Clinical Crossroads

Barrett Esophagus and Risk of Esophageal Cancer
A Clinical Review

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IMPORTANCE Barrett esophagus, a complication of gastroesophageal reflux disease (GERD), predisposes patients to esophageal adenocarcinoma, a tumor that has increased in incidence more than 7-fold over the past several decades. Controversy exists regarding the issues of endoscopic screening and surveillance for Barrett esophagus, treatment for the underlying GERD, and the role of endoscopic eradication therapy.

OBJECTIVES To review current concepts on the pathogenesis, diagnosis, and treatment of Barrett esophagus; to discuss the importance of dysplasia and the role of endoscopic eradication therapy for its treatment; and to review current management guidelines.

EVIDENCE REVIEW MEDLINE and the Cochrane Library were searched from 1984 to April 2013. Additional citations were obtained by reviewing references from selected research and review articles.

FINDINGS Risk factors for cancer in Barrett esophagus include chronic GERD, hiatal hernia, advanced age, male sex, white race, cigarette smoking, and obesity with an intra-abdominal body fat distribution. The annual risk of esophageal cancer is approximately 0.25% for patients without dysplasia and 6% for patients with high-grade dysplasia. High-quality studies have found no significant differences in cancer incidence for patients with Barrett esophagus whose GERD is treated medically or surgically. Endoscopic eradication therapy with radiofrequency ablation significantly reduces the frequency of progression to cancer for patients with high-grade dysplasia.

CONCLUSIONS AND RELEVANCE Endoscopic screening is recommended for patients with multiple risk factors for cancer in Barrett esophagus. For patients with Barrett esophagus without dysplasia, endoscopic surveillance at intervals of 3 to 5 years is recommended, and GERD is treated much as it is for patients without Barrett esophagus. Endoscopic eradication therapy is the treatment of choice for high-grade dysplasia and is an option for low-grade dysplasia. Endoscopic eradication therapy is not recommended for the general population of patients with nondysplastic Barrett esophagus.

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DR SHIP Mr K is a 43-year-old man who has had reflux symptoms for more than 20 years. His symptoms have been severe enough that he wakes from sleep choking. He has often wondered if he was having a heart attack. An esophagogastroduodenoscopy (EGD) performed 11 years ago, when symptoms were resistant to maximal proton pump inhibitor therapy, showed Barrett esophagus. Subsequent EGDs, including 2 in 2012, confirmed that he has short-segment Barrett esophagus with intestinal metaplasia documented in some esophageal biopsy specimens. No biopsy specimens have shown dysplasia.

His medical history is significant for attention-deficit/hyperactivity disorder, allergic rhinitis, eczema, and hemorrhoids. His medications include extended-release amphetamine-dextroamphetamine, 20 mg/d, and esomeprazole magnesium, 40 mg twice per day. He has no drug allergies.

Mr K works as a high school history teacher and lives with his wife and 2 children. He has a 15-pack-year tobacco history and quit at age 30 years. He drinks alcohol 2 to 3 times a week.

On examination, Mr K appeared well, weighed 226 lb, and was 6 ft 4 in tall. His blood pressure was 132/70 mm Hg and his pulse was 62/min. His abdomen had active bowel sounds and was soft and non-

tender, without organomegaly. The remainder of his examination findings were normal.

Mr K: His View

I started getting heartburn really early on in my teen years. When I did manual labor, if I was bending over, I would get a tremendous searing pain in my chest. I took vast quantities of Tums [calcium carbonate] to try and cool the symptoms. I remember many nights being up in the middle of the night and my chest really hurting and trying to sleep sort of in an upright position. At age 18, I didn't know any better—I would eat a large pizza at 10 o'clock. I had tremendous pain.

EMR *endoscopic mucosal resection*

GERD *gastroesophageal reflux disease*

H_2RA *histamine 2 receptor antagonist*

NSAID *nonsteroidal anti-inflammatory drug*

PPI *proton pump inhibitor*

RFA *radiofrequency ablation*

I am taking 40 mg of Nexium [esomeprazole] daily. I have been taking it at that strength for a long time, but it's changed everything. It's almost completely eliminated the symptoms. I worry, though, because I remember seeing a few articles recently that suggested that maybe the medication isn't so good for you. I wonder if maybe it's actually masking some of the damage that's there.

I am concerned that I have been taking a medicine that has allowed me not to modify my diet. I am worried that I have been causing myself further damage. I also wonder if maybe I shouldn't be taking this much and that maybe my diet should be different. I have tried to avoid eating late at night, although I don't always. I avoid certain foods, trigger foods.

My doctor told me that if I develop cancer, they have a laser and they can burn the cancerous cells and they heal into totally normal cells. And so I tell myself that it doesn't even matter if I get precancerous dysplasia; they'll just use the laser and turn the cells back into normal cells. I want to be serious but I do not know if this poses a real threat to my life. I am not sure I have been treating the diagnosis with the care it deserves.

I wonder whether if I did get dysplasia, is the laser the way to go? What are the options if I do get dysplasia?

