Barrett Esophagus

Mark Splittgerber, MD, Vic Velanovich, MD*

KEYWORDS

• Barrett esophagus • Gastroesophageal reflux • Barrett prevention
• Esophageal adenocarcinoma prevention • Endoscopic ablation • Esophagectomy

KEY POINTS

- Barrett esophagus has a prevalence of 1.6% of the general population and an incidence of 9.9/1000 patients/year. Gastroesophageal reflux, male gender, Caucasian race, and obesity are the primary risk factors.
- Duodenogastroesophageal reflux is the primary causative agent.
- Screening should be considered for high-risk populations.
- Endoscopic radiofrequency ablation is the preferred treatment modality for high-grade dysplasia and should be considered for low-grade dysplasia.
- Esophagectomy should only be considered for persistent high-grade dysplasia or high suspicion of invasive carcinoma.

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 article is to review the disease Barrett esophagus with emphasis on current clinical management.

EPIDEMIOLOGY AND RISK FACTORS

Prevalence

It is difficult to know the true prevalence of Barrett esophagus because many individuals are asymptomatic and, therefore, will never be evaluated. Prevalence may also vary from location to location based on variable population risk factors. However, the best estimate of the population prevalence of Barrett esophagus is 1.6% of the general population.[1] Although probably related to GERD, the prevalence of Barrett esophagus has increased, paralleling the increase in esophageal

Division of General Surgery, University of South Florida, Tampa, FL, USA
* Corresponding author. Division of General Surgery, One Tampa General Circle, F145, Tampa, FL 33606.
E-mail address: vvelanov@health.usf.edu

Surg Clin N Am 95 (2015) 593–604
http://dx.doi.org/10.1016/j.suc.2015.02.011 **surgical.theclinics.com**
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Abbreviations

AGA	American Gastroenterological Association
EMR	Endoscopic mucosal resection
GERD	Gastroesophageal reflux disease
HGD	High-grade dysplasia
LGD	Low-grade dysplasia
OR	Odds ratio
PDT	Photodynamic therapy
PPI	Proton pump inhibitor
RFA	Radiofrequency ablation

adenocarcinoma; the true cause is unknown.[2] In a study conducted in Sweden, symptomatic subjects had a prevalence of Barrett esophagus of 2.3%, compared with 1.4% in asymptomatic individuals.[3] Paradoxically, patients with short-segment Barrett esophagus seem to have more frequent and intense symptoms than did those with long-segment Barrett esophagus.[4]

Incidence

The incidence of Barrett esophagus is even more difficult to estimate than its prevalence. Most studies have relied on follow-up of patients who have manifestations of GERD or calculations based on estimates. The Kalixanda study[5] of a general Swedish population initially found endoscopic or histologic diagnosis of GERD and nonerosive reflux disease, of these patients 9.7% of patients with nonerosive reflux disease 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.[6] The overall incidence of Barrett esophagus was 9.9 per 1000 person-years.[6]

The incidence of Barrett esophagus seems to be increasing. A study from Northern Ireland by Coleman, and colleagues[7] found that the annual incidence from 2002 to 2005 was 62.0 per 100,000 persons per year, showing an increase 159% compared with 1993 through 1997. This incidence increased most markedly in patients younger than 60 years, especially in men younger than 40 years. Two studies from The Netherlands also documented a similar increased incidence.[6,8]

Risk Factors

Risk factors for the development of Barrett esophagus include GERD, obesity, male gender, Caucasian ethnicity, and increasing age (**Box 1**). Smoking might increase the risk of Barrett esophagus, whereas *Helicobacter pylori* infection, and specific "healthy" dietary factors may lower the risk.[9] Nelsen and colleagues[10] compared 50 Barrett esophagus patients to matched controls with CT to determine 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.

Tobacco smoking increases the risk of 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).[11] Increasing pack-year history of smoking increased the risk of Barrett esophagus. There was synergy of smoking with GERD with the attributable proportion of disease among individuals who ever smoked and had heartburn or regurgitation was 0.39 (95% CI, 0.25–0.52).[11]

Box 1
Risk factors for GERD

- GERD
- Male gender
- Caucasian race
- Obesity
- Smoking
- Diet

Abbreviation: GERD, gastroesophageal reflux disease.

