

CLINICAL—ALIMENTARY TRACT

Late Recurrence of Barrett's Esophagus After Complete Eradication of Intestinal Metaplasia is Rare: Final Report From Ablation in Intestinal Metaplasia Containing Dysplasia Trial



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BACKGROUND & AIMS: The goal of treatment for Barrett's esophagus (BE) with dysplasia is complete eradication of intestinal metaplasia (CEIM). The long-term durability of CEIM has not been well characterized, so the frequency and duration of surveillance are unclear. We report results from a 5-year follow-up analysis of patients with BE and dysplasia treated by radiofrequency ablation (RFA) in the randomized controlled Ablation of Intestinal Metaplasia Containing Dysplasia (AIM) trial. **METHODS:** Participants for the AIM Dysplasia trial (18–80 years old) were recruited from 19 sites in the United States and had endoscopic evidence of non-nodular dysplastic BE ≤ 8 cm in length. Subjects ($n = 127$) were randomly assigned (2:1 ratio) to receive either RFA (entire BE segment ablated circumferentially) or a sham endoscopic procedure; patients in the sham group were offered RFA treatment 1 year later, and all patients were followed for 5 years. We collected data on BE recurrence (defined as intestinal metaplasia in the tubular esophagus) and dysplastic BE recurrence among patients who achieved CEIM. We constructed Kaplan-Meier estimates and applied parametric survival analysis to examine proportions of patients without any recurrence and without dysplastic recurrence. **RESULTS:** Of 127 patients in the AIM Dysplasia trial, 119 received RFA and met inclusion criteria. Of those 119, 110 (92%) achieved CEIM. Over 401 person-years of follow-up (mean, 3.6 years per patient; range, 0.2–5.8 years), 35 of 110 (32%) patients had recurrence of BE or dysplasia, and 19 (17%) had dysplasia recurrence. The incidence rate of BE recurrence was 10.8 per 100 person-years overall (95% CI, 7.8–15.0); 8.3 per 100 person-years among patients with baseline low-grade dysplasia (95% CI, 4.9–14.0), and 13.5 per 100 person-years among patients with baseline high-grade dysplasia (95% CI 8.8–20.7). The incidence rate of dysplasia recurrence was 5.2 per 100 person-years overall (95% CI 3.3–8.2); 3.3 per 100 person-years among patients with baseline low-grade dysplasia (95% CI 1.5–7.2), and 7.3 per 100 person-years among patients with baseline high-grade dysplasia (95% CI 4.2–12.5). Neither BE nor dysplasia recurred at a constant rate. There was a greater probability of recurrence in the first year following CEIM than in the following 4 years combined. **CONCLUSIONS:** In this analysis of prospective cohort data from the AIM Dysplasia trial, we found BE to recur after CEIM by RFA in almost one third of patients with baseline dysplastic disease; most recurrences occurred during the first year after CEIM. However, patients who achieved CEIM and

remained BE free at 1 year after RFA had a low risk of BE recurrence. Studies are needed to determine when surveillance can be decreased or discontinued; our study did not identify any BE or dysplasia recurrence after 4 years of surveillance.

Keywords: LGD; Low Grade Dysplasia; HGD; High Grade Dysplasia; Prognostic Factor; Long-term Outcome.

Barrett's esophagus (BE) is a precancerous state defined by the replacement of normal esophageal squamous mucosa by intestinal metaplasia. This metaplastic change predisposes to the development of esophageal adenocarcinoma. BE is thought to progress to esophageal adenocarcinoma via a series of steps beginning with non-dysplastic BE, progressing to low-grade dysplasia (LGD), and on to high-grade dysplasia (HGD). LGD and HGD carry an increased risk of progression and malignant transformation compared with non-dysplastic BE.^{1–3} Eradication of dysplastic BE with endoscopic ablative techniques such as radiofrequency ablation (RFA) is commonly performed to reduce the risk of malignant progression.^{4,5} Dysplastic BE can usually be treated to complete eradication of intestinal metaplasia (CEIM).⁶

After CEIM, patients undergo surveillance where serial endoscopy is performed to assess for recurrence of BE.^{7,8} Per recent guidelines, patients with HGD who have been treated to CEIM enter a surveillance program with 3-month intervals for the first year, 6-month intervals in the second year, and then annually thereafter. For LGD, the first year interval is 6 months and then annually thereafter. Research

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Abbreviations used in this paper: AIM, Ablation of Intestinal Metaplasia Containing Dysplasia trial; BE, Barrett's esophagus; CE-D, complete eradication of dysplasia; CEIM, complete eradication of intestinal metaplasia; CI, confidence interval; HGD, high grade dysplasia; LGD, low grade dysplasia; RFA, radiofrequency ablation.

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EDITOR'S NOTES**BACKGROUND AND CONTEXT**

Radiofrequency ablation is an effective treatment for Barrett's esophagus (BE) with dysplasia, but we have little information about long-term outcomes with this procedure.

NEW FINDINGS

Patients treated with radiofrequency ablation for dysplastic BE have >30% chance of having recurrent BE within 5 years. Most recurrences are responsive to further endoscopic therapy. Almost all recurrences happen in the first 2 years following therapy.

LIMITATIONS

This study was performed in tertiary centers expert in the care of BE.

IMPACT

Many patients with BE who undergo RFA will require repeat treatment. Endoscopic surveillance of patients with BE treated with radiofrequency ablation will likely be of diminishing value as the time since ablation grows.

to date has consistently demonstrated low rates of recurrence after CEIM.⁹⁻¹² However, discontinuing surveillance remains a contentious area, in large part because follow-up of BE patients in most prior studies is only 1 to 2 years,¹⁰⁻¹² leaving the long-term risk of recurrence and progression of BE in doubt.

