Barrett’s Esophagus: Diagnosis, Surveillance, and Endoscopic Management

Case Study and Commentary, Michelle H. Lee, MD, and Sharmila Anandasabapathy, MD

ABSTRACT

- **Objective:** To discuss diagnosis, surveillance, and management strategies for Barrett’s esophagus.
- **Methods:** Literature review.
- **Results:** Barrett’s esophagus has gained recognition as the premalignant precursor for esophageal adenocarcinoma. The progression of Barrett’s esophagus may involve the development of low-grade dysplasia and high-grade dysplasia before the eventual development of a neoplasm. The challenges to screening include the inability to predict who has Barrett’s esophagus prior to endoscopy, the lack of evidence demonstrating improved mortality and the cost-effectiveness of endoscopic screening. The recommendation for endoscopic surveillance of Barrett’s esophagus is based on the poor overall survival rate for esophageal adenocarcinoma when it is diagnosed at a late stage. Current treatment options for Barrett’s esophagus include surveillance, endoscopic resection, endoscopic ablation therapy and surgical resection.
- **Conclusion:** Esophageal adenocarcinoma has been rapidly increasing in incidence in the United States and other countries over the last 30 to 40 years [1]. Barrett’s esophagus has gained recognition as the premalignant lesion for adenocarcinoma and is believed to be the major risk factor, with a 20-fold increased risk in the development of esophageal adenocarcinoma when compared to patients without the condition [2-4]. The reported rate of progression of Barrett’s esophagus to esophageal adenocarcinoma range from 0.12% to 0.5% per year [3,5–7].

Barrett’s esophagus is diagnosed in approximately 10% to 15% of patients with reflux symptoms who are undergoing endoscopy [1]. Barrett’s esophagus is defined as a change in the distal esophageal epithelium of any length that can be recognized as columnar type mucosa at endoscopy (Figure 1) and is confirmed to have intestinal metaplasia by biopsy of the esophagus (Figure 2). If the characteristic “salmon-colored” tongues of Barrett’s esophagus are observed on standard light endoscopy, 4-quadrant biopsies should be taken every 1 to 2 cm throughout the Barrett’s segment [8]. The progression of Barrett’s esophagus may involve the development of low-grade dysplasia and high-grade dysplasia before the eventual development of a neoplasm. Because the average age at diagnosis of esophageal adenocarcinoma is in the sixth and seventh decades of life [9], a clear understanding of the diagnosis and treatment options of Barrett’s esophagus is essential in the care of the aging population.

**CASE STUDY**

**Initial Presentation**

A 68-year-old man with a body mass index of 33 is referred to a gastroenterologist for evaluation of gastroesophageal reflux disease. He endorses a history of intermittent substernal burning sensation for the last 6 years.

From the Division of Gastroenterology, The Mount Sinai Medical Center, New York, NY.
BARRETT’S ESOPHAGUS

**What are indications for screening for Barrett’s esophagus?**

**Screening**

A screening test should have the ability to detect a premalignant or early malignant lesion, thereby offering the opportunity for intervention and reduced morbidity and mortality. While screening for Barrett’s esophagus in selected patients has been endorsed by certain gastrointestinal societies [10], the challenges to screening include the inability to predict who has Barrett’s esophagus prior to endoscopy, the lack of evidence demonstrating improved mortality and the cost-effectiveness of endoscopic screening. The rationale supporting screening for Barrett’s esophagus has been based on decision- and cost-analysis studies [11,12] but is limited by the absence of controlled, supportive data.

