HHS Public Access

Author manuscript

Am J Gastroenterol. Author manuscript; available in PMC 2023 June 07.

Published in final edited form as:

Am J Gastroenterol. 2016 January ; 111(1): 30–51. doi:10.1038/ajg.2015.322.

ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus

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Abstract

Barrett's esophagus (BE) is among the most common conditions encountered by the gastroenterologist. In this document, the American College of Gastroenterology updates its guidance for the best practices in caring for these patients. These guidelines continue to endorse screening of high-risk patients for BE; however, routine screening is limited to men with reflux symptoms and multiple other risk factors. Acknowledging recent data on the low risk of malignant progression in patients with nondysplastic BE, endoscopic surveillance intervals are attenuated in this population; patients with nondysplastic BE should undergo endoscopic surveillance no more frequently than every 3–5 years. Neither routine use of biomarker panels nor advanced endoscopic imaging techniques (beyond high-definition endoscopy) is recommended at this time. Endoscopic ablative therapy is recommended for patients with BE and high-grade dysplasia, as well as T1a esophageal adenocarcinoma. Based on recent level 1 evidence, endoscopic ablative therapy is also recommended for patients with BE and low-grade dysplasia, although endoscopic surveillance continues to be an acceptable alternative. Given the relatively common recurrence of BE after ablation, we suggest postablation endoscopic surveillance intervals. Although many of the recommendations provided are based on weak evidence or expert opinion, this document provides a pragmatic framework for the care of the patient with BE.

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Specific author contributions: All authors contributed in the analysis and interpretation of evidence, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

Potential competing interests: None.

Guarantor of the article: Nicholas J. Shaheen, MD, MPH, FACG.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

Recent population studies suggest that gastroesophageal reflux disease (GERD) is increasing in prevalence, both in the United States and worldwide (1,2). The diagnosis of GERD is associated with a 10–15% risk of Barrett's esophagus (BE), a change of the normal squamous epithelium of the distal esophagus to a columnar-lined intestinal metaplasia (IM). Risk factors associated with the development of BE include long-standing GERD, male gender, central obesity (3), and age over 50 years (4,5). The goal of a screening and surveillance program for BE is to identify individuals at risk for progression to esophageal adenocarcinoma (EAC), a malignancy that has been increasing in incidence since the 1970s (6,7).

The purpose of this guideline is to review the definition and epidemiology of BE, available screening modalities for BE detection, rationale and methods for surveillance, and available treatment modalities including medical, endoscopic, and surgical techniques. In order to evaluate the level of evidence and strength of recommendations, we used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (8). The level of evidence ranged from "high" (implying that further research was unlikely to change the authors' confidence in the estimate of the effect) to "moderate" (further research would be likely to have an impact on the confidence in the estimate of effect) to "low" (further research would be expected to have an important impact on the confidence in the estimate of the effect and would be likely to change the estimate) or "very low" (any estimate of effect is very uncertain). The strength of a recommendation was graded as "strong" when the desirable effects of an intervention clearly outweighed the undesirable effects and as "conditional" when there was uncertainty about the tradeoffs. We used meta-analyses or systematic reviews when available, followed by clinical trials and cohort and case–control studies. In order to determine the level of evidence, we entered data from the papers of highest evidence into the GRADE program (accessible at www.gradepro.org). For each recommendation, a GRADE table was constructed, and the evidence rated. Recommendation statements were structured in the "PICO" format (patient population involved, intervention or Indicator assessed, comparison group, and patient-relevant outcome achieved) when possible. The aggregate recommendation statements are in Table 1.

As part of this guideline preparation, a literature search was conducted using Ovid MEDLINE from 1946 to present, EMBASE 1988 to present, and SCOPUS from 1980 to present using major search terms and subheadings including "Barrett esophagus," "Barrett oesophagus," "epithelium," "goblet cells," "metaplasia," "dysplasia," "precancerous conditions," "adenocarcinoma," "radiofrequency," "catheter ablation," "early detection of cancer," "mass screening," and/or "esophagoscopy," The full literature search strategy is demonstrated in Supplementary Appendix 1 online.

DIAGNOSIS OF BE

Recommendations

1. BE should be diagnosed when there is extension of salmon-colored mucosa into the tubular esophagus extending ≥1 cm proximal to the gastroesophageal junction (GEJ) with biopsy confirmation of IM (strong recommendation, low level of evidence).

2. Endoscopic biopsy should not be performed in the presence of a normal Z line or a Z line with <1 cm of variability (strong recommendation, low level of evidence).

3. In the presence of BE, the endoscopist should describe the extent of metaplastic change including circumferential and maximal segment length using the Prague classification (conditional recommendation, low level of evidence).

4. The location of the diaphragmatic hiatus, GEJ, and squamocolumnar junction should be reported in the endoscopy report (conditional recommendation, low level of evidence).

5. In patients with suspected BE, at least 8 random biopsies should be obtained to maximize the yield of IM on histology. In patients with short (1–2 cm) segments of suspected BE in whom 8 biopsies may be unobtainable, at least 4 biopsies per cm of circumferential BE, and one biopsy per cm in tongues of BE, should be obtained (conditional recommendation, low level of evidence).

6. In patients with suspected BE and lack of IM on histology, a repeat endoscopy should be considered in 1–2 years of time to rule out BE (conditional recommendation, very low level of evidence).

Summary of evidence

Establishing a diagnosis of BE.—BE has been traditionally defined as the presence of at least 1 cm of metaplastic columnar epithelium that replaces the stratified squamous epithelium normally lining the distal esophagus. The reason why such segments <1 cm have been classified as “specialized IM of the esophagogastric junction” (SIM-EGJ) and not BE is because of high interobserver variability, as well as the low risk for EAC. Patients with SIM-EGJ have not demonstrated an increase in the development of dysplasia or EAC in large cohort studies after long-term follow-up, in contrast with patients with segments of IM >1 cm (9).

The definition of BE has varied depending upon the requirement for the presence of IM on endoscopic biopsy. The presence of IM has traditionally been a requirement for the diagnosis of BE in the United States. On the other hand, guidelines from the United Kingdom have considered BE to be present if there was visual evidence of columnar-lined epithelium (CLE) on endoscopic examination and biopsies demonstrated columnar metaplasia, regardless of the presence of IM (10). The debate regarding the requirement of IM on biopsy from CLE segments has derived from the apparently differential risk of developing EAC in CLE containing IM compared with non-IM CLE. Large population-based cohort studies have demonstrated a substantially lower EAC risk in subjects with columnar metaplasia without IM compared with those with IM (11). However, not all studies have corroborated this finding (12). Although DNA content abnormalities appear to be comparable in both metaplastic epithelium without goblet cells compared with metaplastic epithelium with goblet cells, other studies suggest that cancer most commonly occurs in columnar metaplasia with goblet cells compared with columnar metaplasia without goblet cells (11,13,14). Even if the rate of EAC is markedly higher in CLE containing IM, another

complicating factor is sampling error leading to misclassification of IM-containing CLE as non-IM CLE. The yield for IM correlates directly with the number of endoscopic biopsies obtained. In a large retrospective study, the yield for IM was 35% if 4 biopsies were obtained, and up to 68% after 8 biopsies were performed (15). Despite the incompletely elucidated risk of EAC in non-IM CLE, and acknowledging the potential for sampling error, we continue to suggest that only CLE containing IM be defined as BE, given the apparent differential cancer risk between CLE containing IM and CLE without IM. Until and unless further work substantiates a markedly elevated risk of EAC in non-IM CLE patients, it is unwise to give these patients a disease diagnosis that has a documented negative impact on insurance status and quality of life (16,17).

IM of cardia is very common, being described in up to 20% of asymptomatic subjects presenting for routine open access endoscopic examinations (18). Studies have suggested that IM of the cardia is not more common in BE patients compared with controls (19), and that the natural history of IM at the EGJ is associated with *Helicobacter pylori* infection and not associated with EAC (20). Based on this information, biopsy of a normal or slightly irregular EGJ is not recommended.

The location of the EGJ has been defined as the anatomic region where the distal extent of the tubular esophagus is in contact with the proximal extent of the gastric folds. The location of the proximal extent of the gastric folds can be affected by respiration, air insufflation during endoscopy, and esophageal and gastric motility. For this reason, some Japanese endoscopists have chosen to define the location of the EGJ based on the distal limit of the lower esophageal palisade vessels (21). Using this methodology, however, the lower esophageal palisade vessel has been described to be lower than the EGJ in the majority of patients, translating to short segments of CLE without IM. In a comparative study of the two methods performed in Japan, investigators concluded that the proximal extent of the gastric folds was more accurate compared with the palisade vessels (22). The diaphragmatic hiatus is identified as an indentation of the gastric folds that is apparent during upper endoscopy with inspiration.

Any segment of BE measuring >3 cm has been classified as long-segment BE, with segments <3 cm classified as short-segment BE (23). It is recommended that a uniform classification be used to facilitate diagnosis, but to date usage of a standard classification system has not been demonstrated to change patient management. The Prague classification, described initially in 2006, uses assessment of the circumferential and maximum extent of the endoscopically visualized BE segment as well as endoscopic landmarks (Figure 1) (24). Applying this system prospectively, there were high reliability coefficients (RCs) for recognition of BE segments >1 cm (RC 0.72), locations of the EGJ (RC 0.88), and diaphragmatic hiatus (RC 0.85), but not for BE segments <1 cm (RC 0.22). In addition to usage of the Prague classification, it is recommended that all three landmarks, including the diaphragmatic hiatus, EGJ, and squamocolumnar junction, be mentioned in every endoscopic report. Isolated islands of columnar mucosa were not included in the Prague classification and should be reported separately in the endoscopy report. There are no data to suggest that a confirmatory endoscopic examination is of utility in 1 year after diagnosis, as long as a sufficient number (up to 8) of biopsies are obtained during the initial

examination from the Barrett's segment (15). Therefore, in situations where BE is suspected, we recommend acquiring 4 biopsies every 2 cm of segment length, or a total of at least 8 biopsies if the segment is <2 cm, at the initial exam.

In patients with suspected BE on endoscopy without confirmation of IM despite adequate number of biopsies, a repeat examination could be considered in 1–2 years of time based on a longitudinal cohort study demonstrating that ~30% of these patients can be expected to demonstrate IM on a repeat examination (25).

EPIDEMIOLOGY AND NATURAL HISTORY OF BE

Summary statements

What are the risk factors for BE?

