Review Article

A narrative review of endoscopic therapies in Barrett's esophagus

Nour Hamade[1], Prateek Sharma[2,3]

[1]Department of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, IN, USA; [2]Department of Gastroenterology and Hepatology, Veteran Affairs Medical Center, Kansas City, MO, USA; [3]Department of Gastroenterology and Hepatology, University of Kansas School of Medicine, Kansas City, KS, USA

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Correspondence to: Nour Hamade, MD. Department of Gastroenterology and Hepatology, Indiana University School of Medicine, IN, USA. Email: nhamade@iu.edu.

Abstract: Endoscopic therapy has largely replaced esophagectomy in the management of neoplastic lesions [high grade dysplasia (HGD) and early cancer] in patients with Barrett's esophagus (BE). This change has improved the cost of treatment and decreased patient's morbidity while maintaining comparable efficacy to surgery. A multitude of endoscopic techniques (resective and ablative) exist to completely eradicate the Barrett's segment. Resective modalities such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are mostly used for visible or nodular Barrett's lesions. Ablative modalities, such as radiofrequency ablation (RFA), cryoablation, and argon plasma coagulation (APC), are used to treat flat Barrett's lesions. These resective and ablative modalities can be used alone or in combination to yield high rates of eradication. While more head to head trials are still needed to compare current modalities, the choice of technique can depend on several factors including the lesion morphology, Barrett's segment length, the circumferential BE extent, side effect profile of treatment, availability of tools, as well as the physician's expertise. In this review, we discuss when BE lesions can and should be treated endoscopically, provide an overview and comparison of the available endoscopic treatment modalities, updated research on upcoming technologies, and how these therapies can be positioned to treat BE in different clinical settings.

Keywords: Ablation; resection; dysplasia; eradication

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Introduction

Barrett's esophagus (BE) is the only known precursor to esophageal adenocarcinoma (EAC), with progression thought to occur in a stepwise fashion from non-dysplastic BE (NDBE), to low grade dysplasia (LGD), to high grade dysplasia (HGD), and finally, to EAC (1). Therapy is indicated in patients with HGD and intramucosal cancer (IMC), and select cases of LGD and submucosal cancer, to halt progression to invasive cancer and ultimately improve mortality (2). In the last 2 decades, Barrett's endoscopic therapy (BET) has revolutionized the management of dysplastic BE. Prior to the availability of BET, treatment was traditionally performed with esophagectomy, a procedure with high complication rates ranging between 30–50% (3). As such, this has been largely replaced by BET which carries lower cost and lower procedural morbidity and mortality (4). Several endoscopic therapeutic techniques are currently available that either resect tissue such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) or ablate tissue such as radiofrequency ablation (RFA), cryotherapy, or argon plasma coagulation (APC) (1,2). While these techniques have not yet been compared in head to head trials, data is accumulating to better inform best therapeutic practices in different patient populations. In this review, we

will describe how each of these techniques is positioned in the treatment and management of BE lesions. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/aoe-20-73).

Methods

We conducted a literature search in 'PubMed' and 'Google Scholar' since year of inception of both databases till present day, with focus on articles published in the last 15 years (i.e., between 2005 and 2020). We included articles published in full text as society guidelines or original papers (i.e., meta-analyses, retrospective and prospective cohort studies, randomized control trials) written in the English language.

To treat or not to treat?

The decision of whether to treat a segment of BE relies primarily on the presence or absence of dysplasia and patient preference.

NDBE

At the present time, there is insufficient data to risk stratify BE patients without dysplasia, i.e., which patients will progress and likely benefit from BET. As such, currently, surveillance every 3–5 years is recommended for NDBE patients as per various GI society guidelines, and BET is not recommended in this patient population (1,2).

