

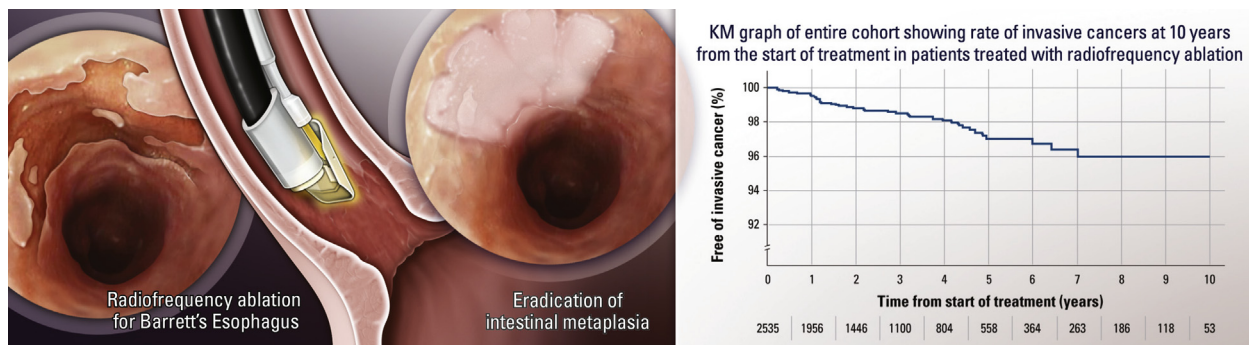


Endoscopic eradication therapy for Barrett's esophagus-related neoplasia: a final 10-year report from the UK National HALO Radiofrequency Ablation Registry (CME)

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GRAPHICAL ABSTRACT



Background and Aims: Long-term durability data for effectiveness of radiofrequency ablation (RFA) to prevent esophageal adenocarcinoma in patients with dysplastic Barrett's esophagus (BE) are lacking.

Methods: We prospectively collected data from 2535 patients with BE (mean length, 5.2 cm; range, 1-20) and neoplasia (20% low-grade dysplasia, 54% high-grade dysplasia, 26% intramucosal carcinoma) who underwent RFA therapy across 28 UK hospitals. We assessed rates of invasive cancer and performed detailed analyses of 1175 patients to assess clearance rates of dysplasia (CR-D) and intestinal metaplasia (CR-IM) within 2 years of starting RFA therapy. We assessed relapses and rates of return to CR-D (CR-D2) and CR-IM (CR-IM2) after further therapy. CR-D and CR-IM were confirmed by an absence of dysplasia and intestinal metaplasia on biopsy samples taken at 2 consecutive endoscopies.

Results: Ten years after starting treatment, the Kaplan-Meier (KM) cancer rate was 4.1% with a crude incidence rate of .52 per 100 patient-years. CR-D and CR-IM after 2 years of therapy were 88% and 62.6%, respectively. KM relapse rates were 5.9% from CR-D and 18.7% from CR-IM at 8 years, with most occurring in the first 2 years. Both were successfully retreated with rates of CR-D2 of 63.4% and CR-IM2 of 70.0% 2 years after retreatment. EMR before RFA increased the likelihood of rescue EMR from 17.2% to 41.7% but did not affect the rate of CR-D, whereas rescue EMR after RFA commenced reduced CR-D from 91.4% to 79.7% ($\chi^2 P < .001$).

Conclusions: RFA treatment is effective and durable to prevent esophageal adenocarcinoma. Most treatment relapses occur early and can be successfully retreated. (Gastrointest Endosc 2022;96:223-33.)

(footnotes appear on last page of article)

The incidence of esophageal adenocarcinoma (EAC) continues to rise in the Western world,^{1,2} but 5-year survival has only shown modest improvement in the past 40

years despite advances in diagnosis and therapeutics.³ Dysplasia arising in Barrett's esophagus (BE) is the only known premalignant condition of EAC, albeit with a low

risk of progression to invasive cancer.⁴ Improvement in patient access, referral pathways, and ultimately endoscopic imaging have led to an increased number of patients being detected at an early stage where potentially curative intervention can be initiated.

Surgery with esophagectomy and lymph node clearance was previously the standard treatment for high-grade dysplasia (HGD). Although this remains the intervention of choice for patients with locoregional disease, mortality and morbidity remain significant,^{5,6} and therefore over the past 20 years there has been a paradigm shift in pursuing a minimally invasive approach focused on organ preservation to treat early-stage disease and avoid the adverse events related to surgery while also delivering curative treatment. Endoscopic eradication therapy (EET) appears to confer a similar medium-term survival rate for intramucosal cancer (IMC; stage T1a) disease as esophagectomy and is increasingly used in older and less fit patients.⁷

The initial treatment modality for early-stage esophageal neoplasia is endoscopic resection to remove and accurately stage visible neoplasia. Several large-scale series have shown short- and medium-term success with this approach.^{8,9} A drawback of monotherapy is the risk of metachronous neoplasia arising in the residual metaplastic BE of up to 20%.¹⁰ As a result, a dual EET therapeutic algorithm is now widely implemented with clearance of visible neoplastic lesions by endoscopic resection followed by field ablation of the entire BE field to remove both neoplasia and intestinal metaplasia. Several ablative techniques have been explored including yttrium-aluminum garnet laser and argon plasma coagulation,¹¹ but radiofrequency ablation (RFA) has gained the most traction because of high-quality safety and efficacy data showing short- and medium-term success and durability.^{8,12}

Since the introduction of RFA in 2005, consensus has developed among most international societies that after endoscopic resection, field ablation with RFA is indicated to achieve clearance of disease and ensure long-term safety from progressing to invasive cancer.^{13,14} A significant proportion of patients with dysplastic BE do not initially have any visible lesions. It remains unclear whether RFA should be used as monotherapy in this group. Furthermore, because of the relatively recent introduction of RFA to mainstream clinical practice, long-term follow-up data (>5 years) are lacking. Long-term outcomes in patients with and without initially visible lesions are crucial to understand the risks and benefits of a minimally invasive approach to manage this high-risk patient group.