Here we present the final report of the Ablation of Intestinal Metaplasia Containing (AIM) Dysplasia trial, representing 5 years of follow-up after initial treatment in a randomized controlled trial of RFA of dysplastic BE. The aim of this study was to assess the rate of recurrence of BE in prospectively followed patients who had presented with dysplasia and then achieved CEIM.

Methods

The AIM Dysplasia Trial

Participants for the AIM Dysplasia trial were recruited at 19 US sites. Eligibility criteria included age (18 to 80 years) and endoscopic evidence of non-nodular dysplastic BE ≤ 8 cm in length. A central pathology laboratory confirmed histologic grade. Previous endoscopic mucosal resection was permissible at least 8 weeks before entry, provided that subsequent endoscopy demonstrated non-nodular dysplasia. Exclusion criteria included pregnancy, active esophagitis or stricture, history of esophageal malignancy, varices, uncontrolled coagulopathy, or life expectancy of <2 years as judged by the investigator.

Subjects were randomly assigned in a 2:1 ratio to receive either RFA or a sham endoscopic procedure. Randomization was stratified by grade of dysplasia (LGD vs HGD) at study entry and endoscopic length of BE (<4 cm vs 4-8 cm). All underwent upper endoscopy, esophageal intubation with a study catheter, measurement of the esophageal inner diameter, and in-room assignment of treatment group (RFA vs sham) using a computer-generated block randomization sequence. In

subjects assigned to RFA, the entire BE segment was ablated circumferentially. In the sham arm, the study catheter was removed and the procedure terminated.

RFA subjects could receive up to 4 RFA sessions in the first year, performed at 0, 2, 4, and 9 months based on interval biopsy results, and 1 RFA session in the second year (15 months). An initial treatment was performed with a HALO360 device, the circumferential balloon catheter, with settings of 12 joules/cm² and 300 watts (BARRX Medical, Inc, Sunnyvale, CA, now Medtronic, Sunnyvale, CA). Any necessary follow-up treatments of residual BE were performed with a HALO90 focal ablation device. After achieving CEIM, subjects underwent endoscopy with biopsy at 6 and 12 months (LGD arm), or 3, 6, 9, and 12 months (HGD arm). Endoscopic biopsies were performed with maximum-capacity or jumbo forceps in 4 quadrants every 1 cm throughout the original length of BE, with the most distal biopsies 3-5 mm above the gastric folds, plus directed biopsies of any visible abnormalities.

After completion of the 12-month assessment, subjects in the sham arm were offered cross-over to active (RFA) treatment. Because subjects initially assigned to sham spent 12 months without ablative therapy, the earliest CEIM endoscopy in the sham group occurred after the patient had been in the study for at least 14 months, 2 months after their first RFA.

Subjects demonstrating CEIM at 2 years after initial treatment were eligible for participation in a 3-year study extension. The purpose of this extension was to assess the long-term durability of changes induced by RFA, and outcomes associated with treatment. Subjects who did not achieve CEIM at 2 years were offered a single salvage RFA treatment at that time with repeat biopsy 2 months later. Those with CEIM at repeat biopsy were then eligible for the study extension. The study extension provided for 3 additional years of follow-up for these subjects (to a total of 5 years), with annual surveillance endoscopies with biopsies identical in methodology to the primary protocol. All subjects in the trial extension were maintained on esomeprazole 40 mg twice daily. All institutions' ethics committees approved the protocols for both the parent trial and the extension. The trial was performed in accordance with the Declaration of Helsinki. Further details of patient selection and have been published previously.^{4,10}

Statistical Methods

We examined rates of any recurrence and dysplastic recurrence among AIM Dysplasia trial patients who achieved CEIM. Any recurrence is defined as the first recurrence with intestinal metaplasia, dysplasia, or adenocarcinoma. Dysplastic recurrence is defined as the first recurrence with dysplasia or adenocarcinoma. For the primary analysis, CEIM was defined as a single endoscopy visit without endoscopic evidence of BE and with biopsies negative for intestinal metaplasia or dysplasia. Sensitivity analysis was performed with a definition of CEIM requiring 2 such endoscopy visits. Descriptive statistics were reported as mean and standard deviation for continuous variables and as number and percentage for categorical variables. We calculated the proportion of patients who achieved CEIM, who experienced recurrence, who experienced progression, and who achieved second CEIM.

We constructed right-censored survival curves for any recurrence and for dysplastic recurrence after CEIM and compared the incidence of recurrence between patients with

baseline LGD and HGD using the Wilcoxon Rank-Sum test. We used the Kaplan-Meier estimate of the survival function to examine proportions and 95% confidence intervals (CI) of patients without recurrence in the overall population and stratified by baseline histologic grade continuously and at annual intervals of 1 through 5 years. We examined the Epanechnikov Kernel-Smoothed estimate of the hazard function with optimal and arbitrary bandwidth settings to examine changes in recurrence rate over time.¹³ We calculated incidence rates and 95% CI of recurrence and dysplastic recurrence using a Poisson model.

We also fit parametric failure time models with an exponential distribution, Weibull distribution, and spline functions to examine changes in the rate of recurrence over time.¹⁴ We also calculated the proportion and 95% bootstrap CI of patients with CEIM at each annual visit allowing interim retreatments. Bootstrap CIs were performed with 10,000 replicates using the Mersenne-Twister random number generator.