Although attempts have been made to identify the appropriate screening population for Barrett’s esophagus, no guidelines have been established. Studies have attempted to predict Barrett’s esophagus with clinical and demographic features comparing patients with the disease to controls with gastroesophageal reflux disease (GERD) [13]. Age greater than 50 [14], GERD [8], longer duration of GERD symptoms [15–19], male gender [20], and white race [21] have been associated with Barrett’s esophagus, although recently, rates of Barrett’s esophagus have been rising in females [22]. While the only consistent predictor across various studies was the presence of heartburn, the sensitivity remains poor [13]. Furthermore, studies demonstrate that up to 40% of patients with esophageal adenocarcinoma do not experience reflux symptoms and therefore would not be included in the targeted screening population [23–25]. Moreover, a Veterans Administration study noted that older patients with Barrett’s esophagus had significantly lower symptom severity scores when compared with younger patients with similar pathology, with scores similar to those of asymptomatic controls [26]. This atypical clinical presentation further complicates the determination of appropriate screening groups. Additionally, there is conflicting evidence supporting a mortality benefit from screening and surveillance of Barrett’s esophagus [8]. Some retrospective studies have suggested a survival benefit in patients undergoing endoscopy prior to diagnosis of adenocarcinoma [27–34], while other studies have failed to demonstrate an overall mortality benefit in patients undergoing Barrett’s surveillance [35–39].

Given the inability to identify high-risk groups, as well as the lack of proven benefit of endoscopic surveillance in patients in whom Barrett’s esophagus is identified, screening for Barrett’s esophagus in the general population is not recommended at this time (Table 1). The American Gastroenterological Association (AGA) recommends tailoring screening for Barrett’s esophagus to patients based on risk factors rather than reflux symptoms alone [8]. On the other hand, the American Society for Gastrointestinal Endoscopy recommends that screening esophagogastroduodenoscopy should be considered in patients with chronic, longstanding GERD (> 5 years) [10]. The American College of Gastroenterology guidelines state that the use of screening in selective populations at higher risk remains to be established and should therefore be individualized [13]. However, alarm symptoms such as dysphagia, weight loss and anemia should prompt primary care physicians to refer patients to a gastroenterologist for an endoscopic evaluation.

---

Figure 1. Barrett’s esophagus on endoscopy.
Surveillance

Although there is a lack of randomized trials supporting the value of surveillance endoscopy in patients with Barrett’s esophagus, it is still practiced by the vast majority of endoscopists and endorsed by all major professional gastrointestinal societies [13]. The recommendation for endoscopic surveillance is based on the poor overall survival rate for esophageal adenocarcinoma when it is diagnosed at a late stage [40]. Moreover, multiple cohort studies have demonstrated that esophageal cancers detected in patients in surveillance protocol are associated with longer survival than those diagnosed on an initial endoscopy for alarm symptoms [8].

Patients undergoing surveillance endoscopy should be maintained on proton pump inhibitors, with the goal of decreasing esophageal inflammation and enabling better endoscopic and pathological examination of Barrett’s esophagus [41]. If initial pathologic examination demonstrates Barrett’s esophagus without dysplasia, a second endoscopy should be performed within 2 years. Subsequent surveillance can be performed at 3- to 5-year intervals (Table 2) [42]. Patients are maintained on proton pump inhibitors based on the hypothesis that neutralization of esophageal acid exposure would remove mucosal irritation, and subsequently reduce the risk of progression to high-grade dysplasia or adenocarcinoma [39]. In addition, some studies have demonstrated that antireflux surgery can provide control over GERD symptoms in Barrett’s esophagus [43,44]. Studies have demonstrated that more than 20% of cancers reported in prospective surveillance studies arose in patients lacking dysplasia on initial endoscopy; thus, continued surveillance is recommended even in the absence of dysplasia on both baseline endoscopies [45].

When biopsies demonstrate low-grade dysplasia, repeat endoscopy should be done within 6 months, with biopsies taken every 1 cm to ensure that a higher grade of dysplasia is not present. Low-grade dysplasia warrants annual endoscopies. If no dysplasia is noted on 2 consecutive studies, then a 3-year interval can be followed [13]. Low-grade dysplasia should be confirmed by an expert gastrointestinal pathologist, secondary to the high degree of inter-observer variation [46]. The endoscopic treatment of non-dysplastic Barrett’s esophagus is not generally recommended. Low-grade dysplasia is a more controversial area. While some studies have demonstrated eradication of low-grade dysplasia with ablative therapy [47], the long-term efficacy and benefits have not been demonstrated [8].

