REVIEW ARTICLE

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Barrett's Esophagus

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N Engl J Med 2014;371:836-45.
DOI: 10.1056/NEJMra1314704

It has been estimated that 5.6% of adults in the United States have Barrett's esophagus,[1] the condition in which a metaplastic columnar mucosa that confers a predisposition to cancer replaces an esophageal squamous mucosa damaged by gastroesophageal reflux disease (GERD).[2] GERD and Barrett's esophagus are major risk factors for esophageal adenocarcinoma, a deadly tumor whose frequency in the United States has increased by a factor of more than 7 during the past four decades.[3,4] The metaplastic columnar mucosa of Barrett's esophagus causes no symptoms, and the condition has clinical importance only because it confers a predisposition to cancer.

PATHOGENESIS

Metaplasia, the process wherein one adult cell type replaces another, is a consequence of chronic tissue injury.[5] In patients with chronic esophageal injury from GERD, Barrett's metaplasia develops when mucus-secreting columnar cells replace reflux-damaged esophageal squamous cells. The cells that give rise to this metaplasia are not known. It has been proposed that GERD might induce alterations in the expression of key developmental transcription factors, causing mature esophageal squamous cells to change into columnar cells (transdifferentiation) or causing immature esophageal progenitor cells to undergo columnar rather than squamous differentiation (transcommitment).[5,6] In a rat model of reflux esophagitis, metaplasia develops from bone marrow stem cells that enter the blood and settle in the reflux-damaged esophagus.[7] Studies in mouse models have suggested that metaplasia might result from upward migration of stem cells from the proximal stomach (the gastric cardia)[8] or from proximal expansion of embryonic-type cells at the gastroesophageal junction.[9] It is not clear which of these processes contribute to the pathogenesis of Barrett's esophagus in humans.

DIAGNOSIS

The diagnosis of Barrett's esophagus requires findings on endoscopy that columnar mucosa extends above the gastroesophageal junction, lining the distal esophagus, plus esophageal-biopsy results that confirm the presence of columnar metaplasia.[2] Endoscopically, the gastroesophageal junction is identified as the most proximal extent of gastric folds, and the columnar mucosa is salmon-colored and coarse, in contrast to the pale, glossy esophageal squamous mucosa (Fig. 1). The extent of esophageal columnar metaplasia determines whether long-segment or short-segment Barrett's esophagus (≥3 cm or <3 cm of columnar metaplasia, respectively) is diagnosed.[10] However, authorities disagree on the histologic type of columnar mucosa that establishes a diagnosis of Barrett's esophagus.

U.S. gastroenterology societies require esophageal biopsies showing intestinal metaplasia with goblet cells (also called specialized intestinal metaplasia or specialized columnar epithelium) for a definitive diagnosis of Barrett's esophagus

