Background: Barrett esophagus (BE) continues to be a major risk factor for developing esophageal adenocarcinoma.

Methods: We review the risk factors, diagnosis, and management of BE, with an emphasis on the most current endoscopic diagnostic modalities for BE.

Results: Novel diagnostic modalities have emerged to address the inadequacies of standard, untargeted biopsies, such as dye-based and virtual chromoendoscopy, endoscopic mucosal resection, molecular biomarkers, optical coherence tomography, confocal laser endomicroscopy, volumetric laser endomicroscopy, and endocytoscopy. Treatment of BE depends on the presence of intramucosal cancer or dysplasia, particularly high-grade dysplasia with or without visible mucosal lesions.

Conclusions: Recent advances in endoscopic diagnostic tools demonstrate promising results and help to mitigate the shortcomings of the Seattle protocol. Future research as well as refining these tools may help aid them in replacing standard untargeted biopsies.

Introduction

Barrett esophagus (BE) is a condition that has been controversial ever since Barrett first described it in 1950 — from the definition to its appropriate surveillance, treatment, and management.1 As defined by the American Gastroenterological Association, BE involves any extent of metaplastic columnar epithelium predisposed to developing cancer that then replaces the stratified squamous epithelium normally lining the distal esophagus.2 Intestinal metaplasia is required for the diagnosis of BE because intestinal metaplasia is the only type of esophageal columnar epithelium that predisposes a person to malignancy.2 DNA content abnormalities may occur with equal frequency and extent in the metaplastic columnar epithelium regardless of the presence of goblet cells.3 BE is a major risk factor for developing esophageal adenocarcinoma, and the incidence of esophageal adenocarcinoma continues to rise in Western countries.4

The underlying etiology of BE is not well characterized; however, in the majority of cases, it is associated with a combination of acid and bile reflux, even in the absence of symptoms. Esophagitis is secondary to gastroesophageal reflux disease (GERD) is a common medical condition in Western countries, with up to 30% of adults experiencing heartburn at least once per month; of those, one-third has evidence of esophagitis during endoscopic evaluation.5 Approximately 10% of patients have esophagitis that progresses to BE.5,6 Addressing the pathological changes in the mucosa and the underlying etiology are the basis of BE treatment.

Predicting the Disease Evolution

A large, prospective, multicenter study of GERD with more than 6,000 participants showed that age, male sex, Caucasian race, increased body mass index, long-standing reflux disease and smoking were consistently and independently related to GERD.7 A large body of literature indicates that GERD is also an independent factor for the development of BE.8-11 Use of statins, aspirin, or nonsteroidal anti-inflammatory drugs may be associated with a decreased risk of BE.12,13 BE is one of the most common premalignant lesions affecting more than 2% of the adult population, strongly predisposing them to esophageal adenocarcinoma.14,15 Esophageal cancer has a 5-year survival rate of less than 15%, making it a deadly cancer.16 In clinical practice, the presence of dysplasia is the most important useful factor for identifying patients at increased risk for developing esophageal adenocarcinoma.17

Metaplasia–Dysplasia–Carcinoma Sequence

The formation of intestinal metaplasia appears to start with an injury to the esophageal mucosa due to gastric refluxate, which causes the desquamation
of squamous cells (Fig 1). This action causes stem cells to migrate from the epithelial-mesenchymal junction toward the luminal surface. Here, the behavior of the stem cells is modified by the refluxate, which causes a selected lineage of resistant cells that then populate the neoesophageal mucosa. Barrett segments may also develop from the upward progression of the cardia mucosa, in part because Barrett glands replicate the organization of the gastric glands — an observation made when analyzing the architecture of the stem cells and the pattern of the gene expression.

In cases of low-grade dysplasia (LGD) in BE, the epithelium reveals enlarged nuclei with an increased nucleus-to-cytoplasm ratio, stratification of the nuclei, mucin depletion, partial loss of nuclear polarity, and lack of surface maturation (Fig 2). This becomes markedly increased in high-grade dysplasia (HGD) in BE, with an increased nucleus-to-cytoplasm ratio and increased nuclear pleomorphisms with prominent nucleoli, full-thickness nuclear stratification, and loss of polarity (Fig 3).