We have previously published short- and medium-term data from the UK National HALO RFA registry,^{12,15,16} which is a UK-wide database of patients referred for RFA of dysplastic BE or IMC related to underlying BE. It is a multi-center registry that collects data prospectively from 28 specialist centers in the United Kingdom. We present

here the final report focusing on 10-year outcomes collected within this prospective registry.

The primary aim of this study was to determine 10-year cancer progression in patients undergoing EET for BE. Secondary aims were understanding the durability of complete remission of dysplasia (CR-D) and complete remission of intestinal metaplasia (CR-IM) together with rates of relapse from these states and success rates of further therapy when the problems recurred.

METHODS

Inclusion criteria

We included patients in whom low-grade dysplasia (LGD), high-grade dysplasia (HGD), or IMC was confirmed histologically by 2 expert GI pathologists before patients began EET from the inception of the UK registry in January 2008 until December 2018. Only men and nonpregnant women over age 18 years with no contraindications to endoscopy were considered for enrollment. All patients gave written informed consent. Patients were required to attend for treatment and surveillance procedures at regular intervals.¹² Data were entered by each site into a dedicated web-based database.

Ethical approval was granted by the Joint University College London/University College London, Hospital Committee on the Ethics of Human Research (REC REF 08/H0714/27). The UK registry is registered at ISRCTN 93069556. The 10 highest recruiting sites were all subjected to data review by the primary site. This ensured high-quality data entry and review. These patients were included in more detailed analyses.

Pre-enrollment staging

The specialist Barrett's endotherapy center performing EET restaged all patients at enrollment. The extent of BE was measured using the Prague classification.¹⁷ Optical enhancement, chromoendoscopy, and EUS were used at the discretion of the operator. The BE segment was sampled using the Seattle protocol.¹⁸

Histologic diagnosis was categorized using the modified Vienna classification¹⁹ either on biopsy specimens or EMR specimens. Two expert GI pathologists at each site reviewed all histology to ensure consensus. These processes were consistent and followed our previous publications.^{12,15,16} The registry endoscopy protocol, training of operators, technical details regarding RFA procedure, and postprocedure follow-up are detailed in our initial publication.¹²

Definitions and clinical endpoints

CR-D was defined as all biopsy samples clear of dysplasia at 2 consecutive endoscopies. CR-IM was defined as all biopsy samples clear of intestinal metaplasia at 2 consecutive endoscopies together with residual tongues of glandular

TABLE 1. Number of patients reaching clearance of dysplasia and of intestinal metaplasia within specific time frames from the start of radiofrequency ablation treatment

Month	Clearance of dysplasia		Clearance of intestinal metaplasia	
	No. of patients reaching the endpoint	Additional patients included relative to previous time cutoff	No. of patients reaching the endpoint	Additional patients included relative to previous time cutoff
15	898		328	
18	980	82	488	160
21	1014	34	628	140
24	1031	17	729	101
30	1054	23	877	148
36	1058	4	923	46

mucosa measuring <3 cm and the absence of dysplasia. This definition aims to fulfill both UK and U.S. approaches, which differ on the criteria for the diagnosis of BE.^{20,21}

We applied a 24-month cutoff from commencement of therapy to our cohort. This excluded a small number of patients from subsequent analyses because their treatment continued beyond this time, although some of these patients did subsequently reach CR-D and CR-IM. This ensured that our relapse data reflected typical modern practice (Table 1). Invasive cancer was defined as histology showing submucosal adenocarcinoma (stage T1b) or greater, which is not considered amenable to endoscopic therapy.^{20,22}

Relapse from CR-D was defined as biopsy sample-proven recurrence of dysplasia at a single endoscopy. Similarly, relapse from CR-IM followed the successful clearance of intestinal metaplasia. We calculated the time to achieve CR-D and CR-IM after relapse, defined as CR-D2 and CR-IM2, respectively.

We performed an analysis on the entire cohort to assess the risk of developing invasive cancer. More detailed analysis was conducted on patients from the 10 highest recruiting sites. This included time to invasive cancer and time to CR-D and CR-IM plus subsequent relapses. This was to ensure robust and accurate long-term follow-up data. In addition, rates of dilatation during EET and rescue therapy, including argon plasma coagulation, yttrium-aluminum garnet laser, and EMR during or after RFA, were calculated.

Exclusion criteria

Thirty-eight patients in the registry had previously failed an earlier type of endotherapy or photodynamic therapy and were excluded from detailed analyses. Patients were excluded from all analyses except time to invasive cancer from the start of RFA therapy if the duration of follow-up was <18 months from recruitment.

