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Barrett's Esophagus: Diagnosis and Management

Swathi Eluri, MD, MSCR and **Nicholas J. Shaheen, MD, MPH**

Center for Esophageal Diseases and Swallowing, Division of Gastroenterology and Hepatology, University of Nousing a new validated NBI classification systemrth Carolina, Chapel Hill, NC

INTRODUCTION

Barrett's esophagus (BE) is characterized by a change of the normal stratified squamous epithelium lining the esophagus to a metaplastic columnar epithelium with goblet cells. The prevalence of BE is estimated to be 1.5% in the general population [1, 2] and as high as 15% in those with gastroesophageal reflux disease (GERD) [3, 4]. Other risk factors associated with BE are older age, male sex, smoking, central obesity, and white race [5–10]. There also appears to be an increased genetic pre-disposition among those with first-degree relatives with BE [11].

BE is a known precursor to esophageal adenocarcinoma (EAC), and oncogenesis is thought to occur through a sequential progression from metaplasia to dysplasia to carcinoma. The risk of developing EAC is as high as 7% per year in those with high-grade dysplasia (HGD) [12] and 0.7% per year in low-grade dysplasia (LGD). However, reports of EAC risk in LGD are highly disparate, ranging from risks approximating that of non-dysplastic BE (NDBE), to risks of progression to HGD or EAC of 10% per year or more [8, 13–16]. EAC is associated with high mortality and is increasing in incidence in the western world [17–19]. Risk factors for progression of BE to EAC include increasing degree of dysplasia, increasing age, increasing BE segment length, male sex, and smoking, among others [20]. Therefore, there is a need to optimize screening, surveillance, and treatment of high-risk BE with the ultimate goal of decreasing the disease burden and mortality associated with EAC.

In this review article, we will briefly discuss the diagnostic criteria and endoscopic screening for BE. We will then review the indications and performance of endoscopic surveillance, with an emphasis on possible new directions to improve the performance of surveillance. We will conclude with a discussion of the management of BE, with an emphasis on the indications, technique, and outcomes of endoscopic therapy for BE.

Correspondence: Swathi Eluri MD, MSCR, 4119B Bioinformatics Building, 130 Mason Farm Rd, Chapel Hill, NC 27599-7080, Phone: (919) 843-7893, swathi.eluri@unchealth.unc.edu.

DIAGNOSIS

Diagnostic Criteria

Current guidelines recommend that the diagnosis of BE should be based on the presence of columnar epithelium ≥1 cm proximal to the gastroesophageal (GE) junction with biopsies consistent with intestinal metaplasia (IM) [8]. This is in contrast to British diagnostic criteria, where confirmation of IM is not required for diagnosis [21]. The relationship between the presence of IM and progression to EAC has been conflicting [22–24], and complicated both by sampling error [25] and interobserver variability among pathologists [26]. Studies have shown that there is a significant increase in the likelihood of finding IM with increasing number of biopsy samples taken during endoscopy [27].

As a result, the recommended number of random biopsy samples are 4 samples for every 2 cm of BE segment length or 8 for segment length <2 cm in those with suspected BE [28]. In addition, a normal or mildly irregular Z-line should not be routinely biopsied because IM of the cardia is common in chronic GERD patients [29] and has not been definitively demonstrated to imply an increased risk of EAC [30, 31]. In terms of BE classification, a segment >3 cm is defined as long-segment BE and segment <3 cm as short-segment BE. The Prague classification [32] describing the circumferential and maximum extent of BE is used for standardized reporting, in addition to endoscopic landmarks such as the diaphragmatic hiatus, gastroesophageal junction, and the squamocolumnar junction [8].

Screening

The primary goal of screening is to identify patients with BE. However, the question of who to screen is complex, because >90% of patients who develop EAC have no prior history of BE, and the traditional practice of screening GERD patients misses a substantial group destined to develop EAC, because approximately 40% of EAC patients do not have a history of chronic GERD [33–35]. Despite these shortcomings, screening guidelines have traditionally focused on a sub-set that is at higher risk for BE and EAC, which include men with chronic GERD symptoms and 2 additional risk factors including age >50, white race, central obesity, smoking history, and family history [8]. Although risk-stratification models [36–38] have been developed to aid in determining who to screen for BE, these models need further validation and their role in clinical practice is currently limited.

The most commonly used screening modality for BE is conventional per oral upper endoscopy with biopsy samples from any endoscopically visible columnar mucosa in the tubular esophagus. Limitations of endoscopy for screening are that it is an invasive procedure requiring a specialist and that it is costly [39]. Brush cytology sampling might reduce cost, increase the surface area that can be analyzed, and be used in combination with molecular markers to aid in risk-stratification. Wide-area transepithelial sampling (WATS) uses computer-assisted analysis of an abrasive transepithelial brush biopsy to sample a larger surface area, to help overcome the issue of sampling error. When WATS is used in conjunction with 4-quadrant biopsies, there is on average a 40% incremental yield of dysplasia and metaplasia detection in 2 prospective trials [40, 41]. In addition, there is high interobserver agreement [42] for detection of not only BE (κ=0.88) and HGD/EAC

(κ=0.95), but also for LGD (κ=0.74), in contrast to the low inter-observer agreement with traditional 4-quadrant biopsies [43]. However, this technology is currently used as an adjunct to per oral endoscopy, meaning that costs associated with endoscopy are not avoided.

