Curr Treat Options Gastro (2019) 17:171–186
DOI 10.1007/s11938-019-00226-5

Endoscopy (P Siersema, Section Editor)

Durability of Endoscopic Treatment for Dysplastic Barrett's Esophagus

Craig C. Reed, MD, MSCR
Nicholas J. Shaheen, MD, MPH[*]

Address
[*]Center for Esophageal Diseases and Swallowing and Center for Gastrointestinal Biology and Disease, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina School of Medicine, CB#7080, Chapel Hill, NC, 27599-7080, USA
Email: nshaheen@med.unc.edu

Published online: 10 May 2019

This article is part of the Topical Collection on *Endoscopy*

Keywords Barrett's esophagus · Dysplasia · Ablation · Long-term results · Durability

Abstract

Purpose of review This review discusses the durability of the neo-squamous esophageal epithelium following endoscopic eradication therapy of dysplastic Barrett's esophagus. Our review will focus primarily on patients treated with radiofrequency ablation; however, we describe the known durability of cryotherapy. Additionally, we discuss the utility of novel imaging technologies and the efficacy of chemopreventive medications following endoscopic ablation.

Recent findings Mounting data describe the durability of the post-ablation esophagus. Dysplastic Barrett's esophagus and adenocarcinoma following ablation are rare. New data emphasize that most recurrent disease occurs in the initial year following treatment. Additionally, recent publications suggest that a much-attenuated surveillance interval may provide adequate detection of neoplasia with many fewer surveillance endoscopies.

Summary Future guidelines will likely liberalize surveillance intervals following endoscopic eradication therapy. Additionally, further longitudinal studies will need to assess the length of time for which surveillance is indicated. The utility of chemopreventive strategies and adjunctive imaging modalities in the maintenance and surveillance of the post-ablation esophagus also remain unclear and will be areas for future investigation.

Introduction

Barrett's esophagus (BE) is a premalignant condition whereby intestinal metaplasia (IM), a specialized columnar epithelium, replaces the usual stratified squamous epithelium of the distal esophagus [1•]. BE represents a commonly encountered finding. In population-based cohort studies, the prevalence of BE was 1–2% [2, 3] and 15% [4] in all patients referred for endoscopy and in patients referred specifically for symptoms of gastroesophageal reflux, respectively. BE also increases the risk for esophageal adenocarcinoma (EAC) [1•]. Once diagnosed with EAC, less than 20% of patients survive to 5 years [5].

Significant advances have occurred in the management of BE over the last two decades. These advances include new techniques for endoscopic resection and ablation, collectively termed endoscopic eradication therapy (EET) [6–8]. Radiofrequency ablation (RFA) is the most frequently utilized EET given its substantial evidence base, efficacy, and infrequent complications [9]. High-quality data from clinical trials consistently show that EET reliably produces complete eradication of intestinal metaplasia (CEIM) and dysplasia with an acceptable safety profile [7, 10]. Moreover, newer data derived from cohort studies [11–15], RCTs [16], and systematic reviews [17•, 18] describe the long-term durability of the neo-squamous esophageal epithelium following EET. Though IM not infrequently recurs in the post-ablation esophagus [12, 19], most recurrent IM is amenable to further EET [12] and is associated with a benign course [20].

In this review, we discuss the durability of the neo-squamous esophageal epithelium following EET of dysplastic BE. The available body of literature will focus our discussion on patients treated with RFA, though the durability of cryotherapy will be briefly considered. In addition, we discuss the use of novel imaging technologies in the surveillance of BE following CEIM, as well as the efficacy of chemopreventive strategies in the prevention of recurrent disease.

Variable definitions are utilized to describe the durability of the post-ablation neo-squamous esophagus

Significant heterogeneity exists in the literature describing the durability of the post-ablation esophagus. This heterogeneity principally derives from three sources. First, no consensus definition of CEIM exists. In addition, investigators variably define recurrent disease. Finally, the designs of the relevant studies also differ. Variable surveillance protocols, patient populations, and treatments underscore the latter point.

