Threshold evaluation for optimal number of endoscopic treatment sessions to achieve complete eradication of Barrett's metaplasia

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ABSTRACT

Background Endoscopic eradication therapy (EET) is the standard of care for Barrett's esophagus (BE)-associated neoplasia. Previous data suggest the mean number of EET sessions required to achieve complete eradication of intestinal metaplasia (CE-IM) is 3. This study aimed to define the threshold of EET sessions required to achieve CE-IM.

Methods The TREAT-BE Consortium is a multicenter outcomes cohort including prospectively enrolled patients with BE undergoing EET. All patients achieving CE-IM were included. Demographic, endoscopic, and histologic data were recorded at treatment onset along with treatment details and surveillance data. Kaplan–Meier analysis was performed to define a threshold of EET sessions, with 95%CI, required to achieve CE-IM. A secondary analysis examined predictors of incomplete response to EET using multiple logistic regression and recurrence rates.

Results 623 patients (mean age 65.2 [SD 11.6], 79.6% male, 86.5% Caucasian) achieved CE-IM in a mean of 2.9 (SD 1.7) EET sessions (median 2) and a median total observation period of 2.7 years (interquartile range 1.4–5.0). After three sessions, 73% of patients achieved CE-IM (95% CI 70%–77%). Age (odds ratio [OR] 1.25, 95%CI 1.05–1.50) and length of BE (OR 1.24, 95%CI 1.17–1.31) were significant predictors of incomplete response.

Conclusion The current study found that a threshold of three EET sessions would achieve CE-IM in the majority of patients. Alternative therapies and further diagnostic testing should be considered for patients who do not have significant response to EET after three sessions.

Introduction

Barrett's esophagus (BE) is the replacement of stratified squamous epithelium with metaplastic columnar epithelium in the distal esophagus. BE is the only known precursor condition for esophageal adenocarcinoma and portends a 30–40-fold higher risk [1]. BE-associated neoplasia in thought to develop in a stepwise fashion from low grade dysplasia (LGD), high grade dysplasia (HGD), and intramucosal carcinoma to invasive esophageal adenocarcinoma [2–5]. Endoscopic eradication therapy (EET) of BE-associated neoplasia, including endoscopic mucosal resection (EMR) and radiofrequency ablation (RFA), is the current standard of care for treatment of BE-associated neoplasia [6–10]. EET has evolved extensively since inception, and recent studies have shown a > 90 % rate of complete eradication of dysplasia and complete eradication of intestinal metaplasia (CE-IM) [11–14]. However, the exact number of EET sessions required to achieve CE-IM is unclear and is likely to vary significantly depending on several patient and endoscopic factors. Previous studies have suggested that CE-IM should be achieved within three EET sessions and that the requirement for more than three EET sessions should be considered an incomplete response to treatment [15, 16]. We have previously demonstrated that incomplete response to EET can be attributed to uncontrolled reflux burden, warranting further investigation with physiologic testing [17].

The number of EET sessions required to achieve CE-IM has significant implications. In addition to the risks and costs of additional sessions for the patient, there is a significant resource burden to the healthcare system. Hence, it is important to understand the optimal number of EET sessions by which CE-IM should be achieved and identify modifiable risk factors in patients who cross this threshold. The primary aims of this study were: 1) to define a maximum threshold of EET sessions required to achieve CE-IM, and 2) to identify predictors of incomplete response to EET.

Methods

Study design

All data were collected as part of the Treatment with Resection and Endoscopic Ablation Techniques for BE (TREAT-BE) Consortium. TREAT-BE is a multicenter prospective observational cohort including patients undergoing EET for BE at four tertiary care referral centers (Northwestern Memorial Hospital, University of Colorado, Washington University St. Louis, and University of California, Los Angeles). Patients were enrolled in the study from 2011 through 2018, with approval from institutional review boards at all participating institutions. All patients aged ≥ 18 years with BE who underwent EET and achieved CE-IM during the study period were included. Patients who were lost to follow-up (defined as no communication for 1 year), refractory (referred for alternate treatment strategies) or died due to unrelated causes were excluded. Clinical data collected for this study included: baseline demographics, clinical risk factors for BE (smoking, family history), comorbidities (e. g. hyperlipidemia, diabetes), and medication use (e. g. proton pump inhibitors [PPI], statins, aspirin). Referring endoscopy reports were analyzed to identify pre-treatment histology, Barrett's segment length, Prague criteria [18], use of advanced imaging techniques, and surveillance biopsy technique. Finally, details specific to EET were also recorded including Prague criteria, visible lesion detection, use of advanced imaging, type of EET, and final pathology.