Diets high in fiber and "good" fats reduce the risk of Barrett esophagus. Greater 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 a lower risk. 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.[12]

Some social issues may be associated with Barrett esophagus. German patients with Barrett esophagus and adenocarcinoma tend to have higher incomes.[13] Barrett esophagus seems to be less prevalent among persons of Asian, Caribbean, African, Middle Eastern, and South American origin.[14] African Americans with Barrett esophagus are less likely than whites to have long-segment disease (12% vs 26%) and dysplasia (0% vs 7%).[15]

Progression to Adenocarcinoma

Progression of Barrett esophagus is primarily dependent on histologic grade (**Box 2**). Nondysplastic epithelium progresses at a rate of 3.86 per 1000 persons per year,[16] low-grade dysplasia (LGD) at 7.66 per 1000 persons per year,[16] and high-grade dysplasia (HGD) at 146 per 1000 persons per year.[17] The progression rate of HGD seems to be lower than the occult carcinoma rate discovered in esophagectomy specimens of HGD of 30%.[18] Age, male gender, and Barrett metaplasia length only modestly increase the risk of progression to carcinoma.[19,20] Current smoking, former smoking, and more than 40 years of smoking increased the risk of progression to HGD and esophageal adenocarcinoma; current alcohol use did not, but former alcohol use did.[19,21]

Multiplex familial kindreds, defined as families with 3 or more members with Barrett esophagus or esophageal adenocarcinoma,[21] have a younger median age at diagnosis of esophageal adenocarcinoma (57 vs 62 years old) and a lower body mass

Box 2
Progression to esophageal adenocarcinoma related to histologic grade of Barrett esophagus

- Nondysplastic Barrett esophagus: 3.86 per 1000 persons per year
- Low-grade dysplasia: 7.66 per 1000 persons per year
- High-grade dysplasia: 146 per 1000 persons per year

index.[22] It is estimated 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.[23]

Acid and Bile Esophageal Reflux

Development of Barrett esophagus is related to abnormal acid and bile exposure. Specifically, duodenogastroesophageal reflux seems to be an important driver of Barrett esophagus.[24] Esophageal exposure to both acid and duodenogastroesophageal reflux 100% in patients with complicated Barrett esophagus, 89% with uncomplicated Barrett esophagus, 79% with esophagitis, and 50% without esophagitis. There was a correlation between acid exposure and bilirubin absorbance.[25] Nevertheless, the exact mechanism by which bile acids produce mucosal damage is not certain.

DIAGNOSIS

The definition of Barrett esophagus remains controversial. The proximal displacement of the squamocolumnar junction is essential for the diagnosis, but there are different methodologies used to identify the gastroesophageal junction.[26] Identification of the "palisade" of vessels in the lower esophagus with identification of the top of the gastric folds and the diaphragmatic pinch, constitute the essential endoscopic landmarks. Endoscopically, Barrett esophagus appears as a salmon-colored epithelium extending proximal from the gastroesophageal junction (**Fig. 1**A). In cases where the border between the abnormal Barrett epithelium and normal squamous epithelium is difficult to distinguish, narrow band imaging can bring out the distinction (see **Fig. 1**B). Barrett esophagus length should be classified using the Prague system based on circumferential and total length of metaplasia. For example, if 2 cm of esophagus is involved circumferentially with Barrett metaplasia and there is an additional 2 cm tongue of Barrett metaplasia extending from this, this would be classified as C2M4.

In Europe, the histologic diagnosis is based on detection of any type of glandular mucosa with goblet cells,[27] whereas in the United States, intestinal metaplasia with periodic acid-Schiff–positive staining goblet cells is the most widely used histologic criteria. The key basis for this recommendation is the increased incidence of

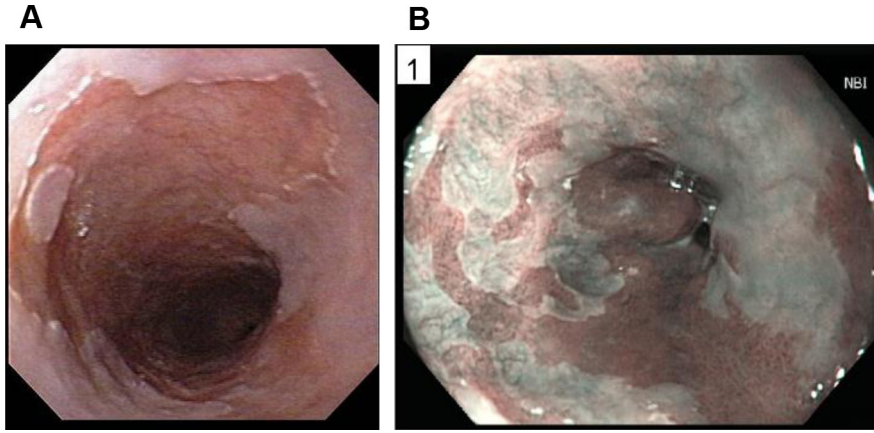


Fig. 1. (*A*) Endoscopic view of Barrett esophagus using white light. (*B*) Endoscopic view of Barrett esophagus using narrow band imaging.

