Intestinal Metaplasia Recurs Infrequently in Patients Successfully Treated for Barrett's Esophagus with Radiofrequency Ablation

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Abstract

Objectives—Radiofrequency ablation (RFA) of Barrett's esophagus (BE) is safe and effective in eradicating dysplasia and intestinal metaplasia and may reduce rates of esophageal adenocarcinoma (EAC). We assessed rates of and risk factors for disease recurrence after successful treatment of BE with RFA.

Methods—We performed a retrospective cohort study of patients who completed RFA for dysplastic BE or intramucosal carcinoma (IMC), achieved complete eradication of dysplasia (CE-D) or intestinal metaplasia (CE-IM), and underwent subsequent endoscopic surveillance at a single center. Rates of disease recurrence and progression were determined. Patients with and without recurrent disease were compared to determine risk factors for recurrence.

Results—262 subjects underwent RFA during the study period. Of these, 119 and 112 patients were retained in endoscopic surveillance after CE-D and CE-IM, respectively. Median observation time was 397 days (range: 54-1668 days). Eight patients (7% of those with CE-IM) had recurrent disease after a median of 235 days (range 55-1124 days). Progression to IMC (n=1) or EAC (n=2) occurred in 3 of these 8 patients, all of whom had pre-ablation high-grade dysplasia (HGD). Five patients had recurrence of non-dysplastic BE (n=3), low-grade dysplasia (n=1), and HGD (n=1).

During 155 patient-years of observation, recurrence occurred in 5.2%/year, and progression occurred in 1.9%/year. No clinical characteristics were associated with disease recurrence.

Conclusions—In patients with BE and dysplasia or early cancer who achieved CE-IM, BE recurred in ~5%/year. Patient characteristics did not predict recurrence. Subjects undergoing RFA for dysplastic BE should be retained in endoscopic surveillance.

INTRODUCTION

Barrett's esophagus (BE) affects 1-2% of the general population (1, 2), and is the precursor lesion of esophageal adenocarcinoma (EAC), a cancer with a marked increase in incidence over the past four decades (3-5). Endoscopic ablative therapy is frequently performed to treat dysplastic BE with the aim of permanently eliminating dysplasia and intestinal metaplasia (IM) to prevent neoplastic progression. Recent studies of radiofrequency ablation (RFA) for BE with dysplasia have demonstrated that RFA is safe and effective, with low complication rates, high rates of complete eradication of dysplasia (CE-D) and intestinal metaplasia (CE-IM), and a potential decrease in progression to cancer (6-9).

While RFA safely and effectively eradicates dysplasia and IM, the durability of the neosquamous epithelium that regenerates is not well understood. This is especially true of subjects with the most severe disease, those with high-grade dysplasia (HGD), and those with intramucosal adenocarcinoma (IMC). The few studies that report on the durability of successful response to treatment with RFA are limited by small sample sizes and short periods of follow-up (10-15). A recent multicenter, randomized, sham-controlled trial reported on the durability of RFA in dysplastic BE and found that dysplasia remained eradicated in >85% of patients and IM in >75% of patients after 3 years, without RFA re-treatment (16). However, only 54 of the 106 subjects in this trial had HGD; the remainder had low-grade dysplasia (LGD).

The aim of this study was to determine rates of disease recurrence and progression following successful eradication of dysplasia and IM in BE with dysplasia or IMC following RFA therapy. We also sought to determine factors associated with disease recurrence following CE-IM.

METHODS

Patient eligibility and data collection

We performed a retrospective study of adult patients who completed RFA therapy for BE with LGD, HGD, or IMC and underwent subsequent endoscopic surveillance at University of North Carolina (UNC) Hospitals between 2006 and 2011. Subjects who received an upper endoscopy (EGD) with RFA between January 1, 2006 and November 1, 2011, were identified by review of our electronic endoscopic database (Provation MD, Wolters Kluwer, Minneapolis, MN). One of two investigators (HK, WB) then reviewed each subject using the electronic medical record (WebCIS, UNC Health Care System) to determine eligibility for inclusion. All institutional health information and imported external records were abstracted. Patients were excluded if they never had treatment with RFA; were treated with RFA for a non-BE-related disease; did not have a pre-ablation histology of LGD, HGD or IMC; did not complete RFA therapy; or did not enter surveillance at UNC Hospitals with CE-D or CE-IM. Patients were considered to be under surveillance if they received at least 1 EGD after a post-RFA EGD demonstrated CE-D or CE-IM. All eligible patients were included in the surveillance cohort and were examined to determine durability of response to RFA treatment.

Pertinent data were extracted from clinical, endoscopy, and pathology reports for each subject and included demographic information (age, gender, race, body mass index), pertinent medical history (erosive esophagitis, peptic stricture), substance use (alcohol, tobacco), medication use (anti-secretory therapy, non-steroidal anti-inflammatory drugs), EGD findings (length of BE, hiatus hernia, erosions, ulcers, nodules), pre-ablation histology, treatment provided, ablation outcomes, and durability outcomes.

