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 GERD.\(^3\),\(^4\) Other risk factors associated with BE are older age, male sex, smoking, central obesity, and white ethnicity.\(^5\),\(^6\)\(^7\),\(^8\) There also appears to be an increased genetic predisposition among those with first-degree relatives with BE.\(^1\)

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 those with low-grade dysplasia (LGD). However, reports of EAC risk in LGD are highly disparate, ranging from risks approximating that of nondysplastic BE to risks of progression to HGD or EAC of 10% per year or more.\(^8\),\(^15\),\(^16\) 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.

**DIAGNOSIS**

**Diagnostic criteria**

Current guidelines recommend that the diagnosis of BE should be based on the presence of columnar epithelium \(\geq1\) cm proximal to the gastroesophageal junction, with biopsy results consistent with those of intestinal metaplasia (IM).\(^8\) This is in contrast to British diagnostic criteria, in which confirmation of IM is not required for diagnosis.\(^2\) The relationship between the presence of IM and progression to EAC has been conflicting\(^2\),\(^24\) and complicated by sampling errors\(^25\) 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 is 4 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 call for routine biopsy, because IM of the cardia is common in patients with chronic GERD,\(^29\) and chronic GERD has not been definitively demonstrated to imply an increased risk of EAC.\(^30\),\(^31\) In terms of BE classification, a segment \(>5\) cm is defined as long-segment BE, and a segment \(<3\) cm is defined as short-segment BE. The Prague classification,\(^32\) describing the circumferential and maximal 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 whom to screen is complex,
because >90% of patients whom develop EAC have no history of BE, and the traditional practice of screening patients with GERD 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 subset of people who are at higher risk for BE and EAC, which includes men with chronic GERD symptoms and 2 additional risk factors including age >50, white race, central obesity, smoking history, and family history.\(^{53}\) Although risk-stratification models\(^ {56-58}\) have been developed to aid in determining who to screen for BE, these models need further validation, and their role in clinical practice currently is 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 uses computer-assisted analysis of an abraded transepithelial brush biopsy to sample a larger surface area to help overcome the issue of sampling error. When wide-area transepithelial sampling was used in conjunction with 4-quadrant biopsies, there was 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 not only of BE (κ = 0.88), HGD, and/or EAC (κ = 0.95), but also for LGD (κ = 0.74), in contrast to the low interobserver 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 and single-fiber endoscopy. Transnasal endoscopy uses a smaller-caliber endoscope, which is inserted into the esophagus orally or nasally without the need for sedation.\(^ {44}\) Transnasal endoscopy may be comparable to standard endoscopy for detection of BE and for the quality of biopsy specimens.\(^ {54-57}\) In addition, transnasal endoscopy 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 esophagoscopy (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 endoscopes are smaller in diameter (1.6 mm) compared with transnasal endoscopy and allow for narrow-band imaging (NBI) but do not provide operator control or the ability to collect biopsy samples.\(^ {50}\)

There are nonendoscopic screening devices for BE that are designed to obtain tissue for histologic evaluation. The Cytosponge (Medtronic, New Haven, Conn) is a gelatin-coated sponge attached to a string, which collects cytology 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,\(^ {4}\) but the diagnostic accuracy is still being validated.

Esophageal capsule endoscopy, another noninvasive capsule device, has shown conflicting data as to its 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 can provide additional information regarding the microscopic features and architecture of the esophageal wall, and it is being investigated.\(^ {50}\)

**Surveillance**

Surveillance in BE is aimed at early detection of dysplasia. Dysplasia is categorized as nondysplastic BE, indeterminate dysplasia, LGD, HGD, or carcinoma.\(^ {56}\) The presence of dysplasia should be confirmed by a second pathologist expert in GI histopathology, because of a high degree of interobserver variability.\(^ {56}\) The degree of dysplasia dictates recommended surveillance intervals. Patients with nondysplastic BE 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 (Fig. 1).

Careful endoscopic examination of esophageal mucosa and obtaining an adequate number of biopsy samples is vital for effective surveillance.\(^ {37,58}\) Longer mucosal inspection time has been associated with increased detection of HGD and/or 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 may be beneficial.\(^ {60,65}\) A standardized biopsy protocol for surveillance includes random 4-quadrant biopsies every 2 cm in nondysplastic BE 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, 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 has 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 at present (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 requires fewer biopsies.67,68 In addition, the type and regularity of mucosal and vascular patterns found by using NBI can identify dysplasia in patients with BE with 80% sensitivity and 88% specificity by using a new validated NBI classification system 69 (Fig. 2).

