Diagnosis and Surveillance of Barrett's Esophagus

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Introduction

Norman Barrett (1903–1979), a pioneering British thoracic surgeon, is widely recognized for his contributions to understanding gastroesophageal reflux and for describing the abnormal presence of columnar-lined esophagus in the presence of esophagitis [1]. Although coined Barrett's esophagus (BE), Barrett did not claim to be the first to describe the esophageal pathology and believed initially that the stomach was being drawn up by contractions of the esophagus rather than herniating through the hiatus. Later, he corrected his observations and recognized the importance of the sliding hiatus hernia and its effect on esophagitis [2]. He also made the original observation that the severity of the symptoms, such as pain, was not always proportional to the extent of esophageal inflammation [3].

Today, Barrett's esophagus is considered the most important risk factor for developing esophageal adenocarcinoma (EA), which has increased in incidence since the 1970s [4, 5]. The rationale for screening and surveillance of BE is to improve survival of EA through early detection of cancer. Guidelines on management are based on making an accurate histopathologic diagnosis of BE, which is obtained by performing a biopsy of the distal esophagus endoscopically. The relative risk of cancer is dependent on the histopathologic tissue types identified (i.e., nondysplastic vs low- or high-grade dysplasia) as well as the length of the segment of BE noted endoscopically. It is important to recognize that endoscopic surveillance has the potential for sampling error and the distribution of dysplasia and cancer can be highly variable. Moreover, surveillance programs can be expensive and time consuming. Understanding risk factors for BE, progression to EA, diagnostic criteria, and

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histopathology is important in order to optimize resource utilization for screening and surveillance.

Risk Factors

Barrett's esophagus has been identified in approximately 1–2% of the population and in 15% of patients with chronic gastroesophageal reflux disease (GERD) [6–8]. Patients with GERD symptoms present for greater than 5 years have a higher likelihood of having BE (odds ratio (OR) 3.0, 95% confidence interval (CI) 1.2–8.0), and the likelihood increases with symptoms that are present for greater than 10 years (OR 6.4, 95% CI 2.4–17/1) [9]. Likewise, patients with early onset of GERD symptoms (i.e., weekly symptoms before the age of 30 years) have a higher likelihood of BE when compared to those that did not (OR 31.4, 95% CI 13.0–75.8) [9]. Presence of a hiatal hernia can also increase the risk of BE (OR 3.94, 95% CI 3.02–5.13) [10]. Male gender has been identified as a risk factor for BE, and a meta-analysis demonstrated that the overall pooled male/female ratio among patients with BE was 1.96:1 (95% confidence interval (CI) 1.77, 2.17/1) [11]. Compared to Caucasians, African Americans have a lower likelihood of BE (OR 0.34, 95% CI 0.12–0.97), indicating that Caucasian race is also a strong risk factor for BE [12]. Central obesity can contribute to an increased risk for BE when compared with patients with a normal body habitus (OR 2.0, CI 1.5–2.6), and this relationship persists after adjusting for BMI and GERD and is also consistent in both men and women [13, 14]. BE is more common in first- or second-degree relatives of patients with BE when compared to controls (24% vs 5% $p < 0.005$), and the association remains strong after adjusting for age, gender, and body mass index (OR 12, 95% CI 3.3–44.8) [15]. Although smoking is associated with a greater risk for BE compared with non-smokers (OR 1.44, 95% CI 1.20–1.74), alcohol use has not been demonstrated to be a significant risk factor for BE [16, 17]. Risk factors for BE have been summarized in Table 27.1.

Risk factors associated with the presence of dysplasia or EA in patients with BE include older age and length of BE segment. There is a reported 3.3% increase in dysplasia per year in patients diagnosed with BE [18]. Furthermore, in patients with a BE segment length of over 3 cm, there is a 14% risk of dysplasia for each additional centimeter of BE present. Other risk factors for developing neoplasia in the

Table 27.1 Risk factors for Barrett's esophagus

1. GERD
2. Age
3. Hiatal hernia
4. Male gender
5. Caucasian race
6. Family history of BE (first- or second-degree relatives)
7. Smoking

GERD gastroesophageal reflux disease, *BE* Barrett's esophagus

presence of BE include central obesity and tobacco usage. It is important to note that there are certain medications that have been associated with reducing the risk of progression of BE to dysplasia including proton-pump inhibitors (PPIs), aspirin, nonsteroidal anti-inflammatory agents, and statins [19–21].

