Management of Barrett Esophagus Following Radiofrequency Ablation

Craig C. Reed, MD, MSCR, and Nicholas J. Shaheen, MD, MPH

Dr Reed is a clinical instructor of medicine and Dr Shaheen is a professor of medicine and epidemiology in the Division of Gastroenterology and Hepatology in the Department of Medicine at the University of North Carolina School of Medicine in Chapel Hill, North Carolina.

Address correspondence to:
Dr Nicholas J. Shaheen
University of North Carolina School of Medicine
CB #7080
Chapel Hill, NC 27599-7080
Tel: 919-966-2513
Fax: 919-843-2508
E-mail: nshaheen@med.unc.edu

Abstract: Radiofrequency ablation (RFA) effectively treats dysplastic Barrett esophagus (BE), reduces the risk of esophageal adenocarcinoma (EAC), and infrequently produces complications. Complications of RFA include chest discomfort, esophageal stricturing, and bleeding. However, chest discomfort is usually transient and mild, strictures are generally amenable to dilation, and clinically significant bleeding is rare. Following RFA, intestinal metaplasia recurs at a rate of approximately 10% per patient year of follow-up time. Postablation dysplastic BE and EAC are rare. Moreover, recurrent disease is generally responsive to further endoscopic therapy and is associated with a benign clinical course. Although RFA is effective at producing low rates of postablation EAC and dysplastic recurrence, data suggest that current consensus guidelines for postablation surveillance are overly aggressive, as they mirror those for treatment-naive cohorts. Future guidelines may attenuate surveillance intervals, reducing the burden of endoscopic surveillance while providing for adequate detection of recurrent disease. Additional studies are needed to determine the length of time patients should ultimately remain in surveillance programs. Uncertainty exists regarding the appropriate application of chemopreventive measures (including proton pump inhibitors, aspirin, and statins) and novel imaging and sampling modalities (such as optical coherence tomography and wide-area transepithelial sampling) to reduce the risk of recurrent disease and sampling error, respectively. These uncertainties represent targets for future investigations.

Keywords
Barrett esophagus, dysplasia, radiofrequency ablation, complications, durability

Barrett esophagus (BE) is a premalignant condition of the esophagus with the potential to progress to esophageal adenocarcinoma (EAC). The condition is characterized by intestinal metaplasia (IM), a specialized columnar epithelium, supplanting the typical stratified squamous epithelium of the distal esophagus.[1] The prevalence of BE is estimated to be 1% to 2% of all patients referred for upper endoscopy[2,3] and as high as 15% of all patients referred for symptoms of gastroesophageal reflux disease.[4] EAC ultimately

develops in approximately 1 of 300 patients with BE each year.[5] Incident EAC portends a poor prognosis, with most patients not surviving beyond 5 years.[6]

Endoscopic eradication therapy (EET) represents the standard of care for treatment of BE with dysplasia and early neoplastic changes.[7-9] EET comprises multimodal techniques for endoscopic resection (eg, endoscopic mucosal resection and endoscopic submucosal dissection) coupled with endoscopic ablation (eg, radiofrequency ablation [RFA] and cryotherapy). Of the ablative EET modalities, RFA is the most commonly utilized.[10] A large volume of peer-reviewed data that consistently document high rates of complete eradication of intestinal metaplasia (CEIM) and dysplasia, reduction in the risk of EAC, and low rates of complications have established RFA as the preferred EET modality.[8,11]

Ample data from studies of clinical care,[12-16] clinical trials,[17,18] and systematic reviews[19,20] describe the clinical course of patients after obtaining CEIM. Recurrent IM postablation is not rare.[13,21] However, as additional EETs may be utilized in most scenarios,[13] recurrent disease typically follows a benign clinical course.[22]

This article reviews the management of patients with BE following RFA with CEIM, focusing on the definitions utilized to identify CEIM, recurrence rates following CEIM, endoscopic surveillance techniques, the management of recurrent disease, and the utility of chemopreventive agents in the postablation setting, as well as the more common complications of RFA and their treatment. The current body of literature centers the discussion on RFA; however, this article briefly describes the available data regarding the long-term efficacy and side effects associated with cryotherapy.