While only patients who achieved CEIM were included for Kaplan-Meier analyses of recurrence, analysis of the proportion of patients with CEIM at selected time intervals included all treated patients. The durability analysis was performed in 2 ways, 1 that considered any recurrence a permanent failure, demonstrated in Kaplan-Meier analyses, and a second that allowed for patients to be re-treated and re-gain CEIM, represented in tabular form. All statistical analyses were performed using SAS software (SAS version 9.4; SAS Institute Inc, Cary, NC).

Results

Inclusion and Censoring of Patients in the Surveillance Cohort

Of 127 patients initially randomized in the AIM Dysplasia trial, 64 had LGD and 63 had HGD. After cross-over, 119 received RFA and were included for analysis of the proportion with CEIM. Of these 119, 110 (92%) achieved CEIM and were included for analysis of recurrence

(Figure 1). These 110 patients had an average age of 66 years and were predominantly male (87%) and white (95%) (Table 1). Patients were observed for 401.1 person-years (mean, 3.6 years per patient; range, 0.2–5.8 years) after they achieved CEIM.

Of 110 patients entering surveillance, 5 were lost to follow-up during the first 2 years and 6 were ineligible because of not being in CEIM at the 2-year visit. The 5 losses to follow-up consisted of 2 subjects who had progression of disease during treatment, 1 because of diagnosis of amyotrophic lateral sclerosis, and 2 who were unreachable. Of the remaining 99 patients eligible for the study extension at the end of year 2, 2 dropped out because their site did not participate in extension, 4 died of unrelated causes, 2 could not be reached, and 16 subjects declined to participate in the extension. The remaining 75 enrolled in the study extension and returned for the year 3 visit.

Any Recurrence of Intestinal Metaplasia, Dysplasia, or Progression to Adenocarcinoma

Over 324.5 person-years of follow-up (mean, 2.9 years per patient; range, 0.2–5.5 years), 35 of 110 (32%) patients experienced any recurrence. Among patients with baseline LGD, 14 (26%) had recurrence, while 21 (38%) with baseline HGD had recurrence. The incidence rate of any recurrence was 10.8 (95% CI 7.8–15.0) per 100 person-years overall, 8.3 (95% CI 4.9–14.0) per 100 person-years among patients with LGD, and 13.5 (95% CI 8.8–20.7) per 100 person-years among patients with HGD. Patients with baseline HGD had a numerically higher rate of any recurrence than patients with baseline LGD, but were not at a statistically significant increased risk of any recurrence with a rate ratio of 1.63 (95% CI 0.83–3.20) compared with patients with baseline LGD (Figure 2). Of the 35 recurrences, 10 (29%) had subsquamous intestinal metaplasia on 1 or more fragments from the biopsy level with

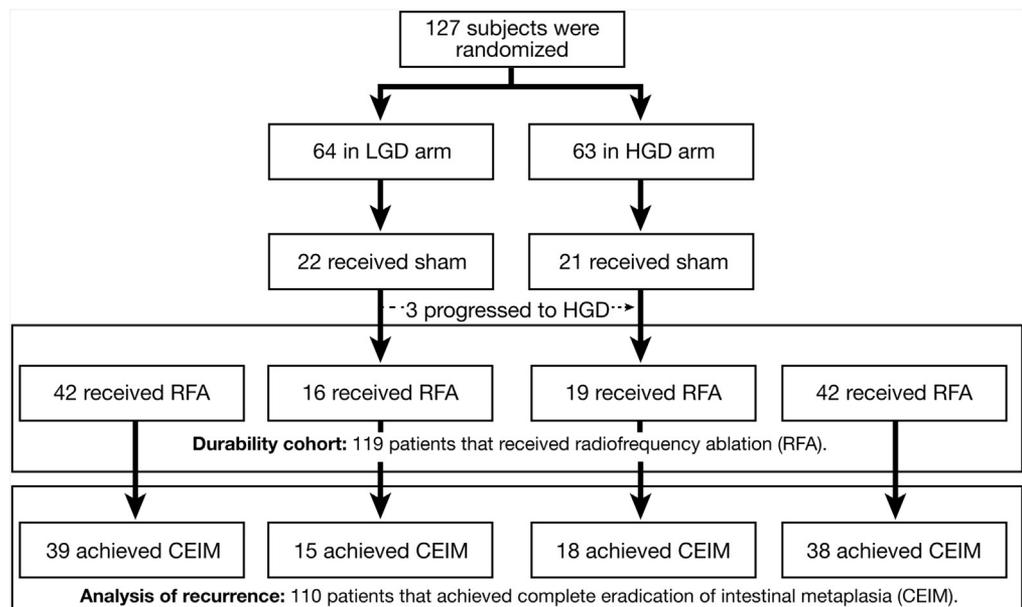


Figure 1. Inclusion of 119 patients in the durability cohort allowing interim “touch-up” treatments and 110 patients in the analysis of recurrence not allowing “touch-up” treatments.

Table 1. Baseline Characteristics of Patients in the Analysis of Recurrence (N = 110)

Age, y (mean ± SD)	66.2 ± 8.5
Male sex, n (%)	96 (87.3)
Race - white, n (%)	105 (95.5)
BMI (mean ± SD)	29.2 ± 5.3
Years with BE prior to enrollment (mean ± SD)	5.5 ± 5.0
Years with dysplasia prior to enrollment (mean ± SD)	2.5 ± 2.9
Prague C length, cm (mean ± SD)	2.4 ± 2.5
Prague M length, cm (mean ± SD)	3.7 ± 2.7
Baseline characteristics of patients in the durability cohort (N = 119)	
Age, y (mean ± SD)	66.0 ± 8.9
Male sex, n (%)	102 (85.7)
Race - white, n (%)	113 (95.0)
BMI (mean ± SD)	29.2 ± 5.3
Years with BE prior to enrollment (mean ± SD)	5.4 ± 4.9
Years with dysplasia prior to enrollment (mean ± SD)	2.4 ± 2.8
Prague C length, cm (mean ± SD)	2.4 ± 2.5
Prague M length, cm (mean ± SD)	3.7 ± 2.7

recurrence. Of these 10 recurrences showing subsquamous metaplasia, 4 had 1 or more biopsies from the same endoscopy showing recurrence with no subsquamous metaplasia. Therefore, 6 out of the 35 recurrences were solely subsquamous (4 non-dysplastic BE, 1 indefinite for dysplasia, and 1 with LGD). No recurrence with subsquamous intestinal metaplasia was higher than LGD. Six (17%) of the recurrences were on targeted biopsies and these consisted of 2 patients with adenocarcinoma, 1 with HGD, 1 with LGD, and 2 with intestinal metaplasia recurrence.

