Barrett's Esophagus

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Norman Rupert Barrett

This is to acknowledge that Dr. Spechler has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Spechler will be discussing off-label uses of proton pump inhibitors in his presentation.

Biographical Information

Stuart Jon Spechler, M.D. is Chief of the Division of Gastroenterology at the VA North Texas Healthcare System, Professor of Medicine, holder of the Berta M. and Cecil O. Patterson Chair in Gastroenterology, and Co-Director (along with Dr. Rhonda Souza) of the Esophageal Diseases Center at The University of Texas Southwestern Medical Center at Dallas. Before coming to Dallas in 1997, Dr. Spechler was Director of the Center for Swallowing Disorders at the Beth Israel Deaconess Medical Center and Harvard Medical School. Dr. Spechler's clinical and translational research has focused primarily on disorders of the esophagus, especially gastroesophageal reflux disease and its complications including Barrett's esophagus and esophageal adenocarcinoma. He described the condition known as "short-segment Barrett's esophagus" in 1994, and he has chaired three VA Cooperative Studies on gastroesophageal reflux disease. Dr. Spechler has published more than 300 scientific reports, editorials, review articles, and book chapters on esophageal disorders. He has served on the editorial boards of numerous journals including Gastroenterology, Gut, Alimentary Pharmacology and Therapeutics, and Diseases of the Esophagus. He is the lead author of the American Gastroenterological Association's latest technical review and medical position statement on the management of Barrett's esophagus.

Purpose and Overview

The purpose of this presentation is to provide physicians a state-of-the-art review on the pathogenesis, epidemiology, diagnosis and treatment of Barrett's esophagus. Areas of exceptional controversy are highlighted including international disagreements on diagnostic criteria for Barrett's esophagus, screening and surveillance practices, and endoscopic eradication therapy for dysplastic and non-dysplastic Barrett's esophagus.

Educational Objectives

1. Identify the diagnostic criteria for Barrett's esophagus.
2. Recognize key epidemiological features of Barrett's esophagus.
3. Understand the controversies surrounding screening and surveillance programs for Barrett's esophagus.
4. Comprehend the principles of endoscopic eradication therapy.
5. Formulate a management strategy for patients who have Barrett's esophagus with and without dysplasia.

Barrett's esophagus is named for Norman Rupert Barrett, an Australian-born surgeon who drew attention to the condition that now bears his name in a report published in the British Journal of Surgery in 1950.[1] Barrett's esophagus now is defined as the condition in which a metaplastic columnar mucosa predisposed to develop adenocarcinoma replaces an esophageal squamous mucosa that has been damaged by gastroesophageal reflux disease (GERD).[2] The frequency of esophageal adenocarcinoma has increased more than seven-fold over the past four decades in the United States[3,4] (Figure 1) and, presently, it is estimated that 5.6% of adult Americans are at risk for this tumor because they have Barrett's esophagus.[5]

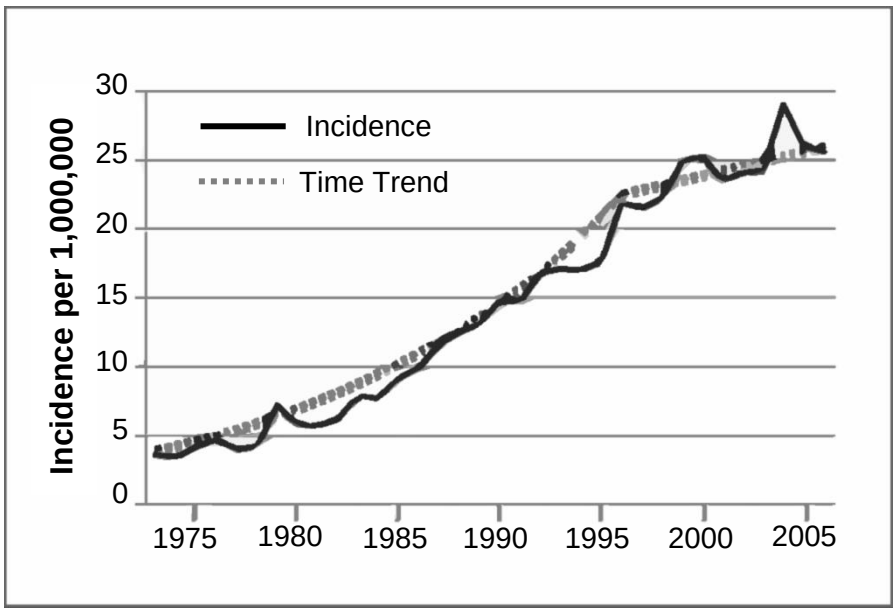

Figure 1. Incidence of esophageal adenocarcinoma in the United States (from reference 3).

Pathogenesis

Barrett's esophagus results from metaplasia, the process in which one adult cell type replaces another in response to chronic tissue injury.[6] With chronic esophageal injury from GERD, Barrett's metaplasia develops when columnar cells replace reflux-damaged esophageal squamous cells. Presumably, these mucus-secreting columnar cells are more resistant to injury by refluxed gastric juice than the native esophageal squamous cells.

