Review Article

Goals of endoscopic eradication therapy in Barrett's esophagus: a narrative review

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Abstract: Barrett's esophagus is a premalignant condition, and endoscopic eradication therapy is indicated upon development of early neoplasia. Therapy consists of endoscopic resection for visible lesions, if present, followed by endoscopic ablation for remaining flat Barrett's epithelium. Since Barrett's esophagus with early neoplasia in itself is asymptomatic disease, the ultimate goal of endoscopic eradication therapy is to prevent progression to advanced cancer: a disease stage with limited treatment options and a poor prognosis. The preventive nature of endoscopic treatment may give rise to debate about the preferred endpoint to pursue. Establishment of a careful balance between the benefits of endoscopic eradication therapy against its risks, such as complications and other adverse events, may help to define the optimum endpoint for each individual patient. To date, various endpoints have been used in regular practice and different endpoints are used in clinical studies. The most important differences between these endpoints are whether all visible Barrett's epithelium is eradicated or all dysplasia and cancer; and whether the endpoint is assessed on endoscopic examination only or with histologic confirmation. In this narrative review, we aim to evaluate these different endpoints of endoscopic eradication therapy with potential advantages and limitations, and present three clinical vignettes each with a different suggestion for an appropriate treatment endpoint.

Keywords: Barrett's esophagus; Barrett's dysplasia; Barrett's neoplasia; endoscopic eradication therapy; radiofrequency ablation

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Introduction

Barrett's esophagus (BE) is a premalignant condition characterized by the replacement of normal squamous epithelium in the distal esophagus with columnar-lined epithelium with specialized intestinal metaplasia (IM). Esophageal adenocarcinoma (EAC) is thought to develop through a stepwise sequence, from non-dysplastic BE progressing to low-grade dysplasia (LGD), high-grade dysplasia (HGD), early EAC (T1) and eventually advanced EAC (T2+) (1). Considering the poor prognosis of advanced EAC despite invasive treatments such as chemoradiation or esophagectomy with or without (neo)adjuvant therapy (2,3), endoscopic eradication therapy (EET) for BE is performed with the main objective to prevent advanced disease stages

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and ultimately death.

EET involves ablation of all flat BE epithelium, preceded by endoscopic resection (ER) for visible lesions, if present. Currently, radiofrequency ablation (RFA) is the most widely used ablative modality. For patients with non-dysplastic BE, the risk of malignant degeneration is low, with an estimated annual progression rate to cancer of 0.3–0.5% per year (4,5). Consequently, these patients are subjected to endoscopic surveillance every 3–5 years instead of EET (6,7). Once dysplasia develops, either LGD or HGD, the risk for progression to EAC is considerable. For LGD confirmed by an expert gastrointestinal pathologist the risk of progression to HGD or adenocarcinoma is 5–13% per year (8-10), whereas for HGD the risk for progression to cancer is 10-19% per year (1,11). Given these risks, BE containing LGD or worse is considered an indication for EET (6,7). In addition, BE remaining after ER of a lesion containing HGD or early EAC is also identified as an indication for EET in order to prevent metachronous lesions (12-15), even if the residual epithelium is non-dysplastic (6,7).

It is important to realize that early BE neoplasia is usually asymptomatic and therefore the main goal of treatment is to prevent future progression to advanced EAC. This "prophylactic" nature of EET may give rise to debate about the preferred endpoint. Should we, for instance, always initiate RFA after ER of an early BE cancer, or may eradication of visible neoplasia or dysplasia be sufficient in selected patients? Once we decide to initiate RFA, should we strive for complete eradication of all endoscopically visible BE, or should we continue until every single metaplastic cell is ablated? In the following narrative review, we aim to evaluate available literature and discuss the optimum goal of EET. At the end of this paper, we will discuss three clinical scenarios based on three medical vignettes, all three with a different appropriate treatment endpoint.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/aoe-2020-etbe-04).