BE is relatively common, but the development of dysplasia and adenocarcinoma occurs in a small number of those affected. Once intestinal metaplasia develops, persons with BE are at increased risk for developing dysplasia and adenocarcinoma when compared with the general population. This underscores the principal clinical importance of BE, particularly because the prevalence of adenocarcinoma has increased in the United States and Europe during the past 20 years. BE is estimated to carry a risk of cancer 30 to 125 times greater than that for an age-matched population. In a meta-analysis by Yousef et al, the overall estimate of cancer incidence in BE was 4.1 cases per 1,000 person-years (3.9 per 1,000 person-years using high-quality study data), and the incidence of combined cancer and HGD was 9.1 per 1,000 person-years (7.7 per 1,000 person-years using high-quality study data).

Based on these data, the risk of developing or dying from esophageal carcinoma from BE is relatively low, but the diagnosis of BE can have psychological and financial implications on the affected patients, in part due to the limited treatment options available and poor survival rates once the cancer is diagnosed. Patients with BE report a worse quality of life than the general population, and receiving a diagnosis of BE can cause psychological distress and increase life and health care insurance premiums.

**Diagnosis**

**White Light Endoscopy**

Standard of care for the diagnosis of BE is endoscopic evaluation performed with white light endoscopy (WLE) with 4-quadrant biopsy specimens taken every 2 cm as necessary.
described by the Seattle protocol (Fig 4; Table). The American Gastroenterological Association also recommends that 4-quadrant biopsy specimens be obtained every 1 cm in patients with known or suspected dysplasia; however, doing so may require additional biopsy procedures, longer procedure times, and increased cost. This technique is also subject to sampling error, thus resulting in a low diagnostic uncertainty rate between 1% and 10%, suboptimal disease management, and decreased adherence to practice guidelines.

The mosaic of BE dysplasia is widely recognized (Fig 5). Areas of HGD and microscopic carcinoma are often small, making differentiation between these lesions difficult on biopsy. Therefore, other diagnostic tools have been sought to solve the shortcomings of standard, untargeted biopsies for diagnosing BE.

**Chromoendoscopy**

Chromoendoscopy is a technique that utilizes dyes in

<table>
<thead>
<tr>
<th>Endoscopic Technique</th>
<th>Method</th>
<th>Comment</th>
<th>Limitation</th>
</tr>
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<tbody>
<tr>
<td>WLE with random biopsies</td>
<td>4-quadrant biopsy specimens obtained every 1–2 cm in patients with known or suspected dysplasia (Seattle protocol)</td>
<td>Wide availability, Low cost, Ease of use and integration into standard endoscopy with no additional risks</td>
<td>May require larger number of biopsies, longer procedures times, and increased cost, Sampling error with low diagnostic uncertainty</td>
</tr>
<tr>
<td>Dye</td>
<td>Utilizes dyes (methylene blue or acetic acid) with WLE to enhance visibility of high-grade dysplasia, intestinal metaplasia, and cancer</td>
<td>Increased diagnostic yield compared with WLE, Well tolerated, Low cost, Ease of use and integration into standard endoscopy with no additional risks</td>
<td>Larger, prospective studies warranted, Dysplasia can still be missed</td>
</tr>
<tr>
<td>Virtual</td>
<td>Enhances the endoscope through special filter inside scope, narrowing bandwidth of light that illuminates tissue with light at specific wavelengths, thus allowing enhancement of the underlying vasculature Various modalities used (eg, narrow band imaging)</td>
<td>Increased diagnostic yield compared with WLE, Fewer biopsies and more effective at targeting biopsies, Ease of use and integration into standard endoscopy with no additional risks, Same efficiency as dye-based method, but more decreased time expenditure, No studies show that one modality is better over another</td>
<td>Larger, prospective studies warranted, Dysplasia can still be missed</td>
</tr>
<tr>
<td>Endoscopic mucosal resection</td>
<td>Local snare excision of lesion down to the submucosal level allows depth of tumor invasion to be histologically identified</td>
<td>Useful as “giant biopsy” given large amount of surface area it can resect in presence of raised mucosal lesions, May also serve as tool for staging purposes</td>
<td>Differentiating depth of invasion is important, as inaccurate diagnosis may lead to inappropriate treatment</td>
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Fig 4. — White light endoscopy in Barrett esophagus.