Pre-treatment evaluation and procedural protocol

All patients had an initial consultation visit to discuss BE and dysplasia, its risk of progression to cancer, and the risks and benefits of different treatment options including continued endoscopic surveillance, ablative therapy, and, in the case of HGD or IMC, esophagectomy. Prior to the first visit, the worst histologic grade of BE was determined by review of original pathology records. An expert gastrointestinal pathologist reviewed all cases, and if findings between the initial pathology report and the secondary review were discordant, an additional expert gastrointestinal pathologist reviewed the case with histologic classification by consensus.

Patients with BE and LGD were offered RFA followed by endoscopic surveillance, or endoscopic surveillance alone. Patients with BE and HGD or IMC were offered RFA followed by endoscopic surveillance, esophagectomy, or, in the case of HGD, endoscopic surveillance alone. Patients with BE and HGD or IMC who opted for RFA had pre-treatment staging by EGD and endoscopic ultrasound to exclude invasive disease (submucosal infiltration, lymph node or metastatic spread) that would preclude curative endoscopic treatment. If the BE segment contained nodularity, endoscopic mucosal resection (EMR) was performed prior to beginning RFA therapy. Nodules were defined endoscopically as any contoured irregularity and elevation of the mucosa without breaks, including Paris classification 0-I and 0-IIa lesions (17). All resections were performed using either the Olympus 18 mm oblique cap kit (Olympus America, Center Valley, PA) or the Duette device (Cook Medical, Winston-Salem, NC). EMR performed with the Olympus device was preceded by submucosal injection of saline, while EMR with the Duette device was performed without prior injection. If the BE segment was not nodular, RFA was performed as outlined below. RFA therapy was initiated two months after all nodular lesions were removed by EMR, and if pathology specimens did not reveal submucosal infiltration of EAC. Twice daily proton pump inhibitor therapy was prescribed to all patients prior to and throughout RFA treatment.

Radiofrequency ablation was performed using the HALO^{360} device (BARRX Medical, Sunnyvale, CA) for circumferential disease and the HALO^{90} device for focal lesions. Standard procedural technique was used as previously described (8). Patients returned every two months for repeat EGD to assess treatment response. EMR was performed if patients developed nodular disease during the treatment period. Patients with non-nodular residual disease underwent focal RFA treatment. Treatment was continued in this manner until no visible BE was observed on white-light and narrow band imaging endoscopy. At this point, treatment was considered complete and four-quadrant biopsies were taken from just distal to the gastroesophageal junction and at 1 cm intervals along the length of the original BE segment. Subjects were then offered continued endoscopic surveillance to monitor their condition, either at our institution, or, for those not living locally, follow-up with their referring gastroenterologist.

The date of these esophageal biopsies marked the "index date," the date when the surveillance period began. Surveillance EGDs at our institution were performed using narrow band imaging and four-quadrant biopsies just distal to the gastroesophageal junction and at 1 cm intervals along the length of the original BE segment. Separate biopsy samples

were obtained for any visible BE during surveillance. Patients who had pre-ablation LGD received surveillance EGDs every 6 months for one year, and if patients were disease-free after one year, they were followed-up annually thereafter. From 2006-2009, patients who had pre-ablation HGD or IMC received surveillance EGDs every 3 months for one year, then every 6 months for the second year, and were followed-up annually thereafter. From 2009 to the present, any patient who achieved CE-IM received surveillance EGDs every 6 months for one year and then yearly, regardless of baseline histology. Physicians and patients may have deviated from the surveillance protocol depending on individual clinical considerations. No further RFA treatments were administered unless patients experienced disease recurrence, at which point RFA re-treatment was considered.

Outcomes and statistical analysis

Upon completion of therapy, all biopsy specimens were analyzed by an expert gastrointestinal pathologist to assess for the presence of residual BE and degree of dysplasia. Any reading of dysplasia was subsequently confirmed by a second histological analysis by an expert gastrointestinal pathologist. Outcomes upon treatment completion included CE-D and CE-IM. CE-D was defined as the absence of dysplasia from all esophageal biopsies, and CE-IM was defined as complete endoscopic resolution with the absence of IM from all esophageal biopsies. Throughout the surveillance period, biopsy specimens were similarly examined to determine the presence of any recurrent IM or dysplasia.

Two separate cohorts were analyzed: patients that achieved CE-D (with or without CE-IM) and the subset of patients that achieved CE-IM. Primary durability outcomes included recurrent disease and progressive disease. For the CE-IM cohort, recurrent disease was defined as any recurrence of IM with or without dysplasia. For the CE-D cohort, recurrent disease was defined as recurrence of any grade of dysplasia, not including non-dysplastic (ND) BE. Progressive disease was defined as recurrence at a worse level than pre-treatment histology. As patients actively under surveillance are scheduled to undergo EGD at least yearly, those who had not undergone an EGD within the 15 months prior to the conclusion of this study were considered lost to follow-up. The characteristics and clinical courses of each patient with recurrent disease were described.