Significant data entry gaps were defined as time intervals of >18 months between 2 consecutive endoscopies despite a patient continuing to have dysplasia or time intervals between 2 therapeutic endoscopies >1 year before primary endpoints were reached. In these cases, the patient's

data were censored at the endoscopy before the data gap for all analyses except when reviewing the time to developing invasive cancer.

Statistical analysis

For time-dependent data, a Kaplan-Meier (KM) survival analysis with the log rank test was calculated for each of the primary endpoints using Microsoft Excel (Excel 2010; Microsoft, Redmond, Wash, USA) and R Studio (R Studio 1.2.1335; R Studio PBC, Boston, Mass, USA) software. Other data were assessed for normality, after which parametric or nonparametric tests were applied.

We report the cancer outcomes for 2535 patients recruited to the UK National Registry between April 2008 and December 2018. Patients underwent 18,371 procedures at 28 sites. We also report rates of CR-D and CR-IM and relapse from these endpoints for 1175 patients (Fig. 1).

Demographic data for all patients from sites that were included in the detailed analyses are shown in Table 2. Before therapy, LGD was the highest histologic grade for 225 patients, HGD for 624 patients, and IMC for 326 patients. The LGD group contained the fewest patients, which likely reflects UK guidelines that only recommended RFA for LGD in 2015. The mean length of the BE segment was 5.2 cm (range, 1-20).

RESULTS

Invasive cancer

One year after patients had started RFA therapy, the KM rate of invasive cancer in the entire cohort of 2535 patients was .5%. After 2 years of follow-up this rate was 1.2% and at 10 years was 4.1% (Fig. 2). There was no difference in rates of invasive cancer among the 10 sites included in the primary analysis and the other sites (log rank $P = .81$).

During follow-up, 41 patients (1.6%) developed invasive cancer. Four were initially being treated for LGD (.7% of the LGD cohort), 24 for HGD (1.8%), and 13 for IMC

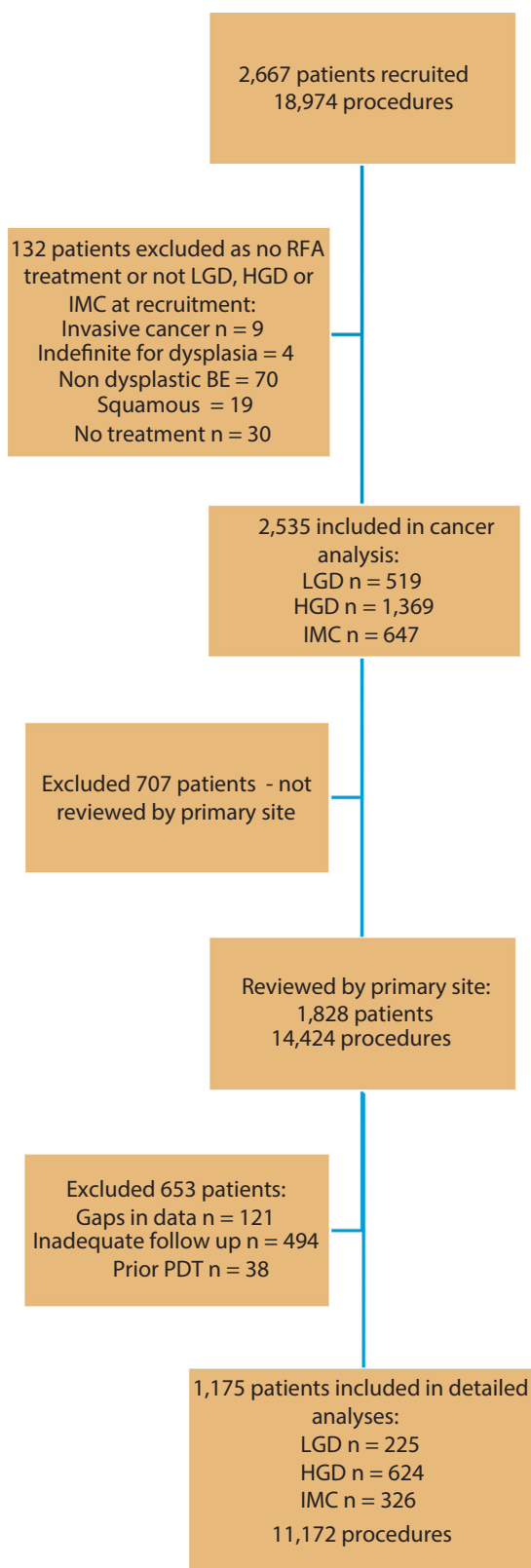


Figure 1. Flow diagram indicating included and excluded patients.

(2.0%) ($\chi^2 P =$ not significant). Of these 41 patients, 22 progressed to invasive cancer within 18 months of initiating EET.

Eleven of the 41 patients initially achieved CR-D at 2 consecutive endoscopies but subsequently relapsed to invasive cancer after a median of 3.4 years (interquartile range [IQR], 1.9-4). The other 30 patients never achieved CR-D and developed invasive cancer after a median 433.5 days (IQR, 310-765). They received a median of 2 ablations (IQR, 2-3.75) before developing cancer.

Follow-up time for the entire cohort was 7856 patient-years, a crude incidence rate of .52 per 100 patient-years. The crude incidence rate in patients with LGD was .20 per 100 patient-years, and the combined crude incidence rate in patients with HGD and IMC was .63 per 100 patient-years. This difference was significant ($\chi^2 P = .015$).

