade dysplasia and *then* intervene. Physician, *"Primum Non Nocere* — First Do No Harm."

Risk of Cancer is Low

The word "dysplasia" in Barrett's esophagus appears to strike inordinate fear. We live in an age where fear is used routinely to motivate behavior. The reality is that the risk of progression from LGD to cancer is quite low. Again, the best estimate comes from the same multi-center prospective database, which shows that the rate of progression of LGD to cancer is approximately 0.6% a year, not much higher than the 0.4% to 0.5% per patient year risk of progression for non-dysplastic BE.[2] Given the low lifetime risk of developing cancer in this elderly man with comorbid conditions, ablative therapy is unnecessary at this point. Reassure the patient, continue surveillance, and intervene only if and when he develops high-grade dysplasia. Physician, *"Primum Non Nocere* — First Do No Harm."

Ablative Therapy is Not Completely Benign

Forget that ablative therapy requires repeated sessions, on average 3.5 treatment sessions and (at times) up to eight sessions for complete ablation. Forget that therapy is costly, up to $15,000 for ablation. Forget that ablative therapy does not eliminate the necessity for continued surveillance. Forget that patients under surveillance may develop hidden sub-squamous cancers after ablative therapy. Forget that 6% of patients develop strictures with ablative therapy that require dilation. Forget that we do not yet know the long-term safety of ablative therapy. The major reason to avoid ablative therapy in this patient with LGD is the serious potential for morbidity. The multicenter trial of published in the *New England Journal of Medicine* reported three serious adverse events in 84 BE patients with low- or high-grade dysplasia randomized to ablative therapy.[3] Even one case of serious gastrointestinal hemorrhage is "one case too many" for a benign condition with a low risk of progression to cancer. Physician, *"Primum Non Nocere* — First Do No Harm."

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MODERATOR

Gary W. Falk, MD, MS, FASGE
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After reviewing the pro and con expert arguments, moderator and Barrett's esophagus expert Gary W. Falk, MD, MS, FASGE poses the following questions:

1. Is there an ideal candidate for RFA with LGD?
2. Which patients with LGD are clearly not candidates for RFA? That is, assuming it may be appropriate in some but not all individuals, how would you decide who should be treated? (For example, we do not colonoscope or endoscope every patient.)
3. Two recent studies warrant comment and can perhaps put this in scientific perspective — I would like Drs. Fleischer and Chak to comment on the following studies:
    a. Risk Factors for Progression of Low-Grade Dysplasia in Patients with Barrett's Esophagus. Wani S, Falk GW, Post J, et al. *Gastroenterology*. 2011 June 29 [e-publication ahead of print].
    b. Low-Grade Dysplasia in Barrett's Esophagus: Overdiagnosed and Underestimated. Curvers WL, ten Kate FJ, Krishnadath KK, et al. *Am J Gastroenterol*. 2010 Jul;105:1523-30.
4. Considering these studies, are there any clear risk factors for progression of LGD that would help here?

PRO

David E. Fleischer, MD
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Dr. Fleischer responds:

I will start by commenting on the two relevant papers to which Dr. Falk alluded. They are both important because they report upon the progression of LGD to HGD or EAC (early adenocarcinoma). In the study by Wani et al., 27 out of 210 patients progressed to either HGD or EAC in a 6.2 year follow-up. In the Curvers et al. study, 85% of patients progressed to high-grade dysplasia or carcinoma in 109 months. Although the incidence of progression is different in the two studies, perhaps an even more important aspect of the studies is that they indicate the difficulty in making the LGD diagnosis shared by both community and expert pathologists. This disagreement, even among expert pathologists, makes it challenging for clinicians to make treatment decisions based on pathology and to determine the likelihood of disease progression. Although the pathologic diagnosis of LGD is not straightforward, once the diagnosis is confirmed, it appears that progression to HGD/EAC is common.

The Road to Understanding

Clinicians and pathologists are beginning to understand the necessity of precise biology. To underscore that dilemma is the widespread concern that even non-dysplastic Barrett's (ND-BE) is neoplastic. Authorities point out that ND-BE meets the definition of a neoplasm because it consists of hyperproliferative epithelium that shows independence from growth signal regulation, disruption of architecture, widespread clonal abnormalities, increased inability to avoid program cell death (apoptosis), and lack of spontaneous regression without intervention.

In the future, it is likely that molecular/biologic markers will replace histology for diagnosing dysplastic Barrett's esophagus. However, we are currently not at that point. To correctly treat this (or any) patient with low-grade dysplasia, one must affirm the following:

- That the diagnosis of LGD is correct
- The likelihood of LGD progressing to HGD/EAC
- That the endoscopic treatment for eliminating LGD is effective and durable
- The safety profile and complications of that treatment

Back to Dr. Falk's questions; I will assume that the diagnosis of LGD is correct and I will base my answer on both the Wani and Curvers study:

Question 1: Since patients with LGD have as high as an 85% chance of progressing to HGD/EAC, all patients with LGD would be candidates for RFA.

Question 2: Patients would not be candidates if they have problematic comorbidities and/or are not interested in endoscopic therapy.

Questions 3-4: Since I would suggest treatment for all appropriate LGD patients, the issue of risk factors for progression is less relevant to me clinically, but as I review the literature there is no firm data that define risk factors for progression to LGD. My own view that RFA is appropriate treatment for Barrett's esophagus patients with LGD is emboldened by the fact that four major GI/surgical societies (ASGE, AGA, ACG, and SAGES) have endorsed the position that "RFA should be an option for treatment of Barrett's containing LGD."