1. The known risk factors for the presence of BE include the following:
    a. Chronic (>5 years) GERD symptoms
    b. Advancing age (>50 years)
    c. Male gender
    d. Tobacco usage
    e. Central obesity
    f. Caucasian race
2. Alcohol consumption does not increase risk of BE. Wine drinking may be a protective factor.
3. BE is more common in first-degree relatives of subjects with known BE.

What are the risk factors associated with dysplasia and development of EAC in patients with BE?

1. The known risk factors for the development of neoplasia in BE include:
    a. Advancing age
    b. Increasing length of BE
    c. Central obesity
    d. Tobacco usage
    e. Lack of nonsteroidal anti-inflammatory agent use
    f. Lack of PPI use
    g. Lack of statin use.

What is the cancer risk in BE, based on degree of dysplasia?

1. The risk of cancer progression for patients with nondysplastic is ~0.2–0.5% per year.

2. For patients with low-grade dysplasia (LGD) the annual risk of progression to cancer is ~0.7% per year.
3. For patients with high-grade dysplasia (HGD), the annual risk of neoplastic progression is ~7% per year.
4. The majority (>90%) of patients diagnosed with BE die of causes other than EAC.

Summary of evidence

Risk factors for BE.—BE has been detected in ~15% of patients with chronic GERD (26) and in ~1–2% of population subjects (Table 2) (27,28). In a population-based study from Sweden, the authors found that severe and chronic GERD were risk factors for the development of EAC; however, 40% of the cohort with esophageal cancer reported no prior history of GERD symptoms (29). In subjects with GERD, symptom duration has been shown to be a risk factor for the presence of BE. In a cohort study examining duration of GERD symptoms and risk for BE (30), 77 (11%) of 701 patients with GERD symptoms were found to have BE on upper endoscopy. Compared with patients with GERD symptoms for <1 year, the odds ratio (OR) for BE increased to 3.0 (95% confidence interval (CI) 1.2–8.0) and 6.4 (95% CI 2.4–17.1) when symptoms were present for >5 and >10 years, respectively. A meta-analysis further demonstrated that the OR for the association of GERD symptoms and BE was 2.9 (95% CI 1.9–4.5) with significant heterogeneity between studies. When stratified by length of BE, the heterogeneity resolved, demonstrating a strong association between GERD and long-segment BE (OR 4.9, 95% CI 2–12) but no association with short-segment BE (OR 1.2, 95% CI 0.8–1.7) (31).

Increasing age is a risk factor for BE. In a retrospective study using the CORI (Clinical Outcomes Research Initiative) database, the yield of BE in white men with GERD was 2% in the third decade of life, but increased to 9% in the sixth decade (4). Early age of onset of GERD symptoms may also be associated with BE. In a VA study, patients reporting frequent (defined as at least weekly) GERD symptoms starting before the age of 30 years had the highest risk of BE (OR 15.1, 95% CI 7.91–28.8), and risk increased linearly with earlier age at onset of symptoms (P=0.001). The risk of BE also increased with cumulative GERD symptom duration (P=0.002) (32).

Male gender has been consistently identified as a risk factor for BE and EAC. A meta-analysis demonstrated an overall pooled male/female ratio of 2:1 (95% CI 1.8–2.2) (33). The risk of development of EAC is also significantly higher in men. In a study using the SEER (The Surveillance, Epidemiology, and End Results) database, women composed only 12% of all EACs. In this study, the risk of EAC in women with GERD symptoms was approximately equivalent to the risk of breast cancer in men (3.9 per 100,0000 at age 60 years) (34).

Tobacco usage has been demonstrated to be a risk factor for BE in a recent meta-analysis based on 39 studies and 7,069 BE patients. Any smoking during a patient’s lifetime was associated with a greater risk for BE compared with non-GERD controls (OR 1.4, 95% CI 1.2–1.7), but not when compared with patients with chronic GERD (OR 1.2, 95% CI

0.8–1.9), suggesting that the increased risk of BE associated with tobacco usage may be mediated via increasing GERD (35).

In contrast to tobacco usage, alcohol consumption has not been demonstrated to be significantly associated with the risk for development of BE (36,37). In fact, there are data suggesting a possible protective effect of wine consumption, with ORs ranging from 0.44 (95% CI 0.2–0.99) to 0.71 (95% CI 0.52–0.98) (37,38).

The presence of obesity is an independent risk factor for BE and EAC (39). However, it appears that a central pattern of obesity, rather than overall body fat content (measured by BMI), is the primary risk factor for BE. In a meta-analysis (3), patients with central adiposity had a higher risk for BE compared with patients with normal body habitus (OR 2.0, 95% CI 1.5–2.6) and this relationship persisted after adjustment for BMI and GERD, suggesting a reflux independent role for central obesity in BE pathogenesis. Indeed, overall body fat content is not associated with BE risk (40). Central obesity is a risk factor for BE in both men and women (41).

The presence of a family history of BE has been identified as another potential risk factor for BE (42). A cohort study demonstrated that BE was markedly more common in first- or second-degree relatives of subjects with BE compared with controls (24% vs. 5%, $P<0.005$). After adjusting for age, gender, and body mass index, the presence of family history was strongly associated with BE (OR 12, 95% CI 3.3–44.8) (42). In a subsequent study, endoscopic screening was offered to first-degree previously uninvestigated relatives of subjects with BE. The overall diagnostic yield was 20% (43). Single-nucleotide polymorphisms on gene loci, which may confer increased susceptibility to BE development, have recently been described (44–47).

Caucasian race appears to be a strong risk factor for BE. Although the evidence for lower prevalence of BE in African Americans compared with Caucasians is consistent (48,49), the results of studies comparing BE incidence in Hispanics and non-Hispanic whites are inconsistent, likely reflecting the heterogeneity of the Hispanic population (49,50).

Other risk factors for BE have also been reported. Disease conditions such as metabolic syndrome (51), type 2 diabetes mellitus (52), and sleep apnea (53) have been identified as potential BE risk factors. *H. pylori* infection, particularly infection with Cag A+ strains, is associated with a decreased risk of BE in some studies (54,55).

Risk factors associated with dysplasia and EAC in patients with BE.

Advancing age and increasing BE segment length are known risk factors for the presence of dysplasia in patients with BE. In a multicenter study of 309 BE patients (5 with cancer, 11 with HGD, and 29 with LGD), the risk factors for prevalent dysplasia included age (3.3% increase in dysplasia per year and BE segment length over 3 cm (risk increase of 14% per cm of BE present) (56).

In patients with known BE, a variety of medications have been associated with reduced risk of progression to dysplasia and/or esophageal cancer including proton pump inhibitors (PPIs), aspirin, nonsteroidal anti-inflammatory agents, and statins. A meta-analysis based

on 7 studies with 2,813 patients demonstrated a 71% reduced risk of HGD and/or EAC with PPI users (OR 0.3, 95% CI 0.1–0.8). No significant effect was shown for H_2RA usage in two studies (57). In another meta-analysis of 9 observational studies of 5,446 participants (605 with HGD or EAC), usage of cyclooxygenase inhibitors, aspirin, and nonaspirin cyclooxygenase inhibitors was associated with reduced risk for HGD and EAC independent of duration of therapy (58). By means of their antiproliferative, proapoptotic, antiangiogenic, and immunomodulatory effects, statins may prevent cancer development and growth. In a meta-analysis of 5 studies including 2,125 BE patients (312 EAC cases), statin usage was associated with a 41% reduction in EAC risk (adjusted OR 0.6, 95% CI 0.45–0.78) with the number needed to treat of 389 to prevent 1 case of EAC (59).

Cancer risk in BE based on degree of dysplasia.

A recent meta-analysis published in 2012 demonstrated lower risk for progression of nondysplastic BE than previously reported (Table 3) (60). It included 57 studies and demonstrated that the pooled annual incidence of EAC was 0.33% (95% CI 0.28–0.38%). In patients with short-segment BE reported from 16 studies, the annual cancer risk was 0.19%.

For patients with LGD, a meta-analysis examined 24 studies. In this cohort, pooled annual incidence rates were 0.5% (95% CI 0.3–0.8) for EAC alone and 1.7% (95% CI 1.0–2.5) for HGD and/or EAC combined (61). However, there was considerable heterogeneity in these results and when stratified by the LGD/BE ratio as a surrogate for pathology quality, the incidence rate for EAC was 0.76% per year for a ratio of <0.15 and 0.32% per year for a ratio of >0.15. This finding suggests that in settings where the diagnosis of LGD is made more liberally, and perhaps overcalled, there is a lower risk of progression.

The risk of EAC for patients with HGD was examined in a meta-analysis of 4 studies and 236 patients. The weighted annual incidence rate was 7% (95% CI 5–8) (62). However, the AIM-Dysplasia trial that randomized 127 patients with dysplasia to ablation therapy compared with surveillance reported a much higher yearly progression rate of 19% in the HGD surveillance arm (63). This rate is similar to a second randomized trial that also required confirmation of HGD by a second expert pathologist, again suggesting that the rigor with which the histology is validated likely predicts the subsequent EAC risk (64).

What are the common causes of death in subjects with BE?

Most BE patients die of other causes than EAC. A meta-analysis reported mortality rates from 19 studies in 7,930 patients (65). There were 88 deaths because of EAC and 1,271 deaths because of other causes, resulting in a pooled incidence rate of fatal EAC of 3/1,000 person-years (95% CI 2–4). In 12 studies reporting cause-specific mortality, 7% of deaths (64/921) were from EAC, and 93% (857/921) because of other causes. The most common causes included cardiac disease in 35%, followed by pulmonary disease in 20% and other malignancies in 16% of the cohort.

SCREENING FOR BE

Recommendations

7. Screening for BE may be considered in men with chronic (>5 years) and/or frequent (weekly or more) symptoms of gastroesophageal reflux (heartburn or acid regurgitation) and two or more risk factors for BE or EAC. These risk factors include: age >50 years, Caucasian race, presence of central obesity (waist circumference >102 cm or waist–hip ratio >0.9), current or past history of smoking, and a confirmed family history of BE or EAC (in a first-degree relative) (strong recommendation, moderate level of evidence).

8. Given the substantially lower risk of EAC in females with chronic GER symptoms (when compared with males), screening for BE in females is not recommended. However, screening could be considered in individual cases as determined by the presence of multiple risk factors for BE or EAC (age >50 years, Caucasian race, chronic and/or frequent GERD, central obesity: waist circumference >88 cm, waist–hip ratio >0.8, current or past history of smoking, and a confirmed family history of BE or EAC (in a first-degree relative)). (strong recommendation, low level of evidence).