Alternative endoscopic techniques for screening include transnasal endoscopy (TNE), and single-fiber endoscopy. TNE uses a smaller-caliber scope and is inserted into the esophagus orally or nasally without the need for sedation [44]. TNE has been shown to be comparable to standard endoscopy for detection of BE and for the quality of biopsy specimens [45–47]. In addition, TNE is well tolerated and has demonstrated efficacy in a community setting [44, 48, 49]. However, most gastroenterologists have limited experience with transnasal approaches, which require good nasopharyngeal anesthesia, and knowledge of pertinent landmarks. Endoscopes with a disposable sheath (EndoSheath; Vision Sciences, Orangeburg, NY) and disposable esophagoscopes (EG scan; IntroMedic, Seoul, South Korea) may be limited by the quality of images generated, a problem likely to be addressed by continuing technological advances. Single-fiber endoscopy is smaller in diameter (1.6 mm) compared with TNE and allows for NBI imaging but does not provide operator control or the ability to collect biopsy samples [50].

There are also non-endoscopic screening devices for BE that are designed to obtain tissue for histologic evaluation. The Cytosponge is a gelatin-coated sponge attached to a string and collects cytologic specimens from the esophageal mucosa when withdrawn and may have the potential to replace traditional endoscopic screening in a cost-effective manner [51]. Preliminary data showed a sensitivity of 73% to 90% for identifying BE when used in combination with immunohistochemistry staining for trefoil factor 3 (TFF3) [4], but the diagnostic accuracy is still being validated.

Esophageal capsule endoscopy (ECE), another non-invasive capsule device, has shown conflicting data as to effectiveness in BE diagnosis [52–54] without being more cost-effective [55] and, as a result, is not commonly used for screening. Tethered capsule endomicroscopy (TCE) can provide additional information regarding the microscopic features and architecture of the esophageal wall, and is currently being investigated [50].

Surveillance

Surveillance in BE is aimed at early detection of dysplasia. Dysplasia is categorized as NDBE, indeterminate, LGD, HGD, or carcinoma [56]. The presence of dysplasia should be confirmed by a second pathologist expert in GI histopathology, due to a high degree of inter-observer variability [56]. The degree of dysplasia dictates recommended surveillance intervals. Patients with NDBE are recommended to have a repeat endoscopy in 3 to 5 years, and those with indeterminate dysplasia are recommended to undergo a repeat examination in 3 to 6 months after optimization of proton pump inhibitor therapy [8]. Patients with LGD can undergo eradication therapy, although ongoing endoscopic surveillance is an acceptable alternative for LGD. Those with a higher degree of dysplasia should be considered for endoscopic eradication therapy (Figure 1).

Careful endoscopic examination of esophageal mucosa and obtaining an adequate number of biopsy samples is vital for effective surveillance [57, 58]. Longer mucosal inspection time

has been associated with increased detection of HGD/EAC [59]. In addition, highly dysplastic lesions in BE are more often found in the right side of the esophagus, so particular attention to this area maybe beneficial [60–63]. A standardized biopsy protocol for surveillance includes random 4-quadrant biopsies every 2 cm in NDBE and every 1 cm in dysplastic BE [64], in addition to targeted sampling of focal mucosal abnormalities. Any mucosal abnormalities noted on surveillance should be sampled; among those with a history of dysplasia, endoscopic mucosal resection (EMR) is recommended for optimal disease staging [65]. Empiric data demonstrate that in current practice, a majority of patients often do not undergo adequate biopsies when surveillance is performed leading to decreased dysplasia detection [66].

A variety of endoscopic imaging techniques have been developed to improve visualization of the esophageal mucosa for detection of dysplasia and neoplasia, although none has been adopted for wide-scale routine use presently (Table 1). The current criterion standard for both screening and surveillance is use of high-resolution white-light endoscopy (HD-WLE). NBI increases detection of dysplasia when compared with HD-WLE and also requires a lower number of biopsies [67, 68]. In addition, the type and regularity of mucosal and vascular patterns using narrow-band imaging (NBI) have recently been shown to identify dysplasia in BE patients with 80% sensitivity and 88% specificity using a new validated NBI classification system [69] (Figure 2). Autofluorescence imaging (AFI) can detect mucosal abnormalities with high sensitivity but poor specificity compared with HD-WLE [70]. In one prospective study, despite using tri-modal imaging with HD-WLE, NBI, and AFI, 10% of patients had advanced lesions that were not visibly apparent and were only detected on random biopsies [71]. Magnifying endoscopy with chromoendoscopy has been shown to improve detection of both IM and dysplasia by enhancing mucosal visibility [72–76]. Confocal laser endomicroscopy (CLE) can increase the yield of dysplasia detection [77–79] with good accuracy [80, 81] compared with random biopsies but is limited by longer procedure times, cost, and the restricted time for mucosal inspection before the injected fluorescein dye obscures visualization. Unlike CLE, modalities such as VLE can image a larger surface area in a short period of time and can identify sub-squamous BE [82], making it a potentially useful tool for surveillance. However, other than case reports and series [83, 84], VLE's role and efficacy in BE surveillance is not completely elucidated.

Whether these advanced imaging techniques may obviate the need for random esophageal biopsies is a matter of great interest. The "Imaging in Barrett's Esophagus Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI)" initiative [85] by ASGE, established minimum performance thresholds for an imaging modality with targeted biopsies to replace the need for random biopsies in BE. To meet PIVI performance thresholds, an imaging technology in combination with targeted biopsies should have a sensitivity of ≥90% and negative predictive value (NPV) of ≥98% for detection of HGD/EAC, and a specificity of 80% to replace random biopsy protocol. Acetic acid chromoendoscopy, NBI, and endoscope-based CLE currently meet these criteria for BE surveillance and are endorsed by ASGE for use in surveillance of NDBE by experienced operators to obtain targeted biopsies [86].