Statistical analysis was performed using Stata software (version 12.0; StataCorp LP, College Station, TX). Descriptive statistics were performed for patients entering the surveillance period upon achieving CE-IM. Categorical variables were reported as counts and percentages. Continuous variables were reported as means and standard deviations or medians and interquartile ranges for non-normally-distributed variables. Comparisons between groups were performed using Fisher's exact test for categorical variables and Student's t-test or Wilcoxon rank-sum test for continuous variables. Kaplan-Meier survival analyses were performed to determine the rates of disease recurrence. For these Kaplan-Meier analyses of dysplasia-free and intestinal metaplasia-free survival, any recurrent dysplasia or IM, respectively, was considered a failure, even if subsequent RFA resulted in a recurrent complete eradication. Comparisons between rates were performed using the log-rank test. The UNC Institutional Review Board approved this study.

RESULTS

In all, 262 patients received RFA for BE during the study period. Of these, 244 had a pre-treatment diagnosis of either dysplastic BE or IMC. Of 188 patients who completed treatment for BE with dysplasia or IMC, 183 achieved CE-D, and 168 achieved CE-IM (Figure 1). Within these groups, 119 and 112 patients entered endoscopic surveillance, respectively, at our institution, with the remainder opting to undergo surveillance with their local gastroenterologist due to proximity. Subjects returning to their referring

gastroenterologist for surveillance were not significantly different from those pursuing surveillance at UNC with respect to demographics or pre-treatment histology. Baseline characteristics of the 112 patients who achieved CE-IM and underwent surveillance are reported in Table 1. The mean age was 64.1 ± 10.9 years, 79.5% were male, 111 of the 112 (99.1%) patients were Caucasian, and the mean length of BE was 4 cm. Patients with IMC were more likely to have had pre-ablation erosive esophagitis or to have received EMR at any time. Patients underwent a mean of 3.0 ± 1.5 RFA sessions, and 63.4% received circumferential therapy. Patients were followed in surveillance for a median of 397 days (range 54-1668). Five patients were lost to follow-up.

In those under endoscopic surveillance following CE-D and CE-IM, an analysis of durability was performed using Kaplan-Meier estimation. As demonstrated in Figure 2A, of the 119 patients who attained CE-D and enrolled in endoscopic surveillance at our institution, 85% of patients remained free of dysplasia at a median follow-up of 393 days with no additional therapy. Dysplasia did not recur in any subject treated for LGD; in those treated for HGD or IMC, dysplasia recurred in 4.2% per year (Figure 2B), with a median time to recurrence of 173 days. All 5 recurrences of dysplasia were among those who had achieved CE-IM with RFA. Of the 112 patients followed after CE-IM, 80% remained free of IM (Figure 3A). Only 1 patient with pre-ablation LGD had recurrent IM (2.4% per year); whereas 5 with pre-ablation HGD and 2 with pre-ablation IMC had recurrent IM (5.5% per year and 9.4% per year, respectively) (Figure 3B). Among patients experiencing IM recurrence, IM recurred at a median of 235 days into surveillance (range 55-1124).

Among the 8 patients who experienced recurrence of IM following CE-IM, most had a benign clinical course (Table 2). In 5 of these patients, the histologic grade at the time of recurrence was at or below the pre-treatment grade. Of these, 3 had histologic recurrence, but no endoscopic evidence of recurrent BE. One of the other 2 patients had an "irregular z-line" only, and the other had a small isolated island of BE. In all of these cases, the pathologist described the histologic recurrence as "sparse," "minute," or within "one fragment". In no case was the recurrent BE noted to be sub-squamous. Three of the 8 patients experiencing recurrence of IM were re-treated with RFA for NDBE (n=1), LGD (n=1), and HGD (n=1), and all subsequently had CE-IM. The two other patients who experienced recurrence but not progression had NDBE at recurrence and continued endoscopic surveillance.

All 3 patients who had histologic progression (i.e. grade at the time of recurrence greater than the pre-treatment grade) had pre-treatment HGD. One developed a single, visible, 5 mm island of IMC, which was successfully treated with EMR. Another developed IMC within an endoscopically normal-appearing gastroesophageal junction and shortly thereafter progressed to EAC, which was subsequently treated successfully with esophagectomy. One had an acute MI just prior to his scheduled yearly endoscopy, which was therefore cancelled. He became symptomatic from a fungating esophageal mass 20 months after his prior negative endoscopy and was subsequently diagnosed with metastatic EAC. He died after systemic chemotherapy and radiation. During 155 total years of observation, the rate of any recurrence was 5.2% per year, the rate of recurrence with HGD or worse histology was 2.6% per year, the rate of recurrence with EAC was 1.3% per year, and the rate of death from EAC was 0.6% per year.

