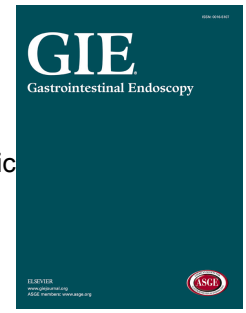

Learning curves and the influence of procedural volume for the treatment of dysplastic Barrett's

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Learning curves and the influence of procedural volume for the treatment of dysplastic Barrett's

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Contributors

GL, RJH and LBL were involved in the study concept and design. GL, SM and AG performed the statistical analysis and interpretation of data. GL, RJH and LBL were involved in drafting of the manuscript. All authors were involved in the acquisition of data and approved the final manuscript.

Competing interests

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Ethics approval

Ethical approval was granted by the Joint UCL/UCLH Committee on the Ethics of Human Research (REC REF 08/H0714/27).

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Abstract

Background and Aims

Endoscopic resections (ER) and radiofrequency ablation (RFA) are the established treatments for Barrett's-associated dysplasia and early esophageal neoplasia. The UK RFA Registry collects patient outcomes from 24 centers in the United Kingdom and Ireland treating patients. Learning curves for treatment of Barrett's dysplasia and the impact of center caseload on patient outcomes is still unknown.

Methods

We examined outcomes of 678 patients treated with RFA in the UK Registry using risk-adjusted CUSUM plots to identify change points in complete resolution of intestinal metaplasia (CR-IM) and complete resolution of dysplasia (CR-D) outcomes. We compared outcomes between those treated at high- (>100 enrolled patients), medium- (51-100) and low- (<50) volume centers.

Results

There was no association between center volume and CR-IM and CR-D rates, but there were lower recurrence rates in high-volume versus low-volume centers (Log Rank p=0.001).There was a significant change-point for outcomes at 12 cases for CR-D (reduction from 24.5% to 10.4%; P<0.001) and at 18 cases for CR-IM (30.7% to 18.6%; P<0.001) from RA-CUSUM curve analysis.

Conclusion

Our data suggest that 18 supervised cases of endoscopic ablation may be required before competency in endoscopic treatment of Barrett's dysplasia can be achieved. The difference in outcomes between a high-volume and low-volume center does not support further centralization of services to only high-volume centers.

Introduction

Endoscopic eradication therapy (EET) for Barrett's associated neoplasia is well established. Current guidelines recommend endoscopic mucosal resection (EMR) of visible lesions and ablative therapy for flat dysplasia and residual Barrett's esophagus (BE) after resection (1). The most commonly used ablative technology used for this purpose is radiofrequency ablation (RFA). This combined approach has been demonstrated to achieve complete resolution of dysplasia (CR-D) in 81% to 92% in clinical trials and complete resolution of intestinal metaplasia (CR-IM) in 62% to 87% by 12 months (2,3).

Current guidelines recommend that "Endoscopic therapy of Barrett's neoplasia should be performed at centers where endoscopic and surgical options can be offered to patients, and a minimum of 30 supervised cases of ER and 30 cases of endoscopic ablation should be performed to acquire competence in technical skills, management pathways and adverse complications(1)." A study of trainees learning ER reported a significant adverse event rate in the first 20 procedures, although the majority of these were cap-assisted ER rather than multiband mucosectomy ER (4). Previous work published by our group has demonstrated improvements in patient outcomes over time (5) and previous analysis of national EMR rates has demonstrated a short learning curve for proficiency in terms of mortality and major adverse events (6). There is, however, limited evidence regarding the learning curve for RFA. The quality indicators for Barrett's endotherapy (QBET) publication suggested that centers should be performing >40 EET cases per year (7).

The UK RFA Registry prospectively collects data from 24 sites in the United Kingdom and Ireland with a variety of experience. Hospitals performing higher volume of surgery for upper gastrointestinal cancers have adjusted mortality rates 25% to 41% lower than those performing a low volume of surgery (8). Proposed reasons include the concentration of specialist infrastructure and high levels of technical expertise located at these centers (9). It is unclear whether the effect of caseload volume seen with surgical centers is seen in centers that provide EET for Barrett's dysplasia.

The aims of this study were to establish the proficiency gain on CR-D and CR-IM rates for the EET of Barrett's dysplasia, identify whether a proficiency-gain curve exists for the treatment of BE dysplasia and assess the effect of hospital procedure volume on outcomes.