Recurrence With Dysplasia or Progression to Adenocarcinoma

Over 363.1 person-years of follow-up (mean, 3.3 years per patient; range, 0.2–5.7 years) 19 (17%) experienced dysplastic recurrence. The incidence rate of dysplastic recurrence was 5.2 (95% CI 3.3–8.2) per 100 person-years overall, 3.3 (95% CI 1.5–7.2) per 100 person-years among patients with LGD, and 7.3 (95% CI 4.2–12.5) per 100 person-years among patients with HGD. Patients with baseline HGD had a numerically higher rate of dysplastic recurrence than patients with baseline LGD, but were not at a statistically significant increased risk of dysplastic recurrence with a rate ratio of 2.24 (95% CI 0.85–5.89) compared with patients with baseline LGD. Of the 35 patients with recurrence, 24 (69%) went on to achieve second CEIM after further endoscopic therapy. Of the 19 patients with dysplastic recurrence, 14 (74%) achieved second CEIM. During surveillance, 4 (7%) patients with LGD and 2 (4%) with HGD had progression of dysplasia to a condition worse than their baseline histologic grade.

Change in the Rate Of Recurrence Over Time

There was a greater probability of any recurrence or dysplastic recurrence in the first year following CEIM than in the following 4 years combined (Table 2). Fitting time to any recurrence and dysplastic recurrence to an exponential distribution, which assumes a constant rate of recurrence, produced a poor fit, indicating that recurrence did not occur at a constant rate. A Weibull distribution significantly improved fit, yielding an estimated shape parameter k of

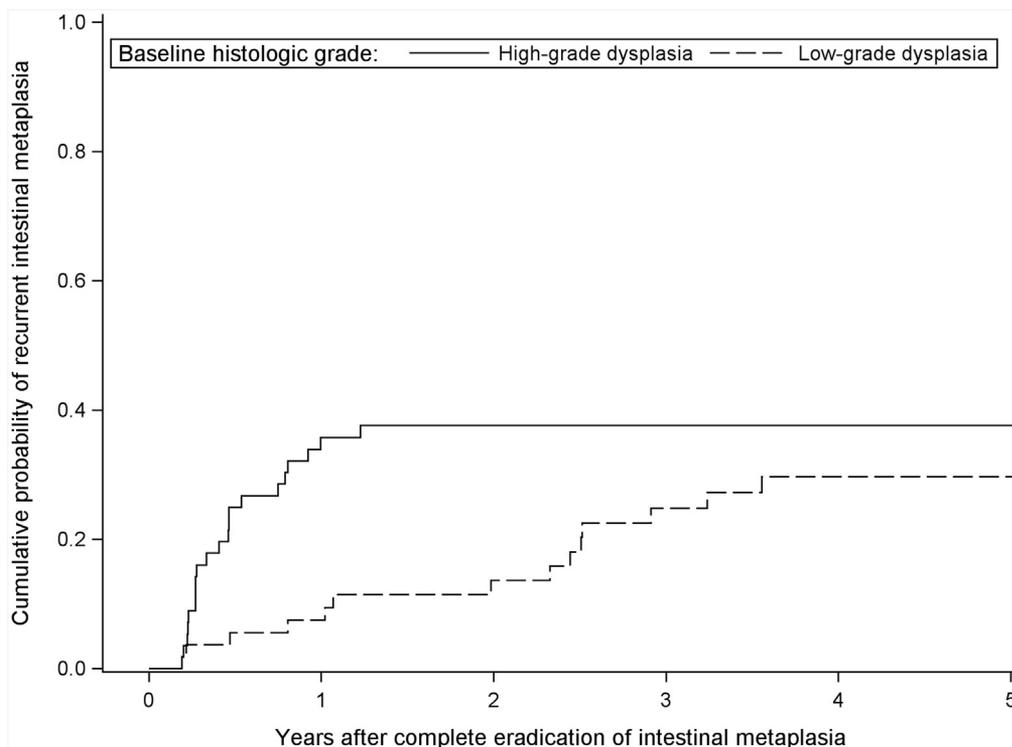


Figure 2. Estimated proportion of subjects with any recurrence stratified by baseline histologic grade after CEIM not allowing interim “touch-up” treatments.

