Barrett esophagus: epidemiology, pathogenesis, diagnosis, and management

Introduction

Barrett esophagus is a change in the normal squamous epithelium of the esophagus to specialized columnar-lined epithelium. Barrett esophagus is of interest to surgeons in that it is associated with gastroesophageal reflux disease (GERD) and is a risk factor for esophageal adenocarcinoma. Beyond that, nearly every other aspect of Barrett esophagus has been an area of controversy among surgeons, gastroenterologists, pathologists, and epidemiologists. The purpose of this monograph is to review the information available on the epidemiology, pathogenesis, diagnosis, and management of Barrett esophagus.

Epidemiology and risk factors

Prevalence

It is difficult to truly know the overall prevalence and incidence of Barrett esophagus. This is due to the fact that many individuals with Barrett metaplasia are asymptomatic and, therefore, will never be evaluated for the presence of Barrett esophagus. Also, different populations are at risk and, therefore, prevalence may vary from location to location. The best estimate of the population prevalence of Barrett esophagus is 1.6% of the general population.\(^1\) It is generally considered that the prevalence of Barrett esophagus has increased and this increase has occurred in parallel to the frequency of esophageal adenocarcinoma in men, which has quadrupled in the past few years. The cause is unknown, but it might be linked to an increase in incidence of gastroesophageal reflux, with its association with Barrett esophagus.\(^2\) In a study conducted in Sweden with the objective of validating the Gastrointestinal Symptom Rating Scale, a random selection of 1000 individuals underwent endoscopy.\(^3\) Patients with symptoms of reflux had an overall prevalence of Barrett esophagus of 2.3%, whereas the prevalence in asymptomatic individuals was 1.4%. Patients with symptoms seem to have a higher incidence of Barrett esophagus, with 1 study identifying 13.2% of symptomatic patients with Barrett metaplasia.\(^4\) Paradoxically, patients with short-segment Barrett esophagus had more frequent and intense symptoms than did those with long-segment Barrett esophagus.\(^5\) Among patients undergoing endoscopy for any reason, Barrett esophagus was rare in children and tended to become more prevalent with age.\(^6\) Nevertheless, in a series of patients from a tertiary care clinic, approximately 25% of patients with Barrett esophagus were younger than 50 years.\(^7\) Men and Caucasians appear to have a higher prevalence of Barrett esophagus than other groups.\(^6\)
The “typical” patient with Barrett esophagus is the middle-age, white male, overweight, with several years history of GERD-related symptoms.

**Incidence**

The incidence of Barrett esophagus is even more difficult to estimate than prevalence. As with prevalence, there are few studies that have taken a general population and subjected them to repeat endoscopic examination solely for the purpose of determining the incidence of Barrett esophagus. Therefore, most studies have relied on follow-up of patients who have manifestations of GERD or calculations based on estimates. The Kalixanda study of a general Swedish population initially found endoscopic or histologic diagnosis of GERD and nonerosive reflux disease (NERD), of these patients 9.7% of patients with NERD progressed to erosive esophagitis, and 1.8% to Barrett esophagus. In patients initially with erosive esophagitis, 13.3% progress to a more severe grade and 8.9% to Barrett esophagus. The overall incidence of Barrett esophagus was 9.9 per 1000 person years. Erosive esophagitis was independently associated with progression to Barrett esophagus (relative risk ratio 5.2; 95% confidence interval [CI] 1.2-22.9). Patients with Los Angeles (LA) C/D esophagitis were at greatest risk for developing Barrett esophagus at 2 years: 5.8% vs 1.4% for LA A/B and 0.5% for NERD. A 5-year follow-up of the ProGERD study showed 5.9% of patients with NERD, 12.1% of patients with LA A/B, and 19.7% of patients with LA C/D progressed to Barrett esophagus. In another study from California, with a mean follow-up of 3.4 ± 2.2 years, none of 412 patients with nonerosive GERD and 5 of 103 (4.9%) patients with erosive GERD developed Barrett esophagus.

Another study highlights the issue that the incidence of Barrett esophagus also depends on how this condition is diagnosed. Specifically, Barrett esophagus can be diagnosed by endoscopic white-light visual inspection, enhanced endoscopic visual inspection (such as chromoendoscopy or high-definition endoscopy), or endoscopic biopsy with either regular or “jumbo” biopsy forceps, with either spot or systematic biopsy protocols. Therefore, the incidence can be calculated based on the rate for a given population, rate for a set number of endoscopies, and the rate for a set number of endoscopies with biopsies. Using this model, Coleman and colleagues calculated the annual Barrett esophagus incidence rates in Northern Ireland. They found that the annual incidence from 2002-2005 was 62.0 per 100,000 persons, 3.5 per 100 upper endoscopies, and 35.4 per 100 endoscopic biopsies.

The incidence of Barrett esophagus appears to be increasing. The previously mentioned study of Coleman and colleagues documented an increase in incidence of 159% from the time period of 1993-1997 to 2002-2005. This elevation exceeded corresponding increases in rates of endoscopies and biopsies. The incidence of Barrett esophagus increased most markedly in patients younger than 60 years, and most notable in men younger than 40 years. Two studies from the Netherlands also documented a similar increased incidence; the increases appeared to be independent of increasing use of endoscopy. Although these studies were from European countries, the factors driving this increasing incidence are also present in North America.

**Risk factors**

**Demographics**

Barrett esophagus is not uniformly distributed among the general population and, as such, there are risk factors for its development. Risk factors for the development of Barrett esophagus include GERD, obesity, male gender, Caucasian ethnicity, and increasing age. Smoking might increase the risk of Barrett esophagus, whereas *Helicobacter pylori* infection, and specific “healthy” dietary factors may lower the risk. Similarly, patients with intestinal metaplasia of the gastroesophageal junction had substantially lower risk of progression to cancer. Patients with Barrett esophagus were older, heavier, had more severe reflux symptoms, and had a
higher prevalence of advanced neoplasia compared with patients with intestinal metaplasia of the gastroesophageal junction.\textsuperscript{17}

**Obesity**

The rapid increase in the incidence of esophageal adenocarcinoma in the United States from approximately 4.2 per 100,000 to 4.8 per 100,000,\textsuperscript{18} an increase of approximately 14%, indicates that there are nongenetic factors (eg, behavioral and environmental) which are playing a larger role in the pathogenesis of this malignancy. There is clearly an association between esophageal adenocarcinoma, GERD, and Barrett esophagus.

The epidemic of obesity is the single most important factor implicated in the pathogenesis of GERD and esophageal adenocarcinoma. In a retrospective study among Veterans Affairs patients in 2005, Stein and colleagues\textsuperscript{19} concluded that a higher body mass index increases the risk of GERD symptoms and erosive esophagitis, independent of demographic features and dietary intake. Crowell and colleagues\textsuperscript{20} reported on a 5-fold increase in the likelihood of demonstrating an abnormal total acid exposure time among obese patients using a 48-hour pH study.

Several factors predispose obese individuals to GERD. Abdominal or visceral fat appears to increase the risk for both GERD (erosive esophagitis) and adenocarcinoma.\textsuperscript{21} Adipokines are proposed to play a central role in the genesis of reflux and possibly adenocarcinoma.\textsuperscript{15} In 2012, Nelsen and colleagues\textsuperscript{22} collected data from 50 patients with Barrett esophagus and matched controls. Computed tomography scan imaging was used to determine the gastroesophageal junction fat area, visceral fat area, and abdominal circumference. Visceral and gastroesophageal junction fat were significantly greater among patients with Barrett esophagus (odds ratio [OR] 6.0; 95% CI 1.3-27.7) independent of body mass index. Additionally, the same factors were statistically associated with increased esophageal inflammation compared with those without these factors ($P = 0.02$).

**Behavior and lifestyle**

Certain behaviors increase the risk of developing Barrett esophagus. Subjects with Barrett esophagus were significantly more likely to have ever smoked cigarettes than the population-based controls (OR 1.67; 95% CI 1.04-2.67) or GERD controls (OR 1.61; 95% CI 1.33-1.96). Increasing pack-year history of smoking increased the risk of Barrett esophagus. There was a synergism of smoking with GERD as a risk factor for Barrett esophagus; the attributable proportion of disease among individuals who ever smoked and had heartburn or regurgitation was 0.39 (95% CI 0.25-0.52).\textsuperscript{23}

**Diet**

Diet is also suspected as a risk factor for the development of Barrett esophagus. In a case-control study of the Kaiser Permanente Northern California population, higher intake of omega-3 fatty acids (OR 0.46; 95% CI 0.22-0.97), polyunsaturated fat, total fiber (OR 0.34; 95% CI 0.15-0.76), and fiber from fruits and vegetables (OR 0.47; 95% CI 0.25-0.88) were associated with Barrett esophagus. Higher meat intakes were associated with a lower risk of long-segment Barrett esophagus (OR 0.25; 95% CI 0.09-0.72). Conversely, higher trans-fat intakes were associated with increased risk of Barrett esophagus (OR 1.11; 95% CI 1.03-1.21). Total fat intake, barbecued foods, and fiber intake from sources other than fruits and vegetables were not associated with Barrett esophagus.\textsuperscript{24}

**Socioeconomic status**

Interestingly, in a study from Germany, Barrett esophagus and adenocarcinoma tend to occur slightly more often in subjects with higher income.\textsuperscript{25} The causes for this are unclear, although the lifestyle choices may influence this trend.

Ethnic origin also appears to influence Barrett esophagus. Mimicking GERD, Barrett esophagus appears less prevalent among persons of Asian, Carribean, African, Middle Eastern,
and South American origin. In a study of University of Florida, Jacksonville's endoscopic database, African Americans with Barrett esophagus are less likely than whites to have long-segment disease (12% vs 26%) and less likely to have dysplasia (0% vs 7%).

Progression to adenocarcinoma

Although it is clear that Barrett esophagus increases the risk of esophageal adenocarcinoma, quantifying the exact risk has been difficult. First, it must be remembered that 40% of patients with esophageal adenocarcinoma do not report a history of GERD symptoms. Whether this represents true lack of reflux or just “silent” reflux is unclear. Certainly, there are a substantial proportion of patients with Barrett esophagus that do not manifest any symptoms of reflux. In fact, those patients with longer segments of Barrett esophagus are more likely to be asymptomatic than patients with shorter segments of Barrett esophagus. Therefore, by necessity, estimation of the incidence of progression to adenocarcinoma must begin with patients with known Barrett esophagus.

Risk factors

Risk factors for the progression of Barrett esophagus to adenocarcinoma are related to both histologic grade of the Barrett esophagus and nonhistologic factors. A recent systematic review set the risk as 6.3 per 1000 person years, with a 95% CI of 4.7–8.4 per 1000 persons and substantial heterogeneity of the data. Age, male gender, and Barrett metaplasia length only modestly increase the risk of progression to carcinoma.