Diagnosis

Barrett's esophagus is diagnosed by identifying the presence of columnar-lined intestinal metaplasia (IM) in the distal esophagus, which is normally lined by stratified squamous epithelium (Fig. 27.1). The diagnosis is achieved by performing upper endoscopy and obtaining biopsies of salmon-colored mucosa that extends greater than 1 cm proximal to the gastroesophageal junction (GEJ). In patients with long segments (>2 cm) of suspected BE, eight random biopsies should be obtained.

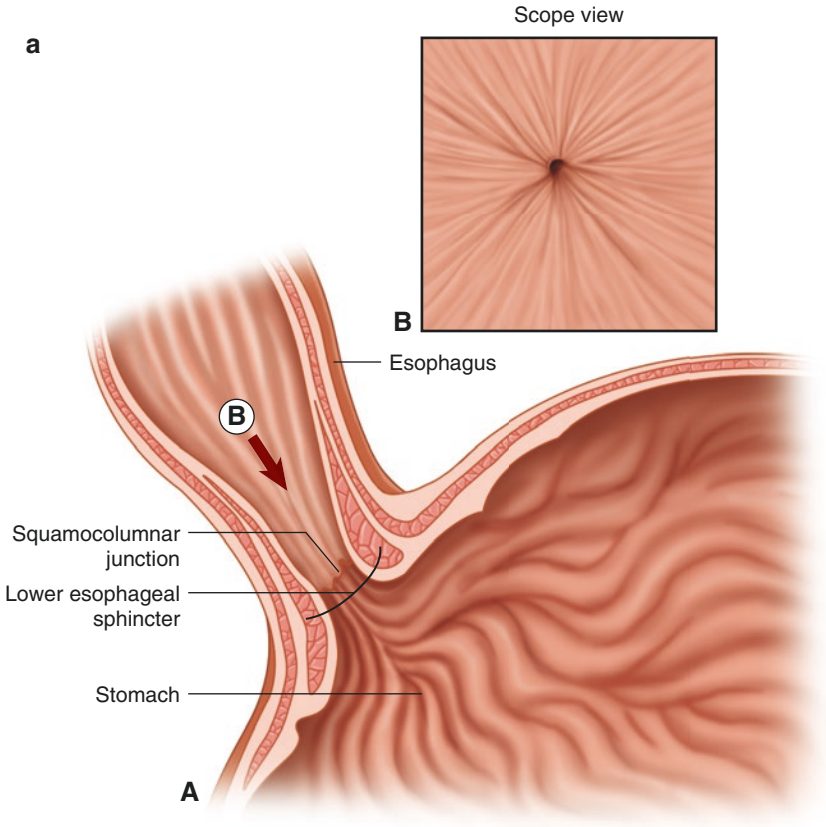


Fig. 27.1 (**a**) Endoscopic view of the gastroesophageal junction with a normal Z-line (squamocolumnar junction). (**b**) Endoscopic view of the gastroesophageal junction with Barrett's esophagus