Auto-fluorescence imaging can detect mucosal abnormalities with high sensitivity but poor specificity compared with HD-WLE.70 In 1 prospective study, despite using trimodal imaging with HD-WLE, NBI, and auto-fluorescence imaging, 10% of patients had advanced lesions that were not visibly apparent and were detected only 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 can increase the yield of dysplasia detection77-79 with good accuracy80,81 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 confocal laser endomicroscopy, modalities such as VLE (volumetric laser endomicroscopy) can image a larger surface area in a short period of time and can identify subsquamous 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 the Barrett’s Esophagus Preservation and Incorporation of Valuable Endoscopic Innovations initiative85 (PIVI) by the American Society for Gastrointestinal Endoscopy (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 of ≥98% for detection of HGD and/or EAC and a specificity of 80% to replace the random biopsy protocol. Acetic acid chromoendoscopy, NBI, and endoscope-based confocal laser endomicroscopy currently meet these

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**Figure 1.** Schematic for management of non-nodular Barrett’s esophagus. Surveillance upper endoscopy at 1-year intervals is an acceptable alternative to endoscopic eradication therapy. T1a esophageal adenocarcinoma is amenable for endoscopic therapy. (Image reproduced with permission). BE, Barrett’s esophagus; LGD, low-grade dysplasia; HGD, high-grade dysplasia; EAC, esophageal adenocarcinoma; PPI, proton-pump inhibitor.
criteria for BE surveillance and are endorsed by ASGE for use in surveillance of nondysplastic BE 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 among tumors, it is quite possible that only the most indolent disease is detected by surveillance endoscopy. Consistent with concerns about overestimation 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 U.S. 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

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Description</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Image</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD-WLE</td>
<td>HD-WLE is the current criterion standard for both screening and surveillance of BE</td>
<td>40%-64%</td>
<td>98%-100%</td>
<td>![Image](67, 79, 150)</td>
<td>67, 79, 150</td>
</tr>
<tr>
<td>NBI</td>
<td>NBI visually emphasizes vascular patterns allowing for better differentiation between columnar and squamous tissue in the esophagus</td>
<td>94%*</td>
<td>94%*</td>
<td>![Image](85, 150)</td>
<td>85, 150</td>
</tr>
<tr>
<td>CMB</td>
<td>Endoscopic evaluation of mucosa after application of dyes or contrast agents</td>
<td>64%*</td>
<td>96%*</td>
<td>![Image](85, 150)</td>
<td>85, 150</td>
</tr>
</tbody>
</table>

(continued on the next page)
intervention in dysplastic disease may be underappreciated. 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 patients with BE 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 compliance with recommended biopsy protocols, sampling errors, and interobserver variability in degree of dysplasia among pathologists.25,27,43,97 As a result, adjunct techniques to improve risk stratification, such as wide-area transepithelial sampling,41 with computer-aided

### TABLE 1. Continued

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Description</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Image</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic acid</td>
<td></td>
<td>97%*</td>
<td>85%*</td>
<td><img src="image1.png" alt="Image" /></td>
<td>85, 150</td>
</tr>
<tr>
<td>AFI</td>
<td>Relies on spectroscopic characteristics of light to induce fluorescence of biomolecules that can be used to detect mucosal abnormalities</td>
<td>37%-50%</td>
<td>61%-92%</td>
<td><img src="image2.png" alt="Image" /></td>
<td>150-153</td>
</tr>
<tr>
<td>CLE</td>
<td>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</td>
<td>90%*</td>
<td>90%*</td>
<td><img src="image3.png" alt="Image" /></td>
<td>85, 154</td>
</tr>
</tbody>
</table>

(continued on the next page)
TABLE 1. Continued

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Description</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Image</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT</td>
<td>Uses light waves to generate cross-sectional images of the esophageal epithelial and subepithelial tissue architecture</td>
<td>68%-83%</td>
<td>75%-82%</td>
<td></td>
<td>155, 156</td>
</tr>
</tbody>
</table>

