

CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on Endoscopic Treatment of Barrett's Esophagus With Dysplasia and/or Early Cancer: Expert Review



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DESCRIPTION: The purpose of this best practice advice article is to describe the role of Barrett's endoscopic therapy (BET) in patients with Barrett's esophagus (BE) with dysplasia and/or early cancer and appropriate follow-up of these patients.

METHODS: The best practice advice provided in this document is based on evidence and relevant publications reviewed by the committee. **BEST PRACTICE ADVICE 1:** In BE patients with confirmed low-grade dysplasia, a repeat examination with high-definition white-light endoscopy should be performed within 3–6 months to rule out the presence of a visible lesion, which should prompt endoscopic resection. **BEST PRACTICE ADVICE 2:** Both BET and continued surveillance are reasonable options for the management of BE patients with confirmed and persistent low-grade dysplasia. **BEST PRACTICE ADVICE 3:** BET is the preferred treatment for BE patients with high-grade dysplasia (HGD). **BEST PRACTICE ADVICE 4:** BET should be preferred over esophagectomy for BE patients with intramucosal esophageal adenocarcinoma (T1a). **BEST PRACTICE ADVICE 5:** BET is a reasonable alternative to esophagectomy in patients with submucosal esophageal adenocarcinoma (T1b) with low-risk features (<500- μ m invasion in the submucosa [sm1], good to moderate differentiation, and no lymphatic invasion) especially in those who are poor surgical candidates. **BEST PRACTICE ADVICE 6:** In all patients undergoing BET, mucosal ablation should be applied to 1) all visible esophageal columnar mucosa; 2) 5–10 mm proximal to the squamocolumnar junction and 3) 5–10 mm distal to the gastroesophageal junction, as demarcated by the top of the gastric folds (ie, gastric cardia) using focal ablation in a circumferential fashion. **BEST PRACTICE ADVICE 7:** Mucosal ablation therapy should only be performed in the presence of flat BE without signs of inflammation and in the absence of visible abnormalities. **BEST PRACTICE ADVICE 8:** BET should be performed by experts in high-volume centers that perform a minimum of 10 new cases annually. **BEST PRACTICE ADVICE 9:** BET should be continued until there is an absence of columnar epithelium in the tubular esophagus on high-definition white-light endoscopy and preferably optical chromoendoscopy. In case of complete endoscopic eradication, the neosquamous mucosa and the gastric cardia are sampled by 4-quadrant biopsies. **BEST PRACTICE ADVICE 10:** If random biopsies obtained from the neosquamous epithelium demonstrate intestinal metaplasia/dysplasia or subsquamous intestinal metaplasia, a repeat endoscopy should be performed and visible islands or tongues should undergo targeted focal ablation. **BEST PRACTICE ADVICE 11:** Intestinal metaplasia of the gastric cardia (without residual columnar epithelium in the tubular esophagus) should not warrant additional ablation therapy. **BEST PRACTICE ADVICE 12:** When consenting patients for BET, the most

common complication of therapy to be quoted is post-procedural stricture formation, occurring in about 6% of cases. Bleeding and perforation occur at rates <1%. **BEST PRACTICE ADVICE 13:** After complete eradication (endoscopic and histologic) of intestinal metaplasia has been achieved with BET, surveillance endoscopy with biopsies should be performed at the following intervals: for baseline diagnosis of HGD/esophageal adenocarcinoma: at 3, 6, and 12 months and annually thereafter; and baseline diagnosis of low-grade dysplasia: at 1 and 3 years. **BEST PRACTICE ADVICE 14:** Endoscopic surveillance post therapy should be performed with high-definition white-light endoscopy, including careful inspection of the neosquamous mucosal and retroflexed inspection of the gastric cardia. **BEST PRACTICE ADVICE 15:** The approach to recurrent disease is similar to that of the initial therapy; visible recurrent nodular lesions require endoscopic resection, whereas flat areas of columnar mucosa in the tubular esophagus can be treated with mucosal ablation. **BEST PRACTICE ADVICE 16:** Patients should be counseled on cancer risk in the absence of BET, as well as after BET, to allow for informed decision-making between the patient and the physician.

Keywords: Barrett's Esophagus; Dysplasia; Endoscopic therapy; Esophageal Adenocarcinoma.

The purpose of this best practice advice article from the Clinical Practice Update Committee of the American Gastroenterological Association (AGA) is to describe the role of Barrett's endoscopic therapy (BET) in patients with Barrett's esophagus (BE) with dysplasia and/or early cancer, as well as the appropriate follow-up in patients who have undergone such therapy. The target audience is all gastroenterologists and endoscopists, and the target patient population is adults with confirmed dysplastic BE and/or early esophageal adenocarcinoma (EAC).

Abbreviations used in this paper: AGA, American Gastroenterological Association; BE, Barrett's esophagus; BET, Barrett's endoscopic therapy; CE-D, complete eradication of dysplasia; CE-IM, complete eradication of intestinal metaplasia; CI, confidence interval; EAC, esophageal adenocarcinoma; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; GEJ, gastroesophageal junction; HD-WLE, high-definition white-light endoscopy; HGD, high-grade dysplasia; LGD, low-grade dysplasia; RFA, radiofrequency ablation; RR, relative risk.