Histology

Progression to carcinoma is dependent on the histologic grade of the dysplasia. Nondysplastic metaplasia has an incidence of progression of 3.86 per 1000 person years, whereas low-grade dysplasia (LGD) had an incidence of 7.66 per 1000 person years. The incidence of esophageal adenocarcinoma in nondysplastic Barrett esophagus is approximately 1 per 300 patients per year. The incidence in short-segment Barrett esophagus is 1 per 500 patients per year. In a Danish population-based study, the incidence of esophageal adenocarcinoma in nondysplastic Barrett esophagus was 1 per 1000 person years and in LGD it was 5.1 per 1000 person years. In patients undergoing esophagectomy for high-grade dysplasia (HGD), occult carcinoma was found in 30% of patients. However, when patients with HGD were observed, the detection rate of adenocarcinoma was 14.1 per 100 person years and a progression rate of 4.2 per 100 person years after excluding prevalent cases. The risk of prevalent esophageal adenocarcinoma (ie, identifying carcinoma with first endoscopy discovering HGD) was lower with previous surveillance, unifocal HGD, diagnosis at a university hospital, endoscopic resection, or ablation, and higher when patients were 65-75 years old. Risk factors which increase the likelihood that occult carcinoma is present in HGD include nodularity and multilevel presence of HGD.

Behavior and lifestyle

Tobacco and alcohol have been investigated in the progression of Barrett esophagus to adenocarcinoma. In patients with Barrett esophagus, current smoking increased the risk of progression to HGD and esophageal adenocarcinoma (OR 2.03; 95% CI 1.29-3.17), whereas alcohol consumption did not. Another study demonstrated that being a former smoker (OR 2.6; 95% CI 1.1-6.4), current smoker (OR 3.7; 95% CI 1.4-9.9), smoking more than 40 years (OR 4.7; 95% CI 1.7-13), and being a former alcohol user (OR 3.4; 95% CI 1.2-10) were risk factors, whereas being a current alcohol user did not increase the risk of progression.

Familial and genetic factors

Family history is associated with the risk of progression to esophageal adenocarcinoma. Multiplex familial Barrett esophagus kindreds are defined as families with 3 or more members with Barrett esophagus or esophageal adenocarcinoma. Using this definition, in familial
Barrett esophagus, the median age at diagnosis of esophageal adenocarcinoma was younger (57 vs 62 years old) and with lower body mass index.\textsuperscript{38} This group previously showed that 7.3% of individuals with Barrett esophagus, esophageal adenocarcinoma, or gastroesophageal junction carcinoma have familial Barrett esophagus (ie, at least 1 first or second degree relative). Specifically, they found that 6.2% of patients with Barrett esophagus, 9.5% of patients with esophageal adenocarcinoma, and 9.5% of patients with gastroesophageal junction adenocarcinoma have a first or second degree relative with familial Barrett esophagus.\textsuperscript{39} Therefore, although it is clear that there is a subset of Barrett-related pathology associated to family risk, this is a small minority of patients.

**Effect on life expectancy**

The American Gastroenterological Association’s (AGA) Medical Position Panel’s consensus position is that although deaths from esophageal adenocarcinoma clearly occur with increased frequency in patients with Barrett esophagus, on an actuarial basis, the effect on overall life expectancy for the individual patient is low.\textsuperscript{27} Interestingly, this same panel suggests that mortality from cardiovascular disease may increase. Therefore, a policy of seeking out and treating Barrett esophagus to specifically reduce the incidence of esophageal adenocarcinoma is not warranted. Nevertheless, there are specific groups of patients with Barrett esophagus (those with HGD) that would benefit from treatment, and others, such as those with LGD, who could possibly benefit.

**Barrett esophagus and quality of life**

Barrett esophagus affects patients’ quality of life. Patients with Barrett esophagus report a poorer quality of life. It is unclear whether this is due to anxiety about cancer or GERD symptoms.\textsuperscript{27,40} Barrett esophagus causes psychological stress in many patients and may increase financial burdens.\textsuperscript{27,40}

One study of how Barrett esophagus affected patients’ assessed patient-determined utility scores.\textsuperscript{42} In this study, a utility score of 0 was equal to death and a score of 1 equaled perfect health. Patients gave Barrett esophagus without dysplasia a utility score of 0.95, postesophagectomy with dysphagia a score of 0.92, postphotodynamic therapy with no dysphagia a score of 0.93, postphotodynamic therapy with dysphagia a score of 0.91, and intensive endoscopic surveillance a score of 0.90.\textsuperscript{41} It is interesting that the least invasive management option was given the worst score. A systematic review of quality of life studies of Barrett esophagus up to 2009 showed that whether quality of life was measured with generic, broad-based instruments, or disease- or organ-specific instruments patients with Barrett esophagus had worse quality of life scores.\textsuperscript{42} In a study of patients randomized to sham vs radiofrequency ablation (RFA) of Barrett esophagus with HGD, the majority of subjects with Barrett esophagus reported worries regarding esophageal cancer (71% RFA and 85% sham) and esophagectomy (61% RFA and 68% sham). Subjects reported depression, impaired quality of life, worry, stress, and dissatisfaction with the condition of their esophagus.\textsuperscript{43}

Therefore, in addition to the cancer risk, the presence of Barrett esophagus affects the quality of life of patients with this condition. The presence of Barrett esophagus places patients in the difficult position of their life insurance rates being increased by life insurance companies because the companies view this as possibly affecting their longevity, yet unable to get ablative treatment funded by their medical insurance companies because these companies do not recognize Barrett esophagus as a medical risk. Therefore, a patient’s quality of life is affected not only by health-related issues, but also by financial-related issues.

**Pathogenesis of Barrett esophagus**

The precise sequence of events leading to intestinal metaplasia in the esophagus has not been determined. The process of metaplastic change is rarely observed in vivo and there are no
reliable, physiological animal models. Similar to other premalignant conditions, Barrett esophagus requires both a genetic predisposition (first “hit”) coupled with environmental exposure (second “hit”). In Barrett esophagus, these metaplastic changes are most likely a form of protective mechanism in response to chronic inflammation or tissue injury.

Transdifferentiation

Transdifferentiation and altered squamous stem cell differentiation are the 2 mechanisms that best explain the presence of columnar cells with intestinal metaplasia in the distal esophagus typically lined with stratified squamous epithelium (Fig 1).

To better understand transdifferentiation, a review of esophagus embryogenesis is important. Esophageal explants from 8 fetuses (12-16 weeks of gestation) were cultured in serum-free media up to 21 days by Menard and Arsenault in 1987. Between 12 and 16 weeks of gestation, stratified columnar ciliated epithelium is present. The morphology remains unchanged for the first 5 days in culture after which vacuolization in the upper-half layer occurs, leading to a lifting off of the ciliated layer and flattening of the cells underneath. Stratified squamous epithelium replaces the stratified ciliated columnar epithelium at 20-25 weeks, a process that begins in the midesophagus and proceeds both caudad and cephalad. These findings indicate that stratified squamous epithelium may originate or transdifferentiate from the underlying stratified columnar epithelium.

The abnormal development of columnar from stratified squamous epithelium in Barrett esophagus may represent a reverse transdifferentiation from the normal “specialized” lining back to an abnormal “primitive” lining. This may be the initial step followed by identification of intestinal metaplasia in the transdifferentiated columnar epithelium. Evidence against

Fig. 1. Possible cells of origin for Barrett metaplasia. If the metaplastic process occurs by altered differentiation of a mature squamous esophageal epithelial cell (shaded cells in gray in the mucosal layer) without requiring proliferation, it is called transdifferentiation. Alternatively, the cell of origin may be an undifferentiated cell with the capacity to form multiple cell lineages: a so-called “stem cell.” These stem cells may be of tissue or bone marrow origin. The tissue-derived stem cells may be located in the basal compartment of the interpapillary layer or in the submucosal gland duct. In either case, the trigger for columnar differentiation seems to depend on surface epithelial damage from luminal factors (acid and bile acids). (From Fitzgerald.)
transdifferentiation comes from the observation that new squamous epithelium can develop after ablation treatment in which the Barrett epithelium has been completely eliminated.47

**Metaplastic columnar stem cells**

The more commonly accepted pathogenetic mechanism involves metaplastic columnar cell stem cell development from local (squamous epithelium stem cell) or bone marrow source (bone marrow–derived stem cell). The stem cell origin of Barrett esophagus can explain the persistence of Barrett esophagus and predisposition to developing adenocarcinoma.48 The proposed origins of these altered metaplastic stem cells are from 4 sites. First, they may originate from the basal cell layer of the squamous epithelium and undergo altered differentiation into metaplastic columnar stem cells.44 Second, stem cells originating from the gastroesophageal junction may proliferate in response to acid and duodenogastroesophageal reflux (DGER); this is substantiated in the mouse model.49 Third, stem cells from the neck of the esophageal submucosal glands may migrate to and proliferate in the surface of the distal esophagus after the squamous mucosa injury.50 Lastly, a bone marrow stem cell may migrate into the injured epithelium and undergo metaplastic transformation into columnar cells.50 These changes may be mediated by activation or inactivation of transcription factors and modulation of signaling pathways at the cellular level (Fig 2).48 This figure illustrates how gastroesophageal reflux can produce genetic alterations, which result in increased production of transcription factors promoting intestinal cell differentiation (metaplasia) and decreased production of transcription factors promoting squamous cell differentiation.

**Cytokines**

The role of cytokines as they relate to genetic alteration in Barrett esophagus has been described by Souza and colleagues51 in both animal and human cell line studies. In the rat model of acid-bile mucosal injury (produced by anastomosis of the duodenum to the proximal stomach), the presence of inflammatory cells and inflammatory histologic changes precede the presence of mucosal injury seen on endoscopy.51 An increase in interleukin (IL)-8 secretion from epithelial cells begins on the second day after exposure and continues until the fifth day. Utilizing experimental designs with media from the exposed cells, the following observations were made: there was increased migration of T cells and neutrophils and introduction of anti-IL-8 antibodies into the media reduced neutrophil migration. These findings suggest that IL-8 is involved in the proinflammatory response.51

An important gene involved in Barrett esophagus pathogenesis is CDX2. Huo and colleagues52 found CDX2 messenger RNA (mRNA) in 7 of 10 esophageal squamous biopsy specimens from patients with Barrett esophagus, but found only 1 of 10 such specimens from patients who had GERD without Barrett esophagus.52 They concluded that acid and bile salts induce CDX2 mRNA and protein expression in esophageal squamous cells from patients with Barrett esophagus, but not from GERD patients without Barrett esophagus.51

Likewise, unconjugated bile acids potently stimulated COX-2 expression and increased intracellular reactive oxygen species, whereas reactive oxygen species scavengers blocked COX-2 induction and the signaling pathways involved in immortalized Barrett esophagus and esophageal adenocarcinoma cells in an in vivo model.53 The proposed roles of cytokines are represented in Figure 3.15 In brief, mucosal damage after exposure to duodenogastric reflux is mediated by cytokine release from the exposed epithelium and not due directly to injury from exposure to the refluxate.