Table 2. Kaplan-Meier Estimates of the Cumulative Incidence and 95% CL of Recurrence of BE-Associated Neoplasia by Year Following CEIM not Allowing Interim "Touch-up" Treatments

Year	HGD at baseline		LGD at baseline		Combined surveillance cohort	
	Events	Cumulative incidence % (95% CL)	Events	Cumulative incidence % (95% CL)	Events	Cumulative incidence % (95% CL)
Any recurrence						
First	20	35.8 (23.2, 48.3)	4	7.5 (0.4, 14.6)	24	22.0 (14.2, 29.8)
Second	1	37.7 (24.9, 50.4)	3	13.7 (4.2, 23.1)	4	26.0 (17.7, 34.3)
Third	0	37.7 (24.9, 50.4)	5	24.8 (12.5, 37.1)	5	31.4 (22.5, 40.4)
Fourth	0	37.7 (24.9, 50.4)	2	29.7 (16.5, 43.0)	2	33.8 (24.5, 43.0)
Fifth	0	37.7 (24.9, 50.4)	0	29.7 (16.5, 43.0)	0	33.8 (24.5, 43.0)
Recurrence with LGD or higher						
First	10	17.9 (7.8, 27.9)	2	3.8 (0.0, 8.7)	12	10.9 (5.1, 16.7)
Second	2	21.7 (10.8, 32.6)	1	5.7 (0.0, 11.9)	3	13.8 (7.3, 20.3)
Third	0	21.7 (10.8, 32.6)	2	10.1 (1.7, 18.6)	2	16.1 (9.0, 23.1)
Fourth	1	24.1 (12.6, 35.6)	1	12.7 (3.1, 22.4)	2	18.6 (10.9, 26.2)
Fifth	0	24.1 (12.6, 35.6)	0	12.7 (3.1, 22.4)	0	18.6 (10.9, 26.2)
Recurrence with HGD or higher						
First	7	12.5 (3.8, 21.2)	1	1.9 (0.0, 5.4)	8	7.3 (2.4, 12.2)
Second	0	12.5 (3.8, 21.2)	1	3.8 (0.0, 9.0)	1	8.3 (3.1, 13.4)
Third	0	12.5 (3.8, 21.2)	2	8.2 (0.5, 16.0)	2	10.5 (4.6, 16.4)
Fourth	2	17.1 (6.8, 7.4)	1	10.9 (1.8, 20.0)	3	14.2 (7.2, 21.1)
Fifth	0	17.1 (6.8, 7.4)	0	10.9 (1.8, 20.0)	0	14.2 (7.2, 21.1)
Recurrence with intramucosal adenocarcinoma						
First	2	3.6 (0.0, 8.4)	0	0.0 ^a	2	1.8 (0.0, 4.3)
Second	0	3.6 (0.0, 8.4)	1	2.0 (0.0, 5.9)	1	2.8 (0.0, 5.9)
Third	0	3.6 (0.0, 8.4)	0	2.0 (0.0, 5.9)	0	2.8 (0.0, 5.9)
Fourth	0	3.6 (0.0, 8.4)	0	2.0 (0.0, 5.9)	0	2.8 (0.0, 5.9)
Fifth	0	3.6 (0.0, 8.4)	0	2.0 (0.0, 5.9)	0	2.8 (0.0, 5.9)

Abbreviations: BE, Barrett's esophagus; CEIM, complete eradication of intestinal metaplasia; CL, confidence limits; HGD, high grade dysplasia; LGD, low grade dysplasia.

^aConfidence limits are omitted when no events occurred.

0.62 (95% CI 0.55–0.71) for any recurrence and 0.53 (95% CI 0.45–0.65) for dysplastic recurrence. The shape parameter was significantly < 1 , demonstrating decreasing rates of recurrence and dysplastic recurrence over time. The rates of recurrence with HGD and mucosal adenocarcinoma recurrence also decreased with time after CEIM, but this did not reach statistical significance.

Examination of Kaplan-Meier estimates (Figures 2 and 3) and the smoothed hazard function (Figure 4) show an increased rate of recurrence at the 3- and 6-month visits immediately after CEIM was achieved. Thereafter, the predicted rate of recurrence for each subsequent year decreased to a plateau. Whether rates decreased to a constant plateau or continued to decrease in years 4 and 5 was sensitive to the model chosen for parametric survival analysis or the smoother bandwidth in the case of the smoothed hazard function.

Proportion of Patients With Current Remission of Intestinal Metaplasia

Patients in this trial received a prescribed surveillance endoscopy protocol, with further endoscopic therapy for recurrences. An additional important outcome in describing the durability after CEIM is the proportion of patients with

CEIM or complete eradication of dysplasia (CE-D) allowing for patients to receive retreatment. Tabular estimates by year show that among 73 patients completing 5 years of surveillance, 72 (99%) had CE-D and 66 (90%) had CEIM, when allowing for intervening treatment of recurrences (Table 3).

Sensitivity analysis

Our sensitivity analysis defining CEIM as 2 clean endoscopies did not significantly alter these findings. Even after requiring 2 negative endoscopies for CEIM, subjects still had a higher rate of recurrence in year 1 of follow-up than the subsequent 4 years combined (Supplementary Table 1, Supplementary Figures 1–3).

Discussion

In this prospective, multicenter study assessing the 5-year risk of recurrence of BE among patients with dysplastic BE at baseline, the vast majority were successfully treated to CEIM. However, recurrence after CEIM was common, occurring in 32% of the cohort. Of 35 recurrence events, 24 occurred in the first year and none during the fifth year. While some portion of this decline is attributable