Defining Post–Radiofrequency Ablation Surveillance Cohorts

Patients with BE treated with EET enter into endoscopic surveillance following CEIM. However, no consensus definition of CEIM exists, and, as such, what constitutes a postablation surveillance cohort varies within the literature. Discrepant definitions largely manifest out of concern over sampling error associated with random biopsies. For example, some investigators define CEIM as 2 negative biopsy sessions following EET,[13] while the majority define it as 1 negative biopsy session following EET.[12,23,24] Variable definitions of CEIM add heterogeneity to the literature and complicate its synthesis and interpretation.

The use of multiple biopsy sessions to denote CEIM may reduce sampling error; however, no data describe the "right" number of negative biopsy sessions. Moreover, no matter how many negative biopsy sessions are required for CEIM, residual sampling error persists. Articles[12,23,24] analyzing data from the AIM Dysplasia (Ablation of Intestinal Metaplasia Containing Dysplasia) trial[8] and the US RFA Patient Registry,[25] which define CEIM as 1 negative biopsy session, also conducted sensitivity analyses defining CEIM as 2 negative biopsy sessions. These analyses did not find a meaningful difference in rates of recurrent disease comparing CEIM as defined by 1 or 2 negative biopsy sessions.[12,24] As such, we favor defining CEIM following a singular negative biopsy session, acknowledging that some portion of patients thus identified will, in fact, be falsely labeled as free of disease.

Variable Definitions Denoting a Durable Response to Radiofrequency Ablation Following Complete Eradication of Intestinal Metaplasia

Management of patients with BE obtaining CEIM predicates upon an understanding of the natural history of the postablation esophagus. However, similar to variable definitions describing CEIM, heterogeneity exists in what constitutes a durable response to treatment post-CEIM.

Regarding durability of treatment response, definitions largely differ by the location in which recurrent disease is detected. Definitions include histopathologic abnormalities only found within the tubular esophagus[14] and histopathologic abnormalities located within both the tubular esophagus and cardia,[26] as well as histopathologic abnormalities found solely within the cardia.[22] Most investigators do not consider IM of the cardia to be recurrent disease. IM of the cardia is found in approximately 20% of patients with chronic symptoms of gastroesophageal reflux disease without BE.[27] Moreover, the available natural history data of IM of the cardia without dysplasia suggest that the risk of progression to malignancy is low. IM of the cardia with dysplasia, however, suggests recurrent disease or dysplasia missed prior to ablation as a consequence of sampling error. As such, most investigators consider dysplasia of the cardia to be a failure of EET and, thus, disease recurrence. We favor a definition of recurrent disease including all post-RFA surveillance biopsies with IM or dysplasia found in the tubular esophagus, as well as any finding of dysplasia in the cardia. Such a definition encompasses all likely important esophageal and cardiac findings while excluding IM of the cardia, which is a highly prevalent condition of unclear clinical significance. Inconsistent study designs, biopsy protocols (eg, location and number), and patient populations further compound the synthesis of the literature pertinent to the durability of the postablation esophagus.

Table 1. Recommended Time After Complete Eradication of Intestinal Metaplasia to Perform Endoscopic Surveillance Based on New Data

Risk Category	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Low-grade dysplasia	1 year	3 years	>5 years[a]	a	a	a	a	a
High-grade dysplasia or intramucosal carcinoma	3 months	6 months	1 year	2 years	3 years	4 years	5 years	>5 years

[a]Surveillance times were estimated to a limit of 5 years for the higher risk categories and 7 years for the lower risk categories to avoid extrapolation beyond the data.

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Endoscopic Surveillance Intervals for Patients Obtaining Complete Eradication of Intestinal Metaplasia

Consensus guidelines, which are largely informed by cohort studies and expert opinion,[14,22] endorse indefinite endoscopic surveillance at intervals defined by the highest pretreatment histologic grade pre-CEIM.[1] In the current American College of Gastroenterology guidelines,[1] patients with baseline high-grade dysplasia (HGD) or intramucosal carcinoma (IMC) are recommended to undergo endoscopic surveillance every 3 months in the first year following CEIM, every 6 months in the second year, and yearly thereafter. Surveillance intervals for baseline low-grade dysplasia (LGD) are every 6 months in the first year post-CEIM followed by annual examinations.

