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Challenges in Endoscopic Therapy of Dysplastic Barrett's Esophagus

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Abstract

Purpose of review Barrett's esophagus (BE) is the only known measurable factor associated with esophageal adenocarcinoma. The development of endoscopic eradication therapy (EET) has transformed the way BE is managed. Given the fairly recent development of EET, its role in BE is still evolving.
Recent findings This paper discusses the challenges that endoscopists face at the preprocedural, intraprocedural, and postprocedural stages of BE management. These include challenges in risk stratification, dysplasia detection, ablation methods and dosimetry, choice of resection technique, and management of refractory disease.
Summary Despite the advances in EET in BE, there remain challenges that this review focuses on. Future research into these challenges will optimize ablation techniques and strategies in the future.

Introduction

Barrett's esophagus (BE) is defined as a conversion of the distal esophagus from normal squamous mucosa to specialized columnar intestinal metaplasia. It is the only known measurable factor associated with esophageal adenocarcinoma (EAC), a cancer with a 5-year survival rate of less than 20% [1, 2]. BE is thought to progress to EAC through the following histologically identifiable stages 1) intestinal metaplasia (IM), 2) low-grade dysplasia (LGD), 3) high-grade dysplasia (HGD), 4) intramucosal cancer, and 5) invasive cancer. Intestinal metaplasia, LGD, and HGD each have a different probability of progressing to EAC. In a 2008 study using the

United Kingdom's National Barrett's Esophagus Registry, IM was estimated to have a risk of progression to adenocarcinoma of about 0.59% annually [3]. HGD has been shown to be linked to an annual risk of progression to EAC of approximately 6% [4].

The development of endoscopic eradication therapy (EET) has transformed the way BE is managed and has replaced esophagectomy as the gold standard of care in patients with LGD, HLD, and intramucosal cancer [5–7]. The goal of EET has been to reduce the progression of Barrett's esophagus to EAC, to prevent metastasis in patients with mucosa-limited adenocarcinoma, to prevent the need for esophagectomy, and to improve survival rates. Given the fairly recent development of EET, its role in Barrett's esophagus is still evolving. Although society guidelines provide direction in regard to endoscopic management [6,7,8••,9,10], there are a number of challenges that still remain when treating these patients. This paper will discuss the preprocedural, intraprocedural, and postprocedural challenges facing endoscopists who treat dysplastic Barrett's esophagus.

Preprocedural challenges

There are several preprocedural challenges in the endoscopic management of Barrett's esophagus including risk stratification of patients for determination of ablation candidates, interobserver variability in staging of dysplasia, unclear role of EET in treatment of LGD, as well as limitations in discussing optimal treatment options with patients.

Risk stratification

The role of biomarkers as a risk stratification tool in BE is still unclear. Despite this uncertainty, they are starting to be used in clinical practice for risk stratification purposes. Many studies have looked at various biomarkers and their role in management of BE [11]. Many biomarkers such as the expression pattern of p53, genetic polymorphisms, and hypermethylation of p16 have been looked at extensively and may be promising in risk stratifying patients, predicting prognosis, and guiding therapy [12–15]. Despite many studies, no single biomarker has shown to be superior to histologic identification of dysplasia [12,13,16,17], which is still the best measurement of disease progression in patients with BE and is currently the gold standard in determining which patients are ideal candidates for EET [8••]. Ongoing studies are needed to better define the role of biomarkers in treatment of BE.

Despite being the gold standard in guiding therapy, histologic identification of BE has its challenges as well. There is significant interobserver variability in the diagnosis of LGD, which makes determining appropriate management for these patients difficult [18•]. A recent retrospective study in the Netherlands found that of 147 patients diagnosed with LGD in the community, 85% were diagnosed with no dysplasia upon second review by two expert GI pathologists [19]. Even among expert pathologists, there is suboptimal agreement between LGD even after consensus meetings [20]. The interobserver disparity among pathologists makes determining prognosis as well as appropriate therapy challenging. However when pathologists agree on the diagnosis of LGD, there is an increased risk of progression of disease [21•]. This suggests that patients suspected to have BE, especially those with LGD, should have their biopsies confirmed by expert pathologists prior to treatment. The most recent guidelines reflect this [22•].