Fig 5. — High-definition white light endoscopy in Barrett esophagus.
combination with WLE to better visualize the mucosal surface of the gastrointestinal tract (see Table). The most commonly used dye is methylene blue, which is actively absorbed by the mucosa (peak absorption, 670 nm) by intestinal metaplasia. It is topically applied to the mucosal surface to enhance visibility for HGD, intestinal metaplasia, and cancer. Results from early studies evaluating the diagnostic advantage of methylene blue have shown that it is similar to conventional biopsy in its detection of specialized intestinal metaplasia and indefinite/LGD, while others have shown that methylene blue may be superior to random biopsy for identifying intestinal metaplasia, but not dysplasia or carcinoma. A meta-analysis of 450 participants in 9 studies did not significantly increase the detection of specialized intestinal metaplasia and dysplasia with methylene blue compared with WLE by the Seattle protocol.

Acetic acid has also been used to produce a transient whitening effect caused by protein acetylation.

### Table. — Endoscopic Diagnosis of Barrett Esophagus (continued)

<table>
<thead>
<tr>
<th>Endoscopic Technique</th>
<th>Method</th>
<th>Comment</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autofluorescence and molecular biomarkers</td>
<td>Autofluorescence endoscopy incorporates real-time, wide-angle view allowing back-and-forth switch between standard white light imaging and autofluorescence endoscopy</td>
<td>Provides equivalent diagnostic rates of accuracy for dysplasia compared with current gold standard therapy with reduction in number of biopsies</td>
<td>Low-quality evidence for their use Cannot be used to confirm diagnosis or predict which patients are at risk for progression</td>
</tr>
<tr>
<td>OCT</td>
<td>High-resolution, cross-sectional imaging technique that provides visualization of internal microstructure of tissues using measurements of optical backscattering or back reflection</td>
<td>Useful in guiding targeted biopsies in areas with higher probability of dysplasia</td>
<td>Imaging depth limited by optical attenuation from tissue scattering and absorption, allowing ≤ 3 mm of depth to be achieved in most tissues Low-contrast images High interobserver and intraobserver variations between image interpretation and prediction of pathology</td>
</tr>
<tr>
<td>CLE</td>
<td>Combination of endoscopy with microscopic imaging of gastrointestinal mucosa</td>
<td>Real-time assessment of gastrointestinal mucosa Improves diagnostic yield and helps guide therapeutic treatment through targeting of lesions Requires fewer biopsies with better diagnostic yield</td>
<td>Requires specialized equipment and training Only available at large academic institutions</td>
</tr>
<tr>
<td>Volumetric laser endomicroscopy</td>
<td>Variant of OCT Allows visualization of comprehensive, simultaneous images of distal esophagus using laser instead of sound waves OCT laser beam helically scanned across long length of esophagus (~6 cm in 1–2 min) using miniature optics in center of 2.5-cm diameter, transparent balloon-centering catheter</td>
<td>Real-time assessment with comprehensive, simultaneous images of distal esophagus Fills the gap between endoscopic ultrasonography and CLE in resolution and imaging depth Has 10-µm resolution and 3-dimensional imaging to 3.5 mm in muscularis propria Performed at faster frame rate of 100× than OCT</td>
<td>Biopsies cannot be excised during the scan because the dataset is continuously acquired through inflated balloon, but new targeting system may improve localization for biopsy site Larger, multicenter prospective trials warranted Head-to-head comparisons needed with other endoscopic modalities</td>
</tr>
<tr>
<td>Endocytoscopy</td>
<td>Involves real-time visualization of superficial mucosa using high-level ≤ ×1400, necessitates use of mucosal staining to assess cytological and architectural features of superficial mucosa</td>
<td>May be useful as adjunctive technique for targeted assessment of already identified lesions</td>
<td>Not practical for wide-field screening of mucosa given restrictive sampling area Uses optical lens alone, limited to visualization of superficial mucosa</td>
</tr>
</tbody>
</table>

CLE = confocal laser endomicroscopy, OCT = optical coherence tomography, WLE = white light endoscopy.
and tissue edema, with dysplasia retaining color faster than BE and squamous mucosa. Studies have shown that acetic acid detects neoplasia better and more often than standard random biopsy, requiring 15 times fewer biopsies per neoplasia detected and equivalent rates of sensitivity and specificity to that of histological analysis. However, a high false-positive rate of 19.6% was noted in 1 study, and the other study was not a randomized or blinded-controlled trial. In another meta-analysis, dye-based chroendoendoscopy increased the diagnostic yield of dysplasia by 35%, and testing for difference in yields of detection of dysplasia between virtual chroendoendoscopy and chroendoendoscopy failed to detect any significant differences between the 2 modalities. However, the possibility of inadequate or uneven surface application of either methylene blue or acetic acid creating inconsistent results is a limitation of the method.