Study definitions

BE was defined by endoscopic extension of salmon-colored mucosa in the distal esophagus above the gastroesophageal junction, along with presence of intestinal metaplasia (IM) with goblet cells on endoscopic biopsies. Hiatal hernia was defined as small (< 2 cm), medium (2–4 cm), or large (> 4 cm). Patients with dysplasia were confirmed by two expert gastrointestinal pathologists prior to EET. Patients with nondysplastic BE were offered EET if they had risk factors for progression to dysplasia (age < 50 years and long-segment disease or family history of esophageal adenocarcinoma in first-degree relative). CE-IM was defined as absence of endoscopically visible BE plus absence of IM on all surveillance biopsies (four-quadrant biopsies performed every 1–2 cm from the gastroesophageal junction and entire pre-treatment BE length) after completion of EET [13, 14]. Recurrence of IM and recurrence of dysplasia were defined as presence of IM or dysplasia, respectively, on surveillance biopsies in tubular esophagus, or new squamocolumnar junction after achieving CE-IM. We have previously defined incomplete responders as patients requiring more than three sessions of ablative therapy to achieve CE-IM [17].

Treatment and surveillance protocols

All patients were prescribed twice-daily PPI therapy at the initiation of EET. Endoscopy was performed with high-definition endoscopes (EVIS EXERA GIF-HQ, 180/GIF-HQ 190; Olympus, Center Valley, Pennsylvania, USA) with careful inspection of the Barrett's segment before deciding upon treatment modality. The Barrett's segment was inspected with high definition white-light endoscopy and narrow-band imaging to detect visible lesions. Anatomical landmarks were recorded including location of visible lesions, diaphragmatic pinch, top of the gastric folds, and top of the IM. The total length of BE was recorded to document the extent of disease.

EMR was performed during EET for all identified visible lesions with a wide margin to ensure complete resection. EMR was performed predominantly using multi-band mucosectomy devices (Duette Multi-Band Mucosectomy device – Cook Medical, Limerick, Ireland; and Captivator EMR device – Boston Scientific Ltd., Marlborough, Massachusetts, USA). These devices use a transparent cap pre-loaded with multiple rubber bands, attached to the endoscope tip and a controller attached to the accessory channel. The lesion to be resected is suctioned into the transparent cap and the rubber band is deployed at the base to create a pseudopolyp. A snare is then used to resect the pseudopolyp underneath the rubber band using electrocautery. The EMR specimens were evaluated in detail, including tumor differentiation and presence of lymphovascular invasion when relevant, by expert pathologists at each institution.

RFA was then performed at 2–3-month intervals using the Halo 360 balloon or the Halo 90 Ultra device for long-segment BE (> 3 cm), or the Halo 90 focal ablation device for short-segment BE (< 3 cm), using 12 J/cm^2 energy, until all endoscopically visible BE was eradicated. The original Barrx 360 RFA balloon catheter system (Covidien, Sunnyvale, California, USA) including a balloon catheter (4-cm cylindrical balloon with a 3-cm RFA electrode) and a soft sizing balloon was used from 2011 until 2016. The sizing balloon was first introduced over a guidewire to measure the inner diameter of the esophagus. The appropriately sized ablation catheter (18, 22, 25, 28, or 31 mm) was then introduced over the guidewire to perform two sets of circumferential ablations using a pre-determined energy setting (12 J/cm^2). The transparent cleaning cap was used to remove all coagulative debris between the two ablations (1-Clean-1). The Barrx 360 express RFA balloon catheter (Medtronic Co., Minneapolis, Minnesota, USA) was used from 2016 and included a self-adjusting balloon electrode catheter that eliminates the need to size the esophagus. This device has an 8-cm-long balloon and 4-cm electrode, which reduces the procedure time significantly. The treatment regimen used for Halo 90 Ultra device was two ablations (12 J/cm^2) with cleaning using transparent cap in between ablations (1-Clean-1). For Halo 90 focal ablation catheter and through-the-scope RFA catheter, we performed four ablations (12 J/cm^2) in total, with cleaning after the second ablation (2-Clean-2).

Circumferential ablation of the gastroesophageal junction and gastric cardia was performed during each RFA session. The remaining BE islands were also treated with RFA.

