Ther Adv Gastroenterol
2020, Vol. 13: 1–11
DOI: 10.1177/1756284820924209

Indications, contraindications and limitations of endoscopic therapy for Barrett's esophagus and early esophageal adenocarcinoma

Carol Rouphael, Mythri Anil Kumar, Madhusudhan R. Sanaka and Prashanthi N. Thota

***Abstract*:** Endoscopic eradication therapy (EET) has revolutionized management of Barrett's esophagus (BE)-associated neoplasia, traditionally treated by esophagectomy, which carries very high mortality and morbidity. EET, usually performed in the outpatient setting, has a safe risk profile. It is indicated in patients with BE with high-grade dysplasia and intramucosal cancer, confirmed, and persistent low-grade dysplasia, and in highly selected cases of non-dysplastic BE and submucosal cancers. Multiple EET modalities are available and can be categorized into two groups: ablation therapies and resection techniques with resection techniques usually reserved for nodular/raised lesions or lesions with suspected neoplasia. Patients usually require multiple ablation sessions with a goal of achieving complete eradication of metaplasia. Despite very good results, EET has its limitations and is not 100% effective: it targets a small subset of patients along the spectrum of BE and esophageal adenocarcinoma, as most patients with esophageal adenocarcinoma remain asymptomatic until the disease has progressed to advanced stages. Post-ablation surveillance is mandatory, as recurrences are common. An area of concern is buried metaplasia reported to occur following ablation therapy and thought to be from *de novo* growth of metaplastic tissue underneath the neosquamous epithelium, following ablation. The focus of this review article is to present the indications, contraindications and limitations of EET.

Keywords: Barrett's esophagus, endoscopic therapy, ablation, cryotherapy, resection

Received: 21 January 2020; revised manuscript accepted: 15 April 2020

Correspondence to:
Prashanthi N. Thota
Department of Gastroenterology and Hepatology, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195-5243, USA
thotap@ccf.org

Carol Rouphael
Mythri Anil Kumar
Madhusudhan R. Sanaka
Department of Gastroenterology and Hepatology, Cleveland Clinic, Cleveland, OH, USA

Introduction

Barrett's esophagus (BE) is defined as an extension of metaplastic columnar epithelium of at least 1 cm above the gastroesophageal junction, replacing the stratified squamous epithelial lining of the esophagus, with biopsy-proven intestinal metaplasia.[1] It is a result of chronic mucosal injury due to gastroesophageal reflux disease (GERD) and is estimated to be present in up to 15% of GERD patients.[2] BE is of significance due to its increased risk of progressing to esophageal adenocarcinoma (EAC), especially in the presence of dysplasia. While non-dysplastic BE (NDBE) carries a small annual risk of progressing to EAC (0.3%),[3] the risk increases to 0.5% in the presence of low-grade dysplasia (LGD)[4] and 7% with high-grade dysplasia (HGD).[5]

Up until the last 2 decades, esophagectomy was the standard of care for BE with HGD and intramucosal cancer (IMC), with up to 95% 5-year survival rates, but very high complication rates ranging between 30% and 50%.[6] Over the last 2 decades, however, there has been a shift towards endoscopic eradication therapies (EETs) considering their lower procedural morbidity and mortality, decreased cost and similar survival rates when compared with radical esophagectomy. The main principle behind EET is that under maximal acid suppression, there is regeneration of normal esophageal squamous mucosa after ablating BE.[6] This concept was first confirmed using endoscopic laser treatment more than 20 years ago.[7] Since then, multiple EET modalities were developed and can be categorized into resection techniques and ablation techniques. In this review, we will provide a brief overview of the various EET modalities available and focus on indications, contraindications and limitations of EET.

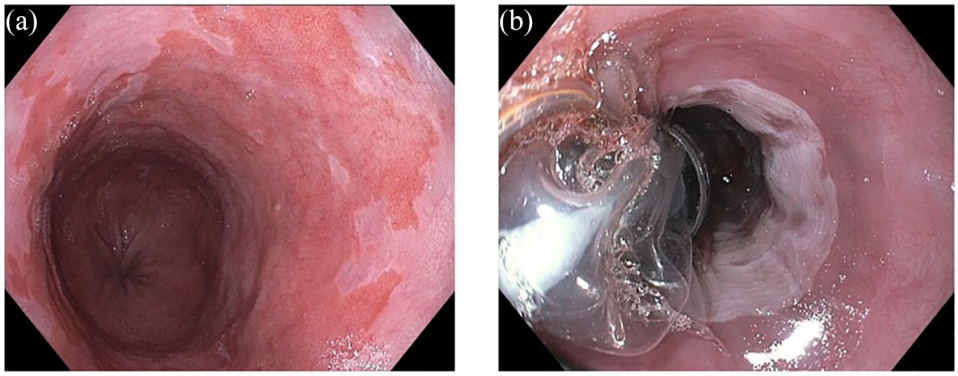

Figure 1. Barrett's mucosa prior to and after ablation.
(a) Barrett's mucosa prior to ablation and (b) after ablation with RFA 360 express catheter.
RFA, radiofrequency ablation.

EET techniques for BE

EET can be categorized into (a) ablation techniques that utilize thermal, photochemical or radiofrequency energy for destruction of abnormal tissue, and (b) resection techniques that involve removal of abnormal tissue and therefore provide tissue for histological examination. Radiofrequency ablation (RFA) is the most widely used ablation technique for BE with flat mucosa. The efficacy has been established with a randomized controlled trial and therefore it remains the preferred modality. There is less evidence for other ablation modalities such as cryotherapy and argon plasma coagulation (APC); however, they are useful in specific instances, such as refractory disease, in the presence of strictures and treatment of residual small islands of BE, etc.