Surveillance has been shown to be beneficial in identifying EAC at earlier stages and in improving mortality in several retrospective studies [33, 87–89]. However, these studies are susceptible to lead-time and length-time biases. Given differences in growth rates between tumors, it is quite possible that only the most indolent disease is detected by surveillance endoscopy. Consistent with concerns about over-estimation of the effectiveness of surveillance, no survival benefit from surveillance was noted in a case–control study from the Northern California Kaiser Permanente population [90] or in the US Veterans Health Administration [91]. Even if surveillance is effective, the cost-effectiveness of this intervention has been questioned [92, 93]. Of note, all these studies focus on survival benefit after EAC diagnosis in those undergoing surveillance and do not assess the benefit of preventing EAC from endoscopic eradication of dysplasia. Given that recent guidelines suggest endoscopic therapy before the development of EAC [8, 94, 95], the impact of intervention in dysplastic disease may be under-appreciated. Therefore, despite conflicting evidence on the effectiveness of surveillance, it is a recommended practice in the management of BE [8].

Current surveillance strategies based on histologic tissue analysis are not without limitations. There is evidence that a meaningful proportion of BE patients in a surveillance program can progress to EAC despite having no history of dysplasia [87, 96], highlighting the limitations of current surveillance in accurately risk-stratifying individuals. Several potential sources of error include lack of adherence to recommended biopsy protocol, sampling error, and interobserver variability between pathologists of degree of dysplasia [25, 27, 43, 97]. As a result, adjunct techniques to improve risk-stratification, such as WATS [41] with computer-aided analysis to overcome limitations with sampling error, as well as biomarkers, have been explored. Although early data on this technology suggest that its use adjunctive to standard biopsy protocols might increase detection of dysplasia, its operating characteristics are not completely defined, and its application adds time and expense to the procedure.

Molecular biomarkers have been investigated to identify individuals with BE who are at an increased risk of progressing to EAC (Table 2). Because BE is thought to develop from a dysplasia to carcinoma sequence, the degree of genetic aberration can be used to predict disease progression [98]. Molecular abnormalities such as chromosomal aneuploidy or tetraploidy, hypermethylation of p16, loss of heterozygosity of p53, and microRNA expression, among others, have been associated with progression to HGD or EAC [99–104]. Panels of markers have also been tested to increase the predictive ability carcinogenesis [105]. All these markers are based on histologic tissue and thus cannot overcome the limitation of sampling error. Therefore, attempts have been made to develop serum biomarkers, including interleukins, EAC-specific proteins, and serum microRNAs with mixed results [38, 106, 107]. To date, none of these markers are routinely used in BE risk-stratification with the exception of immunohistochemical testing of p53, which is recommended by the British Society of Gastroenterology Guidelines (BSG) as an adjunct to analysis of biopsy samples during BE surveillance [21].

MANAGEMENT

Chemoprevention

The utility of chemopreventive agents in BE is unclear. Because those with baseline dysplasia are often treated with endoscopic ablation and those with NDBE have a very low risk of progression, the safety and cost-effectiveness of long-term use of any agent for chemoprevention needs to be justified. Currently, it is recommended that all patients with BE, regardless of the presence of GERD symptoms, be treated with once daily PPI based on evidence [108] that progression to neoplasia is reduced compared with no PPI therapy or with the use of H2 receptor blockers. Although the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with a diminished incidence of EAC [109], and a reduced the risk of progression to EAC in BE patients by up to 30% [110], the bleeding risk associated with NSAIDs may outweigh these benefits and, therefore, they are not currently recommended as a chemopreventive strategy in BE [8].

Endoscopic Therapy

Once the diagnosis of BE is confirmed, further management is dictated by the degree of dysplasia (Figure 2). In HGD, endoscopic eradication therapy appears to be associated with a decreased risk of subsequent adenocarcinoma compared with surveillance endoscopy, and may have a similar all-cause mortality rate when compared with esophagectomy [111, 112]. There is also evidence [16] that treating LGD [14] with endoscopic eradication therapy results in a lower rate of progression to HGD or EAC during a 3-year follow-up period. Currently there are differences among professional society guidelines regarding management of BE with LGD. Although the ACG and AGA recommend consideration of endoscopic eradication therapy for LGD confirmed by a second pathologist, the BSG suggests endoscopic surveillance [8, 21, 95]. At this time, routine endoscopic eradication therapy is not recommended for NDBE, given the low risk of progression to neoplasia [113], the small but real risk of procedure-related adverse events, and the costs inherent in the procedures [114, 115]. In general, before initiating treatment, overall patient health, including other comorbidities, need to be considered, particularly in those with LGD, where the rates of progression to EAC are low.

There are multiple endoscopic therapies available for BE eradication, including resection and ablation modalities. The presence of irregular, raised or nodular esophageal mucosa within BE is associated with higher rates of malignancy [116], so initial resection of these areas with either EMR or endoscopic submucosal dissection (ESD) [117, 118] is necessary to determine depth of invasion for staging and selection of further therapy [119]. EMR can be performed by band ligation technique or with an endoscopic resection cap and the use of a snare for resection. Both techniques are comparable, but in a head to head comparison, band ligation was found to be less costly, more time effective, and with fewer adverse events [120]. Compared with EMR, ESD offers a more controlled and precise resection of the target area and, for larger lesions, determination of adequacy of resection at the lateral margins. In general, because the deep margin of the resection is the most important clinically actionable data from mucosal resection, and because most centers see small volumes of

subjects needing ESD, for most Western endoscopists, the focus should be on performing quality EMR.