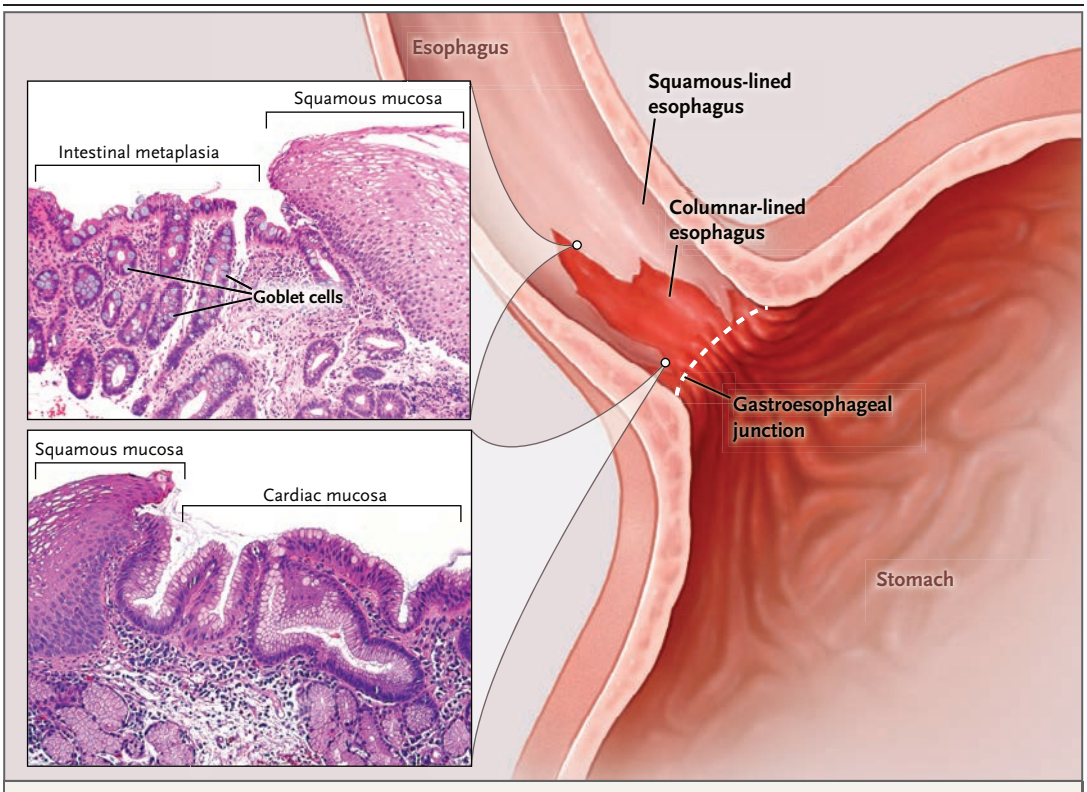

Figure 1. Diagnostic Features of Barrett's Esophagus.

The diagnosis of Barrett's esophagus requires endoscopic evidence that columnar mucosa extends above the gastroesophageal junction and lines the distal esophagus, plus esophageal-biopsy results that confirm the presence of columnar metaplasia. Endoscopically, the gastroesophageal junction is identified as the most proximal extent of the gastric folds (dashed white line). Salmon-colored columnar mucosa extends in tongue-shaped projections above the gastroesophageal junction, lining the distal esophagus. A biopsy specimen obtained at the level of the upper white dot reveals the junction between esophageal stratified squamous epithelium and intestinal metaplasia with distinctive, intestinal-type goblet cells, which establishes the diagnosis of Barrett's esophagus. Intestinal metaplasia may not be uniformly distributed throughout the entire columnar-lined esophagus, however. In this example, a biopsy specimen taken from the columnar-lined esophagus closer to the gastroesophageal junction (at the level of the lower white dot) shows cardiac mucosa composed of mucus-secreting columnar cells without goblet cells. Some gastroenterology societies (e.g., the British Society of Gastroenterology) accept evidence of cardiac mucosa alone as diagnostic of Barrett's esophagus, but U.S. gastroenterology societies require evidence of intestinal metaplasia for a definitive diagnosis. Photomicrographs (hematoxylin and eosin) provided by Drs. Kevin Turner and Robert Genta.

(Fig. 1).[11-13] This intestinal metaplasia is a well-established risk factor for adenocarcinoma.[12] However, some other societies, including the British Society of Gastroenterology, also consider esophageal biopsies that show cardiac mucosa (comprising mucus-secreting columnar cells without goblet cells) to be diagnostic of Barrett's esophagus.[14] Cardiac mucosa, although traditionally considered the normal lining of the gastric cardia, can have intestinal-type histochemical features and abnormalities in DNA content,[15,16] and it appears to be a GERD-induced metaplasia in some, if not all, cases.[17] Nevertheless, it is not clear that cardiac mucosa is an important risk factor for adenocarcinoma.[18] Thus, the major issue underlying disagreement on histologic criteria for the diagnosis of Barrett's esophagus is whether the condition should be defined as a histologic curiosity (a mucosal metaplasia, irrespective of its clinical importance) or as a medical condition (a mucosal metaplasia that confers a predisposition to cancer). U.S. gastroenterology societies have taken the latter position.