The complete eradication of dysplasia and intestinal metaplasia defines success in the application of EET. However, given concern over sampling error intrinsic to random biopsies, some investigators have required two negative biopsy sessions to define complete eradication, while others require only one such exam. For instance, papers analyzing data from the AIM Dysplasia Trial [21, 22•] and the US RFA Patient Registry [11] required complete histologic and endoscopic remission of IM on a single biopsy session following treatment to define CEIM. Alternatively, papers from the Barrett's Esophagus Translational Research Network (BETRNet) Consortium required at least two sessions with histologic and endoscopic remission of IM to define CEIM [12]. Though the latter definition may partially mitigate sampling error, no data objectively describe an ideal number of biopsy sessions devoid of recurrent disease. Certainly, if two is better than one, three should be better than two. Therefore, by using this rationale, it is difficult to know the "right" definition of durability, and no matter which number is chosen, the specter of residual sampling error persists, albeit to a presumably lesser degree. Furthermore, papers from the AIM

Dysplasia Trial and US RFA Patient Registry also conducted sensitivity analyses assessing the impact on recurrent rates of disease using the alternative definition of CEIM, and these rates did not differ significantly [11, 22•]. These sensitivity analyses argue that a definition incorporating a single normal endoscopy session optimizes the amount of follow-up time without markedly impairing data quality.

Investigators also variably define recurrent disease, and these differences pertain to anatomic loci. Some investigators have defined recurrent disease as IM or dysplasia located solely within the tubular esophagus [13], while others have termed recurrent disease to be IM located within both the tubular esophagus and the gastroesophageal junction and cardia [23], or even disease located solely in the cardia [20]. Significant uncertainly exists as to the optimal disease definition for recurrent disease. Dysplasia confined to the cardia following CEIM may suggest recurrent disease or dysplasia missed on pre-CEIM biopsies, owing to sampling error. Because few investigators contest the clinical relevance of dysplasia of the cardia, most clinicians consider this finding to be a failure of EET, and therefore include it in a definition of recurrent disease. IM of the cardia, on the other hand, is common place in patients with chronic GERD; approximately 20% of patients with chronic GERD symptoms without BE have non-dysplastic IM of the cardia [24]. The natural history of IM of the cardia is unclear, and the clinical data we do have on this entity suggest that, at least in the chronic GERD population, the risk of malignant progression is low. Therefore, the finding of IM of the cardia alone on surveillance biopsies after CEIM is not considered recurrent disease by most investigators. It is important to further note that in order to discover dysplasia or IM of the cardia, one must take biopsies of the cardia, and biopsy regimens in durability studies have varied considerably both in number and location.

Subsquamous Barrett's esophagus following endoscopic eradication therapy

Buried BE, also known as subsquamous IM, refers to the presence of IM beneath a normal layer of squamous esophageal epithelium (Fig. 1). Debate exists regarding the malignant potential of this finding. Moreover, the rate of detection of subsquamous IM following CEIM varies drastically by EET modality and means of detection. For instance, rates of buried BE post-RFA and photodynamic therapy have been estimated at 0.9% and 14.2%, respectively [24–26]. The addition of a novel imaging technology, such as three-dimensional optical coherence tomography, increased detection to as high as 63% of patients [27].

Though the prevalence of buried Barrett's esophagus remains in dispute, this finding apparently represents a benign lesion in the vast majority of patients. Subsquamous EAC following CEIM has seldom been reported despite a large body of literature. Furthermore, the risk of subsquamous IM appears to decrease following endoscopic ablation. Data from the AIM Dysplasia Trial showed that, using a highly protocolized standard biopsy technique, the prevalence of subsquamous IM decreased from 25.2 to 5% and subsequently 3.8% following 12 and 24 months of surveillance post-RFA [7]. For these reasons, although subsquamous IM is a common occurrence after apparently successful EET, the clinical significance remains unclear. Because of the unclear significance of this finding, the most appropriate clinical response to subsquamous IM is similarly not understood. While some endoscopists further treat such patients with EET,