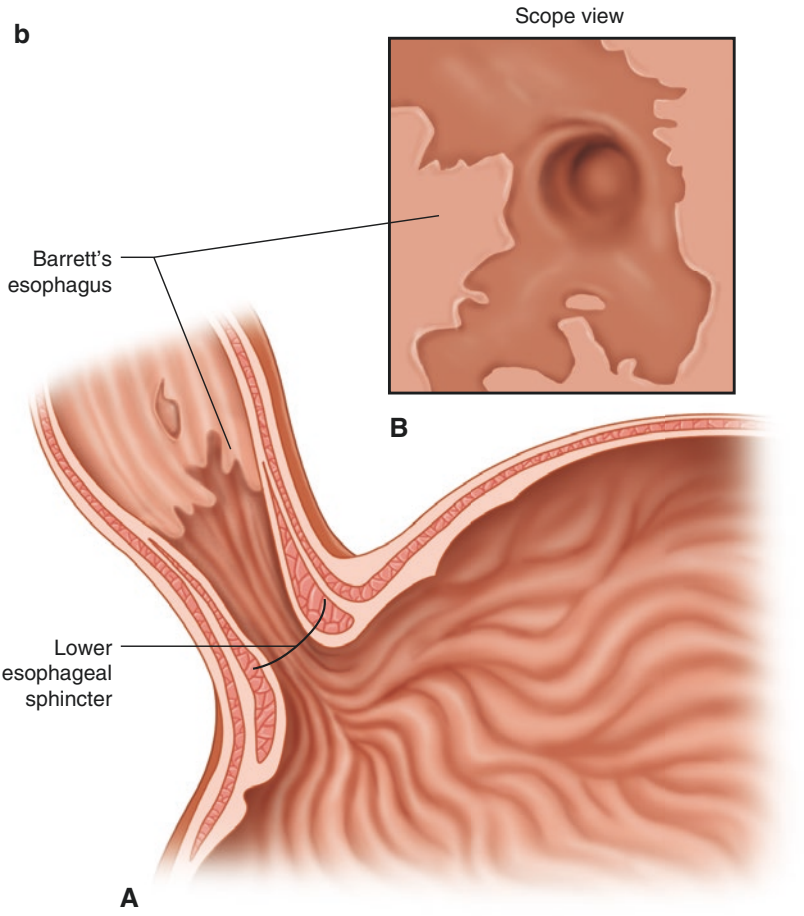


Fig. 27.1 (continued)

In patients with short segments (1–2 cm) of suspected BE, eight biopsies may not be possible, and so at least four biopsies per centimeter of circumferential BE and one biopsy per centimeter in tongues of BE should be obtained [18]. The location of the diaphragmatic hiatus, GEJ, and squamocolumnar junction (Z-line) should be reported by the endoscopist. In the presence of BE, the endoscopist should also describe the extent of metaplastic change using the Prague classification (Fig. 27.2) [22]. Assessment of the extent of BE on endoscopy is clinically important because more extensive disease is associated with a higher risk of dysplasia and EA.

High-definition, high-resolution white light endoscopy is the most common modality used for diagnosis. Alternatively, transnasal endoscopy is considered as an alternative to conventional upper endoscopy for BE screening [23, 24]. A wide variety of image enhancement techniques have been studied, such as methylene blue staining, acetic acid staining, indigo carmine staining, autofluorescence endoscopy,

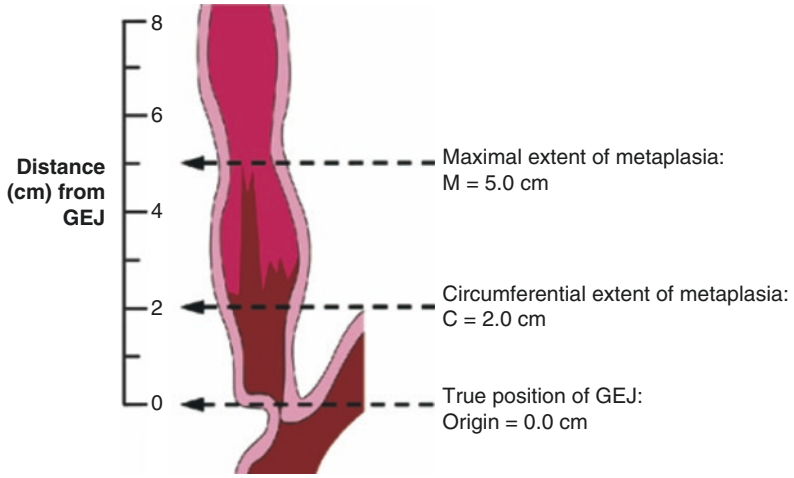


Fig. 27.2 Illustration of the Prague classification for Barrett's esophagus. (Adapted from Sharma et al. [22]). C, extent of circumferential metaplasia; M, maximal extent of metaplasia including the gastroesophageal junction (GEJ). The area of Barrett's esophagus is classified as C2M5

confocal laser endomicroscopy, volumetric laser endomicroscopy, spectroscopy, and molecular imaging. However, none of these methods have been determined to be superior. Electronic chromoendoscopy with either narrow-band imaging (NBI) or post-processing software systems allows for detailed imaging of the mucosal and vascular surface patterns in BE without the need for dye. When compared to high-definition white light endoscopy, NBI demonstrated no difference in the number of patients detected with dysplasia or neoplasia; however, fewer biopsies were required for NBI [25]. A meta-analysis evaluating the utility of electronic chromoendoscopy also suggested that this technology may increase the detection of dysplasia [26].