Weighing the benefits and risks of endoscopic eradication therapy

In considering EET for BE-related neoplasia, its benefits should be carefully balanced against the risks. The main benefit of EET is the prevention of advanced cancer, e.g., the situation in which a patient that would have progressed to advanced, symptomatic cancer or death if he or she was not treated with EET, did not progress to advanced cancer upon EET. The chance of achieving this benefit upon EET is determined by a mixture of disease related factors, efficacy of treatment, and a patient's life expectancy.

The most important disease related factor is the grade of the histologic abnormalities. For flat BE, the risk of progression is 10–19% for HGD and 5–13% for LGD per patient-year (1,8-11). When the diagnosis of LGD is confirmed in subsequent endoscopies, the risk of malignant progression is even believed to be increased (8,16). Remaining BE after ER for a visible lesion has shown to progress in 11–30% of cases during 3 years of follow-up (FU) (12-15). In addition, it has been shown that longer BE segments are associated with a higher risk for progression (10,17-21), with a reported risk ratio (RR) of 1.11 (95% CI: 1.01–1.20) per cm increase in length (10). Other disease related risk factors for neoplastic progression include known duration of BE of ≥10 years (RR 3.2; 95% CI: 1.3–7.8), and presence of reflux esophagitis (RR 3.5; 95% CI: 1.3–9.5) (10).

The potential benefit of EET logically also depends on its efficacy. RFA, currently considered the gold standard for endoscopic ablation, is highly effective and may successfully eradicate BE in 77–93% of patients (8,11,22,23), with sustained eradication of neoplasia during ≥5 years of FU in 93–96% of patients (24,25). Still, some patients treated with RFA will not achieve complete eradication (7–23%) or will develop recurrent neoplasia during FU (4–7% of the successfully treated patients) (8,11,22-25).

Finally, the life expectancy of the individual patient plays an important role in his or her chance to benefit from EET. Even in HGD, progression to advanced cancer may take years, so a patient has to live "long enough" to experience benefits of treatment. A 50-year-old, fit patient with LGD has a considerably higher life-time risk of developing advanced EAC as compared to a 85-year-old patient with significant comorbidity with the same degree of dysplasia.

Ultimately, potential benefits of EET should be balanced against the risk of complications and other adverse events. Even although RFA is generally safe and most complications are mild, treatment is not free of adverse effects. Esophageal stricture is the most common complication (4–14%), which is usually resolved after 2–3 endoscopic dilatations (8,11,22,26-29), but might require multiple dilation sessions in individual patients. Furthermore, retrosternal pain and/or dysphagia requiring analgesics may occur after RFA, with a typical duration of 4–8 days (11,30). Other possible adverse events include bleeding, laceration, and perforation (26-28). Ablative therapy is also associated with the possible risk of persistent

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Table 1 Overview of landmark studies on efficacy of radiofrequency ablation in Barrett's esophagus

First author	Year of publication	Study design	Treatment	Patients, n	BE segment	Median maximum BE length, cm	Baseline histology, n (ND/LGD/HGD/EAC)	Primary endpoints, %
Shaheen	2009	Prospective, multicenter, randomized	RFA *vs.* sham procedure	127 (84 *vs.* 43)	Flat BE	4.6 *vs.* 5.3	–/64/63/–	CE-D 86.0 CE-IM 77.4
Gupta	2013	Retrospective, multicenter	RFA +/– ER	448	BE +/– lesion	4.1	63/67/269/49	CE-IM 56.0
Haidry	2013	Retrospective, multicenter	RFA +/– ER	335	BE +/– lesion	5.8	–/12/241/82	CE-D 81.0 CE-BE 62.0
Phoa	2014	Prospective, multicenter, randomized	RFA *vs.* endoscopic surveillance	136 (68 *vs.* 68)	Flat BE	4.0 *vs.* 4.0	–/136/–/–	CE-D 92.6 CE-IM 88.2
Phoa	2016	Prospective, multicenter	RFA +/– ER	132	BE +/– lesion	6.0	51/45/36/–	CE-Neo 92.0 CE-IM 87.0