EPIDEMIOLOGY

In individual patients, the extent of Barrett's metaplasia varies with the severity of underlying GERD.[19] Untreated patients with long-segment Barrett's esophagus typically have severe GERD with erosive esophagitis, whereas short-segment Barrett's esophagus is not associated with GERD symptoms or endoscopic signs of reflux esophagitis.[1,20] Presumably, short-segment Barrett's esophagus develops as a consequence of protracted acid reflux involving only the most distal portion of the esophagus, a phenomenon that can be documented in apparently healthy persons.[21] Short-segment Barrett's esophagus was not widely recognized until 1994,[22] and earlier studies generally involved patients with long-segment disease exclusively. More recent studies have involved varying proportions of patients with long-segment and short-segment Barrett's esophagus, and the proportion can profoundly influence the frequency of associated GERD symptoms and complications.

Proposed risk factors for Barrett's esophagus are listed in Table 1 (also see the Supplementary Appendix). The condition typically is discovered

Table 1. Proposed Risk Factors and Protective Factors for Barrett's Esophagus and Esophageal Adenocarcinoma.*

Factor	Risk Factor for Barrett's Esophagus	Risk Factor for Esophageal Adenocarcinoma
Older age	Yes	Yes
White race	Yes	Yes
Male sex	Yes	Yes
Chronic heartburn	Yes	Yes
Age <30 yr at onset of GERD symptoms	Yes	—
Hiatal hernia	Yes	Yes
Erosive esophagitis	Yes	Yes
Obesity with intraabdominal fat distribution	Yes	Yes
Metabolic syndrome	Yes	Yes
Tobacco use	Yes	Yes
Family history of GERD, Barrett's esophagus, or esophageal adenocarcinoma	Yes	Yes
Obstructive sleep apnea	Yes	—
Low birth weight for gestational age	Yes	No
Preterm birth	No	Yes
Consumption of red meat and processed meat	Yes	Yes
Human papillomavirus infection	No	Yes
	Protective Factor for Barrett's Esophagus	**Protective Factor for Esophageal Adenocarcinoma**
Use of nonsteroidal antiinflammatory drugs	Yes	Yes
Use of statins	Yes	Yes
Helicobacter pylori infection	Yes	Yes
Diet high in fruits and vegetables	Yes	Yes
Exposure to ambient ultraviolet radiation	—	Yes
Breast-feeding for parous women	—	Yes
Tall height	Yes	Yes

* A dash indicates that studies have not addressed the question of whether the specified factor is associated with an increased risk or has a protective effect. Citations for the information in this table are provided in the Supplementary Appendix, available at NEJM.org. GERD denotes gastroesophageal reflux disease.

during endoscopy in white patients 50 years of age or older, either by intention (during screening endoscopy for GERD symptoms) or by chance (during endoscopy for conditions unrelated to GERD). Barrett's esophagus is two to three times as common in men as in women, is uncommon in blacks and Asians, and is rare in children.[23,24] Other important risk factors include obesity (with a predominantly intraabdominal fat distribution) and cigarette smoking, and there is a familial form of Barrett's esophagus, which accounts for 7 to 11% of all cases.[25] Most conditions associated with Barrett's metaplasia are also risk factors for esophageal adenocarcinoma.[26] Conversely, factors that might provide protection against Barrett's esophagus include the use of nonsteroidal antiinflammatory drugs, gastric infection with *Helicobacter pylori*, and consumption of a diet high in fruits and vegetables.

No single risk factor yet identified can account for the profound increase in the incidence of esophageal adenocarcinoma in Western countries during the past 40 years, a period when GERD and Barrett's esophagus appear to have increased only modestly in frequency.[27,28] There has been a steep rise in the frequency of central obesity, which might contribute to Barrett's carcinogenesis by promoting GERD and by increasing the production of hormones that promote cell proliferation, such as leptin and insulin-like growth factors.[29,30] *H. pylori* infection, which may protect the esophagus from GERD by causing a gastritis that reduces gastric acid production, has declined in frequency during the same period when esophageal adenocarcinoma has risen in developed countries.[31] Another hypothesis links the rising incidence of esophageal adenocarcinoma with increased dietary intake of nitrate, which has resulted from the widespread use of nitrate-based fertilizers.[32]

