This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author’s clinical recommendations.

**Barrett’s Esophagus**

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A 55-year-old obese white man has had frequent heartburn for more than 10 years. He has treated himself with a histamine $H_2$-receptor antagonist, which provides only partial relief. He decided to consult a physician after reading a magazine article warning that heartburn causes cancer of the esophagus. The patient has no other medical problems, dysphagia, or recent, unexplained weight loss, and the findings on physical examination are unremarkable. An endoscopy reveals columnar epithelium lining the distal 5 cm of the esophagus. Esophageal-biopsy specimens show specialized intestinal metaplasia with inflammation and “possible dysplasia.” How should this patient’s condition be managed?

**The Clinical Problem**

Barrett’s esophagus is the condition in which columnar epithelium replaces the squamous epithelium that normally lines the distal esophagus (Fig. 1). The condition develops when gastroesophageal reflux disease damages the squamous esophageal mucosa and the injury heals through a metaplastic process in which columnar cells replace squamous ones. The abnormal columnar epithelium that characterizes Barrett’s esophagus is an incomplete form of intestinal metaplasia (called specialized intestinal metaplasia) that predisposes patients to adenocarcinoma. Esophageal adenocarcinoma develops in approximately 0.5 percent of patients with Barrett’s esophagus per year. This is a tumor found predominantly in white men, among whom the frequency of esophageal adenocarcinoma has inexplicably quadrupled over the past few decades. Although gastroesophageal reflux disease is the main recognized risk factor for this cancer, presumably because it causes Barrett’s esophagus, it is not clear whether the rising incidence of the tumor is due to an increasing frequency of gastroesophageal reflux disease in the general population.

The diagnosis of Barrett’s esophagus is based on the endoscopic findings of columnar epithelium lining the distal esophagus and confirmed by the presence of specialized intestinal metaplasia in esophageal-biopsy specimens. To document the finding of columnar epithelium in the distal esophagus, the endoscopist must identify both the squamocolumnar and gastroesophageal junctions (Fig. 2). The juxtaposition of pale squamous epithelium and reddish columnar epithelium forms a visible line called the $Z$ line or the squamocolumnar junction. The gastroesophageal junction, the point at which the esophagus ends and the stomach begins, is the most proximal part of the gastric folds. Often, the $Z$ line and the gastroesophageal junction coincide (Fig. 2A). When the $Z$ line is located above the gastroesophageal junction (Fig. 2B), there is a columnar lined segment of esophagus.

For decades, Barrett’s esophagus was identified predominantly in patients with severe gastroesophageal reflux disease on the basis of the finding of long seg-

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ments of columnar epithelium extending more than 3 cm above the gastroesophageal junction. In 1994, specialized intestinal metaplasia was reported in biopsy specimens from short segments of esophageal columnar epithelium, even in patients with no evidence of gastroesophageal reflux disease.\textsuperscript{5} Since then, Barrett’s esophagus has been categorized according to the extent of the metaplastic lining.\textsuperscript{6} Patients who have segments of specialized intestinal metaplasia in the esophagus measuring 3 cm or more have traditional, or long-segment, Barrett’s esophagus, whereas those with shorter segments have short-segment disease. It is not clear whether these two types have the same pathogenesis and natural history, or whether short-segment disease progresses to long-segment disease. Although logic and indirect evidence suggest that the risk of cancer should vary with the extent of esophageal metaplasia, this contention has not been proved.\textsuperscript{7} Currently, short-segment and long-segment Barrett’s esophagus are managed similarly.

Figure 2. The Use of Endoscopic Landmarks to Distinguish Normal Esophagus (Panel A) from Barrett’s Esophagus (Panel B). The squamocolumnar junction, or Z line, is the visible line formed by the juxtaposition of squamous and columnar epithelia. The gastroesophageal junction is the imaginary line at which the esophagus ends and the stomach begins. The gastroesophageal junction is identified endoscopically as the most proximal part of the gastric folds. In normal esophagus, the squamocolumnar junction and gastroesophageal junction often coincide, and there is no columnar epithelium between the two (Panel A). The inset in Panel A shows normal stratified squamous epithelium. In Barrett’s esophagus, the squamocolumnar junction is proximal to the gastroesophageal junction (Panel B). The area between the two junctions consists of columnar epithelium with specialized intestinal metaplasia (inset in Panel B). Modified from Spechler\textsuperscript{4} with the permission of the publisher. (Inset in Panel A, hematoxylin and eosin, ×80; inset in Panel B, hematoxylin and eosin, ×100.) Photomicrographs provided by Dr. Edward Lee.