**Virtual Chroendoendoscopy**

Virtual chroendoendoscopy encompasses a set of digitally enhanced imaging techniques achieved with the use of optical filters or selective wavelengths of light to highlight vessel and mucosal patterns. Narrow band imaging is a type of virtual chroendoendoscopy that enhances the diagnostic capability of the endoscope through a special filter inside of the scope, thus narrowing the bandwidth of light that illuminates tissue with light at specific wavelengths. This technique creates blue light of wavelengths corresponding to the hemoglobin absorption band (415 nm), and, because the light does not deeply penetrate, the underlying vasculature is enhanced, producing contrast between the vessels and surrounding mucosa (Fig 6). Use of narrow band imaging has been evaluated in BE and compared with WLE, and these results have showed that it is superior to WLE. Narrow band imaging detected significantly more patients with dysplasia and higher grades of dysplasia with fewer biopsy samples than WLE. A meta-analysis and systematic review, which included 7 studies on virtual chroendoendoscopy, found that virtual chroendoendoscopy increased the diagnostic yield for identifying dysplasia or cancer in patients with BE by 34% compared with WLE with random biopsies. Narrow band imaging is not better at visually diagnosing dysplasia, but this technique has proven to be more effective at targeting biopsies, thus reducing the number of biopsy passes. This is the main practical application of narrow band imaging — namely, allowing the health care professional to focus on the tissue, find suspicious lesions, perform target biopsies, and avoid performing 4-quadrant biopsies. Overall, narrow band imaging increases diagnostic yield and requires fewer biopsies than WLE.

**Other Imaging Modalities**

Proprietary models, including i-Scan imaging (Pentax, Tokyo, Japan), Fuji Intelligent Chromo Endoscopy (Fujifilm, Tokyo), and the Storz Professional Image Enhancement System (Karl Storz, Tuttingen, Germany), are imaging modalities that use software-based processing to alter the wavelength ranges of reflected light to obtain different effects on surfaces, tissues, and vessel enhancement. By contrast to narrow band imaging, these proprietary modalities offer different filter options that allow the health care professional to visualize tissue and surface structures in a selective and accentuated manner.

For example, Hoffman et al found that i-Scan has significantly higher diagnostic yield for identifying specialized columnar epithelium, thus resulting in fewer biopsies than the random biopsy protocol. It also provides the precise detection of lesions associated with erosive reflux disease via esophagogastroduodenoscopy, and it is superior to standard-resolution colonoscopy and equivalent to chroendoendoscopy using methylene blue when detecting colorectal neoplasia. These virtual imaging modalities may eventually replace dye-based chroendoendoscopy due to their decreased time expenditure and equivalent effectiveness.

**Endoscopic Mucosal Resection**

Endoscopic mucosal resection (EMR) may be used as a diagnostic tool and a therapeutic treatment option for patients with HGD or intramucosal cancer (see Table). It entails the local snare excision of a lesion down to the submucosal level, allowing the depth of tumor invasion to be histologically iden-
Differentiating the depth of invasion is important, as an inaccurate diagnosis could have severe consequences. Patients with neoplasia limited to the mucosa are at a 0% to 3% risk of lymph-node metastasis, while those with submucosal infiltration have an increased risk of lymph-node metastasis of 20% to 30% and require surgical evaluation instead of mucosal resection. An accurate diagnosis depends on an interpretation of the depth of invasion and also on an accurate diagnosis of BE, LGD, and HGD, and should require 2 expert pathologists to read the specimen.