Methods

The treatment protocol for the UK RFA Registry has previously been described (10). The primary outcomes for this study were CR-D and CR-IM at 12 months after RFA treatment started and dysplasia recurrence. Any patient with residual dysplasia or who progressed to cancer during the 12 months after therapy was started was considered to have failed to reach CR-D. Patients who achieved CR-D but had persistent BE at 12 months, even if the length was significantly shorter than at the beginning were deemed as failing to reach CR-IM. Recurrence was defined as patients in whom CR-D was achieved but who later showed histological recurrence of LGD, HGD or IMC on biopsies or EMR specimens.

Most patients were treated initially with a HALO360 device with follow-up treatments using the HALO90 or HALO60 devices. In this study, none of the patients were treated with the newest catheter, the RFA-Express device. Centers with at least one patient who had completed the treatment protocol were included in this analysis.

The outcome data were analyzed according to the order treated at each center. The first group included the first ever 20 patients treated in all centers (hospitals); the second group included the next 21 to 40 patients at each center and the third group all patients treated from 41 onwards. To assess the effect of center volume on outcomes, centers were grouped by the total number of patients entered consecutively on the Registry database. Centers were divided into low-volume (<50 patients), medium-volume (50-100 patients) and high-volume (>100 patients) centers. Unfortunately, data are only available from each center rather than each endoscopist as there may be several endoscopists performing these procedures at each center, and these numbers varied during the course of the study.

The cumulative sum control chart (CUSUM) is an analysis that allows identification of procedural proficiency (11). When applied to a specific therapeutic intervention, it needs to be risk-adjusted. To identify the existence and length of a proficiency-gain curve for RFA a combination of risk-adjusted cumulative sum (RA-CUSUM) and change-point analysis was performed. This allows for identification of proficiency, which is independent of hospital procedural volume. RA-CUSUM curves were plotted for the cumulative difference between the observed and the expected outcome against hospital case number; using the CUSUM equation $S_i=S_{i-1}+(\Sigma i - \Sigma R)$; $S_0=0$: S_i is the cumulative sum, Σi the sum of events at procedure number i, and ΣR the sum of expected events at procedure number i. Therefore, at each case number the curve goes upward if the outcome is worse than expected and down if better than expected. According to the unique anonymised hospital codes within the dataset; the first case in each hospital case series was assigned case one and subsequent case numbers assigned according to ascending date order. The expected outcomes were derived from logistic regression models for each binary outcome; these provided the predicted probability of each outcome in each case.

Previously, multivariate analysis of the UK RFA cohort reported increasing age (OR, 1.316), prior EMR (OR, 1.358) and shorter lengths of BE at baseline (OR, 1.103) were associated with improved CR-D rates, whereas rescue EMR (OR, 0.426) reduced the chance of achieving CR-D (5). The factors used to risk adjust for the RA-CUSUM analysis included increasing age, prior EMR, shorter lengths of BE at baseline and rescue EMR (5). Potential confounding factors (from previous multivariate analysis of the sample population), which were risk adjusted for, in the models were age, entry histology, length of Barrett's esophagus, rescue endoscopic mucosal resection (EMR), and previous EMR.

An inverse relationship was expected between experience and adverse outcomes and the length of the proficiency-gain curve was defined as the number of cases for a sustained improvement in outcome. This was represented graphically on the RA-CUSUM curve as the maximal positive deflection; the point at which outcomes changed from worse than expected to better than expected. The clinical significance of this change point was determined by comparing outcomes before

and after. These binary outcomes were compared using Chi-square and a threshold of significance was set at a p value of less than 0·05.

Data were analyzed using the SPSS version 23 (IBM Corp, Armonk, NY, USA). Comparisons between groups for available data were analyzed using the χ^2 test for categorical variables. Noncontinuous variables underwent a homogeneity test to ensure a normal distribution. After this, a one-way ANOVA was performed, and any results that demonstrated a significance of <0.05 underwent a Tukey post-hoc test. Log rank test was used to compare the difference in the rate of disease recurrence between the groups at latest follow-up.