Complete remission of dysplasia

Within 24 months of initiating EET, 1031 of 1175 patients (88.0%) achieved CR-D. There was no difference in remission rates by initial disease severity with LGD achieving 87.2%, HGD 89.1%, and IMC 86.4% (log rank $P =$ not significant).

Younger patients were significantly more likely to achieve CR-D with a mean age of 66 years (95% confidence interval [CI], 66-67) versus 69 years (95% CI, 67-71) for those who did not (unpaired 2-tailed t test $P = .003$). Patients with shorter BE segments also had a higher clearance of dysplasia, with a median initial maximum length of 4 cm (IQR, 2-7) versus 7 cm (IQR, 4-10) where dysplasia remained (Mann-Whitney U test $P < .0001$).

Relapse from CR-D

The KM rate of relapse from CR-D for the entire cohort was 1.1% at 1 year, 2.7% at 2 years, and 5.9% at 8 years. There was no difference by histologic subtype, with .5% at 1 year for LGD patients, 1.5% for HGD, and .7% for IMC (Fig. 3). At 2 years the relapse rates were 1.2%, 3.5%, and 2.0%, respectively, which increased to 2.2%, 6.8%, and 6.3%, respectively, after 8 years. The log rank score showed a significantly higher relapse for patients with IMC than LGD ($P = .04$), but there was no statistically significant difference between any of the other groups.

Dysplasia relapse rates were not related to patient age or initial length of BE. The mean age of those relapsing from CR-D was 67 years (95% CI, 65-70) versus 66 years (95% CI, 66-67) for those who did not (unpaired 2-tailed t test $P = .51$). The median initial maximum length of BE for those who relapsed was 5 cm (IQR, 3-8) versus 4 cm (IQR, 2-7) for those who did not (Mann-Whitney U test $P = .18$). Most relapses (34/41, 82.9%) occurred within 3 years.

TABLE 2. Demographic and outcome data of all 1175 patients with Barrett's esophagus included in clearance of dysplasia and of intestinal metaplasia analysis of the UK HALO RFA registry

Variable	Value
Age, y	
Mean \pm SD	67.2 \pm 9.4
Range	37.7-90.8
Sex	
Male	970 (83)
Female	205 (17)
Ethnicity	
White	1094 (93)
Missing data	81 (7)
Histologic grade at study entry	
Low-grade dysplasia	225 (19)
High-grade dysplasia	624 (53)
Intramucosal cancer	326 (28)
Length of Barrett's esophagus, cm, mean \pm SD (range)	
Prague classification C	3.2 \pm 3.6 (0-19)
Prague classification M	5.2 \pm 3.4 (1-20)
Received primary EMR (before RFA)	
Yes	646 (55)
No	529 (45)

Values are n (%) unless otherwise defined.

RFA, Radiofrequency ablation; SD, standard deviation.

CR-D after relapse

For patients who were initially successfully treated and then relapsed to dysplasia, CR-D2 was achieved in 54.4% after 1 year and 63.4% after 2 years (Fig. 4).

Complete remission of intestinal metaplasia

Within 2 years of starting therapy, 729 of 1175 patients (62.7%) achieved CR-IM. Initial disease severity did not affect this, with CR-IM achieved by 65.2% of LGD patients, 62.0% of HGD patients, and 63.5% of IMC patients (log rank $P =$ not significant).

CR-IM was more likely in younger patients and in those with shorter lengths of BE (4 cm [IQR, 2-6] vs 6 cm [IQR, 3-8], respectively; Mann-Whitney U test $P < .0001$). Age did not impact the likelihood of CR-IM, which was 66 years (95% CI, 66-67) versus 67 years (95% CI, 66-68), respectively (unpaired 2-tailed t test $P = .08$).

Relapse from CR-IM

The rate of relapse from CR-IM for the entire cohort was 4.2% at 1 year, 10.1% at 2 years, and 18.7% at 8 years. The rate of relapse at 1 year was 3.2% in patients with LGD, 5.2% in patients with HGD, and 2.8% in patients with IMC (Fig. 5). At 2 years the relapse rates were 9.8%, 11.9%, and 11.4%, respectively, which increased to

11.3%, 22.1%, and 14.7%, respectively, after 8 years. The rate of relapse was significantly higher for HGD than for LGD (log rank $P = .004$), but there was no significant difference between IMC and HGD (log rank $P = .481$) or IMC and LGD (log rank $P = .907$).

There was also no significant difference in age or length of BE before RFA of those who relapsed and maintained remission from CR-IM at 66 years (95% CI, 63-68) versus 66 years (95% CI, 66-67; unpaired t test $P = .70$). Similarly, the initial median maximum length of BE was identical at 4 cm (IQR, 2.25-6.75) versus 4 cm (IQR, 2-6; Mann-Whitney U test $P = .45$). Although age and length of BE segment were not predictors of relapse, 78.4% (74) of patients relapsing from CR-IM did so within 2 years.

CR-IM after a previous relapse

For 74 patients who relapsed from CR-IM, the rate of CR-IM2 after further treatment was 46.5% after 1 year and 70.0% after 2 years (Fig. 6). For all secondary outcomes, CR-D, CR-IM, CR-D2, and CR-IM2, the percentage of patients taking proton pump inhibitors was between 80% and 90%. This figure likely under-represents the true figure as we had to rely on documentation at the time of endoscopy. We were unable to show any differences in proton pump inhibitor use between those who relapsed and those who did not.

