

Recent developments in pathogenesis, diagnosis and therapy of Barrett's esophagus

Magnus Halland, David Katzka, Prasad G Iyer

Magnus Halland, David Katzka, Prasad G Iyer, Division of Gastroenterology and Hepatology, Mayo Clinic Rochester, MN 55905, United States

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Correspondence to: Prasad G Iyer, MD, Division of Gastroenterology and Hepatology, Mayo Clinic Rochester, Mayo Clinic, 200 First St. S.W., Rochester, MN 55905, United States. iyer.prasad@mayo.edu
Telephone: +1-507-2844824

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Abstract

The burden of illness from esophageal adenocarcinoma continues to rise in the Western world, and overall prognosis is poor. Given that Barrett's esophagus (BE), a metaplastic change in the esophageal lining is a known cancer precursor, an opportunity to decrease

disease development by screening and surveillance might exist. This review examines recent updates in the pathogenesis of BE and comprehensively discusses known risk factors. Diagnostic definitions and challenges are outlined, coupled with an in-depth review of management. Current challenges and potential solutions related to screening and surveillance are discussed. The effectiveness of currently available endoscopic treatment techniques, particularly with regards to recurrence following successful endotherapy and potential chemopreventative agents are also highlighted. The field of BE is rapidly evolving and improved understanding of pathophysiology, combined with emerging methods for screening and surveillance offer hope for future disease burden reduction.

Key words: Barrett's esophagus; Gastroesophageal reflux disease; Esophageal cancer; Esophagus

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Core tip: This review highlights recent updates in the pathogenesis, diagnosis and therapy for Barrett's esophagus (BE), the pre-malignant lesion for esophageal adenocarcinoma (EAC). The incidence of EAC continues to rise, and prognosis once diagnosed is poor. In this paper we critically reviewed the diagnostic criteria as well as new understanding of risk factors. Comparative recommendations from gastrointestinal societies are presented, and approaches to BE therapy, and management of recurrent BE after ablation is discussed.

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INTRODUCTION

Barrett's esophagus (BE), a metaplastic change of the esophageal mucosa from squamous to columnar mucosa with intestinal metaplasia, is the dominant pre-malignant lesion of esophageal adenocarcinoma (EAC) (Figure 1). The incidence of EAC continues to rise in the western world^[1,2] and thus efforts to prevent EAC by screening and surveillance for BE, coupled with endoscopic therapy for BE related dysplasia/neoplasia is practiced in many clinical settings (Table 1). Despite this, the effectiveness of current strategies in preventing EAC is not well proven^[3,4] as only a small fraction of patients with BE will develop cancer^[1]. Furthermore, up to 95% of EAC develops in patients with no prior diagnosis of BE despite its presence^[5,6]. New developments in the understanding of BE pathogenesis, screening, the neoplastic potential of BE, along with improvements in endoscopic therapeutic options, imaging techniques and molecular markers may impact future EAC mortality. In 2015, however, the management of the individual patient with BE remains challenging and the optimal approach to EAC prevention on a population level remains uncertain^[7].

DIAGNOSTIC CHALLENGES

Correctly defining the presence of BE in patients is crucial before committing patients to lifelong surveillance endoscopy. BE can be found in up to 10%-15% of patients with gastroesophageal reflux (GERD) symptoms who undergo upper endoscopy^[8,9]. In a recent study three gastroenterologists underwent intensive didactic and practical training in accurate identification of gastroesophageal junction (GEJ) landmarks and BE diagnosis which lead to a third of previously diagnosed BE patients being re-classified to have minor squamocolumnar junction abnormalities, but no longer to have BE^[8]. This study demonstrates that misdiagnosis of BE is common in clinical practice. This could likely lead to underestimation of the protective effect of a surveillance program by including patients with intestinal metaplasia of the GEJ or cardia (IMGEJ) frequently misclassified as short segment BE^[10], which is found in up to 15% of the normal population. Furthermore, the risk of progression to EAC in IMGEJ is vastly different when compared to Barrett's as demonstrated by Jung *et al*^[10] who followed 86 patients with IMGEJ for 8 years and no patient progressed to dysplasia or adenocarcinoma. A diagnosis of BE also adds significant financial and psychological burden to patients. Therefore improved diagnostic skills of endoscopists will be crucial to avoid misclassification between intestinal metaplasia at the cardia and BE.