Curvers et al47 evaluated histopathology reports of 147 study patients with a prior diagnosis of LGD. After pathology review, 85% of study patients were downstaged to nondysplastic BE or to indefinite for dysplasia, highlighting that most cases of dysplasia in BE are overdiagnosed.47 However, once LGD was confirmed, a high risk of progression to HGD or carcinoma was seen.47

In a multicenter cohort study by Wani et al,48 138 patients underwent EMR (10.9% LGD; 63% HGD; 26.1% esophageal adenocarcinoma). EMR resulted in a change of the diagnosis in 31.1% of study patients (10.1% upgrade and 21.0% downgrade).48 Although EMR can be used as a diagnostic tool in cases of malignancy or HGD, it is also useful as therapy in HGD and early cancer by acting as a “giant biopsy” sample and, in cases where it does not resect HDG or early cancer, it serves for staging purposes. In the presence of raised mucosal lesions, which are often signs of inflammation but sometimes contain LGD or HGD, or even early cancer, EMR can be a useful diagnostic tool.

Endoscopic ultrasonography (EUS) has also been evaluated for its role in staging. Although EUS is used for staging other types of gastrointestinal malignancy, its use for BE staging is suboptimal and carries the risk of overstaging.49 Its role in distinguishing mucosal from submucosal lesions is limited and, in 1 systematic review, was shown to carry a 65% concordance rate with surgical or EMR staging.49 Thus, EUS has no clinical impact and diagnostic EMR is superior.49 Detectable lesions should be staged with EMR to determine the risk of lymph-node metastasis to help guide treatment options.

**Autofluorescence and Molecular Biomarkers**

Several studies have evaluated the combination of autofluorescence endoscopy and molecular biomarkers as a novel diagnostic tool in BE (see Table). di Pietro et al50 created a 3-biomarker panel to include p53 immunohistochemistry, cyclin A, and aneuploidy, and they demonstrated a strong association with prevalent dysplasia. They concluded that the 3-biomarker panel, in combination with autofluorescence imaging–targeted biopsies, provided an equivalent diagnostic accuracy rate for dysplasia when compared with the gold standard of therapy; a significant reduction in the number of required biopsies was also seen.50

Glycosylation patterns may also be candidate biomarkers for detecting disease progression in BE through the use of fluorescence endoscopes and fluorescent-labeled lectins sprayed onto the mucosal surface of tissue.51 Sturm et al52 showed that fluorescent-labeled peptides with specific binding for esophageal neoplasia could be topically and safely administered using real-time confocal laser endomicroscopy, in addition to showing strong fluorescence in HGD and esophageal adenocarcinoma. However, although biomarkers show promise in assisting with the diagnosis of BE, the quality of evidence for their use is low and cannot be used to confirm the diagnosis or predict which patients will be at risk of disease progression.21

**Cross-Sectional Imaging Techniques**

**Optical Coherence Tomography:** Optical coherence tomography (OCT) uses a low-coherence laser to help the health care professional visualize the internal microstructure of tissues by measuring differences in time delay between light that backscatters from below the tissue surface and a reference beam (see Table). It
was initially developed for ophthalmology, is noninvasive, and analogous to EUS in that it uses a laser instead of sound waves, with air not producing artifacts. Imaging depth is limited by optical attenuation from tissue scattering and absorption, allowing up to 3 mm of depth to be achieved in most tissues. Other limitations include low-contrast imaging and high interobserver and intraobserver variation between image interpretation and prediction of pathology. Imaging of HGD and intramucosal cancer by OCT exhibits more heterogenous structures that correspond to irregular, heterogenous tissue morphology from distorted and cribriform or villiform glandular architectures.

Two prospective studies evaluated OCT, with 1 trial demonstrating a 68% sensitivity rate and an 82% specificity rate for detecting Barrett neoplasia, and the other detecting an 83% sensitivity rate and a 73% specificity rate for detecting HGD and esophageal adenocarcinoma. Overall, OCT can be used to target areas for biopsy with a higher probability of the presence of dysplasia.

OCT has also been used to predict responses to radiofrequency ablation (RFA) for which the BE mucosa was significantly thinner in patients who achieved complete eradication of intestinal metaplasia compared with those without complete eradication at follow up, corresponding to rates of 92.3% sensitivity, 85% specificity, and 87.9% accuracy.

**Confocal Laser Endomicroscopy:** Confocal laser endomicroscopy (CLE) is a novel, endoscopic imaging modality that combines endoscopy with microscopic imaging of the gastrointestinal mucosa (see Table). First described for the diagnosis of BE in 2006 by Kiesslich et al, this fluorescence-aided endomicroscopy of BE uses an argon-ion laser delivered with a wavelength of 488 nm to generate optical, histological slices of 7 µm with a lateral resolution of 0.7 µm. This action allows for real-time, in vivo histology of mucosal layers during endoscopy, with the aim of improving the effectiveness of the surveillance of dysplasia and esophageal adenocarcinoma in BE. Although CLE cannot replace histopathology, this method may improve diagnostic information and guide therapeutic management because of its ability to localize pathology and specifically target lesions in patients with BE.