High-grade dysplasia in flat mucosa should be confirmed by an expert gastrointestinal pathologist and a repeat endoscopy should be performed within 3 months, with biopsies taken every 1 cm. However, high-grade dysplasia with mucosal irregularity should undergo endoscopic mucosal resection due to the increased likelihood of cancer existing in nodularity. In high-grade dysplasia, the 5-year risk of progression to esophageal adenocarcinoma has been shown to range from 16% to 56%; hence, intervention (endoscopic or surgical) is usually recommended for subjects with high-grade dysplasia [13]. Patients with high-grade dysplasia should be advised on various therapeutic options including intensive surveillance, esophagectomy or abla-
tive therapies. Recent guidelines support the endoscopic eradication of high-grade dysplasia with radiofrequency ablation, photodynamic therapy or endoscopic mucosal resection preferentially over surveillance of high-grade dysplasia [8,48].

In patients without dysplasia on surveillance studies, the recommended follow up should be based upon the highest grade of dysplasia previously confirmed. Patients who have undergone ablative treatment should have biopsies over the entire area of ablation, in time intervals indicated for their prior grade of dysplasia until there are 3 negative consecutive studies [13]. Additionally, continued surveillance is still recommended, as Barrett’s esophagus is known to reoccur. Currently there are studies underway evaluating the impact of surveillance endoscopy, with results that should be available in the next few years.

There are some caveats to surveillance protocols. While cost-utility studies have demonstrated that screening may have some benefits, continued surveillance in patients with Barrett’s esophagus is an expensive practice [11]. Additionally, these patients appear to greatly overestimate their risk of develop adenocarcinoma [49], which can be a source of anxiety and decrease overall quality of life.

**Advanced Surveillance Technology**

The current practice of endoscopic surveillance for Barrett’s esophagus has limitations in that biopsies are performed randomly and samples may miss metaplasia, dysplasia and esophageal adenocarcinoma because of the patchy distribution of a Barrett’s segment [50,51]. Advanced endoscopic optical imaging techniques have been developed with the objective of improving the overall accuracy of endoscopic biopsies of Barrett’s epithelium. Narrow-band imaging (electronic chromoendoscopy) uses spectral narrow-band optical filters with a predominance of blue light that highlights mucosal and vascular patterns characteristic of neoplastic tissue [52]. Studies by Kara and Sharma suggest that narrow-band imaging (NBI) has a high sensitivity and specificity for the detection of Barrett’s associated neoplasia: 94% and 75%, and 100% and 99%, respectively [53,54]. However, studies by Curvers and by Herrero have shown that NBI does not improve inter-observer agreement or accuracy over high-definition white light endoscopy, independent of expertise [55, 56].

Confocal laser endomicroscopy integrates a confocal laser microscope into the tip of a standard videoendoscope, allowing for real-time histology during the procedure [57]. In a prospective study by Kiesslich et al, patients with Barrett’s esophagus underwent endoscope-based confocal laser endomicroscopy (eCLE) examination [57]. Barrett’s associated neoplasia could be predicted with a sensitivity of 92.9% and a specificity of 98.4%. Sharma et al published results of a multicenter,
prospective, randomized controlled study in patients with Barrett’s esophagus and associated high-grade dysplasia and adenocarcinoma designed to determine the accuracy of probe-based confocal laser endomicroscopy (pCLE) [58]. The sensitivity and specificity for high-definition white light endoscopy with pCLE was 68.3% and 87.8%, respectively [58]. Multimodality imaging involves the use of more than one advanced imaging modality simultaneously, with the purpose of improving the detection of high-grade dysplasia and esophageal adenocarcinoma. The techniques that have been used in combination are NBI, autofluorescence imaging and high-resolution endoscopy. However the use of these imaging modalities has not been recommended in current guidelines [8].

**Patient Workup**

The patient undergoes an endoscopic evaluation that demonstrates 4 cm of salmon-colored mucosa with no ulcerations or nodules. Random biopsies confirm the diagnosis of Barrett’s esophagus with low-grade dysplasia and multifocal high-grade dysplasia.