The need for intestinal metaplasia for a diagnosis of BE continues to be a point of controversy, particularly between American and European gastroenterology societies. Evidence of an increased risk of progression



Figure 1 Endoscopic picture of gastroesophageal junction with Barrett's esophagus.

to EAC in subjects exhibiting columnar metaplasia with goblet cells (a marker of intestinal differentiation) compared to those without goblet cells is robust, with large population based cohort studies showing substantially different progression risks amongst these two histologic types^[11,12]. Nevertheless, there is some evidence of comparable molecular abnormalities found in columnar esophageal metaplasia with and without goblet cells associated with neoplastic risk in cross sectional studies of Barrett's patients^[13]. Moreover, sampling error and/or a patchy distribution of these cell types may account for a variable appearance of goblet cells on biopsy as repeated biopsies may demonstrate goblet cells in those without goblet cells at baseline. A recent study longitudinally followed 107 patients with columnar lined epithelium (CLE) without metaplasia. At repeat endoscopy after 2 years, 71% had suspected CLE confirmed at repeat endoscopy of which 29% had IM consistent with a BE diagnosis. These data suggest that surveillance may be discontinued in those without goblet cells at a second endoscopic examination after ensuring adequate sampling to detect intestinal metaplasia^[14].

NEW INSIGHTS INTO BARRETT'S PATHOGENESIS AND RISK FACTORS

In addition to the classic risk factors of gastroesophageal reflux, male gender and Caucasian race, other BE risk factors recently identified include obesity^[15], specifically central obesity^[16], metabolic syndrome^[17], and obstructive sleep apnea^[18]. These factors may contribute to BE risk independent of their additive effects on gastroesophageal reflux. More recently it has become clear that the distribution of excess body fat appears important, with central obesity confirmed as an independent predictor of BE^[19] although the effect on progression of BE is less clear^[20]. A recent meta-analysis summarized the findings of 40 studies which examined the association of body mass index (BMI) and central obesity (waist circumference, waist to hip ratio and quantitative measures of visceral

Table 1 Comparison of societal guidelines for screening and surveillance in Barrett's esophagus

	Screening	Surveillance NDBE	Surveillance LGD	Surveillance HGD
AGA ^[104]	Screening for patients with multiple risk factors Age 50 yr or older Male sex White race Chronic GERD Hiatal hernia Elevated body mass index Intra-abdominal distribution of body fat Screening in the general population is not recommended	Recommend surveillance No dysplasia: three to five years	Low-grade dysplasia: 6-12 mo	High-grade dysplasia in the absence of eradication therapy: 3 mo
BSG ^[48]	Endoscopic screening can be considered in patients with chronic GERD symptoms and multiple risk factors (at least three of age 50 yr or older, white race, male sex, obesity) The threshold of multiple risk factors should be lowered in the presence of family history including at least one first-degree relative with Barrett's or OAC	Patients with Barrett's oesophagus shorter than 3 cm, with IM, should receive endoscopic surveillance every 3-5 yr Patients with segments of 3 cm or longer should receive surveillance every 2-3 yr	High resolution endoscopy every 6 mo	Not recommended For HGD and Barrett's-related adenocarcinoma confined to the mucosa, endoscopic therapy is preferred over esophagectomy or endoscopic surveillance
ASGE ^[53]	Endoscopic screening for BE can be considered in select patients with multiple risk factors for BE and EAC, but patients should be informed that there is insufficient evidence to affirm that this practice prevents cancer or prolongs life	Consider no surveillance If surveillance is elected, perform EGD every 3 to 5 years with 4-quadrant biopsies every 2 cm Consider endoscopic ablation in select cases	Confirm with expert GI pathologist Repeat EGD in 6 mo to confirm LGD Surveillance EGD every year, 4-quadrant biopsies every 1 to 2 cm Consider endoscopic resection or ablation	Confirm with expert GI pathologist Consider surveillance EGD every 3 mo in select patients, 4-quadrant biopsies every 1 cm Consider endoscopic resection or RFA ablation Consider EUS for local staging and lymphadenopathy Consider surgical consultation
ACP ^[34]	Upper endoscopy may be indicated among men older than 50 yr with chronic GERD symptoms (symptoms for more than 5 yr) and additional risk factors (nocturnal reflux symptoms, hiatal hernia, elevated body mass index, tobacco use, and intra-abdominal distribution of fat) to detect esophageal adenocarcinoma and be	For surveillance evaluation in men and women with a history of be. In men and women with be and no dysplasia, surveillance examinations should occur at intervals no more frequently than 3 to 5 yr. More frequent intervals are indicated in patients with Barrett esophagus and dysplasia		