Newly Proposed Endoscopic Surveillance Intervals for Patients Obtaining Complete Eradication of Intestinal Metaplasia

The aforementioned surveillance guidelines[1] produced excellent postablation outcomes in patients obtaining CEIM.[28] However, the frequency of endoscopic surveillance following CEIM does not align with the natural history of the postablation esophagus. Current posttreatment surveillance recommendations identically match recommendations for cohorts with untreated dysplastic BE. Because RFA substantially lowers cancer risk, less intensive surveillance may be appropriate following ablation. Data from the AIM Dysplasia trial,[8] US RFA Patient Registry,[25] and United Kingdom National Halo Registry[29] were utilized to assess whether less intensive surveillance intervals following CEIM are reasonable for this cohort.[16,24] Investigators built and validated statistical models to predict the probability of recurrent advanced neoplastic disease (eg, HGD, EAC in both the esophagus and cardia) following CEIM via RFA.[16] Analysis of these data suggested that HGD and IMC overlapped in their estimated risk of recurrence; this was also true for patients with pretreatment nondysplastic BE and indefinite for dysplasia. The combined registries demonstrated annual rates of recurrent neoplastic BE of 0.19% (95% CI, 0.09%-0.40%) for patients with pretreatment nondysplastic BE and indefinite for dysplasia, 1.98% (95% CI, 1.34%-2.93%) for patients with pretreatment LGD, and 5.93% (95% CI, 4.77%-7.36%) for patients with pretreatment HGD or IMC. The investigators chose 2.9% as the acceptable rate of neoplastic recurrence per surveillance endoscopy because it was associated with an estimated rate of invasive EAC of 0.1%, which was their proposed acceptable rate of EAC at any given surveillance endoscopy. Additional analysis of these data allowed the investigators to propose surveillance intervals of 1 and then 3 years after CEIM for patients with baseline LGD to yield a risk of invasive EAC less than 1/1000 at any given surveillance endoscopy. Intervals of 3 months, 6 months, and then annually for 5 years were suggested for patients with baseline HGD or IMC (Table 1). Data limitations did not allow the investigators to extrapolate their findings for baseline HGD or IMC beyond 5 years. These proposed intervals will ideally provide a low rate of recurrent disease with neoplasia while significantly reducing the burden of surveillance endoscopies engendered by current guidelines.

Endoscopic Surveillance Techniques Following Complete Eradication of Intestinal Metaplasia

Once CEIM is achieved, endoscopic surveillance with biopsies represents the standard of care to detect recurrent disease. Inspection should be conducted with high-resolution white-light endoscopy and narrow-band imaging. The gastroesophageal junction and tubular esophagus, including the area of the prior BE segment, should be examined in both antegrade and retrograde views.[1]

A fundamental question in endoscopic surveillance after CEIM is how biopsies should be taken. All guidances suggest that any endoscopic abnormalities in the

neosquamous epithelium or the gastric cardia be sampled and placed in specifically labeled pathology jars. These samples provide the highest yield of recurrent disease in the examination. Current guidelines also suggest that 4-quadrant random biopsies be taken every centimeter through the prior area of BE.[1] However, newer data challenge this paradigm, demonstrating that recurrent disease of the esophagus typically occurs at or adjacent to the gastroesophageal junction. Additionally, when found more than 1 cm from the gastroesophageal junction, recurrent disease of the tubular esophagus is generally visible to white-light endoscopy compared with an incidental histologic finding on random biopsies.[28] Therefore, there is little to no yield of random biopsies more than 2 cm cephalad to the squamocolumnar junction regardless of the length of the BE segment prior to ablation.

Similar to that of the tubular esophagus, recurrent disease of the cardia tends to occur within 1 cm of the gastroesophageal junction.[23] Given the inability of clinicians to reliably identify dysplastic columnar mucosa in the cardia, 4-quadrant random biopsies of the cardia are recommended during routine surveillance endoscopy. A study of 52 initial recurrences following successful RFA found that 33 (63%) recurrences were isolated to the esophagus, 17 (33%) were isolated to the cardia, and 2 (4%) occurred in both the esophagus and the cardia.[23]

When biopsies are obtained, those from the tubular esophagus and gastroesophageal junction should ideally be placed in separate bottles to promote accurate localization and treatment of recurrence. No consensus exists as to the correct number of biopsies needed for adequate surveillance[1]; however, a reasonable approach would be to perform any targeted biopsies and then to perform 6 to 8 random biopsies of the distal 2 cm of the tubular esophagus, as well as 4-quadrant biopsies of the cardia, either straddling the Z line or within 1 cm of the gastroesophageal junction.