STRATEGIES AND EVIDENCE

Screening and Surveillance for Barrett’s Esophagus

A proposed strategy to decrease the risk of death from esophageal cancer is to use endoscopy to screen patients with chronic gastroesophageal reflux disease for Barrett’s esophagus.\textsuperscript{8} Endoscopy shows that 3 to 5 percent of such patients have long-segment disease\textsuperscript{9} and 10 to 15 percent have short-segment disease.\textsuperscript{10} It has been suggested that screening should focus on patients with gastroesophageal reflux disease who have risk factors for Barrett’s esophagus, such as male sex, white race, an age of more than 50 years, and a long history of symptoms (more than five years).\textsuperscript{9} However, such an approach will have a limited impact on the rates of death from cancer, because up to 40 percent of patients with esophageal adenocarcinoma have no history of gastroesophageal reflux disease.\textsuperscript{3} There is little evidence that present screening practices have prevented deaths from esophageal adenocarcinoma.
A recent systematic review of studies of esophageal resections for adenocarcinoma found that less than 5 percent of patients were known to have had Barrett’s esophagus before they sought medical attention for symptoms of cancer.11

Patients with Barrett’s esophagus should undergo regular endoscopic surveillance for curable neoplasia to decrease the risk of death from esophageal cancer.9 Available studies suggest that Barrett’s esophagus does not affect longevity. Proponents of surveillance argue that those studies included predominantly older patients, many of whom died of unrelated diseases; thus, the results may not be applicable to younger patients with Barrett’s esophagus.12

Small, retrospective studies have shown that endoscopic surveillance can detect curable neoplasms in patients with Barrett’s esophagus and that the cancers identified are less advanced than those identified in patients with symptoms of cancer, such as dysphagia and unexplained weight loss.13,14 These results do not prove that surveillance is beneficial, however. Early esophageal cancers can remain asymptomatic for years,15 and invasive therapies such as esophagectomy are associated with substantial rates of morbidity and mortality. In one series of 143 patients with Barrett’s esophagus who were followed for a mean of 4.4 years, for example, surveillance identified only 1 patient with asymptomatic esophageal cancer, and this patient died as a result of the ensuing esophageal surgery.16

A report from the United Kingdom estimated that the cost of detecting one case of esophageal cancer with the use of endoscopic surveillance was approximately $23,000 among male patients with Barrett’s esophagus and $65,000 among female patients.17 A U.S. study estimated that the cost was approximately $38,000, which was lower than the cost of surveillance mammography ($55,000 for each breast cancer detected).18 Both studies, however, used a considerably higher incidence of cancer to calculate surveillance costs than the current estimate of 0.5 percent per year.

A statistical-probability model has also been used to evaluate surveillance strategies in a simulated cohort of 10,000 middle-aged patients with Barrett’s esophagus.19 Assuming an annual incidence rate of esophageal cancer of 0.4 percent, this analysis suggested that endoscopic surveillance every five years was the preferred strategy, costing $98,000 per quality-adjusted year of life gained. Using a different decision model, another group estimated the incremental cost effectiveness of endoscopic surveillance performed every other year at approximately $17,000 per year of life saved.20 With another model, the estimated cost of one-time endoscopic screening for 60-year-old patients with gastroesophageal reflux disease was approximately $25,000 per year of life gained.21 However, it is important to appreciate the limitations of these computer models, which incorporate multiple layers of soft data and questionable assumptions.

Treatment of Gastroesophageal Reflux Disease in Barrett’s Esophagus

The goals of antireflux therapy are to eliminate the symptoms and signs of gastroesophageal reflux disease and to prevent its complications. Usually this approach involves suppressing the secretion of gastric acid through the administration of H₂-receptor antagonists or proton-pump inhibitors.22 Antireflux surgery attempts to create a barrier to gastroesophageal reflux through fundoplication.23 Medical and surgical therapies are highly effective for improving or eliminating the symptoms and signs of gastroesophageal reflux disease, but no antireflux therapy has been proved to decrease the risk of esophageal adenocarcinoma.