Histopathology

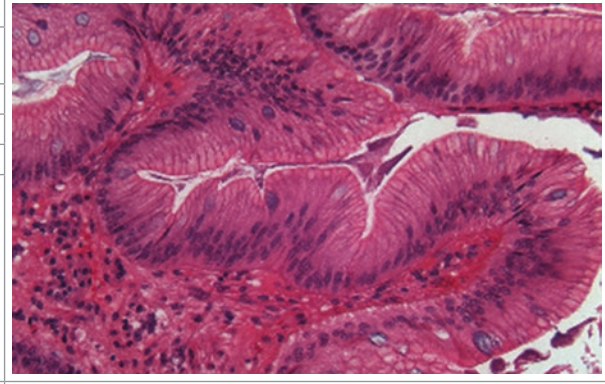
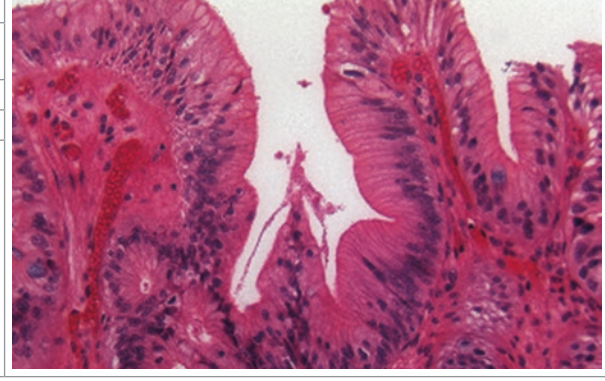
Barrett's esophagus is defined by the presence of intestinal metaplasia within visible columnar epithelium within the esophagus. Intestinal metaplasia refers to the transformation of squamous epithelium into columnar-lined epithelium consisting of goblet cells, which are recognized by a large cytoplasmic vacuole filled with blue-tinted mucin [27]. Alcian blue staining should be applied when there is doubt about the nature of goblet-shaped cells. Distended gastric foveolar cells may appear to be goblet cells ("pseudogoblet" cells), but they do not contain acid mucin and are therefore Alcian blue negative [28]. Additionally, IM identified below the GEJ should not be diagnosed as BE, since the changes are often secondary to *Helicobacter pylori* infection and its significance as a risk factor for EA is not well established [29]. Thus, it is important to obtain biopsies of BE that extends proximally 1 cm or greater from the GEJ and not in the presence of a normal Z-line or a Z-line with less than 1 cm of variability [18].

Neoplastic progression of BE is initiated by gastroesophageal reflux resulting in esophagitis, which in turn causes a subset of patients with IM to develop dysplasia, a precursor to EA. Histologically confirmed dysplasia is associated with a significant increased risk of EA; thus, understanding the degree of dysplasia is of clinical importance. During carcinogenesis, there is a spectrum of morphologic changes that are subdivided into four clinically significant groups: negative for dysplasia, low-grade dysplasia, high-grade dysplasia, and adenocarcinoma. These groups can be differentiated based on cytology, architecture, and degree of surface maturation among cells. Cytologic evaluation involves describing nuclear and cytoplasmic features such as size of nuclei, nuclear polarity, mitotic activity, and pleomorphism. Loss of nuclear polarity is an important feature that distinguishes high-grade dysplasia from low-grade dysplasia. It is evident when the nucleus is tilted, rounded, or horizontal to the basement membrane. Cellular architecture refers to the relationship of glands and lamina propria, which are well-spaced normally and demonstrate mild to marked distortion with crowded glands with dysplasia. Finally, normal cells demonstrate complete maturation, whereas dysplastic cells demonstrate minimal to no maturation. Biopsies with evidence of high-grade dysplasia should be evaluated for co-existing EA, which involves invasion into the lamina propria or muscularis mucosa. Other signs suggestive of EA include single cells in the lamina propria, desmoplasia, cribriform or solid tubular architecture, dilated tubules filled with necrotic debris, extensive neutrophilic infiltrate within the epithelium, ulcerated high-grade dysplasia, and neoplastic tubules incorporated into the overlying squamous epithelium [30]. Table 27.2 summarizes the histopathology of BE.