The latest cytokine to be implicated in the pathogenesis of Barrett esophagus and progression to adenocarcinoma is IL-18.54 A group from Dublin reported that the pattern of associations of IL-18 polymorphisms in patients with disease phenotypes (Barrett esophagus and esophageal adenocarcinoma) is quite similar, suggesting common underlying genetic pathways in both. Moreover, the distribution of these polymorphisms is similar in the control
and the reflux esophagitis group and significantly different from the disease phenotype. The authors propose that these polymorphisms could be used as genetic susceptibility biomarkers of esophageal disease (Barrett esophagus and esophageal adenocarcinoma). In an accompanying editorial, El-Omar and Jankowski note that the era of genome-wide genetic studies to look at risk for progression from Barrett esophagus to esophageal adenocarcinoma is possible in the near future. These wider range genetic studies may achieve clinical applicability after the cost of testing markedly diminishes and the technology becomes more widely available. This parallels the decrease in cost of full-genome sequencing for individual patients which initially was possible only after years of costly and labor-intensive work, but now can be accomplished at a substantially reduced cost of less than $8000 per individual.

**MicroRNA (miR)**

miRs are an endogenous class of 17-25 long noncoding RNAs that play crucial roles in gene regulation and expression. Evidence of their involvement in esophageal adenocarcinoma carcinogenesis is mounting based on differences between miR profiles between normal esophageal lining, Barrett esophagus, and esophageal adenocarcinoma. Fassan and colleagues described distinct patterns of miR expression that were characteristic for each step of progression. These consisted of upregulated levels of miR-215 and miR-182 and concomitant decrease in expression of miR-205, miR-203, and let-7c. Feber and colleagues reported that miR-99b, miR-199a_3p, and miR-199a_5p levels were expressed at higher levels among patients with lymph node metastases. These miR type increased levels were also inversely associated with the patients.
Acid and bile esophageal reflux

There are sufficient data to establish a relationship between abnormal acid exposure and Barrett esophagus. In 1994, Neumann and Cooper\textsuperscript{60} compared the pH studies between 16 patients with uncomplicated Barrett esophagus, 37 patients with reflux esophagitis, and 10 control subjects of comparable age. Barrett esophagus patients differed significantly, with respect to the percentage time the pH was less than 4 and the number of reflux episodes of greater than 5 minutes during the supine period when compared with patients with grade I reflux esophagitis, but not when compared with patients with grade II and III reflux esophagitis. In the same year, Singh and colleagues\textsuperscript{61} concluded that compared with the patients with esophagitis, patients with Barrett esophagus had lower median lower esophageal sphincter pressure (10.5 vs 17.5 mmHg; \(P = 0.013\)), longer median supine transit time (180 vs 13.5 seconds; \(P = 0.0001\)), and higher median percentage of total time with pH less than 4 (48.2 vs 8.7 and 23.2 vs 5.2; \(P < 0.0001\) for distal and proximal esophageal acid exposure, respectively). Additionally, these authors report that there is a strong correlation between the degree of acid exposure in the proximal esophagus and the length of Barrett segment. However, there is an overlap between the amount of acid exposure in patients with esophagitis compared with patients with Barrett esophagus.\textsuperscript{62}

In addition to acid, the importance of DGER was described in a recent review by Richter.\textsuperscript{63} DGER contents include bile acids, lysolecithin, and trypsin. Utilizing pH and bile acid monitoring (Bilitec 2000) in the esophagus, a significant increase in abnormal exposure in patients with complicated Barrett esophagus was shown. Esophageal exposure to both acid and DGER was the most prevalent

![Pathogenesis of Reflux Esophagitis](image)

\textsuperscript{Fig. 3.} An alternative concept for the development of reflux esophagitis. The reflux of gastric juices does not directly damage the esophagus, but rather stimulates esophageal epithelial cells to secrete chemokines that, in turn, through the recruitment of neutrophils and the release of nitric oxides (NO) and reactive oxygen species (ROS), mediate the damage of esophageal mucosa. (From Falk et al.\textsuperscript{15})
reflux pattern (100% in patients with complicated and 89% in patients with uncomplicated Barrett esophagus, 79% in patients with esophagitis, and 50% in patients without esophagitis) (Fig 4). The majority (70%-91%) of DGER episodes occurred in an acidic environment (pH < 4). Linear regression analysis found a significant correlation ($r = 0.73; P < 0.01$) between percentage time for which the pH was less than 4 and percentage time for which bilirubin absorbance level was greater than 0.14. The combination of acid and bile salt induced CDX2 mRNA and protein expression in patients with Barrett esophagus, but not from patients with GERD without Barrett esophagus. The exact mechanism by which bile acids produce mucosal damage is not certain. The most commonly accepted hypothesis suggests that bile acids go across the mucosa because of their lipophilic nature and causes disruption of the membrane structure or interfering with cellular function.

**Esophageal hyposensitivity**

The occurrence of mucosal damage without the expected corresponding severity of symptoms in patients with Barrett esophagus may be partially explained by decreased sensitivity to noxious stimuli which may lead to significant and prolonged, yet undetected exposure. In 1987, Johnson and colleagues evaluated esophageal acid sensitivity in 15 patients with Barrett esophagus and in patients with reflux esophagitis without Barrett esophagus. Patients with Barrett esophagus were less sensitive to esophageal acid perfusion than those with reflux esophagitis without Barrett esophagus (66% vs 100%; $P < 0.05$). Additionally, patients with Barrett esophagus who were acid sensitive took longer to develop pain during acid perfusion ($P < 0.05$), and overall experienced less severe heartburn symptoms ($P < 0.01$) vs those patients with reflux esophagitis. Based on diaries over a 2-week period, patients with Barrett esophagus had less frequent ($P < 0.01$) and less severe ($P < 0.01$) pain episodes.

![Fig. 4](image)

**Fig. 4.** Esophageal exposure to both acid and duodenogastroesophageal reflux was the most prevalent pattern and present in 100% of patients with complicated Barrett, 89% of patients with uncomplicated Barrett, 79% of patients with esophagitis, and 50% of patients with nonerosive esophagitis. (From Richter.)

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**References:**


64. The combination of acid and bile salt induced CDX2 mRNA and protein expression in patients with Barrett esophagus, but not from patients with GERD without Barrett esophagus.

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heartburn symptoms in those with reflux esophagitis. In 2003, Fletcher and colleagues\textsuperscript{67} reported that GERD patients with Barrett esophagus differed from GERD patients without Barrett esophagus in being less sensitive to acid (mean intensity score of 2.3 vs 4.8; \(P<0.05\)) perfusion. Over the past 5 years, advances in modalities of testing indicate that patients with Barrett esophagus may have a hyposensitivity to heat and partly to mechanical stimulation in both the normal and abnormal epithelium. This was demonstrated in a small (\(n=15\)) group of patients with Barrett esophagus. These investigators used a multimodal (mechanical, heat, and electrical) probe to provide stimulation\textsuperscript{68}.

**Genetics**

Whatever the critical mechanisms of injury leading to altered mucosal development, the basic genetic changes appear to be the driving force. Bajpai and colleagues\textsuperscript{69} demonstrated that in immortalized, nonneoplastic Barrett esophagus cell line, repeated exposure to acid and bile leads to the development of columnar epithelium (colonic phenotype). Single exposure to acid and or bile did not change cell phenotypes. However, chronic treatment for at least 2 weeks significantly enhanced (\(P<0.05\)) the expression of colonic phenotype. Bile salt at pH 4 and bile salt followed by acid (pH 4) in succession were the strongest stimulators (\(P<0.01\)) for induction of colonic phenotype cells. The current limitation in discerning these specific genetic mechanisms is the inability to identify the specific genetic code alteration(s) which can reliably predict development of Barrett esophagus or lack of a Barrett esophagus genotype.\textsuperscript{51} Increased COX-2 expression is described or associated with higher degrees of dysplasia.\textsuperscript{70} In an animal model Buttar and colleagues\textsuperscript{71} also demonstrate this increased expression of COX-2.

**Microbiome**

Other potentially significant developments include the type of esophageal microbiome. In 2009, Yang and colleagues\textsuperscript{72} reported a classification of esophageal microbiomes with the use of a bacterial ribosomal RNA gene survey into type I (dominated by genus *Streptococcus* and concentrated in the phenotypically normal esophagus) and type II (containing a greater proportion of gram-negative anerobes and microaerophiles) primarily correlated with the presence of esophagitis and Barrett esophagus). The implications of these differences are difficult to discern at this point because as the authors point out, there are no data on treatment or conversion from type II to type I leading to healing of esophagitis.

**Diagnosis**

**Definition of Barrett esophagus**

In 2012, the definition of Barrett esophagus still remained controversial, with no uniformly accepted criteria. The proximal displacement of the squamocolumnar junction is essential for the diagnosis, but there are different methodologies used to identify the gastroesophageal junction.\textsuperscript{73} The Japanese pioneered identification of the “palisade” of vessels in the lower esophagus. This, in conjunction with identification of the top of the gastric folds and the diaphragmatic pinch, constitute essential landmarks which ideally should be identified during every endoscopy procedure intended for Barrett esophagus identification, detection, or surveillance (Fig 5). In Europe and in a recent review article, the diagnosis of Barrett esophagus based on detection of any type of glandular mucosa in addition to goblet cells is advocated,\textsuperscript{40} however biopsies showing intestinal metaplasia with periodic acid-Schiff positive staining goblet cells remain the most widely used histologic criteria in the United States. The key basis for this recommendation is the increased incidence of esophageal adenocarcinoma among patients with endoscopic Barrett esophagus with intestinal metaplasia compared with patients
who have endoscopic Barrett esophagus without intestinal metaplasia.\textsuperscript{74} This must to be balanced against the high likelihood of identifying intestinal metaplasia among patients with endoscopic Barrett esophagus (another term used is columnar-lined epithelium) during follow-up endoscopies.\textsuperscript{75}

**Length of Barrett esophagus**

Another area of controversy lies in obtaining biopsies among individuals with an endoscopic Barrett segment shorter than 1 cm. Depending on the individual (genetic predisposition or personal history of dysplasia and follow-up after ablation) undergoing evaluation for possible Barrett esophagus, most experts agree that in a patient who presents for endoscopy with a history of GERD, biopsies of 1.0 cm or shorter Barrett esophagus segment are to be carefully considered (based on the negative implications of a Barrett esophagus diagnosis). A balance must be struck between the very low likelihood of adenocarcinoma in Barrett esophagus vs the possibility that adenocarcinoma can arise from short-segment Barrett esophagus (defined as a length of Barrett metaplasia of less than or equal to 3 cm). Classification of Barrett esophagus into short-segment and long-segment Barrett esophagus is helpful but difficult to reproduce and follow longitudinally.