AGA: American Gastroenterology Association; BSG: British Society for Gastroenterology; ASGE: American Society for Gastrointestinal Endoscopy; ACP: American College of Physicians; HGD: High grade dysplasia; GERD: Gastroesophageal reflux; NDBE: Non-dysplastic BE; BE: Barrett's esophagus; LGD: Low grade dysplasia; EAC: Esophageal adenocarcinoma; RFA: Radiofrequency ablation.

fat by cross sectional body imaging) and the risk of erosive esophagitis, BE and EAC, and a reflux and BMI independent effect of central adiposity was again noted^[16].

The exact molecular mechanisms by which central obesity promotes replacement of injured squamous epithelium with columnar metaplasia are the focus of intense research. While increased gastroesophageal reflux disease due to mechanical effects has been proposed as the mediator of this association^[21], a recent study by Lagergren *et al*^[22] support the existence of additional mechanisms. Lagergren *et al*^[22] analyzed data from a population-based Swedish nationwide study of patients with a new diagnosis of EAC or GEJ adenocarcinoma and matched controls and found no evidence that the

increased risk of EAC in obese subjects is mediated by symptomatic reflux alone. However, it is clear that symptoms alone underestimate the severity of reflux in Barrett's patients^[23]. Several studies have assessed the association of smoking and alcohol with BE and EAC^[24-27]. In a recent meta-analysis which included thirty-nine studies comprising 7069 BE patients^[28], having ever-smoked was associated with an increased risk of BE compared with non-gastroesophageal reflux disease controls (OR = 1.44; 95%CI: 1.20-1.74), population-based controls (OR = 1.42; 95%CI: 1.15-1.76), but not GERD controls (OR = 1.18; 95%CI: 0.75-1.86). With regards to alcohol consumption, a recent meta-analysis of population based case-control studies found that there was a no significant association (any vs none, summary

OR = 0.77, 95%CI: 0.60-1.00) between any alcohol consumption and the risk of Barrett's esophagus^[29].

Genetic factors which contribute to BE have also been discovered. Two recent genome wide association studies have identified polymorphisms which are associated with an increased risk of BE and EAC^[30,31]. Associations have been found in 19p13 in CRTC1, whose aberrant activation has been associated with oncogenic activity, as well as 9q22 in BARX1 which encodes a transcription factor which is important in esophageal specification^[31]. Furthermore, polymorphisms near TBX5 and GDF7 which encode for a bone morphogenetic protein and a transcription factors which regulates esophageal development respectively, are associated with an increased risk of BE^[30].

An inverse relationship between *Helicobacter pylori* (*H. pylori*) and BE has been noted in observational studies, but significant heterogeneity between studies exists. In a meta-analysis which focused on only four methodologically robust studies found a relative risk of 0.46 (95%CI: 0.35-0.60) for the development of BE among persons infected with *H. pylori*^[32]. A subgroup analysis of seven studies showed that this effect was stronger for infection with CagA-positive strains (OR = 0.38; 95%CI: 0.19-0.78). Despite this association the increased risk of gastric cancer outweighs the protection against GERD offered by *H. pylori* induced gastric atrophy.