In bivariate analyses, we assessed a variety of clinical, endoscopic, and treatment variables as predictors of recurrence following CE-IM. Patients with recurrence of IM were not statistically different in these characteristics from those who did not recur in bivariate analysis (Table 3). However, numerically, patients with recurrence were younger, with a higher BMI, and with a longer BE length. They were also more likely to have had an

esophageal stricture, erosive esophagitis, a medium or larger hiatal hernia, and a pre-ablation histology of IMC. Multivariate analysis could not be performed due to the small number of recurrences.

DISCUSSION

Endoscopic RFA is an established safe and effective therapy for dysplastic BE and results in a high proportion of CE-D and CE-IM. However, the durability of CE-IM following treatment, especially for subjects with more severe disease (HGD and IMC), is not clear. This study demonstrates that the majority of patients successfully treated with RFA for dysplastic BE or IMC maintain CE-IM after more than a year of follow-up. Of those who developed recurrent IM, most were not histologically worse than the pre-treatment grade, and the area of recurrence was generally small. More than half were in the setting of an endoscopically normal-appearing esophagus or irregular z-line.

This study is the largest to date reporting RFA outcomes and durability in subjects with HGD and IMC. However, several studies have examined the risk of IM recurrence following successful RFA for dysplastic BE (Table 4). Pouw et al. demonstrated that among 43 patients who achieved CE-IM following RFA for HGD or early cancer, 5 (12%) had histologic recurrence immediately distal to a normal-appearing neosquamous columnar junction during a median follow-up of 21 months (10). Only 1 had endoscopic recurrence, and none had recurrent dysplasia. In 2 series, Gondrie et al. reported no visible recurrence among 23 patients with CE-IM following RFA for dysplastic BE (18, 19). One patient had recurrence of focal IM just distal to the neosquamous columnar junction. In a multicenter trial of RFA for HGD or early cancer, 23 of 24 patients achieved CE-IM with EMR and RFA (12). Twenty-three of these patients received EMR prior to RFA, and 2 required salvage EMR after RFA in order to obtain CE-IM. Only 3 patients (13%) who achieved CE-IM had recurrence of IM at 22 months of median follow-up. Again, there was no recurrent dysplasia. The same group reported 2 endoscopic and 3 histologic recurrences without dysplasia among 19 patients (26%) who achieved CE-IM after RFA of BE segments ≥10 cm (13). Mean follow-up was 21 months after treatment completion. In a randomized trial of RFA versus EMR for HGD or early cancer, none of 21 patients who had achieved CE-IM had endoscopic recurrence after a median 15 months of follow-up (14). Four patients had histologic recurrence without dysplasia at the neosquamous columnar junction. Two of these were within single biopsy specimens and were not reproduced on subsequent endoscopies. Vaccaro et al. reported recurrent IM in 15 of 47 patients (32%) who had achieved CE-IM following RFA at a single center (15). Median follow-up in this study was 13.3 months. Four of these recurrences had dysplasia (2 LGD and 2 HGD) at the neosquamous columnar junction, none of which were seen endoscopically, and 1 represented progression from LGD to HGD. In bivariate analysis, a longer baseline BE segment was associated with IM recurrence. Three-year follow-up of a randomized controlled trial of RFA for dysplastic BE showed recurrent IM in 14 of 108 patients who achieved CE-IM (16). Seven of the 14 had recurrence at a normal or irregular z-line. The other 7 consisted of small, isolated islands (n=3) or tongues (n=4). Among the patients with recurrence, only 3.8% of biopsies demonstrated IM.

This study compares favorably with prior studies in that ≥80% were able to maintain CE-D and CE-IM without additional therapy. Moreover, the recurrence rate of 5.2% per year is lower than the calculated rates for the previous studies (Table 4). As in the other studies, recurrence was typically minimal, with little endoscopic evidence of recurrence and few positive biopsies in most cases. In addition, the majority of patients with recurrent IM had uneventful clinical courses. Six (75%) of our recurrences were successfully re-treated endoscopically or kept under surveillance. Nevertheless, despite our overall good outcomes,

1 patient required esophagectomy after progressing to EAC, and 1 progressed to metastatic EAC. The former patient had a large hiatal hernia but no endoscopic evidence of recurrence despite the IMC seen histologically at the gastroesophageal junction. As described above, the latter patient missed surveillance endoscopy due to a cardiac event, but the prior surveillance endoscopy (20 months before his diagnosis of metastatic EAC) showed a normal z-line without histologic abnormality. These two patients each had 9cm of pre-ablation IM (90th percentile), but were otherwise without specific features in their pre-recurrence clinical course that would distinguish them from the remainder of the cohort. Cases such as these reinforce the need for continued surveillance in this patient population. As suggested by Vaccaro et al. (15), the neosquamous columnar junction may be an area at risk for the development of dysplasia or adenocarcinoma. However, the optimal method to prevent such progression is not clear.