Dysplasia detection

Reliably identifying dysplasia in BE is also a challenge for endoscopists, as dysplasia can be focal and flat. Deciding on which advanced imaging tools to use, if any, can be challenging. High definition white light endoscopy (HD-WLE) has been shown to improve sensitivity in detection of Barrett's when compared with standard white light endoscopy and is currently the recommended standard of care when paired with four-quadrant biopsies [6,9,23–25]. Additional tools available are narrow band imaging (NBI), endoscopic and probe based confocal laser endomicroscopy (eCLE and pCLE) systems, and volumetric laser endomicroscopy (VLE). The American Society of Gastrointestinal Endoscopy (ASGE) has established certain research thresholds to be met prior to adoption in clinical practice. To date the advanced imaging modalities that have met these thresholds are NBI, acetic acid chromoendoscopy, and eCLE [26••]. These thresholds have been achieved in academic settings only. This document did not evaluate VLE given its recent release on the market at the time of the document. However, a recent retrospective study provides some data on its potential value in academic centers [27•].

Current guidelines recommend obtaining four-quadrant biopsies at 2 cm sections along the entire length of BE [8••]. A defined systematic biopsy protocol has shown to have higher detection rates of EAC as well as dysplasia compared to random biopsies [28]. However, there are many limitations and challenges to the current guidelines including sampling error and poor compliance and technique. Some studies have looked into the use of a cytology type brush followed by computer-assisted analysis (WATS 3D, CDx Diagnostics, Suffern, NY), which can sample and analyze a large area of mucosa. These studies have been promising and suggest an increase in detection of BE and dysplasia when using this method [29,30]. Current studies have only examined this as an ancillary tool in addition to random biopsies. It should not be used as a stand-alone test. In addition, no study has compared WATS 3D to an external gold standard such as esophagectomy specimens. Finally, compared to standard biopsy specimens, evaluation of the architectural features and differences between surface epithelium and deeper glands is hindered [31,32]. Thus, in practice, it may be difficult to interpret a WATS 3D positive result when other sampling is negative. Thus, more studies are needed that address these issues to determine if it is superior to the currently accepted sampling techniques.

Ablation methods

Before proceeding to EET, it is important to discuss treatment options with patients. However, due to limited studies, it can be difficult to decide and inform patients on various therapies. Esophagectomy was previously considered the gold standard of care for patients with HGD and early EAC. Because of the high risk for serious complications with surgery, there are no randomized controlled trials (RCT) comparing the efficacy of EET and esophagectomy, and no such studies are expected in the future. However, based on other trials, we can deduce that EET is a reasonable alternative. A 2014 population-based study showed similar 2-year and 5-year survival rates in patients who received EET and esophagectomy [33]. One 2011 retrospective cohort study has shown comparable long-term remission rate following surgery and EET of 100% and 98.7% respectively [34]. These results are reassuring in that EET is an acceptable alternative to the surgical management of HGD and Barrett's neoplasia without the morbidity of surgery.

There are also several endoscopic treatment options for ablation of dysplasia that should be discussed with patients. Visible lesions should be endoscopically resected followed by ablation of residual flat Barrett's [8••,35,36••]. Focal resection of visible lesions followed by ablation for complete eradication of BE is favored over radical stepwise endoscopic resection of the BE. A randomized control trial showed comparable rates of complete eradication of dysplasia and intestinal metaplasia; however, the radical resection group had higher complication rates [37]. The two main ablation modalities are radiofrequency ablation (RFA) and cryotherapy. Discussion of these options can be challenging given the lack of comparative studies. Given the options for ablation and resection, it can be confusing to the patient of the ideal approach. Often the patient's anatomy or pain tolerance may dictate which ablation method is chosen. Postprocedural pain is discussed in detail in the postprocedural challenges section. It is our practice to inform the patient about all the ablation and resection methods, and the choice of which ablation platform to use is often made after a detailed inspection of the anatomy. Each ablation method and considerations are listed in the intraprocedural challenges section.