Ablation techniques

(1) RFA:

RFA uses radiofrequency energy to cause tissue injury and necrosis of the metaplastic tissue by applying current in a uniform fashion and at a steady depth to the esophageal mucosa.[6] Circumferential ablation is applied for circumferential BE segments >3 cm in length, using the Barrx 360 Express RFA balloon catheter (Medtronics, Minneapolis, MN, USA) (Figure 1). If <3 cm in length or non-circumferential, focal ablation is applied using Barrx 90 RFA (ablates 260 mm^2), Barrx 90 ultra long RFA (ablates 520 mm^2), Barrx 60 RFA (ablates 150 mm^2), or Barrx channel RFA catheters. The endoscopist first determines which catheter to use depending on the BE segment characteristics. The mucosa is then sprayed with 1% N-acetylcysteine to clean from it any secretions that could interfere with radiofrequency delivery. For circumferential ablation, the catheter was introduced over the guide wire and placed 1 cm above the proximal end of the metaplastic segment. The balloon was then inflated and RFA application was performed once. This was followed by scraping of the ablated mucosa with a cap mounted on the endoscope followed by a repeat application ×1. Regarding focal ablation, the type of catheter used depends on the surface area to be ablated. The catheter was attached to the scope externally in the 12 o'clock position and advanced with endoscopic guidance to the area of interest, where RFA is applied twice. Following ablation, the coagulum was scraped off with the cap attached to the scope and the RFA was reapplied twice.[6,8] RFA was found to be very efficacious for complete eradication of dysplasia (CE-D) and metaplasia (CE-IM) at rates ranging between 92% and 98%, and 88% and 91%, respectively.[9,10] It is worth noting that the studies reporting the efficacy of RFA were performed with a previous-generation 360 RFA balloon instead of the currently available 360 express RFA self-sizing balloon catheter.

(2) APC:

APC was one of the first techniques used for ablation of NDBE. The APC device consists of a contact-free probe that delivers electrical energy through ionized plasma of argon gas to the target tissue at a rate of 1–2 liters/min with energy settings ranging from 30 to 90 watts. Most of the studies performed looked at NDBE with a

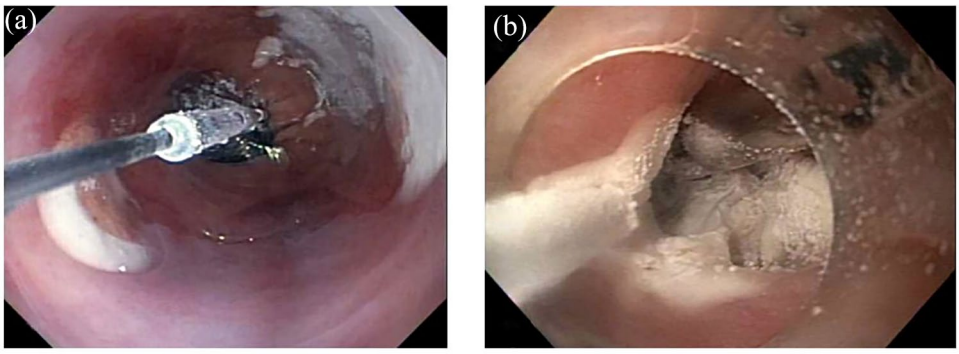

Figure 2. Ablation with the cryoballoon focal ablation system and with TruFreeze cryospray.
(a) Ablation with cryoballoon focal ablation system and (b) ablation with TruFreeze cryospray.

CE-IM rate ranging between 58% and 78%.[11,12] This technique fell into disfavor due to serious complications reported, including buried BE glands, perforation, pneumomediastinum, and bleeding.[6] More recently, Manner and colleagues described a modified technique (APC-Hybrid) that entails injecting normal saline in the submucosa prior to APC ablation with CE-IM noted in 78% of the 60 patients with prior endoscopic mucosal resection (EMR) for BE associated neoplasia.[13]

(3) Cryotherapy:

Cryotherapy comprises spraying cryogen (liquid nitrogen, or nitrous oxide) endoscopically without the need for contact ablation with the catheter (Figure 2). It causes thermal injury by first immediately freezing the cells, followed by apoptosis. The non-contact approach may be useful for the ablation of uneven surfaces such as plaques, nodules or masses. Currently, there are two systems available approved by the United States Food and Drug Administration: (a) the TruFreeze system, which delivers liquid nitrogen and freezes tissues up to −196°C, and (b) the cryoballoon focal ablation system (CbFAS), which uses a cryogenic balloon that requires direct contact with the target tissue using nitrous oxide as cryogen. Long-term results with the TruFreeze system show CE-D in 88–93%, and CE-IM in 75%.[14] In the only reported trial using the CbFAS of 41 patients with BE-associated neoplasia, CE-D and CE-IM rates at 1 year were 95% and 88%, respectively.[15] Cryotherapy is associated with less pain compared with RFA. Strictures have been reported in up to 13% of patients, and perforations have occurred.[6]

(4) Photodynamic therapy (PDT):

PDT uses photochemical energy to destroy metaplastic epithelium. A photosensitizer is administered intravenously (porfimer sodium in the United States) or orally (5-aminolevulinic acid in Europe) and gets concentrated in the tissue with a higher affinity to metaplastic and neoplastic cells. At 48 h after the photosensitizer is administered, the patient undergoes an endoscopy where red light is transmitted through use of balloon-diffusing fibers or optical fibers through the scope. The interaction between red light and the photosensitizer leads to metaplastic tissue destruction by generating superoxide and hydroxyl-free radicals leading to cell apoptosis, with conservation of normal squamous mucosa. Upper endoscopy can be repeated after 2–3 days to assess mucosa and re-treat if needed.[16] Photosensitivity reactions are seen in more than 60% of patients who undergo PDT using porfimer sodium,[16] with esophageal stricture occurring in up to 36% of patients,[17] and hence this technique is mostly abandoned.

