Barrett’s Esophagus

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Barrett’s esophagus is a premalignant lesion detected in the majority of patients with esophageal and gastroesophageal adenocarcinoma — cancers that are associated with a low rate of survival (5-year survival rate, 15 to 20%). The incidence of esophageal adenocarcinoma has been increasing in the United States. In 2009, it is estimated that 16,400 new cases of esophageal cancer will be diagnosed in the United States, of which approximately 60% will be adenocarcinomas. The risk of esophageal adenocarcinoma is 30 to 40 times as high among patients with Barrett’s esophagus as among patients without this condition. The progression of Barrett’s esophagus may involve the development of low-grade dysplasia and high-grade dysplasia before the eventual development of cancer.

Barrett’s esophagus is diagnosed in approximately 10 to 15% of patients with reflux who are undergoing endoscopy; it has also been reported in patients without chronic reflux symptoms, with a prevalence of 5.6% in one report of endoscopic screening. The prevalence of Barrett’s esophagus in the general U.S. population is not known. In a population-based study conducted in Sweden, Barrett’s esophagus was diagnosed in 1.6% of 3000 study participants. If these numbers are applied to the U.S. population, 1.5 to 2.0 million adults may have this premalignant lesion. Risk factors for Barrett’s esophagus include advanced age, male sex, white race, symptoms of reflux, and obesity. Studies have reported inverse associations between the presence of Barrett’s esophagus and consumption of red wine, Helicobacter pylori infection, and black race.

### Strategies and Evidence

**Evaluation**

Although endoscopic screening for Barrett’s esophagus in patients with symptoms of chronic reflux has been suggested by some gastroenterology societies, such screening is controversial. Several cohort and case–control studies have shown that almost half the patients in whom esophageal adenocarcinoma developed had no previous symptoms of heartburn. Although the risk of esophageal adenocarcinoma is elevated among persons with heartburn as compared with the general population,
the absolute risk is still less than 1 case per 1000 person-years. Furthermore, Barrett's esophagus may occur in the absence of symptoms of chronic reflux. Finally, data that show a reduction in deaths from esophageal adenocarcinoma as a result of endoscopic screening are lacking. A recent Clinical Practice article in the Journal discussed this issue.

**DIAGNOSIS**

Barrett's esophagus is a metaplastic change in the esophageal lining from the usual squamous mucosa to columnar epithelium, and is detected on endoscopic examination as a columnar-lined distal esophagus (Fig. 1). In healthy persons, the squamocolumnar junction and the gastroesophageal junction are located at the same level, whereas in patients with Barrett's esophagus, the squamocolumnar junction is displaced proximally. The gastroesophageal junction is evident endoscopically as the top of the gastric folds; the squamocolumnar junction is seen as a transition from the light pink squamous mucosa of the esophagus to the red columnar mucosa of the stomach.

Historically, Barrett's esophagus was arbitrarily classified as short-segment disease (<3 cm) or long-segment disease (≥3 cm) according to the length of the metaplastic epithelium on endoscopic examination. However, it is not clear that such classification is clinically meaningful or alters management. The extent of Barrett's esophagus on endoscopic examination can also be graded with the use of the Prague circumference and maximum (C and M) criteria, a standardized and validated system based on the circumferential and maximal extent of the columnar-lined esophagus. Mucosal biopsy specimens are obtained from the columnar segment to confirm the presence of metaplastic or neoplastic epithelium.

**ENDOSCOPIC SURVEILLANCE**

Given the strong association between Barrett's esophagus and esophageal adenocarcinoma and the high proportion of patients with esophageal carcinoma who present with advanced disease, endoscopic surveillance programs have been established in an effort to diagnose cancer at an early stage in patients with Barrett's esophagus. Case-control and cohort studies have shown that endoscopic surveillance is significantly associated with both an earlier stage of esophageal adenocarcinoma at diagnosis and improved survival. In a population-based cohort study, 11 of 23 patients with cancer detected by means of endoscopic surveillance (48%), as compared with none of the patients with cancer who presented clinically, were alive at 2 years of follow-up (P = 0.001); however, the possibility of lead-time bias makes it impossible to conclude from these findings that surveillance prolongs life. Surveillance of patients with Barrett's esophagus is recommended by all major gastroenterology societies and published guidelines. However, no randomized, controlled trials have evaluated the efficacy of surveillance, and it is not clear whether surveillance reduces the mortality from esophageal cancer. Furthermore, several factors limit the expected benefits of current surveillance strategies, including the low overall incidence of cancer in patients with Barrett's esophagus, the absence of a previous diagnosis of Barrett's esophagus in the majority of patients with esophageal adenocarcinoma, and difficulties in the diagnosis of dysplasia (a high miss rate on evaluation of random biopsy specimens and high variation among pathologists in the interpretation of biopsy findings).