Most current article

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Methods

This article provides practical advice based on the best available published evidence, taking into account recently published systematic reviews and clinical guidelines. This best practice document is not based on a formal systematic review. The best practice advice as presented in this document applies to adult patients with BE and low- (LGD) or high-grade dysplasia (HGD) (confirmed by an expert pathologist) or T1 esophageal cancer.

This expert review was commissioned and approved by the AGA Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership.

Who Should Undergo Barrett's Endoscopic Therapy?

The progression to EAC in BE usually occurs in stepwise fashion from LGD to HGD and EAC, although progression can happen without these intermediate steps. The goal of treatment in BE is to eradicate prevalent dysplasia and/or cancer, to prevent progression to invasive cancer, and ultimately to reduce mortality from EAC. BET is the elimination of the Barrett's epithelium by removal of the tissue (endoscopic mucosal resection [EMR] or endoscopic submucosal dissection [ESD]) and/or by ablation of the tissue (eg, radiofrequency ablation [RFA], cryotherapy, or hybrid argon plasma coagulation).¹ Because of the paucity of evidence supporting BET in nondysplastic BE, current guidelines do not recommend BET in such patients. For this reason, this guidance will concentrate on those with dysplastic BE.

Low-Grade Dysplasia

Histologic diagnosis of LGD in BE has an extremely high inter-observer variability, even among expert pathologists.² To circumvent this limitation, it is recommended that LGD is confirmed by an expert/experienced gastrointestinal pathologist (with special interest in Barrett's pathology and experience in this field) and, once the diagnosis is confirmed, by a repeat endoscopy within 3–6 months while the patient is on optimal acid suppression to evaluate for persistence of LGD and to exclude the presence of synchronous more advanced neoplasia. To better understand the role of BET in LGD patients, it is important to evaluate the progression rates in those with LGD, confirmed LGD, and persistent LGD (found in 2 consecutive endoscopies) undergoing BET vs surveillance endoscopy.

The overall annual progression rate of all patients with LGD to EAC has been reported in a recent meta-analysis as 0.5%.³ On the other hand, several studies have shown confirmation of BE-LGD by more than 1 expert pathologist to be associated with a significantly higher risk of progression to HGD/EAC. Curvers et al⁴ reported a high rate of progression in patients whose LGD was confirmed by the review of an expert panel compared with patients whose LGD was down-graded to nondysplastic BE (annual progression rate 13.4% vs 0.49%). These findings were reproduced by Duits et al,⁵ in a cohort of 293 LGD patients in which expert confirmation of LGD was associated with an annual progression rate of 9.1%

vs 0.6% for down-staged cases. In a study by Kestens et al,⁶ persistence of LGD (LGD present on 2 consecutive endoscopy examinations within 1 year) was associated with higher rates of progression to HGD or EAC (annual progression rate 7.65% vs 2.32%). Regarding the benefit of endoscopic treatment of confirmed LGD, the SURF (Surveillance vs Radiofrequency Ablation) trial directly compared BET using RFA with surveillance for 136 BE patients with confirmed LGD.⁷ Of note, the biopsy diagnosis of LGD was confirmed at minimum by an expert pathologist before study enrollment. When compared with surveillance, ablation was found to reduce the absolute risk of progression to HGD/EAC by 25% ($P < .001$) and to EAC alone by 7.4% ($P = .03$). The annual progression rate of confirmed LGD in this study was in line with the aforementioned studies at 12.5%.

In a recent meta-analysis of 19 studies, with a total of 2746 patients, the impact of BET was evaluated in LGD patients.⁸ This analysis demonstrated a significant reduction of any progression in the RFA arm compared with the surveillance arm (RR 0.14%; 95% confidence interval [CI], 0.04–0.45; $P = .001$; $Q = 2$; $I^2 = 0\%$). However, surveillance alone might also be an acceptable alternative for LGD patients; in these patients, a careful endoscopic follow-up is needed not only to detect progression of dysplasia, but also to assess for missed prevalent higher-grade lesions. For example, in the SURF trial, 14% of patients were excluded because they were up-staged to HGD or cancer upon entry to the trial, with high-definition white-light endoscopy (HD-WLE) required before enrollment. Additionally, annual surveillance (target biopsies of any visible abnormalities and 4-quadrant biopsies every 1–2 cm) usually detects neoplastic progression at a stage amenable to BET and rarely requires esophagectomy. In the SURF trial, no patients randomized to surveillance developed unresectable cancer or cancer-related deaths.

For the optimal management of BE-LGD, establishing an accurate diagnosis is pivotal in risk-stratifying these patients. Data suggest this is best achieved by confirmation of LGD by 1 or more pathologists with expertise in gastrointestinal histology.