Although the presence of dysplasia is an important marker of cancer risk, considerable interobserver variability in the histopathologic interpretation of different degrees of dysplasia exists [31]. Current evidence supports confirmation of dysplasia by a second pathologist with extensive experience in BE interpretation [18]. In some cases biopsies may be indefinite for dysplasia. In these cases, there is pronounced inflammation or loss of surface epithelium along with cytologic atypia characterized by hyperchromasia, overlapping nuclei, irregular nuclear borders, and nuclear stratification. In addition, the cellular architecture is normal with some minimal gland crowding, and surface maturation is present. Given that the changes cannot be definitively described as reactive or neoplastic, repeat endoscopy within 6 months is recommended [27].

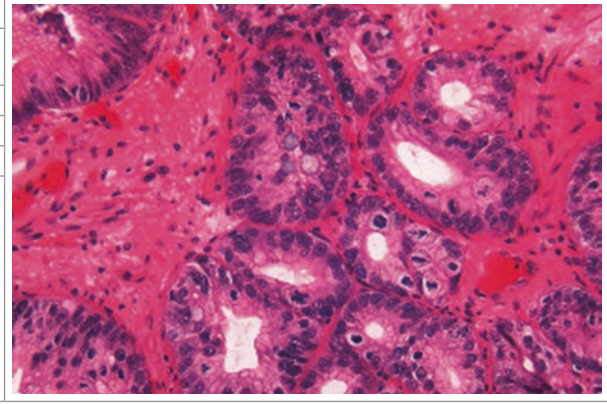
Since grading the degree of dysplasia accurately is important, biomarkers have been investigated in order to improve risk stratification of patients with BE. Specific immunohistochemical stains such as alpha-methylacyl CoA racemase (AMCAR), beta-catenin, cyclin DI, and p53 have shown some promise for differentiating neoplastic progression from reactive changes [32, 33]. Biomarkers that detect aneuploidy, increased tetraploidy, and loss of heterozygosity for chromosome 12p demonstrate some predictive value for neoplastic progression in patients with no dysplasia or low-grade dysplasia on biopsy, but have little utility in patients with high-grade dysplasia [34, 35]. Finally biomarker panels, which include detection of chromosomal abnormalities or tumor-suppressor gene-methylation patterns, have even identified patients with BE who progress to high-grade dysplasia 2 years

Table 27.2 Histopathology of Barrett's and risk of progression to esophageal adenocarcinoma

Histology	Hematoxylin and eosin stain (200×)	Risk of cancer progression
Negative for dysplasia Columnar cell metaplasia with mucin-filled, blue-tinted goblet cells Normal well-spaced glands Regular nuclei Smooth membranes Complete maturation		0.2–0.5% per year
Low-grade dysplasia Increased cellular atypia, hyperchromasia, pleomorphisms, and mitoses Gland crowding Maintained polarity Minimal maturation		0.7% per year

(continued)

Table 27.2 (continued)

Histology	Hematoxylin and eosin stain (200×)	Risk of cancer progression
High-grade dysplasia		7% per year
Nuclear enlargement, prominent pleomorphism, atypical mitoses		
Crowded glands		
Cribriform or budding glands		
Loss of polarity		
No maturation		

Adapted from Shaheen et al. and Booth et al. [18, 27]

before histologic changes were detectable [36]. Despite its promise, biomarkers have yet to be validated in prospective controlled trials, and routine use is not advocated at this time.

Screening and Surveillance

Although Barrett's esophagus is a common condition and considered a precursor to esophageal adenocarcinoma, screening of the general population is not recommended by the American College of Gastroenterology [18]. In a meta-analysis reviewing the risk of EA and mortality in patients with BE, the data suggests that most patients with BE die of causes other than EA, indicating that patients should be counseled appropriately with regard to surveillance and therapeutic options [37]. Screening may be considered in high-risk patients such as men with chronic and/or frequent symptoms of gastroesophageal reflux and two or more risk factors for BE. In females, screening is not recommended but may be considered in individual cases if multiple risk factors for BE or EA are present [18].