Results

Demographics

The first 678 consecutive patients who completed 12-month treatment from the UK RFA registry were included in the analysis (median follow-up 26 months). The baseline characteristics of all patients completing treatment can be seen in Table 1. Over 90% had a diagnosis of HGD or IMC and 53% have had a previous EMR before RFA treatment.

Center Volume

Twenty-four centers reported outcomes on patients who had completed the treatment protocol. Five centers were classed as high-volume centers (total patients completing treatment n=418), 4 were medium-volume centers (n=145) and 15 were low-volume centers (n=115).

Baseline characteristics across the 3 groups of center volumes can be seen in Table 4. Patients were marginally older in low-volume centers compared with high-volume centers (p<0.05). Neither 12-month CR-D nor CR-IM rates were any different between the groups (CR-D 86.4%-89.5%, CR-IM 73.7%-81.1%). The number of treatment sessions performed was higher in the high-volume centers and dysplasia recurrence was significantly lower in these centers compared with

low-volume centers (Log Rank p=0.001). The higher number of treatment sessions was not reflected in the median time taken to complete the protocol.

Rescue EMR during RFA treatment was performed less frequently in medium-volume centers (0% versus high- 5.3% and low-volume 10%, p=0.001), although with no clear effect on CR-D or recurrence rates.

Hospital Experience

Table 3 compares the first 20 patients treated at each site with the next 20 patients at each site and then with those treated afterward. Patients treated after the first 40 cases at each center resulted in fewer rescue EMRs (p=0.016), faster time to completion of the treatment protocol and higher CR-D and CR-IM rates. There is no difference in CR-D or CR-IM rates between the second 20 cases and those performed after 40 cases (p=0.869 and p= 0.398 respectively).

Hospital RA-CUSUM curve analysis

Analysis of the RA-CUSUM curve for incomplete resolution of dysplasia (Figure 1) showed a significant change-point at 12 cases, with a significant reduction from 24.5% to 10.4%; P<0.001 (Table 4). A longer RA-CUSUM curve was seen for incomplete resolution of Barrett's esophagus (Figure 2) with a significant change-point at 18 cases, and a significant reduction from 30.7% to 18.6%; P<0.001 (Table 2).

RA-CUSUM plots were attempted to identify a minimum number of RFA patients that need to be treated at each center each year to maintain the standard of outcomes achieved after 12 to 18 patients. However, due to low numbers performed per year at most centers, no significant findings could be reported.

Discussion

Studies assessing complex surgical procedures repeatedly demonstrate improved survival outcomes in specialist centers (8,12–18). Also, data from the US RFA Registry have demonstrated that higher center volume is associated with fewer procedures required to achieve CR-IM (P <0.001). Furthermore, after an endoscopist has treated 30 cases they required 0.35 fewer endoscopies to achieve CR-IM compared with those who had completed 10 or fewer cases (19). The BSG recommend a minimum of 30 supervised RFA procedures before competency is attained (1), QBET recommends >40 cases (7), although this is based on limited evidence. The TREAT-BE Consortium were unable to recommend a volume of cases per year (20).

Risk-adjusted CUSUM charts have recently been used to identify significant change points in clinical outcomes for EMR during endoscopist proficiency gain using national data (6). We demonstrate that there is a learning curve with a significant change point after 12 and 18 cases for CR-D and CR-IM, respectively.

The UK RFA Registry was set up in 2008. At that time, it was considered that treatment should be completed within 1 year in line with the previously published randomized controlled trial data (21) although increasingly, this arbitrary timepoint is seen as being inappropriate. Nonetheless, all the analyses were carried out using this as it was a primary endpoint for the registry. Previous analysis of the UK RFA registry has demonstrated improved outcomes including lower adverse event rates with time (5) and these data demonstrate a similar effect, that the more cases a center performs, the better the outcome. After treating 40 patients with a combined EMR and RFA approach, outcomes are significantly improved than for the first 20 patients treated in the same center (CR-D 91% versus 79.8%; p=0.001, CR-IM 83.9% versus 71.3% p=0.004).

There are currently limited data to guide requirements for RFA experience before independent practice. Fudman et al (22) performed a retrospective analysis of 417 patients who had been treated by 7 endoscopists with a median RFA volume of 62 patients (range 20–188). The study was performed at 3 teaching centers, and

endoscopists who had treated less than 10 patients were excluded from the analysis. RFA volume (both number of patients treated and number of RFA procedures) correlated with CR-IM rates (rho = 0.85, p=0.014) and in multivariate analysis, higher RFA volume was associated with higher CR-IM rates. However, no association was found between CR-IM rates and yearly endoscopic volume. No data on CR-D rates were reported in this study and there was no common treatment protocol.