BEST PRACTICE ADVICE

1. The reading of LGD in BE should be confirmed by an experienced gastrointestinal pathologist.
2. In BE patients with confirmed LGD, a repeat examination within 3–6 months with HD-WLE and preferably optical chromoendoscopy should be performed to rule out the presence of a visible lesion, which should prompt endoscopic resection (see section on HGD).
3. Both BET and continued surveillance are reasonable options for the management of BE patients with confirmed and persistent LGD.

High-Grade Dysplasia

The rates of progression from flat HGD to EAC are approximately 5%–8% per year. Truly flat HGD is uncommon and the majority of HGD patients will have a visible

lesion seen on HD-WLE.⁹ The presence of ulcerated lesions within HGD should raise suspicion for invasive cancer, and curative BET is probably not feasible. For diagnostic purposes, all visible lesions should be endoscopically resected to rule out invasive adenocarcinoma. There are 2 randomized controlled trials that have evaluated the progression of HGD in BE with or without endoscopic treatment. Overholt et al¹⁰ demonstrated a 2-fold risk of progression to EAC without the use of endoscopic photodynamic therapy (28% in the control group vs 13% in the photodynamic therapy group; $P = .0014$), while the AIM-Dysplasia (Ablation of Intestinal Metaplasia Containing Dysplasia) trial showed an 8-fold risk of progression without RFA (19% in control group vs 2.4% in ablation group; $P = .04$). The effectiveness of BET in patients with HGD was shown in a recent meta-analysis.¹¹ Pooled complete eradication of dysplasia (CE-D) and complete eradication of intestinal metaplasia (CE-IM) rates for focal EMR with RFA were 93.4% (95% CI, 90.8%–96.1%; I^2 , 46%) and 73.1% (95% CI, 63%–83.1%; I^2 , 93.3%), respectively, and for complete EMR were 94.9% (95% CI, 92.2%–97.5%; I^2 , 72%) and 79.6% (95% CI, 75.2%–84.1%; I^2 , 52.48%), respectively. Esophagectomy, the other treatment alternative considered in the past, is a major surgery that confers a high morbidity rate (>30% in most series), with complications such as anastomotic leaks and strictures, pneumonia, prolonged mechanical ventilation, and chronic reflux. There is also up to a 6% chance of mortality with any esophageal resection,^{12,13} although a large series from the Netherlands published this year reported only a 1.7% mortality rate with esophagectomy.¹⁴

BEST PRACTICE ADVICE

1. The reading of HGD in BE should be confirmed by an experienced gastrointestinal pathologist.
2. The diagnosis of flat HGD should prompt a repeat HD-WLE (6–8 weeks) to evaluate for the presence of a visible lesion; these visible lesions should be removed by EMR.
3. BET is the preferred treatment, over esophagectomy, for BE patients with HGD.

Intramucosal Esophageal Adenocarcinoma (T1a Esophageal Adenocarcinoma)

The primary treatment for resectable EAC has been esophagectomy with lymph node dissection to remove the primary cancer as well as metastases to lymph nodes. However, intramucosal EAC, also designated as T1a,¹⁵ is confined to the mucosal layer with a minimal chance of lymph node or distant metastasis (<2%). As mentioned earlier, esophagectomy is a major surgery associated with high morbidity and also a small but real chance of mortality.¹² To our knowledge, there are no randomized controlled trials to date that compare the efficacy of BET with esophagectomy for T1a EAC. However, a meta-analysis of 7 retrospective and prospective studies compared outcomes between esophagectomy and BET for HGD and T1a cancers.¹⁶ This analysis

of 870 patients (510 BET, 360 esophagectomy) found no significant difference in CE-D rates between the 2 modalities (RR, 0.96; 95% CI, 0.91–1.01), but the recurrence rate of dysplasia was higher with BET (RR, 9.50; 95% CI, 3.26–27.75). There were no differences in survival rates at 1, 3, and 5 years between the 2 groups (RR, 0.99; 95% CI, 0.94–1.03), and cancer-related deaths were 0.2% and 0.3%, respectively ($P = .84$). Adverse events were significantly lower in the BET group compared with the surgery group (RR, 0.38; 95% CI, 0.20–0.73; $P = .004$).

BEST PRACTICE ADVICE

BET should be preferred over esophagectomy for BE patients with intramucosal EAC (T1a).

Submucosal Esophageal Adenocarcinoma (T1b Esophageal Adenocarcinoma)

Esophagectomy is the mainstay therapy for submucosal EAC, as the rates of lymph node involvement can be up to 45%.¹⁷ The role of BET in subgroups of patients with submucosal EAC has been studied in a few small trials. In the initial study by Manner et al,¹⁸ 19 patients with minimal submucosal invasion (sm1, invasion limited to the first third of the submucosal layer) were treated with EMR technique and had a CE-D rate of 95%. During a 5-year follow-up, metachronous cancers were found in 5 of 19 patients (26%) who underwent repeat BET with resolution in 4 of 19 patients (21%). Importantly, there were no tumor-related deaths. The same group published a larger study of 66 patients with low-risk sm1 lesions (defined as polypoid or flat with sm1, good to moderate differentiation, and no lymphatic invasion) with a CE-D rate of 87% (53 of 61), metachronous neoplasia rate of 19% (10 of 53), and lymph node metastasis in 1.9% (1 of 53) during a mean follow-up of 47 months. These data suggest that endoscopic management of T1b cancers with favorable characteristics is feasible, and may be an attractive therapeutic option, especially in those at higher risk of complications from esophagectomy. ESD can also be considered in these patients when invasive EAC is suspected, the lesions are large in size and sessile, en bloc resection is required, and local expertise in this technique is available. However, EAC patients being considered for BET should be discussed in a multidisciplinary tumor board setting (involving a gastroenterologist, oncologist, pathologist, and surgeon), taking into account patient preferences and comorbidities.

