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BARRETT'S ESOPHAGUS AND MANAGEMENT MODALITIES

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Abstract: Barrett's esophagus (BE) is characterized by the replacement of the normal stratified squamous epithelium of the distal esophagus with metaplastic columnar epithelium, a process that represents a premalignant transformation with a well-established link to esophageal adenocarcinoma. Chronic gastroesophageal reflux disease (GERD) is the principal risk factor, while additional contributors include Caucasian ethnicity, age over 50 years, central obesity, tobacco exposure, and a history of peptic strictures or erosive esophagitis. Current guidelines recommend selective screening based on risk stratification rather than population-wide programs. The diagnosis of BE requires endoscopic visualization of suspected mucosal changes, systematic biopsy sampling, and histopathological confirmation of intestinal metaplasia. In this review, we aim to synthesize contemporary evidence on the epidemiology, molecular and cellular mechanisms of pathogenesis, and evolving strategies for screening, advanced detection, and therapeutic eradication of Barrett's esophagus.

Keywords: Barrett's esophagus, esophageal adenocarcinoma, intestinal metaplasia, dysplasia, metaplasia

Introduction

Barrett's esophagus (BE) represents a metaplastic alteration of the distal esophageal mucosa, in which the native stratified squamous epithelium is replaced by columnar epithelium with a characteristic salmon-colored appearance extending at least 1 cm proximal to the gastroesophageal junction. This transformation is thought to arise from aberrant mucosal repair following chronic esophageal injury, most commonly associated with gastroesophageal reflux disease. The clinical relevance of BE is considerable, as it constitutes a well-recognized precursor to esophageal adenocarcinoma (EAC), a malignancy with dismal survival outcomes and a rapidly increasing global incidence.

Esophageal cancer overall ranks among the most lethal malignancies worldwide, occupying the seventh position in incidence and the sixth in cancer-related mortality, accounting for approximately one in eighteen cancer deaths in 2020. Epidemiologic estimates of BE prevalence in the United States range between 1.6% and 6.8%, though these figures are subject to methodological limitations, including selection bias toward older or symptomatic patients, exclusion of short-segment BE, reliance on diagnostic coding rather than histopathology, and increased utilization of endoscopy. European data provide more consistent prevalence estimates, with multicenter studies in Southern Europe reporting rates around 1.3% and population-based studies in Sweden identifying BE in 1.6% of subjects. Registry data from the Netherlands and Northern Ireland demonstrate rising incidence trends of both BE and EAC, though these increases may partly reflect greater endoscopic and biopsy activity during the study periods.

Collectively, these findings suggest that the epidemiologic trajectory observed in North America is mirrored across Europe, underscoring the global relevance of BE as a premalignant condition. The objective of this review is to critically appraise contemporary literature on Barrett's esophagus, encompassing epidemiology, molecular pathogenesis, risk stratification, screening strategies, and

advances in diagnostic and therapeutic modalities. By synthesizing current evidence, we aim to provide clinicians with an academically rigorous framework to guide informed decision-making in the management of this condition.

In 2022, the American College of Gastroenterology (ACG) issued updated clinical guidelines for the diagnosis and management of Barrett's esophagus (BE). Although randomized controlled trials have not demonstrated a reduction in esophageal adenocarcinoma (EAC)–related mortality through screening, evidence supports that screening, endoscopic surveillance, and endoscopic eradication therapy can lower the incidence of EAC and facilitate earlier detection. The ACG currently recommends screening in patients with chronic gastroesophageal reflux disease (GERD) who also possess at least three additional risk factors, such as male sex, age greater than 50 years, White race, tobacco use, central obesity, or a family history of BE or EAC in a first-degree relative.