Estimates of the annual incidence of esophageal adenocarcinoma among patients with nondysplastic Barrett's esophagus have ranged from 0.1 to 2.9%, with the highest estimates in studies with evidence of publication bias.[33] Recent, better-quality studies suggest that the risk of esophageal adenocarcinoma in the general population of patients with nondysplastic Barrett's esophagus is only 0.1 to 0.3% per year.[34-37] However, a number of factors influence the risk of cancer for individual patients. For example, cancer risk among men with Barrett's esophagus is approximately twice that among women,[36] the risk is greater with a longer segment of Barrett's metaplasia,[38] and the risk is especially high among persons with certain familial forms of Barrett's esophagus.[39] In addition, the risk appears to decrease with follow-up endoscopies showing no progression to dysplasia.[40]

SCREENING AND SURVEILLANCE FOR BARRETT'S ESOPHAGUS

For decades, the primary strategy for preventing deaths from esophageal adenocarcinoma has been to screen patients with GERD symptoms for Barrett's esophagus with the use of endoscopy and, for patients with Barrett's esophagus on endoscopic screening, to perform regular endoscopic surveillance to detect curable neoplasia.[2] Unfortunately, there is no proof that this strategy is effective, and with an annual cancer incidence of only 0.1 to 0.3%, the logistics of performing a randomized trial to prove that screening and surveillance prevent deaths from esophageal cancer are daunting. Observational studies have shown that patients with Barrett's esophagus–associated cancers diagnosed by means of surveillance endoscopy have earlier-stage tumors and higher survival rates than those whose tumors are discovered because of symptoms such as dysphagia and weight loss.[41,42] However, such studies are highly susceptible to biases that might exaggerate the benefits of surveillance. Some computer-modeling studies have concluded that screening and surveillance can be cost-effective under certain circumstances, but such studies are not definitive.[43,44]

Despite the lack of high-quality evidence to support the practice, medical societies currently recommend endoscopic screening for Barrett's esophagus in patients with chronic GERD symptoms who have at least one additional risk factor for esophageal adenocarcinoma, such as an age of 50 years or older, male sex, white race, hiatal hernia, elevated body-mass index, intraabdominal body-fat distribution, or tobacco use.[2,12,13,45] If the screening examination does not reveal Barrett's esophagus, no further endoscopic screening for the condition is recommended.[13,45] For patients found to have nondysplastic Barrett's metaplasia, whether by screening or by chance, medical societies recommend regular endoscopic surveillance at intervals of 3 to 5 years.[2,11-13]

Nevertheless, there are a number of reasons to question the value of screening and surveillance for Barrett's esophagus.

The screening prerequisite of GERD symptoms limits the usefulness of the practice, because patients with short-segment Barrett's esophagus often have no GERD symptoms, and approximately 40% of patients with esophageal adenocarcinoma report no history of GERD.[46] Studies have shown that less than 10% of patients with esophageal adenocarcinoma have a prior diagnosis of Barrett's esophagus, suggesting that current screening practices are highly ineffective.[47,48] Furthermore, a recent case–control study has challenged the efficacy of surveillance for cancer prevention among patients with Barrett's esophagus.[49] This study compared the frequency of surveillance endoscopy during a 3-year period among 38 case patients (those known to have Barrett's esophagus who subsequently died of esophageal adenocarcinoma) with that among 101 living, control patients with Barrett's esophagus who were matched for age, sex, and follow-up duration. The case patients and controls had nearly identical frequencies of endoscopic surveillance (55% among case patients and 60% among controls), and surveillance was not associated with a decreased risk of death from esophageal cancer (adjusted odds ratio, 0.99; 95% confidence interval [CI], 0.36 to 2.75). However, this relatively wide confidence interval does not exclude the possibility that surveillance was beneficial.

A primary rationale for screening has been to identify patients with Barrett's esophagus, who then will benefit from surveillance. If, as the aforementioned report suggests, surveillance has little benefit, then the practice of screening might be based on a fundamentally flawed premise. Clearly, better methods are needed for risk stratification to identify those patients with Barrett's esophagus who could benefit most from surveillance or other interventions. Advanced endoscopic imaging techniques have been studied for this purpose, including dye-based chromoendoscopy, optical and digital chromoendoscopy, autofluorescence endoscopy, and confocal laser endomicroscopy.[50] In biopsy specimens from patients with Barrett's metaplasia, abnormalities in p53 expression and in cellular DNA content on flow cytometry have been associated with neoplastic progression.[51,52] Cytogenetic abnormalities detected by means of fluorescence in situ hybridization (FISH) and biomarker panels that identify multiple abnormalities in DNA content, gene expression, and DNA methylation have shown promise as predictors of cancer risk, as have some risk-stratification models that incorporate a variety of clinical, histologic, and molecular features.[52-56] However, none of these methods have yet been validated sufficiently to justify routine application in clinical practice.