Standard post-procedure instructions were clear liquid diet for 48 hours followed by mechanical soft diet for 5 days, with Tylenol-codeine (Johnson & Johnson, New Brunswick, New Jersey (USA) and sucralfate as needed for pain. CE-IM was confirmed after EET by standard four-quadrant biopsies every 1–2 cm from the entire pre-treatment length of BE. Surveillance endoscopies were performed as follows: every 6 months for 2 years, then yearly for patients with HGD or intramucosal carcinoma; every 6 months for 1 year, then yearly for patients with LGD; at 6 months, then yearly for 2 years and then every 3 years for patients with nondysplastic BE [6]. Recurrence of IM or dysplasia during surveillance was followed by repeat EET until CE-IM.

Outcomes and statistical analysis

The primary outcome of this analysis was the threshold number of EET sessions (EMR + RFA) required to achieve CE-IM in the majority of patients. To determine this threshold, we performed a Kaplan–Meier analysis, which examines "time to event" data and estimates confidence bands for the product limit curve. Several aspects of the curve may indicate a reasonable threshold: for instance, the lower limit of the 95 %CI for the true probability of CE-IM being above 50 %, the maximal slope of the curve, or incremental changes being higher than the first procedure. Once the optimal number of sessions was determined, based on examining these different criteria, patients who needed additional sessions were considered to have inadequate response to EET, and were recorded as "incomplete responders."

A secondary analysis was performed after excluding patients with nondysplastic BE to determine whether the performance threshold was influenced by inclusion of this group.

Categorical variables were reported as counts and percentages. Age was reported as mean (SD), and length of BE and number of procedures were presented as medians and interquartile ranges (IQRs) due to their skewed distribution. Logistic regression analysis was then performed using the defined threshold to determine factors associated with response to EET. Univariate models were first fit including each patient- and endoscopy-related variable. Although this analysis was exploratory, a type I error rate of 5 % was considered as a guide to determine significant results. The variables that were found to be significant on the univariate model were then included in a multivariate model using stepwise selection to determine a set of potential risk factors for incomplete response. Odds ratios (OR) and Wald 95 %CIs are presented. Data were analyzed using SAS v9.4 (Cary, North Carolina, USA).

Results

Study population and treatment outcomes

A total of 623 patients (mean age 65.2 [SD 11.6] years, 79.6 % male) with BE underwent EET and achieved CE-IM during the study period. All patients were followed until the end of the study period (11/30/2018). The median duration of follow-up was 2.7 years (IQR 1.4–5.0). During the study period, there were 83 additional patients who did not achieve CE-IM. Of these, 72 were lost to follow-up, 5 patients were classified as refractory and referred for alternative treatment strategies, and 6 patients died of other unrelated causes during treatment.

Baseline demographics are presented in ▶ **Table 1**. The median number of EET sessions performed was 2 (range 1–12; mean 2.9 [SD 1.7]). The distribution of the number of total EET sessions is shown in ▶ **Fig. 1**. Overall, 50.6 % of patients (315/623) underwent EMR and 85.6 % (533/623) underwent RFA as part of EET. The distribution of number of ablation and EMR sessions is reported in **Fig. 1 s** in the online-only Supplementary Material.

Threshold number of EET sessions

The total number of EET sessions performed per patient ranged from 1 to 12 (▶ **Fig. 1**). The Kaplan–Meier product limit curve is displayed in ▶ **Fig. 2**. This figure shows that after one EET session, 17 % (95 %CI 15 %–20 %) achieved CE-IM. The maximal slope occurs between two and three sessions. After three sessions, 73 % (95 %CI 70 %–77 %) achieved CE-IM; however, this value increased only to 87 % (95 %CI 84 %–89 %) after a fourth session. From this, it appears that after three sessions, we can be 95 % confident that the true rate of CE-IM is between 70 % and 77 %, and that incrementally, another session would only yield an additional 14 percentage points, which is less than the initial yield after one session. The percentage of patients achieving CE-IM by each session of EET is reported in **Table 1 s**.

In a secondary analysis excluding patients with nondysplastic BE, 70 % (95 %CI 66 %–75 %) of patients achieved CE-IM after three sessions and the maximal slope occurred between two

▶ **Table 1** Baseline demographics.