Primary EMR, dilatation, and rescue therapy

Primary EMR (EMR before any RFA therapy) was performed in 646 of 1175 patients (55.0%). The rate of CR-D at 24 months was unchanged at 87.6% versus 88.1% ($\chi^2 P = .80$) for patients without primary EMR, but rescue therapy was much more likely if an EMR had been done before RFA started, at 41.2% versus 17.2% ($\chi^2 P < .00001$).

Rescue therapy (EMR, argon plasma coagulation, or yttrium-aluminum garnet laser) during or after reaching CR-D was required by 360 patients (30.6%) and primarily consisted of EMR ($n = 351$). CR-D was achieved in 287 patients (79.7%). Compared with 815 patients (69.4%) not undergoing rescue therapy, the overall CR-D was 91.4%. CR-D was significantly lower in the group that required rescue therapy ($\chi^2 P < .001$). The proportion of patients who developed cancer was significantly higher in those undergoing rescue therapy (5.0%) versus those not undergoing rescue therapy (.9%; $\chi^2 P < .00001$).

During and after EET, 144 patients (12%) required ≥ 1 dilatation, 68 required 1, 25 required 2, and 51 required >2 dilatations. Undergoing primary EMR ($\chi^2 P = .018$) and >4 ablative procedures ($\chi^2 P = .03$) were both significant predictors of requiring a dilatation. Length of BE before therapy, requiring rescue therapy, and not achieving CR-D or CR-IM were not significant predictors of requiring a dilatation.

The median number of ablations per centimeter of BE rose with disease severity. Patients with LGD had .80 ablations per cm BE, HGD 1.00 ablations per cm, and IMC 1.19

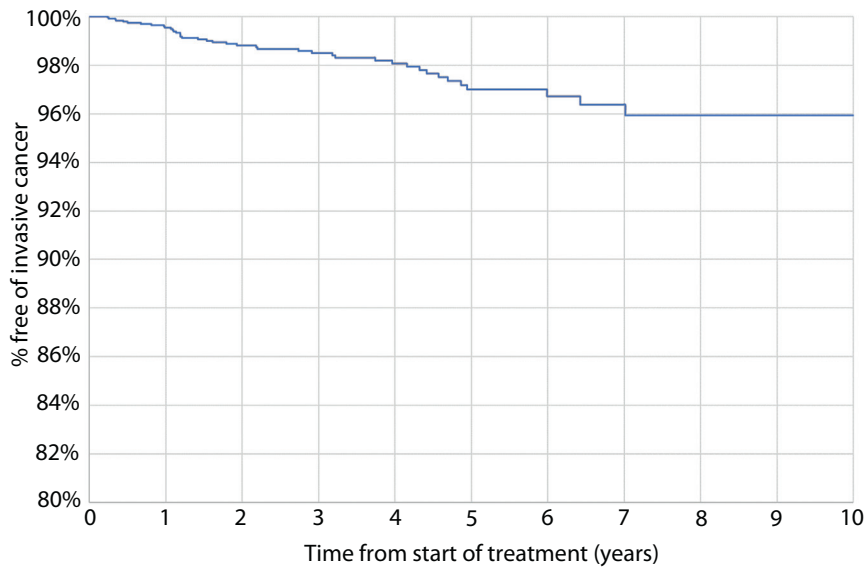


Figure 2. Kaplan-Meier graph of the entire cohort showing the rate of invasive cancers at 10 years from the start of treatment in patients treated with radiofrequency ablation. The y axis is truncated at 80% for ease of viewing. Fifty-three patients reached the 10-year follow-up time point.

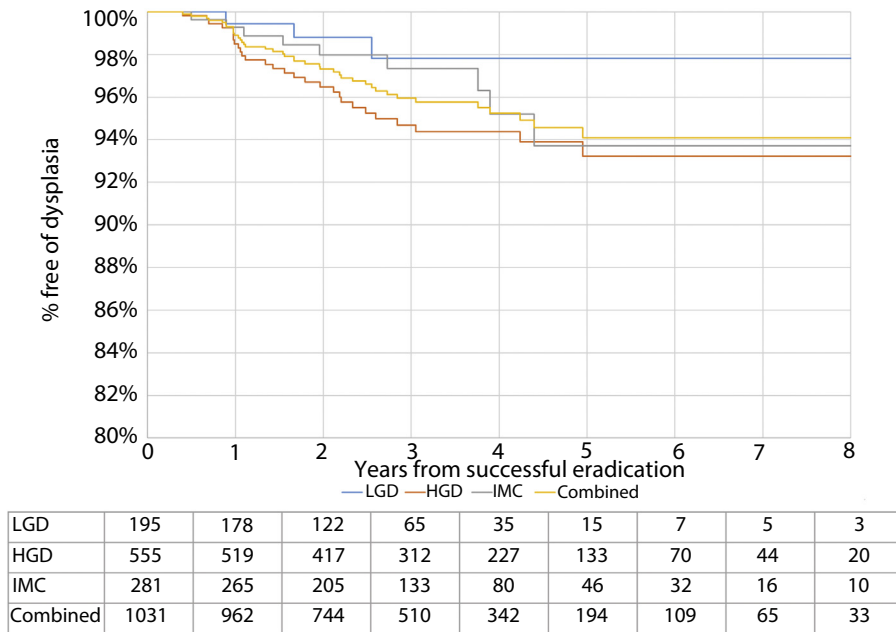


Figure 3. Kaplan-Meier graph showing the rate of relapse from clearance of dysplasia for those patients initially treated for low-grade dysplasia (LGD), high-grade dysplasia (HGD), and intramucosal cancer (IMC). Log rank score between IMC and LGD, $P = .4$. All other comparisons log rank score, $P =$ not significant. The y axis is truncated at 80% for ease of viewing.