UPDATES IN SCREENING

New tools

The role of screening is controversial. Even the leading United States gastroenterology societies differ in recommendations on whether screening should be performed. For example, the American Gastroenterological Association states that screening may be considered in patients 50 years and older with multiple risk factors whereas the American Society for Gastrointestinal endoscopy states that screening should be offered after the pros and cons are discussed. In general, however, most societies agree that the high risk group for BE includes Caucasian men aged 50 and above with chronic reflux symptoms and with other coexisting risk factors such as central obesity and history of smoking^[9,33,34]. Conventional endoscopy for screening is expensive, not widely applicable and is usually performed by a physician. A possible alternative is un-sedated ultrathin endoscopy which avoids ancillary costs of sedation, personnel, recovery time and requirement for time off work and a patient escort^[35,36]. Peery *et al.*^[37] assessed the use of office based trans-nasal endoscopy using a 4.5 mm scope (Vision Sciences, Orangeburg, NY) with a disposable sheath. 426 participants were scoped and 99% completed the examination and no serious

adverse effects were reported. The examination was well-tolerated based on post-procedure surveys. Trans-nasal endoscopy was also compared with standard endoscopy in a randomized cross-over study^[38]. In this study of 95 patients TNE correctly diagnosed 48 of 49 BE cases and thus had a sensitivity and specificity of 0.98 and 1.00, respectively. Furthermore, physician extenders have also been shown to be able to accurately recognize esophago-gastric landmarks and reliably perform BE screening using transnasal endoscopy after a short training program^[39]. A recent study demonstrated that the majority of adults in a population based survey was willing to undergo screening for BE, and that unsedated techniques were preferred by 64% vs 36% for sedated endoscopy^[40].

Another recently described non-invasive screening method has been described using an ingestible sampling device, (Cytosponge)^[41]. This device consists of an ingestible gelatin capsule containing a compressed mesh attached to a string. The brushings obtained by the device are analyzed with an immunological assay for trefoil factor 3, a marker for columnar epithelium with intestinal metaplasia. In the largest study of this device, 501 of 504 patients were able to swallow the capsule with a sensitivity and specificity of 73% and 94%, respectively for detection of BE^[41]. The test also appears cost-effective compared to no screening assuming increased participation when compared to conventional endoscopy^[42]. Trials of other office based devices such as the EG II Scan (Intromedic, Seoul, South Korea), an ultrathin transnasal operator-controllable video capsule based esophagoscope with a disposable delivery system are underway (NCT02066233). Data on patient tolerance and diagnostic accuracy from these trials are awaited.

Novel biomarkers that examine chromosomal alterations, epigenetic markers as well as gene expression markers and microRNAs are all being evaluated^[31,43]. Kendall *et al.*^[44] demonstrated that a high serum leptin was associated with BE among men. Furthermore, Alashkar *et al.*^[39] found that patients with the high serum insulin levels had an increased risk (OR = 2.02, 95%CI: 1.15-3.54) of having BE, indicating a potential role for insulin or insulin-like growth factor in BE pathogenesis. These results were echoed in a case-control study where levels of circulating cytokines including adipokines had a modest association with BE^[45]. A biomarker panel was also recently evaluated in a case-control study of predominantly white male veterans^[45]. A risk prediction model including a multi-biomarker score, derived from serum levels of cytokines and leptin, as well as GERD frequency and duration, age, sex, race, waist-to-hip ratio, and *H. pylori* infection, achieved an area under the curve of 0.85, thus more accurately identifying persons in this population with BE than in previous non-invasive methods^[45-47].