Neoplastic BE

Due to the high inter observer variability in the diagnosis of LGD and variable rates of progression reported in the literature, these patients can consider either undergoing surveillance or be referred for endoscopic therapy, with risk and benefits of each option discussed with the patient to foster a patient centered decision approach (1,2). For patients with HGD/T1 (a) cancer, GI societies recommend endoscopic therapy over esophagectomy given high efficacy rates of eradication along with lower morbidity and mortality associated with BET over surgery (1,2). For T1b cancers, surgery had traditionally been the preferred management given the risk of lymph node metastasis, however, currently endoscopic resection techniques can be considered as an alternative for patients with SM1 tumors (<500 micron submucosal invasion) and low risk features (well-differentiated, size <2 cm, no lymphovascular invasion) especially if they are poor surgical candidates (2). Lesions that are staged beyond T1b (SM1) cannot be treated with BET and require other modalities (1). Caution is advised when determining depth of invasion of lesions as differentiating T1a from T1b can be challenging, and even more so when differentiating SM1 from SM2 invasion, especially in community practice. Rigorous preoperative evaluation of depth of invasion is thus paramount to decide on management options. While EMR can provide information on invasion depth, advanced imaging modalities have also been shown to be helpful. Narrow band imaging in combination with magnifying endoscopy has been shown in a systematic review of ten studies to be superior to white light endoscopy in predicting the invasion depth of superficial squamous cell cancer (5). More studies are needed to show a similar accuracy in BE. EAC patients being considered for endoscopic therapy should be discussed in a multidisciplinary tumor board setting with involvement of a gastroenterologist, oncologist, pathologist, and surgeon.

Which modality to use?

In the following section, we will discuss the role of different endoscopic resective and ablative modalities that can be utilized depending on the length and circumferential extent of the BE segment, as well as, the presence of any visible lesions (*Figure 1*).

Flat dysplasia without visible lesions

Circumferential and/or long segments

It is important to note that more than 80–90% of patients with HGD and/or early EAC within BE will have visible lesions documented on a high quality examination of the esophagus using high definition white light endoscopy and virtual chromoendoscopy (Narrow Band Imaging, Blue Light Imaging, i SCAN) (2). Therefore, it is extremely important to conduct a careful inspection of the BE mucosa prior to proceeding to ablation type therapy without resection. RFA remains the preferred modality of treatment for flat-type, dysplastic BE and is currently recommended by societal guidelines as first-line therapy (1,2).

For circumferential lesions, traditionally the Barrx360 system (Medtronic, Minneapolis, MN, USA) was used, which consisted of an ablation catheter with a 3 cm long