esophageal adenocarcinoma among patients with endoscopic Barrett esophagus with intestinal metaplasia compared with patients who have endoscopic Barrett esophagus without intestinal metaplasia.[28]

Grading of dysplasia is a pathologic determination. There are several possible interpretations from the pathologist[29]:

1. Negative for dysplasia;
2. Positive for dysplasia, either LGD or HGD; or
3. Indefinite for dysplasia.

However, the interobserver variability is substantial. Comparing histologic samples of HGD, intramucosal carcinoma, or submucosal invasive adenocarcinoma, there was consensus among gastrointestinal pathologists (4 out of 7) in 85.9% of the cases, with overall agreement for all 4 diagnostic categories 0.30 kappa score.[30] Therefore, expert review or a review by a panel of experts is essential to ensure the most accurate diagnosis.

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. Chemoprevention is related to either prevention of esophageal acid exposure or modulation of proinflammatory mechanisms. Chemoprevention with proton pump inhibitors (PPIs), statins, and aspirin or nonsteroidal antiinflammatory drugs is based on epidemiologic evidence.[9] Patients who consume aspirin had a reduced prevalence of Barrett esophagus (OR, 0.56; 95% CI, 0.39–0.80).[31] 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).[32] During a median follow-up period of 4.5 years, nonsteroidal antiinflammatory drug and statin use were each associated with a reduced risk of neoplastic progression (hazard ratio, 0.47 and 0.48, respectively) and the combination increased the protective effect (hazard ratio, 0.22).[33]

Screening

For the general population, the American Gastroenterological Association (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.[34]

Treatment

Acid suppression without surveillance is based on the premise that screening has not been shown to improve mortality from adenocarcinoma or to be cost effective.[35] Barbiere and Lyratzapoulos[36] have questioned a variety of assumptions made for these recommendations. Therefore, the recommendation for acid suppression without surveillance should be made with caution and thorough patient counseling.

Acid suppression with surveillance identifies early stage esophageal adenocarcinoma. Because there are no reliable data on the duration of PPI treatment, most practitioners keep patients on PPI therapy indefinitely. Wong and colleagues[37] showed

that 80% of esophageal adenocarcinomas found in patients undergoing surveillance were stage I cancers, compared with only 6.5% in patients who were not in the surveillance program ($P<.001$). These data imply that cancers are indeed found earlier when patients are undergoing surveillance. Although the optimal frequency of surveillance has not been determined, most authorities recommend surveillance at intervals of 3 to 5 years for patients with nondysplastic metaplasia, 6 to 12 months for LGD, and every 3 months for HGD in patients not receiving invasive therapy.[1]

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.[38] Factors to consider in the choice between medical and surgical management include reflux-related symptoms, comorbidities, patient choice, adverse effects of medications, and individual surgeon skill. Biertho and colleagues[39] showed that, in patients with Barrett esophagus who underwent laparoscopic Nissen fundoplication, 33% had complete regression, 21% had a decrease in the degree of metaplasia or dysplasia, and 7% showed progression. No patients developed HGD or adenocarcinoma. A metaanalysis 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.[40] Nevertheless, the evidence that antireflux surgery lowers the risk for progression to adenocarcinoma is mixed.[41–43] 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. **Box 3** states the various treatment options for Barrett esophagus.

Although different types of endoscopic ablative therapies are available, the AGA,[34] the National Institute for Health and Clinical Excellence in the United Kingdom,[44] and the Society of American Gastrointestinal and Endoscopic Surgeons[45] have recommended ablation only with radiofrequency ablation (RFA), photodynamic therapy (PDT), or endoscopic mucosal resection (EMR) for patients with Barrett esophagus with HGD.