BEST PRACTICE ADVICE

BET is a reasonable alternative to esophagectomy in patients with submucosal EAC (T1b) with low-risk features (sm1 [$<500\text{-}\mu\text{m}$ invasion in the submucosa] cancer, good to moderate differentiation, and no lymphatic invasion), especially in those who are poor surgical candidates.

Which Therapy Should Be Applied?

In recent years, there has been a proliferation of devices designed for BET for BE. Our understanding of which devices perform best in a given patient population is

hampered by the paucity of head-to-head data comparing commercially available devices. However, given the available data, best practices for BET are becoming clearer.

First, focal complete endoscopic resection of any visible lesion, no matter how subtle, should be performed. Ideally, if the endoscopist is not trained to perform EMR, referral to an expert is recommended, rather than biopsy. EMR should be followed by ablation of residual flat BE, which is superior to stepwise radical endoscopic resection of the entire BE segment. Although both approaches yield high rates of CE-IM, randomized data demonstrate that radical EMR yields a markedly higher rate of esophageal strictures (88% compared with 14% in the focal EMR group).¹⁹ Although multiple EMR devices exist, it appears that the multiband mucosectomy technique may be preferable. When compared with the EMR cap technique, both techniques yield similar specimens and side effect profiles. However, the multiband mucosectomy technique is both faster and less expensive compared with the cap device.²⁰ Although multiband mucosectomy should be satisfactory for most lesions encountered in the practice of endoscopic eradication therapy, ESD can be considered for lesions with a bulky intramural component that might fill or overflow the cap, as well as those with endoscopic features suggesting submucosal involvement.²¹ Such lesions make up only a small proportion of patients requiring endoscopic eradication therapy and, therefore, should be considered for referral to centers of excellence, especially in Western countries. Regardless of the method used to resect lesions, all visible lesions must be resected before the application of other ablation methods. Failure to resect these areas leaves the patient at risk for residual subsquamous neoplasia, given the superficial nature of the effect of mucosal ablation modalities. In addition, endoscopic resection is the only reliable means of distinguishing mucosal from submucosal cancers and to diagnose lymphatic invasion and poorly differentiated cancers. Ablation of misdiagnosed cancers with any of these features is a suboptimal treatment with potentially adverse outcomes.

Endoscopic Ablation

After successful endoscopic resection of visible abnormalities, the residual flat component of the BE segment should be treated with an endoscopic ablative therapy to achieve CE-IM. Data demonstrate that endoscopic resection of visible lesions followed by endoscopic surveillance of the residual flat segment yields unacceptably high rates (14.5%–36.7%) of recurrent HGD or adenocarcinoma.^{22–24} Therefore, the only acceptable treatment end point for the vast majority of patients with neoplastic BE is complete endoscopic and histologic eradication of all intestinal metaplasia. Regarding the best approach to eradicate flat-type dysplastic BE, multiple devices have documented high rates of CE-IM in case series, retrospective cohorts, and prospective cohorts. Methods studied include photodynamic therapy, argon plasma coagulation,²⁵ hybrid argon plasma coagulation,²⁶ spray cryotherapy,²⁷ balloon-based cryotherapy,²⁸ and RFA.^{1,7} Given the presence of level I evidence

documenting superiority over endoscopic surveillance and the large number of publications documenting efficacy in a variety of treatment settings, societal guidelines recommend RFA as first-line therapy for ablation of flat-type dysplastic BE or BE after resection of visible lesions.^{29–31} As a result of a paucity of head-to-head data comparing alternative ablation modalities, as well as the lack of literature on combinations of modalities, the most appropriate use of alternative ablation modalities in treatment algorithms remains to be determined. With respect to use of RFA, most clinical trials use the balloon device (Barrx 360 RFA Balloon Catheter; Medtronic, Sunnyvale, CA) as initial therapy with BE segments ≥ 3 cm, with subsequent use of a focal device (12 J/cm²; Barrx 90 RFA Focal Catheter; Medtronic) to treat residual metaplasia and dysplasia at 2- to 3-month intervals. The most common treatment algorithm involves a single application of the circumferential device, followed by debridement of the treated area using lavage and a soft cap to remove debris, followed by a second application of the device, the so-called “one-clean-one” algorithm; alternative algorithms may lead to a higher incidence of esophageal strictures or result in lower CE-IM rates. For the focal device, 2 applications in rapid succession are followed by debridement, then 2 additional applications, for a “two-clean-two” algorithm. A recent randomized trial showed that a simplified approach of 3 applications with the focal device without cleaning is noninferior to the two-clean-two approach, saves time, and eliminates the need for cleaning of the ablation zone and catheter.³²