If the resected nodular area shows LGD, HGD, or T1a EAC without lymphatic or vascular involvement, then subsequent endoscopic ablative therapy is recommended [8] for complete eradication of IM (CEIM). Although stepwise, radical complete EMR of the entire BE segment demonstrates high rates of eradication and remission over a 2-year follow-up period [121, 122], stricture rates are demonstrably higher than focal EMR followed by radiofrequency ablation (RFA) [123]. Therefore, combination therapy with EMR followed by ablation is the recommended approach for most patients, and has been shown to eradicate HGD in 86% to 92% of the cases and IM in 62% to 87% of cases [124, 125]. Adverse events of endoscopic resection techniques include bleeding, perforation, and a dose-dependent risk of stricture formation [121, 122].

For non-nodular BE, several ablative options are available, but RFA is the ablative treatment of choice based on efficacy, safety, and availability of a large amount of high-quality data. Radiofrequency energy can be delivered either circumferentially through balloon-based devices or focally through devices attached to the end of the endoscope (Figure 3). RFA is highly effective in eradicating dysplasia in BE patients with 81% of HGD and 91% of LGD achieving complete eradication of dysplasia (CED) at 12 months in a multicenter US randomized controlled trial [111]. The most common adverse events of RFA is post-ablation stricture with a pooled estimate of 5.6% (95% CI, 4.2%–7.4%) [126]. Other rare adverse events include bleeding, perforation and post-procedure chest pain requiring hospital admission for control.

Cryoablation is another effective ablative modality for management of BE, which delivers either liquid nitrogen or carbon dioxide to the intended tissue via a spray catheter inserted though the upper endoscope. A newer device is also available to deliver cryotherapy using nitrous oxide via a self-contained, balloon based system [127]. Cryoablation can achieve complete eradication of HGD in a high proportion of patients with BE in retrospective studies, with good durability during a 24-month follow-up period [128, 129]. Similar efficacy was seen in prospective data with 81% to 94% eradication of HGD [130, 131]. A more recent prospective study showed that cryoablation with pressurized CO_2, when combined with EMR for treatment of BE with nodular neoplasia provided CED in only 44% of the patients [132]. There is a paucity of randomized trials comparing mucosal ablation modalities to each other.

Although photodynamic therapy (PDT) is rarely used currently due to cost and side effects, level 1 evidence exists for the efficacy of PDT in preventing cancer in BE with HGD [133]. In a multicenter study, PDT resulted in eradication of HGD in 77% of the cases with maintenance of remission in 85% during a 5-year follow-up period [133, 134]. Despite this efficacy, use of PDT is limited by high rates of post-ablation strictures with reports as high as 36% and higher procedural cost compared with RFA [134, 135]. Other ablative modalities that are available are argon plasma coagulation (APC) and multipolar electrocoagulation, which have been shown to have similar rates of CEIM [136]. The most frequent use of APC is to treat residual disease after ablation as this can promote sustained remission for a greater

duration after CEIM [137]. Although no head to head comparisons exist, APC has been shown to have similar cost efficacy to RFA [93].

After CEIM, the risk of recurrence of intestinal metaplasia is significant, especially with risk factors such as increasing age, BE segment length, and baseline dysplasia [138] (Figure 4). A recent meta-analysis [139] that assessed all types of endoscopic eradication modalities showed that the annual incidence of recurrent IM was 7.1%, of dysplastic BE was 1.3%, and of HGD/EAC was 0.8%, over more than 10000 patient years of follow-up time. When the analysis was restricted to only treatments with RFA, the annual incidence of recurrent IM was 9.5%, of dysplastic BE was 2%, and of HGD/EAC was 1.2%. There was a similar risk of recurrence in those treated with combination therapy with EMR followed by ablation [140]. Although the recurrence of dysplasia is low, it is not insignificant, and thus it is important for patients who have achieved CEIM and CED to undergo periodic post-ablation surveillance with careful mucosal inspection and both targeted and random biopsies.

Recent work suggests that the highest yield for random biopsies is at the squamocolumnar junction, and that strategies that heavily sample that area might improve the yield of dysplasia without incurring more biopsies or extra costs [141]. The frequency of current surveillance examinations is based on baseline pathology and expert opinion [8]. For patients treated for baseline LGD, one commonly used strategy is to perform surveillance every 6 months for the first year after CEIM, then annually after. For patients treated with baseline HGD, surveillance can be performed every 3 months in the first year after CEIM, every 6 months in the second year after CEIM, and then annually after. Recurrent disease is treated in a similar manner as before initial endoscopic therapy, and success rates of a second CEIM after recurrence of BE are high [138, 142].

Surgical Therapy

Anti-reflux surgery has not been shown to be superior to medical therapy in preventing EAC incidence in BE patients based on 2 meta-analyses [143, 144] and is not recommended for prevention of neoplasia in BE. There is some evidence that post-ablation the neosquamous epithelium is potentially more prone to reflux injury [145], possibly increasing the risk of BE recurrence. A recent study found decreased BE recurrence after RFA with Nissen fundoplication versus PPI therapy, in the subgroup of patients with long-segment BE and a hiatal hernia >3 cm [146]. However, current data as to any incremental benefit of a surgical anti-reflux procedure compared with medical therapy after successful RFA remains inconclusive [147, 148], and in general the indications for consideration of fundoplication after RFA remain similar to those in the general GERD population.