9. Screening of the general population is not recommended (conditional recommendation, low level of evidence).

10. Before screening is performed, the overall life expectancy of the patient should be considered, and subsequent implications, such as the need for periodic endoscopic surveillance and therapy, if BE with dysplasia is diagnosed, should be discussed with the patient (strong recommendation, very low level of evidence).

11. Unsedated transnasal endoscopy (uTNE) can be considered as an alternative to conventional upper endoscopy for BE screening (strong recommendation, low level of evidence).

12. If initial endoscopic evaluation is negative for BE, repeating endoscopic evaluation for the presence of BE is not recommended. If endoscopy reveals esophagitis (Los Angeles Classification B, C, D), repeat endoscopic assessment after PPI therapy for 8–12 weeks is recommended to ensure healing of esophagitis and exclude the presence of underlying BE (conditional recommendation, low level of evidence).

Summary of evidence

Survival of subjects diagnosed with EAC with regional or distant disease remains dismal, at <20% at 5 years (7). The concept of metaplasia–dysplasia–carcinoma progression sequence in BE has led to the hypothesis that screening for BE, institution of endoscopic surveillance to detect dysplasia, followed by endoscopic intervention, will lead to a decreased incidence of EAC (66). In addition to detecting BE, screening also detects prevalent dysplasia or carcinoma that may be treated with endoscopic therapy. The available evidence to support this hypothesis, however, consists of retrospective studies that may be subject to biases.

Indeed, >90% of EACs are diagnosed in patients without a prior BE diagnosis, despite the increasing use of endoscopy (67,68).

Given the number of patients involved, a widely embraced population screening effort could lead to substantial economic costs (from diagnostic tests and need for subsequent surveillance). Economic modeling studies (69) have found BE screening (done by endoscopy) followed by surveillance in hypothetical populations (50-year-old male subjects with GERD symptoms) to be cost effective, with acceptable incremental cost-effectiveness ratios ranging from $10,000 to 50,000/quality-adjusted life-year gained (70,71). Estimates vary among studies, likely because of differences in assumptions (Supplementary Table S1). Three of these studies found that screening with video capsule endoscopy (72,73) or uTNE (74) was cost effective compared with no screening, but that standard endoscopy was preferred over capsule endoscopy. All assumed participation rates of almost 100% and accuracy rates of 100%. This is likely an overestimate with lower participation rates (18–49%) (75–77), and lower accuracy rates for endoscopy (80%) being reported in prior studies (78). Of note, a substantial proportion of BE diagnoses in the community are reversed, likely because of incorrect landmark identification and incorrect targeting of biopsies (79). In addition, the yield of a repeat endoscopy following an initial negative endoscopy for BE is low (2.3%), with esophagitis and male gender being predictors of BE being diagnosed at subsequent endoscopy (80). However, studies report a BE prevalence of 9–12% on repeat endoscopy following treatment of esophagitis with PPIs, making a repeat endoscopy after healing of more severe erosive esophagitis advisable (81,82).

BE screening has several challenges. Although symptomatic GERD is a risk factor for BE and EAC, it is neither a sensitive nor specific marker (29,31). Only 5–15% of subjects with chronic (>5 years) and frequent (weekly or more frequent) reflux have BE (83), and as many as 50% of subjects with BE or EAC do not report chronic reflux symptoms (31,84). Several studies have reported a substantial prevalence of BE in those without reflux symptoms (27,85,86). Indeed, although reflux symptoms are associated with long-segment BE, they may not be consistently associated with short-segment BE (31). Hence, a BE screening strategy based solely on GERD symptoms is likely to be unsuccessful. Women (even those with daily or weekly reflux symptoms) have a low incidence of EAC comparable to that of men without reflux symptoms (34). This may relate to the lower risk of progression to EAC in women with BE compared with men with BE (60,87) and should likely influence the threshold of BE screening in women.

Recent reports have described the creation of prediction or risk scores for BE using a combination of risk factors (5,88). This may enable the synthesis of multiple risk factors into a single clinically applicable parameter and make BE screening more efficient by targeting a high-risk target population. Accuracy for BE prediction, though improved from GERD-only models, remains modest (area under the curve 0.73–81), but is likely to be improved by the addition of other variables such as circulating cytokine levels (89). Validation in larger unselected populations will be critical before widespread use.

Several techniques are available for BE screening. Conventional endoscopy is regarded as the gold standard despite evidence on limitations of accuracy. uTNE as an alternate

modality for BE screening has been found to have comparable performance characteristics to endoscopy for the diagnosis of BE (sensitivity 98% and specificity 100%) (90). The feasibility and safety of uTNE in BE screening in the community has also been demonstrated (75,77). Esophagoscopes with disposable sheaths, eliminating the need for standard disinfection, may be a viable alternative for BE screening (91). Although inability to intubate the nasopharynx and discomfort are limitations of TNE, they occur in a small proportion of subjects, and a substantial majority are willing to undergo the procedure again. Nonphysician providers can be trained to perform this procedure, reducing costs further (92). Esophageal video capsule endoscopy is a well-tolerated, patient-preferred, and non-invasive technique that allows visualization of the distal esophagus. However, because of inadequate accuracy (pooled sensitivity 78% and specificity 73%) (93), it is currently not recommended for BE screening. More recently, a novel gelatin-coated sponge attached to a string that expands to a sphere when swallowed, and is then pulled out, obtaining esophageal cytology samples (Cytosponge), has been described. When combined with a protein marker, trefoil factor 3, a sensitivity of 73% and specificity of 94% for BE diagnosis has been described (76). Although participation rates were low (18%), the device was overall safe and well tolerated. Given its non-endoscopic nature, this device may allow cheaper, more convenient, office-based screening for BE if validated in subsequent studies. This method has also been shown to be cost effective compared with no screening or sedated endoscopy in a modeling study (94).

SURVEILLANCE OF BE

Recommendations

13. Patients should only undergo surveillance after adequate counseling regarding risks and benefits of surveillance (strong recommendation, very low level of evidence).

14. Surveillance should be performed with high-definition/high-resolution white light endoscopy (strong recommendation, low level of evidence).

15. Routine use of advanced imaging techniques other than electronic chromoendoscopy is not recommended for endoscopic surveillance at this time (conditional recommendation, very low level of evidence).

16. Endoscopic surveillance should employ four-quadrant biopsies at 2 cm intervals in patients without dysplasia and 1 cm intervals in patients with prior dysplasia (strong recommendation, low level of evidence).

17. Mucosal abnormalities should be sampled separately, preferably with endoscopic mucosal resection (EMR). Inability to perform EMR in the setting of BE with nodularity should lead to referral to a tertiary care center (strong recommendation, low level of evidence).

18. Biopsies should not be obtained in mucosal areas with endoscopic evidence of erosive esophagitis until after intensification of antireflux therapy to induce mucosal healing (strong recommendation, very low level of evidence).

19. For BE patients with dysplasia of any grade, review by two pathologists, at least one of whom has specialized expertise in gastrointestinal (GI) pathology, is warranted because of interobserver variability in the interpretation of dysplasia (strong recommendation, moderate level of evidence).

20. Use of additional biomarkers for risk stratification of patients with BE is currently not recommended (strong recommendation, low level of evidence).

21. For BE patients without dysplasia, endoscopic surveillance should take place at intervals of 3 to 5 years (strong recommendation, moderate level of evidence).

22. Patients diagnosed with BE on initial examination with adequate surveillance biopsies do not require a repeat endoscopy in 1 year for dysplasia surveillance (conditional recommendation, very low level of evidence).

23. For patients with indefinite for dysplasia, a repeat endoscopy after optimization of acid suppressive medications for 3–6 months should be performed. If the indefinite for dysplasia reading is confirmed on the repeat examination, a surveillance interval of 12 months is recommended (strong recommendation, low level of evidence).

24. For patients with confirmed LGD and without life-limiting comorbidity, endoscopic therapy is considered as the preferred treatment modality, although endoscopic surveillance every 12 months is an acceptable alternative (strong recommendation, moderate level of evidence).

25. Patients with BE and confirmed HGD should be managed with endoscopic therapy unless they have life-limiting comorbidity (strong recommendation, high level of evidence).

Summary of the evidence

Rationale for surveillance.—Survival in EAC is stage dependent and early spread before the onset of symptoms is characteristic of this tumor. Lymph node metastases are a clear prognostic factor for decreased survival (95). Thus, the best hope for improved survival of patients with EAC remains detection of cancer at an early and potentially curable stage.

A number of observational studies suggest that patients with BE in whom EAC was detected in a surveillance program have their cancers detected at an earlier stage with markedly improved survival compared with similar patients not undergoing routine endoscopic surveillance (96–99). Furthermore, nodal involvement is far less likely in surveyed patients compared with nonsurveyed patients. As esophageal cancer survival is stage dependent, these studies suggest that survival may be enhanced by endoscopic surveillance. Recent work from a large Dutch population-based cohort study confirmed that there is a survival advantage for EAC in patients who received adequate endoscopic surveillance compared with patients who were not participating in endoscopic surveillance (100). Similarly, a large Northern Ireland population-based study found that in patients with EAC and a prior diagnosis of BE, survival was enhanced, tumor stage was lower, and tumor grade was lower compared with patients without a prior diagnosis (101). Importantly, these findings were

maintained, although attenuated, after attempting to correct for both lead time and length time bias. On the other hand, a case–control study from the Northern California Kaiser Permanente population found no evidence that endoscopic surveillance improved survival from EAC (102). Although there are no prospective clinical trial data that demonstrate a benefit of endoscopic surveillance, the considerable heterogeneity of available evidence makes it prudent to continue to perform endoscopic surveillance of BE patients.

It is important to recognize, however, that endoscopic surveillance, as currently practiced, has numerous shortcomings. Dysplasia may not be visible endoscopically and the distribution of dysplasia and cancer is highly variable. Even the most thorough biopsy surveillance program has the potential for sampling error. Current surveillance programs are expensive and time consuming. It is well known that adherence to practice guidelines is problematic at best and worsens with longer segment lengths (103). All of these shortcomings likely diminish any benefit from these programs, and efforts to adhere to published standards for the performance of various elements of surveillance are recommended.

Counseling for surveillance.—Before entering into a surveillance program, patients should be counseled about the risks and benefits of this program, including the limitations of surveillance endoscopy as well as the importance of adhering to appropriate surveillance intervals. Other considerations include age, likelihood of survival over the next 5 years, and ability to tolerate interventions including endoscopic therapy, surgery, and medical or radiation oncologic treatments for EAC.