OCT image of IMC/HGD showing disorganized architecture and increased surface reflectivity

| 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%* | | 85, 154 |

VLE images irregular glandular architecture and increased surface reflectivity

| 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% | | 157-159 |

Mean confocal spectra of columnar epithelium, NDBE, and BE with HGD

BE, Barrett’s esophagus; HD-WLE, high definition white light endoscopy; NBI, narrow-band imaging; CMB, chromoendoscopy methylene blue; AFI, autofluorescence imaging; CLE, confocal laser endomicroscopy; OCT, optical coherence tomography; IMC, intramucosal carcinoma; HGD, high-grade dysplasia; VLE, volumetric laser endomicroscopy; NDBE, nondysplastic BE.

*Pooled estimate generated from the American Society for Gastrointestinal Endoscopy Imaging in the Barrett’s Esophagus Preservation and Incorporation of Valuable Endoscopic Innovations analysis85.

analysis to overcome limitations with sampling errors 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. Molecular abnormalities such as chromosomal aneuploidy or tetraploidy, hypermethylation of p16, loss of heterozygosity of p53, and microscopic RNA expression, among others, have been associated with progression to HGD or EAC. Panels of markers also have been tested to increase the predictive ability for carcinogenesis. All these markers are based on histologic tissue and cannot overcome the limitation of sampling error. Therefore, attempts have been made to develop serum biomarkers, including interleukins, EAC-specific proteins, and serum microscopic RNAs with mixed results. 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 as an adjunct to analysis of biopsy samples during BE surveillance.

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 nondysplastic BE 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 a once-daily dose of a proton pump inhibitor (PPI) based on evidence 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 and a reduced risk of progression to EAC in patients with BE by up to 30%, the bleeding risk associated with NSAIDs may outweigh these benefits and, therefore, they are not currently recommended as a chemopreventive strategy in BE.