- **How is Barrett’s esophagus managed?**

In the past, esophagectomy was the standard treatment for Barrett’s esophagus with high-grade dysplasia. Various minimally invasive techniques have been developed, but esophageal resection may still carry a high risk of complications. Esophagectomy has been correlated with a mortality rate which may be as high as 20% in centers with low-frequency esophagectomies [59,60]. However, the mortality rate may be significantly reduced to less than 2% in experienced, high-volume medical centers [61,62]. Various endoscopic therapies have evolved (Table 3), and subsequently, patients now have alternatives to surgical resection for the treatment of high-grade dysplasia or early intramucosal cancers. Furthermore, the efficacy of endoscopic ablation has been demonstrated in multicenter, randomized controlled trials [63–65].

Endoscopic mucosal resection (EMR) involves the removal of the mucosa and typically partial excision of the submucosa [66]. The most commonly used technique is the ER-cap method. The targeted mucosal tissue is elevated by submucosal injection of fluid and the lesion is sucked into the tip of the endoscope, and then resected with a snare. Another option is the ligate-and-cut technique, which does not require submucosal injection and uses a band-ligating device, similar to variceal ligation device. The ER-cap technique allows for large tissue samples, while the band ligation method is faster and less expensive for multiple resections [67].

EMR can be performed to remove focal visible areas of high-grade dysplasia within a Barrett’s segment. It carries the advantage of being both a diagnostic tool, as well as a treatment modality for both high-grade dysplasia and early esophageal adenocarcinoma. Compared to standard endoscopic biopsy methods, EMR enables more precise characterization of neoplasia, less inter-observer variation among pathologists, and more precise evaluation of dysplasia grades and the depths of invasion [48,68,69]. Additionally, EMR can provide more precise staging of submucosal invasion when compared to endoscopic ultrasound [70,71].

Ell et al conducted a single-center prospective study evaluating the efficacy and safety of EMR in patients with low-risk adenocarcinoma of the esophagus arising from Barrett’s epithelium. The primary outcome was complete local remission in a mean follow-up period of 36.7 months. Complete local remission was achieved in 99 of the 100 patients. The study also demonstrated that endoscopic therapy appeared to be superior to surgery with regard to mortality and morbidity, as there were no major complications among the 100 patients. The calculated 5-year survival rate was 98% [72].

Before endoscopic therapy can be considered a curative treatment, the extent of the neoplastic involvement must be determined. Esophageal resections performed on intramucosal carcinomas that do not invade the muscularis mucosae have revealed a less than 5% rate of metastases to lymph nodes [73–76]. Therefore, when neoplastic tissue is confined to the mucosa, endoscopic therapy may be a definitive treatment. Thus, EMR has not only a key role in staging early esophageal neoplasms, but also has a role in determining whether endoscopic therapy is appropriate. Prior to undergoing endoscopic therapy, patients should be made aware of complications such as bleeding, perforation, stricture formation and the possibility of residual metaplasia. Moreover, given reported recurrence rates of adenocarcinoma in 10% to 30% [72,77–83], patients should be informed of the necessity of surveillance after endoscopic therapy.

Radiofrequency ablation (RFA) uses radiofrequency energy emitted from an endoscopic balloon catheter or
a focal ablation device to destroy Barrett’s epithelium. First, the endoscopist determines the diameter of the esophagus with a balloon-measuring device, then an ablation balloon, which is covered with electrodes, is positioned over the esophageal segment to be ablated. Radiofrequency energy is released through the electrodes, producing heat that destroys metaplastic tissue in the muscularis mucosa and superficial submucosa. RFA also has the ability to treat long segments of Barrett’s esophagus [66]. Patients typically return 2 to 3 months after the initial RFA treatment for endoscopic assessment, and any remaining metaplastic tissue is removed using the focal ablation device [66]. There have been an increasing number of studies aimed at evaluating the efficacy and safety of RFA in both dysplastic and nondysplastic Barrett’s epithelium [64,84,85].