Adjunct Technologies for Surveillance of Patients Who Have Obtained Complete Eradication of Intestinal Metaplasia

Random biopsies are prone to sampling error and can miss areas of recurrent disease during surveillance.[1,30-32] Newer imaging and sampling technologies, such as optical coherence tomography (OCT) and wide-area transepithelial sampling (WATS, CDx Diagnostics), are being assessed to address this problem.[33] OCT functions as an optical ultrasound that measures back-scattered or back-reflected light off of a tissue.[34] This permits high-resolution cross-sectional imaging with up to 2 mm of depth. WATS is a brush biopsy technique that employs an abrasive brush to gather a transepithelial specimen.[35] Analysis of the specimen is aided by a computer scan that may identify potentially abnormal cells via their morphology.

Data exist regarding the utility of OCT[36-38] and WATS[39,40] for general endoscopic surveillance of BE but are limited in postablation cohorts. For instance, a single, multicenter, randomized, clinical trial assessed the proportion of patients diagnosed with HGD and EAC using WATS in addition to biopsy sampling compared to biopsy sampling alone.[35] Prior history of esophageal ablation was an exclusion criterion. The researchers found that the addition of WATS led to an absolute increase in the detection of HGD and/or EAC of 14.4% (95% CI, 7.9%-19.3%). In regard to OCT, an observational cohort study assessed a 1000-patient registry to estimate the quantitative performance metrics of OCT for BE.[38] Of the 1000 patients, 238 completed prior BE treatment and had no visible BE or an irregular Z line at follow-up. There were 211 out of 238 (89%) patients with no focally suspicious findings on white-light endoscopy alone. When adding OCT as an adjunct to white-light endoscopy, the researchers found that 103 out of 211 (49%) patients had no suspicious white-light endoscopy or OCT findings. There were ultimately 2 and 0 patients with negative white-light endoscopy and white-light endoscopy plus OCT, respectively, who were later diagnosed with BE-associated neoplasia (1 HGD and 1 EAC).

Treatment of Recurrent Barrett Esophagus Following the Complete Eradication of Intestinal Metaplasia

Recurrent IM and dysplastic BE following CEIM are amenable to further EET.[14,24,26,29] For instance, in one study, 58% of patients with recurrent disease again obtained CEIM following additional EET.[23] Moreover, this number is likely under-representative of the true efficacy of EET in this setting, as 37% of the patients with recurrent disease in this study were still undergoing retreatment at the time of the report, and presumably at least some of these patients additionally reattained CEIM. For the patients in this study who obtained a second CEIM, 13% had an additional recurrence of disease. Ultimately, only a small minority of this cohort (4%) failed EET and progressed to EAC.[23]

Subsquamous Barrett Esophagus Detected During Surveillance Following Complete Eradication of Intestinal Metaplasia

Subsquamous BE after EET, also referred to as buried BE, denotes IM beneath a normal layer of neosquamous esophageal epithelium. The likelihood of detecting subsquamous BE following apparent CEIM depends upon the

particular ablation modality employed and the process of sampling. The proportions of patients with subsquamous BE following RFA and photodynamic therapy have been estimated to be 0.9% and 14.2%, respectively.[27,29,41] However, up to 63% of patients have been found to have subsquamous BE when detected using 3-dimensional OCT.[42] Although a similar study reports disparate findings,[43] it suggests that subsquamous BE is much more common than is understood using random sampling methods of apparently normal neosquamous epithelium.[42]

Despite the relatively high proportion of patients in whom subsquamous BE is found, it likely represents a benign lesion. Supporting this supposition is the low rate of subsquamous EAC found following CEIM, and the decreased risk of subsquamous IM following EET. In one study utilizing data from the AIM Dysplasia trial to assess a postablation surveillance cohort, the prevalence of subsquamous BE decreased from 25.2% pre-EET to 5.0% immediately following CEIM, and ultimately to 3.8% by the end of follow-up.[8] Given the poorly defined clinical course of subsquamous BE, debate exists as to the proper management of this finding. Some investigators recommend retreatment of patients with subsquamous IM, while other investigators provide additional treatment only if dysplasia is present.[44] In the latter scenario, endoscopic mucosal resection of a mucosal abnormality and ablation of any area found on random biopsies to harbor dysplastic subsquamous BE, but without a visible abnormality, is a reasonable strategy.