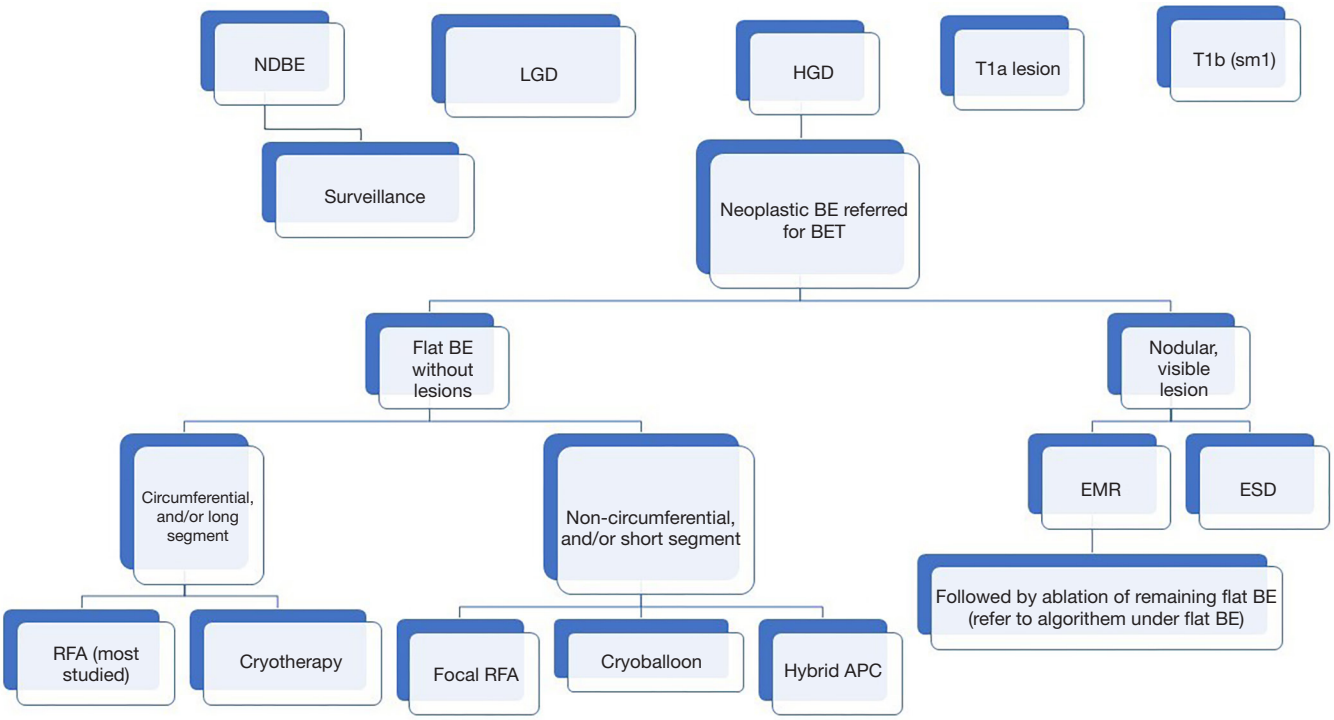

Figure 1 Algorithm for management of Barrett's esophagus with endoscopic eradication therapy.

electrode. After sizing the esophageal inner diameter at multiple levels using a sizing balloon, an appropriately sized ablation catheter was introduced and 2 ablations at 12 J/cm^2 with a cleaning phase in between was performed (6). Using this device, initial studies reported complete eradication of dysplasia (CE-D) rates between 92–98% and metaplasia (CE-IM) ranging between 88–91% (7,8).

More recently, a new self-sizing 360 Express RFA balloon catheter (360 Express, Medtronic, Minneapolis, MN, USA) with a 4 cm electrode has been under study. A pilot study showed that the new system leads to decreased procedure time while maintaining efficacy, however, pronounced esophageal scarring was observed in 23% of patients, with 10% requiring dilation, especially when cleaning was not performed between ablations (9). A recent multicenter cohort study comparing the manual versus self-sizing circumferential balloon catheters found that when the 10 J application was used, there was no significant difference between the 2 devices in terms of stricture formation, rates of and time of CE-IM and CE-D. The self-sizing catheter was again shown to have significantly shorter procedure time (10).

There has also been recent interest in the use of spray or balloon cryotherapy as an ablative modality. Cryoablation is a noncontact method that consist of directed spray of a cryogen, like liquid nitrogen, which causes rapid freezing and thawing. This process causes vascular ischemia, and causes thrombosis, resulting in the necrosis of superficial esophageal mucosa layers. A recent meta-analysis of studies using spray cryotherapy as the primary BET modality included 6 studies with a total of 282 patients and showed CE-IM rate of 69.35% (95% CI: 52.1–86.5%) and CE-D rate of 97.9% (95% CI: 95.5–100%) (11). More recently, cryoballoon ablation was developed to address some of the challenges associated with the spray technique namely the variable ablation depth, unstable positioning of the catheter, and need of a decompression tube to vent accumulated gas from the stomach (12). Until recently, the cryoballoon was designed to treat only focal BE, however, a new cryoballoon (Swipe90 Ablation System; CbSAS90) with a 3 cm long ablation over a quarter of the esophageal circumference, has been under study (13). A recent prospective, multicenter study in the first human application of this device showed that it had comparable procedure times to RFA and was able to eradicate BE effectively with a median BE surface regression percentage of 93% (95% CI: 88–96%), with no

significant adverse events (13). However, more comparative studies between cryotherapy and other modalities are needed before the widespread adoption of this technique as a primary modality of therapy. Currently, it is mostly used as salvage therapy in patients who have previously failed RFA.