Finally, the choice to discontinue antiplatelet therapy prior to EET can be a challenging decision for many cardiac and stroke patients. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have a high risk of bleeding and should not be performed on dual antiplatelet therapy (DAPT) [38,39]. However, the need to discontinue aspirin prior to these procedures is still a topic of controversy given conflicting studies [40]. In regard to ablation, the ASGE considers this a low risk for bleeding [41]. In the 2009 study looking at treatment of dysplasia with RFA, only 1 of 127 patients had an upper GI bleed. This patient was on DAPT during the study [36••]. Similarly, in a 2017 study of 33 patients receiving cryotherapy, only 1 patient had a gastrointestinal bleed also while on dual antiplatelet therapy [42]. In our experience, minor bleeding can be observed with RFA. If discontinuation of DAPT is considered safe by a cardiologist, ablative therapy should be performed off antiplatelet agents.

Intraprocedural challenges

Choice of endoscopic resection technique

Guidelines recommend that all raised or suspicious lesions in BE should be resected [8••]. EMR and ESD are two options available for mucosal resection. EMR allows for en bloc resection of lesions up to 2 cm in size. Larger lesions may require removal in a piecemeal fashion [43]. ESD has higher en bloc resection rates regardless of the size of the lesion [44]. A 2017 RCT comparing the safety and efficacy of EMR and ESD in treatment of HGD or early EAC ≤ 3 cm found that while ESD had higher initial complete and curative resection rates, at 3 months, both EMR (when used with adjunctive ablation) and ESD had comparable rates of remission [45••]. Compared to EMR, however, ESD is known to be technically more difficult and time-consuming [45••] with higher rates of adverse events including bleeding, perforation, and stricturing [38].

Rates of recurrent disease may be lower in ESD compared to EMR. However, this has never been shown in studies. ESD should be reserved for bulky intraluminal lesions that would result in positive vertical margins via EMR and in cases that have a higher chance of submucosal invasion based on endoscopic or EUS appearance [46]. This will allow an optimal histologic specimen to identify for factors of invasion, resection margins, and for lymphovascular invasion. These cases only account for 10% percent of Barrett's cases, and thus it is hard for endoscopists to gain enough experience in this technique for BE management [46]. Given the disadvantages of ESD as well as the low rate of recurrent neoplasia of 4% when treated with EMR followed by RFA [47], EMR is the more reasonable method of resection for early BE neoplasia at this time.

There are also multiple EMR methods to choose from including cap and ligation-assisted EMR. Cap method uses a transparent cap that attaches to the tip of the endoscope. The cap has a special groove on which a snare can be opened and positioned in place. The endoscope is then aligned over the target lesion, and the mucosa is pulled into the cap by suction. The snare is closed over the retracted mucosa, and the lesion is resected using snare electrocautery [43]. Ligation-assisted EMR or band ligation can be used with or without submucosal fluid injection. Similar to the cap method, the mucosa is pulled into the cap. A band is deployed over the mucosa. An electrocautery snare is then used to resect the banded mucosa either above or below the ligation band [43]. There are limited studies comparing the efficacy and safety of these two methods. Available studies suggest that rates of complications and depth of resection are comparable [48,49]. Currently, the decision on which method to use depends on provider preference and experience.

Choice of ablation method

Deciding on the optimal therapeutic ablation method for a given patient is not straightforward. For the treatment of dysplastic BE or the remaining non-raised BE following endoscopic resection, several options are available for ablation including RFA, cryotherapy, and argon plasma coagulation (APC). Photodynamic therapy has fallen out of favor due to the high stricture rate [50] and photosensitivity and thus will not be discussed here.