The utility of surgery, specifically esophagectomy, is more evident in BE patients with advanced neoplasia. In patients with T1a esophageal adenocarcinoma, esophagectomy may be indicated in cases with poorly differentiated tumors, lymphovascular invasion, or cases in which ablation is technically difficult or failed [149]. Traditionally, esophagectomy has been viewed as the standard of care for all patients with T1b esophageal adenocarcinoma. However, the relative merits of esophagectomy and endoscopic therapy in tumors only superficially invasive into the submucosa (T1b sm1) have recently come into question. Although any submucosal invasion has traditionally been considered to be associated with

prohibitively high rates of lymph node involvement to consider endoscopic therapy, recent data suggest that at least a subgroup of such patients may be effectively treated endoscopically [117]. Currently, the precise degree of tumor invasion to preclude endoscopic therapy in a good surgical candidate is unsettled, and data to support endoscopic management of patients with tumors showing superficial submucosal invasion is not yet robust enough to allow definitive conclusions to be drawn.

CONCLUSION

Although only a small proportion of patients with BE develop EAC, the high mortality and cost associated with this outcome drives screening, surveillance, and treatment practices of BE, with the ultimate goal of preventing advanced neoplasia. Despite the technical advances in detection of metaplasia and neoplasia, the incidence of EAC is rising, highlighting inadequacies in current screening and surveillance practices. Because the risk factors of BE and EAC extend beyond a history of GERD symptoms, developing cost-effective screening tools to identify those at risk is imperative. Once individuals with BE are identified, the goal is to prevent progression to EAC through early dysplasia detection and treatment. This must involve better risk stratification in the large pool of BE patients to understand who is at increased risk of progression. The wide range of evolving imaging and therapeutic modalities will likely enhance our ability to detect mucosal abnormalities, but detection of dysplasia is currently based on histology, which has its limitations. The use of biomarkers and risk-stratification models will have utility to identify individuals with BE who are at highest risk of progressing to EAC, and this improved risk stratification can help guide targeted interventions. In terms of treatment, endoscopic ablation or endoscopic resection is efficacious and has an acceptable safety profile for treating BE with early neoplasia. Esophagectomy is generally reserved for advanced cases of EAC, and those failing endoscopic eradication therapy.

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Acronyms

BE	Barrett’s esophagus
GERD	gastroesophageal reflux disease
EAC	esophageal adenocarcinoma
HGD	high-grade dysplasia
LGD	low-grade dysplasia
NDBE	non-dysplastic Barrett’s esophagus
GE	gastroesophageal
IM	intestinal metaplasia

NBI	narrow-band imaging
WATS	Wide-area transepithelial sampling
TNE	transnasal endoscopy
TFF3	trefoil factor 3
ECE	Esophageal capsule endoscopy
TCE	Tethered capsule endomicroscopy
EMR	endoscopic mucosal resection
HD-WLE	high-resolution white-light endoscopy
AFI	autofluorescence imaging
CLE	confocal laser endomicroscopy
PIVI	Preservation and Incorporation of Valuable Endoscopic Innovations
NPV	negative predictive value
NSAIDs	Nonsteroidal anti-inflammatory drugs
BSG	British Society of Gastroenterology Guidelines
ESD	endoscopic submucosal dissection
RFA	radiofrequency ablation
CEIM	complete eradication of intestinal metaplasia
CED	complete eradication of dysplasia
PDT	photodynamic therapy
APC	argon plasma coagulation
LOH	loss of heterozygosity
FISH	fluorescent in-situ hybridization
RR	relative risk
CI	confidence interval
AUC	area under curve
OR	odds ratio
BING	Barrett’s International NBI Group

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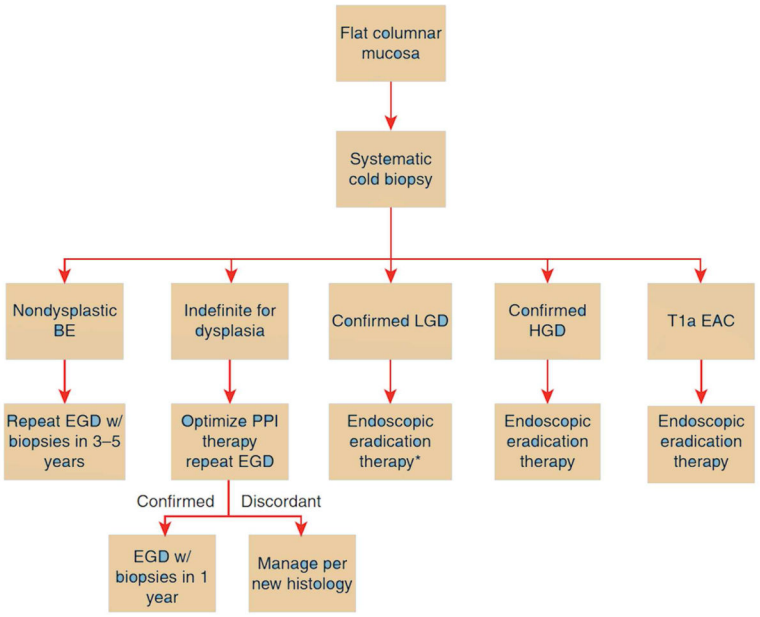


Figure 1.