There are adverse consequences of endoscopic screening and surveillance, in addition to the high cost of endoscopy and the small risk of endoscopic complications. Identification of innocuous neoplastic lesions by means of these procedures might lead to the use of invasive therapies with serious or even fatal complications. Studies have shown that a diagnosis of Barrett's esophagus causes psychological stress, has a negative effect on quality of life, and results in higher premiums for health and life insurance.[12] To date, medical societies have taken the position that, in the absence of definitive data, it is better to err by performing unnecessary screening and surveillance than by forgoing the opportunity to identify curable esophageal neoplasms. It is not clear whether the new data discussed above will influence future recommendations. Despite the many limitations and dubious benefits of screening and surveillance for Barrett's esophagus, these practices are still recommended by medical societies. In general, recommendations for surveillance of established Barrett's esophagus are stronger and more explicit than recommendations for initial screening.

MANAGEMENT OF BARRETT'S ESOPHAGUS

A brief algorithm for endoscopic surveillance and eradication therapy in patients with Barrett's esophagus is provided in Figure 2.

TREATMENT OF GERD

In patients with Barrett's metaplasia, refluxed gastric acid can cause chronic inflammation, double-strand DNA breaks, and increased cell proliferation, all of which may contribute to carcinogenesis.[57] This suggests that GERD should be treated aggressively in patients with Barrett's esophagus, and there is indirect evidence to sug-