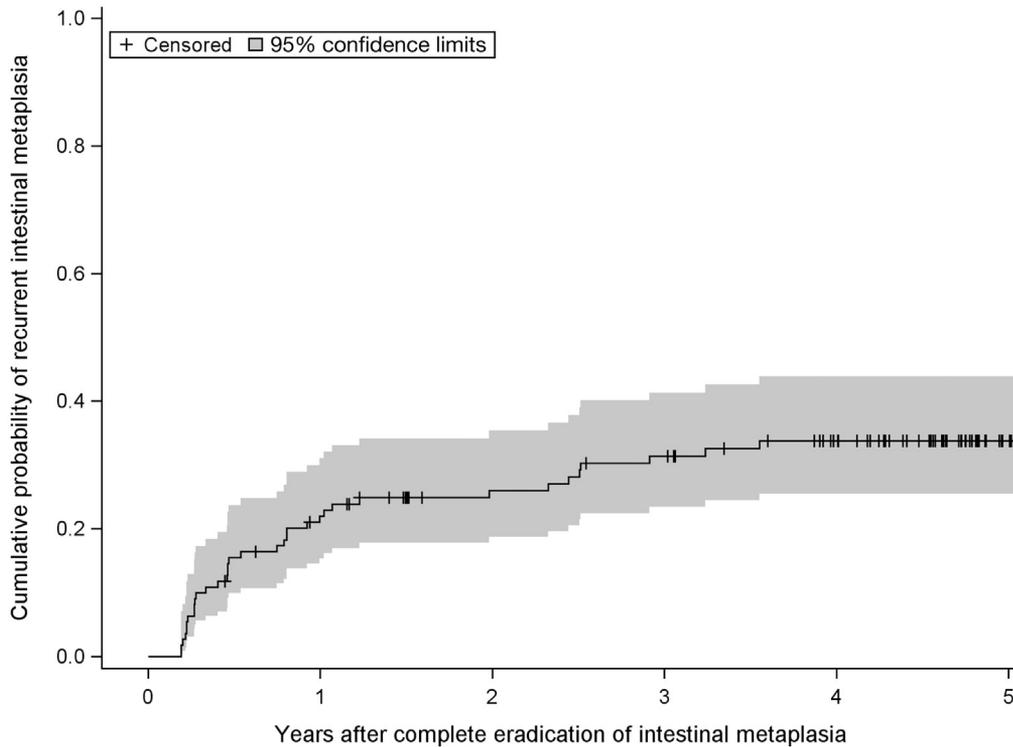


Figure 3. Estimated proportion of subjects with any recurrence after CEIM not allowing interim “touch-up” treatments.

to the fact that not all patients completed 5 years of surveillance, parametric survival analysis suggests 2 distinct phases of recurrence risk, rather than a continuum: an acute phase of elevated risk during the first year that is followed by a longer term trend toward decreased rates of

recurrence over time. While some early recurrence may be because of sampling error, attributing these findings solely to sampling error (and premature declaration of CEIM) is not supported by our sensitivity analysis, where requiring 2 clean endoscopies before CEIM did not meaningfully change

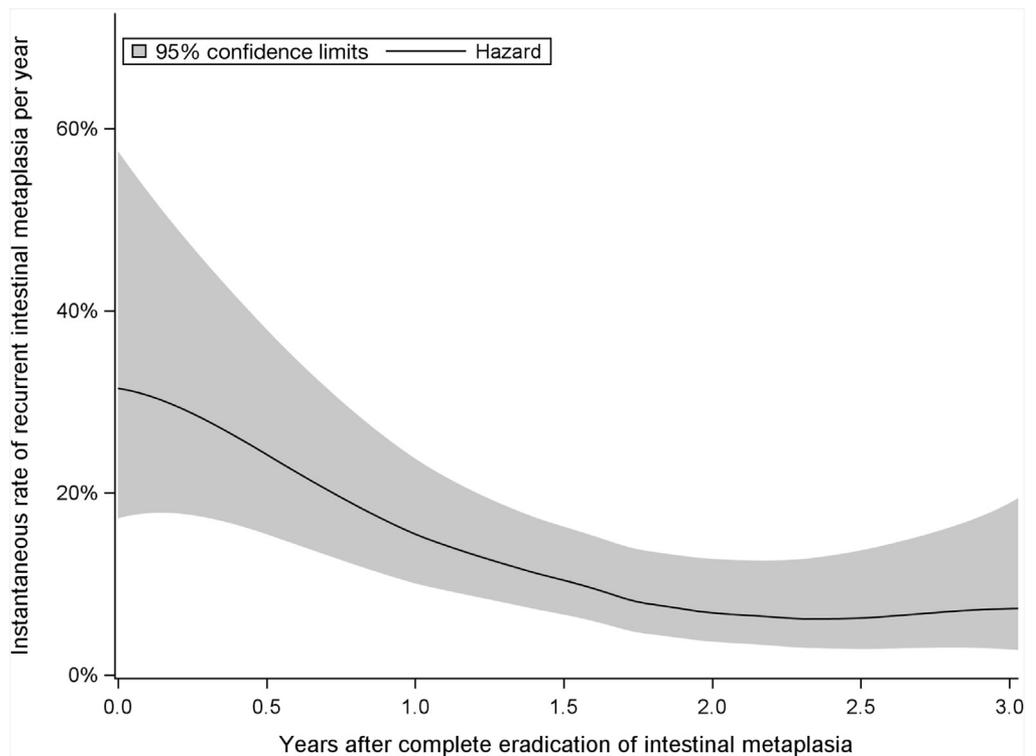


Figure 4. Estimated hazard function, or instantaneous rate, for recurrence of intestinal metaplasia following CEIM not allowing interim “touch-up” treatments.