Esophagogastroduodenoscopy (EGD) with systematic forceps biopsies remains the gold standard for diagnosis. Adjunctive techniques, including wide-area transepithelial sampling (WATS) and advanced imaging modalities such as high-definition white light endoscopy, chromoendoscopy with acetic acid, and electronic chromoendoscopy, have demonstrated improved sensitivity for dysplasia detection, though not all are incorporated into current guidelines. Artificial intelligence–based systems are under investigation in the United States and Europe to enhance neoplasia localization and optimize biopsy targeting. Alternative diagnostic approaches, such as unsedated transnasal endoscopy and capsule sponge devices coupled with molecular biomarkers (e.g., methylated DNA markers, trefoil factor 3), are being explored to reduce cost and procedural risk.

Histopathologic evaluation is critical, with emphasis on identifying and grading dysplasia. The extent of dysplasia correlates with cancer risk, and pathologists are encouraged to report both presence and distribution (focal versus diffuse). Dysplasia in BE is frequently flat and endoscopically occult, most often of intestinal type, though nonintestinal variants such as foveolar and serrated patterns exist. Diagnostic reproducibility remains a challenge, particularly in distinguishing high-grade dysplasia from intramucosal carcinoma.

Diagnostic criteria vary internationally. In the United States, BE requires endoscopic evidence of columnar mucosa extending ≥1 cm proximal to the gastroesophageal junction, with histologic confirmation of intestinal metaplasia containing goblet cells. In contrast, British and Japanese societies accept columnar metaplasia alone, irrespective of goblet cell presence. A hybrid classification has been proposed, allowing pathologists to specify columnar metaplasia with or without goblet cells.

Biopsy protocols are central to surveillance. The ACG recommends a minimum of eight biopsies, obtained in four quadrants at 2-cm intervals for short segments, while the Seattle protocol applies to longer segments (>4 cm), incorporating four-quadrant biopsies every 2 cm (or 1 cm if dysplasia is suspected). Narrow-band imaging (NBI) has shown promise in identifying dysplasia more effectively than random biopsies, though it is not yet guideline-endorsed. Visible or exophytic lesions within BE must be resected endoscopically.

The Prague criteria provide standardized grading of BE extent, documenting circumferential (C) and maximal (M) involvement. For example, a circumferential length of 6 cm and maximal extent of 8 cm is classified as C6M8. Islands of intestinal metaplasia are excluded from this system.

Emerging adjuncts such as WATS-3D have demonstrated increased detection rates of BE and dysplasia compared with forceps biopsies alone, though meta-analyses highlight limitations in

sensitivity. Biomarkers, particularly p53 immunohistochemistry, have shown utility in identifying occult dysplasia and predicting progression risk. TissueCypher, an AI-driven fluorescence-based pathology platform, stratifies patients into risk categories for progression to high-grade dysplasia or EAC, influencing surveillance intervals and therapeutic decisions. Prospective data indicate that TissueCypher results altered management strategies in more than half of patients evaluated.

This evolving landscape underscores the importance of integrating traditional diagnostic standards with advanced imaging, molecular biomarkers, and artificial intelligence to optimize detection, risk stratification, and management of Barrett's esophagus

Barrett's Esophagus Without Dysplasia: Medical and Surgical Management

Medical Therapy

In patients with non-dysplastic Barrett's esophagus (BE), the therapeutic objective is twofold: to alleviate gastroesophageal reflux disease (GERD) symptoms and to reduce the risk of progression to dysplasia and esophageal adenocarcinoma (EAC). Proton pump inhibitors (PPIs) remain the cornerstone of therapy. By irreversibly inhibiting the hydrogen–potassium ATPase pump on gastric parietal cells, PPIs suppress acid secretion and thereby mitigate mucosal injury. Observational and interventional studies have demonstrated that PPI therapy is associated with a significant reduction in the risk of dysplasia development, with longer treatment duration correlating with greater protective effect. Endoscopic follow-up has also shown regression in the circumferential and maximal extent of short-segment BE following sustained PPI use.

Other pharmacologic agents, including aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and statins, have been investigated for chemoprevention. However, current evidence remains inconclusive, and these agents are not recommended for routine use in BE management. Overall, PPIs are well tolerated and remain first-line therapy, offering both symptomatic relief and potential chemopreventive benefit.