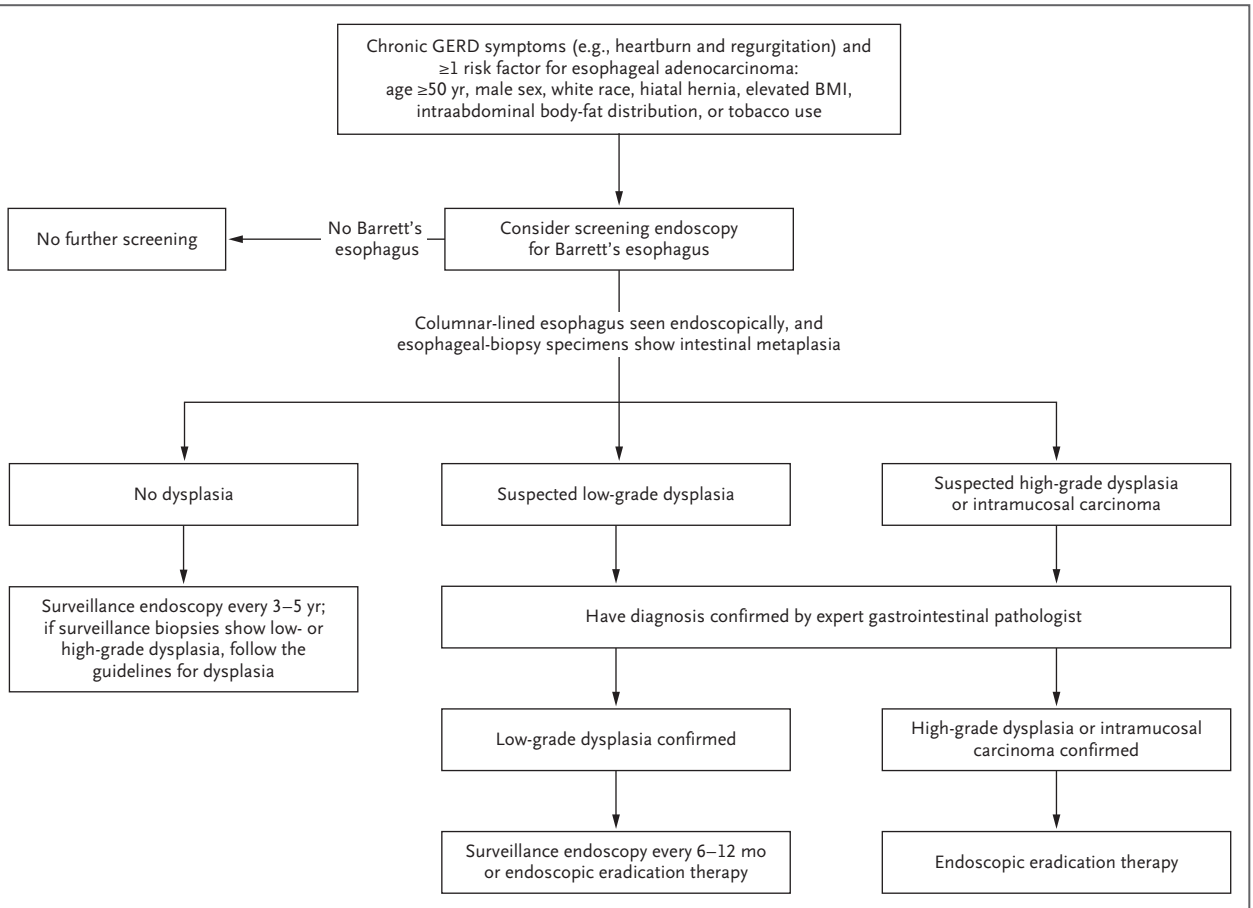

Figure 2. Algorithm for the Screening, Surveillance, and Management of Barrett's Esophagus.

Endoscopy for patients with dysplasia or intramucosal carcinoma should include four-quadrant biopsy sampling at 1-cm intervals and endoscopic resection of mucosal irregularities. If dysplasia or intramucosal carcinoma is discovered and these procedures have not been performed, then repeat endoscopy is recommended before endoscopic eradication therapy is initiated. BMI denotes body-mass index, and GERD gastroesophageal reflux disease.

gest that proton-pump inhibitors (PPIs) decrease the risk of cancer development. For example, a recent cohort study involving 540 patients with Barrett's esophagus who were followed for a median of 5.2 years showed that PPI use was associated with a 75% reduction in the risk of neoplastic progression.[58] Bile acids can also cause double-strand DNA breaks and might contribute to carcinogenesis in patients with Barrett's metaplasia, and PPIs do not prevent bile reflux.[59] Antireflux surgery can prevent reflux of all gastric contents (acid and bile), but the best available data suggest that surgery is not more effective than PPI therapy in preventing cancer.[57] Thus, antireflux surgery is not advised solely for protection against cancer.

Just as in patients who have GERD without Barrett's metaplasia, PPIs are used in patients with Barrett's esophagus to control GERD symptoms and heal reflux esophagitis. For patients who have no symptoms or endoscopic signs of GERD, as is common in short-segment Barrett's esophagus, the issue of whether to use PPIs for chemoprevention remains unresolved and controversial. We believe that the indirect evidence supporting a cancer-protective role for PPIs in Barrett's esophagus is strong enough to warrant conventional-dose PPI treatment for asymptomatic patients after they have been informed of the potential risks and benefits, although this approach is not specifically endorsed by medical societies.

ENDOSCOPIC ERADICATION OF DYSPLASIA

Cancers in patients with Barrett's metaplasia evolve through a series of genetic and epigenetic alterations that activate oncogenes, silence tumor-suppressor genes, and free cells from their normal growth controls. Before cells become malignant, these DNA abnormalities can cause histologic changes in the esophagus that pathologists recognize as dysplasia.[60] Dysplasia is an imperfect biomarker for malignant potential because dysplasia can be patchy and easily missed during routine biopsy sampling of Barrett's esophagus, and the severity of dysplasia is graded with the use of subjective criteria, frequently resulting in interobserver disagreement among pathologists. Despite these shortcomings, dysplasia remains the basis for clinical decision making in cases of Barrett's esophagus.[12] However, medical societies recommend that a diagnosis of dysplasia be confirmed by a second expert pathologist before invasive therapies are initiated.[11-14]