RFA was first developed in 1999 and has been the most studied ablation modality to date. In 2009, in an RCT of 127 patients comparing RFA to sham treatment, 90.5% of patients with LGD had complete eradication of disease following RFA compared to 22.7% in the sham group. Eighty-one percent of patients with HGD had complete eradication compared to 19% in the control group. In this study as well as another RCT, those with LGD treated with RFA had less disease progression and fewer resulting cancers [35,36••]. This has resulted in a shift to treating persistent and confirmed low-grade dysplasia. The pooled complete eradication of intestinal metaplasia (CE-IM) rates for RFA from a meta-analysis of ten studies is 78% while the pooled complete eradication of dysplasia (CE-D) rate was 91% [51•].

Cryotherapy is another primary treatment option for ablation of BE. It is known that RFA is limited to the level of the muscularis mucosa while cryotherapy is able to ablate deeper to the level of the submucosa [52]. This has led to the hypothesis that cryotherapy may have lower recurrence rates than RFA and may be an ideal second-line treatment to RFA-resistant BE. Cryotherapy of the esophagus can be performed using liquid nitrogen spray type (CSA Medical, Lexington, MA, USA) or balloon-based nitrous oxide (C2 CryoBalloon, Pentax Medical, Redwood City, CA, USA) type in which a probe within a balloon sprays cryogen against the balloon that contacts the esophagus (Fig. 1). Liquid nitrogen cryotherapy was first used in patients in 2003, while the balloon-based cryotherapy was first used around 2012. Studies evaluating liquid nitrogen cryotherapy as the primary ablation technique for ablation of dysplastic BE have largely been retrospective [42,52–54]. Prospective studies have been small single arm or registry studies [55–57]. These studies show similar CE-D and CE-IM rates compared to RFA. Nitrous oxide balloon cryotherapy has less literature on its efficacy given its infancy on the market. There are two prospective trials evaluating the efficacy of ablation. The first trial involved 30 patients with small islands of dysplasia of which all islands were successfully ablated (100% CE-IM and CE-D) [58]. The second trial involved 41 patients with or without prior ablation. One-year CE-IM and CE-D rates were 88% and 95% respectively [59]. There is currently an ongoing multicenter prospective trial of over 100 patients.

Currently, the decision on which modality to use depends on a combination of provider preference, ease of use, patient preference, and patient anatomy. RFA can be delivered using a balloon device with 360-degree coverage or with a focal probe device. Intuitively, it would seem that the balloon modality would work best with long segment and circumferential BE while the focal probe would be better for focal lesions or with difficult anatomy such as a hiatal hernia. One recent study in 2015 compared the relative effectiveness of both devices and found that the focal RFA device was more effective in treatment of BE compared with the balloon device even after adjusting for BE length, hernia status, prior EMR, and prior RFA treatments. Initial treatment with the focal device resulted in an 82% reduction in BE length compared to only a 47% reduction with the balloon device. Those that underwent focal RFA also required fewer sessions to achieve remission (3.8 vs. 1.6 sessions, $p < 0.01$) [60]. Cryotherapy also

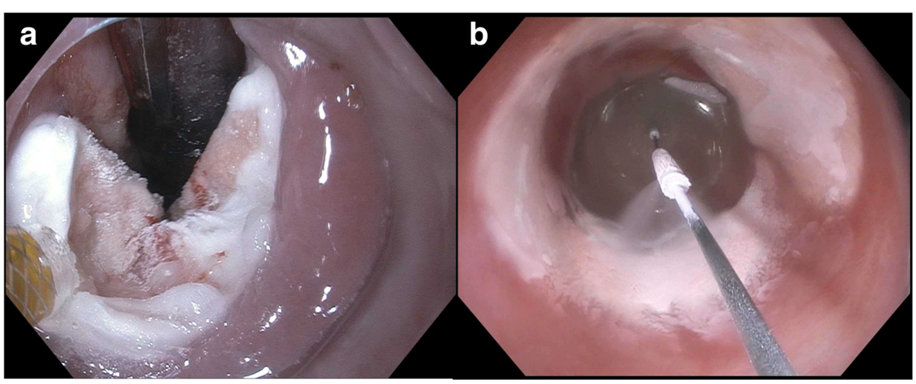

Fig. 1. Cryotherapy for Barrett's esophagus. A) Liquid nitrogen spray cryotherapy of a segment of Barrett's. Note the spray catheter and the decompression tube. B) Nitrous oxide CryoBalloon therapy. Note the probe is within a balloon that is contacting the mucosa.