Resection techniques

Resection techniques are applied for removal of visible lesions or abnormal areas within the BE segment. This provides tissue for histological evaluation and therefore helps in staging, too. Resection is typically followed by endoscopic ablation due to increased risk of metachronous lesions in the remaining BE segment. There are two resection techniques described below:

(1) Endoscopic mucosal resection (EMR):

EMR can be done *via* the ligate-and-cut technique or lift-and-suck technique. With ligate and

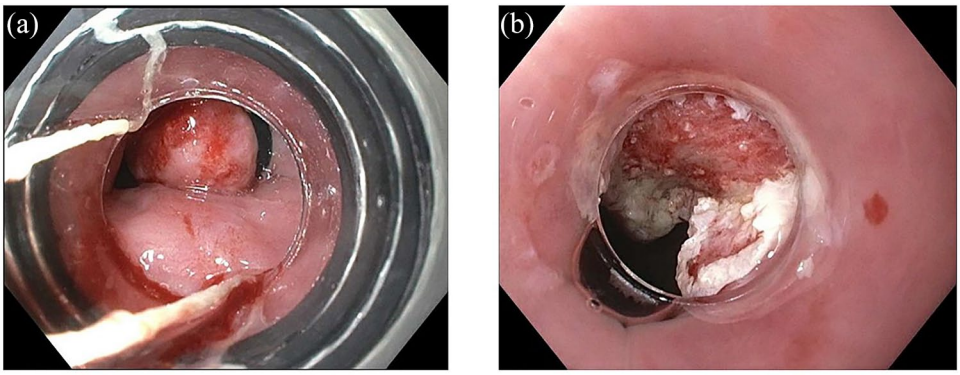

Figure 3. Band placement for EMR with Duette® kit and mucosal defect after EMR.
(a) Band placement for EMR with Duette® kit and (b) mucosal defect after EMR.
EMR, endoscopic mucosal resection.

cut, APC is used to mark a lesion's margins and a modified variceal band ligator is used to suck the lesion into a cap with a rubber band released around it, and the lesion is then resected with a snare (Figure 3). The lift-and-suck technique entails lifting the submucosa with normal saline. Using a cap placed on the endoscope tip, the lesion is suctioned, creating a pseudo-polyp, and a snare is used with cautery to resect the lesion.[6] Focal EMR is used to remove visible lesions in the BE segment and is usually followed by ablation. Stepwise radical EMR is utilized for removal of the entire BE segment by serial EMR. EMR is highly effective, with reported rates of CE-IM of 92–100%.[6]

(2) Endoscopic submucosal dissection (ESD):

ESD enables complete removal of lesions that are too large for *en bloc* EMR. ESD may be considered in selected patients with BE with the following features: large or bulky area of nodularity, lesions with a high likelihood of superficial submucosal invasion, recurrent dysplasia, EMR specimen showing invasive carcinoma with positive margins, equivocal pre-procedural histology, and IMC.[18] This technique was originally developed in Japan for resection of early gastric cancers. After marking the lesion with circumferential coagulation makers, the lesion is lifted by injecting solution into the submucosal space and a circumferential incision is made around the lesion using an electrosurgical knife. The submucosa is dissected and the lesion resected *en bloc*.[6]

Indications for endoscopic eradication therapy in Barrett's esophagus

(1) BE with HGD or IMC:

Any EET involves careful staging with confirmation of dysplasia by a second gastrointestinal pathologist, use of endoscopic ultrasound (EUS) and positron emission tomography (PET) scan in selected cases, and EMR of visible lesions, followed by ablation of flat BE mucosa. The AIM dysplasia trial has established the effectiveness of EET in treatment of BE with HGD with CE-IM of 77%, and CE-D of 81%.[19] The 3-year follow-up results showed CE-D and CE-IM in 98% and 91% patients, respectively.[10] EET is also highly effective for treatment of IMC with no evidence of nodal involvement. In a large series of 1000 patients with IMC treated with EET and followed for up to 5 years, 96.3% were successfully treated by EET, and 3.7% underwent surgery after EET failed. Recurrences developed in 14.5% but were successfully treated by EET in 11.5% leading to a long-term complete remission rate of 93.8%.[20]

Historically, prior to EET, esophagectomy was the only treatment option available for BE with HGD and IMC. Esophagectomy carries a 1–5% mortality risk and a 30–50% morbidity risk, even with expert surgeons,[21] making it a less attractive therapeutic option in the era of EET. There are no randomized control trials comparing EET with esophagectomy. Wu and colleagues performed a meta-analysis including 870 patients with BE with HGD or IMC (T1a).[22] There was no significant difference in remission rate [relative risk (RR)

0.96; 95% confidence interval (CI) 0.91–1.01], neoplasia relate mortality (relative difference 0; 95% CI 0.02–0.01) or overall survival at 1 year, 3, and 5 years (RR 0.99; 95% CI 0.94–1.03, RR 1.03; 95% CI 0.96–1.10, and RR 1.00; 95% CI 0.93–1.06, respectively).The EET group had higher neoplasia recurrence (RR 9.5; 95% CI 3.26–27.25) but had significantly less risk of adverse events (RR 0.38; 95% CI 0.2–0.73).The current guidelines recommend EET for BE with HGD or IMC (T1a) given that the risk lymph-node metastasis is 0% for patients with BE-HGD and close to 2% in those with IMC.[23]