Characteristic	Entire cohort (N = 623)	CE-IM by 3 EET sessions (n = 457)	Incomplete response (n = 166)
Male sex, n (%)	496 (79.6)	358 (78.3)	138 (83.1)
Caucasian race, n (%)	539 (86.5)	394 (86.2)	145 (87.4)
Age, mean (SD), years	65.2 (11.6)	64.5 (11.9)	67.1 (10.3)
Length of BE, median (C, M), cm*	4 (2, 6)	3 (2, 5)	6 (3, 8)
Fundoplication, n (%)	47 (7.5)	28 (6.1)	19 (11.4)
Family history of BE, n (%)	33 (5.3)	27 (5.9)	6 (3.6)
Medications, n (%)			
▪ Aspirin	191 (30.7)	143 (31.3)	48 (28.9)
▪ NSAIDs	63 (10.1)	45 (9.8)	18 (10.8)
▪ Statins	261 (41.9)	182 (39.8)	79 (47.6)
Erosive esophagitis, n (%)	46 (7.4%)	35 (7.7)	11 (6.6)
Visible lesions, n (%)	109 (17.5)	79 (17.3)	30 (18.1)
Hiatal hernia, n (%)	n = 70	n = 56	n = 14
▪ None	11 (15.7)	11 (19.6)	0 (0)
▪ Small	7 (10.0)	7 (12.5)	0 (0)
▪ Medium	38 (54.3)	28 (50.0)	10 (71.4)
▪ Large	14 (20.0)	10 (17.9)	4 (28.6)
Highest histologic grade, n (%)	n = 548	n = 393	n = 155
▪ IM	93 (17.0)	73 (18.6)	20 (12.9)
▪ LGD/Indefinite	164 (29.9)	120 (30.5)	44 (28.4)
▪ HGD	233 (42.5)	159 (40.5)	74 (47.7)
▪ Cancer	58 (10.6)	41 (10.4)	17 (11.0)

CE-IM, complete eradication of intestinal metaplasia; EET, endoscopic eradication therapy; BE, Barrett's esophagus; NSAIDS, nonsteroidal anti-inflammatory drug; IM, intestinal metaplasia; LGD, low grade dysplasia; HGD, high grade dysplasia.
* Prague C & M criteria, where C = circumferential length, M = maximal length of Barrett's mucosa.

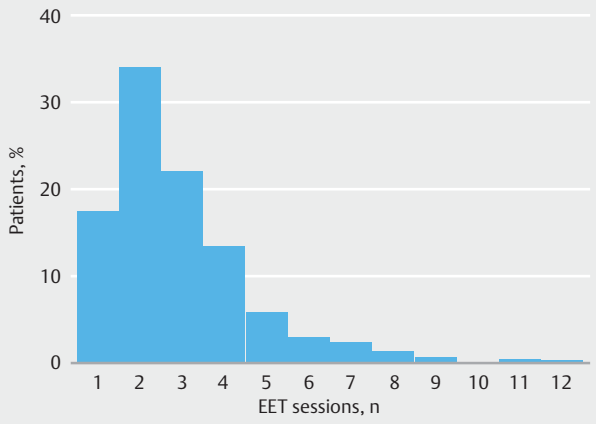
and three sessions, data that are similar to the findings for the entire cohort (**Fig. 2 s, Table 2 s**).

Risk factors for incomplete response

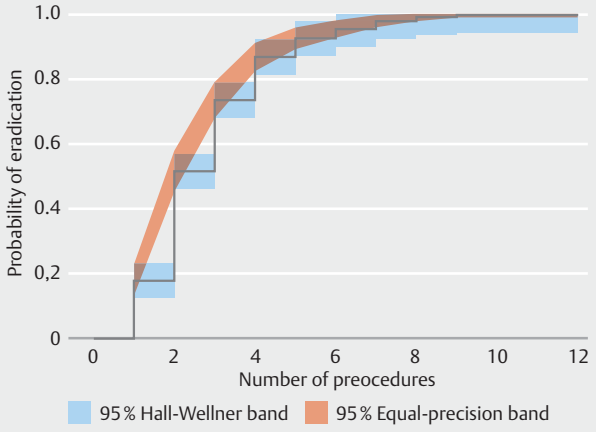
Using the threshold of three EET sessions to achieve CE-IM, univariate and multivariate logistic regression models were fit to determine the risk factors associated with incomplete response. The univariate model showed that age (OR 1.22, 05% CI 1.04–1.43), histology from referral endoscopy showing LGD (OR 2.13, 95%CI 1.03–4.41), HGD (OR 2.71, 95%CI 1.35–5.44), or intramucosal carcinoma (OR 2.41, 95%CI 1.03–5.67), and length of BE (OR 1.25, 95%CI 1.17–1.34) were significantly associated with incomplete response to EET. Stepwise logistic regression models showed that age (OR 1.25, 95%CI 1.05–1.50) and length of BE (OR 1.24, 95%CI 1.17–1.31) remained predictors of incomplete response to EET, although histology was no longer significant after adjustment for those factors (▶ **Fig. 3**).