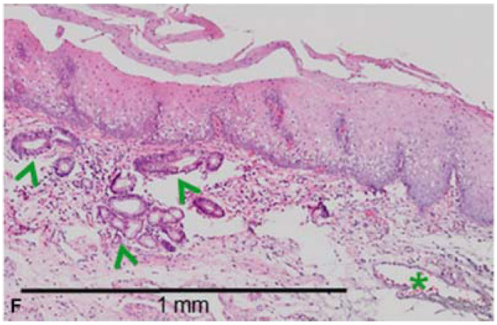

Fig. 1. Arrowheads indicate buried Barrett's glands in a patient with Barrett's esophagus in surveillance following radiofrequency ablation. From Swager A, Boerwinkel D, de Bruin DM, et al. Detection of buried Barrett's glands after radiofrequency ablation with volumetric laser endomicroscopy. Gastrointest Endosc. 2016;83(1):80–8. Figure 3F. Used with permission from Elsevier.

others perform endoscopic surveillance in this population and only intervene further if dysplastic changes are noted.

The durability of the neo-squamous epithelium following the complete eradication of intestinal metaplasia

Data from multiple cohort studies [11–15], RCTs [16, 28, 29], and systematic reviews [17•, 18] describe the durability of CEIM and complete eradication of dysplasia. Though EETs effectively achieve CEIM, recurrent IM is common and occurs in approximately 25% of patients at a rate of 8–10% per patient-year of follow-up [12, 19, 30]. However, most recurrences are associated with a benign clinical course [20], as recurrent dysplastic IM or recurrent BE with histologic progression (i.e., recurrent disease with a histologic grade more advanced to pre-CEIM grade) occurs in a minority of cases [11]. Moreover, EAC is rare in post-ablation surveillance cohorts [31•], and <1% of patients treated with EET require esophagectomy [32].

Overall durability of Barrett's esophagus and incidence of non-dysplastic IM following the complete eradication of intestinal metaplasia

Multiple studies document that the predominant histologic subtype for recurrence after CEIM is non-dysplastic IM. One study analyzing data from the US RFA Patient Registry, a multi-center collaboration documenting outcomes of care for patients treated with RFA for BE at 148 US institutions [11], assessed 1634 patients for 2.4±1.3 years subsequent to CEIM. Of these, 668 (31%) of the cohort had non-dysplastic BE prior to ablation. In this cohort, recurrence of any disease was seen in 334 (20%) patients (Fig. 2a, b). Non-dysplastic or indefinite for dysplasia recurrence accounted for 287/335 (86%) recurrences. Similarly, data from the AIM Dysplasia Trial analyzed the rate of recurrent disease in patients achieving CEIM following EET for dysplastic BE [22•] (Fig. 3a, b). In this trial, 110/127 (92%) subjects achieved CEIM and were subsequently followed for a mean time of 2.9 years (range 0.2–5.5). Of these 110 patients, 35 (32%) experienced any recurrent disease. Twice as many patients in this study recurred with NDBE than with dysplasia. A second study