Recurrent Barrett Esophagus Following Radiofrequency Ablation With the Complete Eradication of Intestinal Metaplasia

Recurrent IM in the tubular esophagus following CEIM is common and is diagnosed in 25% or more of post-EET patients at a rate of 8% to 10% per patient year.[13,21,45] However, only a minority of cases demonstrate recurrence with dysplastic IM, histologic progression (defined as a histologic grade more advanced than prior to EET),[12] EAC,[46] or require esophagectomy.[18] The vast majority of recurrent BE after CEIM is small in terms of surface area involved, and is nondysplastic on histologic sampling. As such, most recurrent disease is associated with a benign clinical course and is amenable to further EET.[22]

As noted, most patients with recurrent disease are found to have nondysplastic IM (Table 2). In a study of 1634 patients included in the US RFA Patient Registry, treated with RFA, and followed for 2.4 ± 1.3 years, any disease recurrence was documented in 334 (20%) patients (Figures 1 and 2).[12] Nearly 90% of these recurrences were nondysplastic or indefinite for dysplasia.[12] Only 34 (10%) recurrences contained dysplasia, with 19 (6%) and 15 (4%) being LGD and HGD, respectively. Disease recurrence data from the AIM Dysplasia trial were evaluated in 110 patients treated with RFA who were followed for 2.9 years (range, 0.2-5.5 years).[24] During this interval, there were 35 (32%) patients with any disease recurrence, of which 19 (17%) were dysplastic recurrences. A systematic review and meta-analysis reported a pooled recurrent disease rate of 8.6 per 100 patient years (95% CI, 6.7-10.5 per 100 patient years).[15] The pooled recurrence rate of dysplastic IM was 1.9 per 100 patient years (95% CI, 1.3-2.5 per 100 patient years).

Risk of disease recurrence also likely varies with time from ablation, with the highest risk being immediately after attaining CEIM, although data from some investigators contest this finding. The AIM Dysplasia trial reported that recurrent disease usually occurred in the first year of surveillance (69%).[24] An additional study reported disease recurrence of 20% and 33% following 1 and 2 years of surveillance, respectively.[13] As opposed to the prior 2 studies, analysis of data from a retrospective cohort concluded that the rate of recurrent disease and the proportion of patients with recurrent disease were constant with time.[23] During 540.6 patient years of follow-up, 218 (24%) patients developed recurrent IM or BE-associated neoplasia. This cohort underwent a mean of 2.32 surveillance endoscopies (standard deviation [SD] ± 1.35 endoscopies). Over this follow-up interval, the patients had a mean time to recurrence of 1.88 years (SD ± 1.42 years) with an annual incidence rate of recurrent disease of 9.6%. Kaplan-Meier analyses showed a constant rate of recurrence over time. Some smaller studies likely have a type II error when attempting to assess the pattern of disease recurrence. If the overall number of recurrences in the cohort are too few, temporal patterns are obscured and it is falsely assumed that rates of recurrence are uniform over time.

Recurrent disease with histologic progression or EAC is uncommon. Data from the US RFA Patient Registry showed that disease recurrence with histologic progression occurred in only 6% (20/334) of patients who experienced a recurrence, which accorded with 1.2% of all treated patients. The other 94% of recurrences demonstrated a histologic grade identical to or lower than the pretreatment histology.[12] An additional study documented that only 1 out of 37 treated patients had recurrent disease with histologic progression.[13] A systematic review assessed the risk for EAC following EET.[15] There were a total of 1000 included relapses, of which 54 (5.4%) were EAC. This proportion, however, is a composite of studies assessing relapses after both RFA and stepwise endoscopic mucosal resection, and, as such, may differ from the true incidence of EAC following RFA specifically.