(2) BE with LGD:

The traditional approach to BE with LGD has been surveillance at 6 months and then every 12 months if pathology is confirmed by a second pathologist. In recent years, there has been a shift toward favoring EET in cases of confirmed LGD. The AIM dysplasia trial was the first study comparing outcomes in LGD patients randomized to RFA *versus* sham ablation and following them for 1 year. Those who underwent RFA had a 5% risk of progressing to HGD as opposed to 14% in the sham ablation group.[19] In the SURF trial, 1.5% of LGD patients treated with RFA progressed to HGD at 3 years, as opposed to 26.5% in the surveillance group, with a number needed to treat of 4.[9] In a meta-analysis including 2746 patients, the RR of disease progression was lower in RFA group compared with surveillance (RR 0.14; CI 0.04–0.45, $p=0.001$) with a number needed to treat of 9.2.[24] Therefore, several gastroenterology societies recommend EET in LGD patients, especially those with confirmed and persistent disease (moderate level of evidence).[1,25–27]

(3) NDBE in selected high-risk patients:

NDBE carries a very low rate of progression to EAC of 0.3% per year.[3] Multiple trials evaluated RFA in successful eradication of NDBE. In a US multicenter prospective study of 70 patients who underwent RFA, 70% had CE-IM at 1 year, 98% at 2.5 years and 92% at 5 years.[28] In another multicenter study of 326 patients with NDBE undergoing ablation therapy, 76% had CE-IM at a mean follow up of 20 months.[29] Despite successful clinical trials in this subgroup of patients, routine EET in NDBE is not recommended due to costs, inability to achieve a 100% eradication rate, risk of recurrence of metaplasia and need for post ablation surveillance (low level of evidence).[1,27] However, certain NDBE patients are at high risk for progression to EAC and therefore, may benefit from preemptive ablation. As a matter of fact, BE length was consistently shown to be a predictor of progression to HGD/EAC.[30,31] In a multicenter outcomes study, the RR of progression to HGD/EAC was found to be increased by 28% for every 1 cm of NDBE.[32] Other considerations include family history of BE or EAC, and young age at BE diagnosis. More recently, Parasa and colleagues developed a validated model, the Progression in Barrett's Esophagus score, to stratify patients into low, intermediate and high risk for disease progression. Once again, male sex, length of BE, baseline LGD, and smoking were identified as predictors of progression.[33] Gastroenterologists should hence consider EET for NDBE on a case-by-case basis, for example, in a young male with long-segment BE, and family history for EAC.[34]

(4) Selected cases of BE with submucosal cancer:

Submucosal infiltration is classified according to depth with submucosa 1 (sm1) representing infiltration in the upper third, sm2 into the middle third and sm3 into the lower third of submucosa.[35] Up until a decade ago, the gold standard for T1b EAC was esophagectomy with lymph node dissection. Early surgical series, however, showed absence of lymph-node involvement in lesions limited to the upper third of the submucosa (sm1).[36,37] In 2008, Manner and colleagues showed that sm1 patients with well-differentiated tumors and no lymphovascular invasion can be treated by EMR. In this study, complete remission was achieved in 95% of cases (18/19) after 5.3 months and after a mean of 2.9 resections. Metachronous carcinomas were found in 28% of cases (5/19) during mean follow up of 62 months which were treated by EMR. Only 1 of the 19 patients was not tumor free after two EMR sessions.[38] The rate of lymph-node metastasis is 0–22% in sm1, 0–30% in sm2, and 20–70% in sm3 EAC.[39] The current guidelines suggest that EET can be considered in patients with T1b sm1 and favorable characteristics such as well-differentiated tumors and lack of lymphatic or vascular invasion.[1]

Contraindications to EET

There are very few absolute contraindications to EET and most are relative.

The general contraindications are:

(1) non-compliance with treatment regimen: EET requires multiple sessions and ongoing post-ablation surveillance. Inability to comply with treatment regimen translates to suboptimal outcomes;
(2) anticoagulant therapy: increases the risk of bleeding after EMR or RFA and hence should be stopped temporarily;
(3) prior radiation therapy: associated with poor healing and increased risk of stricture formation;[40]
(4) persistent reflux esophagitis: leads to poor response to EET and hence needs aggressive acid suppression by medical or surgical means.

Contraindications to ablation techniques

(1) Ablation should be performed on flat mucosa only. Inadvertent RFA over visible lesions instead of EMR may miss invasive cancer and cause inadequate eradication.
(2) RFA in the presence of esophageal varices: may cause unroofing of varices and delayed bleeding after the mucosal necrosis.[8]
(3) Presence of stricture or uneven surface: may lead to poor tissue contact and inadequate ablation with RFA. Cryospray is preferred in those situations.
(4) Cryospray is contraindicated in the presence of food in the stomach, which may clog the venting tube or when there is altered anatomy of stomach such as following gastric bypass, stomach stapling and gastrojejunostomy and in Marfan's syndrome.[41]

Contraindications to EMR

In addition to the general contraindications listed above, EMR of more than 50% of esophageal circumference should be avoided, as it leads to severe stricture formation.

Limitations of EET

While EET has revolutionized treatment of dysplastic BE and early EAC, its scope in the management of the majority of patients with BE is limited. First, all EET modalities are currently performed by advanced endoscopists, and general endoscopists do not get training in EET,[42] which makes this modality restricted to tertiary care centers. There remains a small but significant risk of occult disease which may not be addressed by EET. On another note, it is important to explore the concept of buried BE or submucosal intestinal metaplasia following ablation therapy. In this section, we review the various limitations of EET in patients with BE.