A study by Shaheen et al was the first randomized controlled trial to assess the effectiveness of RFA in eradication of dysplastic Barrett’s esophagus [86]. In this multicenter, sham-controlled trial, 127 patients with Barrett’s esophagus with low- or high-grade dysplasia were randomly assigned in a 2:1 ratio to receive either RFA or a sham procedure and were surveyed with interval endoscopies for a total of 12 months. Primary outcome was complete eradication of dysplasia and intestinal metaplasia at 12 months. Complete eradication of intestinal metaplasia was found in 77.4% of patients in the RFA group, as compared with 2.3% in the control group ($P < 0.001$). Among patients with low-grade dysplasia, complete eradication of dysplasia was observed in 90.5% of patients in the ablation group compared with 22.7% of those in the control group ($P < 0.001$). Among patients with high-grade dysplasia, there was complete eradication of dysplasia in 81% in the ablation group compared with 19% in the control group ($P < 0.001$). The study was not designed to detect a difference in disease progression, yet progression was observed in 16.3% of patients in the control group, as compared with 3.6% of patients in the ablation group ($P = 0.03$). Esophageal neoplasia developed in significantly more patients in the control group (9.3%) when compared to patients in the ablation group (1.2%, $P = 0.045$). The investigators extended their initial findings by following this cohort for a mean 3.05 years in a subsequent study [87].

---

**Table 3. Endoscopic Management of Barrett's Esophagus**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
<th>Benefits</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic mucosal resection [72,82,83,87]</td>
<td>Resection of mucosal and submucosal tissue, allowing for histological evaluation</td>
<td>Spares normal tissue</td>
<td>May require repeat treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allows for precise cancer staging</td>
<td>Risk of perforation, bleeding and stricture formation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Used on visible lesions</td>
</tr>
<tr>
<td>Radiofrequency ablation [64,86,87]</td>
<td>Radiofrequency energy emitted from endoscopic balloon catheter or focal ablation device</td>
<td>Low side-effect profile</td>
<td>Requires multiple sessions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Requires flat surface for successful ablation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lack of long-term remission data</td>
</tr>
<tr>
<td>Photodynamic therapy [63,89]</td>
<td>Photochemical energy generated with laser light and photosensitizer</td>
<td>Treatment in single session</td>
<td>Significant post procedure morbidity</td>
</tr>
<tr>
<td>Multipolar electrocoagulation [90,91]</td>
<td>Thermal energy applied to mucosa</td>
<td>Well tolerated</td>
<td>Not used in treatment of high-grade dysplasia and difficult to use in longer segments</td>
</tr>
<tr>
<td>Argon plasma coagulation [92]</td>
<td>Ionized argon gas delivers monopolar energy</td>
<td>Easy to use</td>
<td>Limited evidence in high-grade dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Risk of residual metaplasia</td>
</tr>
<tr>
<td>Cryotherapy [94]</td>
<td>Endoscopically delivered cryogen (liquid nitrogen or carbon dioxide)</td>
<td>Well tolerated</td>
<td>Only limited, early clinical trial data available</td>
</tr>
</tbody>
</table>

---

570  **JCOM December 2012 Vol. 19, No. 12**  www.jcomjournal.com
were followed for as long as 5 years, depending on their eradication status at 2 years post-ablation. Crossover was permitted between the control and RFA treatment group. After 2 years, 101 of 106 subjects had complete eradication of all dysplasia (95%). Among subjects with initial low-grade dysplasia, dysplasia was eradicated in 51 of 52 (98%) and in those with initial high-grade dysplasia, dysplasia was eradicated in 50 of 54 (93%). After 3 years, dysplasia was eradicated in 55 of 56 of subjects (98%). Kaplan–Meier analysis demonstrated that eradication persists in greater than 85% of patients, without maintenance RFA. Serious adverse events were reported in 4 of 119 subjects (3.4%) with a rate of stricture of 7.6%. This study, as well as others [63,86,88], demonstrates comparable efficacy of RFA compared to other modalities. Additionally, the low complication rate and side effect profile make RFA an appealing treatment option for high-grade dysplasia, especially in elderly patients with multiple comorbidities for whom the risk of surgery may be too high. Furthermore, if ablation does not eradicate high-grade dysplasia, surgery and EMR remain an option.