Schematic for management of non-nodular Barrett's esophagus (BE) [8]. Surveillance upper endoscopy at 1-year intervals is an acceptable alternative to endoscopic eradication therapy. T1a esophageal adenocarcinoma (EAC) is amenable for endoscopic therapy. (Image reproduced with permission).

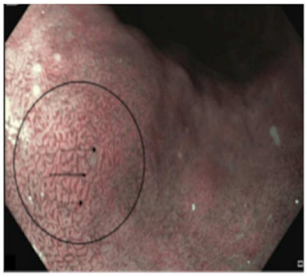
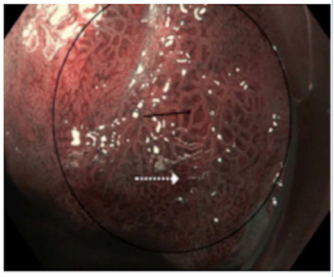
	Regular	Irregular
Mucosal	Circular, ridged, villous, or tubular patterns	Absent or irregular patterns
Vascular	Blood vessels regularly aligned along or between mucosal ridges and/or those showing normal, long, branching patterns	Focally or diffusely distributed vessels not following normal architecture of the mucosa
Endoscopic images using NBI		

Figure 2.

Classification of regular and irregular mucosal and vascular patterns using the validated Barrett's International NBI Group (BING) criteria for detection of high-grade dysplasia and esophageal adenocarcinoma using narrow-band imaging (NBI) in Barrett's esophagus [69]. (Image reproduced with permission).

Figure 3.

Available radiofrequency ablation devices (RFA) include a circumferential device that can be used for ablation of large areas and focal devices comprising a paddle that can either be attached to the tip or placed through the working channel of an upper endoscope. (All rights reserved. Used with the Permission of Medtronic).

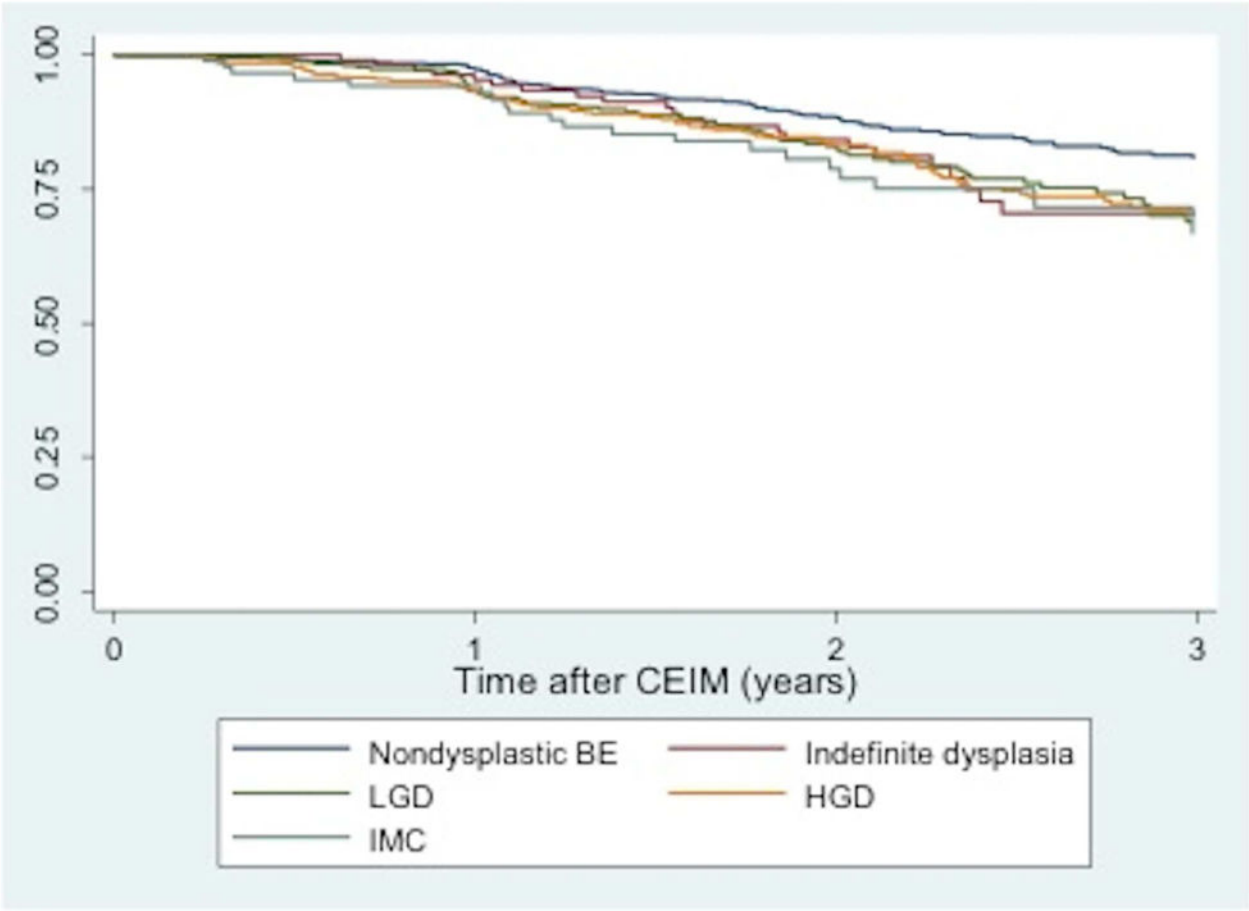
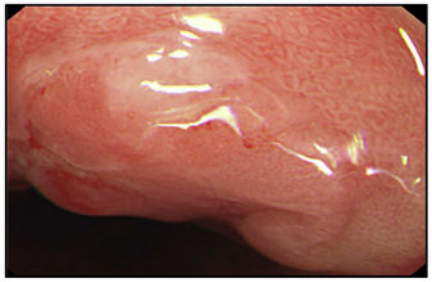
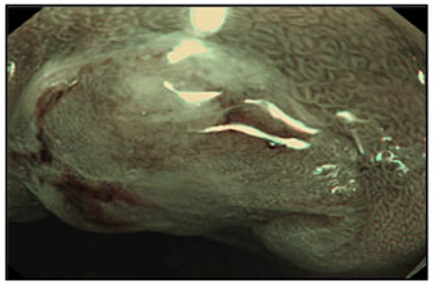
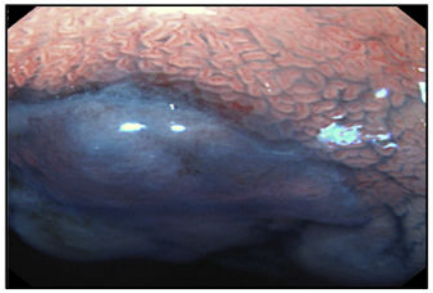