(1) EET is applicable in only a small group of patients:

While the prevalence of BE in the general population is difficult to ascertain, as most patients with BE are asymptomatic, it is estimated to be between 1% and 2% in general population and 5–15% in patients with gastroesophageal reflux symptoms.[2,43] The spectrum of BE disease varies from no dysplasia to advanced EAC. The majority of patients diagnosed with BE on index endoscopy have no dysplasia. LGD is diagnosed in about 10%, HGD in 3%, and EAC in 3% of patients presenting with BE during index endoscopy.[44] EET is beneficial in only a subset of patients with BE, that is, those with dysplasia. On the other end of the spectrum are patients with EAC in whom symptoms do not develop until circumferential involvement or significant penetration into the esophageal lumen occurs,[45] and therefore, are diagnosed at later stages of disease. In spite of BE surveillance and advances in endoscopy, only about 23.7% of EAC are diagnosed at stage I, 20.7% at stage II, 20.4% stage III, and 34.2% at stage IV disease.[46] Since the majority of patients are diagnosed at later stages with disease spread beyond the esophagus, EET is therapeutic in only a small fraction of patients presenting with EAC.

(2) Risk of occult disease in EET-eligible patients:

The esophagus has a rich blood supply and lymphatic drainage. It lacks serosa and is instead covered by loose connective tissue known as adventitia. These factors contribute to extra esophageal spread in early disease with lymph-node involvement seen in 0–2% of patients with IMC and 0–78% of patients with submucosal cancers.[39] The current staging studies available are not 100% accurate and carry a risk of missing occult disease. Staging *via* EUS is recommended once-distant metastatic disease is ruled out by

computed tomography/PET scan. The treatment regimen is determined based on the tumor invasion into esophageal wall, involvement of regional lymph nodes or presence of distant metastases.[47] While EUS is currently considered the most sensitive test for loco-regional staging of EAC, a meta-analysis of 19 international studies comparing EUS findings with surgical specimens found that the pooled sensitivity and specificity of EUS for T1a cancers was 0.85 (95% CI: 0.82–0.88), and 0.87 (95% CI: 0.84–0.90) respectively; and for T1b cancers, sensitivity 0.86 (95% CI: 0.82–0.89) and specificity of 0.86 (95% CI: 0.83–0.89).[47,48] In another study comparing pre-operative EUS findings in 107 patients who underwent esophagectomy for HGD/early EAC, 8.4% of the patients thought not to have lymph node involvement did have pN1 on surgical pathology.[49] These findings raise the possibility of residual lymph-node disease being untreated if these patients were to undergo EET alone. Hence, in patients presenting with HGD or early EAC, careful staging and multidisciplinary evaluation with endoscopists, surgeons and pathologists is necessary before EET is contemplated.

(3) Refractory disease:

EET is highly effective in eradication of BE; however, in a small percentage of patients, BE may be refractory to RFA or progress to a worse grade of dysplasia. Refractory disease is defined as the histological or endoscopic persistence of IM with or without dysplasia after RFA, or progression of disease while undergoing EET. Different cut-off points are used in various studies such as persistence of IM after three RFA sessions,[50] four RFA sessions,[51] or persistence of dysplasia for at least three RFA sessions.[52] The goal of EET is CE-IM and not CE-D, as the latter is associated with a higher rate of recurrences. Therefore, if there is no, or suboptimal, response to one ablative technique, alternative modalities should be tried. Also, in a small percentage of patients, progression to worse-grade disease can occur during EET.[53] Patients and endoscopists need to be aware of this possibility, and meticulous examination should be performed prior to each ablative session.

(4) Buried BE:

A concern associated with endoscopic ablation techniques is the potential persistence of metaplastic areas underneath the newly formed epithelial layer. This entity is known as 'buried metaplasia', 'buried glands', or subsquamous intestinal metaplasia, and is controversial due to its malignant potential. One hypothesis proposed is the inadequate RFA energy delivery leading to incomplete eradication of BE. Another theory proposes the development of new buried glands following ablation therapy.[54] The prevalence of buried metaplasia varied from 25.2% to 72% in some studies.[19,55] The prevalence appears to decrease after ablative therapy. In a systematic review, 0.9% (9/1004 patients) were found to have buried metaplasia after RFA, and 14% (135/953 patients) following PDT.[56] Approximately 20 cases of buried neoplasia have been reported after RFA from 3 months to 4 years.[57] However, the malignant potential of buried metaplasia is thought to be less than BE due to lack of exposure to gastric refluxate.[58]

(5) Recurrence of BE:

After successful CE-IM, recurrence of BE and dysplasia have been reported in many studies. In a pooled analysis, the recurrence of IM appears to be 4.8 per 100 patient- years (95% CI 3.8–5.9), and dysplasia 2.0 per 100 patient-years (95% CI 1.5–2.5).[59] The interval for recurrence also varies, with the highest risk in the first year compared with subsequent years. A meta-analysis reported that IM detection in the first year was 12% (95% CI 8–17%), in the second year, 7% (95% CI 4–11%), and in the third year, 3% (95% CI 1–7%).[60] HGD/EAC detection was 1% (95% CI 0–2%) in the first year after CE-IM compared with 0% per patient-year (95% CI 0–1%) in subsequent years.[60] Also, recurrences are more common after CE-D than CE-IM. In a recent meta-analysis of 40 studies including 4410 patients, with a total follow-up time of 12,976 patient-years, 4061 achieved CE-IM, and 349 CR-D only.[61] Dysplasia recurrence was found to be 5% in the CE-IM group and 12% in the CE-D group. In addition, CE-D patients were three times more likely to have BE with dysplasia recurrence (RR 2.8; 95% CI 1.7–4.6) as well as recurrence of HGD/EAC (RR 3.6; 95% CI 1.45–9.0). While recurrence is common, it is important to note that the majority of the recurrences are NDBE and progression from pre-treatment grading is rare. In a study based on 1634 patients observed for 2.4 ± 1.3 years following CE-IM, 86% (287/335) of the recurrences were NDBE or

indefinite for dysplasia, 6% (19/334) were LGD, and 4% (15/334) were HGD.[62] In most cases, recurrent disease is also amenable to EET, and CE-IM can be achieved.

