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

Nicholas J. Shaheen, MD, MPH, FACG[1], Gary W. Falk, MD, MS, FACG[2], Prasad G. Iyer, MD, MSc, FACG[3] and Lauren Gerson, MD, MSc, FACG[4]

[1]Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [2]Division of Gastroenterology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA; [3]Division of Gastroenterology and Hepatology, Mayo Clinic Minnesota, Rochester, Minnesota, USA; [4]Division of Gastroenterology, California Pacific Medical Center and Department of Medicine, University of California, San Francisco, San Francisco, California, USA.

Am J Gastroenterol advance online publication, 3 November 2015; doi:10.1038/ajg.2015.322

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.

Introduction

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,” “radio- frequency,” “catheter ablation,” “early detection of cancer,” “mass screening,” and/or “esophagoscopy,” The full literature search strategy is demonstrated in Supplementary Appendix 1 online.

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 gastroesopha- geal 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 (condi- tional 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 peri- odic 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 recommenda- tion, 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 ad- ditional 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.

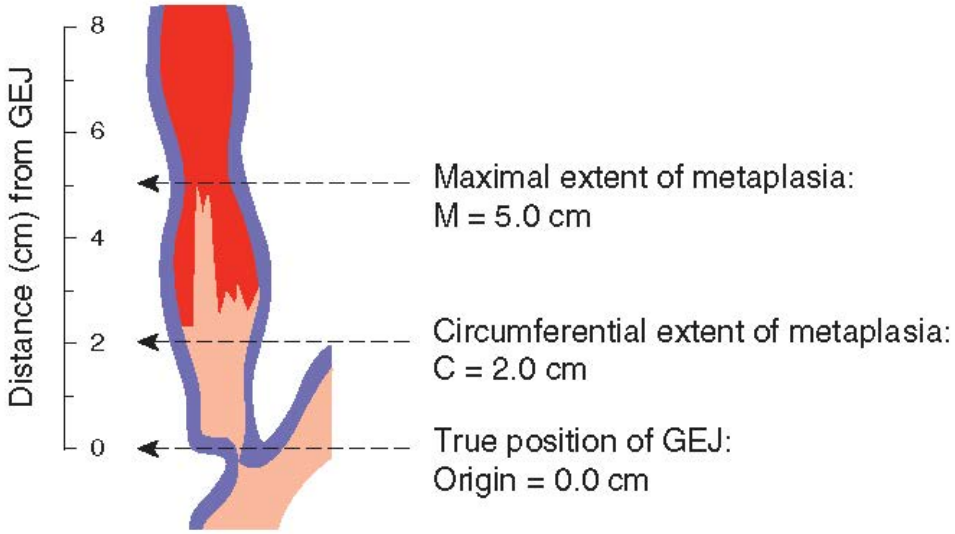

Figure 1. Illustration of Prague Classification for Barrett's esophagus (BE) where C indicates circumferential extent of metaplasia and M indicates maximal extent of metaplasia. Schema shows a C2M5 segment with identification of the gastroesophageal junction (GEJ) below the squamo-columnar junction. Reprinted with permission (24).

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) 1.96 (1.77–2.17)	Rubenstein *et al.* (5)a 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.

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 50 Studies, 14,109 patients	3.3/1,000 person-years 6.3/1,000 person-years	2.8–3.8 4.7–8.4	(60) (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.