**Prague classification**

The use of the circumferential (C) and maximum (M) (Prague) classification which is both easy to learn and reproduced accurately among endoscopists is an important development in the standardization of nomenclature for Barrett esophagus and a more accurate assessment during follow-up for Barrett esophagus. This involves identification of the C and M extent of the

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**Fig. 5.** Drawing depicting sites important to understanding endoscopic anatomy of the esophagogastric junction region. (From Boyce.\textsuperscript{73})
Barrett esophagus segment during endoscopy. Sharma and colleagues\textsuperscript{76} described this system of Barrett esophagus classification to have a very high overall reliability coefficient for rating the C and M extent of the Barrett esophagus segment above the gastroesophageal junction with a value of 0.95 and 0.94, respectively. They also describe a reliability coefficient of 0.75 for endoscopic recognition of Barrett esophagus segments longer than 1.0 cm, whereas for the segments of Barrett esophagus shorter than 1.0 cm, the reliability coefficient was 0.22. Recently, Vahabzadeh and colleagues\textsuperscript{77} demonstrated the validity of the C and M criteria for endoscopic assessment of Barrett esophagus among gastroenterology trainees regardless of the level of training. Eighteen gastroenterology trainees were assessed after a formal teaching module by an expert endoscopist, the overall intraclass correlation coefficients for assessment of the C and M extent of the endoscopic Barrett esophagus segment above the gastroesophageal junction were 0.94 (95% CI 0.89-0.98) and 0.96 (95% CI 0.94-0.98), respectively.

**Sampling**

Another factor to consider in the accurate diagnosis of Barrett esophagus is sampling error, particularly among patients with long-segment Barrett esophagus. Guidelines published in 2011\textsuperscript{40} still advocate obtaining 4 quadrant biopsies every 2 cm randomly (the so-called “Seattle protocol”). Using this protocol would lead to sampling of only 5% of the surface area with Barrett esophagus; furthermore, there is evidence that few endoscopists comply with these recommendations and take markedly fewer biopsies than suggested per cm of Barrett esophagus. In a recent publication by Abrams and colleagues\textsuperscript{78} only 51% of community gastroenterologists adhered to this guideline. The degree of compliance decreased with the increasing length of the Barrett esophagus segment. This study was based on the Caris Diagnostics pathology database.

**Endoscopic technique**

The latest consensus guideline for surveillance of Barrett esophagus by Bennett and colleagues\textsuperscript{79} now recommends the use of high-definition imaging (HDI) with targeted biopsies of every suspicious lesion plus 4 quadrant random biopsies. The use of different techniques and the availability of imaging enhancements have led to renewed enthusiasm in the area of endoscopic diagnosis of Barrett esophagus. In a recent American Society of Gastrointestinal Endoscopy Preservation and Incorporation of Valuable Endoscopic Innovations Committee statement on imaging in Barrett esophagus dated May 2012, the committee\textsuperscript{80} stated that to eliminate the need for random mucosal biopsies during the endoscopic surveillance of patients with nondysplastic Barrett esophagus, an imaging technology with targeted biopsies should have a per patient sensitivity of greater than 90% and a negative predictive value greater than 98% for detecting HGD or esophageal adenocarcinoma compared with the standard (white-light endoscopy [WLE] plus 4 quadrant biopsies). To allow for a reduction in the number of biopsies (vs random 4 quadrant biopsies), the new imaging technology should have a specificity that is at least 80%.

Intuitively, it makes sense that the amount of time spent in inspecting a segment of Barrett esophagus will correlate positively with the yield of Barrett esophagus surveillance. However, this assumption had no published supporting data until recently. Gupta and colleagues\textsuperscript{81} evaluated the effect of Barrett inspection time (BIT) on yield of surveillance among 112 patients in 5 tertiary centers. They report that patients with longer BITs were more likely to have an endoscopically suspicious lesion ($P < 0.001$). Endoscopists with a BIT greater than 1 min/cm of Barrett esophagus detected more patients with endoscopically suspicious lesions (54.2% vs 13.3%, $P = 0.04$).

Conventional or standard WLE uses the full visible wavelength range to produce a red-green-blue (RGB) image.\textsuperscript{82} Standard definition imaging is based on traditional (television)
broadcast format with images in the 4:3 (width:height) aspect ratio. The images are approximately 300,000 pixels (640-pixels wide × 480 lines in height). Recent technological advances have led to further improvements in charge-coupled device technology, resulting in smaller chips with even higher pixel counts and higher resolution. In a technology status report about high-resolution and high-magnification endoscopes, the American Society for Gastrointestinal Endoscopy Technology Assessment Committee states that the general consensus definition of an HD image or display is one with more than 650-720 lines of resolution. There are 2 types of imaging performed: progressive (p) or interlaced (i). With the “p” or progressive imaging, lines are scanned consecutively and the image is generated 60 times per second. However, with “i” or interlaced images, only every other line is scanned, and the image is created in 2 passes at 30 times per second each. As progressive (60 frames/s) scanning provides the number of images captured per second compared with interlaced (30 frames/s) scanning, progressive scanning is thought to be better for video display of fast-moving objects.83

Endoscopic technologies to enhance visualization of mucosal disease

High-resolution WLE or HDI uses charged coupled devices which can capture images with very high pixel density. The widespread use of HDI (1080 lines for horizontal resolution, vertical line resolution dependent on the monitor aspect ratio) has improved visualization of Barrett esophagus. This requires adequate processing capabilities of the video system and HDI resolution capability of the monitor and all connecting cables to allow the display of high-resolution images.

Both standard resolution and high-resolution endoscopes can magnify the images 30-50 ×. High-magnification endoscopes are equipped with an optical zoom mechanism using a movable lens in the endoscope tip. Utilizing optical zoom, a closer or a larger image can be captured while maintaining the image’s display resolution. Electronic magnification, however, simply moves the image closer on the monitor with a drop in image resolution. All 3 major endoscope manufacturers (Fujinon, Pentax, and Olympus) have zoom endoscopes available in the United States capable of high-magnification endoscopy resulting in enlargement of the image up to 150 × (combined optical and digital). Ferguson and colleagues reported no increase in the detection rate for intestinal metaplasia using magnification endoscopy-enhanced guidance for targeting biopsies. This group used an Olympus GIF-160Z magnification endoscope (up to 115 ×) and acetic acid enhancement. Magnification endoscopy is usually used in conjunction with chromoendoscopy (magnification chromoendoscopy) as noted below.

Computed virtual chromoendoscopy: There were 3 electronic image-enhancement technologies available: a narrow-band imaging (NBI) (Olympus America, Inc, Center Valley, PA), the Fujinon intelligent color enhancement system or FICE system (Fujinon, Saitama, Japan), and the Pentax iScan (Pentax Medical Co, Montvale, NJ). In 2012, the FICE system was no longer available in the United States. Switching from WLE to any of these image-enhancement modalities can be accomplished instantaneously by depressing a button in the endoscope or image processor. These imaging technologies target the mucosal vasculature of the gastrointestinal tract.

NBI, the most widely available image-enhancement technology, utilizes optical filters to narrow the bandwidth of transmitted light allowing enhanced selective imaging of deeper structures (ie, submucosal blood vessels). The NBI filter is placed between the RGB filter and the light source. It splits white light into 2 specific lights with narrowed bandwidths; blue (400 ± 430 nm) and green (530 ± 550 nm), whereas the contribution of the red light, which has a longer bandwidth and hence deeper penetration, is reduced. This allows the blue and green lights, which have more superficial penetration, to penetrate the superficial mucosal architecture, leading to enhancement of both the pit patterns and the vasculature. The insertion of the NBI filter between the RGB filter and the xenon lamp is achieved by activating a switch on the scope. The endoscopist can then alternate between WLE and NBI easily at any
time (Fig 6).\textsuperscript{85} Regular mucosal and vascular patterns suggest absence of neoplasia whereas irregularity or abnormal blood vessels or both are features of early neoplasia.\textsuperscript{86} Sharma and colleagues\textsuperscript{87} in a multinational (United States and the Netherlands), randomized, crossover trial among recognized experts in enhanced endoscopic imaging in 2012 compared HD-WLE (Olympus GIF-H180, Center Valley, PA) and NBI for the detection of intestinal metaplasia and neoplasia in patients with Barrett esophagus. Either imaging modality was used during the entire procedure for each patient. A total of 123 patients with Barrett esophagus with a mean age of 62 years, 93% males, and 97% Caucasians were enrolled. The mean circumferential extent of Barrett esophagus was 1.8 cm and the mean maximal extent was 3.6 cm. The authors reported that both HD-WLE and NBI detected intestinal metaplasia in 92% of patients (104 out of 113) with suspected Barrett esophagus. However, using NBI significantly fewer biopsies per patient were reported (3.6 vs 7.6, \textit{P} < 0.0001). Furthermore, during examination with NBI, all areas of HGD and cancer had an irregular mucosal or vascular pattern (Fig 7). Curvers and colleagues\textsuperscript{88} in 2008 reported that the yield for identifying early neoplasia based on WLE still images was 86% for all observers, 90% for experts, and 84% for nonexperts. The authors concluded that the addition of indigo carmine chromoendoscopy, acetic acid chromoendoscopy, or NBI to WLE did not improve interobserver agreement or yield identifying early neoplasia in patients with Barrett esophagus (Fig 8).

Unlike NBI (that uses optical filters), the FICE system is software driven and uses an image processing algorithm that is based on spectral estimation methods. This computerized spectral estimation technology targets the microvessels of the mucosa. This technology arithmetically processes reflected photos into virtual endoscopic images according to a set of narrowed wavelengths.\textsuperscript{89} This system has 3 modes of enhancement: (1) surface enhancement which enhances the structures through recognition of the edges; (2) contrast enhancement which enhances the depressed areas and differences in structure through the colored presentation of low density areas; and (3) tonal enhancement which enhances individual organs through modification of RGB components for each pixel. This system is no longer available in the United States as of 2012.

The Pentax iScan is an endoscopic postprocessing light filter technology that utilizes sophisticated software algorithms. This technology allows image resolution above the high-definition television standard. Detailed analysis is based on vessel (V-mode), pattern (P-mode), or surface architecture (surface enhancement-mode).\textsuperscript{90} This technique for endoscopic image enhancement is the least studied among the 3.

HDI can also be combined with chromoendoscopy to improve detection of Barrett esophagus. Curvers and colleagues\textsuperscript{91} reported a multicenter study utilizing endoscopic trimodal imaging (ETMI). The ETMI system consists of a high-resolution white-light endoscope with optical zoom
This endoscope has 2 separate monochromatic charge-coupled devices: 1 for white-light imaging and NBI and another AFI. This was compared with a standard video endoscopy (SVE) using Olympus (Q-140 and Q160) standard white-light (not high-resolution) endoscopes. Mean (± standard deviation) procedure time of SVE was 15:03 ± 6:42 minutes compared with 25:55 ± 9:33 minutes for ETMI (P < 0.001). Eighty-seven patients with Barrett esophagus underwent ETMI and SVE. No significant difference was observed in overall histologic yield between ETMI and SVE. ETMI had a significantly higher targeted yield compared with SVE because of AFI. However, the yield of targeted biopsies of ETMI was significantly inferior to the overall yield of SVE. Detailed inspection with NBI reduced the false-positive rate of high-resolution endoscopy + AFI from 71%-48% but misclassified 17% of HGD/Ca lesions as not suspicious. The authors concluded that at this stage, ETMI cannot replace random biopsies for detection of lesions or targeted biopsies for characterization of lesions in a high-risk population.