Until recently, the concept of early outpatient consultation to review the significance of BE has not been a point of emphasis in prior practice guidelines (10). Why is this important? First, wide access to the Internet allows patients to obtain information about BE and EAC in an unfiltered manner. Studies to date suggest that patients both over- and under-estimate their cancer risk (16,104). Given the low risk of progression to cancer for most patients with BE and the data suggesting that most BE patients die of causes other than EAC, such counseling should now be part of the ongoing care of these patients to help inform decision making regarding therapeutic options (65).

Surveillance technique.—Endoscopic surveillance should utilize high-resolution/high-definition white light endoscopy to optimize visualization of mucosal detail. Recent work suggests that this is superior to standard-definition white light endoscopy for the detection of dysplastic lesions (105). This should be accompanied by removal of any mucosal debris and careful insufflation and desufflation of the lumen. Part of the examination should also incorporate a retroflexed view of the GEJ. Data demonstrate a direct correlation between inspection time of the Barrett’s segment and detection of patients with HGD/EAC (106). Inspection of the Barrett’s segment should also involve careful attention to the right hemisphere of the segment, extending from the 12 o’clock to 6 o’clock location where early cancer appears to have a predilection to develop (107,108).

The aim of surveillance is detection of dysplasia. The description of dysplasia should use a standard five-tier system: (i) negative for dysplasia, (ii) indefinite for dysplasia, (iii)

LGD, (iv) HGD, and (v) carcinoma (109). Active inflammation makes it more difficult to distinguish dysplasia from reparative changes. As such, surveillance biopsies should only be performed after any active inflammation related to GERD is controlled with antisecretory therapy. The presence of ongoing erosive esophagitis is a relative contraindication to performing surveillance biopsies. Once any inflammation related to GERD is controlled with antisecretory therapy, systematic four-quadrant biopsies at 2 cm intervals along the entire length of the Barrett's segment remains the standard for endoscopic surveillance of nondysplastic BE.

A systematic biopsy protocol clearly detects more dysplasia and early cancer compared with *ad hoc* random biopsies (110,111). Subtle mucosal abnormalities, no matter how trivial, such as ulceration, erosion, plaque, nodule, stricture, or other luminal irregularity in the Barrett's segment, should also be sampled, as there is an association of such lesions with underlying cancer (112). Mucosal abnormalities, encountered in the setting of surveillance of patients with known dysplasia, should undergo EMR. EMR will change the diagnosis in ~50% of patients when compared with endoscopic biopsies, given the larger tissue sample available for review by the pathologist (113). Interobserver agreement among pathologists is improved as well (114). The safety of systematic endoscopic biopsy protocols has been demonstrated (115). The addition of routine cytologic sampling to endoscopic biopsies appears to add little to surveillance biopsies (116). The role of computer-assisted or wide-field "brush biopsy" tissue acquisition for increasing the yield of dysplasia is currently under investigation (117,118). Currently, the finding of subsquamous BE on surveillance biopsies of the untreated patient does not change patient management, based on the most advanced histology found on the combination of targeted and random biopsies.

Advanced endoscopic imaging techniques.—A wide variety of enhancements to endoscopic imaging with white light endoscopy have been studied in recent years to allow for detailed inspection of the Barrett's segment. Electronic chromoendoscopy allows for detailed imaging of the mucosal and vascular surface patterns in BE without the need for chromoendoscopy dye sprays. This may be accomplished with either narrow band imaging that uses optical filters to narrow the band width of white light to blue light or by postprocessing software systems to accomplish similar visualization. Most of the published literature to date have examined narrow band imaging in conjunction with magnification endoscopy. A randomized clinical trial of narrow band imaging vs. high-definition white light endoscopy demonstrated no difference in the number of patients detected with dysplasia or neoplasia. However, fewer biopsies were required for narrow band imaging (119). A recent meta-analysis also suggests that electronic chromoendoscopy may increase detection of dysplasia (120). A wide variety of other image enhancement techniques have been studied including methylene blue staining, acetic acid staining, indigo carmine staining, autofluorescence endoscopy, confocal laser endomicroscopy, volumetric laser endomicroscopy, spectroscopy, and molecular imaging, but none of these methods appear ready for widespread clinical use at present.

Importance of confirmation of dysplasia.—Dysplasia remains the best clinically available marker of cancer risk in patients with BE. However, there is considerable

interobserver variability in the interpretation of dysplasia in both the community and academic settings. That being said, there is reasonable interobserver agreement among GI pathologists for the extremes of dysplasia, namely IM without dysplasia and HGD/EAC (109). There is considerably more difficulty in the interpretation of indefinite for dysplasia and LGD (121). The importance of the confirmation of the diagnosis of LGD comes from two recent studies from the Netherlands. Review by two GI pathologists, with extensive experience in the diagnosis of BE-related neoplasia, found that of 147 patients diagnosed with LGD in the community, 85% of the patients were downgraded to a diagnosis of no dysplasia (122). Further work by that group examined 293 additional patients with LGD diagnosed in the community who had biopsies reviewed by at least 2 GI pathologists and 73% of the cases were downgraded to indefinite for dysplasia or nondysplastic BE (123). Other studies suggest that community-based pathologists have difficulties in the interpretation of both nondysplastic BE and dysplasia (124). Therefore, current evidence supports the importance of having all readings of dysplasia confirmed by a second pathologist with extensive experience in the interpretation of Barrett's associated neoplasia.

Surveillance intervals.—Surveillance intervals are determined by the presence and grade of dysplasia and are currently governed by expert opinion. Given the low risk of progression of BE to EAC, surveillance at 3- to 5-year intervals remains reasonable in patients without dysplasia.

There is a paucity of data to guide the management of BE patients with biopsies indefinite for dysplasia. It is reasonable to use double-dose PPI therapy to decrease any ongoing inflammation. A retrospective study found that indefinite for dysplasia was associated with a similar risk of progression to cancer as was LGD (125). More recent data suggest an especially high risk of progression to higher grades of dysplasia within the first year of diagnosis but a risk comparable to nondysplastic BE after the first year (126). The progression risk may be more pronounced in multifocal indefinite for dysplasia (defined as indefinite for dysplasia in biopsies from more than one level of the esophagus) than in focal indefinite for dysplasia (127). Thus, surveillance in these patients should follow the recommendations for LGD as described below.

If LGD is found, the diagnosis should first be confirmed by a second pathologist with expertise in BE. These patients should also receive aggressive antisecretory therapy for reflux disease with a PPI to decrease the changes associated with regeneration or inflammation. A repeat endoscopy after optimization of acid suppressant therapy may result in downgrading of the LGD reading. If LGD is confirmed and endoscopic therapy not performed, annual surveillance is recommended until two examinations in a row are negative for dysplasia, after which time surveillance intervals for nondysplastic BE can be followed. A protocol of four-quadrant biopsies at 1 cm intervals is advisable, given that anatomic studies suggest that dysplasia can occur in a mosaic pattern and involve small portions of the overall surface area of the esophagus. EMR should be performed if any mucosal abnormality is present in these patients.

If HGD is found, the diagnosis should first be confirmed by a second pathologist with experience in GI pathology. The presence of any mucosal abnormality warrants EMR in

an effort to maximize staging accuracy. If HGD is confirmed, endoscopic intervention is warranted as described below. Figure 2 demonstrates the recommended actions for surveillance endoscopy of nonnodular BE.

Biomarkers of increased risk.—Given the limitations of endoscopic surveillance and histologic dysplasia as a risk stratification tool, molecular markers to identify patients at increased risk for progression have been studied. Abnormalities including DNA content abnormalities, chromosomal abnormalities, gene mutations, methylation changes, and clonal diversity measurements define patients at increased risk for progression to cancer (128–132). These genetic abnormalities appear to occur early in disease development (133).

Recent promising work in a case–control study suggested that aberrant p53 expression defined as absent or increased expression by immunohistochemistry was associated with an increased risk of neoplastic progression (134). However, it appears that no single biomarker is adequate as a risk stratification tool. Given the complexity and diversity of alterations observed to date in the progression sequence, a panel of biomarkers may be required for risk stratification. At the present time, no biomarkers or panels of biomarkers are ready for clinical practice. In order to become part of the clinical armamentarium, biomarkers will have to be validated in large prospective cohorts. Such studies will be challenging given the low overall progression of BE to HGD/EAC.

THERAPY

Recommendations

Chemoprevention.

26. Patients with BE should receive once-daily PPI therapy. Routine use of twice-daily dosing is not recommended, unless necessitated because of poor control of reflux symptoms or esophagitis (strong recommendation, moderate level of evidence).

27. Aspirin or nonsteroidal anti-inflammatory drugs should not be routinely prescribed to patients with BE as an antineoplastic strategy. Similarly, other putative chemopreventive agents currently lack sufficient evidence and should not be administered routinely (conditional recommendation, high level of evidence).

Endoscopic therapy.

28. Patients with nodularity in the BE segment should undergo EMR of the nodular lesion(s) as the initial diagnostic and therapeutic maneuver (see point 17 above). Histologic assessment of the EMR specimen should guide further therapy. In subjects with EMR specimens demonstrating HGD, or intramucosal carcinoma, endoscopic ablative therapy of the remaining BE should be performed (strong recommendation, high level of evidence).

29. In patients with EMR specimens demonstrating neoplasia at a deep margin, residual neoplasia should be assumed, and surgical, systemic, or additional

endoscopic therapies should be considered (strong recommendation, low level of evidence).

30. Endoscopic ablative therapies should not be routinely applied to patients with nondysplastic BE because of their low risk of progression to EAC (strong recommendation, very low level of evidence). Endoscopic eradication therapy is the procedure of choice for patients with confirmed LGD, and confirmed HGD, as noted above (see points 24 and 25).

31. In patients with T1a EAC, endoscopic therapy is the preferred therapeutic approach, being both effective and well tolerated (strong recommendation, moderate level of evidence).

32. In patients with T1b EAC, consultation with multidisciplinary surgical oncology team should occur before embarking on endoscopic therapy. In such patients, endoscopic therapy may be an alternative strategy to esophagectomy, especially in those with superficial (sm1) disease with a well-differentiated neoplasm lacking lymphovascular invasion, as well as those who are poor surgical candidates (strong recommendation, low level of evidence).

33. Routine staging of patients with nodular BE with endoscopic ultrasound (EUS) or other imaging modalities before EMR has no demonstrated benefit. Given the possibility of over-staging and understaging, findings of these modalities should not preclude the performance of EMR to stage early neoplasia (strong recommendation, moderate level of evidence).