The most difficult area to treat during BET is the area of the gastroesophageal junction (GEJ)/“neo-z-line” (ie, the area immediately above the upper end of the gastric folds). This area is less effectively ablated by balloon-based RFA because the gastric folds and widening of the hiatal hernia reduce mucosal contact with the RFA electrodes. Endoscopy is generally not reliable to assess the presence of residual BE in this area. Furthermore, this is also a common site for neoplastic recurrences occur during follow-up. For these reasons, it is extremely important to adequately treat the area of the GEJ/neo-z-line circumferentially with focal/targeted therapy.

BEST PRACTICE ADVICE

1. Resection of visible lesions followed by mucosal ablation is recommended for patients undergoing BET.
2. In all patients undergoing BET, mucosal ablation should be applied to a) all visible esophageal columnar mucosa; b) 5–10 mm proximal to the squamocolumnar junction; and c) 5–10 mm distal to the GEJ, as demarcated by the top of the gastric folds (ie, gastric cardia) using a focal device in a circumferential fashion.

What Are the End Points of Barrett’s Endoscopic Therapy?

Endoscopic ablation sessions are scheduled every 2–3 months until complete endoscopic eradication of all columnar epithelium in the tubular esophagus is achieved.

Adequate assessment of the success of BET requires a completely healed esophageal mucosa and use of HD-WLE and/or optical chromoscopy to detect small islands of columnar epithelium and a retroflexed inspection of the gastric cardia.^{7,33}

Endoscopic assessment of complete endoscopic eradication is reliable for columnar islands in the tubular esophagus and for tongues extending ≥ 1 cm proximal to the gastric folds.³⁴ However, for the area of the gastric cardia (ie, the area at the top of the gastric folds), studies have shown poor inter-observer agreement for endoscopic assessment of BE.³⁴ In addition, a detailed inspection of the gastric cardia, even with optical chromoendoscopy, is unable to detect intestinal metaplasia.³⁵ Therefore, random biopsies of the cardia are required to document the histologic absence of intestinal metaplasia.^{7,33}

After complete endoscopic eradication, most clinical studies have obtained 4-quadrant random biopsies every 1–2 cm throughout the length of the original Barrett's segment. The yield of these biopsies, however, is low when the neosquamous epithelium has been inspected carefully with HD-WLE and preferably optical chromoendoscopy to rule out any residual columnar islands/tongues. Biopsies should be obtained only in the absence of erosive esophagitis. Accidental sampling of small residual columnar islands will yield a histologic diagnosis of "buried Barrett's" in 21% of cases, whereas this finding occurs in 0.01% of biopsies obtained from neosquamous epithelium.³⁶

BEST PRACTICE ADVICE

1. BET should be continued until there is an absence of columnar epithelium in the tubular esophagus on HD-WLE and preferably on optical chromoendoscopy.
2. In case of complete endoscopic eradication, the neosquamous mucosa and the gastric cardia are sampled by 4-quadrant biopsies.
3. If the random biopsies obtained from the neosquamous epithelium demonstrate intestinal metaplasia/dysplasia or subsquamous columnar epithelium, a repeat endoscopy should be performed and visible islands or tongues should undergo targeted focal ablation.
4. Intestinal metaplasia of the gastric cardia (without residual columnar epithelium in the tubular esophagus) should not warrant additional ablation therapy.

What Are the Practical Ground Rules for Effective Barrett's Endoscopic Therapy?

BET sessions are performed preferably at 2- to 3-month intervals to allow for optimal healing of the ablated mucosa.^{33,37} Subsequent ablation should only be performed when the residual BE appears flat, without any exudates or ulceration. If the BE demonstrates residual erosive esophagitis, ablation should be postponed because the edematous mucosa has a thickness greater than the

depth of RFA penetration and visible lesions may be masked and missed. In case of incomplete healing, treatment should be postponed for at least 6 weeks and adequate acid-suppressive therapy should be verified. No biopsies should be taken in this clinical setting because the histologic differentiation of reactive inflammatory changes from residual dysplasia may be difficult. In the absence of endoscopic signs of neoplastic progression (ie, no visible lesions), the indication for ablation will not be altered by the results of the biopsies.

Ablation therapy may consist of multiple 2–3 monthly ablation sessions that may extend over a period of more than 1 year. The worst adverse outcome during the treatment period is failing to recognize and treat an invasive cancer while continuing the ablation sessions. This occurrence may place the patient outside of the window of opportunity for curative endoscopic treatment. Therefore, every ablation session starts with careful endoscopic inspection using HD-WLE and preferably optical chromoendoscopy to exclude the presence of visible abnormalities that require an endoscopic resection instead of the scheduled ablation. Routine biopsies of flat BE are not necessary or recommended before ablation at these sessions, as the blood may inhibit optimal energy transfer to the tissue.

