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# Barrett's Esophagus in 2012: Updates in Pathogenesis, Treatment, and Surveillance

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## Abstract

Barrett's esophagus (BE) is the only established precursor lesion in the development of esophageal adenocarcinoma (EAC) and increases the risk of cancer by eleven fold. It is regarded as a complication of gastroesophageal reflux disease. There is ever increasing body of knowledge on the pathogenesis, diagnosis, treatment and surveillance of BE and its associated dysplasia. In this review, we summarize the latest advances in BE research and clinical practice in the past 2 years. It is critical to understand both the molecular underpinnings of this disorder to comprehend the clinical outcomes of the disease. For clinical gastroenterologists, there is also continuous growth of endoscopic approaches is daunting and further improvements in the detection and treatment of BE and early EAC are anticipated. In the future, we may see the increased role of biomarkers, both molecular and imaging, in both diagnostic and therapeutic strategies for BE.

### Keywords

Barrett's esophagus; esophageal adenocarcinoma; biomarkers; acid reflux; obesity; endoscopic mucosal resection; radiofrequency ablation; photodynamic therapy; cryotherapy; narrow band imaging; confocal laser endomicroscopy; optical coherence tomography

## Introduction

Barrett's esophagus (BE) is the most significant risk factor for esophageal adenocarcinoma (EAC). In the past decades, advances in endoscopic technology have made endoscopic eradication therapy of Barrett's esophagus a safe and efficient alternative to esophagectomy [1]. This shift in treatment paradigm, however, has not been paralleled by improvements in clinical screening and surveillance guidelines. To date, surveillance of BE relies on the acquisition of four quadrant biopsies at set intervals along the BE segment, an approach that is prone to sampling error given the heterogeneous distribution of dysplasia [2]. This is important because detection of dysplasia is used for risk stratification and to guide treatment strategies. Recent years have brought several improvements to these shortcomings with the development of narrow band imaging and other forms of "electronic" chromoendoscopy that can enhance mucosal patterns. Advanced imagining technologies such as confocal laser endomicroscopy and optical coherence tomography hold great promise in real-time detection of dysplasia and targeted biopsy acquisition. The clinical utility of biomarkers for

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risk-stratification is being reevaluated [3]. Improved understanding of the pathogenesis of BE may offer new treatment strategies. Therapies have also undergone expansion in their indications as well as improvements in techniques for widefield resection.

## Updates in Pathogenesis

The focus of recent investigation in BE pathogenesis has focused on the origins of the BE stem cell. This has an importance in the therapy of Barrett's esophagus as abnormal stem cells may lead to the generation of abnormal clones that could be squamous, intestinal type, or even columnar. In an animal model, irradiated female rats were infused with bone marrow cells from male rats [4]. Intestinal metaplasia (IM) developed in female rats after inducing reflux esophagitis. Fluorescence in-situ hybridization (FISH) analysis of IM cells demonstrated presence of Y chromosome that implies that the infused bone marrow may be a source for the IM progenitor cells. Similar results have been reported in donor bone marrow-derived cells. These cells were assessed based on loss of Y chromosomes in male tumor cells [5]. However, the absolute donor origin of these cells can not be ascertained completely as cells can lose the Y-chromosome during the process of tumor progression [6]. One difficulty with this model is that it is established that in any form of major tissue injury, bone marrow stem cells can be recruited and whether this is the majority of the stem cell population unclear.

Esophageal mucosal injury from bile reflux in an acidic environment may lead to the development of BE [7]. In animal models, esophagitis was shown to develop after weeks of acid-bile exposure in addition to caustic injury. Following the exposure to acidic bile salts, interleukin 8 (IL-8) and interleukin-1β concentration were elevated in the esophageal mucosa. This was associated with neutrophils and T-helper type 2 (Th-2) lymphocytic infiltrations which preceded development of erosive esophagitis [8, 9]. Increasing mRNA expression of pro-inflammatory cytokines has also been reported in erosive esophagitis with or without BE. However, mRNA expression for Th-2 cytokines (IL-4, IL-10, and IL-13) was significantly higher in the presence of BE [10]. Current studies suggests that the development of BE may be mediated through IL-4 which triggers *CDX2* which then leads to proliferation of progenitor cells. However, the role of *Th-2* lymphocyte migration to the injury site still remains unclear.