It is not clear which cells give rise to Barrett's metaplasia, but a number of hypotheses have been proposed. It is possible that GERD induces alterations in the expression of key developmental transcription factors that cause mature esophageal squamous cells to change into columnar cells (a process called transdifferentiation), or that cause immature esophageal progenitor cells to undergo columnar rather than squamous differentiation (a process called transcommitment).[6,7] In a rat model of reflux esophagitis, Barrett's metaplasia appears to develop from bone marrow stem cells that enter the blood and settle in the reflux-damaged esophagus.[8] Recent studies in mouse models have suggested that Barrett's metaplasia might result from the upward migration of stem cells from the proximal stomach (the gastric cardia),[9] or from the proximal expansion of a nest of residual, embryonic-type cells that are located at the gastro-esophageal junction (GEJ).[10]

Recent studies from the laboratories of Drs. David Wang and Rhonda Souza on esophageal Hedgehog (Hh) signaling have identified interesting mechanisms that might underlie the pathogenesis of Barrett's esophagus.[7,11] Hh signaling is active in the columnar-lined embryonic esophagus, inactive in the squamous-lined adult esophagus, and reactivated in

Barrett's columnar metaplasia. Overexpression of Sonic hedgehog (Shh) in mouse esophageal squamous epithelium causes the epithelial cells to assume a columnar phenotype.[7] By microarray analysis, Dr. Wang found higher expression of the transcription factor Foxa2 in embryonic (columnar-lined) mouse esophagus than in the postnatal (squamous-lined) mouse esophagus.[11] He used conditionally-activated Shh transgenic mouse esophageal epithelium and Shh knockout embryos to establish that Foxa2 is a Hh target gene in the esophagus. In patients, he found FOXA2 expression in Barrett's metaplasia, but not in esophageal squamous epithelium. In human esophageal squamous cell lines, he showed that Hh signaling upregulated FOXA2 to cause expression of MUC2 (an intestinal mucin found in Barrett's esophagus) and AGR2 (a protein involved in MUC2 processing). These studies demonstrate that Hh signaling in esophageal squamous epithelial cells can induce the expression of genes that determine an intestinal phenotype, an observation supporting either transdifferentiation or transcommitment in the development of Barrett's metaplasia.

Diagnosis

The diagnosis of Barrett's esophagus requires both an endoscopy demonstrating that there is a columnar-lined esophagus, and an esophageal biopsy specimen confirming the presence of columnar metaplasia.[2] Endoscopically, the GEJ is identified as the most proximal extent of the gastric folds, and columnar mucosa has a characteristic salmon-pink color and coarse texture that is unlike the pale, glossy appearance of esophageal squamous mucosa (Figure 2). The endoscopist measures the extent of columnar-lined esophagus to determine whether the patient has long-segment or short-segment Barrett's esophagus (arbitrarily defined as ≥3 cm or <3 cm of esophageal columnar metaplasia, respectively).[12] However, there is international disagreement on the histologic type of columnar mucosa that establishes a diagnosis of Barrett's esophagus.

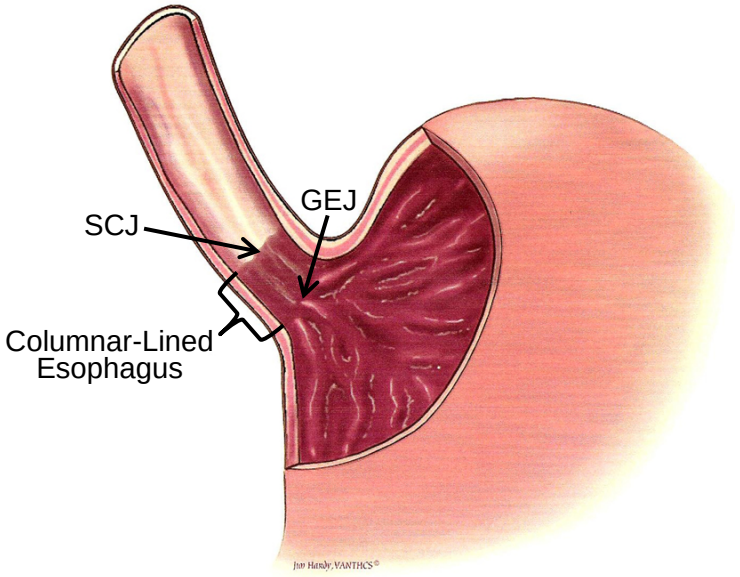

Figure 2. The squamo-columnar junction (SCJ) is recognized as the line formed by the juxtaposition of pale squamous mucosa and pink columnar mucosa. The gastroesophageal junction (GEJ) is identified as the most proximal extent of the gastric folds. When the SCJ is located proximal to the GEJ, the region between the two landmarks is a columnar-lined segment of esophagus.