can be delivered by two different methods, spray, and balloon. However, there are currently no completed studies comparing them. The spray method has been the most widely studied given it has been in use longer. The spray can treat larger areas of BE but is limited by decreased visibility by the cryogen spraying on the endoscope lens. It also requires an external decompression tube for venting of excess gas and capital equipment. Balloon-based cryotherapy is self-venting but may be difficult to position (i.e., GE junction, nodular, or tortuous esophagus) and is only able to treat focal disease of less than 5–6 cm. The addition of a pear-shaped balloon helps overcome ablation challenges at the GE junction. The recently released next generation balloon and catheter will overcome limitations of focal ablation as well as balloon placement issues.

Currently, there are no head-to-head prospective comparison trials of RFA to cryotherapy for primary eradication of dysplastic BE. There is one small retrospective study showing similar CE-D rates but higher CE-IM rates for RFA. However, this study only includes studies from 2006 to 2011 and does not include cryotherapy studies with updated technology or balloon-based cryotherapy [61]. Some anatomy (e.g., circumferential disease) is best ablated with techniques that contact the mucosa, while some anatomy is better suited for focal devices (e.g., focal disease). Non-contact devices are ideal when there is an extremely large hiatal hernia or the esophagus is too large for contact devices.

Deciding on the RFA protocol to be adopted in an endoscopy unit is also challenging. Standard fixed diameter ablation balloon catheters have been replaced by all-in-one self-sizing ablation balloons (Barxx 360 Express Balloon, Medtronic Inc., Minneapolis, MN). Traditionally, circumferential ablation required many steps including sizing of the esophagus to determine the optimal diameter of the ablation balloon to use, ablation of the mucosa, cleaning the ablation zones, and re-ablation. To simplify the protocol, it had been accepted to ablate two times and skip the cleaning step [62]. Optimal energy settings and ablation protocols for the self-sizing express balloon are still evolving [63]. The new balloon sizes and ablates at the same setting so contact with the esophagus is maximized for the entire esophagus; the maximal contact may increase the risk of stricture formation. Determining the optimal number of ablations, correct dosing, and if cleaning steps are needed can be challenging. A recent interim analysis of a RCT showed that ablation two times at 10 J/cm^2 without any cleaning steps may lead to an increased stricture rate (17%) when using the circumferential express balloon versus a standard regimen (10J/cm^2-clean-10J/cm^2) arm [64••]. As a result, this arm of the study was stopped, but enrollment was continued for the 10 J/cm2 × 1 without cleaning arm and the standard arm. Recently published results from a completed RCT for focal ablation comparing a protocol of 3 × 12 J/cm^2 versus a standard regimen with cleaning steps (2 × 15 J/cm^2, cleaning steps, and then 2 × 15 J/cm^2 again) showed the simplified regimen was noninferior to the standard regimen in regard to efficacy and adverse events for focal RFA [65••]. Thus, the conclusion was this should be the preferred regimen. Although this study may allow for an expedited procedure, cleaning with a focal device after ablation does not add much time. However, the cleaning steps after circumferential ablation adds significant time. Thus, the final results of the RCT for the circumferential ablation with the express balloon will provide some clarity.

Fortunately, intraprocedural adverse events such as bleeding and perforation are not encountered often in endoscopic therapy for BE. In studies, these complications have been extremely rare for both RFA and cryoablation. A 2013 meta-analysis found that across 18 studies looking at RFA, bleeding occurred in only 1% of patients [51•]. These studies also show that perforation during or after RFA is extremely rare [36••,51•] with few to no studies reporting any cases. Similar adverse events have been shown in cryoablation. In a 2010 study looking at the safety and efficacy of spray cryotherapy treatment for BE in 98 patients, bleeding was a rare complication (1%), and like in RFA, no perforations were seen in this study [54]. Similar complication rates are also seen in EMR and ESD. In a large safety trial of 681 patients who received EMR, bleeding occurred in 1.2% of patients. No perforations occurred during the study [66]. Studies looking at ESD found a bleeding rate of between 1 and 9%, perforation rate of between 0 and 5%, and stricture rate of between 0 and 60% [45••,67–71].