Endoscopic therapy

Once the diagnosis of BE is confirmed, further management is dictated by the degree of dysplasia (Fig. 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. There also is evidence that treating LGD 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 American College of Gastroenterology (ACG) and the American Gastroenterological Association (AGA)
recommend consideration of endoscopic eradication therapy for LGD confirmed by a second pathologist, the British Society of Gastroenterology suggests endoscopic surveillance. At this time, routine endoscopic eradication therapy is not recommended for nondysplastic BE, given the low risk of progression to neoplasia, the small but real risk of procedure-related adverse events, and the costs inherent in the procedures. In general, before treatment is initiated, overall patient health, including comorbidities, needs to be considered, particularly in those with LGD, where the rates of progression to EAC are low.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Baseline to outcome histology</th>
<th>Mean or median follow-up, y</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53</td>
<td>NDBE to HGD/EAC</td>
<td>6.6</td>
<td>Overexpression—RR: 5.6 (95% CI, 3.1-10.3) Loss—RR: 14.0 (95% CI, 5.3-37.2)</td>
<td>160</td>
</tr>
<tr>
<td>Gene and DNA content abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOH of 17p, 9p, DNA abnormalities</td>
<td>NDBE to EAC</td>
<td>6.7</td>
<td>RR: 38.7 (95% CI, 10.8-138.5)</td>
<td>105</td>
</tr>
<tr>
<td>9p LOH</td>
<td>NDBE to EAC</td>
<td>5.0</td>
<td>RR: 2.6 (95% CI, 1.1-6.0)</td>
<td>161</td>
</tr>
<tr>
<td>17p LOH</td>
<td>NDBE/LGD to EAC</td>
<td>3.0</td>
<td>RR: 16 (95% CI, 6.2-39)</td>
<td>100</td>
</tr>
<tr>
<td>Aneuploidy/tetraploidy</td>
<td>NDBE/LGD to EAC</td>
<td>5.0</td>
<td>RR: 11 (95% CI, 5.8-21)</td>
<td>161</td>
</tr>
<tr>
<td>Panel of LGD, abnormal DNA ploidy, and Aspergillus oryzae lectin</td>
<td>NDBE or LGD to EAC</td>
<td>6.7</td>
<td>Baseline LGD—OR: 3.9 (95% CI, 2.4-6.4) Baseline NDBE—OR: 3.3 (95% CI, 1.8-6.00)</td>
<td>162</td>
</tr>
<tr>
<td>FISH</td>
<td>NDBE to EAC</td>
<td>3.8</td>
<td>p16 loss or aneuploidy—RR: 3.2 (95% CI, 1.3-7.9)</td>
<td>163</td>
</tr>
<tr>
<td>DNA methylation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Promoter methylation of p16, RUNX3, HPP1</td>
<td>NDBE to HGD/EAC</td>
<td>6.3</td>
<td>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)</td>
<td>104</td>
</tr>
<tr>
<td>8-gene methylation panel (p16, RUNX3, HPP1, NELL1, TAC1, SST, AKAP12, and CDH13)</td>
<td>NDBE to HGD/EAC</td>
<td>2.0 or 4.0 y</td>
<td>AUC: 0.84, 80% sensitivity, 70% specificity</td>
<td>164</td>
</tr>
<tr>
<td>4-gene methylation panel (SLC22A18, PIGR, GJA12, and RIN2)</td>
<td>NDBE to EAC</td>
<td>n/a</td>
<td>AUC: 0.99, 94% sensitivity, 97% specificity</td>
<td>165</td>
</tr>
<tr>
<td>miRNAs—192, -194, -196a, and -196b</td>
<td>NDBE to EAC</td>
<td>4.6</td>
<td>71%-85% sensitivity, 50%-71% specificity</td>
<td>103</td>
</tr>
<tr>
<td>Genetic and clonal diversity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shannon LOH diversity index</td>
<td>NDBE to EAC</td>
<td>4.5</td>
<td>RR: 11.0 (95% CI, 5.8-21.0)</td>
<td>166, 167</td>
</tr>
<tr>
<td>Mean pairwise divergence by LOH</td>
<td>NDBE to EAC</td>
<td>5.0</td>
<td>RR: 2.15 (95% CI, 1.67-2.77)</td>
<td>168</td>
</tr>
<tr>
<td>No. of LOH clones</td>
<td>NDBE to EAC</td>
<td>5.0</td>
<td>RR: 1.99 (95% CI, 1.7-2.32)</td>
<td>168</td>
</tr>
<tr>
<td>Proliferation and cell cycle markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclin D</td>
<td>NDBE to EAC</td>
<td>4.3</td>
<td>OR: 6.9 (95% CI, 1.6-29.9)</td>
<td>168</td>
</tr>
<tr>
<td>Mcm2</td>
<td>NDBE/LGD to HGD/EAC</td>
<td>6.0</td>
<td>OR: 136 (95% CI, 7.5-2464)</td>
<td>169</td>
</tr>
</tbody>
</table>

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

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, so initial resection of these areas with either EMR or endoscopic submucosal dissection (ESD) is necessary to determine depth of invasion for staging and selection of further therapy. 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 to have fewer adverse events. 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 patients needing ESD, for most endoscopists in the West, the focus should be on performing quality EMRs.

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

For BE that is not nodular, 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 circumferentially through balloon-based devices or focally through devices attached to the end of the endoscope (Fig. 3). RFA is highly effective in eradicating dysplasia in patients with BE, with 81% of HGD and 91% of LGD achieving complete eradication of dysplasia at 12 months in a multicenter U.S. randomized controlled trial. The most common adverse event of RFA is an after-ablation stricture with a pooled estimate of 5.6% (95% confidence interval [CI], 4.2%-7.4%). Other rare adverse events include bleeding, perforation, and postprocedural 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 through the upper endoscope. A newer device is available to deliver cryotherapy by using nitrous oxide via a self-contained, balloon-based system. 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. Similar efficacy was seen in prospective data with 81% to 94% eradication of HGD. A more recent prospective study showed that cryoablation with pressurized CO₂, when combined with EMR for treatment of BE with nodular neoplasia provided complete eradication of dysplasia in only 44% of patients. There is a paucity of randomized trials comparing mucosal ablation modalities to each other.

Although photodynamic therapy (PDT) rarely is used because of cost and side effects, level 1 evidence exists for the efficacy of PDT in preventing cancer in BE with
HGD. In a multicenter study, PDT resulted in eradication of HGD in 77% of cases, with maintenance of remission in 85% of cases during a 5-year follow-up period. Despite this efficacy, use of PDT is limited by high rates of after-ablation strictures, with reports as high as 36% and higher procedural costs compared with RFA. Other ablative modalities that are available are argon plasma coagulation and multipolar electrocoagulation, which have been shown to have similar rates of complete eradication of IM. The most frequent use of argon plasma coagulation is to treat residual disease after ablation because this can promote sustained remission for a greater duration after complete eradication of IM. Although no head-to-head comparisons exist, argon plasma coagulation can have similar cost efficacy to that of RFA.