A genetically engineered mouse model with overexpression of IL-1B in the squamous foregut with dckl2-GFP labeled stem cells for lineage tracing found that interestingly, cardia stem cells appear to be the source of intestinalized mucosa that migrated proximally into the squamous mucosa [58]. This study may be clinically significant as the source of esophageal stem cells could be in the proximal stomach, an area that has not been well treated in current endoscopic ablation protocols. However, there are important differences between mouse and human systems with two important ones being the presence of a squamous mucosa in the mouse proximal stomach that is constantly exposed to acid. The other issue is that this model has chronic inflammation throughout the squamous mucosa that may decrease the stem cell repopulation from other areas of the esophagus.

## Screening

To date, there is no firm recommendations to support population based screening for BE from any major Society or Guideline [11]. There is a wide latitude of clinical practice on who receives screening for BE [12]. Although GERD remains the strongest risk factor, cost-effectiveness analyses suggest that screening may only be cost-effective on the basis of preventing EAC in patients with BE. The true issue lies on what the real incidence of EAC progression in BE. A recent population-based cohort study of adenocarcinoma in BE report an annual risk of EAC of 0.12% among patients with BE [13]. These recent estimates are

lower than the previous rates which challenges current surveillance guidelines for patients with BE.

## Clinical Risk Stratification

Identifying at-risk population is the first step in establishing cost-effective screening strategy. Progress has been made in understanding clinical risk factors. Gastroesophageal reflux has been the primary risk factor for the development of BE. Its mechanism is not entirely clear and is a subject of a growing body of research. In recent years, the role of other risk factors aside from GERD has been the subject of in-depth study. Bile acid-induced injury in the pathogenesis of BE development is a topic of ongoing research. There are three bile acids: cholic acid (CA), chenodeoxycholic acid (CDCA) and deoxycholic acid (DCA). Amongst these, DCA is the most potent in inducing mucosal injury [14, 15]. Multiple human and animal models have studied their role in BE. Pooled results from in vivo and in vitro studies demonstrate that bile acids are responsible for increasing reactive oxygen species (ROS) leading to oxidative DNA damage and activating the NF-κB pathway for cell death [15, 16]. The impact of oxidative DNA damage is more severe with bile acids as there is concomitant decrease in MnSOD expression which is a scavenger for ROS [14, 17]. The damage from bile acids can be alleviated with the use of N-acetyl-l-cysteine which strengthens the case for ROS-induced injury [15]. Bile acid also induces cytokine-mediated cell damage and may stimulate expression of COX2, BMP4 and MUC2 genes for proliferation of intestinal metaplasia [15]. Another theory which has surfaced recently in the pathogenesis of BE is nitrate-induced injury. Nitrates are found in abundance in human saliva after a nitrate-rich diet and is present in high concentration at the GE junction [18]. Nitrates are converted to nitrites on contact with acid and become more carcinogenic. This occurs at the gastroesophageal junction that conforms to appearance of Barrett's esophagus at the junction. In addition, the industrialization of commercial farming has led to widespread use of nitrate fertilizers whose use mirror the increase incidence in esophageal adenocarcinoma. In addition, investigators have shown increased expression of Epidermal Growth Factor Receptor (EGFR) in nitrate-treated esophageal cells in vitro [19].

Obesity has been known to increase the risk for developing BE but there is on-going debate on whether obesity's contribution is from visceral adiposity versus overall increase in body mass index (BMI). Adipokines associated with visceral obesity have been reported to increased risk of various cancers [20, 21]. To understand the role of visceral obesity in esophageal tumor biology, Howard et al. reported increased expression of leptin and adiponectin receptor in esophageal tumor [22]. Indirect evidence also seems to demonstrate that sleep apnea may be associated BE [23]. Overall, evidence that fat cells are not only metabolically active, but serve as an immune organ has definitely influenced the thought regarding its role in formation of Barrett's esophagus neoplasia. IL6 and IL8 that are cytokines released by adipocytes have been found to be important in the intestinalization process.

Tobacco use is universally recognized as a risk factor for all neoplastic conditions. In a recent meta-analysis, smoking increases the risk of BE by almost 2 times and the risk is dose dependent until 20 pack years and plateaus thereafter [24, 25]. Smoking is also associated with progression of BE to adenocarcinoma [26]. Smoking as risk factor could be considered modifiable risk factor without need for further investigation as smoking cessation has multiple health benefits beyond prevention of EAC.