American gastroenterology societies require that esophageal biopsy specimens show intestinal metaplasia, which is a well-established risk factor for adenocarcinoma, for a definitive diagnosis of Barrett's esophagus (Figure 3).[13-15] Intestinal metaplasia contains mucus-secreting

goblet cells. Some other societies, including the British Society of Gastroenterology, also accept esophageal biopsies showing cardiac mucosa (Figure 4), which contains mucus-secreting columnar cells but no goblet cells, as diagnostic for Barrett's esophagus.[16] Traditionally, cardiac mucosa has been considered the normal lining of the gastric cardia. Despite its lack of goblet cells, however, cardiac mucosa can exhibit intestinal-type histochemical features and DNA content abnormalities,[17,18] and appears to be a GERD-induced metaplasia in some, if not all cases.[19] Unlike intestinal metaplasia, however, it is not clear that cardiac mucosa is an important risk factor for adenocarcinoma.[20,21] Thus, the major issue underlying the international disagreement on histological criteria for Barrett's esophagus is whether the condition should be defined solely as a histological curiosity (a mucosal metaplasia irrespective of its clinical importance) or as a medical condition (a mucosal metaplasia that predisposes to cancer).

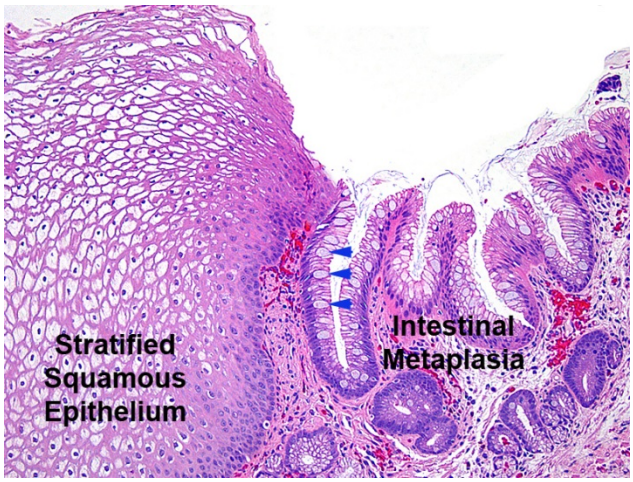

Figure 3. Photomicrograph of a biopsy taken at the squamo-columnar junction showing stratified squamous epithelium adjoining intestinal metaplasia. The arrowheads indicate goblet cells. (Photomicrograph from Reference 2).

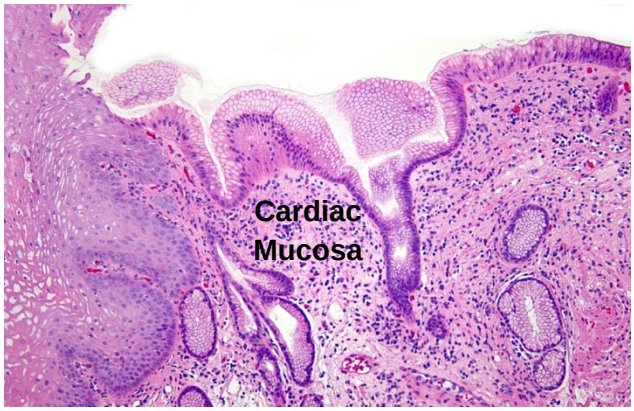

Figure 4. Photomicrograph of a biopsy taken at the squamo-columnar junction showing stratified squamous epithelium adjoining cardiac mucosa, which is comprised almost exclusively of mucus-secreting gastric foveolar-type cells. Photomicrograph courtesy of Dr. Robert Genta.

Epidemiology

Proposed risk factors for Barrett's esophagus and its adenocarcinoma are listed in the table below. Barrett's esophagus typically is discovered in older white patients during

endoscopies performed for the evaluation of GERD symptoms. Often, however, Barrett's esophagus is found serendipitously during endoscopies performed for conditions unrelated to GERD. Barrett's esophagus is more common in men than in women, uncommon in Blacks and Asians, and rare in children.[22,23] Long-segment Barrett's esophagus is strongly associated with chronic heartburn, hiatal hernia and reflux esophagitis, but short-segment Barrett's esophagus has no strong association with these conditions. Obesity that has a predominantly intra-abdominal fat distribution might contribute to the development of Barrett's metaplasia by promoting GERD, and might contribute to the malignant progression of Barrett's metaplasia by increasing the production of pro-proliferative hormones such as leptin and insulin-like growth factors.[24,25] Cigarette smoking is also a risk factor for Barrett's esophagus and its cancer, and there is a familial form of Barrett's esophagus that accounts for 7% to 11% of all cases.[26] Factors that might protect against Barrett's esophagus include the use of non-steroidal anti-inflammatory drugs, gastric infection with *Helicobacter pylori* (which might protect the esophagus from GERD by causing a gastritis that decreases gastric acid production), and consumption of a diet high in fruits and vegetables.