Non-circumferential and/or short segments of BE

Focal and targeted ablation either using the Barrx 90 RFA Focal Catheter, hybrid APC and focal cryotherapy can be used to treat focal lesions or residual BE areas following circumferential RFA treatment. For focal RFA, the catheter is attached to the scope externally at the 12 o'clock position and 2 applications are administered in succession, followed by debridement, and subsequently an additional 2 applications. This method of application has been compared in a randomized trial to a more simplified approach that consists of 3 applications using the focal RFA device without an intermediate cleaning phase and showed that the simplified approach was non-inferior and saved time (14).

APC consists of a non-contact probe that delivers electrical energy transmitted through ionized argon plasma gas. Initially, this technique fell into disfavor due to associated complications such as perforation, bleeding, and pneumomediastinum (15). However, a modified technique of hybrid APC, where normal saline is first injected into the submucosa followed by APC ablation has shown promise with CE-IM of 78% and only 2% stricture rate (16). A randomized trial is currently underway comparing hybrid APC to RFA for the treatment of neoplastic BE.

The focal cryoballoon ablation system has been evaluated to ablate short-segments of BE with each 10-second application resulting in ice patches of 2 cm with studies reporting promising CE-IM and CE-D rates, ranging from 88% to 95% (17). A multicenter, non-randomized trial comparing focal cryotherapy to focal RFA showed that the 2 modalities had comparable BE regression (88% *vs.* 90%, P=0.62), however, the use of cryotherapy was associated with less severity and duration of pain, as well as, less use of analgesics (18).

BE with visible lesions

Complete and focal resection of any visible lesion within the BE segment should be performed using either EMR or ESD. This not only can be curative, but can also distinguish submucosal cancers, lymphatic invasion, and poorly differentiated cancers. EMR is the most commonly used technique for resection of BE cancers in Western countries. Multiple mucosal resection devices exist, including multiband mucosectomy and cap devices. While both yield similar specimens and side effect profiles, the multiband mucosectomy device is preferable as it is less expensive and less time consuming (19). After resection of visible lesions, the remainder of the flat BE mucosa still needs to be treated as data has shown that endoscopic surveillance of the residual flat segment yields unacceptably high rates (14.5–36.7%) of recurrent HGD or adenocarcinoma (20). While stepwise resection can achieve high rates of CE-IM, this is associated with high rates of esophageal strictures (21).

ESD can be considered instead of EMR for lesions with a bulky intramural component, lesions greater than 15 mm, or those with features suggesting submucosal involvement or advanced histology (22). A systematic review and meta-analysis of 524 BE lesions treated with ESD showed a 65% curative resection rate with less than 2% rate of bleeding and/or perforation. Post ESD, recurrence was low at 0.17% at 23 months (23). Compared to EMR, ESD offers *en bloc* resection with more precise histology, higher rates of curative resection (58.8% *vs.* 11.7%, P=0.01), and perhaps lower rates of residual and local recurrence (24).

An important adverse event to anticipate with ESD is esophageal stricture formation which can occur in 10–20% of patients. Risk factors for stricture formation include a mucosal defect >75% of the luminal circumference of the esophagus, a tumor length greater than 30mm, and histologic invasion depth extending greater than M2 (lamina propria). Stricture formation approaches 100% in patients who have had circumferential ESD performed (25).

The most common method to prevent stricture formation is local injection of steroids immediately after performing the ESD. Studies have shown that patients who receive steroid injection have significantly lower rate of stricture formation compared to historical control (10% *vs.* 66%) (26,27).

Overall, ESD requires significant expertise and patients should be considered for referral to centers of excellence, especially in Western countries.

Conclusions

Endoscopic therapy has revolutionized the treatment of neoplastic BE in the past few decades. Multiple techniques, including EMR, ESD, RFA, cryotherapy, and hybrid APC, used alone or in combination, can yield high rates of eradication of neoplasia and metaplasia. The unique merits

of each of these techniques, and patient characteristics wherein one might be preferred over the other, are still not well studied. Head to head comparisons of these different modalities are still needed to better inform endoscopists regarding which technique is better suited for a certain clinical scenario. With multiple innovations already under study, the future of this field appears bright.

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