Table 2. Recurrent Disease by Pre-RFA History in Selected Studies

Study	Pre-RFA History, n (%)						
	Total Patients	NDBE	IND	LGD	HGD	IMC	EAC
Gupta et al[13]							
Pretreatment number	229	NR	NR			NR	
Any post-RFA recurrence	37 (16)						
HR; 95% CI for recurrence				0.66; 0.25-1.76	0.53; 0.23-1.19		0.52; 0.14-1.91
Cotton et al[24]							
Pretreatment number	NR	NR	NR	54	55	NR	NR
Any post-RFA recurrence				14 (26)	21 (38)		
Orman et al[22]							
Pretreatment number	107	NR	NR	23	67	17	NR
Any post-RFA recurrence	8 (7)			1 (4)	5 (7)	2 (12)	
Wolf et al[46]							
Pretreatment number	4982	2346	368	1020	990	195	63
Any post-RFA recurrence	100 (2)	3 (0.1)	2 (0.5)	12 (1)	83 (8)	NR	NR
Small et al[56]							
Pretreatment number	158	NR	NR	NR	95	64	NR
Any post-RFA recurrence	81 (51)				48 (51)	33 (52)	
Pouw et al[57]							
Pretreatment number	24	NR	NR	NR	NR	NR	NR
Any post-RFA recurrence	4 (17)						

EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; HR, hazard ratio; IMC, intramucosal carcinoma; IND, indefinite for dysplasia; LGD, low-grade dysplasia; NDBE, nondysplastic Barrett esophagus; NR, not reported; RFA, radiofrequency ablation.

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Predictors of Recurrent Disease Following Endoscopic Eradication Therapy With Complete Eradication of Intestinal Metaplasia

Of the factors associated with disease recurrence following EET, the strongest and most consistent has been the pretreatment grade of BE. Data from the AIM Dysplasia trial showed an overall recurrence rate of 10.8 per 100 patient years (95% CI, 8.7-15.0 per 100 patient years).[24] Rates of recurrence for patients with baseline LGD and HGD were 8.3 per 100 patient years (95% CI, 4.9-14.0 per 100 patient years) and 13.5 per 100 patient years (95% CI, 8.8-20.7 per 100 patient years), respectively. Rates of dysplastic recurrence also have been found to differ by pretreatment grade of BE. Data from the same AIM Dysplasia trial showed recurrence rates for dysplastic BE to be 3.3 per 100 patient years (95% CI, 1.5-7.2 per 100 patient years) and 7.3 per 100 patient years (95% CI, 4.2-12.5 per 100 patient years) for those with baseline LGD and HGD, respectively.

Although the pretreatment grade consistently associates with posttreatment outcomes, additional predictors of posttreatment outcomes remain poorly defined.[12] Limited data from studies with small sample sizes indicate that age, length of pretreatment BE, Prague circumferential length, and the presence of a large hiatal hernia may increase the risk for recurrent BE following CEIM.[17,19,23]

Chemopreventive Medications and Fundoplication to Mitigate the Risk of Relapse Following Esophageal Ablation

Limited data describe the efficacy of chemopreventive medications to prevent recurrent IM or dysplastic BE following CEIM. Expert consensus promotes tight control of gastroesophageal reflux symptoms[15] and healing of reflux esophagitis[1] to help reduce recurrence. In most cases, experts recommend twice-daily proton pump inhibitors (PPIs) in patients obtaining CEIM. Data from a recent randomized, controlled trial suggest that high PPI dosing safely improves outcomes in patients with BE, although this study was conducted in a cohort that had not undergone EET.[47] Patients motivated to discontinue PPI therapy should be referred for pH testing prior to empiric discontinuation.[48]

Observational studies also suggest that nonsteroidal anti-inflammatory drugs reduce the risk for EAC in the