Optical coherence tomography (OCT) is a form of imaging enhancement analogous to ultrasound B-scanning providing 10 μm resolution with a depth of penetration of 1-3 mm. Unlike endoscopic ultrasound (EUS), OCT does not require a water interface or tissue contact; however, like EUS, real-time scanning is possible. After emitted light encounters tissue, there is scattering. Reflected light is then processed by the emitter to create high-resolution, cross-sectional, or linear images of surface epithelium as well as submucosal structures (using probe-based technology). Images of specialized intestinal metaplasia (SIM) were characterized by the following: (1) absence of the layered structure of normal squamous epithelium or absence of the vertical pit and crypt morphology of normal gastric mucosa, (2) disorganized architecture with inhomogeneous tissue contrast and an irregular surface, and (3) presence of large submucosal glands. The presence of 2 or more of these criteria was defined as diagnostic of SIM. When an experienced, blinded observer prospectively applied the criteria for SIM to the test set, the criteria were found to be 97% sensitive (95% CI 86%-100%) and 92% specific (95% CI 84%-97%) for SIM. The positive predictive value of these OCT criteria for SIM was 84%. This system will be commercially available in the United States with a single use through the scope-probe system beginning in 2013 (NinePoint Medical, Cambridge, MA).
Confocal autofluorescence laser endomicroscopy (CLE) involves the use of a miniaturized laser confocal microscope fitted onto the tip of a conventional videoendoscope which is capable of providing a high-resolution optically sectioned fluorescence digital images of up to a lateral resolution of 0.7 μm and up to 200 μm deep from the surface. This system is capable of visualizing cellular and subcellular structures in the epithelium. The 2 endomicroscopy systems available are: an endoscope-based system using the EC3870CILK (Pentax, Tokyo, Japan); and probe-based confocal autofluorescence laser endomicroscopy, the Cellvizio system (Mauna Kea Technologies, Paris, France). Each probe-based confocal autofluorescence laser endomicroscopy probe is expected to last 20 uses. At present, fluorescent contrast agents are used, as the natural fluorescence of the gastrointestinal mucosa is not sufficient to allow detailed microscopic imaging. Currently, the Food and Drug Administration has not approved any of the available topical or intravenous fluorescent contrast agents for CLE. The most commonly used agent is intravenous fluorescein sodium. This has been used in ophthalmology for several decades and has a very good safety profile. This group also reported an overall accuracy of 96.8% with a sensitivity of 98.1% and a specificity of 94.1% for the prediction of Barrett esophagus and an overall accuracy of 97.4% with a sensitivity of 94.1% and a specificity of 98.5% for the prediction of Barrett esophagus-associated neoplasia. This study was conducted by a group of endoscopists highly trained in CLE.

Endocytoscopy uses a probe or endoscope with ultra-high magnification capability, allowing up to 1400 × magnification and visualization of surface cellular and subcellular structures in the surface epithelium including nuclei, nucleoli, and cytoplasm. Unlike CLE, as this technique

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**Fig. 8.** Four corresponding images obtained with high-resolution white-light endoscopy (A), indigo carmine chromoendoscopy (B), acetic acid chromoendoscopy (C), and narrow-band imaging (D). This area exhibits regular mucosal and vascular patterns with normal vessels situated along the mucosal ridges. This area contained specialized intestinal metaplasia with dysplasia. (From Curvers et al.85)
utilizes the principles of light microscopy, only the most superficial epithelial layer can be visualized. Like CLE, endocytoscopy has both probe-based and endoscope-based systems.

Based on a study by Pohl and colleagues, endoscopic histology using endocytoscopy lacks sufficient image quality to currently be of assistance in identifying neoplastic areas particularly when no macroscopic (endoscopic) evidence of neoplasia is seen. Positive and negative predictive values for high-grade intestinal neoplasia or cancer were 0.29 and 0.87, respectively, for magnification 450 × and 0.44 and 0.83, respectively, for magnification 1125 ×.

The main issues with any “focus-based” technology are: (1) the long duration of examination because of the very small area which can be evaluated at any 1 time; (2) the need for image stabilization to enable good quality image capture; and (3) high cost.

Table 1 summarizes the principles, advantages, disadvantages and availability of these visualization enhancement techniques. Figure 9 illustrates the relative qualitative resolution and penetration of the different endoscopic imaging modalities.

More traditional dye-based imaging enhancements are still available (Table 2); the most rigorously studied among these is methylene blue (0.5% solution). Acetic acid (1.5%-3% dilute white vinegar) with enhanced magnification endoscopy can give a diagnostic accuracy between 52% and 90%. The use of Lugol iodine solution, crystal violet, and indigo carmine in the detection of dysplasia in Barrett esophagus is limited. The widespread availability of enhanced imaging including NBI and magnification endoscopy, which does not require administration of actual dye staining material, has lead to less use of direct dye application. This is based on the dye-based enhanced imaging disadvantages including the need to physically handle and administer a dye; lack of standardization in the technique of applying the dye; and wide variation in the sensitivities and specificities.

Additionally the use of unsedated techniques utilizing small caliber transnasal endoscopes and the esophageal video capsule (PillCam) may lead to more cost-effective screening among

Table 1
Comparison of imaging technologies

<table>
<thead>
<tr>
<th>Technology</th>
<th>White light</th>
<th>HRWLE</th>
<th>Magnification</th>
<th>EUS</th>
<th>OCT/CLE</th>
<th>Spectroscopy</th>
<th>Endocytoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principle</td>
<td>Direct visualization</td>
<td>Higher resolution, direct visualization</td>
<td>Enlargement of image</td>
<td>Ultrasound of varying frequencies</td>
<td>Indirect, focus laser light below the surface, view ultrastructure</td>
<td>Indirect, analysis of light scattered or undergoing fluorescence</td>
<td>Indirect, (similar to OCT), assesses subsurface nuclei, selective detection of light originating from a specific tissue layer</td>
</tr>
<tr>
<td>Advantages</td>
<td>Most available</td>
<td>Widely available</td>
<td>Simple application; can detect dysplasia with higher magnification (up to 150 ×)</td>
<td>Sampling of tissue, staging of malignancy</td>
<td>Good resolution, detection of dysplasia</td>
<td>Possibility of automation, detection of dysplasia or cancer in more accessible area</td>
<td>Good resolution nuclei morphology, possibility of automation</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Lack of penetration</td>
<td>Lack of penetration</td>
<td>Small area examined, image stabilization</td>
<td>Not sensitive for dysplasia</td>
<td>Requires expert interpretation</td>
<td>Development stage</td>
<td>Development stage</td>
</tr>
<tr>
<td>Availability</td>
<td>++ ++ ++</td>
<td>++ ++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>0</td>
</tr>
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</table>

HRWLE, high resolution white light endoscopy; EUS, encoscopic ultrasound; OCT, optical coherence tomography; CLE, confocal autofluorescence endomicroscopy.
the populations at higher risk. In 2011, Chang and colleagues\textsuperscript{97} randomized 20 patients in each group to undergo typical sedated esophagogastroduodenoscopy (EGD), an unsedated transnasal EGD, and video capsule endoscopy (VCE, PillCam2). The authors acknowledge that the study sample size may be small and conclude that both unsedated transnasal EGD and VCE appear to be feasible and acceptable screening methods for Barrett esophagus in the population when compared with sedated EGD. Gralnek and colleagues\textsuperscript{98} in 2008 reported that the PillCam ESO 2 demonstrated excellent visualization of the squamocolumnar junction and compared with standard EGD, the PillCam ESO 2 had good test characteristics with high rates of detection of suspected Barrett esophagus and esophagitis. Although the initial studies suggested that esophageal capsule endoscopy can identify Barrett esophagus in patients accurately, subsequent studies have shown lower accuracy and the lack of cost-effectiveness, resulting in a recommendation that the PillCam ESO 2 (VCE) device cannot be recommended for Barrett esophagus screening at this time.\textsuperscript{97}

**Biopsy interpretation and the role of the pathologist**

**Metaplasia and dysplasia**

Keys to accurate interpretation of Barrett esophagus include (1) communicating the locations from which biopsy specimens are obtained (distance from the incisors above the top of the gastric folds); (2) a description of what is suspected (columnar-lined epithelium or Barrett esophagus); (3) expressing any concerns about the appearance of the mucosa (presence of nodularity or vascular irregularities) from which the biopsy samples are taken; and (4) the

![Fig. 9. Qualitative comparison of resolution or depth penetration for various endoscopic advanced imaging modalities.](image)

The $y$-axis of the figure denotes the depth to which the imaging modality can probe the tissue. The $x$-axis denotes the degree of resolution, with modalities on the right side of the figure providing a higher degree of resolution than those on the left. Chevrons indicate the ability of a modality to penetrate deeper than indicated and increased numbers of chevrons indicate increased penetration ability. WLE, white light endoscopy; HR-WLE, high resolution white light endoscopy; OCT, optical coherence tomography; LSS, light scattering spectroscopy; ESS, elastic scattering spectroscopy; a/LCI, angle-resolved low-coherence interferometry.
number of biopsy samples obtained. All of these factors are under the control of the endoscopist. Without considering all of these issues, interpretation by the pathologist will be difficult. Most of these factors have been discussed in the definition of Barrett esophagus. As stated in the definition of Barrett esophagus, in North America the presence of intestinal goblet cells is widely accepted as a prerequisite for diagnosis of Barrett esophagus. Demonstration of these goblet cells, however, may be difficult. Harrison and colleagues\(^9\) reported that a minimum of 8 biopsy samples are recommended to diagnose Barrett esophagus (containing intestinal goblet cells). Extensive biopsy sampling in the same study (up to 16 biopsy samples) may not yield a Barrett esophagus diagnosis in 25% of the cases. Mixed alcian blue (pH 2.5)/periodic acid-Schiff and hematoxylin-eosin staining is the standard for the diagnosis of intestinal metaplasia.