Definition, Pathogenesis, and Diagnosis

DR SPECHLER Mr K has chronic gastroesophageal reflux disease (GERD) with typical symptoms of heartburn and regurgitation.[1] He also has a serious GERD complication, Barrett esophagus—a condition in which metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus.[2] Barrett esophagus results from metaplasia, the process in which one fully differentiated cell type replaces another. Metaplasia often is a response to chronic inflammation and, in the setting of GERD with chronic reflux esophagitis, columnar cells can replace reflux-damaged esophageal squamous cells.

The pathogenesis of Barrett metaplasia starts with gastroesophageal reflux of acid and bile that damage esophageal squamous cells. It is not known why this damage is repaired through columnar metaplasia rather than by regeneration of more squamous cells. Barrett metaplasia conceivably could result from transdifferentiation, in which squamous cells change into columnar cells through reflux-induced alterations in expression of key developmental transcription factors, or from transcommitment, in which esophageal stem cells (in the basal layer of the squamous epithelium or in the ducts of submucosal glands) that normally differentiate into squamous cells instead differentiate into columnar cells.[3] In a rat model of reflux esophagitis, Barrett metaplasia appears to develop from circulating bone marrow stem cells.[4] Recent research using mouse models has suggested that Barrett metaplasia might result from the proximal migration of stem cells from the gastric cardia[5] or from expansion of a nest of residual embryonic cells at the gastroesophageal junction.[6]

The diagnosis of Barrett esophagus is suspected when an endoscopy reveals columnar mucosa in the esophagus (**Figure 1**). The diagnosis is confirmed when biopsy specimens of that columnar mucosa show specialized intestinal metaplasia with its characteristic goblet cells (**Figure 2**), as they did in Mr K. The distance between the gastroesophageal junction and the most proximal extent of Barrett metaplasia establishes whether there is long-segment (≥3 cm) or short-segment (<3 cm) Barrett esophagus.[7]

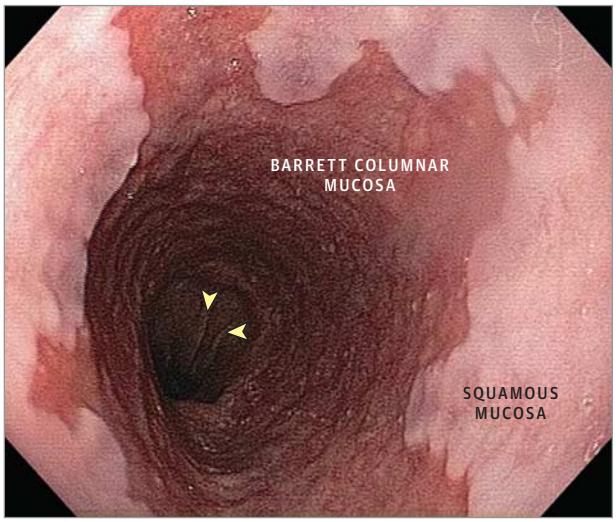
Biopsy specimens taken from the distal esophagus sometimes reveal cardiac mucosa, composed of mucus-secreting epithelial cells. Like specialized intestinal metaplasia with goblet cells, cardiac mucosa can be metaplastic[8] and can exhibit intestinal histochemical features and DNA abnormalities.[9] Consequently, some authorities contend that cardiac mucosa in the esophagus should be considered Barrett esophagus.[9] It is not clear that cardiac mucosa has the same malignant predisposition as intestinal metaplasia in the esophagus, however.[10] For that reason, US gastroenterology societies presently require demonstration of intestinal metaplasia with goblet cells for a definitive diagnosis of Barrett esophagus.[2,11,12]

Risk Factors and Epidemiology

Chronic GERD is a risk factor for Barrett esophagus.[13,14] Long-segment Barrett esophagus is strongly associated with chronic heartburn, hiatal hernia, and severe reflux esophagitis. The frequency of Barrett esophagus increases with age, especially in persons older than 50 years, and the condition is rare in children. A study that reviewed upper endoscopy reports on 6731 pediatric patients found that Barrett esophagus was suspected in only 17 cases (0.25%).[15] Barrett esophagus is 2 to 3 times more common in men than in women, and the condition has a predilection for whites. Most reports suggest that Barrett esophagus is less common in African Americans than in white Americans, and the condition is uncommon in Asians.[16] Obesity is associated with Barrett esophagus, especially obesity with a predominantly intra-abdominal distribution of fat.[17] Cigarette smoking is also a risk factor.[18] Since Barrett esophagus is the precursor of esophageal adenocarcinoma, it is not surprising that these same risk factors apply to that cancer.[19] This patient has several risk factors, including chronic GERD, male sex, and white race.