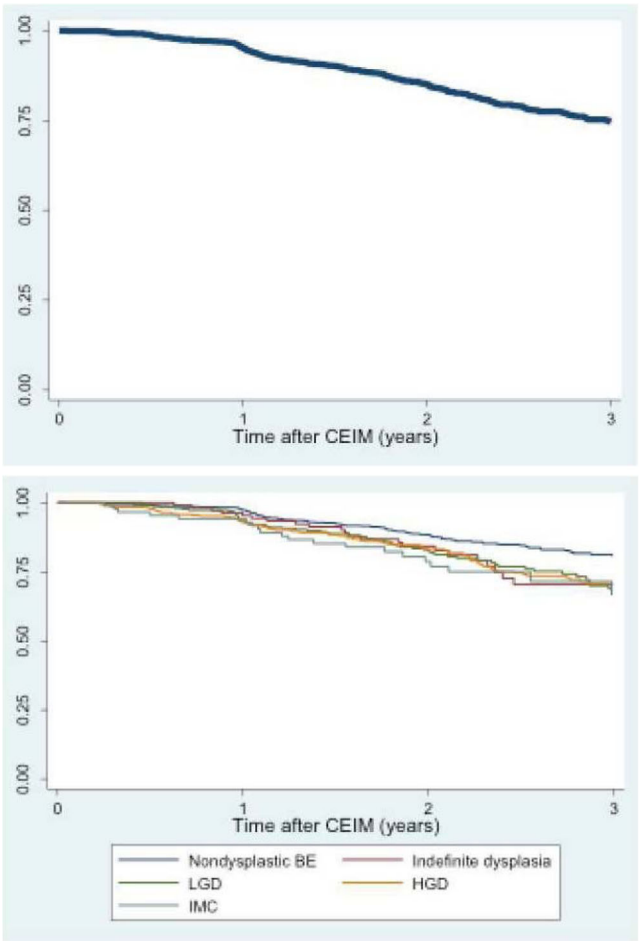

Fig. 2. a Kaplan-Meier plot of intestinal metaplasia recurrence among patients who achieved complete eradication of intestinal metaplasia after RFA (*n*=1634). From Pasricha S, Bulsiewicz WJ, Hathorn KE, et al. Durability and Predictors of Successful Radiofrequency Ablation for Barrett's esophagus. Clin Gastroenterol Hepatol. 2014;12(11):1840–1847. Figure 2a. Used with permission from Elsevier. **b** Kaplan-Meier plot of IM recurrence among patients who achieved CEIM after RFA, with pretreatment histology non-dysplasic BE, low-grade dysplasia (LGD), and high-grade dysplasia (HGD). From Pasricha S, Bulsiewicz WJ, Hathorn KE, et al. Durability and Predictors of Successful Radiofrequency Ablation for Barrett's esophagus. Clin Gastroenterol Hepatol. 2014;12(11):1840–1847. Figure 2b. Used with permission from Elsevier.

of patients in the BETRNet Consortium, additionally, described outcomes for patients treated with RFA [12]. Most of the 448 patients in this study had baseline dysplastic BE; there were 385 (86%) with dysplastic BE or EAC. Ultimately, 229 (51%) achieved CEIM, and 37/229 (16%) patients were found to have recurrent disease. However, the mean follow-up time was short with an average of 3 months (range 0 days–4.6 years) per patient. The majority of the 37 documented recurrences (78%) were also non-dysplastic. Pooled estimates for the overall incidence of recurrent disease have also been reported in systematic reviews and meta-analyses [14]. The overall pooled incidence rate for any recurrent disease following RFA was estimated at 8.6/100 PY (95% CI 6.7–10.5/100 PY).