34. In patients with known T1b disease, EUS may have a role in assessing and sampling regional lymph nodes, given the increased prevalence of lymph node involvement in these patients compared with less advanced disease (strong recommendation, moderate level of evidence).

35. In patients with dysplastic BE who are to undergo endoscopic ablative therapy for nonnodular disease, radiofrequency ablation is currently the preferred endoscopic ablative therapy (strong recommendation, moderate level of evidence).

Surgical therapy.

36. Antireflux surgery should not be pursued in patients with BE as an antineoplastic measure. However, this surgery should be considered in those with incomplete control of reflux on optimized medical therapy (strong recommendation, high level of evidence).

37. In cases of EAC with invasion into the submucosa, especially those with invasion to the mid or deep submucosa (T1b, sm2–3), esophagectomy, with consideration of neoadjuvant therapy, is recommended in the surgical candidate (strong recommendation, low level of evidence).

38. In patients with T1a or T1b sm1 EAC, poor differentiation, lymphovascular invasion, or incomplete EMR should prompt consideration of surgical and/or multimodality therapies (strong recommendation, low level of evidence).

Summary of evidence

No aspect of these guidelines has evolved more since the last guideline iteration than therapeutic aspects of BE (135). Most profound of these changes is our markedly augmented ability to provide effective endoscopic therapy for subjects with neoplastic BE. Aspects of chemoprevention, endoscopic intervention, and surgical evaluation are discussed below.

Chemoprevention.—Data substantiating a chemopreventive effect in the setting of BE are sparse. In part, this paucity of data reflects the low rate of progression to neoplasia in BE (65,136), making intervention studies difficult to perform. In addition, patients who might have previously been considered for chemoprevention, such as those with BE and LGD, are now considered for endoscopic ablative therapy, making the pool of patients who would gain markedly from a chemopreventive agent even smaller.

PPI therapy is common in patients with BE, in part because of the high proportion of those patients who also have symptomatic GERD. In these cases, the use of PPIs is substantiated by the need for symptom control, making consideration of chemoprevention secondary. However, even in patients without reflux symptoms, in whom BE is incidentally found during evaluation of other symptoms and/or signs, the use of PPIs deserves consideration. Several cohort studies now suggest that subjects with BE maintained on PPI therapy have a decreased risk of progression to neoplastic BE compared with those with either no acid suppressive therapy or those maintained on H_2RA therapy (57,137–139). In addition, the risk profile of these medications is favorable in most patients, and the cost of this class of drugs has diminished substantially in recent years because of the availability of generic forms of the medications. These factors, combined with the theoretical consideration that the same inflammation that may be in part be responsible for pathogenesis of BE may also promote progression of BE, make the use of PPIs in this patient population appear justified, even in those without GERD symptoms (57). Given the low probability of a randomized study of PPI use in BE, decisions regarding this intervention will likely rely on these retrospective data and expert opinion.

Some indirect evidence also supports consideration of acetylsalicyclic acid (ASA) as a chemopreventive agent in BE. Patients taking ASA appear less likely to develop esophageal cancer in epidemiological studies (140,141). In additionally, ASA and nonsteroidal anti-inflammatory drugs may inhibit several pathways important in oncogenesis. However, unlike the case with PPIs, the side-effect profile of ASA is not benign, and adverse events including cerebral and GI hemorrhage may be catastrophic. Also, given recent level 1 evidence demonstrating markedly diminished cancer risk in subjects with LGD undergoing endoscopic therapy (142), it is likely that more patients with confirmed LGD will undergo this therapy, as opposed to surveillance endoscopy. If so, these patients will likely not need chemoprevention. Given that the risk of progression in patients with nondysplastic BE is so low, any chemopreventive agent in this group of patients must be very safe to

justify its use. While we await results from a trial randomizing patients with BE to ASA or placebo (143), the current data do not justify the routine use of ASA or other nonsteroidal anti-inflammatory drugs in chemoprevention in BE. However, in the substantial proportion of subjects with BE who are also candidates for ASA use for cardioprotection, additional benefit may be derived from any chemoprotective effect of ASA on their BE.

Endoscopic therapy.—Advances in endoscopic therapy in the past decade have broadened the pool of patients with BE who may be considered for intervention as well as diminished the need for esophagectomy in this patient population. Given the rapid evolution of these technologies, it is important that endoscopists apply evidence-based decision making with respect to the utilization of these technologies.

Consideration of any endoscopic therapy in BE begins with a close inspection of the BE mucosa. The identification of mucosal irregularities including nodularity, ulceration, or flat but irregular mucosal contour is essential to detecting the areas of highest yield for neoplasia. In this role, the adjunct use of a narrow light spectrum imaging technology, such as narrow band imaging, may aid in detecting mucosal irregularity (144). If such irregularity is detected, the next step in the management of that patient should be EMR or endoscopic submucosal dissection, both for therapeutic benefit and to allow staging of the lesion (145,146). Although endoscopic submucosal dissection may provide a more complete understanding of the lateral margins of a lesion, it is technically more demanding, and should only be pursued in settings where the team has expertise in this maneuver. EMR is generally adequate to reveal the depth of invasion, the most important variable in clinical decision making.

The findings of endoscopic resection determine subsequent management of the patient. In patients with a history of nondysplastic BE whose EMR demonstrates no dysplasia, surveillance endoscopy can be resumed. In subjects with LGD or HGD and complete resection of the lesion, the EMR should be generally followed by endoscopic ablative therapy, with the goal of achieving complete eradication of all IM, and thereby decreasing the likelihood of recurrent dysplasia. Figure 3 demonstrates the management of nodular BE.

In patients with nonnodular BE, the utility of ablative therapy is becoming clearer. In patients with BE and HGD, ablative therapy should be preferred over either esophagectomy or intensive endoscopic surveillance because of its proven efficacy (63) and a side-effect profile superior to surgery (147). Recent data demonstrate that in patients with BE and LGD confirmed by a second pathologist, ablative therapy results in a statistically and clinically significant reduction in progression to the combined end point of HGD or EAC, or to EAC alone (142). In contrast, in patients with nondysplastic BE, recent data suggest lower rates of progression than previously believed (68,136,148). Given the low rate of progression in these patients, the low but real rate of complications of endoscopic therapy (149), and the costs associated with its delivery (150), ablative therapy cannot be recommended in patients with nondysplastic BE. Whether these therapies are warranted in subjects judged to have a higher lifetime risk of cancer, such as those with familial BE/EAC and young patients with long segments of BE, is unclear (151–153).

In patients with EAC, depth of invasion decides the curative potential of endoscopic therapy (Supplementary Figure S1). Lesions confined to the mucosa have a very low rate of lymphatic involvement (154,155), making these lesions optimally treated by mucosal resection, followed by a mucosal ablative therapy to eradicate the remaining BE. Lesions with superficial submucosal invasion (T1b sm1) have conflicting data with respect to the likelihood of lymph node invasion (146,156,157), making consideration of surgery and/or multimodality therapy appropriate. However, in subjects at high risk of complications with esophagectomy, endoscopic therapy can be considered as an alternative to more traditional treatments, and reported outcomes of highly selected patients are encouraging (146). If endoscopic therapy is being considered for definitive therapy for such a patient, well-differentiated tumors, as well as those with no lymphovascular invasion, have the best prognosis (154,155). Lesions with invasion into the mid or deep submucosa (T1b sm2 or T1b sm3) are associated with high rates of lymphatic involvement (154,158). Endoscopic therapy performed on such lesions should be considered palliative. Currently, the added value of endoscopic therapy as part of a scheme of multimodality therapy (for instance, endoscopic therapy plus chemotherapy and/or radiotherapy) is not well described in the literature. However, because of the potential of such an approach to provide both local and systemic control of disease, further study is warranted.

The role of imaging modalities such as EUS, positron emission tomography, and computed tomography scanning is becoming clearer. Data demonstrate that a substantial minority of patients with superficial EAC will be both over- and understaged by EUS (159–161). Therefore, the routine use of this modality before EMR is unwarranted, as clinical decision making will rest with the EMR findings. EUS may have a limited role in endoscopic therapy of early esophageal neoplasia in the setting of T1b disease (162). For the subject being considered for endoscopic therapy with T1b disease, evidence of locoregional lymph node involvement, especially if substantiated by fine-needle aspiration, means any attempt at endoscopic therapy would be palliative, and that other modalities need be invoked for curative intent. Given the low likelihood of distant involvement in intramucosal (T1a) cancer or subjects diagnosed with dysplastic BE, positron emission tomography–computed tomography has no demonstrated benefit in these clinical settings. Positron emission tomography–computed tomography may have value after a diagnosis of T1b disease, in detecting distant involvement.

EMR is not adequate as sole therapy for T1a or T1b EAC. Cohort studies document that up to one-third of patients treated with EMR who achieve complete resection of the primary lesion will subsequently develop recurrent HGD or EAC (145). Whether these subsequent lesions represent undetected metachronous lesions or a field effect in the susceptible patient is unclear. However, endoscopic ablative treatment of the remainder of the BE markedly decreases this risk. Therefore, all patients with successful resection of a T1a EAC, as well as any T1b lesions selected for endoscopic therapy, should undergo subsequent ablation of the remainder of the BE segment.

Successful endoscopic ablative therapy is defined as complete eradication of all dysplasia, as well as all IM, in the tubular esophagus. In order to demonstrate this outcome, biopsies in four quadrants at the GEJ, as well as every cm through the extent of previous BE, are taken.

In addition, because several case series report occurrence of neoplasia in the cardia or at the GEJ following successful ablative therapy, surveillance biopsies of the cardia should be routinely performed (163). Because of the sampling error inherent in random biopsies, some authorities have suggested that two negative biopsy sessions be attained before declaring the patient to have achieved complete eradication (164). However, no objective data demonstrate an optimum definition of complete eradication, with respect to number of biopsy sessions free of disease.

The decision of when to call a patient a “failure” of endoscopic ablative therapy depends on the clinical situation of the patient, the amount of progress made with initial attempts at ablation, and the likely mechanism of failure. Data from cohort studies show that even among patients who underwent four sessions of radiofrequency ablation without complete eradication of IM (CEIM), >50% eventually attained this goal with subsequent therapy, suggesting that a concrete number cutoff for failure is not advisable (165).