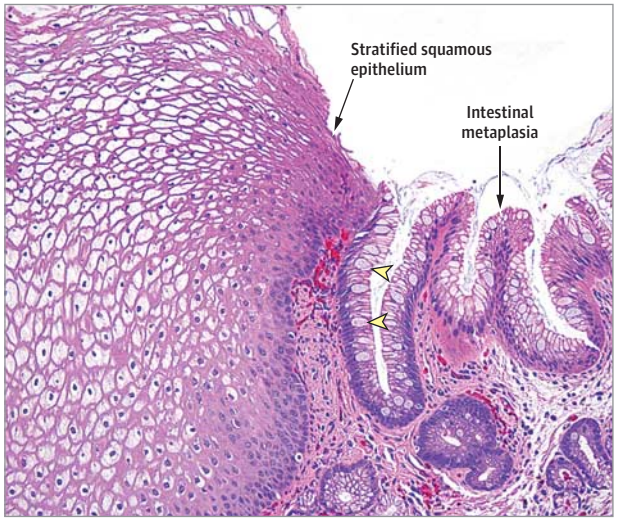
The metaplastic Barrett mucosa causes no symptoms. The condition commonly is discovered during an endoscopy performed for evaluation of symptoms caused by the underlying GERD. Although endoscopic screening of patients with GERD for Barrett esophagus

Figure 1. Endoscopic Image of Barrett Esophagus



Note the contrast between the Barrett columnar mucosa, with its reddish color and velvet-like texture, and the pale, glossy esophageal squamous mucosa. The yellow arrowheads mark the tops of the gastric folds, which identify the level of the gastroesophageal junction.

Figure 2. Photomicrograph of Esophageal Biopsy Specimen Showing the Junction Between Stratified Squamous Epithelium and Specialized Intestinal Metaplasia



The yellow arrowheads identify the prominent goblet cells in the intestinal metaplasia of Barrett esophagus. Hematoxylin-eosin stain, original magnification ×20. Debris in the esophageal lumen was removed using Adobe Photoshop. Photomicrograph reproduced with permission from Robert Genta, MD.

is performed with the assumption that early identification of the condition will decrease morbidity and mortality from esophageal adenocarcinoma, no study yet has validated that assumption definitively. Nevertheless, concern regarding the rapidly increasing incidence of this cancer (see below) has motivated US medical societies to endorse the practice of screening patients with GERD who have multiple risk factors for esophageal adenocarcinoma, as summarized in the **Table**.[1,11,12,20-22] The requirement that patients must have GERD symptoms to consider screening limits the utility of the proposed screening strategies because patients with short-segment Barrett esophagus often have no GERD symptoms.

Short-segment Barrett esophagus was not widely recognized before 1994, when a report documented that 18% of consecutive patients in a general endoscopy unit had specialized intestinal metaplasia at the squamocolumnar junction in the distal esophagus.[23] A number of subsequent reports have confirmed that short-segment Barrett esophagus is common in patients who have endoscopy, irrespective of GERD symptoms. In a Swedish study in which 1000 individuals in the general population were randomly selected to have endoscopy, 16 (1.6%) were found to have Barrett esophagus (5 with long-segment, 11 with short-segment).[24] GERD symptoms were reported by 4 (80%) of the 5 with long-segment Barrett esophagus but by only 5 (45%) of the 11 with short-segment Barrett esophagus. Other studies have confirmed that only approximately half of patients with short-segment Barrett esophagus have GERD symptoms.[25] Reports on Barrett esophagus published before 1994 describe predominantly patients with long-segment disease and severe GERD. More recent studies include many patients with short-segment Barrett having few or no GERD manifestations other than esophageal metaplasia.

The risk of adenocarcinoma appears to vary with the length of esophagus lined by Barrett metaplasia, and patients with long-segment Barrett are at the highest risk of malignancy.[26] Short-segment disease is far more common than long-segment Barrett esophagus, however, and many (if not most) Barrett esophagus cancers in the general population occur in patients with short-segment disease. Because current screening programs for Barrett esophagus cannot identify the 50% of patients with short-segment disease who have no GERD symptoms, these programs can have only limited effect on mortality due to esophageal adenocarcinoma in the general population. Indeed, fewer than 5% of patients presenting with esophageal adenocarcinoma have a prior diagnosis of Barrett esophagus.[27]

The apparent failure of screening programs is distressing because the incidence of esophageal adenocarcinoma in the United States has burgeoned from 3.6 per million in 1973 to 25.6 per million in 2006.[28] The factors responsible for this profound increase are not clear. GERD, Barrett esophagus, and obesity are among the strongest risk factors for esophageal adenocarcinoma. Although the incidence of GERD and Barrett esophagus have increased modestly over the past 30 years,[29,30] this alone cannot account for the 7-fold increased frequency of esophageal adenocarcinoma. Obesity, which has increased substantially, might contribute to Barrett cancers by promoting GERD, and obesity is a risk factor for Barrett esophagus even in the absence of GERD.[31] *Helicobacter pylori* infection can cause gastritis that decreases gastric acid secretion, protecting the esophagus from acid reflux and its complications.[32] The declining rates of *H pylori* infection in Western countries might be contributing to Barrett cancers.[33] Increased dietary nitrate in green leafy vegetables resulting from the widespread use of nitrate-based fertilizers in Western countries following World War II also has been proposed as a risk factor for esophageal cancer.[34]

Cancer Risk and Interventions to Prevent Cancer

Although the incidence of esophageal adenocarcinoma has increased, the estimated cancer risk for patients like Mr K with non-