ablations per cm BE ($P < .0001$, Wilcoxon signed rank test). The number of EMRs per centimeter of BE was also proportional to initial disease severity: LGD, .08 EMRs/cm BE; HGD, .24 EMRs/cm BE; and IMC, .45 EMRs/cm BE ($P < .001$, Wilcoxon signed rank test).

The number of ablative procedures per centimeter of BE was higher for patients achieving CR-D (1.00 vs .64, Wil-

coxon signed rank $P < .001$). The same was true for those reaching CR-IM (1.37 ablations/cm BE vs .83 ablations/cm BE, Wilcoxon signed rank $P < .001$).

We calculated the chance of each successive RFA procedure achieving CR-D if this had not yet been achieved. After a single RFA procedure, CR-D occurred in 12.9%. Procedural success rose progressively for each procedure until

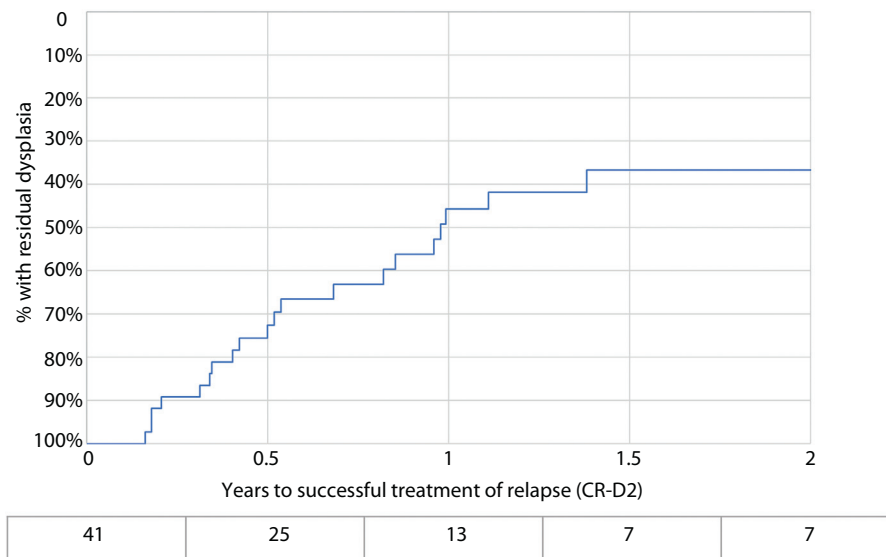


Figure 4. Kaplan-Meier graph showing the rate of the clearance of dysplasia after relapse (CR-D2) in the initial 2 years of therapy (combined for all initial histology types).

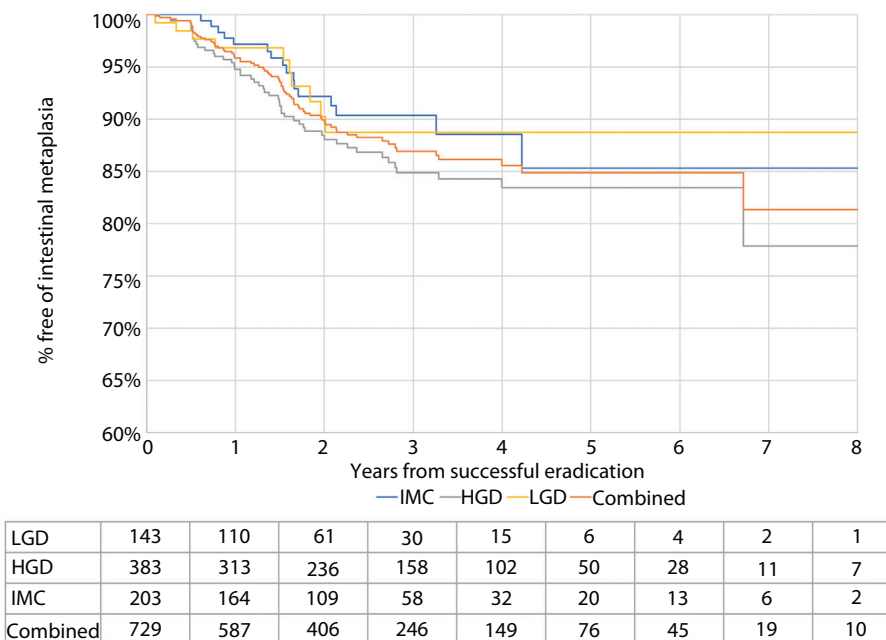


Figure 5. Kaplan-Meier graph showing the rate of relapse from clearance of intestinal metaplasia (CR-IM) for those patients initially treated for LGD, HGD, and IMC. Initial disease severity did not affect the rates of CR-IM. The y axis is truncated at 60% for ease of viewing. *LGD*, Low-grade dysplasia; *HGD*, high-grade dysplasia; *IMC*, intramucosal cancer.

the fifth, where it reached 47.4% of patients still being treated (Fig. 7). Subsequently, the chance of each successive ablation leading to CR-D was reduced.