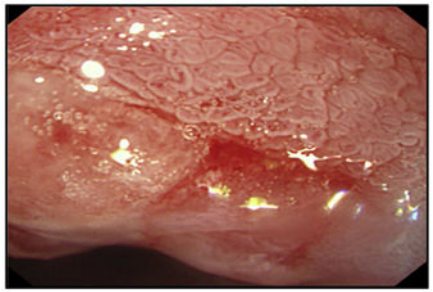
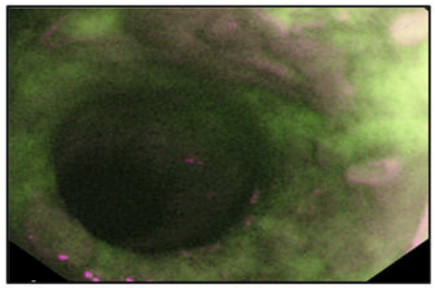
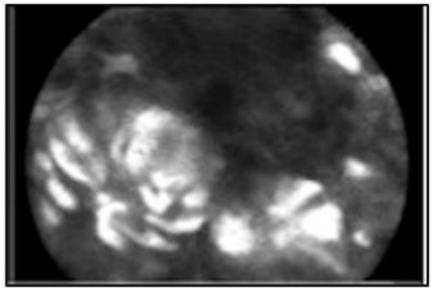
Figure 4.

Kaplan-Meier plot of intestinal metaplasia (IM) recurrence among patients (n=1613) who achieved complete eradication of intestinal metaplasia (CEIM) after RFA, with pretreatment histology non-dysplastic BE (NDBE), low-grade dysplasia (LGD), and high-grade dysplasia (HGD) [138]. (Image reproduced with permission).

Table 1

Endoscopic imaging modalities for detection of dysplasia in Barrett's esophagus

Imaging modality	Description	Sensitivity	Specificity	Image	References
High-definition white light (HD-WLE)	HD-WLE is the current criterion standard for both screening and surveillance of BE.	40–64%	98%–100%	 Endoscopic image of BE with areas of early neoplasia.	[67, 79, 150]
Narrow-band imaging (NBI)	NBI visually emphasizes vascular patterns allowing for better differentiation between columnar and squamous tissue in the esophagus.	94% *	94% *	 Nodular lesions visualized with NBI.	[85, 150]
Chromoendoscopy methylene blue	Endoscopic evaluation of mucosa after application of dyes or contrast agents.	64% *	96% *	 Focal staining of BE mucosa with methylene. blue	[85, 150]

Imaging modality	Description	Sensitivity	Specificity	Image	References
Acetic acid		97% *	85% *	 An irregular white area on Barrett's mucosa after treated with acetic acid.	[85, 150]
Autofluorescence imaging (AFI)	Relies on spectroscopic characteristics of light to induce fluorescence of biomolecules that can be used to detect mucosal abnormalities.	37%–50%	61%–92%	 AFI image of a neoplastic lesion in BE.	[150–153]
Confocal laser endomicroscopy (CLE)	Provides up to a 1000-fold magnification of the esophageal mucosa and allows for real-time histologic evaluation of the esophagus via endoscope and probe-based methods.	90% *	90% *	 Dysplastic BE with intense intracellular fluorescence, heterogeneous cellular sizes and disorganized architecture.	[85, 154]