Due to the small number of recurrences, we were unable to determine predictors of recurrence or progression. However, the median pre-RFA BE length was numerically greater among those who had recurrence (7 vs. 4 cm, p=0.2). Furthermore, the two patients who progressed to EAC had among the longest BE segments in the cohort. Vaccaro et al. found that the baseline BE length was significantly longer in those who developed recurrence (15). The reasons for such an association are unclear, but longer length may be a marker of more severe reflux, or may be a surrogate measure of the likelihood of harboring a more genetically advanced dysplastic clone. There does not appear to be an increased risk of the recurrence for patients who achieve CE-D without CE-IM, as none were seen in this study. However, the small number of patients in this group (n=7) prevents a firm conclusion on this matter. Larger studies are needed to identify predictors of recurrence, which would be valuable to risk stratify patients after ablation in order to better target surveillance efforts.

This study has several limitations. As with other studies on this topic, sampling error is a concern. Although this cohort was found to have CE-IM on biopsy, it is conceivable that residual IM (especially sub-squamous or "buried" IM) might be missed and that patients who never achieved true CE-IM were included in the cohort due to sampling error. In such an instance, subsequent biopsies showing IM would incorrectly classify a patient as recurrent disease when they should have been considered an incomplete initial treatment. Such an error would have the effect of inflating our cohort size at the cost of increasing the recurrence rate. One-third of patients who achieved CE-IM returned to their referring physician for surveillance after treatment completion and were therefore not available for follow-up. A difference in recurrence rate between this group and our cohort would bias our recurrence estimate. However, the pretreatment histology of those receiving follow-up locally was not different from those continuing at our institution, decreasing the concern that baseline differences between the groups might lead to a biased estimate of disease recurrence. Additionally, it is common that recurrence in this group prompts re-referral to our center for management. Therefore, if such a bias exists, it likely results in an over-estimate of recurrence. Given that this is a single-center study, the generalizability of our findings, especially to practice settings with lower volumes of cases, is unclear. It should be noted, however, that similar results have been reported in a cohort of subjects treated in community practice (7). Other limitations of this study include the small number of recurrences that prevents identification of predictors of recurrence, as well as its retrospective nature.

In this study of patients with CE-IM following RFA of dysplastic BE, we found a low rate of IM and dysplasia recurrence. Among those with recurrent IM, most had a benign course, although three cases exhibited progressive disease. One subject, who was unable to attend surveillance endoscopy, developed and died from metastatic esophageal adenocarcinoma. Due to the small number of recurrences, we did not identify any statistically significant

predictors of recurrence. In general, these results should serve to reassure patients and their physicians that, in most cases, RFA induces a durable complete eradication of dysplasia and intestinal metaplasia. At the same time, the few cases of progression point to the need for continued surveillance following treatment. Further follow-up of this cohort and others is needed to identify predictors of IM recurrence so that continued surveillance can be appropriately targeted to the highest risk patients.

Acknowledgments

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STUDY HIGHLIGHTS

WHAT IS CURRENT KNOWLEDGE

- Radiofrequency ablation (RFA) of dysplastic Barrett's esophagus (BE) safely and effectively eradicates dysplasia and intestinal metaplasia and reduces progression to cancer.

- The durability of treatment-induced eradication of intestinal metaplasia is not well understood.

- Risk factors for recurrence of intestinal metaplasia following ablation are unknown.

WHAT IS NEW HERE

- In this cohort of patients who completed RFA for dysplastic BE, recurrence of intestinal metaplasia after complete eradication occurred in 5.2% per year.

- Most patients with recurrence had a benign clinical course.

- Progression of disease occurred in 1.9% per year with associated morbidity and mortality.

- No clinical characteristics were associated with disease recurrence.

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                    │   262 received RFA for BE    │
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                                  │         ┌──────────────────────────────────┐
                                  ├────────▶│  11 with non-dysplastic BE       │
                                  │         │  7 with invasive adenocarcinoma  │
                                  ▼         └──────────────────────────────────┘
                    ┌─────────────────────────────┐
                    │  244 with dysplasia or IMC   │
                    └─────────────────────────────┘
                                  │         ┌──────────────────────────────────────┐
                                  ├────────▶│  34 receiving ongoing therapy at      │
                                  │         │  follow-up                            │
                                  ▼         │  22 lost to follow-up                 │
                    ┌─────────────────────────────┐
                    │   188 completed treatment    │
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| 168 achieved CE-IM | 15 achieved CE-D, but not CE-IM | 5 did not achieve CE-D or CE-IM |

| 56 surveyed by local GI | | 8 surveyed by local GI |

| 112 entered surveillance (CEIM cohort) | 7 entered surveillance | 3 with HGD → esophagectomy 1 with IMC → radiation therapy 1 with LGD → entered surveillance |