Antireflux Surgery (ARS)

For patients with persistent GERD symptoms despite optimal medical therapy, surgical intervention may be considered. Antireflux surgery addresses mechanical contributors to reflux, such as lower esophageal sphincter incompetence, impaired motility, or hiatal hernia. Laparoscopic fundoplication, most commonly Nissen fundoplication, has demonstrated high rates of symptomatic control and is regarded as a safe and effective option.

In obese patients, fundoplication outcomes are less favorable due to increased intra-abdominal pressure and higher rates of wrap disruption. In this population, gastric bypass may be preferred, as it provides both reflux control and weight reduction, though at the expense of higher perioperative risk.

The role of ARS in preventing progression of BE remains controversial. Meta-analyses have not consistently demonstrated a reduction in EAC incidence compared with medical therapy, though some cohort studies suggest regression of dysplasia or metaplasia following surgery. Evidence supporting ARS as a preventive measure is limited by small sample sizes, nonrandomized designs, and short follow-up periods.

Future Directions

While ARS may be considered for symptom control in patients refractory to medical therapy or those unable to adhere to pharmacologic regimens, its role in altering the natural history of BE remains uncertain. Larger, randomized controlled trials with long-term follow-up are needed to clarify whether surgical intervention confers a protective effect against malignant progression. In the interim, ARS should be viewed primarily as a therapeutic option for GERD symptom control rather than a proven strategy for cancer prevention.

Endoscopic Submucosal Dissection (ESD)

ESD is the preferred endoscopic resection technique for Barrett's esophagus–associated lesions larger than 1.5–2 cm, as it enables complete en bloc removal rather than piecemeal excision, thereby facilitating accurate histopathologic assessment. The procedure involves submucosal injection (commonly saline) to elevate the lesion from the muscularis propria, followed by dissection with specialized knives. Despite its advantages, ESD is technically demanding and associated with higher complication rates, including bleeding, perforation, and stricture formation. Retrospective analyses have demonstrated high en bloc resection rates and curative outcomes in patients with high-grade dysplasia (HGD) and early esophageal adenocarcinoma (EAC), underscoring its therapeutic potential in selected cases.

Radiofrequency Ablation (RFA)

RFA is the most widely adopted ablative therapy for nonnodular BE and is considered the standard of care for eradication of dysplasia. The technique delivers high-frequency energy to the esophageal mucosa, inducing controlled tissue necrosis. Balloon-based catheters are used for circumferential ablation of longer segments (>2 cm), while focal catheters target shorter or residual areas. Multiple sessions are often required to achieve complete eradication.

Randomized controlled trials have demonstrated that RFA significantly improves eradication rates of both low-grade and high-grade dysplasia compared with sham procedures, while also reducing progression to cancer. Adverse events are generally manageable, with chest discomfort, dysphagia, strictures requiring dilation, bleeding, and rare perforation being the most reported. Overall, RFA is safe, effective, and well tolerated, making it the preferred modality for dysplastic BE without nodularity.

Discussion

Endoscopic therapy has become the established standard of care for patients with dysplastic Barrett's esophagus (BE). Ablative techniques are highly effective in achieving complete eradication of dysplasia (CE-D) and complete eradication of intestinal metaplasia (CE-IM) in the majority of patients. Among these modalities, radiofrequency ablation (RFA) is the most extensively studied and has consistently demonstrated safety and efficacy across multiple clinical trials.

Despite successful eradication, recurrence of intestinal metaplasia or dysplasia remains an unpredictable risk. Consequently, ongoing endoscopic surveillance following ablation is essential. Most recurrences, when detected in a timely manner, can be managed effectively with repeat endoscopic therapy.

Future directions in the management of BE emphasize the integration of advanced imaging technologies and biomarker-based risk stratification. These innovations hold promise for refining screening strategies, improving surveillance protocols, and enhancing early detection both before and after ablative therapy.

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