The efficacy of antisecretory therapy for gastroesophageal reflux disease is directly related to the degree of acid suppression achieved and inversely related to the severity of the underlying reflux esophagitis.24 Long-segment Barrett’s esophagus is often associated with severe esophagitis, and proton-pump inhibitors are frequently prescribed as first-line treatment.25 Patients with short-segment disease often have only mild esophagitis,4 and in these patients, H₂-receptor antagonists might be sufficient. For patients with Barrett’s esophagus whose symptoms resolve with conventional antisecretory therapy, monitoring of esophageal pH frequently reveals continued acid reflux.26 In fact, 80 percent of patients who are treated with a proton-pump inhibitor twice daily have nocturnal episodes of gastric acid breakthrough, during which stomach pH falls below 4 for more than one hour.27 In some patients, almost complete achlorhydria can be achieved through treatment with high doses of proton-pump inhibitors or the addition, at bedtime, of an H₂-receptor antagonist to a twice-daily regimen of proton-pump inhibitors.28 However, the advisability of such aggressive antireflux therapy for all patients with Barrett’s esophagus remains highly controversial. Advocates of an aggressive approach contend that acid reflux is the main factor contributing to carcinogenesis and that its elimination should prevent cancer.

Some studies have provided support for these hypotheses. Esophageal-biopsy specimens of specialized intestinal metaplasia maintained in organ culture exhibit hyperproliferation when exposed briefly to acid.29,30 Brief exposure to esophageal acid has also been shown to activate the mitogen-activated protein kinase pathways that can increase proliferation and decrease apoptosis in Barrett’s esophagus.31 The expression of proliferating-cell nuclear antigen (a marker of proliferation) was reduced in esophageal-biopsy specimens from patients in whom esophageal acid had been normalized by treatment with a proton-pump inhibitor,
whereas the expression of the antigen was unchanged in specimens from patients who had persistently abnormal acid reflux despite therapy with proton-pump inhibitors. Another study found no significant change in the proliferative activity of Barrett’s esophagus in patients treated with a proton-pump inhibitor for two years, whereas the activity increased significantly in patients who received an H2-receptor antagonist, a less potent suppressor of acid secretion. Finally, therapy with proton-pump inhibitors has been shown to cause partial regression of specialized intestinal metaplasia. These studies all suggest that aggressive acid control may be beneficial. However, the short-term effects of acid on tissues in organ culture may not parallel the long-term effects of acid reflux on Barrett’s esophagus, and the effects of these agents on markers of proliferation may not translate into a decrease in the risk of cancer. Furthermore, areas of apparent regression may have underlying intestinal metaplasia and worrisome proliferative abnormalities.

Some have proposed that fundoplication may be more effective than antisecretory therapy for preventing death from cancer in patients with Barrett’s esophagus. Two recent studies provide little support for that contention, however. In one, a randomized trial of medical and surgical therapies in 247 patients with complicated gastroesophageal reflux disease, esophageal adenocarcinoma developed in 4 of the 165 patients in the medical group (2.4 percent) and 1 of the 82 in the surgical group (1.2 percent) during 10 to 13 years of follow-up; this difference was not statistically significant. Furthermore, the surgical group had an unexplained but significant decrease in survival as a result of a higher than expected number of deaths from heart disease. In the second trial, a large Swedish, population-based cohort study in which patients with gastroesophageal reflux disease were followed for up to 32 years, the relative risk of esophageal adenocarcinoma (as compared with that in the general population) among 35,274 men who received medical antireflux therapy was 6.3 (95 percent confidence interval, 4.5 to 8.7), whereas the relative risk among 6406 men treated with fundoplication was 14.1 (95 percent confidence interval, 8.0 to 22.8).

Dysplasia in Barrett’s Esophagus

Dysplasia is a histologic diagnosis suggesting that one or more clones of epithelial cells have acquired genetic alterations rendering them neoplastic and prone to malignancy. Endoscopic surveillance is performed primarily to identify dysplasia, but it is an imperfect predictor of malignancy. The histologic abnormalities of low-grade dysplasia are not specific for neoplasia because similar changes can occur in normal tissue in response to injury. Among experienced pathologists, the extent of interobserver agreement for the diagnosis of low-grade dysplasia in Barrett’s esophagus may be less than 50 percent. In the case of high-grade dysplasia, in contrast, the extent of interobserver agreement is approximately 85 percent. Since dysplasia has no distinctive gross features, endoscopists collect random samples of esophageal tissue for biopsy; thus, sampling error is a major problem. By the time biopsy specimens show high-grade dysplasia in patients with Barrett’s esophagus, approximately one third of patients already have an invasive cancer. Extensive sampling can reduce this problem but cannot eliminate it.