Recurrence of disease and optimal EET threshold

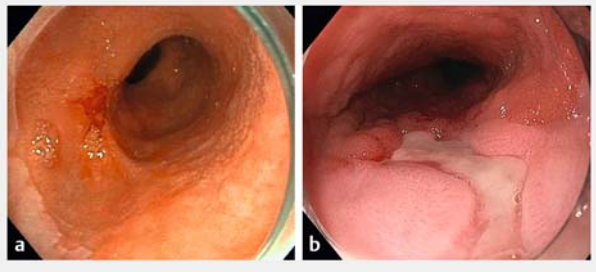
Patients were followed for a median of 1.1 (IQR 0.1–1.9) years after the final EET session to achieve CE-IM. Overall, recurrence of IM was observed in 16.2% (100/616) of patients and recurrence of dysplasia was observed in 5.8% (31/534) of patients. Both rates were higher in the group of patients with incomplete response within three EET sessions. Rates of IM recurrence were 10.9% (49/451) and 30.9% (51/165) in the groups with complete and incomplete response, respectively ($P<0.001$). Additionally, time to recurrence of IM was longer among those with complete response, with relative 5-year recurrence rates of 7.6% and 14.7% (log-rank $P=0.014$). Rates of dysplasia recurrence were 3.4% (13/380) and 11.7% (18/154) in the groups with complete and incomplete response, respectively ($P<0.001$), although there was no difference in the time to recurrence between the responders and incomplete responders, with 5-year recurrence rates of 2.7% and 4.2% (log rank $P=0.120$).



▶ **Fig. 1** Number of endoscopic eradication therapy sessions observed for complete eradication of intestinal metaplasia. EET, endoscopic eradication therapy.



▶ **Fig. 2** Kaplan–Meier (product limit) curve analysis showing number of endoscopic eradication therapy sessions required to achieve complete eradication of intestinal metaplasia.

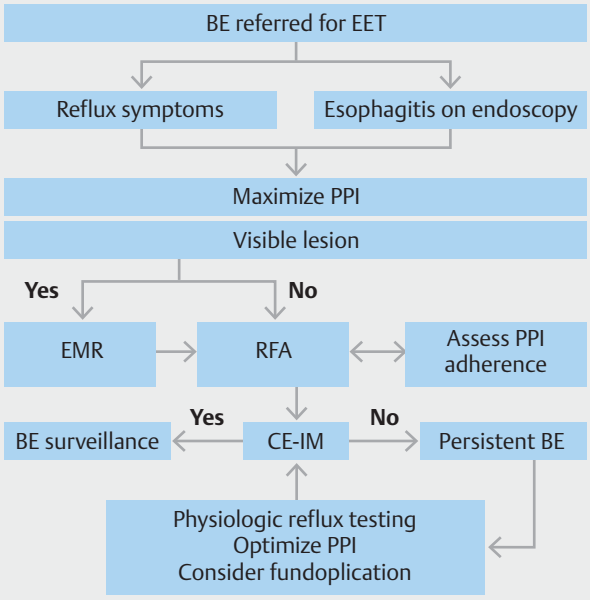


▶ **Fig. 3** Endoscopic images. **a** Long-segment Barrett's esophagus prior to endoscopic eradication therapy (EET). **b** Post-EET image showing incomplete response.

Discussion

The current study from the TREAT-BE Consortium confirms a threshold of three EET sessions by which the majority of patients undergoing EET should achieve CE-IM. We also found age and length of BE to be significant risk factors for incomplete eradication. Previous data have suggested that the majority of patients achieve CE-IM within three ablative sessions, but data assessing this threshold for EET as a whole are lacking. In the US RFA registry, the mean number of RFA sessions required to achieve CE-IM in experienced centers was 2.9 (SD 1.8) [19]. The median number of RFA sessions required in EURO-II trial was 3 (IQR 3–4) [20]. The mean number of RFA sessions required to achieve CE-IM in the UK registry was 2.5 [21]. In our previous report, the mean number of RFA sessions required to achieve CE-IM was 2.2 (SD 1.1) and 29 % of patients failed to achieve CE-IM within three treatment sessions [15]. The current study results are unique in including the total number of treatment sessions (EMR and RFA) to define EET thresholds and predictors of incomplete response, rather than ablation alone as reported in previous studies. We believe using the total number of EET sessions more accurately reflects clinical practice, as many patients will require endoscopic resection prior to ablation therapy.