PDT consists of injecting a light-sensitizing drug into the patient, then exposing the portion of the esophagus to light of a specific wavelength, which then leads to metaplasia and dysplasia cell death.[46] However, eradication of both nondysplastic

Box 3
Treatment options for Barrett esophagus

- Acid suppression without surveillance
- Acid suppression with surveillance
- Antireflux surgery
- Endoscopic ablation
  - Photodynamic therapy
  - Radiofrequency ablation
  - Cryoablation
- Endoscopic mucosal resection
- Ablation with antireflux surgery
- Esophagectomy

metaplasia and HGD and prevention of adenocarcinoma has been variable,[47,48] with issues involving "buried glands." In addition, especially with long segments of Barrett esophagus, stricture formation was up to 40%,[49] with these strictures being difficult to dilate. For these reasons, PDT, although still considered an acceptable treatment, has lost favor.

RFA applies bipolar electrical energy to the mucosal surfaces at energy levels of 10 J for 1 second. With this technique, the mucosa is ablated to the submucosal level.[50,51] Generally, within several weeks to a few months after ablation, the exposed submucosal esophageal surface resurfaces with a "neosquamous" epithelium (**Fig. 2**). Endoscopic RFA is an effective means of eliminating Barrett metaplasia.[47] Using standardized follow-up protocols, complete ablation can be achieved in more than 90% of patients.[52,53] A metaanalysis 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.[54] A landmark randomized trial has demonstrated superiority of endoscopic RFA compared with sham procedure in reducing the progression to adenocarcinoma of HGD.[55] RFA has been shown to be durable,

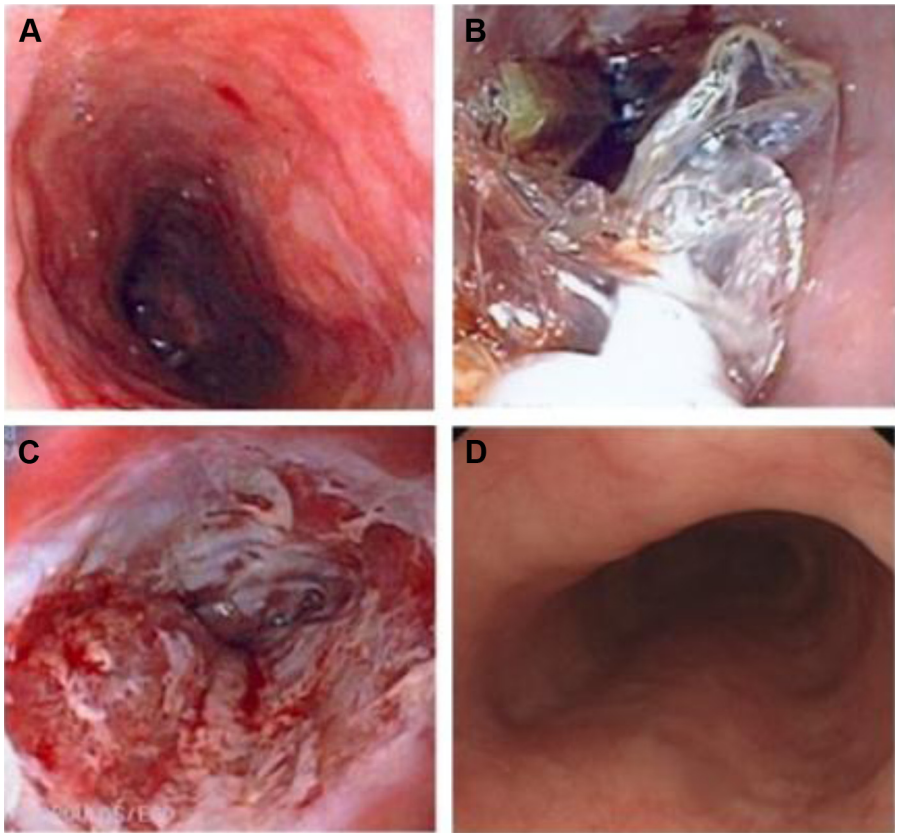


Fig. 2. Steps in radiofrequency ablation of Barrett esophagus. (*A*) Identification of proximal extent of Barrett metaplasia. (*B*) Deflated ablation balloon after ablation completed. (*C*) Immediate ulcer caused by ablation. (*D*) Normal squamous epithelium after completion of healing.