Researchers have assessed the value of other markers of the risk of cancer (e.g., the expression of p53 and flow-cytometric results) and endoscopic techniques for recognizing early neoplasia in patients with Barrett’s esophagus (e.g., staining the mucosa with vital dyes and endoscopic ultrasonography). Currently, there are insufficient data to justify the routine use of any of these approaches in clinical practice. Despite its shortcomings, endoscopy with random sampling for dysplasia remains the clinical standard for managing Barrett’s esophagus.

Natural History of High-Grade Dysplasia

The natural history of dysplasia in Barrett’s esophagus is not well defined. In a recent study of 76 patients with high-grade dysplasia who had no evidence of cancer on an extensive initial evaluation, the five-year cumulative incidence of esophageal cancer was 59 percent. In another study of 100 such patients, esophageal adenocarcinoma was found in 32 percent during eight years of follow-up. A lower rate of esophageal cancer — 16 percent, over a period of 7.5 years — was reported in one study, but this study lacked external confirmation of the diagnosis of high-grade dysplasia.

Some experts have recommended intensive endoscopic surveillance (i.e., every three to six months) for patients with high-grade dysplasia, with invasive therapies withheld until biopsy specimens show unequivocal adenocarcinoma. Relatively few published reports support the safety of this practice, however, and there is concern that the tumors might be incurable by the time surveillance reveals cancer. In one study of 12 patients in whom adenocarcinoma developed during surveillance for high-grade dysplasia, the cancers were deemed potentially curable at the time of detection in all 11 patients who were compliant with the surveillance program. In other small series, 1 of 32 patients and 1 of 4 patients had incurable disease when the cancer was first detected by surveillance endoscopy.

Low-grade dysplasia cannot be diagnosed reliably in patients with Barrett’s esophagus and there are few meaningful data on its natural history. Rates of
progression to high-grade dysplasia or adenocarcinoma within five years range from 10 to 28 percent.41,44,49
Consensus among pathologists regarding the diagnosis of dysplasia was identified as a risk factor for neoplastic progression.41

Fit patients with Barrett’s esophagus who have verified high-grade dysplasia must choose among three proposed management options: esophagectomy, endoscopic ablative therapy, and intensive surveillance. Esophagectomy, the only therapy that can clearly prevent the progression from dysplasia to invasive cancer, is associated with an operative mortality rate of 3 to 12 percent and with a rate of serious operative complications of 30 to 50 percent.50 Endoscopic ablative therapies use thermal or photochemical energy to destroy the metaplastic esophageal epithelium.51 Although endoscopic examination performed a mean of 19 months after photodynamic therapy for dysplasia revealed no evidence of dysplastic epithelium in the majority of patients in one study, minor side effects were frequent, and esophageal strictures developed in approximately one third of the patients.52 Ablative therapies are expensive, and they may not eradicate all of the tissue with a neoplastic predisposition. No study has shown that these treatments decrease the long-term risk of cancer, and thus, endoscopic ablative therapies should be considered experimental.

Helicobacter pylori and Barrett’s Esophagus

*Helicobacter pylori* infection causes a chronic gastritis that is associated with the development of intestinal metaplasia and cancer.53 *H. pylori* does not infect the esophagus, however, and its presence is not associated with an increased risk of Barrett’s esophagus or esophageal adenocarcinoma. In fact, some data suggest that gastric *H. pylori* infection may protect the esophagus from the effects of acid reflux, perhaps by decreasing gastric acidity.53 Currently, routine screening for or treatment of *H. pylori* infection is not recommended in patients with gastroesophageal reflux disease and Barrett’s esophagus.