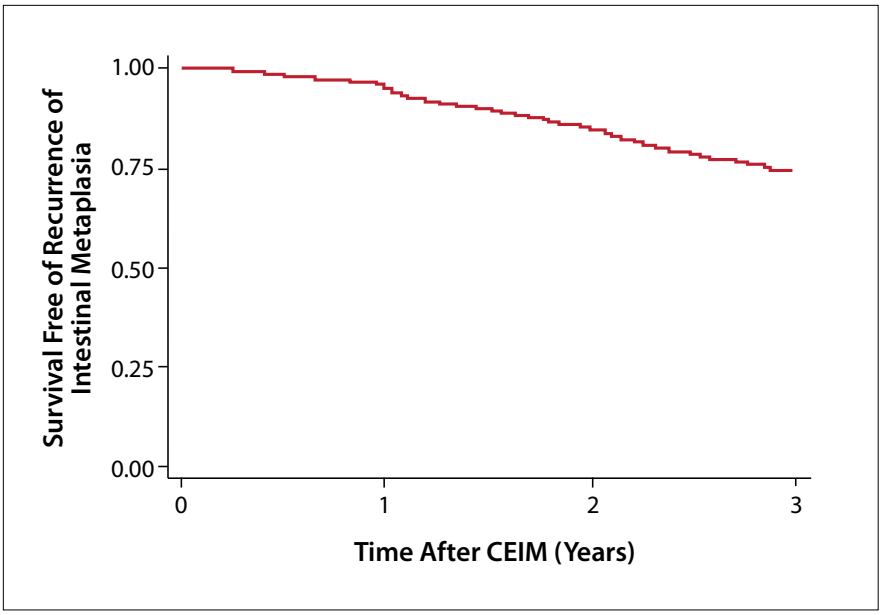

Figure 1. Kaplan-Meier plot of intestinal metaplasia recurrence among patients who achieved complete eradication of intestinal metaplasia (CEIM) after radiofrequency ablation (n=1634).

Modified with permission from Pasricha S et al.[12]

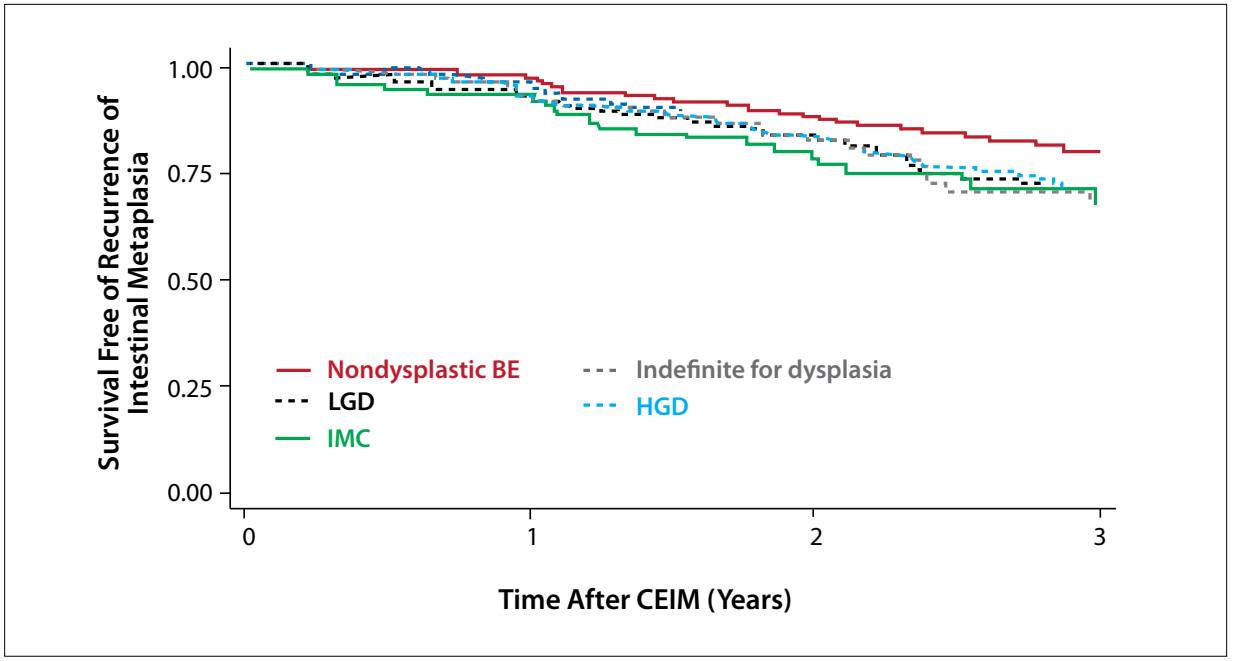

Figure 2. Kaplan-Meier plot of intestinal metaplasia recurrence among patients who achieved complete eradication of intestinal metaplasia (CEIM) after radiofrequency ablation, with pretreatment histology of nondysplastic Barrett esophagus (BE), indefinite for dysplasia, low-grade dysplasia (LGD), high-grade dysplasia (HGD), and intramucosal carcinoma (IMC).