Optimal acid-suppressant therapy is imperative for healing and squamous regeneration during and after BET. A proton pump inhibitor using twice daily dosage is almost uniformly used in all studies.³⁷ European RFA studies have generally added an H₂-receptor antagonist and sucralfate for a short duration after every ablation session.³³ However, comparative studies on the optimal drug regimen are lacking. By maximizing acid-suppressant therapy before ablation, there is no need for a baseline 24-hour pH measurement, although this may be indicated in selected cases (eg, poor squamous regeneration after endoscopic resection, refractory BE, and persistent erosive esophagitis³⁸).

BEST PRACTICE ADVICE

1. Mucosal ablation therapy should only be performed in the presence of flat BE without signs of inflammation and in the absence of visible abnormalities. In case of incomplete endoscopic healing, biopsies should preferably be avoided and ablation therapy should be postponed for at least 6 weeks.
2. Patients should use a proton pump inhibitor at bid dosing throughout the treatment phase.

What Are the Potential Harms of Barrett's Endoscopic Therapy?

Although the entire BE segment can be resected using complete EMR or ESD, multimodal or hybrid/combined therapy is the most widely practiced technique, that is, resection of all the mucosal abnormalities, followed by mucosal ablation. Complications have been associated with all of the evaluated techniques.

A meta-analysis of 37 studies (patients treated with RFA with or without EMR) with 9200 patients found the overall complication rate to be 8.8% (95% CI, 6.5%–11.9%; $P < .0001$). The pooled stricture rate was 5.6% (95% CI, 4.2%–7.4%), bleeding rate was 1% (95% CI, 0.8%–1.3%), and perforation rate was 0.7% (95% CI, 0.3%–2.1%). Significant post-procedure pain was observed in 3.8% (95% CI, 1.9%–7.8%) of the treated patients, although most patients noted some post-procedural chest discomfort.³⁹ Both increasing BE length and prior EMR in the RFA-treated patients were associated with a higher adverse event rate. In a comparison of 9 studies ($n = 774$) of EMR+RFA vs 11 studies ($n = 751$) of complete BE EMR, higher adverse events with a higher stricture rate (33.5% vs 10.2%; OR, 4.73; 95% CI, 1.61–13.85; $P = .005$), bleeding (7.5% vs 1.1%; OR, 6.88; 95% CI, 2.19–21.62; $P = .001$), and perforation (1.3% vs 0.2%; OR, 7.00; 95% CI, 1.56–31.33; $P = .01$) were observed in the complete EMR group compared with the EMR+RFA group.³⁹

BEST PRACTICE ADVICE

1. When consenting patients for BET, the most common complication of therapy to be quoted is post-procedural stricture formation, occurring in about 6% of cases. Bleeding and perforation rates occur at rates $<1\%$.
2. EMR of $>50\%$ of the circumference of BE is associated with higher rates of stricture and therefore extensive resection of flat BE should be avoided.

How Should Patients Be Surveyed Post-Barrett's Endoscopic Therapy?

What Are Appropriate Surveillance Intervals Once Complete Eradication of Intestinal Metaplasia Has Been Achieved?

In the past, strict endoscopic follow-up was deemed necessary in light of recurrence rates of neoplasia elsewhere in the BE of about 30% over 3 years and paucity of long-term follow-up data.^{40,41} Given the excellent outcomes of BET in terms of CE-IM and the low rate of neoplastic recurrence during follow-up, surveillance after achieving CE-IM may be less strict. This might hold even more for patients who have undergone ablation for LGD. Cotton et al⁴² collected data from the US Radiofrequency Ablation Registry (3105 patients) and the UK National Halo Registry (373 patients) to build and validate models to predict the incidence of neoplasia recurrence after initially successful BET. For patients with LGD, a model with surveillance endoscopy at 1 and 3 years after CE-IM, and for patients with HGD/EAC, a model with surveillance endoscopies at 3 months, 6 months, 12 months, and then annually, was associated with identifying surgically unresectable cancers at rates $<1/1000$ endoscopies. Although the model only suggested surveillance at 1 and 3 years post-LGD BET, it may be reasonable to continue surveillance every 2–3 years after that. In a recent multicenter study of 594 patients that achieved CE-IM, 151 developed recurrent BE during a median follow-up of 2.8 years. The cumulative recurrence risk

of any BE within 2 years was 19% and an additional 49% risk over the next 8.6 years, suggesting that recurrences can occur even after long-term follow-up.^{43,44}

BEST PRACTICE ADVICE

After CE-IM (endoscopic and histologic) has been achieved with BET, surveillance endoscopy with biopsies should be performed at the following intervals:

1. Baseline diagnosis of HGD/EAC: at 3, 6, and 12 months and annually thereafter.
2. Baseline diagnosis of LGD: at 1 and 3 year.

How Should Post-Therapy Endoscopic Surveillance Be Performed?