Once the diagnosis of Barrett esophagus is confirmed with adequate sampling, the pathologist is responsible for stating whether or not dysplasia is present. There are several possible interpretations from the pathologist: (1) negative for dysplasia; (2) positive for dysplasia, either LGD or HGD; or (3) indefinite for dysplasia. The original histologic description of dysplasia arose from the concept of dysplasia in inflammatory bowel disease. From

### Table 2

<table>
<thead>
<tr>
<th>Dye technique or image enhancement</th>
<th>Methylene blue</th>
<th>Narrow-band inquiry</th>
<th>Acetic acid in addition to enhanced magnification endoscopy (HRWLE + magnification)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available data</td>
<td>Meta-analysis (n = 450), no significant difference vs random sampling</td>
<td>Meta-analysis (n = 463) 0.88 pooled sensitivity for detection of HGD (using endoscopes not available in the US); Single randomized trial in US NBI w/ HRWLE vs Std WLE favored use of NBI with HRWLE(^48) NBI with magnification endoscopy for differentiation of dysplastic vs nondysplastic lesions (n = 377) pooled sensitivities (0.96) and specificities (0.94) per lesion NBI with magnification endoscopy for identification of intestinal metaplasia in BE (n = 342) pooled sensitivities (0.95) and specificities (0.65) per lesion NBI targeted vs HRWLE with 4 quadrant biopsies favored NBI use because of significantly fewer biopsies needed with similar rates of detection of BE and dysplasia(^87)</td>
<td>Diagnostic accuracy for BE metaplasia ranges from 52%-90%</td>
</tr>
<tr>
<td>Advantages</td>
<td>Widely available and low cost,</td>
<td>Widely available, use in conjunction with magnification endoscopy</td>
<td>AA by itself is widely available, low cost</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Expert center studies</td>
<td>Expert center studies, using different classifications, cost of equipment</td>
<td>Not sensitive for low-grade dysplasia, requires continuous spraying every 2 minutes Expert interpretation</td>
</tr>
<tr>
<td></td>
<td>Wide range of diagnostic sensitivities (32%-98%) and specificities (23%-100%)</td>
<td></td>
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</tbody>
</table>

HRWLE, high resolution white light endoscopy; HGD, high-grade dysplasia; US, ultrasound; NBI, narrow band imaging; BE, Barrett esophagus; AA, acetic acid.
Riddell\textsuperscript{100} dysplasia is defined as the presence of neoplastic epithelium that is confined within the basement membrane of the gland within which it arises. Goldblum\textsuperscript{101} in a review article in 2010 explains this dysplasia categorization in detail. LGD is described by Goldblum as minimal distortion of crypt architecture in which cytologically atypical nuclei are limited to the basal half of the crypts. These atypical nuclei are noted to have variable hyperchromasia, nuclear crowding, and irregular nuclear contours. Goldblum describes HGD as more advanced or severe cytologic and architectural changes found in LGD. The category of “indefinite for dysplasia” is described by Goldblum as a legitimate diagnosis in which differentiation of regenerative changes from true dysplasia, given a background of inflammation or presence of ulceration, may not be possible. Furthermore, Goldblum stated that a diagnosis of indefinite for dysplasia is acceptable even if there is no inflammation, illustrating the difficulty encountered in distinguishing between dysplastic and regenerative changes. Whenever a pathologic diagnosis involving dysplasia is given, there is always a need to have confirmation by an expert pathologist. This is also a situation in which biopsy sampling (adequate number of biopsies) plays an important role in detecting minute foci of dysplasia (Fig 10).

Advanced dysplasia and intramucosal carcinoma

There is even greater controversy in the setting of advanced dysplasia or early-stage adenocarcinoma or HGD vs intramucosal adenocarcinoma (invasion of neoplasia beyond the lamina propria or muscularis propria but not into the submucosal). In 2008, Downs-Kelly and colleagues\textsuperscript{102} from the Cleveland Clinic reviewed slides from 168 patients who underwent esophagectomy for a diagnosis of HGD, intramucosal carcinoma, or submucosal invasive adenocarcinoma. The authors preselected biopsy samples demonstrating the most advanced neoplastic changes that were then reviewed by 7 blinded gastrointestinal pathologists. Overall, there was consensus (4 out of 7) in 85.9\% of the cases, however based on kappa statistics, the overall agreement for all 4 diagnostic categories was only 0.30. The lowest kappa scores were found in the most advanced category (submucosal invasive adenocarcinoma, with a kappa score of 0.14). This strengthens the recommendation that an expert review or a review by a panel of experts is essential to ensure the most accurate diagnosis.

In cases in which there is a discrete lesion (nodular, irregular mucosa), endoscopic mucosal resection (EMR) is recommended to ensure that accurate staging (demonstration of invasion into the submucosal) is possible. This is further discussed in the Rationale for treatment section.

Management of Barrett esophagus

Prevention

There are 2 types of prevention associated with Barrett esophagus: primary prevention of Barrett esophagus and prevention of progression of Barrett esophagus to esophageal adenocarcinoma.

Current interest in primary prevention focuses on lifestyle changes and chemoprevention. Chemoprevention is related to either prevention of esophageal acid exposure or modulation of proinflammatory mechanisms. Although the present status of chemoprevention with proton pump inhibitors (PPIs), statins, and aspirin or nonsteroidal antiinflammatory agents is still uncertain,\textsuperscript{16} there is epidemiologic evidence that is intriguing.

Patients who consume nonsteroidal antiinflammatory drugs (NSAIDs) appear to have a lower risk of the development of Barrett esophagus. In 1 study, current aspirin use reduces the risk of Barrett esophagus (OR 0.56; 95\% CI 0.39-0.80). In a subset analysis, patients who had endoscopies for GERD symptoms had similar results, implying that usage was independent of whether the reflux was symptomatic or not. No associations were found between aspirin use, smoking, or PPI use.\textsuperscript{103}
According to the American College of Gastroenterology, goblet cells are required for a definitive diagnosis of Barrett esophagus. Goblet cells are easily identified in this biopsy of a columnar-lined esophagus (hematoxylin-eosin, original magnification 100 ×) (A). This biopsy of columnar-lined esophagus shows only metaplastic nongoblet cell cardiac-type epithelium, which would not be diagnostic of Barrett esophagus according to the American College of Gastroenterology (hematoxylin-eosin, original magnification 40 ×) (B). This is a focus of Barrett esophagus-related low-grade dysplasia. The focus was recognizable at low magnification due to its hyperchromia, particularly when compared with the adjacent nondysplastic epithelium (hematoxylin-eosin, original magnification 100 ×) (C). This is a focus of Barrett esophagus-related high-grade dysplasia, which shows more profound cytologic atypia than that seen in the focus of low-grade dysplasia depicted in (C). Most gastrointestinal pathologists in Goldblum's group recognize this as high-grade dysplasia (hematoxylin-eosin, original magnification 100 ×) (D). This biopsy was diagnosed as intramucosal adenocarcinoma by all of Goldblum's gastrointestinal pathologists, presumably on the basis of multiple foci of individual cells infiltrating into the lamina propria but not beyond (hematoxylin-eosin, original magnification 100 ×) (E). Three criteria were arbitrarily used to establish a diagnosis of high-grade dysplasia/mucosal adenocarcinoma, including glandular crowding with loss of intervening lamina propria, cribriform growth, or prominent (at least 3) dilated glands with intraluminal necrotic debris (F). (From Goldblum.101)
Regular use of statins was associated with a significantly lower incidence of esophageal cancer in patients with Barrett esophagus (OR 0.45; 95% CI 0.24-0.84). The combination of statins with aspirin further reduced the risk (OR 0.31; 95% CI 0.04-0.69). There is evidence to suggest that statin and NSAID use is synergistic. During a median follow-up period of 4.5 years, NSAID and statin use were each associated with a reduced risk of neoplastic progression (hazard ratio [HR] 0.47 and 0.48, respectively) and the combination increased the protective effect (HR 0.22). It should be emphasized that these are epidemiologic studies and no prospective trials have been conducted.

Screening

The purpose of screening is to identify in asymptomatic patients, disease at a stage when intervention can significantly prolong or enhance life. Therefore, for screening to be effective for Barrett esophagus, the Barrett esophagus screening should identify enough patients at a stage where intervention can significantly reduce the number of lives lost by esophageal adenocarcinoma. Because both GERD and Barrett esophagus increase the risk of esophageal adenocarcinoma, it has been suggested that these individuals should be screened for adenocarcinoma and dysplasia. There are several problems with this strategy. First, approximately 40% of individuals who develop esophageal adenocarcinoma do not have symptoms of GERD. If GERD symptoms are the entrance criteria for screening, then these patients would be excluded immediately. Second, the overall prevalence and incidence of esophageal adenocarcinoma is low, at approximately 10,000 cases per year, whereas the prevalence of GERD-like symptoms is 20%-40% in the general population. Many patients would be screened to find a relatively few cancers. Third, the execution of the screening, namely upper endoscopy, is very operator dependent and varies in its ability to truly identify and exclude adenocarcinoma and dysplasia. Lastly, screening is an invasive procedure. Although endoscopy has an overall low morbidity rate, if applied widely for screening there will be a measurable number of patients harmed and who would have otherwise not benefited from the screening.

Because of these issues, and the lack of any prospectively gathered data, attempts to determine if screening is justified have been more theoretical. In general, for any healthcare policy to be considered cost effective, the cost per quality-adjusted life year gain should be less than $50,000. In a study by Soni and colleagues, screening of patients with GERD at 60 years of age resulted in $24,700 per life year saved. In this study, the only management strategy for HGD was esophagectomy and surveillance after screening was not considered. Inadomi and colleagues found that a strategy of screening patients with GERD at the age of 50 years followed by surveillance of patients with dysplasia resulted in a cost of $10,440 per quality-adjusted life year. These calculations are built for patients at higher risk for Barrett esophagus than the general population. For the general population, the vast majority of whom would be considered low risk for Barrett esophagus and esophageal adenocarcinoma, the AGA does not recommend endoscopic screening for Barrett esophagus. However, in patients with multiple risk factors associated with esophageal adenocarcinoma (age > 50 years, male sex, white race, chronic GERD, hiatal hernia, increased body mass index, and intra-abdominal distribution of fat), the AGA suggests screening for Barrett esophagus may be appropriate. However, definitive recommendations for screening of any patient populations cannot be made with certainty.

Special considerations

Screening for Barrett esophagus in low-risk populations

In 2010, Taylor and colleagues utilized published and publicly available data and Markov computer modeling to estimate the age- and sex-specific incidences of esophageal adenocarcinoma in American white and non-Hispanics with GERD symptoms. They reported an estimated incidence of esophageal adenocarcinoma in women with GERD which is extremely low (3.9 per 100,000 person-years at the age of 60 years). The authors concluded
that women, because of very low incidences of cancer, regardless of the frequency of GERD symptoms, should not be subjected to screening for esophageal adenocarcinoma. In an accompanying editorial, Shaheen\textsuperscript{109} further illustrates the point that a 35-year-old woman with heartburn may have a larger chance of being struck by lightning than developing esophageal adenocarcinoma (risk $< 1$ per 100,000 person-years). Moreover, overutilization of screening for Barrett esophagus is an issue. In 2012, Crockett and colleagues\textsuperscript{110} in a retrospective multicenter study reported that among 235 patients, overutilization of endoscopic screening was present in 65% of the patients. The mean ($\pm$ standard deviation) number of endoscopies per 3-year period was 2.7 $\pm$ 2.6. No patient factors appear to influence this increased number of surveillance endoscopies (education, study site, annual income, and family history of Barrett esophagus or esophageal cancer).