CE-D cohort

Figure 1.
Flow diagram of patients treated for BE with RFA.
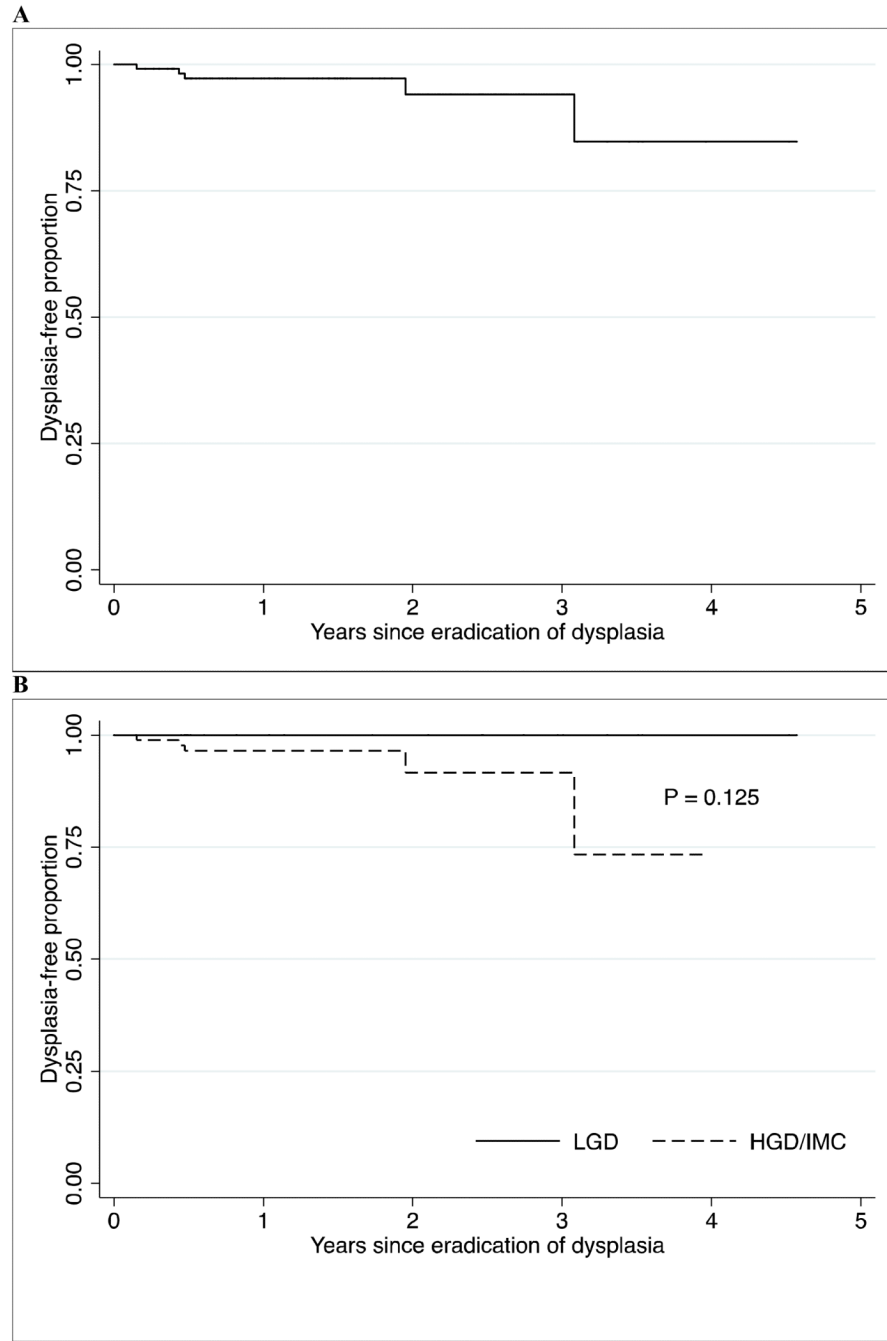
**Figure 2.**
Kaplan-Meier plots of dysplasia recurrence among patients who achieved CE-D after RFA, overall (**A**) and grouped by pre-treatment histology (**B**). P-value based on log-rank test.
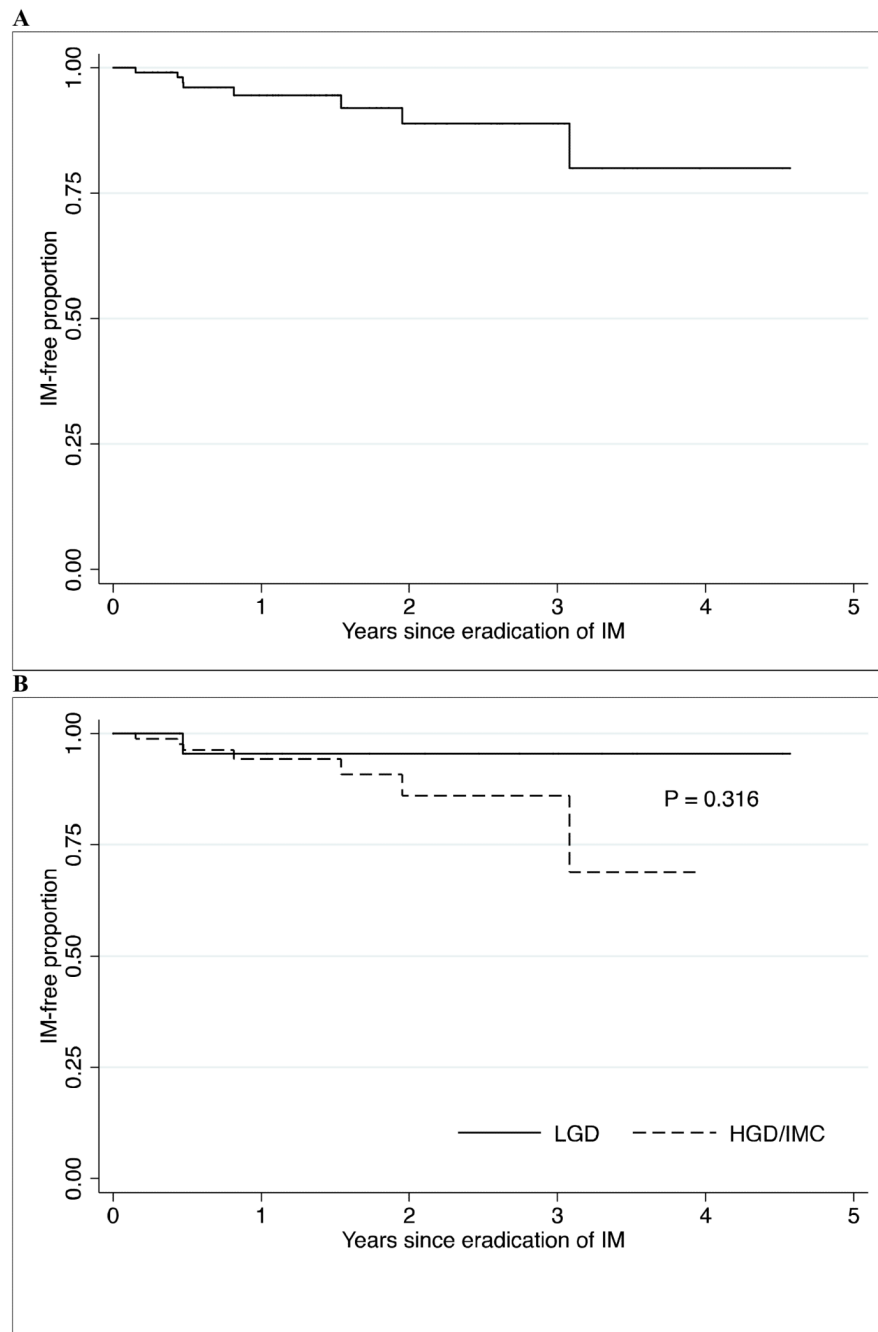
Figure 3.
Kaplan-Meier plot of IM recurrence among patients who achieved CE-IM after RFA, overall (**A**) and grouped by pre-treatment histology (**B**). P-value based on log-rank test.