Table. Comparison of Guidelines on the Management of Barrett Esophagus Published by US Medical Societies

			ACG[a]			
	AGA,[20] 2011	ASGE,[12] 2012	Barrett Esophagus,[11] 2008	GERD,[1] 2013	SSAT,[21] 2005	ACP,[22] 2012
Who to screen for Barrett esophagus	Patients with multiple risk factors for EA[b]	Patients with multiple risk factors for EA[b,c]	Selective populations at higher risk[d]	Patients with GERD at high risk based on epidemiological profile[b]	Patients who require long-term medical therapy for GERD	Men aged >50 y with chronic GERD symptoms (>5 y) and additional risk factors for EA[b]
Recommendation for subsequent screening if first endoscopic screening is negative for Barrett esophagus	NA	Recommend no further endoscopic screening	NA	Repeat endoscopy after 8 wk of proton pump inhibitor therapy if LA grade C or D esophagitis present; otherwise repeat endoscopy not recommended unless new symptoms develop	NA	Recommend no further endoscopic screening
Endoscopic surveillance recommended	Yes	Yes, with qualifications[e]	Yes	Yes	Yes	"May be indicated"
Repeat surveillance endoscopy recommended within 1 y of initial diagnosis of nondysplastic Barrett esophagus	NA	Not recommended	Yes	NA	NA	NA[f]
Surveillance interval for nondysplastic Barrett esophagus	3-5 y	3-5 y	3 y	"According to guidelines"	2 y	3-5 y
Surveillance interval for low-grade dysplasia	6-12 mo[g]	Repeat endoscopy within 6 mo to confirm, then annually[g]	Repeat endoscopy within 6 mo to confirm, then annually until no dysplasia ×2	NA	Annually	NA
Surveillance interval for high-grade dysplasia	Surveillance every 3 mo in the absence of eradication therapy[h]	Surveillance offered only to patients unfit or unwilling to undergo operative or ablative therapy	Surveillance every 3 mo or intervention based on results and patient	NA	Intervention recommended rather than surveillance	NA
Recommendation on how to treat underlying GERD	Same as for patients without Barrett esophagus[i]	NA	Same as for patients without Barrett esophagus[i]	Same as for patients without Barrett esophagus[i]	Same as for patients without Barrett esophagus[i]	NA
Preferred management for high-grade dysplasia	Endoscopic eradication therapy[j]	Endoscopic eradication therapy with endoscopic mucosal resection and/or radiofrequency ablation	Should be individualized with options of surgery, surveillance, endoscopic eradication therapy	NA	Esophageal resection[k]	NA

Abbreviations: ACG, American College of Gastroenterology; ACP, American College of Physicians; AGA, American Gastroenterological Association; ASGE, American Society for Gastrointestinal Endoscopy; EA, esophageal adenocarcinoma; GERD, gastroesophageal reflux disease; LA, Los Angeles classification for reflux esophagitis; NA, not specifically addressed; SSAT, Society for Surgery of the Alimentary Tract.

[a] The ACG has 2 different guidelines (1 on the diagnosis, surveillance, and therapy of Barrett esophagus and 1 on the diagnosis and management of GERD) that address screening and surveillance for Barrett esophagus.

[b] Risk factors for esophageal adenocarcinoma include age ≥50 years, male sex, white race, chronic GERD, hiatal hernia, elevated body mass index, intra-abdominal body fat distribution, nocturnal reflux symptoms, and tobacco use.

[c] The ASGE guideline specifies that "patients should be informed that there is insufficient evidence to affirm that [screening] prevents cancer or prolongs life."

[d] The ACG guideline does not give a specific recommendation for screening but states that "the use of screening in selective populations at higher risk remains to be established and therefore should be individualized."

[e] The ASGE guideline states "We suggest that if patients with nondysplastic Barrett's esophagus are enrolled in an EGD [esophagogastroduodenoscopy] surveillance program, a surveillance EGD should be performed no more frequently than every 3 to 5 years."

[f] The ACP guideline does not specifically address the issue of a 1-year endoscopy but does state that "surveillance examinations should occur at intervals no more frequently than 3 to 5 years."

[g] The guideline indicates that endoscopic eradication is also a valid option for management of low-grade dysplasia.

[h] The AGA guideline recommends endoscopic eradication therapy rather than surveillance for patients with high-grade dysplasia. Surveillance is recommended only in the absence of eradication therapy.

[i] Medications or surgery are used with the goal of eliminating GERD symptoms and healing reflux esophagitis.

[j] Endoscopic eradication therapy includes endoscopic mucosal resection of visible mucosal irregularities and ablation of the remaining Barrett metaplasia. Although the guideline recommends endoscopic ablation with photodynamic therapy or radiofrequency ablation, radiofrequency ablation now is generally considered the ablation procedure of choice.