One possible explanation for this is a fear of malpractice claims. This possibility is supported by a study published by Rubenstein and colleagues\textsuperscript{111} in 2008 in which a survey from 224 gastroenterologists revealed that 21% report being identified as a defendant in at least 1 malpractice suit. These gastroenterologists who had a prior lawsuit had practiced longer and performed a higher volume of endoscopies, but had similar knowledge regarding published screening guidelines compared with those who had not been defendants. Gastroenterologists who had prior lawsuits were more likely to be aggressive in screening and surveillance for Barrett esophagus, with an OR of 3.6 (95% CI 1.1-12) even after controlling for other factors.

**Dysplastic Barrett esophagus in patients with cirrhosis**

There is 1 publication by Raftopoulos and colleagues\textsuperscript{112} in 2011 reporting on the use of esophageal band ligation to eradicate Barrett esophagus (C3M5 by Prague classification) in the context of underlying esophageal varices and cirrhosis. This patient had several areas of HGD.

**Rationale for treatment**

Until Barrett metaplasia progresses to carcinoma, it is a mucosal disease. Therefore, eradication only requires removal of the diseased mucosa, not the entire organ. This concept of removing cancer-prone tissue is not new to surgeons. Table 3 lists examples of premalignant diseases which are treated with “prophylactic” resection prior to the development of malignancy.

With respect to Barrett metaplasia, the value of ablation is dependent on the incidence of progression to invasive carcinoma. Although prevention of esophageal adenocarcinoma is the primary reason to perform ablation, there are other reasons as well. First, ablation may be a cost-effective alternative to observation. Inadomi and colleagues\textsuperscript{113} have shown that for all grades of dysplasia, ablation is more cost-effective than surveillance. This is particularly true when one considers the costs of esophagectomy.\textsuperscript{114} In a sense, ablation can be considered a method to prevent esophagectomy. Although esophagectomy has a high cure rate for adenocarcinoma in a screened Barrett population,\textsuperscript{115} it does come at a cost in quality of life.\textsuperscript{116} In addition, the presence of Barrett esophagus does affect quality of life and ablation

<table>
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<tr>
<th>Disease</th>
<th>Prophylactic surgery</th>
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<tr>
<td>Colonic adenoma</td>
<td>Colonoscopic polypectomy</td>
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<tr>
<td>Ulcerative colitis</td>
<td>Total proctocolectomy with mucosal stripping of rectum</td>
</tr>
<tr>
<td>Familial adenomatous polyps—colon</td>
<td>Total proctocolectomy with mucosal stripping of rectum</td>
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<tr>
<td>Familial adenomatous polyps—duodenum</td>
<td>Pancreas sparing duodenectomy with stripping of duodenal mucosa from pancreas</td>
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<tr>
<td>Hereditary medullary carcinoma</td>
<td>Total thyroidectomy</td>
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<td>BRCA mutations—breast cancer</td>
<td>Bilateral mastectomies</td>
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seems to improve it.\textsuperscript{43} Although it now appears that ablation of Barrett esophagus with HGD is an accepted standard of care,\textsuperscript{117} an argument can be made for ablation of nondysplastic and low-grade dysplastic Barrett esophagus.\textsuperscript{118} This argument centers on the facts that the morphologic evaluation of dysplasia is fraught with error, some studies show a substantial progression rate of LGD to cancer, postablation neosquamous epithelium reveals no molecular abnormalities and is biologically stable, and no other method that reliably reduces cancer risk is durable and eliminates the need for surveillance.

\textbf{Treatment options}

Once Barrett esophagus is discovered, several treatment options are available. For the purposes of discussing treatment options, it will assume that the diagnosis is accurate. As previously stated in the pathology section, if there is any question as to the presence or grade of the Barrett metaplasia or dysplasia, a second expert gastrointestinal pathologist opinion is recommended.

\textit{Acid suppression without surveillance}

After diagnosis, some advocate medical acid suppression without any additional interventions. This is based on the premise that screening for Barrett esophagus has not been shown to improve mortality from adenocarcinoma or to be cost effective.\textsuperscript{119} These authors developed an economic model which suggests that the adverse effect related to screening outweighs any potential benefits of “early” detection of adenocarcinoma.\textsuperscript{119} Even using the “best case” scenario of yearly surveillance for LGD and a 3-month surveillance for HGD, no surveillance is still more cost effective and provides a better quality of life. This is based on the adverse effects of “additional” procedures done after the discovery of Barrett esophagus, especially the adverse effects of esophagectomy. Contrary to some published guidelines, some groups do not recommend screening for adults older than 50 years, regardless of age or duration of heartburn. The AGA 2004 Chicago Workshop concluded that although surveillance can detect curable neoplasia and can be cost effective in selected patients, it may not prolong survival.\textsuperscript{120}

Although acid suppression is important in the management of Barrett esophagus, the dosing of PPIs is an area of disagreement. There is a practice of using “double-dose” PPIs in the management of patients with Barrett esophagus to “maximally” suppress acid production. However, the AGA in a technical review recommends against attempts to eliminate acid exposure with PPIs in doses greater than 1 per day. In addition, they also recommend against antireflux surgery or use of aspirin solely to prevent esophageal adenocarcinoma.\textsuperscript{40}

There is criticism of the methods used in these studies. Barbire and Lyratzapoulos\textsuperscript{121} performed a critical review of 5 studies on the cost-effectiveness of screening and surveillance for Barrett esophagus. They found that none of the studies had data from randomized trials, because such trials do not exist. They concluded that the extant evidence could have underestimated true incremental cost-effectiveness ratios because of optimistic assumptions or failure to consider important and relevant clinical and administrative activities in their modeling. Their first observation is that no study assumed any negative effect on quality of life among patients with Barrett esophagus. Second, the studies seem optimistic in relation to assumed sensitivity and specificity of screening and surveillance. Third, no study seems to have considered organizational arrangements and costs required to successfully run preventive healthcare programs. Lastly, these studies ignored healthcare needs among Barrett esophagus patients for either medical or surgical treatment of GERD-related symptoms, independent of the Barrett esophagus. Given that the arguments for acid suppression without surveillance are theoretical at best and that most professional societies recommend some type of surveillance, the recommendation for acid suppression without surveillance should be made with caution and thorough patient counseling.
Acid suppression with surveillance

The underlying rationale for surveillance is that acid suppression will not eliminate the risk of progression of Barrett esophagus to adenocarcinoma. Even aggressive medical acid suppression does not lead to consistent regression of Barrett esophagus and the rate of progression to adenocarcinoma is approximately 0.25%-0.4% per year. The purpose of surveillance is to identify early-stage esophageal adenocarcinoma. If invasive carcinoma is discovered, then esophagectomy is indicated. Generally, adenocarcinomas discovered while screening for Barrett esophagus are early-stage lesions and have good prognosis (5-year survival > 85%). The identification of early-stage cancer, when treatment is most effective, is the basis for all surveillance recommendations. Because there are no reliable data on the duration of PPI treatment, most practitioners will keep patients on PPI therapy indefinitely, although this practice is neither supported nor refuted by the data. Whether this halts or retards progression of Barrett esophagus to carcinoma has not been definitively demonstrated. One study in a cohort of patients followed with SIM being treated with PPIs, H2-blockers, or fundoplication for a mean of 44.4 ± 9.7 months showed that none of the patients with long-segment Barrett esophagus, 30% of patients with short-segment Barrett esophagus, and 68% of patients with gastroesophageal junction SIM had histologically proven normalization of their epithelium. Therefore, this serves as the basis for continued endoscopic surveillance of patients with Barrett esophagus.

There are data to support this rationale. Wong and colleagues in a review of their surveillance program showed that 80% of esophageal adenocarcinomas found patients undergoing surveillance were stage I cancers, compared with only 6.5% of patients who were not in the surveillance program (P < 0.001). Verbeek and colleagues in a nationwide study of surveillance of Barrett esophagus with HGD determined the rate of prevalent and incident esophageal adenocarcinoma. They defined “prevalent” adenocarcinoma as those found less than 6 months from initial endoscopic diagnosis of HGD. This can be considered a measure of “missed” cancers during the index endoscopy. They defined “incident” adenocarcinomas as those found more than 6 months from the index endoscopy. This can be considered a measure of cancer forming during the surveillance period. They found that the risk of prevalent esophageal adenocarcinoma was lower with previous surveillance (HR 0.7; 95% CI 0.5-0.9), unifocal HGD (HR 0.3; 95% CI 0.2-0.6), diagnosis at a university hospital (HR 0.5; 95% CI 0.3-0.9), prior EMR (HR 0.5; 95% CI 0.3-0.7), or prior endoscopic ablation (HR 0.0; 95% CI 0.0-0.3) and higher when patients were 65-75 years old (HR 1.50; 95% CI 1.04-2.04). These data imply that not only are cancers found earlier when patients are undergoing surveillance, but that fewer cancers are missed.

Although the optimal frequency of surveillance has not been determined, most authorities recommend surveillance at intervals of 3-5 years for patients with nondysplastic metaplasia, 6-12 months for LGD, and every 3 months for HGD in patients not receiving invasive therapy. Nevertheless, surveillance has been practiced in an uneven fashion. One study suggests that surveillance may be overutilized in patients with nondysplastic Barrett undergoing more numbers of endoscopies than was required by generally accepted guidelines. In Australia, simply disseminating screening and surveillance guidelines did not change practice patterns; rather, having “surveillance coordinators” led to an over 90% improvement in adherence to guidelines. Therefore, if surveillance is practiced, knowledge and adherence to guidelines is important.

Antireflux surgery

Antireflux surgery in experienced hands usually in the form of some type of fundoplication, eliminates acid, and bile reflux in more than 90% of patients with Barrett esophagus. As the LOTUS trial has shown, there does not seem to be a superiority between medical management and antireflux surgery in patients with Barrett esophagus. Factors to consider in the choice between medical and surgical management include the effectiveness of the treatment in eliminating reflux-related symptoms, comorbidities affecting the risk for an operative procedure, the desire of the patient to eliminate the need for acid-reducing medications, adverse effects of medications,
effectiveness of the individual surgeon in performing antireflux operations, and the desire of the patient to lower the risk for progression to esophageal adenocarcinoma.