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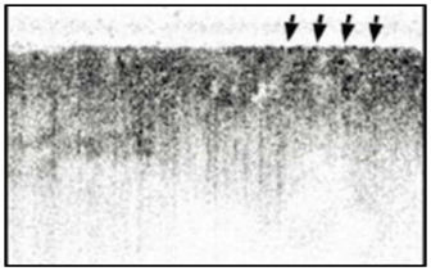
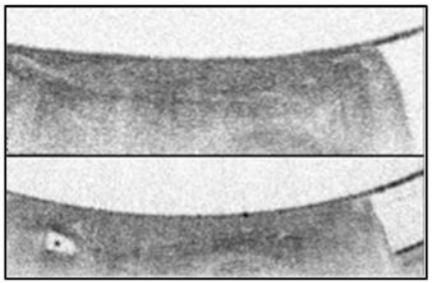
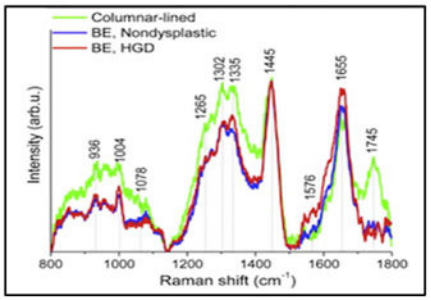
Imaging modality	Description	Sensitivity	Specificity	Image	References
Optical coherence tomography (OCT)	Uses light waves to generate cross sectional images of the esophageal epithelial and sub-epithelial tissue atchitecture.	68%–83%	75%–82%	 OCT image of IMC/HGD showing disorganized architecture and increased surface	[155, 156]
Volumetric laser endomicroscopy (VLE)	Uses OCT to produce fast, high-resolution images to a depth of 3 mm and can scan larger surface areas compared with OCT.	86% *	88% *	 VLE images irregular glandular architecture and increased surface reflectivity.	[85, 154]
Spectroscopy	Include several types such as light-scattering, reflectance and Raman spectroscopy that use scattered light to differentiate abnormal vascular, nuclear, and tissue patterns.	86–90%	85%–90%	 Mean confocal spectra of columnar epithelium, NDBE, and BE with HGD.	[157–159]

BE, Barrett's esophagus.

* Pooled estimate generated from ASGE PIVI analysis [85].

Table 2

Biomarkers for Risk Stratification in Barrett's Esophagus

Biomarker	Baseline to Outcome Histology	Mean or Median Follow-up (Years)	Results	References
Protein Markers				
p53	NDBE to HGD/EAC	6.6 years	Overexpression - RR: 5.6 (95% CI, 3.1–10.3) Loss – RR: 14.0 (95% CI, 5.3–37.2)	[160]
Gene and DNA content abnormalities				
LOH of 17p+9p, DNA abnormalities	NDBE to EAC	6.7 years	RR: 38.7 (95% CI, 10.8–138.5)	[105]
9p LOH	NDBE to EAC	5.0 years	RR: 2.6 (95% CI, 1.1–6.0)	[161]
17p LOH	NDBE/LGD to EAC	3.0 years	RR: 16 (95% CI, 6.2–39)	[100]
Aneuploidy/Tetraploidy	NDBE/LGD to EAC	5.0 years	RR: 11 (95% CI, 5.8–21)	[161]
Panel of LGD, abnormal DNA ploidy, and *Aspergillus oryzae lectin*	NDBE or LGD to EAC	6.7 years	Baseline LGD – OR: 3.9 (95% CI, 2.4–6.4) Baseline NDBE – OR: 3.3 (95% CI, 1.8–6.00)	[162]
FISH				
FISH panel: P16, P53, Her-2/neu, 20q, and MYC, and chromosomal centromeric probes 7 and 17 to detect aneuploidy	NDBE to EAC	3.8 years	p16 loss or aneuploidy - RR: 3.2 (95% CI, 1.3–7.9)	[163]
DNA Methylation				
Promoter methylation of p16, RUNX3, HPP1	NDBE to HGD/EAC	6.3 years	p16 – OR: 1.7 (95% CI, 1.33–2.20), RUNX3 – OR: 1.80 (95% CI, 1.1–2.8) HPP1 – OR: 1.8 (95% CI, 1.1–2.8)	[104]
8-gene methylation panel (p16, RUNX3, HPP1, NELL1, TAC1, SST, AKAP12, and CDH13)	NDBE to HGD/EAC	2.0 or 4.0 years	AUC: 0.84, 80% sensitivity, 70% specificity	[164]
4-gene methylation panel (SLC22A18, PIGR, GJA12, and RIN2)	NDBE to EAC	n/a	AUC: 0.99, 94 % sensitivity, 97 % specificity,	[165]
Gene Expression and MicroRNA (miRNA)				
miRNAs −192, −194, −196a, and −196b	NDBE to EAC	4.6 years	71%–85% sensitivity, 50%–71% specificity	[103]
Genetic and Clonal Diversity				
Shannon LOH diversity index	NDBE to EAC	4.5 years	RR: 11.0 (95% CI, 5.8–21.0)	[166, 167]

Biomarker	Baseline to Outcome Histology	Mean or Median Follow-up (Years)	Results	References
Mean pairwise divergence by LOH		5.0 years	RR: 2.15 (95% CI, 1.67–2.77)	
Number of LOH clones		5.0 years	RR: 1.99 (95% CI, 1.71–2.32)	
Proliferation and Cell Cycle Markers				
Cyclin D	NDBE to EAC	4.3 years	OR: 6.9 (95% CI, 1.6–29.9)	[168]
Mcm2	NDBE/LGD to HGD/EAC	6.0 years	OR: 136 (95% CI, 7.5–2464)	[169]

NDBE, non-dysplastic Barrett's esophagus; LGD, low-grade dysplasia; HGD, high-grade dysplasia; EAC esophageal adenocarcinoma; LOH loss of heterozygosity; FISH fluorescent in-situ hybridization; RR relative risk; CI confidence interval; AUC area under curve; OR odds ratio.