[k] The SSAT guideline states that endoscopic eradication techniques "should be considered experimental at this time … reserved for patients with high grade dysplasia who pose significant operative risks."

dysplastic Barrett esophagus has decreased. In the 1990s, the estimated risk of cancer in nondysplastic Barrett esophagus was 1% per year.[35] This estimate was exaggerated because of publication bias.[36] More recent estimates place the risk at 0.12% to 0.33% per year.[37-40]

Indirect evidence suggest that proton pump inhibitors (PPIs) might help prevent carcinogenesis in Barrett esophagus.[41-45] Mr K, who has taken PPIs for more than a decade, is concerned about their potential risks (**Box 1**).[66] Antireflux surgery, which obviates the risks of PPIs, has been proposed as a better treatment for preventing can-

Box 1. Proposed Risks of Long-term PPI Therapy

Carcinogenesis[a]

Elevated gastrin levels[46]

Gastrin can stimulate proliferation in Barrett mucosa and in the stomach.[47]

Bacterial colonization of the stomach[48]

Bacteria deconjugate bile acids.[49]

Bacteria convert dietary nitrates into carcinogenic N-nitroso compounds.[50]

Accelerated gastric atrophy in patients infected with *Helicobacter pylori*[51]

Atrophy results in gastric intestinal metaplasia, which predisposes to cancer.

Infections

Decreased gastric acid to kill ingested bacteria[52]

Anti-inflammatory effects of PPIs that are independent of their antisecretory effects[53]

Reports of

Increased risk of enteric infections[54]

Increased risk of pneumonia[55]

Increased risk of *Clostridium difficile* colitis[56]

Increased risk of small bowel bacterial overgrowth[57]

Increased risk of spontaneous bacterial peritonitis in cirrhosis[58]

Malabsorption and Metabolism

Decreased absorption of vitamin B_{12}, iron, calcium

Reports of

Increased risk of bone fractures[59]

Increased risk of iron deficiency[60]

Increased risk of hypomagnesemia[61]

Miscellaneous

Reports of

Interstitial nephritis[62]

Microscopic colitis[63]

Decreased efficacy of clopidogrel[64]

Increased risk of food allergy[65]

Abbreviation: PPI, proton pump inhibitor.

[a] No direct evidence has confirmed an increased risk of cancer development due to PPI therapy.

Box 2 . Arguments for and Against Endoscopic Surveillance for Patients With Barrett Esophagus

Against

No randomized clinical trial has shown efficacy in preventing deaths due to esophageal cancer.

Some observational and computer model studies show no reasonable benefit for patients in surveillance programs.[76-78]

Endoscopy has medical risks.

A diagnosis of Barrett esophagus has adverse consequences (eg, anxiety, decreased quality of life, higher life insurance costs).[79,80]

Endoscopy is expensive.

The large majority of patients derive no benefit from surveillance.

For

No randomized clinical trial to establish efficacy will be available in the foreseeable future.

Some observational and computer model studies show reasonable benefit for patients in surveillance programs.[81-84]

The medical risks of elective endoscopy are minimal, and no study has found decreased survival for patients in surveillance programs.[85]

The adverse consequences are far less serious than missing the opportunity to cure esophageal cancer.

Some computer models show reasonable cost-benefit for surveillance in extending life-years.[82-84]

For some patients, surveillance can be lifesaving.

cer in Barrett esophagus because unlike PPIs, fundoplication controls the reflux of bile (which also might contribute to carcinogenesis in Barrett metaplasia).[67] Some uncontrolled trials have shown that patients with Barrett esophagus whose GERD is treated with fundoplication develop less dysplasia and cancer than those treated medically.[68,69] However, antireflux surgery has serious complications, including dysphagia, gas bloat syndrome, diarrhea, and, rarely, death.[70] Furthermore, high-quality studies find no significant differences in cancer incidence between medically and surgically treated patients with GERD and Barrett esophagus.[71-75]