BE, Barrett's esophagus; CE-BE, complete eradication of Barrett's esophagus; CE-D, complete eradication of dysplasia; CE-IM, complete eradication of intestinal metaplasia; CE-Neo, complete eradication of neoplasia; EAC, esophageal adenocarcinoma; ER, endoscopic resection; HGD, high-grade dysplasia; LGD, low-grade dysplasia; ND, no dysplasia; RFA, radiofrequency ablation.

subsquamous Barrett's glands under an overlying layer of neosquamous epithelium, so called buried BE. Although these metaplastic glands may progress to cancer (31), the prevalence of buried BE after RFA is low (0.1%) (32), and the risk of malignant degeneration is believed to be lower compared to unablated epithelium (33). Another important disadvantage of EET are the high costs, which is partly due to the fact that multiple treatment endoscopies are typically required.

The balance between these benefits and risks may determine whether or not EET should be initiated, and may also help to define the optimum endpoint of EET. Although RFA is the most widely adopted ablative modality, other techniques are available, such as argon plasma coagulation (APC) and cryotherapy (34,35). Point estimates for safety, efficacy, or durability may be slightly different for APC and cryotherapy as comparted to RFA, but the same reasoning as outlined in the current paper could be followed to estimate optimum endpoints for that particular technique.

Endpoints for endoscopic eradication therapy

In the current literature on endoscopic eradication of BE-related neoplasia, various endpoints have been used in different studies (*Table 1*) with two flavors: a complete eradication of dysplasia and cancer; or a complete eradication of the entire Barrett's epithelium (*Table 2*). Both endpoints may be assessed either endoscopically (i.e., absence of visible lesions; or absence of all visible BE); or both endoscopically and histologically (i.e., absence of all dysplasia/cancer on random biopsies; or absence of IM on all random biopsies).

Complete eradication of intestinal metaplasia (CE-IM) is the most widely used endpoint in the current literature. In case of CE-IM, all visible BE is endoscopically eradicated with absence of IM on random biopsies from the neosquamous epithelium (NSE) and/or just below the neosquamocolumnar junction (8,11,27,28,36,37). However, random biopsies may be associated with a risk of sampling error and therefore not provide a truly reliable reflection of potential persisting abnormalities. Moreover, the clinical relevance of persisting (buried) IM in the NSE or persisting IM in a normal appearing cardia may be questioned.

CE-BE may therefore be used as an alternative endpoint, provided that all visible Barrett's epithelium is eradicated. Careful endoscopic inspection is of paramount importance for this endpoint. In contrast to CE-IM, CE-BE is assessed endoscopically without histologic confirmation. According to this definition persisting IM in a cardia which is endoscopically normal appearing, is still considered as success (22,35).

An endpoint which is frequently used in endoscopic

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Table 2 Definitions of endpoints

	Complete eradication of dysplasia	Complete eradication of all visible BE
Endoscopic evaluation	**CE-VL "Complete eradication of all visible lesions"**	**CE-BE "Complete eradication of all BE"**
	Complete endoscopic remission of all visible lesions, with only flat BE **remaining**	Complete endoscopic remission of all visible Barrett mucosa. Patients with persisting IM in the cardia are considered as success under this **definition**
Endoscopic + histologic evaluation	**CE-D "Complete eradication of dysplasia"**	**CE-IM "Complete eradication of IM"**
	Random biopsies from the tubular esophagus and cardia show no more dysplasia, independent of whether residual BE **persists**	Complete endoscopic and histologic remission of all visible IM, confirmed in random biopsies from tubular esophagus and **cardia**

BE, Barrett's esophagus; IM, intestinal metaplasia.

studies is complete eradication of dysplasia (CE-D). This applies to the situation where all dysplasia is endoscopically eradicated and random biopsies of remaining BE or from NSE are negative for dysplasia or cancer (8,11,28,36,37). An important limitation of this endpoint is that dysplasia in the remaining BE can easily be missed due to the risk of sampling error.

Finally, we want to introduce an alternative endpoint for EET for specific patient groups: complete eradication of visible lesions (CE-VL). This refers to the condition where all visible lesions are endoscopically eradicated by means of ER, while remaining flat BE (with or without dysplasia) may persist (38).