Table 1

Baseline Characteristics of Patients Under Endoscopic Surveillance Following CE-IM

Characteristic	Overall	LGD	HGD	IMC	p-value
N (%)	112 (100.0)	24 (21.4)	71 (63.4)	17 (15.2)	
Age, years, mean (SD)	64.1 (10.9)	59.2 (12.3)	64.6 (9.6)	68.7 (11.8)	0.26
Male, n (%)	89 (79.5)	16 (66.7)	60 (84.5)	13 (76.5)	0.14
Caucasian, n (%)	111 (99.1)	24 (100.0)	71 (100.0)	16 (94.1)	0.15
BMI, kg/m^2, mean (SD)	30.0 (5.6)	31.7 (5.5)	29.2 (5.6)	30.9 (5.4)	0.97

Substance use
  Tobacco, n (%)
  Alcohol, n (%)
	
	19 (17.0)
	57 (50.9)
		
		0 (0.0)
		13 (54.2)
			
			17 (23.9)
			37 (52.1)
				
				2 (11.8)
				7 (41.2)
					
					0.01
					0.71

NSAID use, n (%)	55 (49.1)	9 (37.5)	39 (54.9)	7 (41.2)	0.29
PPI use, n (%)	110 (98.2)	24 (100.0)	70 (98.6)	16 (94.1)	0.33

EGD findings
  Length of BE, cm, median (IQR)
  Erosive esophagitis, n (%)
  Hiatus hernia, n (%)
	
	4 (2-7)
	4 (3.6)
	101 (90.2)
		
		4.5 (1.5-7)
		0 (0.0)
		21 (87.5)
			
			4 (2-7)
			1 (1.4)
			64 (90.1)
				
				5 (2-6)
				3 (17.7)
				16 (94.1)
					
					0.98
					0.02
					0.26

Treatment characteristics
  Circumferential RFA, n (%)
  EMR, n (%)
	
	71 (63.4)
	39 (34.8)
		