UPDATES IN SURVEILLANCE AND RISK OF PROGRESSION

Currently surveillance is recommended for all patients with BE at intervals depending on the grade of dysplasia. In those without dysplasia, intervals of 3-5 years are suggested^[9,33,48]. In patients with low grade dysplasia (LGD) the interval is shortened to 6-12 mo, and high grade dysplasia (HGD) is generally accepted as a reason to intervene endoscopically or surgically. The rationale behind surveillance is based on estimated risk of progression from non-dysplastic BE to dysplasia and EAC. However, recent large studies have consistently demonstrated a lower than previously estimated annual risk of progression to EAC, and a recent meta-analysis estimated the incidence of EAC in non-dysplastic BE (NDBE) to be 0.33% per year^[11,49,50]. Furthermore, Gaddam *et al.*^[51] recently demonstrated that patients who have had persistence of nondysplastic BE after several surveillance endoscopies may have an even lower risk of progressing to EAC. In this study of predominantly white men, the annual risk of EAC was decreased by 50% and 70% after 3 and 5 consecutive surveillance endoscopies respectively, without dysplasia. These data support the need for revised surveillance intervals for such patients and perhaps even development of "exit-rules" for those at lowest risk as risk stratification evolves.

The risk of progression to EAC in patients with BE with LGD is less well defined^[52,53]. Recently, a meta-analysis found that the annual rate of progression to EAC among patients with LGD is 0.54%, but the authors commented on the wide variability that was observed across studies^[54]. This may be related to the low interobserver agreement for the diagnosis of LGD among pathologists^[55]. However, when LGD is confirmed by three expert gastrointestinal pathologists progression is significantly higher^[56,57]. Staining for aberrant p53 over-expression may help corroborate the presence of dysplasia and has now been recommended as an adjunct to standard histopathological examination in some guidelines^[48]. Because of the variable progression rate of LGD and diagnostic uncertainty, surveillance has been favored over endoscopic intervention until recently. Recently, a randomized trial compared radiofrequency ablation (RFA) vs endoscopic surveillance for patients with LGD^[58]. 136 subjects were randomized to receive RFA or endoscopic surveillance. During a median follow up period of 36 mo 1.5% of patients in the ablation group developed HGD or EAC compared to 26.5% in the control group ($P < 0.001$). The trial was terminated early due to the superiority of ablation, but the external validity of these trial results warrant consideration. First, the progression rate of 11.8% per person-year is higher than that what is observed in community based studies, and second, 28% of patients in the control

group had no dysplasia detected during follow up despite expert pathologists confirming the diagnosis at study entry. This suggests that not all patients with LDG will necessarily benefit from ablation, but that in a small subgroup of patients with persistent and perhaps multifocal confirmed LGD endoscopic ablation may be considered.

Ideally, the ability to non-invasively determine who is at risk of progression would make both ablation and surveillance programs more cost effective. This is particularly prudent as one of the most rigorous studies on the impact of endoscopic surveillance on mortality from EAC failed to find a significant benefit^[59], supporting findings from previous studies^[60,61]. These sobering data urge a review of current clinical practice, and the need for novel approaches in preventing deaths from EAC.