As to the choice of ablative modalities in BE, a wide variety of modalities have been reported to be effective in the eradication of IM. Currently, level 1 evidence for prevention of cancer incidence exists in three clinical scenarios: photodynamic therapy in the setting of BE with HGD, radiofrequency ablation in the setting of HGD, and radiofrequency ablation in the setting of LGD (63,142,166). Given the costs and side-effect profile of photodynamic therapy, as well as the large body of data supporting the safety and efficacy of radiofrequency ablation, this modality appears to be the preferred therapy for most patients. This recommendation may change as further data become available. Promising cohort data on cryotherapy demonstrate high rates of CEIM and neoplasia (167,168).

Surgical therapy.—Several studies have attempted to assess the relative value of surgical antireflux procedures in the prevention of EAC in the setting of BE. One relatively small randomized trial showed no difference in progression outcomes between medical and surgical groups (169), but this result is susceptible to type II error. Meta-analyses on the subject reveal conflicting results, in that some authors have found no difference in cancer risk between medically and surgically managed patients, whereas others show some suggestion of improved outcomes in surgically treated patients (170–172). Given the weak nature of the data, along with the overall very low incidence of cancer in the setting of nondysplastic BE, antireflux surgery should not be considered as an antineoplastic measure in the setting of BE. Therefore, the indications for this procedure in BE patients are the same as those in general GERD patients—principally GERD symptoms or esophagitis not well controlled by medical therapy. With respect to optimizing medical therapy, dosages of PPI beyond twice daily have not been demonstrated to have beneficial effect in patients with BE. We recommend once-daily PPI therapy for patients with BE unless GERD symptoms require twice daily for adequate symptom control.

In contrast, esophagectomy has a well-established role in the care of patients with BE and EAC. It is the treatment of choice for fit candidates with T1b sm2–3 disease, either alone or in combination therapy with radiation and/or chemotherapy. Similarly, in patients with T1a or T1b sm1 EAC and unfavorable prognostic factors, such as poor differentiation or lymphovascular invasion, surgical consultation should be obtained.

MANAGEMENT OF BE AFTER ENDOSCOPIC THERAPY

Recommendations

39. Following successful endoscopic therapy and CEIM, endoscopic surveillance should be continued to detect recurrent IM and/or dysplasia (strong recommendation, low level of evidence).

40. Endoscopic surveillance following CEIM, for patients with HGD or intramucosal carcinoma before ablation, is recommended every 3 months for the first year following CEIM, every 6 months in the second year, and annually thereafter (conditional recommendation, low level of evidence).

41. In patients with LGD before ablation, endoscopic surveillance is recommended every 6 months in the first year following CEIM, and annually thereafter (conditional recommendation, low level of evidence).

42. During endoscopic surveillance after CEIM, careful inspection of the tubular esophagus and GEJ (in antegrade and retrograde views) should be performed with high-resolution white light imaging and narrow band imaging to detect mucosal abnormalities that may reflect recurrent IM and/or dysplasia (strong recommendation, low level of evidence).

43. Treatment of recurrent metaplasia and/or dysplasia should follow guidelines for the treatment of metaplasia/dysplasia in BE before ablation (strong recommendation, low level of evidence).

44. Following CEIM, the goal of medical antireflux therapy should be control of reflux as determined by absence of frequent reflux symptoms (more than once a week) and/or esophagitis on endoscopic examination (conditional recommendation, very low level of evidence).

Summary of evidence

Following CEIM, the recurrence rate for IM is not inconsiderable, with some cohorts demonstrating rates of ≥20% at 2–3 years following CEIM (164,173,174). Though most recurrences are nondysplastic, up to a quarter may be dysplastic, including EAC (164,175). Variability in reported recurrence rates may be partially explained by differences in definitions of recurrence among studies: with some studies reporting recurrences located only in the tubular esophagus (176), whereas others reporting recurrent IM in both the esophagus and the GEJ/cardia (177). The significance of recurrent IM without dysplasia at the GEJ after CEIM is currently unclear. Cohorts treated with either combination therapy (EMR followed by ablation) (178) or single modality therapy (EMR alone) (173) have reported comparable recurrence rates. Recurrence rates also appear to be similar across different ablation modalities, with similar rates being described following cryotherapy (168) and photodynamic therapy for the treatment of dysplastic BE (179).

Careful endoscopic surveillance with biopsies is hence recommended following CEIM to detect recurrent IM. Careful inspection of both tubular esophagus (in the region of the prior BE segment) and the GEJ (on antegrade and retroflexed views) is important. Both the

interval of these examinations and the biopsy protocol are currently based on expert opinion and on intervals reported in published cohort studies (176,180). Endoscopic surveillance for patients with baseline HGD every 3 months in the first year following CEIM, every 6 months in the second year, and annually thereafter is currently recommended. For patients with baseline LGD, endoscopic surveillance is recommended every 6 months in the first year following CEIM, and annually thereafter. Most studies use four-quadrant biopsies every cm throughout the previous BE segment with additional targeted biopsies of any endoscopic abnormality, although this approach has not been compared with other biopsy regimens. There is currently no evidence to support discontinuing surveillance after multiple negative surveillance endoscopies, given reports of recurrent neoplasia several years after CEIM in cohort studies.

Biopsies from the tubular esophagus and GEJ should be obtained in separate bottles to allow localization and treatment of recurrent BE. The optimal number of biopsies needed for adequate surveillance is unknown. Despite concerns regarding depth of biopsies after ablation, the prevalence of subsquamous BE is variable after ablation, with rates ranging from 0.9% after RFA to 14.2% after photodynamic therapy (181). Imaging techniques such as optical coherence tomography suggest a higher prevalence of subsquamous BE, particularly at the GEJ (182), but the significance of this is unclear, despite case reports of subsquamous EACs arising after ablation (175). Some studies suggest that surveillance biopsies obtained after ablation may be too superficial to detect subsquamous BE, with most biopsies not containing lamina propria (183). This has however not been confirmed by other studies (184). It is unclear whether biopsies with large capacity forceps will be more effective at sampling deeper layers of the neosquamous epithelium as compared with regular capacity biopsy forceps. Although neosquamous epithelium may be more permeable than normal squamous epithelium (185), it does not appear to harbor genetic abnormalities (186).

Most recurrent metaplasia and dysplasia, when detected by surveillance, is amenable to endoscopic therapy, including EMR and additional ablation (176,177,180). However, a few cases requiring esophagectomy for invasive carcinoma have been reported (187). Predictors of recurrence are not well defined, with some studies suggesting that older age, a longer preablation BE segment, presence of a larger hiatal hernia (188), and higher grade of dysplasia before ablation are associated with higher rates of recurrence (174).

There is some evidence from uncontrolled observational studies to suggest that incomplete control of reflux may be associated with increased recurrence rates following successful endotherapy (189,190). However, there is currently a lack of conclusive evidence to suggest that high-dose PPI therapy or tight control of reflux (as determined by ambulatory pH monitoring) leads to lower recurrence rates following ablation. Most cohorts reporting follow-up after ablation, however, have continued patients on twice-a-day PPI therapy. Treatment of reflux following successful ablation should follow the same principles as outlined in the section on endoscopic therapy of BE. The goal of medical treatment should be the control of symptoms of reflux and the prevention or healing of esophagitis.

ENDOSCOPIC ERADICATION THERAPY: TRAINING AND EDUCATION

Recommendation

45. Endoscopists who plan to practice endoscopic ablative procedures should additionally offer EMR (strong recommendation, very low level of evidence).

Summary of evidence

There are currently little if any data to determine the exact thresholds for training and education for the performance of endoscopic ablative therapy of BE. Common sense and expert opinion suggest that a number of core competencies are warranted before embarking on endoscopic ablative therapy, the application of which is only one component in the management of these patients (191). Adequate training and expertise in the recognition of mucosal lesions that may harbor neoplasia is critical in order to target such endoscopic abnormalities with EMR. It is well known that EMR of mucosal abnormalities alters the pathologic stage in ~50% of patients with clear management implications (113,192). Furthermore, all randomized clinical trials of radiofrequency ablation required endoscopic resection of mucosal abnormalities before application of radiofrequency ablation. Follow-up after application of radiofrequency ablation also demonstrates the development of nodular lesions in a subset of patients, warranting EMR. Finally, expertise in recognition and management of potential complications of endoscopic therapy, most notably bleeding, strictures, and perforation, are warranted. As such, it makes little sense to offer or train in radiofrequency ablation for flat BE in the absence of training in EMR.

To date, there is little information on the learning curve to acquire these skills. The recent British Society of Gastroenterology guideline statement recommends, based on expert opinion, a minimum of 30 supervised endoscopic resections and 30 ablations for competence (10). For radiofrequency ablation, a single endoscopist case series demonstrated no difference in eradication of IM, complications, and procedure time in the initial 25% vs. later 75% of cases and the initial 50% vs. later 50% of cases (193). On the other hand, work from a multicenter tertiary center consortium found variable CEIM rates ranging from 62 to 88% among seven different endoscopists with a positive correlation between both patient volume and radiofrequency ablation volume and the rate of complete remission of IM (194). However, there was no threshold volume for success. For EMR, a multicenter Dutch study that examined a structured training program for EMR found no difference in complication rates, completeness of resection, and time per resection for the first 10 vs. second 10 resections (195). Of note, only 29% of resections in this study involved the multiband ligator approach, whereas the remainder were performed with the cap technique.

CONCLUSION

Care of the patient with BE has evolved rapidly in the past decade. The above analysis attempts to encapsulate these advances and to present, in a concise manner, “best practices” for the care of these patients. These recommendations should not be construed as practice standards or quality measures—as always, clinical circumstances should dictate the best care for each patient.

These guidelines differ markedly from their predecessor in several areas. These include the expanded use of endoscopic ablative therapy, especially their extension to patients with LGD, based on high-quality level 1 evidence demonstrating diminished risk of progression and/or adenocarcinoma after treatment. In addition, there is further refinement of screening recommendations, based on data demonstrating both a lower risk of EAC in patients with nondysplastic BE and a better understanding of the impact of gender and anthropomorphics on risk. The most important of these changes is the recommendation that females with GERD symptoms no longer undergo routine screening. Finally, surveillance recommendations have been attenuated to recognize the relatively rare occurrence of progression in nondysplastic BE, as well as the unclear nature of benefit inherent in endoscopic surveillance.

It is likely that the development of several technologies will cause further evolution in care of patients with BE. Several areas in particular appear poised for paradigm-shifting advances. These include the evolution of biomarkers to predict risk in BE, the use of advanced imaging and biomolecular technologies to allow recognition of areas of neoplasia within BE, and the advent of less invasive and less expensive modalities for screening patients for BE. All of these areas offer the promise of improved care at reduced costs. Although the time horizon of these developments is unpredictable, it is likely that advances in one or more of these areas will cause marked changes in the next iteration of these guidelines.