Proposed Risk Factors for Barrett's Esophagus and Esophageal Adenocarcinoma

	Risk Factor For BE	Risk Factor For EAC
Older Age	Yes	Yes
White Ethnicity	Yes	Yes
Male Sex	Yes	Yes
Chronic Heartburn	Yes	Yes
Age <30 Years at Onset of GERD Symptoms	Yes	
Hiatal Hernia	Yes	Yes
Erosive Esophagitis	Yes	Yes
Obesity with Intra-Abdominal Fat Distribution	Yes	Yes
Metabolic Syndrome	Yes	Yes
Tobacco Use	Yes	Yes
Family History of GERD, BE, EAC	Yes	Yes
Obstructive Sleep Apnea	Yes	
Birth Weight Small for Gestational Age	Yes	
Pre-Term Birth		Yes
Consumption of Red and Processed Meat		Yes
Human Papillomavirus Infection		Yes

BE=Barrett's esophagus, EAC=Esophageal adenocarcinoma, GERD=Gastroesophageal reflux disease

The reasons underlying the dramatic rise in the incidence of adenocarcinoma are not clear, and no single risk factor yet identified can account for it. Multiple factors appear to be contributing including an increased frequency of GERD, Barrett's esophagus, and obesity along with a decreased frequency of infection by *H. pylori* in the general population of Western countries.[27-29] One interesting hypothesis suggests that the rising incidence of esophageal adenocarcinoma might be due to increased intake of dietary nitrate, most of which comes from green, leafy vegetables.[30] Ingested nitrate is absorbed in the small intestine, concentrated in salivary glands, and secreted in saliva. In the mouth, bacteria reduce the salivary nitrate (NO_3^-) to nitrite (NO_2^-), which is swallowed. When the swallowed nitrite encounters acid in gastric juice, it is converted rapidly to nitric oxide, a toxic molecule. In patients with GERD, nitrite often encounters refluxed gastric acid in the distal esophagus, and studies have shown that nitric oxide generated from dietary nitrate can reach potentially genotoxic concentrations at the

GEJ.[30] After World War II, Western countries sharply increased the use of nitrate-based fertilizers, which conceivably could be contributing to the post-war rise in the frequency of esophageal adenocarcinoma.

Ironically, during the past few decades while the incidence of esophageal adenocarcinoma has been rising so dramatically, the estimated risk of this cancer for patients with non-dysplastic Barrett's esophagus has declined substantially. Older studies suggested that those patients developed cancer at rates as high as 2.9% per year, but many of those older studies were small and suffered from publication bias.[31] Recent large, higher-quality studies suggest that the risk of esophageal adenocarcinoma for the general population of patients with non-dysplastic Barrett's esophagus is only between 0.12% and 0.33% per year.[32-35] However, a number of factors influence cancer risk for an individual patient. Men with Barrett's esophagus develop cancer approximately twice as often as women,[34] the risk varies with the extent of Barrett's metaplasia,[36] the risk is especially high in certain familial forms of Barrett's esophagus,[37] and the risk appears to decrease as follow-up endoscopies find no progression to dysplasia.[38]

Screening and Surveillance for Barrett's Esophagus

To prevent deaths from esophageal adenocarcinoma, medical societies have recommended that certain patients with GERD symptoms should have endoscopic screening for Barrett's esophagus, and that Barrett's patients so identified should have regular endoscopic surveillance to detect curable neoplasia (usually in the form of dysplasia).[2] Unfortunately, there is no proof that this strategy is effective. Observational studies, which are not definitive, have shown that patients with Barrett's cancers diagnosed by surveillance endoscopy tend to have earlier stage tumors and longer survival than those whose tumors are discovered when they cause symptoms such as dysphagia and weight loss.[39,40] Computer modeling studies have concluded that, under certain conditions, screening and surveillance can be cost-effective, but such studies are based on numerous questionable assumptions and cannot be considered definitive.[41,42] In addition to these uncertainties regarding efficacy for cancer prevention, there are a number of potentially adverse consequences of endoscopic screening and surveillance. Endoscopic procedures are expensive, and they have a small risk of serious acute complications such as aspiration, bleeding and perforation. These endoscopies might identify innocuous lesions that lead to hazardous, invasive therapies. Also, a diagnosis of Barrett's esophagus can cause psychological stress, can have a negative impact on quality of life, and can result in higher premiums for health and life insurance.[14]

A number of medical societies recently have published guidelines on screening and surveillance for Barrett's esophagus. The American College of Physicians (ACP) now recommends screening endoscopy for men and women who have heartburn with alarm symptoms, which include dysphagia, bleeding, anemia, weight loss, and recurrent vomiting.[43] The ACP also recommends endoscopy for men and women with typical GERD symptoms that persist despite a therapeutic trial of 4 to 8 weeks of twice-daily proton pump inhibitor (PPI) therapy. The American College of Gastroenterology has suggested that endoscopy is not required for the evaluation of typical GERD symptoms, but that endoscopy is recommended in the presence of alarm symptoms and for screening of patients at high risk for complications (i.e. Barrett's esophagus).[44] The American Gastroenterological Association (AGA) also recommends against endoscopic screening for the general population of patients with GERD.[14] Rather, they recommend screening in patients with multiple risk factors associated with esophageal adenocarcinoma, which include chronic GERD, hiatal hernia, age above 50, male gender, white race, elevated BMI, and intra-abdominal body fat distribution. If the screening examination does not reveal Barrett's esophagus, the ACP and the American Society for Gastrointestinal Endoscopy now recommend no further endoscopic screening for the

condition.[15,43] For patients found to have non-dysplastic Barrett's metaplasia, the societies recommend regular endoscopic surveillance at intervals of 3 to 5 years.[2]