Zemlyak et al (23) retrospectively reviewed 70 consecutive patients treated at a single center by a single endoscopist. Comparing the first 25% of those treated with the last 25%, there was no significant difference in length of procedure, procedures required to achieve CR-IM or adverse event rate. They concluded that "By measure of treatment time, complication rate, and efficacy of therapy, there is minimal or no 'learning curve' for experienced endoscopists." However, the overall rate of adverse events was very low compared with similar studies (2,23) and only 74% had dysplasia.

A larger U.S. registry-based study reported on 5521 patients across 148 institutions undergoing endoscopic therapy for Barrett's (51.7% for dysplasia) (19). Higher-volume centers were associated with higher CR-IM rates ($P < 0.01$) but not CR-D rated ($P = 0.39$); however, the improvement in CR-IM was not significant after multivariate analysis. Center volume was associated with fewer procedures required to achieve CR-IM ($P <0.001$) and after an endoscopist had treated 30 cases they required 0.35 fewer endoscopies to achieve CR-IM compared with those who had completed 10 or fewer cases. The high volume of nondysplastic Barrett's patients in the U.S. Registry may have a significant impact on the learning curve of U.S. operators and make the data difficult to extrapolate to a population for whom RFA is only indicated in the presence of dysplasia.

A recent article assessing EMR proficiency in the United Kingdom using data from a UK Hospital Episode Statistic (HES) database reported a lower 30-day mortality with high-volume endoscopists with a change point of 4 cases seen when comparing 30-day mortality in cancer patients (6). This might suggest that the

learning curve for EMR is even shorter than that for RFA, although it only reports on major adverse events, which are rare in this procedure.

The TREAT-BE Consortium have suggested 80% achieve CR-D at 18 months and 70% CR-IM at 18 months (20). Based on the UK Registry data, CR-D rates for the first 20 patients are just below the 80% threshold recommended at 12 months. We need to perform further analysis to identify whether the patients in the UK Registry meet this threshold.

This study suggests that center volume is not a significant factor in determining successful initial outcomes for the treatment of BE dysplasia with EMR and RFA, namely CR-D (86.4% versus 87.0% versus 89.5%) and CR-IM (73.7% versus 74.9% versus 81.1%). However, dysplasia recurrence is significantly higher in low-volume centers (Log rank 0.001), although these numbers are small (22 cases in the small-volume centers and 58 in the high-volume centers).

Interestingly, medium-volume centers had a significantly lower rescue EMR rate compared with both the high- and low-volume centers. The significance of this finding is unclear and could be interpreted as either medium-volume centers successfully clear all visible dysplasia before commencing RFA, or that they are missing residual disease. Neither explanation explains why ultimately the CR-D and recurrence rates are not significantly different for the medium-volume centers, although a combination of both the above-listed reasons may even out the long-term outcomes. It should also be noted that high- and medium-volume centers are more likely to be academic training centers and that operators may be trainees undergoing training; therefore, this may affect the outcomes compared with low-volume centers that may have greater consistency in operators and technique.

It is important to note that the association between surgical volume and improved outcome has not been consistently agreed. In contrast to the above studies, a UK-based study on individual surgeon volume and lung cancer outcomes did not demonstrate an association between individual surgeon volume and in-hospital mortality (24). This same study highlighted the need to assess the best patient-centered outcome measures, because mortality in lung-cancer patients after

surgery is a rare event. Extrapolating this to the cohort of Barrett's therapy, perhaps a more holistic view of endoscopic treatment for Barrett's should address the future burden of endoscopic surveillance and impact on the quality of life rather than solely on CR-D and CR-IM rates.

This study has several strengths; it is the largest study outside of the United States, assessing 24 centers in the United Kingdom and Ireland, covering the majority of endoscopic therapy that occurs in the United Kingdom for patients with dysplastic BE. The RA-CUSUM plots removes the grouping of centers with similar volumes (such as high-, medium-, or low-volume centers) but assesses each center on the number of patients and the risk adjusted profile of each patient treated to demonstrate a learning curve in the effectiveness of endoscopic therapy for dysplastic BE.