Table 3. Proportion of 119 Patients Treated With RFA With CEIM and CE-D by Year Following First Treatment Allowing Interim "Touchup" Treatments

Year	CE-D		CEIM	
	Number / N ^a	% (95% CL)	Number / N	% (95% CL)
All enrolled patients				
First	103 / 115	89.6 (84.0, 95.2)	90 / 115	78.3 (70.7, 85.8)
Second	101 / 106	95.3 (91.2, 99.3)	99 / 106	93.4 (88.7, 98.1)
Third	74 / 75	98.7 (96.1, 100.0)	71 / 75	94.7 (89.6, 86.9)
Fourth	73 / 77	94.8 (89.8, 99.8)	67 / 77	87.0 (79.5, 94.5)
Fifth	72 / 73	96.8 (96.0, 100.0)	66 / 73	90.4 (83.7, 97.2)
Patients with baseline LGD				
First	53 / 55	96.4 (91.4, 100.0)	45 / 55	81.8 (71.6, 92.0)
Second	51 / 52	98.1 (94.3, 100.0)	51 / 52	98.1 (94.3, 100.0)
Third	39 / 39	100.0 (91.0, 100.0)	36 / 39	92.3 (83.9, 100.0)
Fourth	38 / 40	95.0 (88.2, 100.0)	32 / 40	80.0 (67.6, 92.4)
Fifth	32 / 38	84.2 (72.6, 95.8)	32 / 38	84.2 (72.6, 95.8)
Patients with baseline HGD				
First	50 / 56	89.3 (81.2, 97.4)	45 / 56	80.4 (70.0, 90.8)
Second	50 / 54	92.6 (85.6, 99.6)	48 / 54	88.9 (80.5, 97.3)
Third	35 / 36	97.2 (91.9, 100.0)	35 / 36	97.2 (91.9, 100.0)
Fourth	35 / 37	94.6 (87.3, 100.0)	35 / 37	94.6 (87.3, 100.0)
Fifth	34 / 35	97.1 (91.6, 100.0)	34 / 35	97.1 (91.6, 100.0)

Abbreviations: CE-D, complete eradication of dysplasia; CEIM, complete eradication of intestinal metaplasia; HGD, high grade dysplasia; LGD, low grade dysplasia; RFA, radiofrequency ablation.

^aN is the number of patients remaining at risk at the respective time points.

our findings. Even with this more rigorous definition, over half of recurrence events occurred in the first year of follow-up. Rather, our results suggest a true propensity to early vs late recurrence, lending credence to current recommendations based on expert opinion for aggressive screening during the first year after CEIM, followed by a broader spacing of surveillance timing. The absence of BE recurrence after the fourth year of surveillance suggests that current open-ended surveillance programs may need to be re-evaluated, and that cessation of surveillance for a subgroup demonstrating no recurrence by that point may be possible. However, the relatively small numbers of subjects in this study demand further research to solidify such a recommendation.

In our previous report of AIM Dysplasia trial results, we demonstrated that 95% of patients achieving CEIM had CE-D at 2 years, and 93% had CEIM (our previously published data for year 3 is superseded by the data published here because additional patients completed 3 years of surveillance since the last report).¹⁰ In the current data, 99% still had CE-D and 90% of patients had persistent CEIM, allowing for interim "touch up" treatments. These results indicate that surveillance will protect the vast majority of patients with dysplastic BE from recurrence of high risk disease.

Our BE recurrence frequency is comparable to prior results exploring the rate of recurrence in patients with dysplastic BE.^{11,15-17} However, the shape of the recurrence curve has varied, with some studies suggesting a relatively constant rate of recurrence,¹⁷ while the present data suggest a front-loaded risk of recurrence in year 1. The long

follow-up period of dysplastic BE in the current study is unique in the literature, as is the statistical approach, which tests (and rejects) the hypothesis that the rate of recurrence after ablation is constant.

This study has several limitations. Though use of bootstrap CIs allows a robust estimate of the shape parameter *k*, which indicates decreasing rates of recurrence over time after CEIM, censored data are inherently at risk of bias because of nonrandom censoring. This may result in continued inclusion of patients who, for reasons of genetics, disease, or unknown factors, have easier-to-treat BE. This concern is mitigated by the durability analysis presented here, which allows for retreatment, thus ensuring that patients with more aggressive disease are also well sampled. These data describe treatment and surveillance in expert centers, and their generalizability to community centers is not certain. Finally, biopsy samples included in this study did not sample directly at the top of gastric folds, but rather sampled 0.5 cm proximal to this landmark, which may reduce the sensitivity of sampling for recurrence.

These data demonstrate that, while recurrence of BE after CEIM is common, re-treatment to CEIM is usually achievable, and rates of both CE-D and CEIM out to 5 years are high. Importantly, nearly all recurrence risk occurs in the first year after CEIM. Patients who achieve CEIM after an initial diagnosis of dysplasia can be assured that their risk of malignancy is small. However, it would be premature to recommend stopping surveillance endoscopy at a fixed number of years after CEIM based on this study. Further research will be needed to clarify the long-term risk of BE recurrence and the necessary surveillance interval and

duration. The timing of discontinuing surveillance for BE recurrence remains unclear. While our data suggest that 4 years may be enough, further work with larger numbers of patients treated in real-world settings will be necessary to provide guidance.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at <http://dx.doi.org/10.1053/j.gastro.2017.05.044>.