Post-ablation surveillance intervals

As stated above, the timeline of recurrence has an important bearing on defining surveillance intervals. The current recommendation for patients with baseline HGD/IMC is to undergo surveillance endoscopies every 3 months for the first year, every 6 months in the second year, and annually thereafter after CE-IM. For those with baseline LGD, endoscopy every 6 months in the first year and annually thereafter is recommended.[1] Recently, Cotton and colleagues used data from the US RFA patient registry and UK National Halo Registry to develop a validated model that predicted incidence of neoplasia recurrence after achieving CE-IM by RFA.[63] A dysplastic recurrence risk of 2.9% per visit, which is associated with an estimated risk of 0.1% EAC, was then selected as the cut off to build newly proposed surveillance intervals. According to the model, the authors proposed patients with baseline HGD/IMC undergo surveillance endoscopies at 3 months, 6 months, 1 year, and annually thereafter, as well as those with baseline LGD at 1 year and 3 years after achieving CE-IM. These proposed intervals led to a 38% reduction in the number of surveillance endoscopies, thereby increasing cost effectiveness while not compromising on the very essence of surveillance which is the detection of recurrence of neoplastic lesions. In contrast, another study reported constant incidence rates of NDBE, dysplastic BE, and HGD/EAC during the post-ablation surveillance, with a conclusion that a widening of surveillance intervals requires more evidence before being considered standard practice.[64]

Conclusion

EET has revolutionized management of BE associated neoplasia, transitioning from radical esophagectomy, which carries very high mortality and morbidity, to endoscopic techniques involving ablation and resection of BE, and early EAC with a safer risk profile. EET is indicated in BE patients with dysplasia and IMC. Current research is focused on developing risk prediction models to identify BE patients who are at high risk for neoplastic progression so EET can be offered to them prior to development of neoplasia. In spite of excellent eradication rates, recurrences are common, and hence post-ablation surveillance is mandatory.

Acknowledgements

None.

Authors' contributions

All authors have contributed to designing the study, collecting the data, and drafting the manuscript. All authors approved the final version of the manuscript.

Funding

Prashanthi N. Thota is supported by NIH grants: U54CA163060 and P50CA150964. All other authors received no financial support.

Conflict of interest statement

The authors declare that there is no conflict of interest.

ORCID iD

Prashanthi N. Thota https://orcid.org/0000-0001-7179-4774

References

1. Shaheen NJ, Falk GW, Iyer PG, *et al.* ACG clinical guideline: diagnosis and management of Barrett's esophagus. *Am J Gastroenterol* 2016; 111: 30–50.

2. Ronkainen J, Aro P, Storskrubb T, *et al.* Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology* 2005; 129: 1825–1831.

3. Desai TK, Krishnan K, Samala N, *et al.* The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. *Gut* 2012; 61: 970–976.

4. Singh S, Manickam P, Amin AV, *et al.* Incidence of esophageal adenocarcinoma in Barrett's esophagus with low-grade dysplasia: a systematic review and meta-analysis. *Gastrointest Endosc* 2014; 79: 897–909.

5. Rastogi A, Puli S, El-Serag HB, *et al.* Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. *Gastrointest Endosc* 2008; 67: 394–398.