Postprocedural challenges

Adverse events

The most serious postprocedural challenge facing endoscopists is the management of adverse events and complications following EET. Studies confirm that the most common complications following EET is stricturing secondary to inflammation or due to delayed fibrosis and stenosis. The 2013 meta-analysis looking at the safety of RFA demonstrated that esophageal stricturing occurred in about 5% of patients [51•]. The 2013 study using the UK National Halo RFA registry found higher rates with 10% of patients developing symptomatic dysphagia and/or stricturing requiring dilation [72]. In all studies, esophageal strictures were successfully treated with dilation. In the 2009 RCT looking at the safety and efficacy of RFA in the treatment of dysplastic BE, 6% of patients developed strictures with or without dysphagia which were successfully treated with dilation (mean of 2.6 sessions) [36••]. The postprocedural adverse events for cryotherapy are similar to those for RFA. In the 2010 study looking at the safety and efficacy of spray cryotherapy, stricturing was the most common adverse event (3% overall) [54]. Another study reported closer to 10% of patients treated with cryotherapy developed dysphagia requiring dilation [59].

Postprocedural pain

Postprocedural pain is perhaps the most common self-limited adverse event from ablation. Anecdotally, patients who undergo RFA generally have more pain than patients undergoing cryotherapy. In a multicenter prospective study, RFA was found to be associated with five times greater chance of pain than liquid nitrogen cryotherapy both immediately and 48 h after the procedure. The pain scores between the groups were also similar at 30 days post procedure [73••]. Another prospective study evaluated patients undergoing the CryoBalloon versus RFA [74•]. Pain scores and efficacy of treatment were analyzed. There was no difference in efficacy. However, CryoBalloon had less peak pain and duration of pain than RFA (2 days vs 4 days; $p < 0.01$). CryoBalloon patients used analgesics for 2 days compared to 4 days in the RFA group ($p < 0.01$). Management of pain following EET is a challenge for both providers and patients (see Table 1). Management of pain requires both the optimization of healing through a modified diet and appropriate post procedure medications such as a proton pump inhibitor (PPI), Carafate, and histamine blockers. The addition of pain medications is also recommended depending on the severity of the patient's pain. In patients with an ultra-long segment of BE, it is reasonable to treat each half of the Barrett's at a separate session to minimize pain.

Resistant and recurrent BE

The goal of EET is to eradicate dysplasia and IM and to prevent recurrence of disease. Studies looking at recurrence of disease following treatment has shown varying recurrence rates of 5–40% [51•,75–78]. Life-long surveillance and repeat procedures, assuming a high quality of life for the patient, are needed to maintain remission of BE and prevent recurrence of disease. One 2017 retrospective study of patients successfully treated with RFA found that 24% of patients had recurrence of IM or Barrett's related neoplasia (incidence of 9.6% per year), suggesting these patients continue to have significant risk of recurrence even after complete eradication of disease. This study found that most recurrence occurred in the gastric cardia, and the risk of recurrence was directly correlated with circumferential length (Prague C) rather than maximal length (Prague M) [79].