DISCUSSION

We followed a large cohort of patients for 10 years after commencing RFA therapy, enabling us to publish some of the farthest reaching results. It is well established that endoscopic treatment of dysplastic BE is initially successful

in up to 90% of patients.^{23,24} What is less well understood is how long that benefit lasts and if this contributes to a substantial reduction in progression to cancer.

Our study confirms durable reversal of dysplasia and BE with RFA that reduces cancer risk by more than 90% compared with historical control data of 6% to 19% per annum.²⁵⁻²⁷ The KM rate of progression to EAC in our cohort was <5% after a 10-year follow-up. More RFA is needed for patients with longer segments of BE or more advanced initial disease.

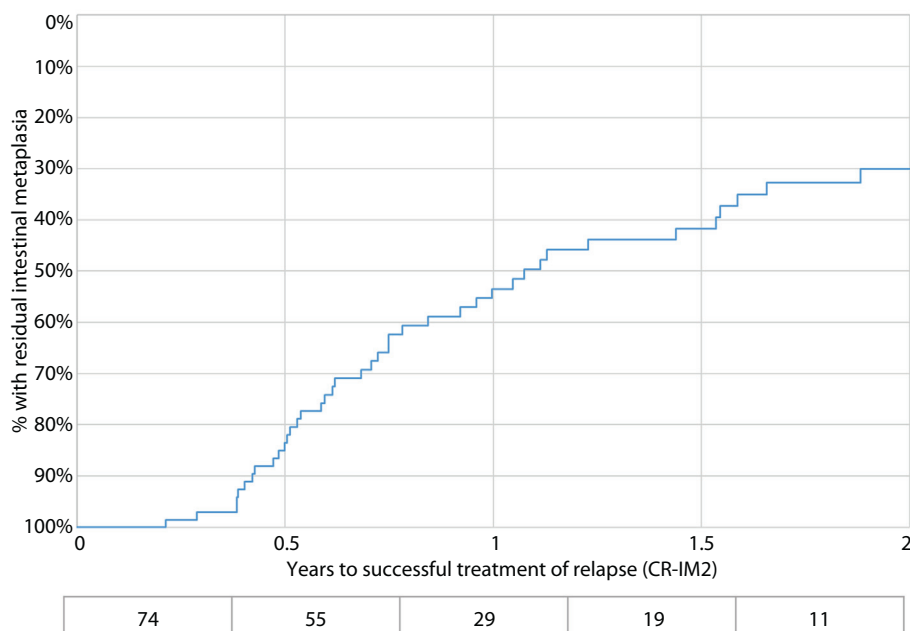


Figure 6. Kaplan-Meier graph showing the rate of clearance of intestinal metaplasia after relapse (CR-IM2) in the initial 2 years of therapy (combined for all initial histology types).

Most relapses occurred within 2 years. Initial disease severity, age, and length of BE before EET were not reliable predictors of relapse from CR-D or CR-IM, but new nodules appearing during RFA that require EMR are associated with a small reduction in treatment success. Finally, we found that even when patients relapse from CR-D and CR-IM, established EET techniques remain efficacious, with over 50% of patients successfully re-treated.

Our work dramatically expands the published literature in long-term follow-up for EET in BE. The U.S. RFA Patient Registry reported a median 2.7-year follow-up of 4982 patients, but only 1305 had dysplasia.²⁸ A systematic review and meta-analysis published this year was only able to report on 794 patients followed for an average of 3.4 years (range, 27-69.7 months),²⁹ highlighting this lack of long-term follow-up.

There is only 1 study, a recently published Dutch study, with 10-year follow-up data on 1386 patients.³⁰ Our larger cohort produced a cancer progression rate of 1.6% at 10 years, an almost identical finding. This compares favorably with the cancer progression rate of 2% published by the U.S. RFA registry. Our rates of relapse from CR-D and CR-IM were higher than those published by the Dutch team. This may be explained by the longer length of BE treated and the lower proportion of patients with LGD in our cohort. Although it is not possible to associate causation between RFA therapy and the incidence of EAC, the incidence of EAC in the United Kingdom was reduced by 3% over the past decade, since the widespread introduction of RFA therapy.

Our study including 2535 patients is the largest study to look at RFA outcomes, either short or

long term. We included data from 28 sites, enabling this study to represent clinical practice across the United Kingdom as well as a range of demographics.

We followed 1175 patients from 10 sites with more precision. This data collection was comprehensive and verified. The authors were able to review every endoscopic procedure, reducing missing data and minimizing individual reporting errors.

Because of the nature of a long-term multicenter study, there was some variability in practice across the sites. Where practice led to large time gaps in data collection, these patients were excluded or censored. This led to a substantial number of exclusions but also enabled a more accurate assessment of the long-term effects of EET in BE. A limitation is that patients were followed by their recruiting site. If patients presented to other hospitals with any of the outcomes or had further therapy, these data were not collected. In addition, approximately 25% of patients were excluded from the detailed analysis because of inadequate follow-up, defined as <18 months. This reflects the high number of patients who dropped out of surveillance programs, either because of older age or patient choice.