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Reprint requests

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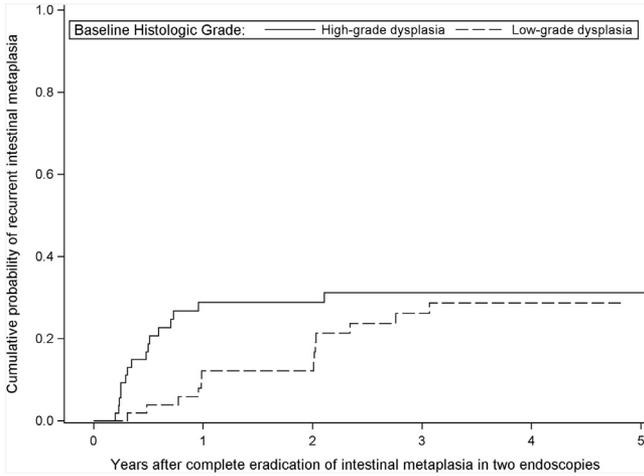
The AIM Dysplasia Trial Group consists of Richard E. Sampliner, David E. Fleischer, Virender K. Sharma, Glenn M. Eisen, M. Brian Fennerty, John G. Hunter, Mary P. Bronner, John R. Goldblum, Ana E. Bennett, Hiroshi Mashimo, Richard I. Rothstein, Stuart R. Gordon, Steven A. Edmundowicz, V. Raman Muthusamy, Kenneth J. Chang, Michael B. Kimmey, Stuart J. Spechler, Ali A. Siddiqui, Rhonda F. Souza, Anthony Infantolino, John A. Dumot, Gary W. Falk, Blair A. Jobe, Robert H. Hawes, Brenda J. Hoffman, Prateek Sharma, and Amitabh Chak.

Conflicts of interest

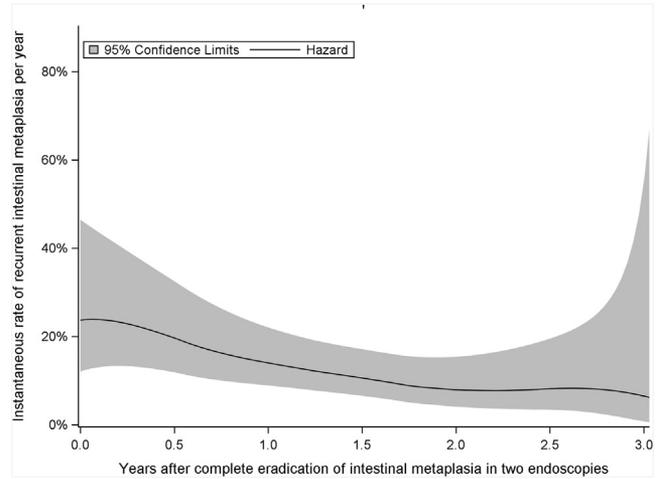
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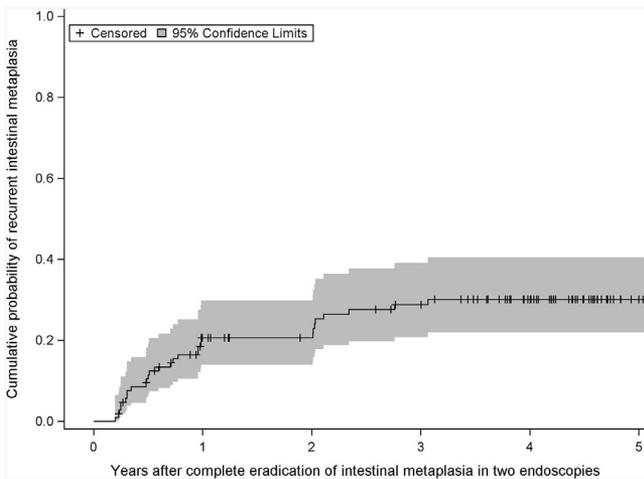
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Supplementary Figure 1. Estimated proportion of subjects with incidence of any recurrence stratified by baseline histologic grade after CEIM defined as 2 clean endoscopies not allowing interim “touch-up” treatments.



Supplementary Figure 3. Estimated hazard function, or instantaneous rate, for recurrence of intestinal metaplasia following CEIM not allowing interim “touch-up” treatments.



Supplementary Figure 2. Estimated proportion of subjects with incidence of any recurrence after CEIM not allowing interim “touch-up” treatments.

Supplementary Table 1. Kaplan-Meier Estimates of the Cumulative Incidence and 95% CL of Recurrence of BE-Associated Neoplasia by Year following CEIM not Allowing Interim "Touch-up" Treatments

Year	HGD at Baseline		LGD at Baseline		Combined Surveillance Cohort	
	Events	Cumulative incidence % (95% CL)	Events	Cumulative incidence % (95% CL)	Events	Cumulative incidence % (95% CL)
Any recurrence						
First	15	28.8 (16.5, 41.2)	6	12.2 (3.0, 21.3)	21	20.6 (12.7, 28.5)
Second	0	28.8 (16.5, 41.2)	0	12.2 (3.0, 21.3)	0	20.6 (12.7, 28.5)
Third	1	31.2 (18.4, 44.0)	6	26.2 (13.3, 39.0)	7	28.8 (19.7, 37.9)
Fourth	0	31.2 (18.4, 44.0)	1	28.7 (15.4, 42.0)	1	30.1 (20.8, 39.4)
Fifth	0	31.2 (18.4, 44.0)	^a	^a	0	30.1 (20.8, 39.4)
Dysplastic recurrence						
First	5	9.6 (1.6, 17.6)	1	2.0 (0.0, 5.8)	6	5.8 (1.3, 10.4)
Second	1	11.7 (2.9, 20.5)	0	2.0 (0.0, 5.8)	1	6.9 (2.0, 11.8)
Third	1	14.1 (4.3, 23.9)	2	6.6 (0.0, 13.9)	3	10.5 (4.3, 16.7)
Fourth	1	16.7 (5.9, 27.3)	1	9.5 (0.5, 18.4)	2	13.2 (6.1, 20.3)
Fifth	0	16.8 (6.1, 27.5)	0	9.5 (0.5, 18.4)	0	13.3 (6.2, 20.4)

Abbreviations: BE, Barrett's esophagus; CEIM, complete eradication of intestinal metaplasia; CL, confidence limits; HGD, high grade dysplasia; LGD, low grade dysplasia.

^aNo subjects remained at risk for this outcome and strata at the 5-year visit.