Advances in endoscopic detection of dysplasia

Detection of dysplasia during routine endoscopy relies on obtaining random biopsies per Seattle protocol^[62] in addition to targeting any visible abnormality. In a study which compared inspection times of less than 1 minute vs longer per 1 centimeter of BE, more patients with endoscopically suspicious lesions (54.2% vs 13.3% $P = 0.04$) and HGD/EAC (40.2% vs 6.7%, $P = 0.06$) were detected with longer inspection time^[63]. Also, some data suggest that neoplastic lesions in BE are more commonly found in the right half of the esophagus compared to the left (84.9% vs 15.1%, $P = 0.001$), with the highest rate in the 12 to 3 o'clock quadrant^[64], and thus particular attention to this anatomical location is important. This observation is not surprising as this is the area of greatest acid exposure and erosive esophagitis^[65]. Newer developments in endoscopic techniques, such as image magnification, chromoendoscopy (dye or filtering techniques which highlight dysplasia) and use of autofluorescence imaging have been evaluated, but have failed to become standard of care either due to lack of efficacy or practicality^[66-70]. For example, a recent study found only a 2% extra yield of autofluorescence compared to high definition white light endoscopy with random biopsies^[68]. The use of autofluorescence combined with magnification narrow band imaging was found^[71] to not be a useful technique for detection of dysplasia. More promise was observed with the first human data of targeted imaging of esophageal neoplasia using a fluorescently labeled peptide^[72]. In this study, a novel peptide which binds to areas of HGD and neoplasia provided 3.8 greater fold fluorescence intensity, and demonstrated 75% sensitivity and 97% specificity for neoplasia. Canto *et al.*^[73] recently evaluated *in-vivo* endoscope based confocal laser endomicroscopy (eCLE, a probe based technique which has resolution to yield close to a histologic view of the epithelium) in a randomized design. Among the 192 patients studied, the addition of eCLE to high

Table 2 Estimated effectiveness and durability of current endotherapies for Barrett's esophagus

	Radiofrequency ablation with or without EMR ^[75,77,78,105]	¹ Cryotherapy ^[79]	Endoscopic mucosal resection ^[80]	Photo-dynamic therapy ^[106,107]
Initial eradication of HGD	90%-95%	100%	90%	81%
Initial CRIM	70%-86%	100%	90%	72%
Recurrence of non-dysplastic Barrett's	13%-33% at 2-3 yr	19% at 36 mo ¹	39.5% at 5 yr	Unknown
Recurrence of dysplasia or cancer	1.6%-11% at 1.5-2.5 yr	3% at 36 mo	6.2% at 5 yr	16%-20% at 2-5 yr
Adverse events	Stricture 4%-11.9%	Stricture 9%	Stricture 47% (widespread EMR)	Stricture 37%

¹The 37.5% required touch up treatment after initial eradication 19% developed recurrent HDG but were successfully re-treated. Study methods: EMR for focal nodular BE, ablation of flat BE with any modality followed by EMR if ablation failed. CRIM: Complete remission from intestinal metaplasia; EMR: Endoscopic mucosal resection; BE: Barrett's esophagus; HGD: High grade dysplasia.

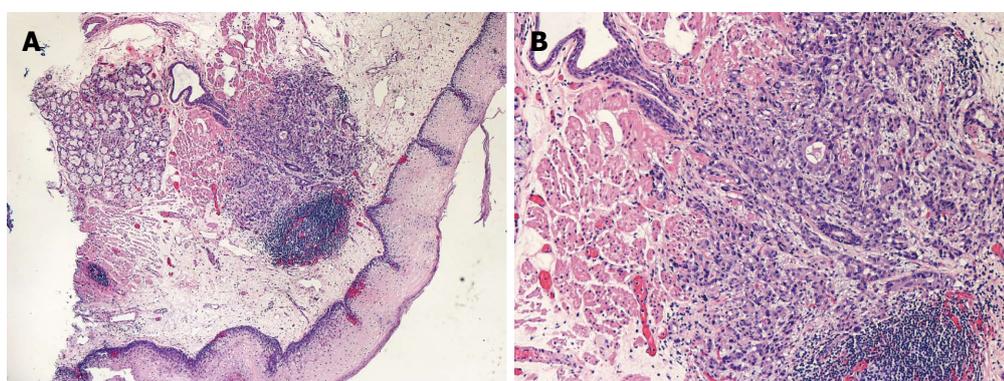


Figure 2 Photomicrograph of endoscopic mucosal resection specimen of neosquamous mucosa showing buried (subsquamous) adenocarcinoma. A: Low magnification of entire endoscopic mucosal resection tissue; B: Medium magnification of submucosal lesion.

definition white light endoscopy and target biopsies led to a lower number of mucosal biopsies and higher diagnosis yield for neoplasia (34% vs 7%, $P = 0.001$), compared with compared high definition white light endoscopy with random biopsies, with but comparable accuracy. The use of such techniques may allow for targeted rather than random biopsies but experience is currently limited to tertiary centers with expert endoscopists. More recently techniques using optical coherence tomography are being developed to allow comprehensive assessment of the BE segment with assessment of the subepithelial layers making this an intriguing technique to study sub-squamous BE^[74].