The prerequisite for GERD symptoms to initiate screening limits the potential benefits of the practice because patients with short-segment Barrett's esophagus often have no GERD symptoms, and approximately 40% of patients with esophageal adenocarcinomas describe no history of GERD symptoms.[45] Furthermore, fewer than 10% of patients found to have an esophageal adenocarcinoma have a prior diagnosis of Barrett's esophagus, suggesting that current screening practices have not been effective.[46,47] For patients found to have Barrett's esophagus by screening, a recent case-control study has raised serious doubts regarding the efficacy of surveillance for cancer prevention.[48] This study compared the frequency of surveillance endoscopy within a 3-year period for 38 cases (patients known to have Barrett's esophagus who subsequently died of esophageal adenocarcinoma) with that of 101 living, control patients with Barrett's esophagus matched for age, sex, and duration of follow-up. If surveillance were an effective cancer prevention strategy, then one would expect the controls (who did not die of cancer) to have had surveillance significantly more often than the cases. However, the cases and controls had nearly identical frequencies of endoscopic surveillance (55% of cases, 60% of controls), and surveillance was not associated with a decreased risk of death from esophageal cancer (adjusted odds ratio 0.99; 95% CI 0.36-2.75). Although this study provides no support for surveillance, the relatively wide 95% confidence interval does not exclude the possibility of a beneficial effect. Nevertheless, since screening is performed to identify Barrett's patients to enroll in surveillance programs and, as this report suggests, surveillance has little benefit, then the practice of screening might be based on a fundamentally flawed premise.

There have been numerous studies exploring methods of risk stratification to identify those Barrett's patients who might benefit most from surveillance or other interventions. These methods have included a number of advanced endoscopic imaging techniques such as dye-based chromoendoscopy, optical and digital chromoendoscopy, autofluorescence endoscopy, and confocal laser endomicroscopy.[49] Abnormalities in p53 expression and cellular DNA content abnormalities in esophageal biopsy specimens have been associated with neoplastic progression.[50,51] Cytogenetic abnormalities detected by fluorescence in-situ hybridization (FISH), and biomarker panels that identify multiple abnormalities in DNA content, gene expression, and DNA methylation have been used to predict cancer risk, as have risk stratification models that incorporate a variety of clinical, histological, and molecular features.[51-55] Unfortunately, none of these modalities has been validated sufficiently to justify its routine application in clinical practice.

Treatment of GERD in Patients with Barrett's Esophagus

Refluxed gastric acid can cause chronic inflammation, double-strand DNA breaks, and increased proliferation, effects that would be expected to promote carcinogenesis in Barrett's metaplasia.[56,57] This suggests that aggressive acid suppressive therapy with proton pump inhibitors (PPIs) might prevent cancer in Barrett's esophagus, and indirect evidence supports this notion. In a recent cohort study of 540 Barrett's patients followed for a median of 5.2 years, for example, PPI use was associated with a 75% reduction in the risk of neoplastic progression.[58] Presently, PPIs are used in Barrett's patients just as they are in patients who have GERD without Barrett's metaplasia - 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 is highly controversial. I feel 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. Before prescribing this treatment, the patient should be informed of the potential risks as well as the benefits of chronic PPI therapy.

Bile acids also can cause double-strand DNA breaks while simultaneously activating NF-κB proteins in Barrett's metaplasia (Figure 5).[59] This NF-κB activation can prevent the apoptosis that otherwise might be induced by DNA damage, thus enabling the survival of cells with potentially carcinogenic DNA damage. PPIs reduce acid reflux, but do not prevent bile reflux. Anti-reflux surgery can prevent reflux of all gastric contents (acid and bile), but high-quality studies suggest that surgery is not more effective than PPI therapy in preventing cancer.[56] Thus, anti-reflux surgery is not advised solely for cancer protection in Barrett's esophagus.

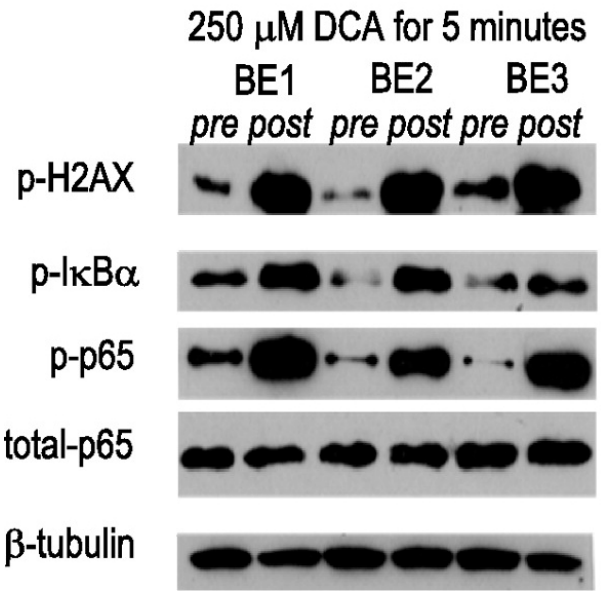

Figure 5. Esophageal perfusion with deoxycholic acid (DCA) increases phosphorylation of H2AX (a marker of DNA damage) and of IκBα and p65 (NF-κB proteins) in Barrett's epithelial cells in vivo. Western blots demonstrate expression of these phosphoproteins before and after esophageal perfusion with DCA in biopsy specimens of Barrett's metaplasia taken from 3 representative patients (BE1, BE2, and BE3) with Barrett's esophagus during endoscopic examinations. 250 μM DCA increased expression of all three phosphoproteins (from reference 59).