Although the precise incidence of cancer in patients with Barrett's esophagus is unknown, cancer does not develop in most patients; recent studies suggest a risk of 0.5% or less annually. In a large multicenter cohort of patients with Barrett's esophagus, the incidence of cancer was 1 case in 212 patient-years of follow-up (0.5% per year). In patients with low-grade dysplasia, incidence rates for esophageal adenocarcinoma range...
from 0.6% to 1.6% per year.\textsuperscript{20,21} The lower end of this range is similar to the incidence in patients with Barrett’s esophagus who do not have dysplasia, whereas cases in which the diagnosis of low-grade dysplasia is based on a consensus by two or more expert pathologists may be associated with progression rates that are higher than those for cases in which consensus is lacking.\textsuperscript{22} Moreover, the majority of patients with low-grade dysplasia detected on endoscopic surveillance do not have evidence of dysplasia on the subsequent endoscopic examination. In contrast, the risk of the development of esophageal adenocarcinoma is high among patients with high-grade dysplasia, with an estimated incidence of 6.6 cases per 100 patient-years (95% confidence interval, 4.9 to 8.2) in a recent meta-analysis.\textsuperscript{23}

A detailed inspection of the metaplastic epithelium with the use of a high-quality video endoscope should be performed. After obtaining target biopsy specimens from any visible mucosal abnormalities (Fig. 2), a systematic four-quadrant biopsy protocol, with specimens obtained every 2 cm along the extent of the Barrett’s esophagus, can increase the yield of both low-grade dysplasia (by 17%) and high-grade dysplasia (by 3%) as compared with randomly obtained biopsy specimens.\textsuperscript{24}

Recommendations regarding surveillance intervals are largely based on longitudinal case series and expert opinion.\textsuperscript{9} For patients without dysplasia in whom two carefully performed endoscopic examinations a year apart have shown no evidence of disease progression, the surveillance interval may be extended up to 3 years. For patients with low-grade dysplasia in whom an advanced lesion has been ruled out, endoscopic surveillance twice during the initial year and annually thereafter is typically recommended (Fig. 3).

**ADVANCED IMAGING TECHNIQUES**

The current practice of endoscopic surveillance in patients with Barrett’s esophagus has limitations. Biopsies are performed randomly and sample only 4 to 6% of the surface area of the metaplastic epithelium, although it is recognized that dysplastic and cancerous lesions within the Barrett’s segment have a focal and patchy distribution. More recently, enhanced optical imaging techniques have been suggested to improve the efficiency and accuracy of endoscopic surveillance (Table 1). Although the majority of these techniques have not been directly compared with standard endoscopy, preliminary results with the use of narrow-band imaging (electronic chromoendoscopy) and confocal laser endomicroscopy suggest a high rate of accuracy (85 to 92%) in the diagnosis of neoplasia in patients with Barrett’s esophagus.\textsuperscript{25,26} Preliminary results from a randomized, controlled crossover trial involving 123 patients with Barrett’s esophagus showed that, as compared with a strategy of performing four-quadrant biopsies every 2 cm with the use of high-definition endoscopy, the use of targeted biopsies with narrow-band imaging identified similar proportions of patients with metaplastic lesions (85% with each procedure) and neoplastic lesions (71% with targeted biopsies and 55% with four-quadrant biopsies, P = 0.15) but involved fewer biopsy specimens per procedure (3.6 vs. 7.6, P<0.001).\textsuperscript{27}
Management

Antireflux Interventions

In patients with Barrett’s esophagus, antireflux interventions are intended to control symptoms of reflux and promote healing of the esophageal mucosa; data showing that these interventions reduce the risk of esophageal carcinoma among these patients are lacking. Indications for antireflux surgery in patients with Barrett’s esophagus are the same as those in patients with chronic re-
Confocal microscopy Uses a single plane of focus with laser microscopy.