6. Singh T, Sanaka MR and Thota PN. Endoscopic therapy for Barrett's esophagus and early esophageal cancer: where do we go from here? *World J Gastrointest Endosc* 2018; 10: 165–174.
7. Salo JA, Salminen JT, Kiviluoto TA, *et al.* Treatment of Barrett's esophagus by endoscopic laser ablation and antireflux surgery. *Ann Surg* 1998; 227: 40–44.
8. Ma GK and Ginsberg GG. Radiofrequency ablation of Barrett's esophagus: patient selection, preparation, and performance. *Gastrointest Endosc Clin N Am* 2017; 27: 481–490.
9. Phoa KN, Van Vilsteren FG, Weusten BL, *et al.* Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. *JAMA* 2014; 311: 1209–1217.
10. Shaheen NJ, Overholt BF, Sampliner RE, *et al.* Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. *Gastroenterology* 2011; 141: 460–468.
11. Ackroyd R, Tam W, Schoeman M, *et al.* Prospective randomized controlled trial of argon plasma coagulation ablation vs. endoscopic surveillance of patients with Barrett's esophagus after antireflux surgery. *Gastrointest Endosc* 2004; 59: 1–7.
12. Manner H, May A, Miehlke S, *et al.* Ablation of nonneoplastic Barrett's mucosa using argon plasma coagulation with concomitant esomeprazole therapy (APBANEX): a prospective multicenter evaluation. *Am J Gastroenterol* 2006; 101: 1762–1769.
13. Manner H, May A, Kouti I, *et al.* Efficacy and safety of Hybrid-APC for the ablation of Barrett's esophagus. *Surg Endosc* 2016; 30: 1364–1370.
14. Ramay FH, Cui Q and Greenwald BD. Outcomes after liquid nitrogen spray cryotherapy in Barrett's esophagus-associated high-grade dysplasia and intramucosal adenocarcinoma: 5-year follow-up. *Gastrointest Endosc* 2017; 86: 626–632.
15. Canto MI, Shaheen NJ, Almario JA, *et al.* Multifocal nitrous oxide cryoballoon ablation with or without EMR for treatment of neoplastic Barrett's esophagus (with video). *Gastrointest Endosc* 2018; 88: 438e2–446e2.
16. Dunn JM, Mackenzie GD, Banks MR, *et al.* A randomised controlled trial of ALA vs. photofrin photodynamic therapy for high-grade dysplasia arising in Barrett's oesophagus. *Lasers Med Sci* 2013; 28: 707–715.
17. Pouw RE, Van Vilsteren FG, Peters FP, *et al.* Randomized trial on endoscopic resection-cap versus multiband mucosectomy for piecemeal endoscopic resection of early Barrett's neoplasia. *Gastrointest Endosc* 2011; 74: 35–43.
18. Draganov PV, Wang AY, Othman MO, *et al.* AGA Institute clinical practice update: endoscopic submucosal dissection in the United States. *Clin Gastroenterol Hepatol* 2019; 17: 16e1–25e1.
19. Shaheen NJ, Sharma P, Overholt BF, *et al.* Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med* 2009; 360: 2277–2288.
20. Pech O, May A, Manner H, *et al.* Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. *Gastroenterology* 2014; 146: 652–660.
21. Heitmiller RF, Redmond M and Hamilton SR. Barrett's esophagus with high-grade dysplasia. An indication for prophylactic esophagectomy. *Ann Surg* 1996; 224: 66–71.
22. Wu J, Pan YM, Wang TT, *et al.* Endotherapy versus surgery for early neoplasia in Barrett's esophagus: a meta-analysis. *Gastrointest Endosc* 2014; 79: 233e2–241e2.
23. Dunbar KB and Spechler SJ. The risk of lymph-node metastases in patients with high-grade dysplasia or intramucosal carcinoma in Barrett's esophagus: a systematic review. *Am J Gastroenterol* 2012; 107: 850–862.
24. Qumseya BJ, Wani S, Gendy S, *et al.* Disease progression in Barrett's low-grade dysplasia with radiofrequency ablation compared with surveillance: systematic review and meta-analysis. *Am J Gastroenterol* 2017; 112: 849–865.
25. Standards of Practice Committee, Wani S, Qumseya B, *et al.* Endoscopic eradication therapy for patients with Barrett's esophagus-associated dysplasia and intramucosal cancer. *Gastrointest Endosc* 2018; 87: 907–931.
26. Di Pietro M and Fitzgerald RC; BSG Barrett's guidelines working group. Revised British Society of Gastroenterology recommendation on the diagnosis andmanagement of Barrett's oesophagus with low-grade dysplasia. *Gut* 2018; 67: 392–393.
27. Sharma P, Shaheen NJ, Katzka D, *et al.* AGA clinical practice update on endoscopic treatment of Barrett's esophagus with dysplasia and/or early cancer: expert review. *Gastroenterology* 2020; 158: 760–769.
28. Fleischer DE, Overholt BF, Sharma VK, *et al.* Endoscopic ablation of Barrett's esophagus: a multicenter study with 2.5-year follow-up. *Gastrointest Endosc* 2008; 68: 867–876.

29. Lyday WD, Corbett FS, Kuperman DA, *et al.* Radiofrequency ablation of Barrett's esophagus: outcomes of 429 patients from a multicenter community practice registry. *Endoscopy* 2010; 42: 272–278.

30. Solanky D, Krishnamoorthi R, Crews N, *et al.* Barrett esophagus length, nodularity, and low-grade dysplasia are predictive of progression to esophageal adenocarcinoma. *J Clin Gastroenterol* 2019; 53: 361–365.

31. Pohl H, Wrobel K, Bojarski C, *et al.* Risk factors in the development of esophageal adenocarcinoma. *Am J Gastroenterol* 2013; 108: 200–207.

32. Anaparthy R, Gaddam S, Kanakadandi V, *et al.* Association between length of Barrett's esophagus and risk of high-grade dysplasia or adenocarcinoma in patients without dysplasia. *Clin Gastroenterol Hepatol* 2013; 11: 1430–1436.

33. Parasa S, Vennalaganti S, Gaddam S, *et al.* Development and validation of a model to determine risk of progression of Barrett's esophagus to neoplasia. *Gastroenterology* 2018; 154: 1282–1289.

34. Lightdale CJ. Radiofrequency ablation for nondysplastic Barrett's esophagus: certainly not for all. *Gastrointest Endosc* 2014; 80: 873–876.

35. Zeki SS, Bergman JJ and Dunn JM. Endoscopic management of dysplasia and early oesophageal cancer. *Best Pract Res Clin Gastroenterol* 2018; 36–37: 27–36.

36. Buskens CJ, Westerterp M, Lagarde SM, *et al.* Prediction of appropriateness of local endoscopic treatment for high-grade dysplasia and early adenocarcinoma by EUS and histopathologic features. *Gastrointest Endosc* 2004; 60: 703–710.

37. Westerterp M, Koppert LB, Buskens CJ, *et al.* Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. *Virchows Arch* 2005; 446: 497–504.

38. Manner H, May A, Pech O, *et al.* Early Barrett's carcinoma with "low-risk" submucosal invasion: long-term results of endoscopic resection with a curative intent. *Am J Gastroenterol* 2008; 103: 2589–2597.

39. Cho JW, Choi SC, Jang JY, *et al.* Lymph node metastases in esophageal carcinoma: an endoscopist's view. *Clin Endosc* 2014; 47: 523–529.