Endoscopic Eradication Therapy for Dysplasia in Barrett's Esophagus

Carcinogenesis in Barrett's metaplasia involves a series of genetic and epigenetic alterations that activate oncogenes, silence tumor suppressor genes, and free cells from their normal growth controls. Before the cells become frankly malignant, the DNA abnormalities that convey growth advantages and autonomy from normal growth controls can cause histological changes in the esophageal mucosa that pathologists recognize as dysplasia.[60] Unfortunately, dysplasia is not an ideal biomarker for malignant potential. Dysplasia can be patchy and easily missed during routine biopsy sampling of Barrett's esophagus, and the severity of dysplasia is graded by subjective criteria. This frequently results in interobserver disagreement among pathologists, particularly when they attempt to distinguish low-grade dysplastic changes from reactive changes. Despite these substantial shortcomings, however, dysplasia remains the basis for clinical decision making in Barrett's esophagus.[14] Medical societies recommend that a diagnosis of dysplasia always should be confirmed by another expert pathologist, especially if invasive therapies are being considered.[2]

High-grade dysplasia progresses to cancer in Barrett's esophagus at a rate considered high enough to warrant intervention.[14] A recent meta-analysis estimated that rate at

approximately 6% per year,[61] but considerably higher rates have been described in therapeutic trials and observational studies.[62,63] Esophagectomy had been the traditional treatment for high-grade dysplasia, but endoscopic resection and ablation techniques now are available to eradicate dysplasia with far less morbidity than esophagectomy and with virtually no mortality.[64] Endoscopic mucosal resection (EMR) uses a diathermic snare to resect a segment of esophageal mucosa and underlying submucosa, and the resected specimen is submitted to the pathologist for evaluation. EMR initially was developed as a therapy to remove neoplastic tissue, but it soon became appreciated that EMR is the most accurate diagnostic procedure available for T-staging early neoplasia in Barrett's esophagus.[65] Unlike EMR, endoscopic ablation techniques deliver thermal or photochemical energy to destroy esophageal mucosa and, therefore, provide no tissue specimen for pathology evaluation. After EMR or ablation of Barrett's metaplasia, patients are treated with PPIs to prevent acid reflux and enable the eradicated mucosa to be re-epithelialized by squamous epithelium. Early studies on EMR and ablation for dysplasia directed these treatments only at the dysplastic areas, and ignored the non-neoplastic Barrett's metaplasia. Subsequent studies suggested that the frequency of metachronous neoplasia could be reduced if all Barrett's metaplasia was eradicated, not just the dysplastic areas.[66] Today, the goal of endoscopic therapy is to eradicate both the dysplastic and non-dysplastic Barrett's metaplasia completely.[64] The term "endoscopic eradication therapy" describes the use of EMR and/or endoscopic ablation to accomplish that goal.

