How to Perform a High-Quality Examination in Patients With Barrett’s Esophagus

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Barrett’s Esophagus: A Precursor Lesion to Adenocarcinoma and the Need for Effective Surveillance

Barrett’s esophagus (BE) is the precursor lesion to esophageal adenocarcinoma (OAC) and can be detected endoscopically. There is a well-established linear progression from nondysplastic BE, through to low-grade dysplasia and high-grade dysplasia.1-3 The 5-year survival of OAC remains low at <20% overall,4 but is particularly poor for patients presenting late in the disease course.5-7 Patients with early neoplasia confined to the mucosa, however, are potential candidates for Barrett’s endoscopic therapy, which has impressive eradication rates of >80% to 90%,6,7 without the attendant morbidity and mortality of surgical management options. The current paradigm for the screening and surveillance of patients with BE involves the endoscopic assessment of their BE segment to identify early neoplastic lesions while they remain amenable to endoscopic therapy. A large meta-analysis demonstrated that a sobering 16.4% to 36.8% of OAC is diagnosed within 1 year after the initial endoscopy.8 This finding highlights the importance to clinicians undertaking BE screening and surveillance that a thorough and careful endoscopic examination is vital to decrease the frequency of missed OAC.

The current gold standard for tissue sampling during endoscopy is the Seattle protocol.9 This involves the systematic assessment of the esophagus starting at the gastroesophageal junction (GOJ) and extending to the squamocolumnar junction. Visible lesions suspicious for dysplasia are target biopsied, macroscopically normal mucosa is then biopsied in each quadrant at 2-cm intervals. Although the Seattle protocol remains the gold standard, it is not without limitations. Tschanz et al10 highlight the susceptibility of the protocol to sampling error. The average BE mucosal surface area is estimated at 14 cm², with random forceps biopsies sampling only around 0.5 cm² of this area, representing just 3.5% of the total surface area. Early BE dysplasia and neoplasia are often highly focal and easily missed with this sampling technique. Moreover, studies have also demonstrated that compliance with the protocol is often poor and worsens with longer segments, with the sensitivity for dysplasia detection ranging widely from 28% to 85%.11 There is an unmet need to develop a system for BE screening and surveillance endoscopy that both improves consistency between endoscopists and that increases the detection rate of early, treatable neoplasia.

Preparing Patients and Identifying the Endoscopic Landmarks in BE

A successful endoscopy begins with thorough preparation. The choice to use conscious sedation with midazolam and fentanyl, monitored anesthesia care, or no sedation remains up to the treating physician and patient, although local resources and staff expertise may also influence the decision. Some studies have suggested that the use of small-caliber endoscopes in nonsedated patients may be used to deliver endoscopies with success comparable with sedated endoscopies,12 suggesting that in selected patients an unsedated endoscopy with topical anesthesia does not preclude a high-quality examination. It is strongly recommended, however, that all patients who may undergo therapeutic procedures during their Barrett’s assessment, or who are particularly anxious, should receive sedation. The endoscopic assessment of a patient with BE begins with a careful assessment of the esophagus from the GOJ to the proximal squamocolumnar junction. Accurate identification of the GOJ is essential to ensure that patients with intestinal

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metaplasia in the cardia, a normal finding in around 20% of people, are not labelled as having BE and subjected to unnecessary surveillance endoscopies despite a minimal risk of progression to OAC.13 The top of the visible gastric folds should be identified as the anatomic landmark of the GOJ, the position from which measurements of visible columnar tissue should begin. The presence of palisade vessels can also be used to identify the top of the gastric folds.14

To standardize the reporting of endoscopic and histologic findings in patients with BE, the Prague classification is used (Figure 1). The Prague classification is a consensus-driven, validated reporting criteria that requires endoscopists to detail the location of the top of the gastric folds, the proximal extent of both the circumferential BE segment (C) as well as the maximal extent of any tongues (M) or islands.15 Accurate recording of the Prague classification is vital for a number of reasons. First, the length of the Barrett’s segment determines the intervals at which patients without evidence of dysplasia should undergo endoscopic surveillance.16–18 Second, if dysplastic tissue is identified incidentally on biopsies, it provides subsequent endoscopists with an anatomic location to which they should give particular focus or direct therapy at later assessments. Once the initial assessment and measurements have been completed, target biopsies are taken from areas that seem to be macroscopically suspicious for neoplasia that become apparent with high-definition white light endoscopy or the enhanced imaging modalities discussed herein. To complete the protocol, endoscopists then take random forceps biopsies across the 4 quadrants of the esophageal mucosa as per the Seattle protocol, starting at the GOJ and then every 2 cm until the proximal border of the BE segment is reached.