Supplementary Material

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Financial support:

Shaheen receives research funding from Covidien, CSA Medical, NeoGenomics, GI Dynamics, Takeda Pharmaceuticals, and CDx Diagnostics. Gerson receives research funding from CDx Diagnostics and is a consultant for Takeda Pharmaceuticals, Endogastric Solutions, Mederi Therapeutics, and Medigus. Iyer receives research funding from Intromedic Inc. Falk receives research funding from CDx Diagnostics.

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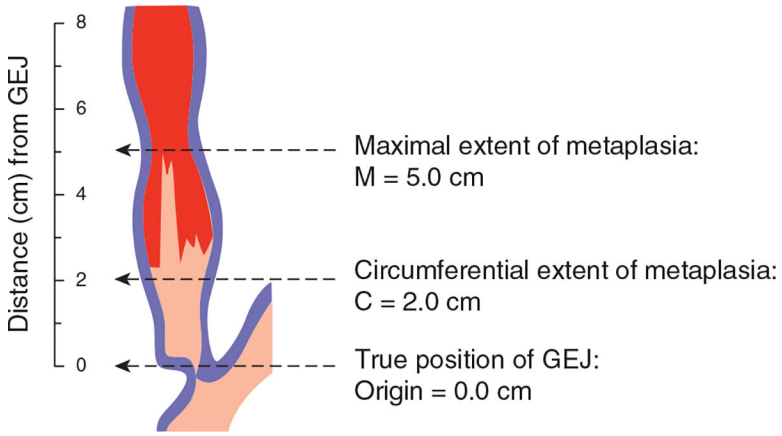

Figure 1.

Illustration of Prague Classifi cation for Barrett's esophagus (BE) where C indicates circumferential extent of metaplasia and M indicates maximal extent of metaplasia. Schema shows a C2M5 segment with identifi cation of the gastroesophageal junction (GEJ) below the squamocolumnar junction. Reprinted with permission (24).

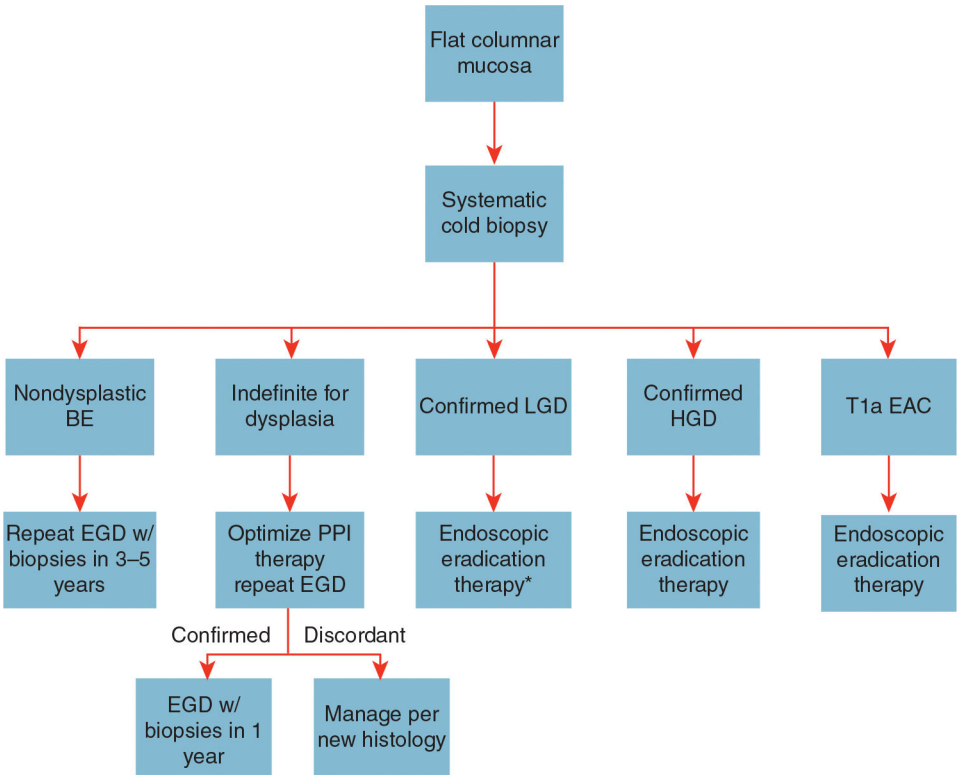

Figure 2.

Management of nonnodular Barrett's esophagus (BE). *Although endoscopic eradication therapy is associated with a decreased rate of progression, surveillance upper endoscopy at 1-year intervals is an acceptable alternative. The above schema assumes that the T1a esophageal adenocarcinoma (EAC) displays favorable characteristics for endoscopic therapy, including well-differentiated histology and lack of lymphovascular invasion. EGD, esophagogastroduodenoscopy; HGD, high-grade dysplasia; LGD, low-grade dysplasia; PPI, proton pump inhibitor.

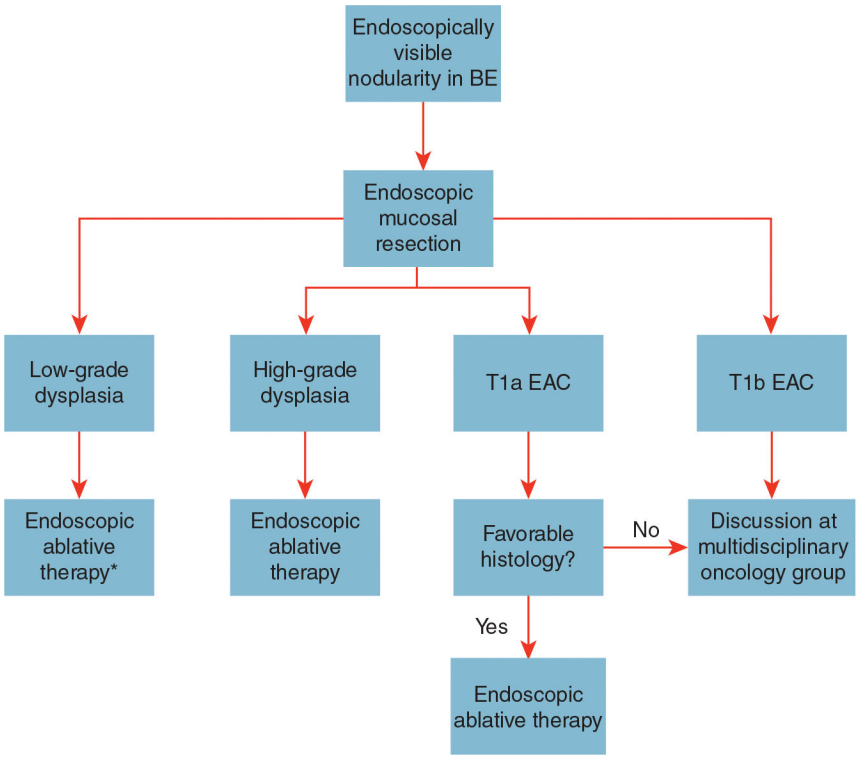

Figure 3.

Management of nodular Barrett's esophagus (BE). *Little data exist on the clinical course of patients with low-grade dysplasia (LGD) managed by endoscopic surveillance following endoscopic mucosal resection (EMR), although this is an alternative treatment strategy. Endoscopic submucosal dissection is an alternative to EMR. Favorable histology consists of no lymphatic or vascular invasion and moderate- to well-differentiated disease. EAC, esophageal adenocarcinoma.

Table 1.

Recommendation statements

Diagnosis of BE

1. BE should be diagnosed when there is extension of salmon-colored mucosa into the tubular esophagus extending ≥1 cm proximal to the gastroesophageal junction with biopsy confirmation of IM (strong recommendation, low level of evidence).

2. Endoscopic biopsy should not be performed in the presence of a normal Z line or a Z line with <1 cm of variability (strong recommendation, low level of evidence).

3. In the presence of BE, the endoscopist should describe the extent of metaplastic change including circumferential and maximal segment length using the Prague classification (conditional recommendation, low level of evidence).

4. The location of the diaphragmatic hiatus, gastroesophageal junction, and squamocolumnar junction should be reported in the endoscopy report (conditional recommendation, low level of evidence).

5. In patients with suspected BE, at least 8 random biopsies should be obtained to maximize the yield of IM on histology. In patients with short (1–2 cm) segments of suspected BE in whom 8 biopsies are unattainable, at least 4 biopsies per cm of circumferential BE, and one biopsy per cm in tongues of BE, should be taken (conditional recommendation, low level of evidence).

6. In patients with suspected BE and lack of IM on histology, a repeat endoscopy should be considered in 1–2 years of time to rule out BE (conditional recommendation, very low level of evidence).

Screening for BE

7. Screening for BE may be considered in men with chronic (>5 years) and/or frequent (weekly or more) symptoms of gastroesophageal reflux (heartburn or acid regurgitation) and two or more risk factors for BE or EAC. These risk factors include: age >50 years, Caucasian race, presence of central obesity (waist circumference >102 cm or waist-hip ratio (WHR) >0.9), current or past history of smoking, and a confirmed family history of BE or EAC (in a first-degree relative) (strong recommendation, moderate level of evidence).

8. Given the substantially lower risk of EAC in females with chronic GER symptoms (when compared with males), screening for BE in females is not recommended. However, screening could be considered in individual cases as determined by the presence of multiple risk factors for BE or EAC (age >50 years, Caucasian race, chronic and/or frequent GERD, central obesity: waist circumference >88 cm, WHR >0.8, current or past history of smoking, and a confirmed family history of BE or EAC (in a first-degree relative)) (strong recommendation, low level of evidence).

9. Screening of the general population is not recommended (conditional recommendation, low level of evidence).

10. Before screening is performed, the overall life expectancy of the patient should be considered, and subsequent implications, such as the need for periodic endoscopic surveillance and therapy, if BE with dysplasia is diagnosed, should be discussed with the patient (strong recommendation, very low level of evidence).

11. Unsedated transnasal endoscopy (uTNE) can be considered as an alternative to conventional upper endoscopy for BE screening (strong recommendation, low level of evidence).

12. If initial endoscopic evaluation is negative for BE, repeating endoscopic evaluation for the presence of BE is not recommended. If endoscopy reveals esophagitis (Los Angeles Classification B, C, D), repeat endoscopic assessment after PPI therapy for 8–12 weeks is recommended to ensure healing of esophagitis and exclude the presence of underlying BE (conditional recommendation, low level of evidence).