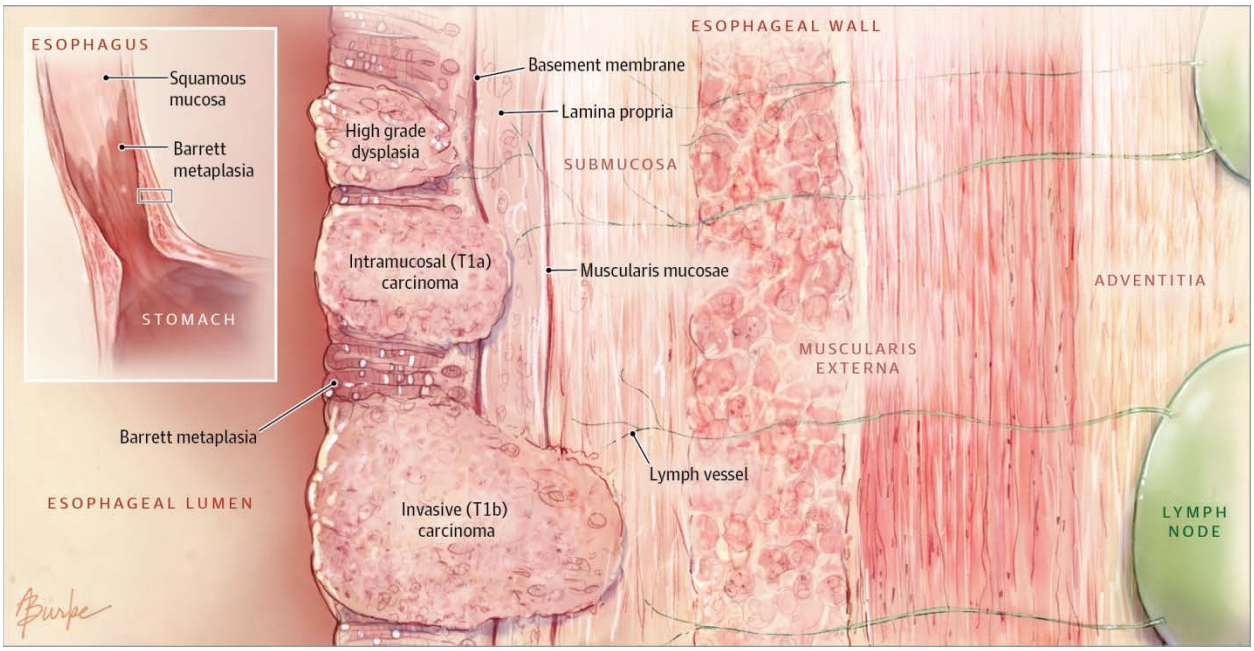

Figure 6. Schematic showing the esophageal wall and grading of esophageal neoplasms. Since endoscopic eradication therapy cannot cure tumors that have metastasized to lymph nodes, this therapy is recommended only for patients with mucosal neoplasms (high-grade dysplasia and intramucosal carcinoma), for whom the risk of lymph node metastases is only 1% to 2% (from Reference 2).

Endoscopic eradication therapy cannot cure neoplasms that have metastasized to regional lymph nodes. Such metastases are present in 1-2% of patients with mucosal neoplasms (high-grade dysplasia or intramucosal adenocarcinoma) in Barrett's esophagus, but in >20% of patients with invasive carcinomas that extend deep into the submucosa (Figure 6).[67] Consequently, endoscopic therapy generally is used only to treat mucosal neoplasms. There have been randomized, controlled trials showing that endoscopic eradication of dysplasia in Barrett's esophagus with photodynamic therapy (PDT) or radiofrequency ablation (RFA, which

uses radiofrequency energy to destroy the mucosa) significantly decreases the rate of progression to cancer.[62,63] Although these techniques have not been compared head-to-head in a prospective trial, RFA appears to achieve superior rates of dysplasia eradication and cancer prevention with easier administration and far fewer side effects than PDT. Consequently, RFA presently is the ablative procedure of choice for dysplasia in Barrett's esophagus. RFA generally requires several endoscopic sessions to achieve complete eradication of metaplasia, and the most common serious side effect is esophageal stricture, which develops in approximately 5% of cases.[68]

Low-Grade Dysplasia

The management of low-grade dysplasia in Barrett's esophagus is a particularly contentious issue, largely because investigations on its natural history have yielded disparate results. The aforementioned difficulties in establishing the diagnosis of low-grade dysplasia confound comparisons among studies. In one study of 147 patients with low-grade dysplasia diagnosed at community hospitals, for example, expert pathologists confirmed the diagnosis in only 15% of cases.[69] There was considerable progression of neoplasia in the patients with confirmed low-grade dysplasia, however, with a cumulative risk of neoplastic progression of 85% at 109 months. The risk of neoplastic progression was dramatically lower in an American study of 210 patients with low-grade dysplasia followed for a mean of 6.2 years, for whom the annual rate of neoplastic progression was only 1.83%.[70]

In a recent, randomized trial of RFA *vs.* endoscopic surveillance for 136 patients with confirmed low-grade dysplasia followed for 3 years, RFA reduced the risk of progression to high-grade dysplasia or adenocarcinoma by 25% (1.5% for RFA *vs.* 26.5% for surveillance; 95% CI 14.1%-35.9%, P<.001).[71] Noting these results, the study's monitoring board decided to terminate the study early on the grounds that RFA was clearly superior to surveillance for preventing neoplastic progression of low-grade dysplasia, and because they felt that there was potential for patient safety issues if the trial continued. Although this might appear to be a "slam-dunk" for RFA, a number of issues raised in this study suggest otherwise. First, RFA was inconvenient and expensive, requiring a median of 3 ablation sessions per study patient to eradicate all Barrett's metaplasia, and 12% of patients so treated developed esophageal strictures that required dilation. In addition, 28% of patients in the surveillance group had no dysplasia detectable on follow-up. It is not clear whether this represents true regression of dysplasia or biopsy sampling error, but this observation suggests that approximately one-quarter of the apparent successes of RFA might be attributable to this same phenomenon. Finally, no patient in the surveillance group developed an unresectable tumor, and none died of cancer. Therefore, it is not clear that RFA improved patient outcomes. For patients with low-grade dysplasia confirmed by at least two expert pathologists, gastroenterology societies presently recommend either a program of endoscopic surveillance at intervals of every 6 to 12 months, or endoscopic ablation therapy.[2]

RFA for Non-Dysplastic Barrett's Metaplasia

Noting the success of RFA in preventing the neoplastic progression of dysplasia, some have proposed that RFA should be offered to all patients with Barrett's esophagus, dysplastic and non-dysplastic. [72] They argue that endoscopic surveillance does not work, and that RFA is a safe and effective technique for eradicating Barrett's metaplasia. However, it should be noted that the efficacy of RFA for preventing cancer in non-dysplastic Barrett's esophagus has not been established, and at least two observations suggest that the cancer risk might not be eliminated, even for patients in whom RFA has eradicated all endoscopically-visible Barrett's metaplasia. First is the observation that patients with Barrett's esophagus frequently have metaplastic glands in the lamina propria underneath esophageal squamous epithelium, a condition called subsquamous intestinal metaplasia (SSIM) (Figure 7). Another reason to

suspect that RFA might not eliminate cancer risk is the observation that Barrett's metaplasia can recur over time.