Spend at Least 1 Minute Inspecting Each Centimeter of BE Mucosa, With Particular Focus on the Right Wall and Proximal Segment

The time spent inspecting the esophagus impacts the quality of BE endoscopy and the endoscopic yield for neoplasia detection. Clinicians should spend time thoroughly assessing the mucosa, and excess mucus should be removed using a mucolytic solution delivered by water jet through the endoscope. Typically, a 2% solution of simethicone or N-acetylcysteine is used to both remove mucous and reduce bubble formation. The esophagus should be assessed only partially insufflated between waves of peristalsis. Subtle lesions can often be missed with overinsufflation owing to lesions being flattened, and can also be missed within the folds of an underinsufflated esophagus. Inspection time of the BE mucosa is significantly associated with improved detection of early lesions. Gupta et al19 demonstrated that both identification of suspicious lesions and detection rate of high-grade dysplasia/OAC improved when endoscopists inspected each centimeter of the BE segment for >1 minute (high-grade dysplasia/OAC detection rate of 40.2% vs 6.7%). Endoscopy units should take such findings into account, particularly when planning workflow, because patients undergoing BE endoscopies may require longer appointment times to be booked to facilitate a more detailed examination.

Figure 1. Prague classification measurements from the gastroesophageal junction. A, Extent of circumferential (C) Barrett’s esophagus (BE). B, maximal (M) extent of BE segment including tongues.

Figure 2. (A) Non-dysplastic Barrett’s oesophagus. (B) Subtle high grade dysplastic lesion. (C) Intramucosal adenocarcinoma.
Several studies have also demonstrated a spatial predilection for early BE-associated neoplasia, which should guide the endoscopists focus during surveillance. Early cancers are more commonly seen on the right wall of the esophagus within the proximal segment; particular focus should, therefore, be given to these areas.

Identifying and Describing Early Neoplastic Lesions in BE

Early neoplastic lesions are focal, subtle, and may be easily missed at endoscopy. The presence of disordered pit patterns, depressions, or nodularity with associated dilation and formation of aberrant vessels should prompt a more focused evaluation to improve dysplasia detection. If visible lesions suspicious for early neoplasia are detected, clinicians should record their findings based on the Paris classification. This simple classification divides lesions into 3 broad categories—flat, depressed, and protruding—with further subcategorization based on the mucosal color and the appearance of vessels.

The Paris classification of endoscopically visible lesions is also informative for clinicians when planning endoscopic therapy. Paris Ila and Iib lesions are typically associated with early neoplastic disease confined to the mucosa in 83% to 100% of cases. Depressed lesions are associated with a higher rate of neoplastic invasion into the submucosal layer. Thomas et al demonstrated only 66% of Paris IIc lesions are confined to the mucosa. Clinicians working in centers where endoscopic therapies for early neoplasia are unavailable should ensure that the position, size, and Paris classification of lesions are recorded. Biopsies should be taken of the lesion to establish a histologic diagnosis, after which the patient should be referred to a tertiary center.

For clinicians performing endoscopic mucosal resection, the macroscopic appearances of lesions should be considered carefully. Depressed, ulcerated lesions may invade the submucosa, with the attendant risk that local lymph node metastases are present. Endoscopists treating these lesions should consider cross-sectional imaging or endoscopic ultrasound examination with fine needle aspiration of local nodes to ensure that patients in whom endoscopic mucosal resection would be futile receive a prompt referral for surgical intervention.

Adjuncts to Endoscopic Examination: Conventional and Virtual Chromoendoscopy

To enhance the subtle mucosal and vascular abnormalities that may indicate the presence of early neoplasia, both conventional and virtual chromoendoscopy have been used. The topical application of dyes may improve the distinction of dysplastic and nondysplastic tissue. Unlike in the colon, methylene blue and indigo carmine have demonstrated disappointing results for highlighting Barrett’s dysplasia. However, acetic acid spray applied to the esophageal mucosa during endoscopy is promising. After the application of a dilute (1.5%-3.0%) acetic acid solution, clinicians should observe the mucosa, which under normal circumstances turns white within seconds as cellular proteins denature in the acidic pH. This color change highlights mucosal patterns more clearly, facilitating a more sensitive and specific identification of potentially neoplastic areas. Furthermore, when observed for a period of up to 2 minutes, the premature loss of aceto-whitening in areas of the mucosa and the speed at which it disappears is also associated with the presence of early neoplasia. The application of acetic acid can improve the diagnostic yield of target biopsies by 14.7-fold compared with random biopsies, with a meta-analysis by Coletta et al demonstrating a sensitivity and specificity of 92% and 96%, respectively. A more recent study has shown sensitivities of up to 99% when using acetic acid to identify abnormal areas of mucosa. Although its use is not endorsed for standard clinical practice, clinicians in centers without advanced imaging technologies should consider adding acetic acid to their practice because it represents a safe and effective adjunct to Barrett’s biopsies.