Liquid nitrogen spray cryotherapy as a salvage technique after failed RFA has been evaluated retrospectively in full manuscript form in two studies with good CE-D (72% and 75%) and acceptable CE-IM rates (50% and 31%) when taking into account the difficult to treat cohort [80,81]. A meta-analysis published in 2018 of 11 studies and 148 patients who received cryotherapy for persistent BE after treatment with RFA showed that 76% (95% CI, 57.7–88.0) of patient achieved CE-D following treatment with cryotherapy [82•]. There are no studies

Table 1. Treatment of post-operative pain and optimization of healing

Expected symptoms after treatment (may last up to 2 weeks)	Chest pain or discomfort Sore throat Dysphagia or odynophagia Low grade fever (< 101)
Recommended postprocedural diet	First 24 h: liquid diet Day 2–7: soft diet Avoid alcohol and very hot or cold liquids and food Avoid all breads, rice, crackers and meats for 1 week
Postprocedural medications	1) Proton pump inhibitor: 40 mg twice a day to be taken 1–2 h prior to a meal until complete eradication of disease 2) Carafate: 1 g three times a day 3) H2-blocker: 40 mg at night 4) Avoid aspirin and NSAIDs for at least 7 days
Pain Management 0 = no pain 10 = severe pain	1) Mild (1–4): Tylenol 325–650 mg every 4–6 h (3000 mg maximum per day) 2) Moderate-severe (5–10): add narcotic medication 5 mg hydrocodone every 4–6 h as needed Or OxyContin 10 mg every 12 h as needed

looking at management of how to manage failures of primary cryotherapy treatment. Crossover to RFA is a reasonable approach. Endoscopic resection of focal areas is also an option.

Finally, the role of acid suppression must be considered in the management of refractory BE. GERD is known to be associated with BE, and reflux control is an important part of BE management [83]. However, symptom assessment is a poor measure of reflux control with most patients being asymptomatic [83]. Consequently, pH testing for resistant disease has been gaining more acceptance [84••]. If a patient is refractory to ablation therapy, pH testing and appropriate measures if positive (e.g., optimization of medical therapy or fundoplication/hiatal hernia repair) should be taken. Studies have shown that control of reflux is necessary for complete eradication in patients undergoing EET. A study showed that the presence of even mildly uncontrolled reflux prior to ablation (measured by 24-h impedance pH testing) was a risk factor for persistent IM postablation with RFA [85•]. A study by the same authors showed that the mean number of RFA sessions required to achieve CE-IM was decreased and the time to recurrence of disease was increased when RFA was used with concurrent PPI treatment as part of the management of BE [84••]. This same study showed that the only significant predictor of recurrence was the presence of a hiatal hernia, likely because of its association with persistent reflux [84••]. Figure 2 displays a simple algorithm for endoscopic eradication therapy with incorporation of pH testing, and acid control [84••]. If the patient does not