Modified with permission from Pasricha S et al.[12]

general patient population.[49,50] Data from a factorial design, randomized, controlled trial assessed whether aspirin in combination with a high- or low-dose PPI reduces the time to progression in a cohort with BE. However, this study was not specifically addressing patients with BE following CEIM, and aspirin was not found to be significantly better than no aspirin when considering time to disease progression (P=.068).[47] In

light of the established side effects of nonsteroidal anti-inflammatory drugs and aspirin and unclear utility in a clinical setting, it is currently inadvisable to pursue the routine use of such medications for chemoprevention in postablation cohorts.[1]

Data utilized from the US RFA Patient Registry compared the safety and efficacy of RFA for patients receiving PPIs alone with patients taking PPIs in addition to prior fundoplication.[25] Prior fundoplication was not found to affect the safety or efficacy outcomes of RFA. Patients with a prior fundoplication were found to have similar adverse events and treatment efficacy relative to patients without prior fundoplication. Limited observational data suggested that individuals with prior fundoplication were more likely to have a durable response to EET, although such an assertion remains inconclusive.[51]

Common Complications Following Endoscopic Eradication Therapy

RFA is associated with a favorable side-effect profile, especially when compared to alternative EETs such as photodynamic therapy and endoscopic mucosal resection. Chest pain is commonly reported and is an anticipated side effect of RFA. In the AIM Dysplasia trial, patients in the ablation arm reported a median pain score of 23 on a 100-point visual analogue scale on the day treatment was received.[8] The median chest discomfort reported by these patients decreased to 0 by day 8 following ablation. Patients are typically discharged with a topical analgesic (eg, viscous lidocaine) and/or a narcotic analgesic for their pain. Strictures are also a common occurrence following RFA, being documented in 5% to 10% of patients. For instance, in the AIM Dysplasia trial, 5 (6%) patients developed an esophageal stricture following a mean of 3.5 RFA sessions. These patients were all successfully treated with dilation.[8] Additional complications of RFA, including perforation, bleeding, and death, are uncommon. A systematic review and meta-analysis that included 37 studies and 9200 patients reported a pooled risk of adverse events attributed to RFA of 8.8%; these events were largely strictures (5.6%), followed by bleeding (1%) and perforation (0.6%).[52]

The Known Durability and Complications of Cryotherapy in Patients Obtaining Complete Eradication of Intestinal Metaplasia

Cryotherapy represents an alternative EET modality to RFA. The method utilizes liquid nitrogen, nitrous oxide, or carbon dioxide (ie, the cryogen), delivered either through a catheter or inside a balloon, to ablate affected tissue.

Data describing the long-term durability of cryotherapy following CEIM are limited.[53] A single-center, retrospective cohort study reported on outcomes at 3 and 5 years following liquid nitrogen spray cryotherapy.[53] This cohort comprised 50 patients with baseline HGD who were followed for 3 years and 40 patients who were followed for 5 years after treatment. Of the 50 patients who were followed for 3 years, 90% (45/50) and 60% (30/50) obtained complete eradication of dysplasia and CEIM, respectively, following initial cryotherapy. Among the 45 patients with complete eradication of dysplasia and 30 patients with CEIM, 24% (11/45) and 40% (12/30) had recurrent dysplasia and IM at 3 years, respectively. For the 40 patients who were followed for 5 years, the durability of complete eradication of dysplasia was 92%, and the durability of CEIM was found to be 81%. Two patients developed EAC, and no deaths were reported over this time interval.

The comparative side-effect profiles of RFA and cryotherapy are poorly understood due to the paucity of head-to-head data. RFA results in treatment-related strictures in approximately 5% to 10% of patients. Cryotherapy is thought to leave the tissue architecture of the superficial squamous epithelium intact, which may result in a smaller proportion of patients developing ablation-associated stenosis; however, the validity of this supposition is as of yet unclear. Moreover, patients undergoing cryotherapy may also develop less posttreatment pain.[54] Any comparative conclusions must be viewed as tentative and await further data.

Summary

RFA represents an effective modality with infrequent post-procedural side effects. As such, it remains the preferred treatment strategy and standard of care for patients with BE and early neoplastic changes. Following CEIM, recurrent IM is common, but recurrent dysplastic BE and EAC are rare. New data describing the clinical course of the post-CEIM esophagus suggest that surveillance intervals should be attenuated following ablation. In the setting of disease relapse, recurrence is generally amenable to treatment with further EET. Complications following RFA, including pain, strictures, and bleeding, are also transient, treatable, and rare, respectively. Future studies are likely to continue to refine surveillance intervals, inform the need for indefinite surveillance protocols, define the utility of chemopreventive agents, and describe the efficacy of novel sampling techniques and imaging modalities in the postablation patient population.

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