The rate at which high-grade dysplasia progresses to cancer in patients with Barrett's esophagus is considered high enough to warrant intervention.[12] One meta-analysis has estimated that rate at approximately 6% per year,[61] but considerably higher rates have been reported in therapeutic trials.[62,63] Until recently, the standard treatment for high-grade dysplasia was esophagectomy, but endoscopic resection and ablation techniques are now available to eradicate dysplasia. The risk of complications is much lower with these new techniques than with esophagectomy, and the risk of death is virtually nil.[64] For endoscopic mucosal resection, a diathermic snare is used to resect a segment of esophageal mucosa and underlying submucosa, which is submitted for pathological evaluation. This procedure is used both as a therapy to remove neoplastic mucosa and as the most accurate means available to delineate the depth of invasion (T staging) of early neoplasia in patients with Barrett's esophagus.[65] In contrast, endoscopic ablation techniques, which use thermal or photochemical energy to destroy esophageal mucosa, provide no tissue specimens. After endoscopic mucosal resection or ablation of Barrett's metaplasia, patients are treated with PPIs to prevent acid reflux, which allows for re-epithelialization of the eradicated area by squamous epithelium.

Studies suggest that among patients with dysplasia that is treated endoscopically, the frequency of metachronous neoplasia is reduced if all metaplasia is eradicated, not just dysplastic areas.[66] Consequently, the goal of contemporary endoscopic therapy is to eradicate both dysplastic and nondysplastic Barrett's metaplasia completely.[64] The term "endoscopic eradication therapy" refers to the use of endoscopic resection, ablation, or both to achieve that goal.

Unlike esophagectomy, endoscopic eradication therapy does not have the potential to cure neoplasms that have metastasized to regional lymph nodes. Such metastases are present in less than 2% of patients with Barrett's esophagus who have mucosal neoplasms (high-grade dysplasia or intramucosal adenocarcinoma) but in more than 20% of those with tumors that extend deep into submucosa.[67] Consequently, endoscopic therapy is generally used to treat mucosal neoplasms only. Randomized, controlled trials have shown that endoscopic eradication of dysplasia in patients with Barrett's esophagus with the use of photodynamic therapy or radiofrequency ablation (in which radiofrequency energy destroys the mucosa) significantly reduces the rate of progression to cancer.[62,63] Although these techniques have not been compared directly in a prospective trial, radiofrequency ablation appears to result in similar, if not superior, rates of dysplasia eradication and cancer prevention, with easier administration and fewer side effects than photodynamic therapy. Consequently, radiofrequency ablation is the ablative procedure of choice for dysplasia in patients with Barrett's esophagus. Radiofrequency ablation generally requires several endoscopic sessions to achieve complete eradication of metaplasia, and the most common serious side effect is esophageal stricture, which occurs in approximately 5% of patients who undergo the procedure.[68]

MANAGEMENT OF LOW-GRADE DYSPLASIA

Investigations of the natural history of low-grade dysplasia in patients with Barrett's esophagus have yielded disparate results, probably because difficulties in establishing the diagnosis confound comparisons among studies. In one study involving 147 patients with low-grade dysplasia diagnosed at community hospitals, for example, expert pathologists who reviewed the biopsy slides confirmed the diagnosis in only 15% of cases.[69] Among patients with confirmed disease, the cumulative risk of neoplastic progression was 85%

at 109 months. In contrast, the annual rate of neoplastic progression was only 1.8% in a study involving 210 patients with low-grade dysplasia who were followed for a mean of 6.2 years.[70]

In a recent randomized trial of radiofrequency ablation versus endoscopic surveillance that involved 136 patients with confirmed low-grade dysplasia who were followed for 3 years, radiofrequency ablation reduced the risk of progression to high-grade dysplasia or adenocarcinoma by 25 percentage points (1.5% with radiofrequency ablation vs. 26.5% with surveillance; 95% CI, 14.1 to 35.9 percentage points; P<0.001).[71] In the surveillance group, however, 28% of patients had no dysplasia detected during follow-up, unresectable tumors did not develop in any of the patients, and there were no cancer-related deaths. Consequently, it is not clear that radiofrequency ablation is the best management strategy for low-grade dysplasia, although it is the one we favor. For patients with confirmed low-grade dysplasia, gastroenterology societies currently recommend either endoscopic surveillance at intervals of 6 to 12 months or endoscopic ablation therapy.