Autofluorescence imaging Detects change in fluorescence from alteration in the content of cellular molecules such as NADPH and collagen, with neoplastic tissue showing differential fluorescence (color).

Narrow-band imaging (electronic chromoendoscopy) Uses spectral narrow-band optical filters with predominance of blue light rather than the complete white-light spectrum; this highlights mucosal and vascular patterns indicative of neoplastic tissue.

Magnification endoscopy Uses optical magnification (up to ×70–100) to visualize subtle mucosal patterns and lesions within the Barrett's segment.

Chromoendoscopy Sprays various stains (e.g., methylene blue, indigo carmine), over the esophageal mucosa to accentuate the contrast between the metaplastic and nonmetaplastic epithelium.

Table 1. Advanced Imaging Techniques for Barrett's Esophagus.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-resolution, white-light endoscopy</td>
<td>Uses a charge-coupled device with up to 1 million pixels and high-resolution components</td>
<td>Becoming the default standard, given improvements in the quality, clarity, and resolution of white-light imaging</td>
</tr>
<tr>
<td>Magnification endoscopy</td>
<td>Uses optical magnification (up to ×70–100) to visualize subtle mucosal patterns and lesions within the Barrett's segment</td>
<td>Evaluated in case series; not directly compared with standard endoscopy and tedious to use, since it allows visualization of very focal areas</td>
</tr>
<tr>
<td>Chromoendoscopy</td>
<td>Sprays various stains (e.g., methylene blue, indigo carmine), over the esophageal mucosa to accentuate the contrast between the metaplastic and nonmetaplastic epithelium</td>
<td>Has been tested in randomized, controlled trials with varying results; relatively inexpensive to use; challenges include variability in use of stains and spray catheter, and lack of standardization of technique</td>
</tr>
<tr>
<td>Narrow-band imaging (electronic chromoendoscopy)</td>
<td>Uses spectral narrow-band optical filters with predominance of blue light rather than the complete white-light spectrum; this highlights mucosal and vascular patterns indicative of neoplastic tissue</td>
<td>Relatively easy to use and tested in randomized, controlled trials showing yield that is similar to that of routine biopsies; difficulty with pattern recognition and learning curve</td>
</tr>
<tr>
<td>Autofluorescence imaging</td>
<td>Detects change in fluorescence from alteration in the content of cellular molecules such as NADPH and collagen, with neoplastic tissue showing differential fluorescence (color)</td>
<td>Allows broad-based imaging; high false positive rates, subjective color interpretation, and lack of commercial availability</td>
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<tr>
<td>Confocal microscopy</td>
<td>Uses a single plane of focus with laser microscopes, allowing for real-time viewing of cellular details</td>
<td>High-quality and detailed imaging of Barrett's glands and cells; challenges include imaging of very focal areas, intravenous fluorescence agent, and image interpretation</td>
</tr>
</tbody>
</table>

flux (e.g., a lack of response to or an inability to tolerate proton-pump inhibitors); the presence of Barrett's esophagus should not be viewed as an indication for antireflux surgery. In a multicenter trial in Europe, 554 patients with symptoms of chronic reflux, including 60 patients with Barrett's esophagus, were randomly assigned to either laparoscopic antireflux surgery or a proton-pump inhibitor (esomeprazole at a dose of 20 to 40 mg daily, adjusted according to symptoms). At 3 years, symptoms and quality-of-life measures did not differ significantly between the groups, although the surgical group had significantly better esophageal pH control. Progression of Barrett's esophagus was not studied. The primary goal of both treatment with proton-pump inhibitors and surgery is symptom control; 24-hour pH monitoring to document normalization of exposure to esophageal acid is not routinely recommended.

Whereas some retrospective cohort studies have shown associations between the use of more rigorous acid suppression (with proton-pump inhibitors) and a decreased risk of or delay in the progression to neoplasia, the data are inconsistent. Proton-pump–inhibitor therapy does not reliably lead to regression of the metaplastic epithelium. Furthermore, a meta-analysis of 34 studies of antireflux interventions in patients with Barrett's esophagus showed no significant difference in the risk of esophageal cancer between patients who underwent antireflux surgery and those who received medical therapy.