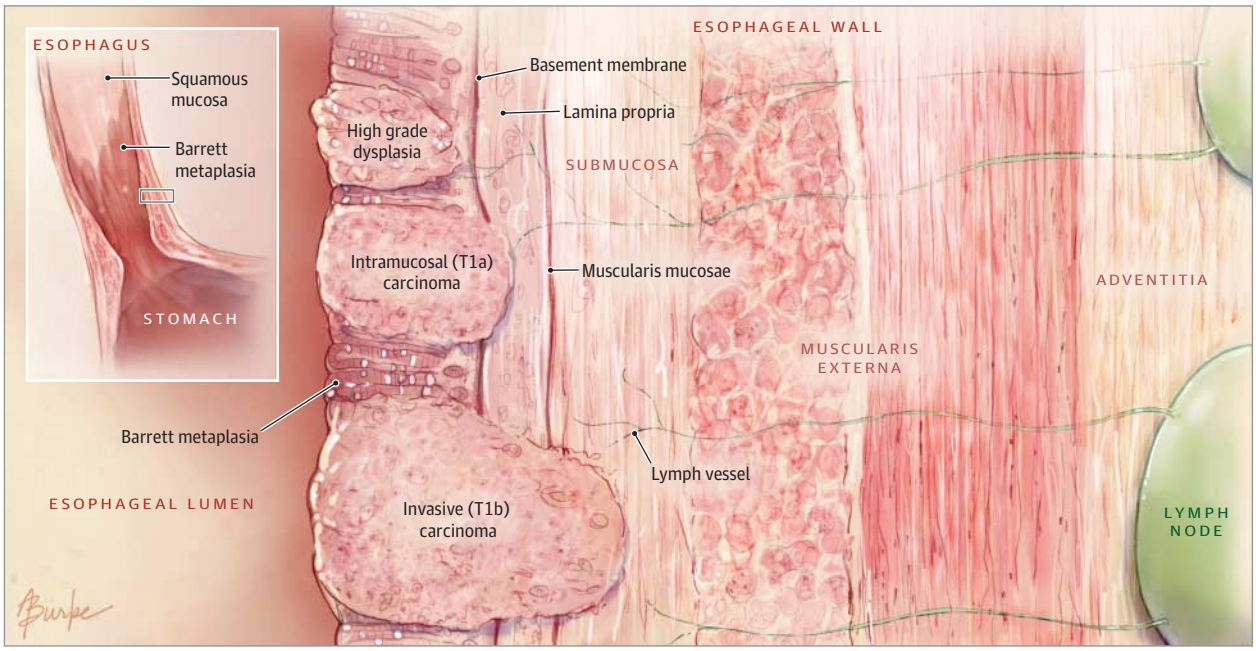
Medical societies agree that therapy (with medication or surgery) is indicated to treat GERD symptoms and to heal reflux esophagitis in patients with Barrett esophagus (Table). The guidelines generally assume that most patients take PPIs but do not endorse the prescription of antireflux surgery or PPIs in unusually high doses solely for cancer prevention. The guidelines do not specifically address the issue of whether patients without GERD symptoms or reflux esophagitis should be treated with PPIs.

Endoscopic surveillance for dysplasia in Barrett esophagus is a widely practiced but unproven cancer prevention strategy (**Box 2**).[85] Medical society guidelines generally endorse regular endoscopic surveillance (Table). Surveillance intervals recommended in these guidelines are based on computer modeling studies (Box 2) and expert opinion. Patients like Mr K, without dysplasia, are recommended to undergo endoscopy every 3 to 5 years.[11,12,20,22] Nonsteroidal anti-inflammatory drugs (NSAIDs) can exert antitumor effects through the inhibition of cyclooxygenase 2 and through actions independent of cyclooxygenase inhibition. Indirect evidence suggests that NSAID use might decrease the risk of esophageal adenocarcinoma.[2] NSAIDs can have dangerous adverse effects, however, and presently, the use of NSAIDs solely for chemoprevention in Barrett esophagus is discouraged.[20]

Dysplasia and Endoscopic Eradication Therapy

Cancers develop in Barrett metaplasia through a sequence of genetic and epigenetic alterations activating oncogenes and silencing tumor suppressor genes, resulting in cellular growth advantage and other physiologic abnormalities.[86] These same DNA alterations can cause the histological changes of dysplasia. Dysplasia has

Figure 3. Schematic of the Esophageal Wall and Grading of Esophageal Neoplasms



Endoscopic eradication therapy cannot cure tumors that have metastasized to lymph nodes. Endoscopic eradication therapy is recommended for patients with mucosal neoplasms (high-grade dysplasia and intramucosal carcinoma), for whom the risk of lymph node metastases is only 1% to 2%. For invasive tumors that breach the muscularis mucosae to enter the submucosa, the risk of lymph node metastases is higher than 10% and endoscopic therapy generally is not recommended.

numerous shortcomings as a biomarker, but despite a decades-long search for a better one, dysplasia remains the most useful clinical biomarker for malignant potential in Barrett esophagus.[2]

High-grade dysplasia in Barrett esophagus is associated with a 6% per year incidence of cancer,[2] justifying intervention.[20] Traditionally, management of patients with high-grade dysplasia involved choosing between esophagectomy and intensive endoscopic surveillance. Recently, high-quality studies proved the utility of endoscopic eradication therapy. The American Gastroenterological Association (AGA) and American Society for Gastrointestinal Endoscopy (ASGE) now recommend endoscopic eradication therapy rather than surveillance for patients with confirmed high-grade dysplasia in Barrett esophagus (Table).[12,20]

Endoscopic eradication therapy removes and/or ablates all of the metaplastic and dysplastic Barrett mucosa. Unlike esophagectomy, endoscopic therapy cannot cure cancers with lymph node metastases (**Figure 3**). For neoplasms confined to the esophageal mucosa (ie, high-grade dysplasia and intramucosal carcinoma), the risk of lymph node metastases is only 1% to 2%.[87] Therefore, endoscopic eradication therapy is appropriate. For tumors with submucosal invasion, the risk of lymph node involvement exceeds 10% and endoscopic treatment generally is not recommended.[88] Consequently, accurate tumor (T) staging is crucial for determining the appropriate therapy for early neoplasms in Barrett esophagus.