## Screening Modalities

The conduct of cost-effective BE screening and surveillance programs would also have to rely on cost-effective screening and surveillance strategies. Screening modalities could

broadly be divided into endoscopic and non-endoscopic. White-light endoscopy for population based screening for BE has not been proven cost effective. At this point, use of chromoendoscopy and newer endoscopes with trimodal imaging capacity have potential to increase detection rate but are time consuming and expensive and unlikely to be suitable for population based screening. Unsedated transnasal endoscopy (TNT) is a potentially cheaper alternative for screening. Recent studies evaluated its feasibility in office-setting, tolerability and diagnostic accuracy.[27, 28] The TNT has sensitivity of 0.91 and 1.00 specific in BE detection and feasible in primary-care office setting.[27], [55] Among non-endoscopic modalities for screening, cytosponge coupled with immunocytochemistry assay for trefoil factor 3 has been reported recently. Esophageal sampling is performed using a ingestible device (cytosponge). It can be perfromed in office setting and is devoid of serious adverse effects but sensitivity is not optimal in short segment BE.[29] In a microsimulation mathematical model, cytosponge has been demonstrated to be potentially cost effective and reduce mortality in 50-year or older patients with symptomatic GERD.[30]

By providing low cost, safe and effective screening modalities only then can we justify screening of BE in a population-based approach. At this point, future of screening for BE appears to be in non-endoscopic modalities and IM detection would be combination of cytology with biomarkers in high risk patients.

## Treatment

The treatment of dysplastic BE with endoscopic techniques continuous to benefit patients who would have likely undergone esophageal surgical resection. Various treatment modalities are being refined with on-going prospective studies that aim to validate both efficacy and durability of achieving complete remission of dysplasia. In general, both ablative and mucosal resection techniques are being combined to achieve better outcomes that are almost comparable to standard surgical esophagectomy without subjecting patients to increased post-surgical comorbidities and altered quality of life after esophagectomy

### Endoscopic Mucosal Resection

Nodular lesions in dysplastic BE can be resected through either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). Endoscopic resection techniques offer the dual the advantage of dysplasia resection and tissue acquisition for histology. The tissue obtained through EMR has better accuracy and interrater agreement for histopathological assessment for the degree for dysplasia when compared with forceps biopsy sampling [31]. In a recent multicenter retrospective cohort study, Pech et al. compared endoscopic resection to esophagectomy. Complete remission of neoplasia was achieved by 75 (98.7%) patients treated with endoscopic resection with a low rate of complication. In contrast, the esophagectomy group had 32% of patients develop major complications after surgery [32]. In conjunction with proper surveillance, endoscopic therapy has been shown to produce similar outcomes to surgical resection. Current studies show that EMR is successful in achieving complete remission of dysplasia in over 90% cases. Clinically significant bleeding may occur in less than 4% of cases; and stricture formation in 6%, especially with wide-field EMR [33, 34].

### Radiofrequency Ablation

Radiofrequency Ablation (RFA) is currently the leading modality for mucosal ablation. Its method of superficial thermal injury is generated by a high-frequency electromagnetic field from regularly-spaced electrodes in an endoscopically-attached ablation catheter. The efficacy of RFA has been reported in a multicenter, sham-controlled randomized trial. Complete eradication of dysplasia was achieved in 91% of cases with low grade dysplasia

while 81% was achieved for those with high grade dysplasia [35]. In non-dysplastic BE, RFA achieved complete remission of intestinal metaplasia in 98.4%. RFA is a relatively safe procedure with esophageal stricture formation in about 6–8% of patients which were successfully treated endoscopically. There are infrequent cases of bleeding and mediastinitis are also reported [35–37]. In a retrospective analysis of patients in our center, stricture formation was not significantly increased even with concomitant EMR for nodular lesions [38].

The long-term durability of RFA has being evaluated by various centers. In non-dysplastic BE, complete remission of intestinal metaplasia is maintained for over 4 years and recurrence of IM has good response to focal RFA.[39] In dysplastic BE, complete remission of IM is sustained in over 75% patients at 3 years follow-up while longer term outcomes are not available at this point.[37] In our tri-institutional multicenter NIH sponsored collaboration, of patients developed recurrence of IM 24 months following complete remission of intestinal metaplasia with 22% of these recurrences having dysplasia. Although most of these were endoscopically managed, our current experience underlines the need for continued surveillance even after successful RFA [40].