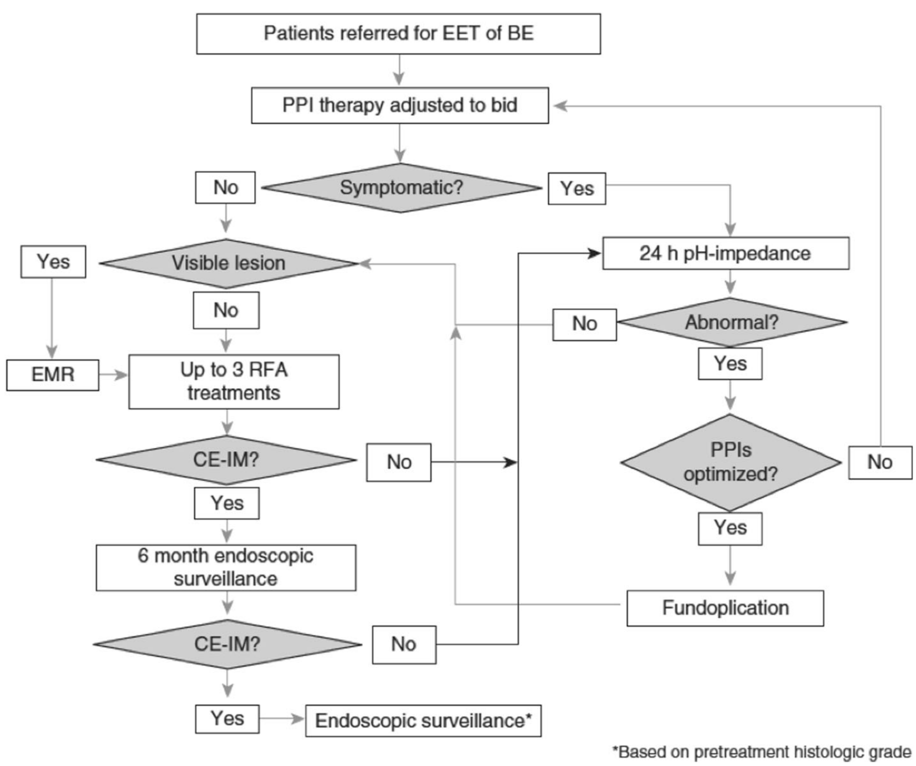

Fig. 2. Algorithm for endoscopic eradication therapy, pH testing, and fundoplication. Reproduced with permission from Springer Nature [82•].

have an adequate response to RFA after three sessions while on twice a day PPI, then pH testing can be performed. If pH testing for RFA refractory disease is positive, then fundoplication can be considered after medical optimization, which has been shown to lead to decreased rates of recurrence of IM compared to post-EET PPI treatment alone (9.1% vs. 20%) in a small uncontrolled study [86]. In our practice, we treat RFA-refractory disease with cryotherapy and maintain twice a day PPI therapy. If there is lack of response to cryotherapy, then, we initiate pH testing.

Conclusion

Endoscopic eradication therapy has replaced esophagectomy for dysplastic BE and is now the recommended treatment for LGD, HGD, and intramucosal cancer. Endoscopic management of Barrett's esophagus currently is an evolving field with a growing body of literature that has allowed providers to make evidence-based decisions. While much is known about the disease and many therapeutic options are available, there still remain many preprocedural, procedural, and postprocedural challenges that have been discussed in this review. This is an evolving field and further research efforts will help define an optimal strategy for these challenges in the future.

Authors' contributions

Conception and design (AJT, AC)
Analysis and interpretation of the data (AJT, AC)
Drafting of the article (AJT, AC)
Critical revision of the article for important intellectual content (AJT, AC)
Final approval of the article (AJT, AC)

Compliance with Ethical Standards

Conflict of Interest
Arvind Trindade reports personal fees as a consultant from Pentax Medical and CSA Medical.
Aurada Cholapranee declares no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

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Papers of particular interest, published recently, have been highlighted as
- • Of importance
- •• Of major importance

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This retrospective study of 255 patients with a primary diagnosis of LGD demonstrated that interobserver variability for LGD is high, a problem that makes it difficult to determine the appropriate management for these patients. This study concluded that as the number of pathologists (up to three pathologists in the study) who agreed on a diagnosis of LGD increased the risk of developing high-grade dysplasia (HGD) and adenocarcioma (EAC) increased.

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This is a letter to the editors commenting on the interim findings of an ongoing randomized controlled multicenter

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A simplified RFA regimen of 3 × 15 J/cm2 without cleaning has been shown to be as effective as the standard regimen of 2 × 15 J/cm^2 with cleaning; however, it has been showed to be associated with higher stricturing rates. This randomized non-inferiority study looks at a new lower radiofrequency energy regimen of 3 × 12J/cm^2 without cleaning versus the standard regimen for focal treatments. The results of this study demonstrated that the lower energy simplified version was noninferior to the standard regimen with no increase in adverse events or stricturing.

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This multicenter prospective study compared focal RFA with liquid nitrogen spray cryotherapy and found that RFA was associated with five times greater odds of pain immediately following the procedure as well as 48 hours postprocedure compared to cryotherapy.

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This multicenter cohort study looked at the efficacy as well as the degree of postprocedural pain in focal cryoballoon therapy versus RFA. This study found no difference in efficacy for treatment of short-segment BE. However, cryotherapy was associated with less reported pain as well as fewer analgesic use compared with RFA.

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This meta-analysis of 11 studies and 148 patients looked at the efficacy of cryoablation as salvage therapy in patients with persistent BE despite prior initial RFA treatment. The study found that cryotherapy successfully achieved CE-D and CE-IM (76% and 46% respectively) in this patient population.

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