After complete eradication of IM, the risk of recurrence of IM is significant, especially with risk factors such as increasing age, BE segment length, and baseline dysplasia (Fig. 4). A recent meta-analysis 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 and/or EAC was 0.8%, over more than 10,000 patient years of follow-up time. When the analysis was restricted to treatments with RFA only, the annual incidence of recurrent IM was 9.5%, of dysplastic BE was 2%, and of HGD and/or EAC was 1.2%. There was a similar risk of recurrence in those treated with combination therapy with EMR followed by ablation. Although the recurrence of dysplasia is low, it is not insignificant, and thus it is important for patients who have achieved complete eradication of IM and complete eradication of dysplasia to undergo periodic after-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. The frequency of current surveillance examinations is based on baseline pathology and expert opinion. For patients treated for baseline LGD, 1 commonly used strategy is to perform surveillance every 6 months for the first year after complete eradication of IM, then annually after. For patients treated with baseline HGD, surveillance can be performed every 3 months in the first year after complete eradication of IM, every 6 months in the second year after complete eradication of IM, and then annually after. Recurrent disease is treated in a similar manner as before initial endoscopic therapy, and success rates of a second complete eradication of IM after recurrence of BE are high.

**Surgical therapy**

Anti-reflux surgery has not been shown to be superior to medical therapy in preventing EAC incidence in patients with BE based on 2 meta-analyses and is not recommended for prevention of neoplasia in BE. There is some evidence that after ablation the neosquamous epithelium is potentially more prone to reflux injury, 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. However, current data as to any incremental benefit of a surgical anti-reflux procedure compared with medical therapy after successful RFA remain inconclusive, 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. 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. 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 are 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.

REFERENCES
Barrett’s esophagus: diagnosis and management


900 GASTROINTESTINAL ENDOSCOPY Volume 85, No. 5 : 2017 www.giejournal.org


1. Management of a patient with newly diagnosed non-dysplastic Barrett’s should include
   a. Therapy with bid PPI
   b. Therapy with PPI only if GERD symptoms are present
   c. Therapy with once daily PPI for all patients
   d. H2RA therapy or PPI therapy for all patients

2. A patient is diagnosed with Barrett’s esophagus, 4 quadrant biopsies at 2cm interval yield no dysplasia, next endoscopy should be in
   a. 6 months
   b. 1-2 years
   c. 3-5 years
   d. 5-10 years

3. A patient with Barrett's is found to have LGD on endoscopy, best next step should be
   a. increase PPI dose, repeat in 3 months with 4 quadrant biopsies every 2cm
   b. get a second pathology opinion
   c. recommend endoscopic eradication therapy
   d. a and b above

4. Risk of developing adenocarcinoma of the esophagus/year in patients with Barrett's is up to
   a. 2.5% in LGD, 15% in HGD
   b. 0.7% in LGD, 25% in HGD
   c. 0.7% in LGD, 7% in HGD
   d. 5% in LGD, 25% in HGD

5. Patients with HGD in a nodular lesion should proceed to endoscopic eradication therapy of dysplastic epithelium.

6. 85% of patients who develop esophageal adenocarcinoma had a history or heartburn

7. When doing post IM eradication surveillance EGD, target most biopsies to the squamo-columnar junction

8. After complete eradication of IM, recurrence rate of IM is 7.1%/y and recurrent dysplasia is 1.3%/yr

9. Long segment Barrett’s is defined as >3cm

10. Patients with <2cm of mucosa suspicious for Barrett’s should undergo 4 biopsies for diagnosis, those with >2cm should undergo 8 biopsies.

11. Irregular Z line with intestinal metaplasia should be classified as Barrett’s

12. Patients with confirmed indefinite for dysplasia biopsies despite optimized PPI therapy should undergo repeat endoscopies with biopsies every year

13. After complete IM eradication in a patient with HGD, next EGD should be done in 6 months