UPDATES ON OUTCOMES OF ENDOTHERAPY FOR BE AND MANAGING RECURRENCE

How durable is endotherapy?

An increasing number of patients now undergo endoscopic ablative therapy for BE. Techniques include thermal ablation with radiofrequency ablation (RFA), freezing of BE tissue with liquid nitrogen or endoscopic mucosal resection (EMR). In a recent study where patients with non-dysplastic BE were presented a simulated scenario which compared endoscopic

ablation with chemoprevention of EAC, 78% vs 53% ($P \leq 0.1$) preferred ablation^[65]. Table 2 presents an estimate of efficacy and durability of current endotherapies for BE. RFA, liquid nitrogen spray cryotherapy and EMR all have acceptable success rates for eliminating HGD and IM in the short to medium term. A systematic review of studies assessing efficacy and durability of RFA found that complete eradication of dysplasia (CE-D) and complete remission from intestinal metaplasia was achieved in 91% and 76% respectively^[75]. However, IM recurred in 13% over an average follow up of 18 mo. EAC developed in 9 of 3802 patients during 20.5 mo of treatment (0.1% per year). More recently, Orman *et al*^[76] reported a lower recurrence rate of 5.2% per year, but this study was limited by relying on a single, negative endoscopy utilizing Seattle -protocol biopsies. Several larger studies which assessed durability of remission of intestinal metaplasia of longer time periods are now delivering more sobering results^[77,78] reporting higher recurrence rates. A recurrence rate of 33% at 24 mo following complete remission has been found. 25% of the recurrences were dysplastic and 50% occurred at the GEJ. All except one were treated endoscopically. These data highlight the need for careful endoscopic surveillance following successful BE eradication. Less data exist for the long term outcomes of liquid nitrogen

spray cryotherapy after successful ablation, but in one such study of 32 patients a rigorous surveillance program was employed^[79]. 37.5% of patients needed treatment for recurrence during surveillance.

Outcomes of endoscopic mucosal resection of BE and early esophageal cancer are also encouraging, although recurrence of BE is common. Almond *et al*^[80] reported outcomes of 90 patients who underwent widespread EMR with the aim of eradicating BE, with ablative procedures used as an addition during follow up. CE-IM was achieved in 90% of patients, but during follow 5 years of follow up NDBE recurred in 39.5% and neoplastic BE was found in 6.2%. In another study of 81 patients who underwent EMR for esophageal lesions (50% HGD and 50% EAC) the complete eradication rate of HGD was 84% at a median follow up of 3.25 years^[81]. The cancer specific survival was 100%. More recently, a meta-analysis compared the safety and efficacy of endotherapy vs surgery for early neoplasia in BE in 7 retrospective studies which included a total of 870 patients^[82]. No difference between endotherapy and esophagectomy was seen with regards to neoplasia remission rate (RR = 0.96, 95%CI: 0.91-1.01) and overall survival rate at 1, 3 and 5 years (5 years survival RR = 1.00, 95%CI: 0.93-1.06). Endotherapy was associated with a higher neoplasia recurrence rate (RR = 9.50, 95%CI: 3.26-27.75), but fewer major adverse events (RR = 0.38; 95%CI: 0.20-0.73). Furthermore, a recent randomized trial examined the use of argon plasma coagulation therapy to residual non-neoplastic BE with PPI compared with standard surveillance and PPI^[83]. The number of secondary lesions was 1 in the ablation group (3%), and 11 in the surveillance group (36.7%), leading to significantly higher recurrence-free survival for the patients undergoing ablation ($P = 0.005$). The most significant problem with circumferential EMR is the occurrence of esophageal strictures in up to 40% of patients^[75].