The endoscopic assessment of the esophagus post-therapy should follow the same principles as the endoscopic assessment at the end of the treatment phase. This requires the use of HD-WLE and preferably optical chromoendoscopy to detect small islands and tongues of columnar epithelium, absence of erosive esophagitis (which may mask residual BE), and a careful retroflexed inspection of the gastric cardia, with particular focus on the area within 5–10 mm.^{7,33} The latter is especially important because most recurrences after CE-IM occur at the cardia and can be easily overlooked during inspection with the endoscope in the antegrade position.

Endoscopic surveillance post therapy should include a careful inspection of the neosquamous mucosa with targeted biopsies of any visible abnormality. In the absence of esophageal columnar mucosa (islands/tongues) and visible abnormalities within the neosquamous mucosa, most clinical studies have obtained 4-quadrant random biopsies every 1–2 cm throughout the length of the original Barrett's segment. The yield of these biopsies, however, is low. Although the majority of recurrences are detected in the distal 2 cm of the esophagus, the entire neosquamous mucosa should be sampled starting immediately above the GEJ.

The clinical consequences of finding cardia intestinal metaplasia during post-ablation follow-up are uncertain. Cardia intestinal metaplasia is found in up to 25% of adult patients in the absence of endoscopic evidence of Barrett's when sampled at a single endoscopy with 1–2 biopsies from the cardia.⁴⁵ Most post-ablation follow-up studies have found a high rate of intestinal metaplasia on a per-patient basis (30%–50%) based on multiple follow-up endoscopies with 4 random biopsies per session.^{33,46} In the majority of cases, however, intestinal metaplasia is detected in a single biopsy and only at a single occasion and not during further follow-up.^{33,46} In addition, the diagnosis of post-ablation focal intestinal metaplasia in the cardia occurs randomly in time during follow-up, which argues against residual or recurrent disease.

BEST PRACTICE ADVICE

1. Endoscopic surveillance post therapy should be performed with HD-WLE, including careful inspection of the neosquamous mucosal and retroflexed inspection of the gastric cardia.

2. During surveillance post-therapy, 4-quadrant biopsies should be obtained from the gastric cardia and the esophageal neosquamous mucosa to rule out intestinal metaplasia and dysplasia.

How Should Post-Therapy Recurrences Be Managed?

Outcomes data demonstrate that recurrence of intestinal metaplasia in the tubular esophagus after initially successful ablative therapy is a common event. Generally, this is in the form of columnar islands and/or tongues in the tubular esophagus. Large prospective cohorts and meta-analyses suggest that the rate of recurrence is approximately 8%–10% per patient-year of follow-up, and may occur more commonly early in follow-up than in later years.^{47–51} Most recurrent intestinal metaplasia is found in the area of the esophagus just proximal to the top of the gastric folds.⁵² Additionally, dysplasia may be discovered in surveillance biopsies of the cardia during follow-up. The extent to which this dysplasia represents true de novo disease, as opposed to prevalent disease not addressed by initial ablative therapy, is unclear. However, these findings emphasize the importance of circumferential treatment of the gastric cardia during endoscopic treatment sessions to address prevalent cardia disease. In general, the approach to recurrent disease is similar to that of the initial therapy. In a recent cohort study evaluating the risk factors for recurrence post CE-IM after BET, on multivariate analysis, baseline dysplasia (hazard ratio, 1.71; 95% CI, 1.03–2.84) and long-segment BE (hazard ratio, 1.59; 95% CI, 1.01–2.51) were associated with increased risk of BE recurrence.⁵¹ On the other hand, BET performed at high-volume facilities (>10 ablation procedures annually) was associated with reduced risk of BE recurrence compared to low-volume centers (<3 ablation procedures annually) (hazard ratio, 0.19; 95% CI, 0.05–0.68).⁵¹

In the absence of visible lesions (which require endoscopic resection) any recurrent columnar epithelium in the tubular esophagus can be treated effectively by any ablation tool (eg, RFA, argon plasma coagulation, and cryotherapy). Biopsies of flat areas suspicious for recurrent disease will lead to partial removal and may hamper targeted ablation at the subsequent endoscopy.

BEST PRACTICE ADVICE

1. BET should be performed by experts in high-volume centers that perform a minimum of 10 new cases annually.
2. The approach to recurrent disease is similar to that of the initial therapy; visible recurrent lesions require endoscopic resection, whereas flat areas of columnar mucosa in the tubular esophagus can be treated with mucosal ablation.

Multiple investigators have considered the cost and quality of life implications of ablative therapy for dysplastic and nondysplastic BE. The most commonly compared alternative strategies included endoscopic surveillance,^{53–57}

and in the case of baseline BE with HGD, surgical esophagectomy.^{53,55,56,58} Without exception, all analyses suggest that ablative therapy with RFA is cost-effective for the management of BE with HGD, providing higher quality-adjusted life expectancy than surgery. In most analyses, BET is dominant, meaning it not only provides a higher life expectancy, but it does so at a lower cost than surgery. The incremental cost-effectiveness of ablative therapy is more variable in studies as lesser degrees of dysplasia are studied, owing to the smaller risks of progression in BE with LGD and nondysplastic BE. Most studies suggest that ablation of BE with LGD is cost-effective compared with endoscopic surveillance.^{53,55–57} Some analyses of ablation of nondysplastic BE suggest that this maneuver might be cost-effective, especially if endoscopic surveillance can be omitted after successful ablation⁵⁶; however, others suggest it to be prohibitively expensive due to the low rate of progression of nondysplastic BE to EAC.⁵⁵ These analyses are often sensitive to the baseline rates of progression, the degree of protection against cancer attributed to the intervention, the efficacy of surveillance strategies to avert cancer, and other poorly understood factors.