We reviewed the differences between patients with early and more advanced disease extensively. The median length of BE was higher in the group with LGD than for those with HGD and IMC, yet the number of EMRs per centimeter of BE was lower, suggesting those with LGD needed less EET therapy than those with more advanced disease. This argues for earlier therapy, which would be easier to perform and require fewer treatment episodes.

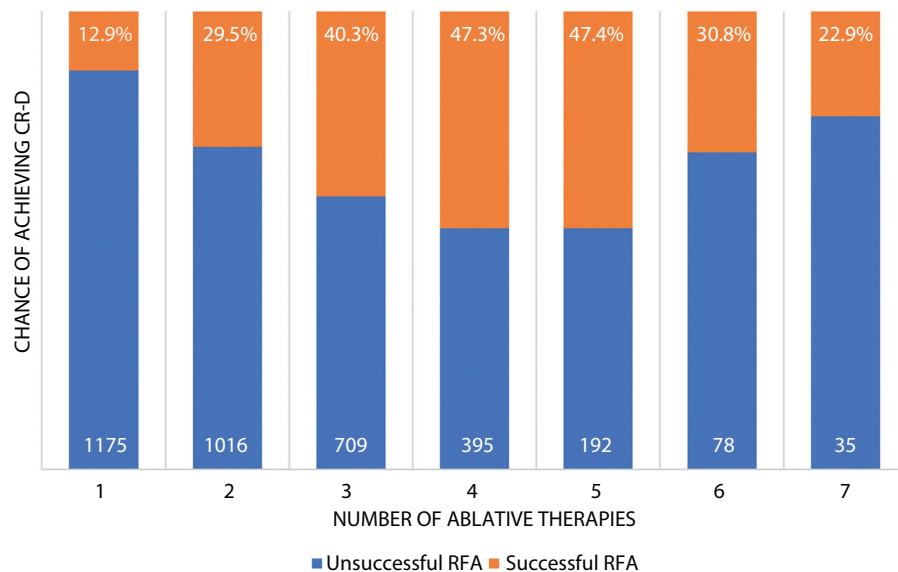


Figure 7. Likelihood of treatment success for each radiofrequency ablation (RFA) procedure.

Implications for clinical practice

EET is primarily used to prevent progression to EAC. In our cohort of 2535 patients, only 41 patients developed invasive cancer throughout the entire study period. For patients with HGD the crude incidence was .53 per 100 patient-years, which is a 10-fold reduction in cancer incidence compared with a meta-analysis calculating annual cancer risk.³¹ The crude incidence rate for IMC was .97 per 100 patient-years. This compares favorably with the original randomized controlled trial.^{24,27}

Our results at 8 years show low rates of relapse to dysplasia across all histologic subgroups, with most of these relapses occurring within 2 years of completion of EET. Age and length of BE segment at the start of EET were not found to be predictors of relapse risk, suggesting that these should not be used to stratify the risk of recurrence. It was also possible to successfully treat most patients who relapsed. These data suggest that continuing annual surveillance endoscopies, as recommended by societal guidelines,^{20,32} beyond 2 years may offer little additional benefit while providing no evidence that the histologic subtype before EET should be used to guide surveillance intervals.³³ Our findings confirm our previous work in recommending more intense earlier surveillance, which is reduced over time.³⁴

We may be undertreating those with longer segments of BE. Although the number of ablative procedures per patient is comparable between those who achieve CR-D and those who do not, the number of ablative procedures per centimeter of BE is higher for patients achieving CR-D than for those not achieving this. For CR-IM this difference is even more substantial. Coupled with what is already understood about cancer progression risks, this suggests we should be more active in our treatment of individuals

with longer BE segments and those with high-grade disease (either HGD or IMC).

In our cohort with a median maximum BE length of 5.2 cm, the likelihood of achieving CR-D reduces rapidly after 5 ablative episodes, suggesting that these patients may have refractory disease and alternative intervention should be considered. This must be understood in the context of additional risk of stricturing with further procedures. In this cohort the risk of stricturing after EET requiring dilatation remained within limits suggested by a consensus publication.³³ In addition, these data must be considered alongside the established literature that reports longer segments of BE typically require more therapy.³⁵

Some endoscopists have advocated endoscopic submucosal dissection as routine treatment.³⁶ This technique is harder to learn than EMR and has a higher risk profile. Our work suggests that EMR with RFA should remain the standard of care, although in specific circumstances operators might want to consider endoscopic submucosal dissection, particularly for patients who develop new lesions after RFA has commenced. However, even here, the success of rescue EMR is still very high.

CONCLUSIONS

We have shown long-term benefit of EET in reducing rates of invasive cancer in a large cohort of patients, with RFA alone achieving excellent results in selected patients. Durability was high, with most relapses occurring shortly after completion of therapy and being treatable with the same modality. EET with RFA is now firmly established as the primary therapy for dysplastic BE.

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Abbreviations: BE, Barrett's esophagus; CR-D, clearance of dysplasia; CR-D2, clearance of dysplasia after relapse; CR-IM, clearance of intestinal metaplasia; CR-IM2, clearance of intestinal metaplasia after relapse; EET, endoscopic eradication therapy; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; IQR, interquartile range; IMC, intramucosal carcinoma; KM, Kaplan-Meier; LGD, low-grade dysplasia; RFA, radiofrequency ablation.

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