All eradication therapies rely on the replacement of BE with neosquamous epithelium but the durability and functional characteristics of this tissue are less clear. In a recent study, biopsies of the neosquamous epithelium exhibited dilated intracellular spaces and defective barrier function^[84]. The molecular profile on FISH analysis is also different in neosquamous epithelium when compared to native type^[85]. Finally, it is also important to note that the existence of "sub squamous" intestinal metaplasia occurs in up to 5%-30% of patients undergoing ablation which may lead to neoplasia^[86] (Figure 2). For all these reasons, ongoing surveillance despite successful eradication is recommended until the long term behavior and durability of the neosquamous epithelium has been further delineated.

Updates on chemoprevention

The role of chemoprevention in BE remains con-

troversial. Non-steroidal anti-inflammatory agents, statins and metformin have all been studied as potential chemopreventative agents in BE^[87-89]. Previous studies have produced conflicting results with regards to a potential role of NSAIDs in preventing neoplastic progression of BE^[88,90,91], and no protective role against the development of BE itself has been observed^[92]. No interventional trials till date have examined the role of NSAIDs in chemoprevention, and thus currently the overall risk-benefit ratio is estimated from observations studies, and routine use is not currently recommended^[93]. Metformin has shown *in vitro* effects on esophageal cancer cells^[94], but clinical data on adenocarcinoma appear negative^[95]. In a recent trial of 74 patients with BE, twelve week administration of metformin for 12 wk did have an effect on cell proliferation as measured by levels of pS6K1, compared with placebo^[96]. Statins, which have a proven role in primary and secondary prevention for cardiovascular disease, may also prevent development of EAC through inhibition of proliferation and induction of apoptosis among esophageal cancer cells. Previous association studies have also found an inverse relationship between statin use and EAC^[87,88]. A recent nested case-control study found that in addition to the inverse association between statin prescription and EAC (OR = 0.58, 95%CI: 0.39-0.87, $P < 0.01$) a robust dose and duration response was observed^[97]. Furthermore, a recent meta-analysis of observational study found an 28%) reduction in the risk of esophageal cancer among patients who took statins (adjusted OR = 0.72; 95%CI: 0.60-0.86)^[98]. This adds further weight to the potential chemo protective role of statins, although no data from a randomized controlled trial are currently available. Proton pump inhibitors are frequently prescribed to patients with BE to control reflux symptoms, but given the role of acid damage in BE pathogenesis a potential protective role for progression has been postulated^[99]. Conversely, given the rise in serum gastrin produced by PPIs a potential for oncogenesis could also be present. Epidemiological studies of a potential association between acid-suppressive therapy and progression to EAC have produced conflicting results^[100,101]. A recent meta-analysis pooled data from seven observational studies and found that PPI use associated with a 71% reduction in risk of EAC or high grade dysplasia (adjusted OR = 0.29; 95%CI: 0.19-0.79)^[102]. Thus, PPIs, which is already universally prescribed to BE patients, may have a significant chemo protective effect and further randomized trials are warranted. A recent study also suggests that the use of PPIs might be a cost-effective approach assuming a minimum risk reduction in EAC of 19%^[103].

CONCLUSION

Current efforts at preventing deaths from esophageal

adenocarcinoma by screening for and surveying BE come at a great cost to society. New insights into BE pathogenesis, coupled with the development of non-invasive risk assessment tools will hopefully lead to more focused and effective non-invasive screening programs in a well-defined population. The currently available endotherapies for HGD and early cancer appear to be effective and are less morbid than surgery, but identifying patients who are most likely to benefit from these therapies is currently challenging. The ability to predict which patients are less likely to progress to cancer, and thus may not need ongoing surveillance is emerging, and will be crucial for cost-effectiveness of current surveillance strategies. Chemoprevention, including use of PPI's, statins and anti-inflammatory medications may become important public health strategies to help hamper the overall disease burden from esophageal cancer on a population basis.

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