Select retrospective reports found that CLE was an effective tool for guiding endoscopic therapy in the setting of BE. A multicenter, randomized controlled trial conducted by Canto et al included 192 study patients with BE compared high-definition WLE alone with random biopsy and high-definition WLE with CLE and targeted biopsy. Adding CLE to high-definition WLE increased the rate of sensitivity from 40% to 96% without significantly compromising the rate of specificity (92%); it also tripled the diagnostic yield for neoplasia and obviated the need for biopsy in 65% of study participants. CLE also changed the treatment plan in 36% of these study patients. Overall, the trial results demonstrated significantly enhanced rates of diagnostic yield and accuracy, leading to an 80% reduction in mucosal biopsy specimens by enabling more selective tissue sampling.

A systematic review and meta-analysis by Gupta et al compared the diagnostic accuracy of CLE with random biopsy and included 7 prospective studies (N = 345 participants; N = 3,080 lesions). Although CLE had good rates of diagnostic accuracy for detecting HGD and esophageal adenocarcinoma, the researchers concluded that CLE might not replace the standard of care, given its relatively low sensitivity rate and negative predictive value. However, this study was performed prior to the study by Canto et al, so those study data were not included in their meta-analysis.

The majority of these studies also included a higher overall prevalence of HGD and esophageal adenocarcinoma than is seen in clinical practice, and they were focused on academic centers not otherwise generalizable to community-based physicians.

As a tool, CLE can be used to decrease unnecessary mucosal biopsies, improve targeting of HGD and neoplasia, and to potentially alter the diagnosis and management of BE. However, because this modality requires specialized equipment and training, and because it is mainly used in large academic centers, CLE has not yet been deemed sufficient to replace the Seattle protocol. Thus, additional, larger prospective studies are warranted.

**Volumetric Laser Endomicroscopy:** Volumetric laser endomicroscopy (VLE) is an emerging endoscopic tool that is a variant of OCT, a cross-sectional imaging technique, that can be used to simultaneously view comprehensive images of the distal esophagus (see Table). An OCT laser beam is helically scanned over a long length of esophagus (~6 cm) in 1 to 2 minutes using miniature optics in the center of a 2.5-mm diameter, transparent balloon-centering catheter. VLE attempts to fill the need between EUS and CLE in resolution and imaging depth: It has 10-µm resolution and 3-dimensional imaging to 3.5 mm in the musculis propria. It is also performed at a faster frame rate of 100 times than OCT. One limitation is that biopsy samples cannot be excised during the scan because the dataset is continuously acquired through an inflated balloon; however, this limitation can be resolved by placing visible marks on the esophagus to delineate tissues corresponding to regions of interest.

A pilot feasibility study performed with 22 participants looked at the effectiveness of VLE for image-guided biopsy in the setting of BE. This modality uses a laser with a different wave length to create 2 burning marks, with the abnormality seen on VLE in the middle, and doing so helps the health care
professional target biopsy/EMR the area. When com-
pared with histopathological interpretations, the rates
of accuracy for diagnosing tissue between cautery
marks were 67% for independent readers, 93% for VLE
intent-to-biopsy, and 100% for corrected VLE post-
marking images.67 No adverse events from VLE and la-
sor marking were seen.67

Thus, preliminary data in BE are promising and
could be useful for “buried” BE. However, larger,
multicenter, prospective trials are warranted and
head-to-head comparisons are needed with other en-
doscopic modalities.