These results have significant clinical implications. These data provide a well-defined reference standard for clinicians performing EET and for the use of further diagnostic testing or consideration of an alternative treatment strategy. Patients in whom CE-IM is not achieved within this threshold of three EET sessions should undergo further diagnostic investigation to identify factors that may contribute to the incomplete response (e. g. uncontrolled reflux burden). We have previously demonstrated that the dominant factor for incomplete response to EET is adequate reflux control [15, 17]. The presence of ongoing acid reflux on 24-hour pH-impedance testing despite twice-daily PPI therapy was associated with inadequate response to RFA and persistent IM [17]. By three ablations, 64.9 % of patients (24/37) achieved CE-IM and were defined as complete responders. Moreover, we observed that total reflux events, weakly acid reflux events (pH 4–7), and weakly alkaline reflux events (pH ≥ 7) were significantly higher in incomplete responders (>3 ablation sessions to achieve CE-IM) compared with complete responders [17]. Adequate reflux control is critical to the success of EET (▶ **Fig. 4**). Assessment of reflux control is an essential component for treating physicians throughout the treatment process. This begins with ensuring the patient is asymptomatic and has no endoscopic evidence of esophagitis prior to starting therapy. This continues with reconciliation of medication compliance at every visit and recognition of endoscopic signs of suboptimal reflux control (esophagitis). Finally, the threshold we have defined provides an opportunity for the treating physician to assess medication compliance, adherence, or consider an alternative treatment modality (e. g. cryotherapy). In the current study, the effect of age and BE segment length are likely to point to a greater reflux burden and to simply reflect the greater surface area of treatment needed. Interestingly, the highest grade of dysplasia in the BE segment was



▶ **Fig. 4** Proposed algorithm for endoscopic eradication therapy and reflux testing.

not found to be a predictor of incomplete response, probably due to aggressive EMR use for visible lesions (50.6 % of the total cohort) followed by RFA.

In addition, we have previously demonstrated lower rates of recurrence in patients managed using a strict anti-reflux regimen compared with controls who were managed per standard of care (recurrence of IM: 4.8 % vs. 10.9 %; P <0.04) [15]. The regimen included: 1) twice-daily PPI therapy throughout EET; 2) confirming adherence and compliance to PPI therapy at each visit; and 3) physiologic reflux testing using 24-hour pH-impedance testing in patients who do not achieve CE-IM within three sessions. Of the patients who were incomplete responders (required>3 sessions), CE-IM was achieved in 93.7 % (mean of 1.1 [SD 0.4] ablative sessions) after modification of therapy based on physiologic testing. In the current study, we also demonstrated that patients who do not achieve CE-IM by the optimal threshold of three EET sessions had a higher rate of recurrence of disease. While this was not a primary aim of the current study, it is likely that the factors responsible for incomplete response and recurrence may be similar.

The threshold remained unchanged when patients treated with nondysplastic BE were excluded, highlighting the generalizability of these findings regardless of pretreatment diagnosis.

Our study has several limitations. First, patients underwent EET at tertiary care high-volume centers with expert endoscopists, and comparable results may not be reproducible in the community setting. However, this study does provide reference standards for the number of sessions required to achieve CE-IM, failure of which should prompt investigation into underlying causes. Second, about 15 % of patients underwent EET for high risk nondysplastic BE, which may not be offered universally. However, there was no difference in our threshold when these patients were excluded. Third, the role of other ablative techniques such as cryotherapy was not assessed in our cohort. Future studies should determine whether non-RFA-based ablation modalities are more efficient and require a smaller number of sessions to achieve CE-IM, as they serve as alternative strategies for patients not responding to RFA. Fourth, early instructions for use of RFA suggested a maximal treatment area of 8 cm per session which, while not in the TREAT-BE protocol, could have resulted in more sessions being required to achieve CE-IM. Fifth, just under 50 % of our cohort had pretreatment histology of HGD or intramucosal carcinoma, which may account for the lower rate of EMR compared with European studies. Sixth, we excluded patients who did not achieve CE-IM during the study period, as the majority of these were lost to follow-up and inclusion of these patients might inappropriately support our primary outcome.

In conclusion, the current study found that a threshold of three EET sessions would achieve CE-IM in the majority of patients. Failure to achieve this should prompt further diagnostic evaluation to determine the underlying cause of incomplete response, such as uncontrolled reflux, and consideration of alternative endoscopic therapeutic modalities.

Competing interests

The authors declare that they have no conflict of interest.

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