Consensus statement by the AGA recommends that RFA, with or without EMR, should be considered as a therapeutic option in select patients with non-dysplastic Barrett’s esophagus who are at increased risk for progression of disease [8,42]. However, specific criteria defining that population have not yet been defined.

Other ablative techniques include photodynamic therapy (PDT), cryotherapy, multipolar electrocoagulation (MPEC) and argon plasma coagulation (APC). PDT is an ablation technique that uses photosensitizing energy generated from the interaction of laser light and an intravenously-administered photosensitizer. This interaction leads to the formation of toxic, singlet oxygen molecules that destroy neoplastic tissue. Common side effects of PDT include photosensitivity reactions in > 60%, and stricture formation in up to 36% [63,89]. Because of this side effect profile, PDT is less frequently used as first line treatment for high-grade dysplasia. MPEC involves the application of thermal energy to the mucosa using an electrode-tipped catheter that is advanced through the working channel of the endoscope [90, 91]. MPEC is not practical for ablating large areas of mucosa. Additionally, there is a lack of data establishing the efficacy of MPEC on the treatment of neoplasia in Barrett’s esophagus. Likewise, APC is a non-contact technique that delivers monopolar energy to the tissue by using ionized argon gas [66]. However, the recurrence rate of Barrett’s esophagus after APC has been reported to be as high as 66% [92]. Given the newer ablative techniques such as RFA and PDT, both APC and MPEC have fallen out of favor for the eradication of Barrett’s esophagus [66].

The newest technology available is cryotherapy, which involves the use of an endoscopically delivered cryogen to inflict tissue injury [92]. Two systems exist utilizing either liquid nitrogen or carbon dioxide. Tissue destruction occurs in 2 phases: an immediate phase, caused by freezing of the cells, followed by a delayed phase where cells undergo apoptosis [93]. Cryotherapy can be sprayed without direct contact to mucosal surfaces and therefore may be beneficial for application to uneven surfaces. While data on cryotherapy is still limited, long-term clinical trials are underway.

**Patient Treatment and Follow-up**

The patient is started on a proton pump inhibitor and undergoes RFA for the treatment of high-grade dysplasia. Follow-up endoscopy demonstrates eradication of high-grade dysplasia.

**CONCLUSION**

While the survival rate from esophageal adenocarcinoma has improved in recent years, the 5-year survival rate is still only 15% to 20% [45]. Physicians caring for the aging population must maintain a high index of suspicion for Barrett’s esophagus in patients experiencing longstanding symptoms of reflux, and it is crucial for the physician to refer any patient in whom they suspect Barrett’s esophagus or a possible gastrointestinal malignancy to a gastroenterologist. The benefits of screening remain controversial despite continued widespread clinical practice, given the inability to identify high-risk groups, as well as the lack of proven benefit of endoscopic surveillance in patients in whom Barrett’s esophagus is identified. Further studies are needed to clearly define the populations that would benefit from screening protocols. Patients with dysplasia or cancer should be seen in a center with expertise in the disease. Current treatment options for Barrett’s esophagus include surveillance, endoscopic resection, endoscopic ablation therapy and surgical resection. The treatment needs to be individualized and patient factors such as age, coexisting medical conditions and personal preference, as well as the expertise available in the patient’s community must be taken into consideration. Esophageal characteristics such
as the length of Barrett’s segment, presence of visible lesions and the presence of multifocal lesions will also guide treatment options [66]. At the current time, patients who are found to have Barrett’s esophagus with high-grade dysplasia or intramucosal esophageal neoplasia have the option of choosing minimally invasive procedures, which appear to have comparable efficacy to surgery, with the benefits of lower morbidity and mortality.

Corresponding author: Sharmila Anandasabapathy, MD, Div. of Gastroenterology, The Mount Sinai Medical Center, One Gustave Levy Place, Unit 1069, New York, NY 10029, sharmila.anandasabapathy@mountsinai.org.

Financial disclosures: None.

REFERENCES


BARRETT’S ESOPHAGUS