Endocytoscopy
Endocytoscopy involves real-time visualization of
the superficial mucosa using high-level magnifica-
tion.62 Endocytoscopy uses an optical lens alone and is limited to visualiza-
tion of the superficial mucosa.68 Endoscopic visual-
ization of subcellular structures, such as nuclei, ne-
cessitates the use of mucosal staining with either
methylene or toluidine blue, which is then washed off
prior to imaging. Diagnosis involves assessing sever-
al cytological and architectural features such as cell
density, size, and arrangement, as well as the size and
shape of nuclei and the nucleus-to-cytoplasm ratio.69
Neoplastic features typically involve an increase in
cellular density and marked heterogeneity in nuclear
staining and size in comparison with orderly cellular
arrangement and homogenous staining of the normal
squamous epithelium.69

When Pohl et al70 assessed the rate of accuracy of
endocytoscopy in patients presenting for BE surveil-
lance, they found that endocytoscopy resulted in a
high proportion of unusable imaging due to subopti-
mal image quality, fair interobserver agreement, and
a poor diagnostic specificity rate. Overall, endocytos-
copy lacked sufficient image quality to assist with the
identification of neoplastic areas.70

Treatment for Mucosal Pathology Changes
Nondysplastic
BE is a complication of uncontrolled GERD, so patients
with BE must be given medications that effectively
treat GERD. Not all patients with GERD require en-
doscopy to screen for BE, but the presence of multiple,
well-established risk factors can be used to identify in-
dividuals with increased risk of developing BE. These
factors include age (≥ 50 years), male sex, white race,
chronic GERD, hiatal hernia, elevated body mass in-
dex, and an intra-abdominal distribution of fat.2

Once the diagnosis of BE has been confirmed, the
health care professional must take several factors into
consideration to determine the appropriate manage-
ment of BE (beyond controlling GERD). The most ac-
cepted approach is based on the presence of dysplasia
and the degree of that finding (LGD and HDG): En-
doscopic surveillance is recommended by most of the
gastroenterology societies worldwide, even though no
data support the reduction of esophageal adenocar-
cinoma due to this practice.71 The management of non-
dysplastic BE has been controversial, and guidelines
recommend continued surveillance endoscopy every
3 to 5 years.2 Controlled trials are lacking to show that
endoscopic eradication therapy of BE without dyspla-
sia is more effective at reducing esophageal adenocar-
cinoma or more cost effective than surveillance.

In our opinion, patients with numerous clinical and
demographic risk factors for neoplastic progression of
BE, including age, sex, ethnicity, obesity, alcohol use,
smoking, and long-segment BE, may need to be consid-
ered on a case-by-case basis given the lack of controlled
trials, but these patients likely do have an increased risk
of progression to HGD or adenocarcinoma.

Dysplastic
When the presence of dysplasia has been confirmed by
2 pathologists (preferably 1 is an expert in gastrointes-
tinal pathology), the management plan can vary based
on the degree of dysplasia.

For patients with LGD, endoscopic surveillance
can be continued in 6 to 12 months as recommended
by societal guidelines.2 In addition, endoscopic eradi-
cation therapy can be considered with photodynamic
therapy, cryoablation, or RFA. A large body of litera-
ture is dedicated to ablation therapy for BE, and, giv-
en its high rate of effectiveness, its low adverse-event
profile, and its easier treatment protocol (for physicians
and patients alike), RFA appears to be the preferred
modality of treatment.72,73 In 1 randomized control tri-
al, RFA resulted in reduced risk of neoplastic progres-
sion in patients with BE who had a confirmed diagno-
sis of LGD during 3 years of follow-up.74

Patients with BE and HGD represent a challenging
group due to their risk of malignancy. Although esoph-
agectomy has been the gold standard treatment for pa-
ients with HGD or intramucosal cancer, a paradigm
shift is taking place to using endoscopic procedures
given the higher morbidity and mortality rates associ-
ated with surgical resection.75-77 Most patients with BE
also have significant comorbidities, which medically
preclude them from undergoing such surgical inter-
ventions.78 Therefore, endoscopic ablative procedures
have been advocated as alternative and minimally in-
vasive treatment modalities.

With the presence of HGD, it is important for the
health care professional to evaluate the BE mucosa
for any abnormalities. If irregularities are detected in
the area with BE, then abnormal mucosa should be re-
sected by means of EMR. EMR can aid in the histologi-
cal diagnosis and is often used to treat patients with
HGD.68 However, a limitation to focal resection is its
high rate of synchronous and recurrent lesions, ranging from 14% to 47%, which tends to increase with longer durations of observation.79 Therefore, complete Barrett eradication EMR (CBE-EMR) was developed at select centers with the curative intent of removing all HGD or intramucosal cancer in patients with BE to reduce such risks.79 A long-term follow-up study of 24 patients for 28 months evaluated CBE-EMR for the treatment of HGD and intramucosal cancer and found the method to be a safe and effective, long-term treatment option.80 CBE-EMR with close endoscopic surveillance has also been demonstrated to be an effective treatment modality for HGD and intramucosal cancer.79 However, a limitation to CBE-EMR is its increased risk for esophageal strictures: The post-EMR stricture rate has been reported to range from 4% to 70%.81 Risk factors for stricture formation depend on the size of the lesion excised and the number of lesions, with larger lesions and removal of several lesions associated with a higher risk of esophageal strictures.81 Although CBE-EMR carries a significant rate of stricture development, strictures can be treated by endoscopic dilation.