Endoscopic mucosal resection (EMR), an important component of endoscopic eradication therapy, uses a diathermy snare or endoscopic knife to remove a segment of esophageal mucosa with submucosa. Although EMR was initially developed as a therapeutic technique to remove mucosal tumors, it is now recognized as a valuable modality for T staging early Barrett neoplasms. Computed tomography and endoscopic ultrasonography are not as effective as EMR for such staging. There is an excellent correlation between preoperative EMR T staging of early Barrett neoplasms and postoperative T staging from examination of esophagectomy specimens.[89] Consequently, nodular lesions in Barrett esophagus are removed by EMR for T staging prior to performing endoscopic ablation.[2] If the EMR specimen shows submucosal invasion, then further endoscopic therapy is not advised. Treatments intended to cure adenocarcinomas with submucosal invasion generally involve a combination of chemoradiation therapy and surgery.[90]

Endoscopic ablation techniques use thermal or photochemical energy to destroy Barrett metaplasia. After ablation, patients receive PPIs to heal the injured mucosa with squamous epithelium rather than with the regeneration of Barrett metaplasia. The preferred ablation technique uses a radiofrequency generator to inflict a thermal injury.[91] Radiofrequency ablation (RFA) is performed using a balloon catheter system inflicting a circumferential mucosal injury or using a smaller, paddle-shaped device to destroy localized segments of metaplasia.

In a multicenter sham-controlled trial of RFA, 127 patients with dysplasia in Barrett esophagus (64 with low-grade, 63 with high-grade) were randomized to receive either RFA (ablation group) or a sham endoscopic procedure (control group).[92] At 1 year, intention-to-treat analyses revealed complete eradication of low-grade dysplasia in 90.5% of patients in the ablation group compared with 22.7% of those in the control group ($P<.001$). Similarly, complete eradication of high-grade dysplasia was found in 81.0% of patients in the ablation group compared with 19.0% of those in the control group ($P<.001$). Complete eradication of intestinal metaplasia was

found in 77.4% of all patients in the ablation group compared with 2.3% of those in the control group (*P*<.001). In addition, patients in the ablation group had less progression in their degree of neoplasia (3.6% vs 16.3%; *P*=.03) and fewer cancers noted 1 year later (1.2% vs 9.3%; *P*=.045). Serious complications occurred in 6 (7%) of the 84 patients who received ablation, including 1 upper gastrointestinal hemorrhage and 5 esophageal strictures.

In one report, complete neoplasia eradication was achieved in 97% of 349 patients undergoing endoscopic therapies for mucosal cancer in Barrett esophagus.[93] During a mean follow-up of 64 months, metachronous neoplasms were discovered in 21%. A retrospectively identified major risk factor for these metachronous lesions was failure to eradicate the residual, nonneoplastic Barrett epithelium. Thus, it is now recommended that all of the Barrett mucosa, not just the apparent neoplastic foci, be eradicated during endoscopic treatment.[2,20]

Controversy exists regarding the management of low-grade dysplasia because there are contradictory data about its natural history and poor agreement among pathologists regarding the diagnosis. In a Dutch study in which pathology slides for 147 patients who had low-grade dysplasia diagnosed at community hospitals were reviewed by 2 expert pathologists, the experts confirmed the diagnosis in only 15% of cases.[94] When the diagnosis was downgraded to "no dysplasia" or "indefinite for dysplasia," neoplastic development was unusual. But when low-grade dysplasia was confirmed by the experts, the cumulative risk of neoplastic progression was 85% at 109 months. In a recent US study of 210 patients with low-grade dysplasia followed up for a mean of 6.2 years, the annual rate of progression was only 0.4.%, and consensus among the pathologists regarding the diagnosis of low-grade dysplasia was not associated with neoplastic progression.[95] Both the AGA and ASGE recommend RFA as a therapeutic option for treating selected patients with confirmed low-grade dysplasia in Barrett esophagus (Table).

What Does the Future Hold?

The role of endoscopic ablation for nondysplastic Barrett esophagus needs resolution. Proponents argue that Barrett metaplasia can be neoplastic even without obvious dysplasia, that the efficacy of endoscopic surveillance as a cancer prevention strategy is questionable, and that the safety and efficacy of RFA already have been established in high-quality studies on the treatment of dysplasia.[96] Some even have proposed that the current practice of limiting RFA only to Barrett esophagus with dysplasia would be like limiting polypectomy only to colon polyps that are large or clearly malignant.[97]

Before endoscopic ablation is routinely recommended for nondysplastic Barrett esophagus, a number of issues need resolution. The frequency and importance of "buried metaplastic glands" is unclear. If all of the Barrett metaplasia is not destroyed by ablation, then the partially ablated mucosa might heal with an overlying layer of new (neo)squamous epithelium. This buries metaplastic glands with malignant potential in the lamina propria, where they are hidden from the endoscopist. Cancers developing in buried glands after the ablation of dysplastic Barrett esophagus have been reported.[98] Although early reports suggested that buried glands occurred infrequently after RFA, more recent studies using optical coherence tomography found metaplastic glands present in the lamina propria of most patients with Barrett esophagus both before and after RFA.[99]