Surveillance of BE

13. Patients should only undergo surveillance after adequate counseling regarding risks and benefits of surveillance (strong recommendation, very low level of evidence).

14. Surveillance should be performed with high-definition/high-resolution white light endoscopy (strong recommendation, low level of evidence).

15. Routine use of advanced imaging techniques other than electronic chromoendoscopy is not recommended for endoscopic surveillance at this time (conditional recommendation, very low level of evidence).

16. Endoscopic surveillance should employ four-quadrant biopsies at 2 cm intervals in patients without dysplasia and 1 cm intervals in patients with prior dysplasia (strong recommendation, low level of evidence).

17. Mucosal abnormalities should be sampled separately, preferably with endoscopic mucosal resection. Inability to perform endoscopic mucosal resection in the setting of BE with nodularity should lead to consideration to referral to a tertiary care center (strong recommendation, low level of evidence).

18. Biopsies should not be obtained in mucosal areas with endoscopic evidence of erosive esophagitis until after intensification of antireflux therapy to induce mucosal healing (strong recommendation, very low level of evidence).

19. For BE patients with dysplasia of any grade, review by two pathologists, at least one of whom has specialized expertise in GI pathology, is warranted because of interobserver variability in the interpretation of dysplasia (strong recommendation, moderate level of evidence).

20. Use of additional biomarkers for risk stratification of patients with BE is currently not recommended (strong recommendation, low level of evidence).

21. For BE patients without dysplasia, endoscopic surveillance should take place at intervals of 3 to 5 years (strong recommendation, moderate level of evidence).

22. Patients diagnosed with BE on initial examination do not require a repeat endoscopy in 1 year for dysplasia surveillance (conditional recommendation, very low level of evidence).

23. For patients with indefinite for dysplasia, a repeat endoscopy after optimization of acid suppressive medications for 3–6 months should be performed. If the indefinite for dysplasia reading is confirmed on this examination, a surveillance interval of 12 months is recommended (strong recommendation, low level of evidence).

24. For patients with confirmed low-grade dysplasia and without life-limiting comorbidity, endoscopic therapy is considered as the preferred treatment modality, although endoscopic surveillance every 12 months is an acceptable alternative (strong recommendation, moderate level of evidence).

25. Patients with BE and confirmed high-grade dysplasia should be managed with endoscopic therapy unless they have life-limiting comorbidity (strong recommendation, high level of evidence).

Therapy

Chemoprevention

26. Patients with BE should receive once-daily PPI therapy. Routine use of twice-daily dosing is not recommended, unless necessitated because of poor control of reflux symptoms or esophagitis (strong recommendation, moderate level of evidence).

27. Aspirin or NSAIDs should not be routinely prescribed to patients with BE as an antineoplastic strategy. Similarly, other putative chemopreventive agents currently lack sufficient evidence and should not be administered routinely (conditional recommendation, high level of evidence).

Endoscopic therapy

28. Patients with nodularity in the BE segment should undergo endoscopic mucosal resection of the nodular lesion(s) as the initial diagnostic and therapeutic maneuver (see point 17 above). Histologic assessment of the EMR specimen should guide further therapy. In subjects with EMR specimens demonstrating HGD, or IMC, endoscopic ablative therapy of the remaining BE should be performed (strong recommendation, high level of evidence).

29. In patients with EMR specimens demonstrating neoplasia at a deep margin, residual neoplasia should be assumed, and surgical, systemic, or additional endoscopic therapies should be considered (strong recommendation, low level of evidence).

30. Endoscopic ablative therapies should not be routinely applied to patients with nondysplastic BE because of their low risk of progression to EAC (strong recommendation, very low level of evidence). Endoscopic eradication therapy is the procedure of choice for patients with confirmed LGD, and confirmed HGD, as noted above (see points 24 and 25).

31. In patients with T1a EAC, endoscopic therapy is the preferred therapeutic approach, being both effective and well tolerated (strong recommendation, moderate level of evidence).

32. In patients with T1b EAC, consultation with multidisciplinary surgical oncology team should occur before embarking on endoscopic therapy. In such patients, endoscopic therapy may be an alternative strategy to esophagectomy, especially in those with superficial (sm1) disease with a well-differentiated neoplasm lacking lymphovascular invasion, as well as those who are poor surgical candidates (strong recommendation, low level of evidence).

33. Routine staging of patients with nodular BE with EUS or other imaging modalities before EMR has no demonstrated benefit. Given the possibility of over- and understaging, findings of these modalities should not preclude the performance of EMR to stage-early neoplasia (Strong recommendation, moderate level of evidence).

34. In patients with known T1b disease, EUS may have a role in assessing and sampling regional lymph nodes, given the increased prevalence of lymph node involvement in these patients compared with less advanced disease (strong recommendation, moderate level of evidence).

35. In patients with dysplastic BE who are to undergo endoscopic ablative therapy for nonnodular disease, radiofrequency ablation is currently the preferred endoscopic ablative therapy (strong recommendation, moderate level of evidence).

Surgical therapy

36. Antireflux surgery should not be pursued in patients with BE as an antineoplastic measure. However, this surgery should be considered in those with incomplete control of reflux symptoms on optimized medical therapy (strong recommendation, high level of evidence).

37. In cases of EAC with invasion into the submucosa, especially those with invasion to the mid or deep submucosa (T1b, sm2–3), esophagectomy, with consideration of neoadjuvant therapy, is recommended in the surgical candidate (strong recommendation, low level of evidence).

38. In patients with T1a or T1b sm1 adenocarcinoma, poor differentiation, lymphovascular invasion, or incomplete endoscopic mucosal resection should prompt consideration of surgical and/or multimodality therapies (strong recommendation, low level of evidence).

Management of BE after endoscopic therapy

39. Following successful endoscopic therapy and complete elimination of intestinal metaplasia (CEIM), endoscopic surveillance should be continued to detect recurrent IM and/or dysplasia (strong recommendation, low level of evidence).

40. Endoscopic surveillance following CEIM, for patients with HGD or IMC before ablation, is recommended every 3 months for the first year following CEIM, every 6 months in the second year, and annually thereafter (conditional recommendation, low level of evidence).

41. In patients with LGD before ablation, endoscopic surveillance is recommended every 6 months in the first year following CEIM, and annually thereafter (conditional recommendation, low level of evidence).

42. During endoscopic surveillance after CEIM, careful inspection of the tubular esophagus and gastroesophageal junction (in antegrade and retrograde views) should be performed with high-resolution white light imaging and narrow band imaging to detect mucosal abnormalities that may reflect recurrent IM and/or dysplasia (strong recommendation, low level of evidence).

43. Treatment of recurrent metaplasia and/or dysplasia should follow guidelines for the treatment of metaplasia/dysplasia in BE before ablation (strong recommendation, low level of evidence).

44. Following CEIM, the goal of medical antireflux therapy should be control of reflux as determined by absence of frequent reflux symptoms (more than once a week) and/or esophagitis on endoscopic examination (conditional recommendation, very low level of evidence).

Endoscopic eradication therapy: training and education

45. Endoscopists who plan to practice endoscopic ablative procedures should additionally offer endoscopic mucosal resection (strong recommendation, very low level of evidence).

BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; EMR, endoscopic mucosal resection; EUS, endoscopic ultrasound; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; GI, gastrointestinal; HGD, high-grade dysplasia; IM, intestinal metaplasia; IMC, intramucosal carcinoma; LGD, low-grade dysplasia; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

Table 2.

Risk factors for BE (estimates drawn from meta-analyses where available)

Risk factor	OR (95% CI)	Reference
Age (per 10-year increment)	1.53 (1.05–2.25)	Rubenstein *et al.* (5)[a]
	1.96 (1.77–2.17)	Cook *et al.* (33)
Race/ethnicity		
AA vs. Caucasian ethnicity	0.34 (0.12–0.97)	Abrams *et al.* (49)
Hispanic vs. Caucasian ethnicity	0.38 (0.18–0.84)	Abrams *et al.* (49)[b]
Hispanic vs. Caucasian ethnicity	1.1 (0.4–2.7)	Keyashian *et al.* (50)[c]
GERD symptoms		
Frequency (weekly vs. less frequent)	2.33 (1.34–4.05)	Rubenstein *et al.* (5)[a]
Duration (>5 years vs. <1 year)	3.0 (1.2–8.0)	Lieberman *et al.* (30)
Age of onset (weekly symptoms, <30 years vs. later)	31.4 (13.0–75.8)	Thrift *et al.* (32)
Obesity		
Overall	1.98 (1.52–2.57)	Singh *et al.* (3)[d]
Increased WC	1.58 (1.25–1.99)	Singh *et al.* (3)
Increased WHR	2.04 (1.49–2.81)	Singh *et al.* (3)
Smoking		
Current/past use vs. never	1.44 (1.20–1.74)	Andrici *et al.* (35)
Pack years of cigarette use	1.99 (1.21–3.29)	Cook *et al.* (196)
Family history		
(BE, EAC, or GEJAC in first- or second-degree relative)	12.23 (3.34–44.76)	Chak *et al.* (42)
Hiatal hernia (overall)	3.94 (3.02–5.13)	Andrici *et al.* (197)
Short-segment BE	2.87 (1.75–4.7)	Andrici *et al.* (197)
Long-segment BE	12.67 (8.33–19.25)	Andrici *et al.* (197)

AA, African American; BE, Barrett's esophagus; CI, confidence interval; EAC, esophageal adenocarcinoma; GEJAC, gastroesophageal junction adenocarcinoma; GERD, gastroesophageal reflux disease; OR, odds ratio; WC, waist circumference; WHR, waist–hip ratio.

[a] In men only.

[b] In Hispanics from Dominican Republic.

[c] In Hispanics from Mexico.

[d] GERD and BMI independent association.

Table 3

Cancer risk based on degree of dysplasia

Dysplasia type	Studies/patients	Incidence	95% CI	References
ND to EAC	57 Studies, 11,434 patients	3.3/1,000 person-years	2.8–3.8	(60)
	50 Studies, 14,109 patients	6.3/1,000 person-years	4.7–8.4	(65)
ND to EAC or HGD	602 patients	4.8/1,000 person-years	0.3–7.8	(198)
LGD to EAC	24 Studies, 2,694 patients	5.4/1,000 person-years	3–8	(61)
LGD to EAC or HGD	17 Studies, 1,064 patients	173/1,000 person-years	100–250	(61)
HGD to EAC	4 Studies, 236 patients	7/100 patient-years	5–8	(62)

CI, confidence interval; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; LGD, low-grade dysplasia; ND, nondysplastic.