Following endoscopic resection, argon-plasma coagulation may significantly reduce the neoplasia recurrence rate compared with a surveillance-alone strategy for the management of residual Barrett epithelium. In a study by Manner et al,82 63 study patients with HGD or intramucosal cancer curatively resected by endoscopy had a significantly high recurrence-free survival rate with ablation of residual Barrett segment by argon-plasma coagulation during a follow-up of 2 years in a randomized control trial.82 However, a longer follow-up duration is warranted.

If a patient has BE with HGD and no mucosal abnormalities are present, then RFA may be considered an appropriate treatment option. RFA was first described in 2004 by Ganz et al,83 and it involves a balloon-based, bipolar electrode that creates a circumferential, thin-layer epithelial ablation zone within the esophagus. The principle is to deliver high power at about 300 W in a short period of time (< 300 milliseconds).84 RFA typically extends into depths of 700 μm, with the concept that Barrett tissue will not extend into the submucosa; this also decreases a patient’s risk of bleeding, fibrosis, and strictureting.84

RFA, which is a relatively conservative approach, has been advocated by some investigators given its lower rates of morbidity and mortality when compared with more invasive treatment options such as surgical resection.85 RFA has also been found to be more effective and less costly than endoscopic surveillance in HGD.86

One multicenter, randomized, sham-controlled study showed a high rate of complete eradication of dysplasia and intestinal metaplasia with decreased disease progression.87 In HGD, complete eradication of dysplasia was seen in 81% of study patients with RFA compared with 19% in the control population. A total of 2.4% study patients with RFA progressed to esophageal cancer compared with 19% in the control group.87 A meta-analysis and systematic review found that ablation may be associated with a reduced incidence of cancer, with the greatest benefit observed in patients with BE with HGD.88 In our opinion, use of RFA should be advocated in patients with HGD without mucosal abnormalities given the effectiveness of RFA in treating this patient population.

Studies evaluating RFA preceded by EMR have shown this combination method to also be a safe and effective treatment option, including in patients with BE (≥ 10 cm); however, given the longer-length BE, the combination method was found to be more challenging in this patient population.89,90 Thus, it should be performed in centers with staff members who have experience in BE imaging and therapy.

We consider cryoablation to be an alternative treatment option for HGD or intramucosal cancer. It uses low-pressure liquid nitrogen to eradicate precancerous or cancerous tissue. In our opinion, the procedure is easier to perform when compared with other treatment modalities, and it relatively lacks any patient discomfort.

Data are limited, but current studies show promising results for either the downgrading of pathology or complete eradication.91,92 A prospective, pilot study revealed the reversal of BE in all 11 study patients at 6 months of follow-up.93 Longer-term results have demonstrated complete eradication of HGD at 100% after 2 years of follow-up in 32 participants.94 However, additional long-term studies are warranted; in addition, lack of uniformity for applying liquid nitrogen to esophageal mucosa and its effectiveness as a treatment option are still existing concerns.

Conclusions

Barrett esophagus is a major risk factor for developing esophageal adenocarcinoma, a cancer with increasing incidence and a dismal 5-year survival rate.16 Significant advances have been made in endoscopic modalities to improve diagnostic yield, rates of accuracy, and better guidance for therapeutic management. Based on preliminary studies, confocal and volumetric laser endomicroscopy have both shown promising results for endoscopic diagnosis and therapeutic guidance of Barrett esophagus. Endoscopic mucosal resection has also evolved as a diagnostic and therapeutic tool, thus allowing for more accurate staging to help guide treatment options and better select patients for esophagectomy. These endoscopic tools help to mitigate the shortcomings of the Seattle protocol, which is the current standard of care. With additional future studies and increasing use, they may
References