Antireflux surgery does seem to promote resolution of Barrett metaplasia. Biertho and colleagues\textsuperscript{129} in a follow-up of patients with Barrett esophagus who underwent laparoscopic Nissen fundoplication showed that with a mean follow-up of 4.2 ± 2.6 years, 33% had complete regression, 21% had a decrease in the degree of metaplasia or dysplasia, 39% had no change, and 7% showed progression. No patients developed HGD or adenocarcinoma. A meta-analysis of antireflux surgery compared with medical treatment in GERD patients with Barrett esophagus demonstrated a pooled estimate of 15.4% of patients who have undergone antireflux surgery will have regression of Barrett esophagus compared with 1.9% of medically managed patients.\textsuperscript{130} In addition to promoting regression of Barrett esophagus, there are reports that suggest that antireflux surgery lowers the risk for progression to adenocarcinoma.\textsuperscript{131,132} Evidence is mixed, however. A Swedish population-based study, comparing 35,274 men given medical therapy with 6406 who underwent fundoplication, found that the relative risk in the former group for adenocarcinoma was 6.3 (95% CI 4.5-8.7) and it was 14.1 (95% CI 8.0-22.8) in the fundoplication group.\textsuperscript{133}

Therefore, although antireflux surgery can successfully treat reflux-related symptoms in patients with Barrett esophagus, caution should be used when discussing its role in Barrett regression or protection against progression to adenocarcinoma.

Endoscopic ablation

Although different types of endoscopic ablative therapies are available and are discussed, it is important to emphasize that several organizations including the AGA,\textsuperscript{134} the National Institute for Health and Clinical Excellence in the United Kingdom,\textsuperscript{135} and the Society of American Gastrointestinal and Endoscopic Surgeons\textsuperscript{136} have recommended ablation in the form of RFA, photodynamic therapy (PDT), or EMR for patients with Barrett esophagus with HGD.

Photodynamic therapy. PDT was once a popular method of ablating Barrett esophagus. This process consisted of injecting a light-sensitizing drug into the patient, then exposing the portion of the esophagus to light of a specific wavelength which would then lead to metaplasia and dysplasia cell death.\textsuperscript{137} However, PDT was found not to have the effectiveness in eliminating Barrett esophagus as hoped. Eradication of both nondysplastic metaplasia and HGD has been variable,\textsuperscript{138} with issues involving “buried glands.” That is, after treatment, a layer of normal-appearing squamous epithelium is present but under this layer, Barrett metaplastic cells persist. In a randomized trial of PDT using porfimer sodium plus omeprazole vs omeprazole only, there was a significant difference in favor of PDT in complete eradication of HGD at any time during the follow-up period. However, although the occurrence of adenocarcinoma was lower in the PDT group (13%) compared with the PPI group (28%), one would still have to be concerned about a relatively high rate of adenocarcinoma development in the PDT group.\textsuperscript{139} In addition, especially with long segments of Barrett esophagus, stricture formation was unacceptably high, with some studies reporting a stricture incidence of nearly 40%.\textsuperscript{140} In addition, these strictures were difficult to dilate and can provide lifelong problems for these patients. For these reasons, PDT, although still considered an acceptable treatment, has lost favor.

Multipolar electrocoagulation. MPEC uses an endoscopic multipolar electrical probe (the “gold” probe), which is used to control gastrointestinal hemorrhage. This technique applies electrical energy at the 50 W range so that all surfaces of Barrett metaplasia are treated. Using this technique in combination with long-term medical acid suppression, Allison and colleagues\textsuperscript{141} had an initial complete eradication in 132 of 139 patients, and complete eradication after retreatment in 5 of 7 patients. Kovacs and colleagues\textsuperscript{142} studied 27 patients treated with MPEC and lansoprazole; 81% had eradication of their Barrett esophagus with 41% developing dysphagia as the most common side effect. Menon and colleagues\textsuperscript{138} in their systematic review
determined that complete eradication with this technique at 3 months is 88%. Although MPEC is an effective technique, it is very much operator dependent as it requires that the endoscopist carefully apply treatment to all surfaces containing Barrett metaplasia.

Argon plasma coagulation. APC produces a flow of ionized argon plasma, which generates a high-frequency monopolar current to Barrett surfaces under direct vision. APC is simply another form of electrocoagulation. A systematic review has shown that APC appears to be more effective than photodynamic therapy, with 3-month complete eradication rates in the high 80% range. Complication rates, such as stricture formation and bleeding are relatively low, but odynophagia rates are more than 10%.

Laser ablation. Laser is an acronym for “light amplification by stimulated emission of radiation.” This light energy is generated by a variety of sources including argon, neodymium:yttrium-aluminum-garnet, potassium titanyl phosphate, and potassium titanyl phosphate:yttrium-aluminum-garnet. In their systematic review, Menon and colleagues identified 7 noncomparative studies of laser ablation of Barrett esophagus. Stricture formation occurred in 4.4%, perforation in 1.5%, and bleeding in 1.5% of patients, with a complete eradication rate of 77% within 3 months. There were no long-term studies. Bright and colleagues in a randomized trial of laparoscopic antireflux surgery alone vs antireflux surgery and argon laser ablation showed that the addition of laser ablation increased the complete eradication rate to 70% from 20% of the laser treated patients, 10% developed stricture.

Overall, the use of lasers in the ablation of Barrett esophagus has gradually fallen out of favor due to lower eradication rates and higher complication rates.

Radiofrequency ablation. Endoscopic RFA has been one of the best studied methods of ablating Barrett esophagus. RFA applies bipolar electrical energy to the mucosal surfaces at frequencies at the radio level. The energy applied is 10 Joules for 1 second. With this technique, the mucosa is ablated to the submucosal level. Generally, within several weeks to a few months postablation, the exposed submucosal esophageal surface resurfaces with a “neosquamous” epithelium (Fig 11).

Endoscopic RFA is an effective means of eliminating Barrett metaplasia. If it is used, a standardized follow-up protocol is needed because ablation is complete with a single treatment in only approximately 70% of patients. Most protocols have a follow-up endoscopy at 3 months when any remaining metaplasia is ablated, with a further follow-up endoscopy at 1 year. Certainly, although there is good evidence that complete ablation can be achieved in more that 90% of cases, there are limited data for risk reduction of esophageal adenocarcinoma in these patients. It appears that a synthesis of the available data favors RFA over photodynamic therapy as the primary ablative therapy for Barrett esophagus.

A meta-analysis and systematic review of the incidence of adenocarcinoma in patients with Barrett esophagus treated with ablative therapies compared with historical controls showed a reduction in carcinoma progression in nondysplastic metaplasia, in LGD, and especially in HGD. A landmark randomized trial has demonstrated superiority of endoscopic RFA compared with sham procedure. This large, multicenter, randomized trial showed that endoscopic RFA can eliminate Barrett esophagus with HGD and reduce the risk of esophageal adenocarcinoma. To achieve these results a strict protocol of follow-up endoscopy is required to ensure that the dysplastic epithelium has been completely ablated. The evidence has been so compelling that the National Institute for Health and Clinical Excellence of the United Kingdom in its August 2010 guidance update recommends to “consider using RFA alone or photodynamic therapy alone for flat high-grade dysplasia.”

RFA has been shown to be durable. Shaheen and colleagues published a 3-year follow-up study showing that at 3 years, complete eradication of intestinal metaplasia was persistent in 91% of patients with intestinal metaplasia, 96% of patients with HGD, and 100% of patients with LGD. Any disease progression (e.g., from intestinal metaplasia to LGD) occurred in 1 per 73
patient years of follow-up, whereas progression to adenocarcinoma occurred in 1 per 181 patient years of follow-up. These data imply that not only is initial eradication successful, recurrence of Barrett esophagus is low. However, we have previously shown that attempts at ablation of longer segments of Barrett esophagus lead to a higher rate of both persistent and recurrent metaplasia compared with segments shorter than 3 cm in length. Vaccaro and colleagues also showed that after complete eradication, more than 30% of patients will be found to have Barrett metaplasia as some point in their posttreatment follow-up. Titi and colleagues demonstrated sub-squamous dysplasia and even development of adenocarcinoma after eradication with RFA. Therefore, it is still an open question as to whether or not a patient with Barrett esophagus should or should not be in a posttreatment surveillance program.

Cryoablation. Cryoablation of Barrett esophagus is a noncontact method of cryotherapy. It involves endoscopically directed spray of liquid nitrogen at \(-196^\circ C\) directly onto the Barrett epithelium (Fig 12). Recent studies have shown that complete eradication of Barrett HGD occurs in 68%-97% of patients, whereas complete eradication of intestinal metaplasia occurs in 57% of patients and eradication of intramucosal adenocarcinoma occurs in 80%. Therefore, although cryoablation appears to be effective in Barrett eradication, it is not as well studied as RFA and yet to be determined if it is an alternative or complementary treatment for Barrett esophagus.

Endoscopic mucosal resection. EMR is a valuable technique to remove nodular Barrett esophagus with HGD. The technique is most useful when either a visible nodule is present or only a short segment of Barrett epithelium is seen. One particular advantage of EMR (compared with radioablation) is that it provides a substantial tissue specimen that can be reviewed by a pathologist for the presence of adenocarcinoma. As EMR can also be used for Tis or T1a esophageal adenocarcinoma, the presence of cancer does not necessarily preclude its use. However, a preprocedure EUS is essential to ensure that the submucosa is not involved. In addition, it has now become clear that endoscopic mucosal resection can be combined with RFA to allow for resection of the nodular component of Barrett HGD with ablation of the remaining field of flat Barrett metaplasia.

Ablation with antireflux surgery. Endoscopic RFA has been used in conjunction with antireflux operations. There are 3 basic issues involved in combining endoscopic Barrett esophagus ablation and antireflux surgery. First, if a fundoplication is already present, will ablation lead to failure of the antireflux operation? We performed ablation in patients with preexisting fundoplications for symptomatic GERD and found that there was no change in reflux symptoms after ablation. Second, is it efficient to perform endoscopic ablation in conjunction with an antireflux operation? Goers and colleagues reported that combining ablation with

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**Fig. 11.** Barrett esophagus prior to ablation (A). Sloughed esophageal epithelium immediately after radiofrequency ablation (B). Neosquamous epithelium approximately 3 months after ablation (C). (Courtesy of Covidien, Mansfield, MA.)
fundoplication reduces the overall number of procedures that a patient must undergo. Lastly, the presence of a fundoplication reduce the recurrence of Barrett esophagus. We compared patients who underwent ablation with a fundoplication with those who did not have a fundoplication and found the recurrence rate was in fact less in patients who had a fundoplication.\textsuperscript{160} This is consistent with the findings of Krishnan and colleagues\textsuperscript{161} who also have shown that recurrence after RFA was related to uncontrolled reflux. Therefore, there should be no hesitancy in combining these procedures.

Resection

At 1 time, esophagectomy was considered a reasonable approach to patients with HGD. The rationale is that 20\%-40\% of patients with HGD on biopsy will actually harbor an early-stage adenocarcinoma.\textsuperscript{162,163} Although esophagectomy can be performed with very low mortality, morbidity is still high.\textsuperscript{138} Even if the operation is accomplished without morbidity, the detrimental effects on quality of life are significant.\textsuperscript{164} Therefore, esophagectomy should be reserved only for patients for whom ablation has not led to durable eradication of HGD or if suspicion for carcinoma is high.

References