Management of Neoplastic Barrett's Esophagus

Multimodal endoscopic eradication therapy involves the removal of visible neoplastic lesions by means of endoscopic mucosal resection (Fig. 4), followed by eradication of the remaining metaplastic epithelium with the use of mucosal ablative techniques such as photodynamic therapy, radiofrequency ablation, cryoablation, and argon plasma coagulation. Endoscopic mucosal resection has been used for both diagnostic and therapeutic purposes. As a diagnostic tool, this procedure has been shown to be superior to mucosal biopsies and results in a change in the histologic diagnosis and clinical management in approximately 25% of patients. The patients with Barrett's esophagus who are most likely to benefit from endoscopic eradication therapy are those with esophageal adenocarcinoma limited to the mucosa and those with high-grade dysplasia. Esophagectomy has tradi-
tionally been the primary treatment in patients with high-grade dysplasia because of a high reported prevalence of coexisting esophageal adenocarcinoma (up to 40% in some surgical series) and a high risk of progression of high-grade dysplasia to cancer. However, a recent systematic review showed a 12.7% prevalence of invasive esophageal cancer among patients undergoing esophagectomy for high-grade dysplasia; this prevalence was lower than previous estimates. In the absence of visualization of abnormal mucosal lesions during endoscopy, the prevalence decreased to 3.0%. Furthermore, metaplastic epithelium may recur after removal of the entire Barrett’s esophagus segment by means of radical subtotal esophagectomy; in one surgical case series, 47% of patients had subsequent evidence of a columnar-lined esophagus. Moreover, even in centers with expertise in performing the procedure, esophagectomy is associated with substantial morbidity (with complications in 30 to 50% of patients, including cardiac complications, pneumonia, and anastomotic leak or stricture) and mortality (1 to 5%).

The use of endoscopic eradication therapy in patients with high-grade dysplasia is supported by the results of two randomized, controlled trials. In one trial involving 208 patients, the proportion of patients in whom high-grade dysplasia remained completely eradicated at 5 years was significantly higher in the group of patients randomly assigned to photodynamic therapy and omeprazole (20 mg twice daily) than in the group randomly assigned to omeprazole alone (77% vs. 39%, P<0.001); the group receiving photodynamic therapy also had lower rates of progression to cancer (15% vs. 29%, P = 0.03), although the trial was not designed to test this outcome. In a multicenter, randomized, sham-controlled trial involving 63 patients, the rate of complete eradication of high-grade dysplasia was significantly higher in the group of patients assigned to radiofrequency treatment than in the control group (81% vs. 19%, P<0.001), as was the rate of complete eradication of the entire Barrett’s esophagus (74% vs. 0%, P<0.001). Among patients with esophageal adenocarcinoma, endoscopic eradication therapy should be considered only for those with mucosal disease, in whom the rate of lymph-node metastasis is extremely low (≤3%); once the cancer invades the submucosa, the risk of lymph-node metastasis at diagnosis increases to 20 to 25%. In a cohort of more than 200 patients with mucosal esophageal adenocarcinoma who were followed

Figure 4. Endoscopic Mucosal Resection.
Removal of early cancer with the use of endoscopic mucosal resection is shown in a patient with Barrett’s esophagus.
for a mean of 5.1 years after endoscopic eradication therapy, the 5-year survival rate was 87%.42

Endoscopic eradication therapy is not currently recommended in patients with nondysplastic Barrett’s esophagus. Because of the overall low risk of esophageal adenocarcinoma among patients with Barrett’s esophagus, if the procedure is confirmed to be preventive, the estimated number of patients who would need to be treated to prevent one case of esophageal adenocarcinoma would be 250 or more. In addition, the potential complications of endoscopic eradication therapy (an overall rate of 10 to 15%, with complications including chest pain, odynophagia, strictures, perforation, and bleeding), as well as the lack of evidence that endoscopic eradication therapy prevents the development of cancer and that the eradication is durable, underscore the need for more data.