However, in conclusion, I emphasize that the Curvers et al. results are more consistent with my own experience as a practitioner throughout the past 30 years.

Amitabh Chak, MD, FASGE
University Hospitals Case Center

Dr. Chak responds:

Interpretation is an "Art"

The questions raised by Dr. Falk are at the very heart of this debate. The diagnosis of LGD is only meaningful diagnosis if it reliably identifies individuals who are at significantly increased risk for progression to cancer. Pathologic interpretation of LGD is clearly an "art," not a science. Your expert GI pathologist will likely not agree with my expert GI pathologist.[1] Studies that have attempted to identify additional risk factors for predicting progression in LGD have either failed,[2] been unsatisfactory for clinical application,[3, 4] or have been based on pathologists' reinterpreting the diagnosis of LGD[5]. Clearly,

the development of objective biomarkers that are more reliable than p53[3, 4] is the "holy grail." It has been suggested that when two expert pathologists agree on the diagnosis of LGD, then the risk of progression is much higher.[5] This risk factor, however, is clearly based on the subjectivity of individual pathologists at a specific institution and cannot be universally applied to all pathologists — expert or not.

So, returning to the question of whether there are patients with LGD who should be ablated, my answer is that the decision must be *individualized*. In my view, a young patient with a long segment of BE with multiple foci of LGD is more worrisome to me than a patient with a short segment of BE who has LGD noted in one small focus. A patient who has multiple biopsies showing LGD on his incident endoscopy is more worrisome than a patient who develops LGD after many years of surveillance. I would consider ablating LGD in what I consider high-risk patients, especially if the patient was interested in ablative therapy. Do I have an evidence base to support this view? Certainly not, but much of medicine has to be practiced without solid evidence. Depend on advice from your friendly neighborhood gastrointestinal pathologist. Not all LGD is the same. And always remember, *"Primum Non Nocere* – First Do No Harm."

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Dr. Falk concludes:

At the End of the Day . . . Summary Points

As referenced in the discussion above, one can take one of two competing approaches to low-grade dysplasia and easily justify either approach with logical arguments. This is typically the case when the data to guide clinical decision making are insufficient or conflicting. This calls to mind the debate that took place for many years in the approach to high-grade dysplasia, surgery versus continued surveillance — a debate that no longer seems to exist with the advent of well-done clinical trials and observational studies examining the role of ablative therapies and the high risk of progression to cancer in patients with high-grade dysplasia.

Low-grade dysplasia, however, represents a different situation because it is a more nuanced situation than high-grade dysplasia. The natural history of low-grade dysplasia is still poorly understood. First, the diagnosis is often transient. In part, this may be due to the high degree of interobserver variability in establishing this diagnosis and the variable biopsy protocols by which these patients are followed, resulting in issues related to tissue sampling. While the majority of patients with low-grade dysplasia do not progress to adenocarcinoma or high-grade dysplasia, a subset of these patients do progress to a higher-grade lesion. The recent studies cited above come to very different conclusions regarding risk of progression. A systematic review prior to these studies suggested an intermediate risk of progression to cancer with a weighted average incidence rate of 1.69% per year.[1] Factors thought to be associated with progression to cancer include

consensus agreement among two or more pathologists, as well as extent of low-grade dysplasia.[2]

The recent study by Wani et al. referenced above suggests that the risk for progression to the combined endpoints of high-grade dysplasia and adenocarcinoma is 1.83% per year with no possible predictors of progression. On the other hand, the progression rate to cancer for confirmed low-grade dysplasia in the study by Curvers et al. was 13.4% per year. However, it is absolutely necessary to emphasize that the Curvers et al. study also found that 85% of patients diagnosed with low-grade dysplasia in the community were downgraded to no dysplasia when slides were reviewed by expert pathologists.

Finally, in the randomized controlled trial of RFA from the *New England Journal of Medicine*, it is important to recognize that all 64 patients with low-grade dysplasia had their diagnosis confirmed by a central pathology reading at the Cleveland Clinic prior to participation in the study.[3] By intention-to-treat analysis, complete eradication of low-grade dysplasia was accomplished in 90%, complete elimination of intestinal metaplasia was accomplished in 81%, and progression to high-grade dysplasia occurred in 5% at 12 months. The results of RFA are most impressive, but the caveats of pathologic confirmation and progression in a subset of patients should still be kept in mind.

So, at the end of the day, what should you do?

First, expert review of slides is mandatory. Once confirmed, a repeat endoscopy with 4 quadrant biopsies at 1 to 2 cm intervals should be carried out to both confirm the diagnosis and exclude a higher-level lesion. If low-grade dysplasia is multifocal and confirmed by expert gastrointestinal pathologists, it is entirely reasonable to consider RFA. However, it is still premature to use RFA in patients with low-grade dysplasia when biopsy specimens are not reviewed by expert pathologists since many of these specimens will be downgraded to non-dysplastic Barrett's esophagus. Patients need to understand that progression to a higher-level lesion may still occur and cancer risk is not eliminated completely by RFA. Furthermore, it is important to emphasize that the majority of patients with low-grade dysplasia never progress on to a higher-level lesion.

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