Several endoscopic companies have incorporated virtual chromoendoscopy systems into their endoscopes. The underlying principle of virtual chromoendoscopy is the use of novel optical filters and/or postprocessing technologies, built into the endoscope and operated with toggle buttons by the endoscopist, to enhance mucosal and vascular patterns seen at endoscopic assessment. This enhancement is typically achieved using narrow wavelengths of light to highlight the deep and superficial mucosal vasculature, as well as to provide better contrast of subtle mucosal patterns. Three main virtual chromoendoscopy modalities are currently available; narrow band imaging (Olympus, Tokyo, Japan), the i-Scan imaging system (Pentax, Tokyo, Japan), and blue light imaging (Fujifilm, Tokyo, Japan).

Validated classification systems exist for these virtual chromoendoscopy modalities; all typically stratify lesions as dysplastic or nondysplastic based on mucosal or vascular patterns. Nondysplastic BE mucosa has regular appearing gyric, elongated pit patterns. The microvasculature when visible should appear ordered, not diluted or branching, and should follow the pattern of folds between pits. Markers of early neoplasia include identification of more disordered and crowded pit patterns, with the microvasculature becoming more dilated, aberrant, and densely packed as a marker of early neoplasia.

The BING criteria, devised by Sharma et al, demonstrated the potential of narrow band imaging as a replacement for conventional chromoendoscopy. Using a simple mucosal and vessel classification system they showed an accuracy of 92%, and sensitivity and specificity of 91% and 93%, respectively, in the identification of early dysplastic lesions on still images. Several studies have shown that i-Scan can improve neoplasia detection in patients with BE. Haidry et al demonstrated an accuracy of 83% when combining i-Scan with magnification and acetic acid. Importantly, this study assessed the detection in real-time videos of endoscopic surveillance to more closely model the clinical application of this technology. Blue light imaging represents another new addition to the gastroenterologist’s arsenal. Bhandari et al validated a classification system for
mentoring, education, and training corner

Improving Barrett’s Endoscopy in Day-to-Day Practice

The successful delivery of high-quality Barrett’s screening and surveillance is multifactorial and endoscopists should be properly trained to recognize subtle visible abnormalities associated with early neoplasia. Enough time should be allowed for a thorough assessment of the entire Barrett’s mucosa, with a particular focus on areas considered high risk for neoplasia such as the GOJ, right wall, and proximal end of the segment. Clinicians should report their findings according to the Prague and Paris classifications to improve consistency and to guide endoscopists should Barrett’s endoscopic therapy be needed. Most important, the Seattle protocol remains the standard for obtaining biopsies of the BE segment. Given the evidence that it improves the detection rates of early neoplasia, clinicians should ensure that they follow it rigidly, paying particular attention to take systematic biopsies throughout the entire Barrett’s segment.

References


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1. Markers of early neoplasia using NBI include
   a. Elongated pit pattern
   b. Dilated microvasculature
   c. Crowded distorted pit pattern
   d. Densely packed vasculature

**True or False**

2. An anatomic landmark of the gastroesophageal junction is the top of the gastric folds

3. Mucosal observation time of at least 1 minute per centimeter of Barrett’s esophagus (with naps in between) is recommended

4. Prior to EMR of depressed lesions, EUS with lymph node biopsy should be considered to assess extent of disease

5. The use of NBI and careful mucosal inspection obviates the need for the Seattle biopsy protocol

6. Intestinal metaplasia of the cardia is a normal finding in about 20% of cases and can be confused with Barrett’s esophagus

7. Acetic acid spray may enhance detection of dysplastic lesions in Barrett’s esophagus

8. Maximal insufflation is recommended to enhance detection of subtle lesions

9. Early adenocarcinomas are more frequent on the right wall of the esophagus, within the proximal segment of the Barrett’s epithelium

10. Methylene blue and indigo carmine have been found to increase the detection rate of dysplastic lesions in Barrett’s esophagus