Goals for endoscopic eradication therapy

In our opinion, the final goal of EET in BE-related neoplasia depends on the benefit-risk balance of an individual patient. We will now provide three medical vignettes each with the suggestion for an appropriate endpoint. These vignettes will serve as a framework for a discussion of the underlying literature.

Medical vignette 1

An upper endoscopy was performed in a 52-year-old, fit male patient with complaints of dyspepsia, showing a C3M4 BE with a visible nodular lesion which was radically removed by means of endoscopic mucosal resection (EMR). Histopathologic assessment of the ER specimen showed a T1m3 cancer, and random biopsies of the residual flat BE contained HGD.

Given the reported risk of metachronous lesions of 11–30% in the remaining Barrett's segment regardless of the presence of dysplasia (12-15), the presence of HGD in the residual flat BE, and the anticipated long life-expectancy in this patient, it might be best to strive for complete eradication of all visible BE by means of RFA. When RFA was introduced in 2008, the effects of treatment were assessed endoscopically by absence of visible BE with histological confirmation of absence of IM in random biopsies from NSE and cardia. Over recent years, most guidelines have dropped the need for NSE biopsies, since more and more studies showed that any abnormal findings such as buried BE, are uncommon and are of low clinical relevance (22,32,39,40). Thus, in terms of the optimal endpoint for the tubular esophagus, endoscopic assessment that confirms absence of visible BE would be sufficient.

Assessment of an "adequately treated" cardia is more complicated. The key question is whether a histologic confirmation of absence of IM by random cardia biopsies (i.e., CE-IM) is essential or whether endoscopic inspection with absence of BE (i.e., CE-BE) will be sufficient. While in both situations all visible Barrett's epithelium is eradicated, persisting IM in a normal appearing cardia is considered as treatment success under the definition of CE-BE.

At the level of the esophagogastric junction, adequate endoscopic assessment of a complete eradication of BE may be challenging. It may be hard to distinguish a small persisting rim of Barrett's epithelium (i.e., 5–10 mm) from a normal squamocolumnar junction by endoscopic inspection alone. Moreover, an adequate inspection for the presence of visible abnormalities requires careful endoscopic inspection in both antegrade and retroflexed position, which is difficult

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for less experienced endoscopists. In addition, a clear definition of an "endoscopically normal" z-line is lacking, and the assessment is therefore dependent on the discretion and experience of the endoscopist. Obtaining random biopsies just below the neo-squamocolumnar junction may overcome these limitations and provide a more reproducible and accurate endpoint. On the other hand, random biopsies from the cardia have an inevitable risk of sampling error which still introduces heterogeneity. Most importantly, the clinical relevance of IM in random cardia biopsies, even if a rim of BE persists, is subject to debate. It is not an uncommon phenomenon, being reported in 11–35% of patients treated with RFA (22,24,25,29,41,42). The finding of persisting cardia IM could however not be reproduced in 66–89% of patients during a median of 3–5 FU endoscopies within 2–6 years (22,24,25,42). In addition, patients with persisting IM in the cardia do not seem to have a higher risk for malignant progression. A recent retrospective cohort study observed 124 patients with cardia IM in an endoscopically normal appearing cardia after EET. During median 4 years of FU, none of these 124 patients progressed to neoplasia as compared to 38 of the 1,030 (4%) patients without persisting cardia IM in the remaining cohort (42). Of note, cardia IM may also be found in 4–18% in healthy individuals without BE (43-48), which is not considered pre-malignant, and it is generally accepted that this is not an indication for routine FU (49,50).

Although these data seem to support the perception that IM in the cardia is clinically irrelevant, some important issues main unsolved. The studies that reported FU rates after IM all were performed in expert centers, and it is unknown whether outcomes will be comparable in less experienced centers. Furthermore, there are no studies that compare a cohort where patients were sampled with a cohort without sampling. This is important, since one may argue that performing biopsies forces the endoscopists to look longer and better. On the other hand, obtaining high-quality cardia biopsies is an art on its own and one may question whether we want to advice biopsies, not for the histological outcomes, but solely to compensate for inadequate inspection.