Previous studies in this field have focused on either EMR as a stand-alone procedure or RFA in isolation (6,23). This analysis does not differentiate between the 2 procedures but assesses outcomes of all patients treated for dysplasia. The learning curves described in this study are a composite of both EMR and RFA treatment. This approach is endorsed in BSG guidance (1) and is considered the best current treatment for dysplasia arising in Barrett's.

As with any registry study, although a treatment protocol is advised, it may not always be adhered to. Multiple sites across the United Kingdom and Ireland enter data from the Registry. Clinical pressures result in significant variation in RFA treatment intervals and sessions within 12 months, and in this analysis there was a higher number of RFA sessions in higher-volume centres.

The UK registry does not require central pathology review of biopsy specimens and EMR samples that may be important because variation among pathologists has been well documented (25,26).

The UK RFA Registry has been collecting data since 2008. During this time, the management of dysplasia arising in BE has changed; there is a greater focus on lesion detection and resection before RFA treatment begins, and there have been

advancements in lesion detection, recognition and interpretation due to higher quality imaging. More recently, low-grade dysplasia is now treated with RFA whereas previously it would have been monitored and most importantly, treatment success has improved with time (5).

It should also be noted that significant numbers of patients have not completed the 12-month protocol; either they are still currently receiving treatment, or they have been lost to follow-up during the course of treatment.

Previous meta-analysis suggested surgical volume rather than center volume is the most important factor for outcomes in upper GI surgery (27). The Registry does not allow sufficient breakdown of the data as to who performed each RFA session. Outcomes recorded are per center and therefore unable to distinguish whether the endoscopy unit (with nursing and administrative staff and the management system) or the individual endoscopists ability that we are measuring. However, most small centers have a single endoscopist, and only the larger centers may have more than one endoscopist. Other factors that may impact on center outcomes may not just be related to the endoscopist and endoscopy staff but also to administrative-related factors such as ensuring availability of endoscopy lists and nursing support around the process of treating dysplasia and regular contact with patients as well as better structured multidisciplinary team discussions. These factors are not recorded, however, in the Registry data.

Conclusion

This study suggests that fewer than 20 cases of endoscopic ablation may be required before competency in treating Barrett's dysplasia can be achieved, and that the difference in outcomes between a high-volume and low-volume center does not support further centralization of services to only high-volume centers.

Table 1: Table of baseline characteristics of patients who have completed treatment with RFA in the UK RFA Registry

Total number of patients competed treatment	678
Sex (M)	82.2%
Median Age (Range)	68 (39-91)
Median Initial Length (Range)	5 cm (1-20 cm)
Prior EMR	53.0%
Rescue EMR	5.1%
Entry Histology	
- IMC	24.4%
- High Grade Dysplasia	69.5%
- Low Grade Dysplasia	6.0%
Mean number of RFA Treatments (Range)	2.5 (1-7)
Median time to protocol completion (months)	11.5
CR-IM	76.7%
CR-D	85.3%
Dysplasia recurrence	12.7%
Median time in follow up (months)	13.3

Table 2: Efficacy of RFA on the basis of center experience

	Low Volume n=115	Medium Volume n=145	High Volume n=418	Significance
Sex (M)	88.1%	80.4%	81.4%	NS
Age	69.7	68.4	67.3	NS
Initial Length (M)	5.1	5.2	5.7	NS
Prior EMR	57.6%	56.6%	50%	NS
Rescue EMR	10.1%	0%	5.3%	**Tukey post-hoc test** Low vs Medium 0.001 Low vs High 0.205 Medium vs High 0.112
Entry Histology				NS
- IMC	27.1%	23.8%	23.7%	
- HGD	69.5%	67.1%	70.2%	
- LGD	3.4%	9.1%	6.1%	
Median number of RFA Treatments	2.1	2.4	2.7	**Tukey post-hoc test** Low vs Medium 0.038 Low vs High <0.001 Medium vs High 0.048
Median time to protocol completion (months)	11.4	11.7	12.1	NS
CR-IM	73.7%	81.1%	74.9%	NS
CR-D	86.4%	89.5%	87.0%	NS
Dysplasia recurrence	19.1%	13.3%	14.0%	Log Rank Medium vs High 0.237 Low vs High 0.001 Low vs Medium 0.066