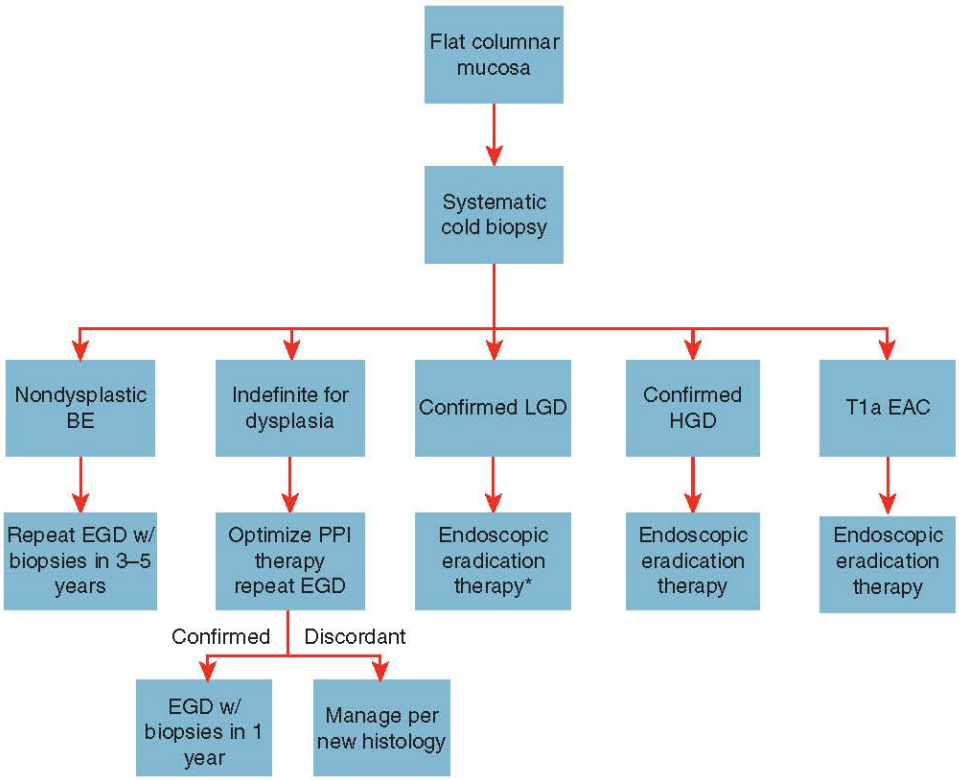

Figure 2. Management of nonnodular Barrett's esophagus (BE). *Although endoscopic eradication therapy is associated with a decreased rate of progression, surveillance upper endoscopy at 1-year intervals is an acceptable alternative. The above schema assumes that the T1a esophageal adenocarcinoma (EAC) 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.

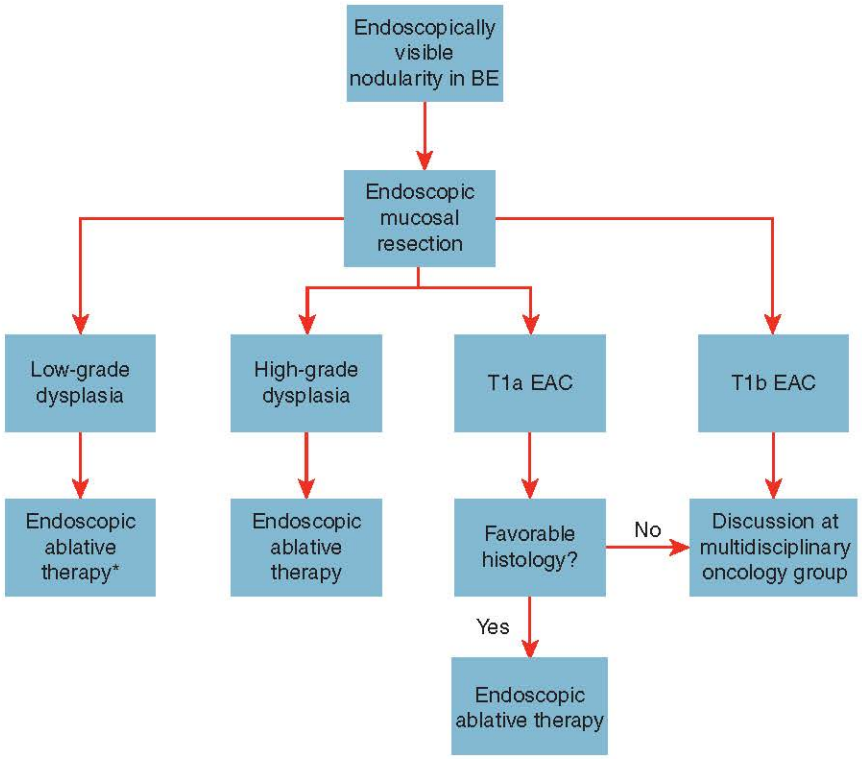

Figure 3. Management of nodular Barrett's esophagus (BE). *Little data exist on the clinical course of patients with low-grade dysplasia (LGD) managed by endoscopic surveillance following endoscopic mucosal resection (EMR), although this is an alternative treatment strategy. Endoscopic submucosal dissection is an alternative to EMR. Favorable histology consists of no lymphatic or vascular invasion and moderate- to well-differentiated disease. EAC, esophageal adenocarcinoma.