Areas of Uncertainty

Data are lacking from randomized, controlled trials assessing the benefits of screening to detect Barrett’s esophagus among patients with gastroesophageal reflux or of surveillance endoscopic examinations among patients with a diagnosis of Barrett’s esophagus. Data from placebo-controlled or sham-controlled trials of the effects of medical, surgical, and endoscopic therapies on the incidence of esophageal adenocarcinoma and mortality are also lacking. In addition, the optimal techniques for surveillance and the optimal surveillance intervals for patients with and those without dysplasia are unclear. Although epidemiologic and experimental studies have suggested a potential role of nonsteroidal antiinflammatory drugs, aspirin, and selective cyclooxygenase-2 inhibitors in preventing esophageal cancer, confirmatory data from large randomized trials are not available.43 A randomized, controlled trial investigating the effects of aspirin and proton-pump–inhibitor therapy on neoplastic progression in patients with Barrett’s esophagus is ongoing (ClinicalTrials.gov number, NCT00357682).44 Given the low overall risk of neoplastic progression of Barrett’s esophagus, there is an interest in biomarkers that might identify persons at particular risk for the development of cancer. Among biomarkers reported to be predictive of neoplastic progression are abnormalities in the tumor-suppressor genes CDKN2A (which encodes the cyclin-dependent kinase inhibitor p16INK4a) and TP53 (which encodes tumor protein p53), and the presence of tetraploidy or aneuploidy in epithelial cells.45 In two large prospective studies, the 5-year cumulative incidence of esophageal adenocarcinoma among patients with Barrett’s esophagus was 43% in patients with aneuploidy, 56% in patients with tetraploidy, and 5% in patients without aneuploidy or tetraploidy.46,47 However, data are needed from large prospective studies to confirm the predictive value of these and other markers, and they are not currently used in routine clinical management.

Guidelines

Table 2. Guidelines for the Management of Barrett’s Esophagus.

<table>
<thead>
<tr>
<th>Organization</th>
<th>Screening Recommended</th>
<th>Histologic Examination Required for Diagnosis</th>
<th>Surveillance Intervals for Nondysplastic Barrett’s Esophagus</th>
</tr>
</thead>
<tbody>
<tr>
<td>American College of Gastroenterology</td>
<td>No†</td>
<td>Yes</td>
<td>3 yr</td>
</tr>
<tr>
<td>American Society for Gastrointestinal Endoscopy</td>
<td>Yes</td>
<td>Yes</td>
<td>3 yr</td>
</tr>
<tr>
<td>British Society of Gastroenterology</td>
<td>No</td>
<td>No</td>
<td>2 yr</td>
</tr>
<tr>
<td>French Society of Digestive Endoscopy</td>
<td>Not indicated</td>
<td>Yes</td>
<td>&lt;3 cm, 5 yr; 3–6 cm, 3 yr; &gt;6 cm, 2 yr</td>
</tr>
<tr>
<td>Society for Surgery of the Alimentary Tract</td>
<td>Yes</td>
<td>Yes</td>
<td>2 yr</td>
</tr>
</tbody>
</table>

* For patients with Barrett’s esophagus, proton-pump–inhibitor therapy, antireflux surgery, or both are generally recommended for the control of symptoms of reflux and treatment of esophagitis.
† Screening is not recommended for the general population. In selective populations at increased risk, the decision about screening should be individualized.

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CONCLUSIONS AND RECOMMENDATIONS

Patients with Barrett's esophagus, such as the patient described in the vignette, should be informed that they are at increased risk for the development of esophageal adenocarcinoma but that this risk is low. Acid-suppressive therapy (proton-pump inhibitors), antireflux surgery, or both are useful in controlling symptoms of reflux and healing erosive esophagitis in patients with Barrett's esophagus, but there is currently no conclusive evidence that such therapies reduce the risk of neoplastic progression. Endoscopic surveillance with detailed inspection and systematic biopsies is recommended for most patients with Barrett's esophagus, but decision making should take into account the patient's age, coexisting conditions, life expectancy, and the lack of conclusive evidence that surveillance reduces mortality from esophageal adenocarcinoma. In patients with nondysplastic Barrett's esophagus, after at least two endoscopic examinations with no evidence of disease progression, surveillance periods can probably be extended to 3 years. In patients with high-grade dysplasia, endoscopic therapies or surgical resection should be considered.

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REFERENCES