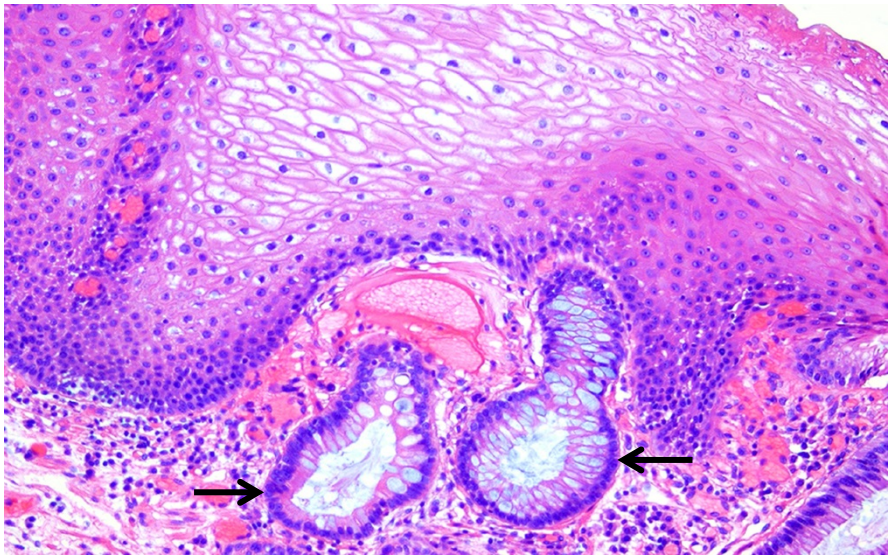

Figure 2. Subsquamous intestinal metaplasia (SSIM). Note the metaplastic, intestinal-type glands (arrows) in the lamina propria underneath the squamous epithelium. Photomicrograph courtesy of Dr. Robert Genta.

SSIM is not visible to the endoscopist because it is hidden by an overlying layer of squamous epithelium, which also might protect the SSIM from destruction by RFA. SSIM used to be called "buried glands" because the condition was assumed to result from an ablation procedure that: 1) did not destroy all of the Barrett's glands and 2) healed with an overlying layer of neo-squamous epithelium that buried the incompletely-ablated glands in the lamina propria.[73] However, more recent evidence suggests that foci of SSIM are present near the squamo-Barrett's junction in most patients both before and after RFA. One study using optical coherence tomography (a microscopic imaging technique that samples an area some 60 times larger than a standard endoscopic biopsy forceps) found foci of SSIM near the squamo-Barrett's junction in 13 of 18 patients (72%) before RFA, and in 10 of 16 patients (63%) after Barrett's metaplasia appeared to be completely eradicated by RFA.[74] In another study of 110 patients who had widespread EMR (EMR performed with the intent of removing all Barrett's metaplasia) to treat dysplasia or intramucosal carcinoma, 98% had SSIM found in at least one EMR specimen that crossed the junction between squamous and Barrett's mucosa, and the SSIM was neoplastic in 60% of those specimens.[75] The rate at which SSIM progresses to malignancy is not known, but cancers have been found in this condition.[76]

A number of studies have documented that Barrett's metaplasia can recur over time. Early studies suggested that the post-RFA recurrence rate was low, but more recent studies have documented recurrences of Barrett's metaplasia, sometimes with dysplasia and cancer, in up to 33% of patients at 2 years.[77] A recent report from the United Kingdom has described a "real-world" experience with EMR and RFA for the treatment of 335 patients with mucosal neoplasia in Barrett's esophagus.[78] There was a one-year protocol during which the patients received a mean of 2.5 RFA treatments aimed at eradicating all Barrett's metaplasia. At the end of that year, 81% had complete eradication of dysplasia, but only 62% had complete eradication of Barrett's metaplasia. 3% had progressed to invasive cancer, and 9% had developed esophageal strictures that required dilation, with one esophageal perforation. Furthermore, a Kaplan-Meier analysis of patients who had achieved complete eradication revealed a

recurrence rate of approximately 60% by 48 months. The long-term cancer risk associated with recurrent Barrett's metaplasia after RFA is not known.

With the frequency and importance of SSIM and recurrent Barrett's metaplasia yet undetermined, the efficacy of RFA for long-term cancer prevention in non-dysplastic Barrett's esophagus is not clear. Consequently, even after apparently successful, complete eradication of metaplasia by RFA, regular surveillance endoscopy still seems advisable. One study used a decision analytic Markov model to explore the cost-effectiveness of RFA for 50 year-old men with Barrett's esophagus, and concluded that RFA was cost-effective for those with dysplasia, but not for those with non-dysplastic Barrett's metaplasia.[79] At this time, I do not recommend RFA for the general population of patients with non-dysplastic Barrett's esophagus.

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