Table 3: Efficacy of RFA on the Experience (0-20, 21-40, >40) – entry criteria and outcomes

	Cases 1-20 n=316	Cases 21-40 n=164	Cases >40 n=198	Significance
Sex (M)	84.5%	77.6%	82.4%	NS
Age	68.4	66.7	67.8	NS
Initial Length (M)	5.5	5.4	4.7	NS
Prior EMR	55.2%	50.3%	51.8%	NS
Rescue EMR	7.3%	5.5%	1.5%	χ^2 test 0.016
Entry histology				One-way ANOVA 0.023
- IMC	27.2%	23.2%	21.1%	
- HGD	69.9%	66.5%	71.4%	
- LGD	2.8%	10.4%	7.5%	
Median no. of RFA Treatments	2.5	2.6	2.5	NS
Median time to completion of protocol (months)	12.1	12.9	10.9	Tukey post-hoc test 1st 20 vs 2nd 20 0.345 1st 20 vs 3rd 20 0.045 2nd 20 vs 3rd 20 0.003
CR-IM	71.3%	78.2%	83.9%	0.004 Tukey post-hoc test 1st 20 vs 2nd 20 0.203 1st 20 vs 3rd 20 0.003 2nd 20 vs 3rd 20 0.398
CR-D	79.8%	89.1%	91.0%	0.001 Tukey post-hoc test 1st 20 vs 2nd 20 0.017 1st 20 vs 3rd 20 0.001 2nd 20 vs 3rd 20 0.869
Dysplasia recurrence	15%	12.8%	11.6%	Log rank = 0.259

Table 4: Analysis of outcomes before and after change-points in RA-CUSUM curves.

Outcome	All patients	Change-point (CP)	CR-D Failure rate before CP	CR-D Failure rate after CP	*P* value
Unable to achieve CR-D	100/678	12 cases	24.5%	10.4%	<0.001
Unable to achieve CR-IM	159/678	18 cases	30.7%	18.6%	<0.001

Figure 1: RA-CUSUM curve for CR-D after RFA, showing a significant change-point at 12 cases, and reduction from 24.5% to 10.5%; P<0.001.

Figure 2: RA-CUSUM curve for CR-IM after RFA, showing a significant change-point at 18 cases, and reduction from 30.7% to 18.6%; P<0.001.

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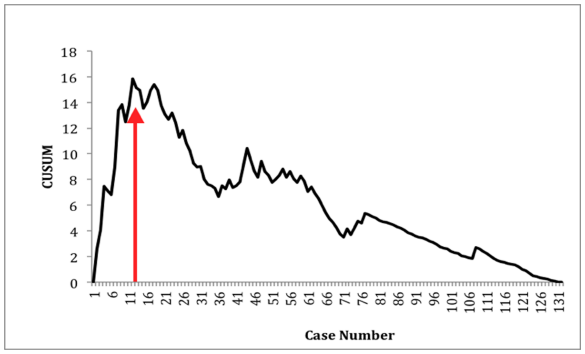

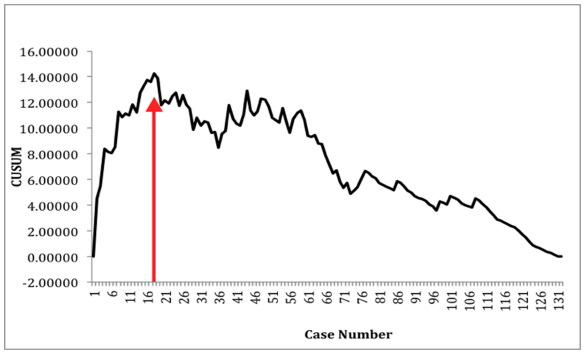

Acronyms and Abbreviations

BE - Barrett's esophagus

CR-IM - Complete resolution of intestinal metaplasia

CR-D - Complete resolution of dysplasia

EET - Endoscopic eradication therapy

ER - Endoscopic resections

LGD - Low grade dysplasia

HGD - High Grade dysplasia

IMC - Intramucosal cancer

QBET - Quality Indicators for Barrett's endotherapy

RA-CUSUM - Risk adjusted – Cumulative sum control chart

RFA - Radiofrequency ablation