There are scant data regarding quality of life and other patient reported outcomes with respect to endoscopic eradication therapy. Patients with dysplastic BE undergoing eradication therapy with EMR and RFA report decreased worry about esophageal cancer or the prospect of undergoing esophagectomy.⁵⁹ Patients with HGD or T1 EAC also reported better quality of life on standard measures, such as the 36-Item Short Form Survey and the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 compared with similar patients treated surgically. However, they did report higher scores on a scale of worry about cancer recurrence, the Worry of Cancer Scale.⁶⁰ In general, patients with BE tend to overestimate their risk of adenocarcinoma,^{61,62} and appear to be accepting of endoscopic intervention, even if the effectiveness of this intervention was much lower than is commonly reported.⁶²

BEST PRACTICE ADVICE

Patients should be counseled on cancer risk in the absence of BET, as well as after BET, to allow for informed decision-making between the patient and the physician.

Future Directions

To more accurately define the use of BET as a treatment for BE, the first step that is needed is improved standardization. This starts with pathologic definitions, particularly for LGD. As we noted, interpretation of BE with LGD is highly variable from pathologist to pathologist, and poorly reproducible. In the future, we will either need more precise morphologic definitions of LGD or, better yet, molecular markers associated with LGD, such as P53, TP53, and/or aneuploidy, that better predict progression and validate features of LGD morphology.

A second area in need of standardization is in defining the distal border of the BE segment up to which mucosal ablation should be applied. This topic remains problematic,

given the technical difficulty of delineating the distal border and the concern that recurrent intestinal metaplasia and/or dysplasia may arise from this area of the BE.⁶³ In the AIM Dysplasia study, the “entire BE segment was ablated.” In contrast, in another large multicenter study, “In addition to treating the original BE segment, all patients had ablation therapy directed to their gastroesophageal junction.”¹ Yet, in another important RFA study by Phoa et al, “at each ablation session, the gastroesophageal junction was ablated circumferentially, irrespective of its endoscopic appearance.”⁷ As recurrences after CE-IM occur most commonly in the distal esophageal segment,⁴⁸ it is essential to uniformly define the distal margin of therapy and, as important, to better understand the metaplastic potential of the gastric cardia.

Future scrutiny of our endoscopic techniques needs to address the biologic concept of whether we are effectively obliterating extant esophageal stem/progenitor cells and diverting newly formed stem/progenitor cells from a metaplastic and neoplastic pathway. As the location of the esophageal stem cell is not clearly known, it is not a safe assumption that we are able to eradicate this area, which may provide a robust explanation for the relatively high rate of recurrences after CE-IM. Whether this is a fault of inadequate depth of BET or failure to eradicate the source of Barrett’s stem/progenitor cells is unclear.

Another important area of BET in BE that merits further exploration is distinguishing undiagnosed but incompletely treated BE and dysplasia from a recurrence of dysplasia and cancer along with development of markers for recurrence. With the appearance of metaplasia and/or dysplasia after CE-IM, the assumption has been made that this is “disease recurrence,” especially within the first year. This rapidity of development is counterintuitive, given the postulated years of sequential molecular changes required for cancer to develop in BE.^{7,37,64} As a result, these data may indicate a failure to obliterate extant metaplasia and dysplasia when detected rather than recurrent disease. These data could not only lead us to ensure more complete eradication techniques in the future, but might change surveillance intervals after CE-IM has been achieved. Finally, it is also not clear whether we should be confident in the restitutive function of the neosquamous mucosa. Analysis of this type of mucosa demonstrates positivity for CDX2 staining, a marker of intestinal differentiation well-recognized in intestinal metaplasia.⁶⁵ It remains to be determined whether this mucosa has its own metaplastic risk or is as functional as native esophageal squamous mucosa to adequately protect underlying stem cells from reflux and putative intestinal differentiation. An important clue to this issue might be the high level of acid suppression required to regenerate neosquamous esophageal mucosa and prevent recurrence of intestinal metaplasia.⁶⁶

Given the expense and time required for careful and continual surveillance after BET, the future must define improved means of risk-stratifying patients for therapy who are at highest risk for cancer development and for risk of recurrence after CE-IM. Potentially, we may use a panel of patient characteristics (such as the Progression in Barrett’s Esophagus score), pre-ablation tissue characteristics (eg,

baseline grade of dysplasia), and the post-therapy molecular makeup of the epithelium to help risk-stratify our patients.

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