The durability of the neosquamous epithelium that replaces the ablated Barrett metaplasia is unknown. Early reports suggested that Barrett metaplasia recurred infrequently after RFA. A recent study of 47 patients with complete eradication of Barrett metaplasia by RFA found that 15 (32%) had Barrett metaplasia detected on subsequent endoscopies performed during a follow-up period of 5 to 38 months.[100] Radiofrequency ablation generally requires several endoscopic procedures to achieve complete eradication of Barrett metaplasia, entailing substantial expense and inconvenience. Radiofrequency ablation has a complication rate that is low but not trivial, and the efficacy of RFA in reducing the already low rate of cancer development in nondysplastic Barrett esophagus is not established. Since the frequency and importance of buried glands and recurrent Barrett metaplasia remains unclear, RFA does not eliminate the need for endoscopic surveillance. For all of these reasons, the AGA recommends against endoscopic eradication therapy for the general population of patients with Barrett esophagus without dysplasia.[2,20]

Recommendations for Mr K

I recommend that Mr K continue the PPI therapy that has controlled his symptoms and endoscopic signs of GERD for many years. I would not recommend that the dose of PPI be increased or that other antisecretory medications be added with the intent of reducing esophageal acid exposure even further. I also would not recommend performing esophageal pH monitoring to document that his antisecretory medication has eliminated esophageal acid exposure or to titrate the dose of that medication. In addition, I would not recommend an antireflux operation with the expectation that this surgery would be more effective than PPI therapy for preventing cancer. With a number of endoscopic surveillance procedures showing no dysplasia in Barrett esophagus, I estimate Mr K's risk of developing esophageal adenocarcinoma at approximately 0.25% per year. I recommend that he have regular endoscopic surveillance performed at intervals of every 3 to 5 years, as suggested by medical societies, provided that esophageal biopsy specimens continue to show no evidence of dysplasia. Finally, I do not recommend prophylactic endoscopic ablation of Mr K's nondysplastic Barrett metaplasia at this time.

Questions and Discussion

QUESTION What are your thoughts on using NSAIDs for chemoprophylaxis in Barrett esophagus?

DR SPECHLER There is substantial evidence to suggest that aspirin and other NSAIDs protect against cancer in Barrett esophagus. NSAIDs decrease proliferation and increase apoptosis in esophageal cancer cells and, in animal models of GERD, NSAIDs decrease the development of Barrett esophagus and cancer.[101,102] Epidemiological and observational studies also have found that NSAID use is associated with a decreased risk of esophageal cancer.[103,104] It is not clear that this cancer-preventive benefit outweighs the consider-

able risks of these medications, however, and the AGA presently recommends against the use of NSAIDs solely for cancer prevention in Barrett esophagus. Interestingly, cardiovascular deaths are more common than deaths due to esophageal adenocarcinoma in patients with Barrett esophagus; therefore, the AGA recommends that these patients should have screening to identify cardiovascular risk factors for which aspirin therapy is indicated.

QUESTION This patient had 2 surveillance endoscopies within 6 months, yet the guidelines that you discussed recommend surveillance at intervals of 3 to 5 years. As a primary care physician, I struggle with this issue that endoscopy seems to be performed at intervals far shorter than those suggested in the guidelines.

DR SPECHLER Your point is well taken. In some cases, there might be good reason to perform surveillance at intervals shorter than those recommended in the guidelines. For example, technical or anesthesia issues during an endoscopy might prevent adequate biopsy sampling of the Barrett esophagus. Those cases should be exceptions rather than the rule, however, and it is clear that some endoscopists perform surveillance more often than recommended without good justification. Although the gastrointestinal medicine societies all have similar guidelines on Barrett surveillance, there are some differences regarding surveillance intervals. For example, the American College of Gastroenterology's current guideline recommends that repeat endoscopy should be performed within 1 year of the first diagnosis of nondysplastic Barrett esophagus, whereas the latest guideline from the ASGE specifically discourages this practice.

QUESTION Would you comment on the use of histamine 2 receptor blockers for patients with Barrett esophagus?

DR SPECHLER In general, GERD in patients with Barrett esophagus is managed the same as GERD in patients without Barrett esophagus. The histamine 2 receptor antagonists (H_2RAs) can be useful for controlling some GERD symptoms, especially those that are mild and intermittent. However, H_2RAs are not effective for healing erosive esophagitis, and tachyphylaxis to their antisecretory effects develops quickly when H_2RAs are taken regularly. Patients who have Barrett with erosive esophagitis should be treated with PPIs or, occasionally, antireflux surgery, and there is little role for H_2RAs in those cases. For patients who have Barrett esophagus with nonerosive reflux disease, it might be possible to achieve adequate symptom control with H_2RAs alone. As I discussed, however, there is considerable indirect evidence that PPIs protect against Barrett cancers, and many experts recommend PPIs for all patients with Barrett esophagus, even those without GERD symptoms and endoscopic signs. For patients taking PPIs, there is little benefit in adding an H_2RA. After a discussion of the risks with my patients with Barrett esophagus, I usually recommend that they take PPIs and, therefore, rarely prescribe H_2RAs for those patients.

ARTICLE INFORMATION

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