		18 (75.0)
		4 (16.7)
			
			45 (63.4)
			20 (28.2)
				
				8 (47.1)
				15 (88.2)
					
					0.19
					<0.01

Surveillance characteristics
  Follow-up, days, median (range)
  EGDs, median (IQR)
	397
	(54-1668)
	2 (1-2)
		397.5
		(54-1668)
		2 (1-4)
			340
			(55-1446)
			2 (1-2)
				496
				(97-892)
				2 (1-2)
					
					0.63
					0.45

Table 2

Characteristics and Clinical Course of Patients with Recurrent Disease

	Age (yrs)	Sex	Pre-Treatment Histology	Total Treatment Sessions	Surveillance EGDs	Days to Recurrence	EGD at Recurrence	Histology at Recurrence	Clinical Course	Final Histology
	69	F	LGD	5	2	172	Grade B esophagitis, no visible BE	NDBE	RFA and subsequent CEIM	Squamous
	55	M	HGD	3	2	297	Irregular z-line	Sparse NDBE	Not retreated due to comorbidities; under surveillance	NDBE
Recurrence	81	M	IMC	3	2	561	No visible BE	Minute focus of NDBE	Not retreated; under surveillance	NDBE
	65	M	HGD	2	1	159	No visible BE	Sparse LGD	RFA and subsequent CEIM	Squamous
	41	M	IMC	4	2	712	Small island of BE	1 fragment of HGD	RFA and subsequent CEIM	Squamous
	46	M	HGD	2	1	173	5 mm island of BE, regular z-line	IMC with negative margins	EMR on date of recurrence	Squamous
Progression	71	M	HGD	3	1	55	Large hiatal hernia, no visible BE	IMC at GE junction; EAC 2 months following recurrence	Successful esophagectomy	EAC
	57	M	HGD	4	3	1124	Large esophageal mass	EAC	Metastatic disease treated with systemic chemotherapy and radiation; deceased	EAC

Table 3

Characteristics of Patients With and Without Recurrent Disease

Characteristic	Recurrence (n=8)	No Recurrence (n=99)	p-value
Age, years (SD)	60.7 (13.4)	64.1 (10.8)	0.40
Male, n (%)	7 (87.5)	77 (77.8)	1.00
Caucasian, n (%)	8 (100.0)	98 (99.0)	1.00
BMI, kg/m^2, mean (SD)	32.2 (4.7)	29.9 (5.8)	0.28

Substance use
   Tobacco, n (%)
   Alcohol, n (%)
	
	2 (25.0)
	3 (37.5)
		
		16 (16.2)
		53 (53.5)
			
			0.62
			0.47

NSAID use, n (%)	4 (50.0)	47 (47.5)	1.00
History of prior stricture, n (%)	1 (12.5)	6 (6.1)	0.43

EGD findings
   Length of BE, cm, median (IQR)
   Erosive esophagitis, n (%)   Medium or large hiatus hernia, n (%)
   Intact Nissen fundoplication, n (%)
   Nodular BE, n (%)
	7 (3-8.5)
	1 (12.5)
	6 (75.0)
	0 (0.0)
	2 (25.0)
		4 (2-7)
		3 (3.0)
		60 (60.6)
		6 (6.1)
		27(27.3)
			0.19
			0.27
			0.71
			1.00
			1.00

Pre-treatment histology, n (%)
   LGD
   HGD
   IMC
	
	1 (12.5)
	5 (62.5)
	2 (25.0)
		
		22 (22.2)
		62 (62.6)
		15 (15.2)
			0.75

EMR during treatment, n (%)	3 (37.5)	34 (34.3)	1.00
Circumferential RFA during treatment, n (%)	5 (62.5)	63 (63.6)	1.00
Erosive esophagitis during treatment, n (%)	2 (25.0)	16 (16.2)	0.62
Total treatment sessions, median (IQR)	3 (2.5-4)	3 (2-4)	0.96
RFA treatment sessions, median (IQR)	3 (2.5-3.5)	3 (2-4)	0.78

Table 4

Prior Studies Reporting Recurrence in Patients with CE-IM After Successful RFA for Dysplastic BE

Author	Year	Patients under surveillance, n	Median length of follow–up, months	Recurrence, n (%)	Recurrence rate, %/year[*]
Pouw (10)	2008	43	21	5 (12%)	6.6
Gondrie (18)	2008	11	14	1 (9%)	7.8
Gondrie (19)	2008	12	9.5	0 (0%)	0.0
Pouw (12)	2010	23	22	3 (13%)	7.1
Herrero (13)	2011	19	21 (mean)	5 (26%)	15.0
van Vilsteren (14)	2011	21	15	4 (19%)	15.2
Vaccaro (15)	2011	47	13.3	15 (32%)	28.8
Shaheen (16)	2011	108	36	14 (13%)	4.3

[*] Estimate of recurrence rate calculated as (number of recurrences)/(number of patients under surveillance × median follow-up)