40. Sanfilippo NJ, Hsi A, DeNittis AS, *et al.* Toxicity of photodynamic therapy after combined external beam radiotherapy and intraluminal brachytherapy for carcinoma of the upper aerodigestive tract. *Lasers Surg Med* 2001; 28: 278–281.

41. Greenwald BD and Dumot JA. Cryotherapy for Barrett's esophagus and esophageal cancer. *Curr Opin Gastroenterol* 2011; 27: 363–367.

42. Komanduri S, Muthusamy VR and Wani S. Controversies in endoscopic eradication therapy for Barrett's esophagus. *Gastroenterology* 2018; 154: 1861e1–1875e1.

43. Thrift AP. Barrett's esophagus and esophageal adenocarcinoma: how common are they really? *Dig Dis Sci* 2018; 63: 1988–1996.

44. Parasa S, Desai M, Vittal A, *et al.* Estimating neoplasia detection rate (NDR) in patients with Barrett's oesophagus based on index endoscopy: a systematic review and meta-analysis. *Gut* 2019; 68: 2122–2128.

45. Bird-Lieberman EL and Fitzgerald RC. Early diagnosis of oesophageal cancer. *Br J Cancer* 2009; 101: 1–6.

46. Tramontano AC, Chen Y, Watson TR, *et al.* Esophageal cancer treatment costs by phase of care and treatment modality, 2000–2013. *Cancer Med* 2019; 8: 5158–5172.

47. DaVee T, Ajani JA and Lee JH. Is endoscopic ultrasound examination necessary in the management of esophageal cancer? *World J Gastroenterol* 2017; 23: 751–762.

48. Thosani N, Singh H, Kapadia A, *et al.* Diagnostic accuracy of EUS in differentiating mucosal versus submucosal invasion of superficial esophageal cancers: a systematic review and meta-analysis. *Gastrointest Endosc* 2012; 75: 242–253.

49. Bergeron EJ, Lin J, Chang AC, *et al.* Endoscopic ultrasound is inadequate to determine which T1/T2 esophageal tumors are candidates for endoluminal therapies. *J Thorac Cardiovasc Surg* 2014; 147: 765–771; discussion 771–773.

50. Komanduri S, Kahrilas PJ, Krishnan K, *et al.* Recurrence of Barrett's esophagus is rare following endoscopic eradication therapy coupled with effective reflux control. *Am J Gastroenterol* 2017; 112: 556–566.

51. Trindade AJ, Inamdar S, Kothari S, *et al.* Feasibility of liquid nitrogen cryotherapy after failed radiofrequency ablation for Barrett's esophagus. *Dig Endosc* 2017; 29: 680–685.

52. Sengupta N, Ketwaroo GA, Bak DM, *et al.* Salvage cryotherapy after failed radiofrequency ablation for Barrett's esophagus-related dysplasia

is safe and effective. *Gastrointest Endosc* 2015; 82: 443–448.

53. Thota PN, Arora Z, Dumot JA, *et al.* Cryotherapy and radiofrequency ablation for eradication of Barrett's esophagus with dysplasia or intramucosal cancer. *Dig Dis Sci* 2018; 63: 1311–1319.
54. Kohoutova D, Haidry R, Banks M, *et al.* Esophageal neoplasia arising from subsquamous buried glands after an apparently successful photodynamic therapy or radiofrequency ablation for Barrett's associated neoplasia. *Scand J Gastroenterol* 2015; 50: 1315–1321.
55. Zhou C, Tsai TH, Lee HC, *et al.* Characterization of buried glands before and after radiofrequency ablation by using 3-dimensional optical coherence tomography (with videos). *Gastrointest Endosc* 2012; 76: 32–40.
56. Gray NA, Odze RD and Spechler SJ. Buried metaplasia after endoscopic ablation of Barrett's esophagus: a systematic review. *Am J Gastroenterol* 2011; 106: 1899–1908.
57. Castela J, Serrano M, Ferro SM, *et al.* Buried Barrett's esophagus with high-grade dysplasia after radiofrequency ablation. *Clin Endosc* 2019; 52: 269–272.
58. Basavappa M, Weinberg A, Huang Q, *et al.* Markers suggest reduced malignant potential of subsquamous intestinal metaplasia compared with Barrett's esophagus. *Dis Esophagus* 2014; 27: 262–266.
59. Fujii-Lau LL, Cinnor B, Shaheen N, *et al.* Recurrence of intestinal metaplasia and early neoplasia after endoscopic eradication therapy for Barrett's esophagus: a systematic review and meta-analysis. *Endosc Int Open* 2017; 5: E430–E449.
60. Sawas T, Iyer PG, Alsawas M, *et al.* Higher rate of Barrett's detection in the first year after successful endoscopic therapy: meta-analysis. *Am J Gastroenterol* 2018; 113: 959–971.
61. Sawas T, Alsawas M, Bazerbachi F, *et al.* Persistent intestinal metaplasia after endoscopic eradication therapy of neoplastic Barrett's esophagus increases the risk of dysplasia recurrence: meta-analysis. *Gastrointest Endosc* 2019; 89: 913–925.
62. Pasricha S, Bulsiewicz WJ, Hathorn KE, *et al.* Durability and predictors of successful radiofrequency ablation for Barrett's esophagus. *Clin Gastroenterol Hepatol* 2014; 12: 1840–1847.
63. Cotton CC, Haidry R, Thrift AP, *et al.* Development of evidence-based surveillance intervals after radiofrequency ablation of Barrett's esophagus. *Gastroenterology* 2018; 155: 316e6–326e6.
64. Sami SS, Ravindran A, Kahn A, *et al.* Timeline and location of recurrence following successful ablation in Barrett's oesophagus: an international multicentre study. *Gut* 2019; 68: 1379–1385.