After initial diagnosis of BE, management and surveillance should be performed depending on the degree of dysplasia. In patients with suspected BE and a lack of IM on histology, a repeat endoscopy should be performed in 1–2 years' time. For patients with BE without dysplasia, endoscopic surveillance should be performed every 3–5 years. In patents with BE and indefinite dysplasia, a repeat endoscopy should be performed in 3–6 months after the patient has been placed on acid-suppressive therapy. Patients with low-grade dysplasia may undergo endoscopic therapy or surveillance every 12 months. If endoscopic therapy has been performed, surveillance is recommended every 6 months in the first year following complete elimination of IM followed by yearly endoscopic surveillance thereafter. Meanwhile, patients with high-grade dysplasia should be managed with endoscopic therapy followed by endoscopic surveillance every 3 months for the first year following complete elimination of IM, every 6 months in the second year, and yearly thereafter. Figure 27.3 summarizes surveillance recommendations. Endoscopic surveillance should be performed by obtaining four-quadrant biopsies at 2 cm intervals without dysplasia and 1 cm intervals in patients with prior dysplasia [18].

A variety of endoscopic ablative therapies have been reported to eradicate IM in patients with BE. Radiofrequency ablation can be performed in the setting of low-grade and high-grade dysplasia and is currently the modality of choice [38]. Photodynamic therapy can be performed in patients with BE with high-grade dysplasia only but has a higher cost and side-effect profile [39]. Endoscopic mucosal resection (EMR) is performed when mucosal nodularity or ulcerations are detected. If low- or high-grade dysplasia is discovered, ablative therapy can be performed followed by surveillance. In the case of EA, lesions confined to the mucosa have a low rate of lymphatic involvement, and thus mucosal resection followed by ablative therapy to eradicate the remaining BE is considered acceptable treatment [18]. Otherwise, esophagectomy is the treatment of choice for candidates with T1a or T1b EA with poor differentiation and/or lymphovascular invasion. Antireflux surgery has

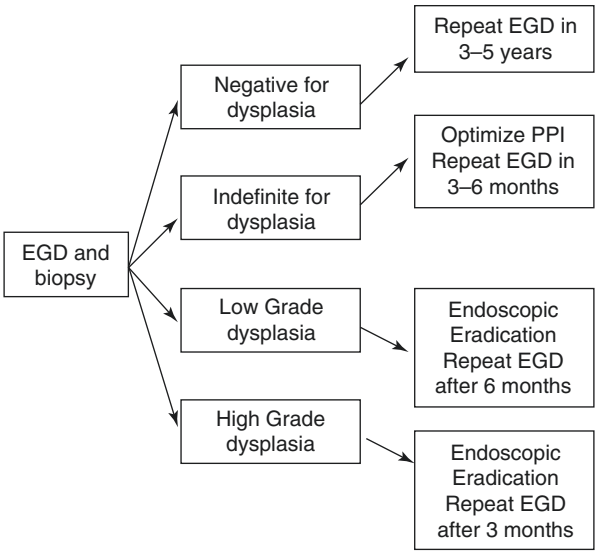


Fig. 27.3 Endoscopic surveillance of Barrett's esophagus according to histopathologic diagnosis. **EGD* esophagogastroduodenoscopy, *PPI* proton-pump inhibitor

demonstrated complete or partial regression of Barrett's mucosa with dysplasia regressing in nearly half of the patients at 5 years [40, 41]. However, the ACG does not consider antireflux surgery as an antineoplastic measure and only recommends surgery in patients with BE and GERD symptoms who are not well controlled by medical therapy [18]. To date, there has been no evidence to demonstrate the effectiveness of BE regression with magnetic sphincter augmentation devices. However, such prosthetic devices appear to result in pH normalization, cessation of PPI use, and improved quality of life in studies with 5-year follow-up [42].

Summary

Barrett's esophagus is a common condition that increases the likelihood for esophageal adenocarcinoma. Routine screening is not recommended for the general public but should be considered in patients with known risk factors. High-definition, high-resolution white light endoscopy with biopsy remains the gold standard for diagnosis, and the degree of dysplasia noted on histology dictates management.

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