All in all, we feel that we cannot (yet) recommend to abandon random cardia biopsies. In our country, random cardia biopsies are obtained during the first FU endoscopy upon eradication of BE to confirm the completeness of EET. In case these cardia biopsies show persisting IM, one additional focal RFA is performed at the level of the cardia. This is based on expert opinion and there is no data to support this strategy. During subsequent FU, random cardia biopsies are not repeated, but inspection is leading. In case of visible abnormalities, targeted biopsies or direct ER is performed. This treatment strategy is a balance between the fact that persisting IM in the cardia most likely has no malignant potential and the fact that residual Barrett's epithelium is easily missed if the cardia is merely assessed endoscopically.

As a side note, if the esophagus after RFA repeatedly regenerates with BE and not with squamous epithelium, it may be justified to adjust the desired endpoint of EET. Predictive factors for a poor response after RFA include regeneration of a prior ER scar with BE, increasing baseline BE length, presence of reflux esophagitis, pre-treatment esophageal narrowing and a higher BMI (28,51,52). Suppose the ER scar of this 52-year-old, male patient with remaining C3M4 BE is completely regenerated with Barrett's mucosa and we perform one circumferential RFA treatment after which C3M3 BE persists under double douse PPI. We believe that cessation of EET should strongly be considered at this point. Upon a finding of poor squamous regression after the first RFA, the chance of obtaining a complete eradication of BE is much lower than initially estimated (52). In these cases, CE-D or CE-VL might emerge early during treatment as an acceptable finish line for endoscopic therapy.

Medical vignette 2

A 68-year-old, otherwise healthy male patient with long-standing severe complaints of gastroesophageal reflux disease, was diagnosed with a grade C reflux esophagitis according to LA Classification (53). High dose PPI was prescribed and 2 months later, the esophagitis was completely healed and a C10M11 flat type BE was identified. Initially, no dysplasia was found on random biopsies and patient entered endoscopic surveillance. During the third surveillance endoscopy, a visible nodular lesion was detected which was removed by means of EMR. The ER specimen showed a T1m2 EAC, and random biopsies of the residual flat BE contained no dysplasia. During consecutive FU, both the ER scar and all biopsies sites were completely regenerated with Barret's mucosa.

To prevent metachronous lesions in the remaining non-dysplastic Barrett's segment, EET would consist of RFA for this patient (6,7). The main concern here is the chance of successful RFA. Although a considerable proportion of patients with long-segment BE will achieve CE-BE after RFA, this treatment is more likely to fail in these

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patients (28,52). Moreover, in this particular patient the prior ER scar regenerated with BE and not with squamous epithelium, which is also a strong predictive factor for a poor response to RFA (51,52). It is important to realize that the burden of RFA treatment may be significant, especially in patients with a long-segment BE. In order to reach CE-BE, longer Barrett's segments may require more RFA sessions and a prolonged treatment time (27,28) with a higher risk for esophageal stenosis. Therefore, CE-D may be a valid alternative in selected patients with non-dysplastic residual BE.

Upon CE-D, endoscopic surveillance remains essential to detect neoplastic progression at an early stage, still allowing for endoscopic treatment with curative intent. Careful inspection of the BE segment by a dedicated endoscopist, preferably in the setting of a Barrett's expert center is warranted (54), with targeted biopsies from visible abnormalities if present, and random biopsies according to the Seattle protocol. If during FU flat dysplasia develops, especially if this finding is repeated on a subsequent endoscopy, initiation of RFA should again be discussed with the patient, taking into consideration the age reached by the patient when dysplasia is detected, and the patient's comorbidity at that moment in time.

Medical vignette 3

A 74-year-old male patient with severe comorbidity (i.e., diabetes, hypertension and renal insufficiency requiring hemodialysis) was referred for upper endoscopy after complaints of heartburn that did not respond to high dose PPI. Patient was diagnosed with C4M7 BE containing a T1m2 cancer which was radically removed by EMR. A C3M7 BE remained with HGD in random biopsies.