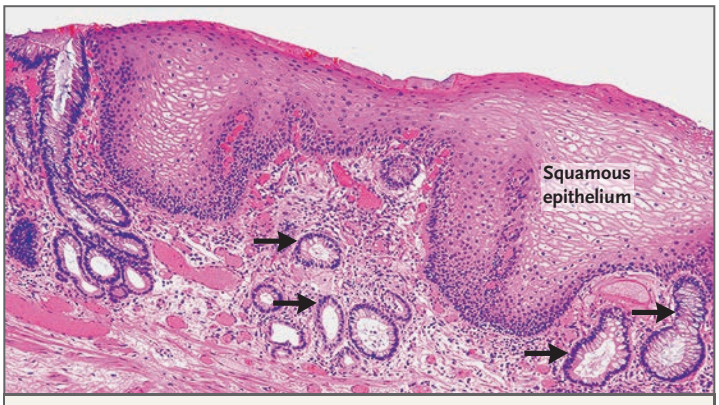

Figure 3. Subsquamous Intestinal Metaplasia.

Numerous metaplastic, intestinal-type glands are evident in the subepithelial lamina propria (arrows). In this location, subsquamous intestinal metaplasia is hidden from the endoscopist and possibly protected from radiofrequency ablation by the overlying layer of squamous epithelium. Photomicrograph (hematoxylin and eosin) provided by Dr. Amy Noffsinger.

RADIOFREQUENCY ABLATION OF NONDYSPLASTIC BARRETT'S METAPLASIA

Some physicians have proposed that radiofrequency ablation should be offered to all patients with Barrett's esophagus, dysplastic or nondysplastic, arguing that endoscopic surveillance is not an effective cancer-prevention strategy and that radiofrequency ablation is safe and effective for eradicating Barrett's metaplasia.[72] However, the efficacy of radiofrequency ablation for preventing cancer in patients with nondysplastic Barrett's esophagus has not been established in long-term studies, and there are at least two reasons why the risk of cancer may not be eliminated, even when radiofrequency ablation eradicates all visible evidence of Barrett's metaplasia. First, patients with Barrett's esophagus frequently have metaplastic glands in the lamina propria underneath the esophageal squamous epithelium, usually within 1 cm of its junction with metaplasia (Fig. 3).[73] The overlying squamous epithelium hides this subsquamous intestinal metaplasia from the endoscopist and may protect it from radiofrequency ablation. The rate at which subsquamous intestinal metaplasia progresses to a malignant state is not known, but cancers have been found in these subsquamous metaplastic glands.[74,75]

Another reason to suspect that radiofrequency ablation might not eliminate the risk of cancer is the observation that Barrett's metaplasia can recur over time. Early studies suggested that the recurrence rate after radiofrequency ablation was low, but more recent studies have shown recurrences of Barrett's metaplasia, sometimes with dysplasia and cancer, in up to 33% of patients at 2 years.[76] The long-term cancer risk associated with recurrent Barrett's metaplasia after radiofrequency ablation is not known.

Since the frequency and importance of subsquamous intestinal metaplasia and recurrent Barrett's metaplasia have not yet been determined, the efficacy of radiofrequency ablation for cancer prevention in patients with nondysplastic Barrett's esophagus is not clear. These uncertainties suggest that patients should continue to undergo endoscopic surveillance even after apparently successful eradication of metaplasia by means of radiofrequency ablation. One study used a decision-analytic Markov model to explore the cost-effectiveness of radiofrequency ablation for 50-year-old men with Barrett's esophagus and concluded that it was cost-effective for those with dysplasia but not for those with nondysplastic metaplasia.[77] At this time, we do not recommend radiofrequency ablation for the general population of patients with nondysplastic Barrett's esophagus.

Dr. Spechler reports receiving consulting fees from Takeda Pharmaceuticals USA, Ironwood Pharmaceuticals, and Torax Medical. Dr. Souza reports receiving consulting fees from Ironwood Pharmaceuticals and Otsuka America. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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