complete eradication of intestinal metaplasia 91%, 96% for HGD, and 100% for LGD, with no disease progression occurring in 1 per 73 patient-years of follow-up and progression to adenocarcinoma occurring in 1 per 181 patient-years.[56] However, ablation of longer segments of Barrett esophagus is associated with a higher rate of both persistent and recurrent metaplasia compared with segments shorter than 3 cm in length.[52] A recent randomized, controlled trial comparing surveillance to RFA in patients with LGD demonstrated at 3 years of follow-up a reduction in the progression to adenocarcinoma from 8.8% in the surveillance group to 1.5% in the RFA-treated group.[57]

Cryoablation involves endoscopically directed spray of liquid nitrogen at −196°C directly onto the Barrett epithelium.[58] Complete eradication of Barrett HGD has been reported in 68% to 97% of patients,[59,60] of intestinal metaplasia occurs in 57%,[60] and intramucosal adenocarcinoma in 80%.[59] Nevertheless, cryoablation is not as well-studied as RFA and is yet to be determined if it is an alternative or complementary treatment.

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. A particular advantage of EMR is that it provides tissue pathologic review. EMR can also be used for Tis or T1a esophageal adenocarcinoma. However, an endoscopic ultrasound examination is essential to ensure that the submucosa is not involved.[47] EMR 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.[61]

Endoscopic RFA has been used in conjunction with antireflux operations. First, RFA in patient with preexisting antireflux operation was associated with no change in reflux symptoms after ablation.[62] Second, combining endoscopic ablation with an antireflux operation reduces the overall number of procedures that a patient must undergo.[63] Last, the presence of a fundoplication reduces the recurrence or persistence of Barrett esophagus.[64] This is consistent with the findings of Krishnan and colleagues,[65] who also have shown that recurrence after RFA was related to uncontrolled reflux.

Esophagectomy was considered a reasonable approach to patients with HGD. The rationale was that 20% to 40% of patients with HGD on biopsy will actually harbor an early stage adenocarcinoma.[66,67] Although esophagectomy can be performed with very low mortality, morbidity remains high. Even if the operation is accomplished without morbidity, the detrimental effects on quality of life are significant.[68] Therefore,

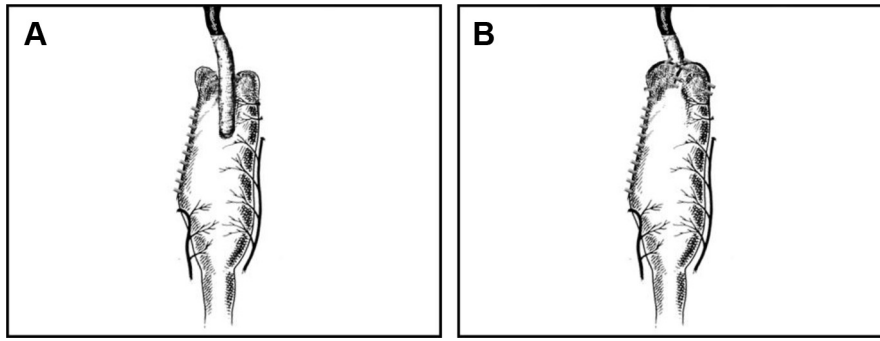


Fig. 3. (*A*) Creation of 2 gastric flaps at the apex of the gastric remnant to be used in the fundoplication. (*B*) The gastric flaps are brought around the anastomosis and sutured together to create the fundoplication.

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. When esophagectomy is performed for Barrett esophagus, vagus-preserving esophagectomy should be considered.[69] The addition of a fundoplication after an esophagectomy has been shown to decrease the incidence of recurrent Barrett esophagus in the remnant esophagus from 18% to 6%.[70] The type of fundoplication used involves created gastric flaps from the apex of the gastric remnant, then creating the esophagogastrostomy inferior to the flaps, then bringing the flaps around to create the fundoplication (**Fig. 3**).

SUMMARY

Although there are many unanswered questions with Barrett esophagus, we can safely say that the incidence is increasing, chemoprevention strategies for the prevention of Barrett metaplasia and its progression to adenocarcinoma may be in the offing, surveillance should be considered for all patients who are discovered to have Barrett esophagus, RFA is the treatment of choice for those with HGD and strongly considered in those with LGD, EMR should be the treatment of choice for patients with nodular high-grade Barrett esophagus, and, finally, vagal-sparing esophagectomy reserved for patients with persistent HGD or a strong suspicion of carcinoma, with consideration of a concomitant fundoplication.

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