In patients with significant comorbidity and a limited life expectancy, we think that eradication of cancer may be preferred over obtaining a complete eradication of BE or dysplasia. In this particular patient, we would be very reluctant to initiate RFA. Instead, we would restrict EET to ER of visible neoplastic lesions only. In general, in patients who underwent ER for neoplasia in BE, metachronous lesions developed in the residual flat BE in up to 30% during the first 3 years (12-15). However, the patient described above might simply not live long enough to become symptomatic of an advanced cancer that at this moment still has to arise from a new metachronous lesion; a process that will take several years. Therefore, a much higher recurrence and/or progression risk may be accepted depending on age and severity of comorbidity.

This is supported by a large retrospective cohort study that included 963 patients who underwent an ER for mucosal cancer. During a mean FU of 56 months 140 patients (15%) developed a neoplastic recurrence, which was curatively treated endoscopically in 82% (115/140). Of the patients with a neoplastic recurrence, 15% (21/140) were considered to have failed endoscopic therapy, after which they were referred to surgery (n=14), continued with non-curative endoscopic treatment (n=6), died from metastatic disease (n=1) or were lost to follow-up (n=1) (14). Similar results were seen in a recent retrospective cohort study showing that none of 95 patients, who were not additionally treated after ER for varying reasons, progressed to advanced cancer during a median FU of 25 months. Overall, 17 patients (18%) progressed to either HGD or low-risk EAC (annual progression risk of 8%), of whom all were successfully treated endoscopically with either ER for a visible lesion (14/17) or ablation for flat HGD (3/17) (38).

One step further, in some patients we may also decide to perform no further follow-up at all. As an example, suppose the 74-year-old patient with C4M7 BE has a colon cancer pT3N2M1 with limited treatment options. In that case, there is a substantial chance that this patient will die from the consequences of the colon cancer rather than from potential development of metachronous dysplasia, that will progress to advanced cancer. Discontinuing endoscopic surveillance may then emerge as a justifiable alternative, and in this particular patient one might even debate the usefulness of the ER of the index early cancer. In the aforementioned retrospective study following 95 patients who were treated with ER monotherapy, endoscopic surveillance was stopped in 62 patients (65%) due to comorbidity and anticipated limited life-expectancy. During the following median 44 months after endoscopic surveillance was stopped, no symptomatic advanced EAC or tumor-related death occurred among these 62 patients (38).

Conclusion and recommendations

EET is performed with the main goal to prevent progression to advanced cancer and related death. Given the prophylactic nature of this treatment, we believe that it is essential to carefully balance the benefits of EET (i.e., prevention of progression to advanced cancer) against its risks (i.e., complications and adverse events) for each

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individual patient.

In patients with a significant risk of metachronous lesions and considerable life-expectancy, we believe that the anticipated success of EET outweighs its associated risks. Therefore, we recommend to strive for complete eradication of all endoscopically visible BE, and to obtain random biopsies from the normal appearing cardia after EET, since residual Barrett's epithelium at this region is easily missed.

In cases where less than half of the BE regenerates with squamous epithelium after a single RFA treatment, the likelihood of achieving CE-BE is decreased (52) and an adjustment of the pursued endpoint of EET may be considered (i.e., CE-D or CE-VL). One step further, we believe it may be even justified to withhold any RFA treatment if non-dysplastic BE persists after ER of a visible lesion, in patients who are expected to have a poor response to RFA and/or are at high risk for stenosis (i.e., long Barrett segments with persistent reflux esophagitis). In these patients, eradication of all dysplasia with subsequent endoscopic surveillance may be a valid alternative, since careful endoscopic inspection may enable the detection of BE-related neoplasia at an early stage with further endoscopic treatment still possible.

Finally, in patients with a limited life-expectancy it may be best to strive for eradication of visible neoplasia by means of ER, with the choice for subsequent endoscopic surveillance depending on age and severity of comorbidity. These patients will then still benefit from EET in terms of reducing the risk of advanced cancer stages, but will not be exposed to the substantial burden associated with RFA.

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