### Cryotherapy

There has been a recent interest in the use of cryotherapy for BE. Cryotherapy is a non-contact ablation technique which uses alternating cycles of rapid freezing and slow thawing to disrupt cell membrane and induce endothelial damage. At this point, the literature on cryoablation for dysplastic BE is limited mostly to retrospective observation which shows dysplasia eradication in over 80% and complete remission of intestinal metaplasia over half of the treated patients [41–43]. The alternate mechanism of thermal injury in cryoablation makes it an attractive alternative for patients who may not respond to RFA. The evidence for using cryoablation is mostly from retrospective studies again [44, 45]. In our center, cryotherapy has been used in a small series of patients who failed to eradicate dysplasia even after RFA. We have preliminary data to suggest significant improvement in length of BE and dysplasia grade [46].

## Surveillance

Current recommendations for endoscopic surveillance intervals are based on an annual risk of EAC of 0.5. [47]. The decreasing estimates of EAC progression in BE makes screening less cost-effective with the currents strategy of endoscopic evaluation with biopsies. The newer and advanced endoscopic imaging modalities which could differentiate dysplastic mucosa from normal mucosa more accurately have the potential for improving effectiveness of surveillance.

Narrow-band imaging (NBI) seems to decrease the need for random biopsies with better dysplasia detection [48]. Combination of imaging have been attempted to increase detection with mixed results. Endoscopic tri-modal imaging is a combination of high-resolution endoscopy, autofluorescence imaging (AFI), and NBI. It has shown to increase the targeted yield but no increase in overall yield when compared with standard video endoscopy [49]. Adding probe-based confocal laser endomicroscopy to high definition white-light endoscopy has shown to increase neoplasia detection in realtime [50]. Current surveillance guidelines do not recommend incorporation of these technologies in routine clinical practice. The real time evaluation of BE is a major initiative of the American Society for Gastrointestinal Endoscopy. We anticipate guidelines that will highlight the need for high quality endoscopic evaluation in conjunction with high-yield biopsy acquisition.

The role of biomarkers in surveillance for neoplastic progression of BE is also being explored as an adjunct to current endoscopic and histologic screening and surveillance strategies. The use of dysplasia in biopsy alone is not an accurate and cost-effective means to stratify patients at increased risk of EAC progression. Biomarkers can provide a second layer of validation that can make prognosticate better than traditional biopsies acquired during endoscopy. One of the most common genetic mutations in EAC is loss of heterozygosity in p53 gene and is independent predictor of progression to EAC [51]. Another set of biomarkers studied for progression to EAC is aberrant DNA methylation of tumor suppression genes. Methylation biomarkers have shown excellent performance in predicting EAC with area under the receiver operating curve of 0.84 in a multicenter study [52]. In a recent population based study, abnormal DNA ploidy, and Aspergillus oryzae lectin has shown to increase the odds of detecting dysplasia with each factors by 3.7 [53]. Mutation in mitochondrial DNA has been previously postulated in carcinogenesis and recently found to be strongly associated with progression of dysplasia in BE. Deletion of 4977bp in mitochondrial DNA (mtDNA) has been found to be significantly higher concentration in BE segment when compared to neighboring tissue. The frequency of this deletion is more often with progression of dysplasia but not in EAC. This suggest possible role of the mtDNA in progression of the IM into dysplasia.[54, 55]. In another prospective cohort study, selenoprotein P concentration was found to be positively correlated with risk of EAC with hazard ratio of 3.95 but not the serum selenium concentration.[56]

To date, there are several biomarkers each with different performance characteristics and lacking large-scale prospective studies to be validated for routine clinical practice. A needs-assessment survey of the U.S. gastroenterologists highlights the current limitation of BE screening and surveillance. Participants in the survey uniformly showed interest in a FISH-based testing for BE if proven accurate to be an acceptable adjunct to current histology for stratification of BE patients undergoing surveillance.[57]

## Conclusion

Our understanding of BE and the development of dysplasia has come a long way. The need to screen and treat dysplasia in BE is driven by the poor outcomes of EAC and the morbidity associated with surgical esophageal resection. In spite of multiple studies highlighting well-established risk factors for BE, there is still no cost-effective population-based strategies for BE screening. Newer modalities such as cytology obtained without need for endoscopy are being investigated. In contrast, endoscopic treatment strategies for BE complicated by dysplasia have emerged as effective alternatives to surgical esophageal resection. The issue of surveillance after endoscopic treatment is important given the recurrence rates that have been seen in single and multi-center studies.

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