**AREAS OF UNCERTAINTY**

No study has established that endoscopic screening and surveillance programs for Barrett’s esophagus decrease the rates of death from cancer, and decisions regarding the optimal interval for surveillance are based on conjecture and questionable models. Treatment of gastroesophageal reflux disease has not been proved to affect the risk of adenocarcinoma among patients with Barrett’s esophagus. Consequently, it is not clear whether to prescribe only the minimal amount of medication necessary to control the symptoms of gastroesophageal reflux or to prescribe aggressive antireflux therapy in order to abolish acid reflux. Although dysplasia is an imperfect biomarker for malignant conditions, random sampling of esophageal tissue for dysplasia remains the clinical standard. The role of endoscopic ablative therapies in Barrett’s esophagus is not clear. Finally, there are limited data on the safety and efficacy of intensive endoscopic surveillance for patients with high-grade dysplasia.

**GUIDELINES**

A number of organizations have published guidelines regarding the management of Barrett’s esophagus.8,54-57 Perhaps the most comprehensive are those of the American College of Gastroenterology (available at [http://www.acg.org](http://www.acg.org)). According to these guidelines, treatment of esophageal reflux in patients with Barrett’s esophagus should be the same as that in patients with gastroesophageal reflux disease who do not have Barrett’s esophagus. Patients with Barrett’s esophagus should undergo surveillance endoscopy and biopsy at intervals that are based on the presence or absence and grade of dysplasia. Patients without dysplasia should undergo endoscopy every two to three years. When low-grade dysplasia is found, endoscopy should be repeated after 6 and 12 months and then yearly thereafter if there has been no progression. When high-grade dysplasia is identified, the diagnosis should be confirmed by an experienced pathologist. If the diagnosis is confirmed, the American College of Gastroenterology endorses either of two management strategies: intensive endoscopic surveillance (every three months) or esophagectomy.

The International Society for Diseases of the Esophagus and the consensus panel of the Society for Surgery of the Alimentary Tract, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy do not specifically endorse intensive endoscopic surveillance for high-grade dysplasia and instead recommend that fit patients with this lesion be considered for esophagectomy.54,55 The guidelines of the American College of Gastroenterology do not explicitly address the role of endoscopic ablative therapies for high-grade dysplasia, but the consensus panel concluded that these techniques require further study and should be limited to patients enrolled in clinical trials.57

**CONCLUSIONS**

Endoscopic screening for Barrett’s esophagus should be considered for patients who have chronic symptoms of gastroesophageal reflux disease (i.e., symptoms that have lasted for more than five years). The group at highest risk for cancer consists of obese white men over the age of 50 years. Among black and Asian women, the risk of cancer in association with Barrett’s esophagus is so low that it probably does not warrant even the small risk associated with endoscopy, if the procedure is performed solely to screen for Barrett’s esophagus.
Evidence that aggressive antireflux therapy reduces the risk of cancer is insufficient to warrant the substantial expense and inconvenience of the therapy in routine clinical practice. Antireflux therapy should be prescribed only as needed for the symptoms and signs of gastroesophageal reflux disease.

A management algorithm for Barrett’s esophagus is shown in Figure 3. This strategy assumes that patients have undergone an initial endoscopic examination with biopsy specimens obtained in four quadrants at intervals of no more than 2 cm throughout the area of Barrett’s esophagus. If sampling of tissues during the initial endoscopy is not adequate or if there is any question regarding the degree of dysplasia, the examination should be repeated. If inflammation is interfering with the histologic assessment of dysplasia, as it was in the patient described in the case vignette, intensive antireflux therapy (at the least, twice-daily treatment with a proton-pump inhibitor) for 8 to 12 weeks should be given, and endoscopic biopsy should then be repeated to confirm the diagnosis.

The American College of Gastroenterology recommends that endoscopic surveillance be performed every two to three years in patients without dysplasia, on the basis of an estimated incidence of cancer in patients with Barrett’s esophagus of 1 to 2 percent per year. Recent studies suggest that the true incidence of cancer is approximately 0.5 percent per year. Therefore, less frequent surveillance — every three to five years — seems appropriate in patients without dysplasia.

Because studies of intensive endoscopic surveillance for high-grade dysplasia are limited and have involved primarily older patients, caution is warranted in applying the results of these studies to younger patients. Intensive endoscopic surveillance may be a valid alternative to immediate esophagectomy for older patients with high-grade dysplasia who can comply with this approach. For patients who are infirm, too old, or unwilling to undergo esophagectomy, endoscopic ablative therapy may be a reasonable alternative if the procedure is performed as part of a study protocol. Finally, the clinician should bear in mind that these recommendations have not been validated by studies demonstrating that this strategy prolongs survival or enhances the quality of life.

REFERENCES