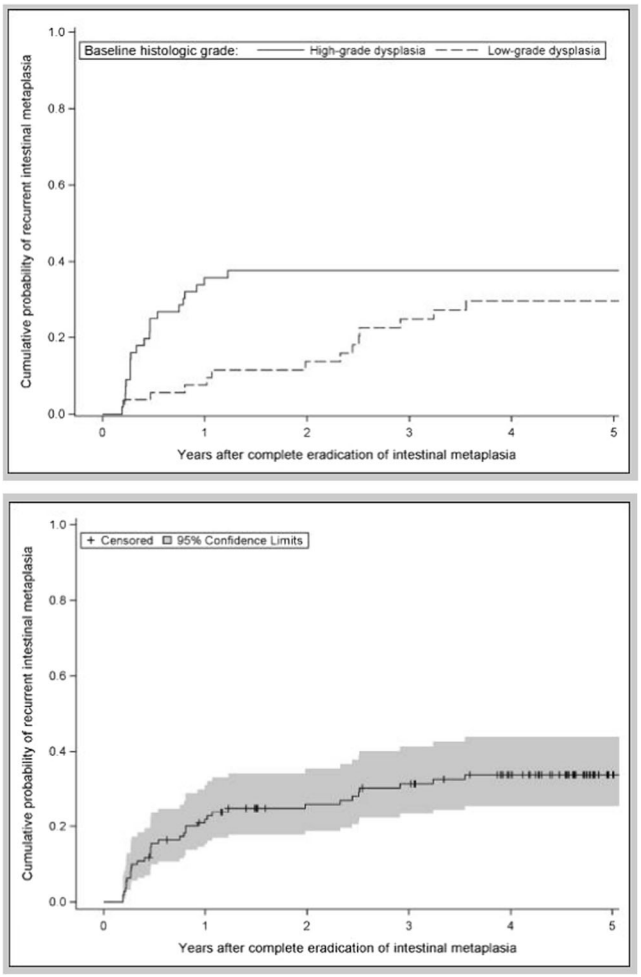

Fig. 3. a Estimated proportion of subjects with any recurrence of intestinal metaplasia recurrence stratified by baseline histologic grade after complete eradication of intestinal metaplasia now allowing interim "touch-up" treatments. From Cotton CC, Wolf WA, Overholt BF, et al. Late Recurrence of Barrett's Esophagus After Complete Eradication of Intestinal Metaplasia is Rare: Final Report From Ablation in Intestinal Metaplasia Containing Dysplasia Trial. *Gastroenterology*. 2017;153(3):681–688. Figure 2. Used with permission from Elsevier. **b** Estimated proportion of subjects with any recurrence after complete eradication of intestinal metaplasia not allowing interim touch-up treatments. From Cotton CC, Wolf WA, Overholt BF, et al. Late Recurrence of Barrett's Esophagus After Complete Eradication of Intestinal Metaplasia is Rare: Final Report From Ablation in Intestinal Metaplasia Containing Dysplasia Trial. *Gastroenterology*. 2017;153(3):681–688. Figure 3. Used with permission from Elsevier.

Recurrence of dysplastic Barrett's esophagus following the complete eradication of intestinal metaplasia

As opposed to non-dysplastic recurrent disease, dysplastic disease following CEIM with RFA is a rarer finding. In the aforementioned US RFA Registry study [11], there were 34/334 (10%) recurrences containing dysplasia. Low-grade dysplasia (LGD) and high-grade dysplasia (HGD) comprised 19 (6%) and 15 (4%) of these findings. In the paper by Cotton et al. assessing data from the AIM Dysplasia Trial, following 363.1 person-years of follow-up (mean 3.3 years per patient), there were 19 (17%) dysplastic recurrences. The overall incidence rate

Table 1. Recurrent disease by preradiofrequency ablation histology in selected studies. From Reed CC, Shaheen NJ. Natural History of the Post-ablation Esophagus. Dig Dis Sci. 2018;63(8):2136–2145. Table 1. Used with permission from Springer Nature

Study	Preradiofrequency ablation histology, *n* (%)						
	Total patients	NDBE	IND	LGD	HGD	IMC	EAC
Gupta et al. [12]							
Pretreatment number	229	NR	NR			NR	
Any post-RFA recurrence	37 (16)						
HR and 95% CI				0.66 (0.25, 1.76)	0.53 (0.23, 1.19)		0.52 (0.14, 1.91)
Cotton et al. [22•]							
Pretreatment number	NR	NR	NR	54	55	NR	NR
Any post-RFA recurrence				14 (26)	21 (38)		
Orman et al. [20]							
Pretreatment number	107	NR	NR	23	67	17	NR
Any post-RFA recurrence	8 (7)			1 (4)	5 (7)	2 (12)	
Small et al. [48]							
Pretreatment number	158	NR	NR	NR	95	64	NR
Any post-RFA recurrence	81 (51)				48 (51)	33 (52)	
Wolf et al. [31•]							
Pretreatment number	4982	2346	368	1020	990	195	63
Post-RFA EAC	100 (2)	3 (0.1)	2 (0.5)	12 (1)	83 (8)	–	–
Small et al. [48]							
Pretreatment number	24	NR	NR	NR	95	64	NR
Any post-RFA recurrence	81 (51)				48 (51)	33 (52)	
Pouw et al. [49]							
Pretreatment number	24	NR	NR	NR	NR	NR	NR
Any post-RFA recurrence	4 (17)						

NDBE non-dysplastic Barrett's esophagus, *IND* indeterminate for dysplasia, *LGD* low-grade dysplasia, *HGD* high-grade dysplasia, *IMC* intramucosal carcinoma, *EAC* esophageal adenocarcinoma, *RFA* radiofrequency ablation, *HR* hazard ratio, *95% CI* 95% confidence interval for recurrence, *NR* not reported

of dysplastic recurrence was 5.2/100 PY (95% CI 3.3–8.2) [22•]. Of the 37 patients included within the BETRNet Consortium study with documented recurrence, 8/37 (22%) were dysplastic [12]. These individual findings were reflected in the pooled estimated recurrence rate of dysplastic IM described in a systematic review and meta-analysis of 1.9/100 PY (95% CI 1.3–2.5/100 PY) [14].

Risk of disease recurrence stratified by pretreatment histologic grade

The most severe pretreatment grade of BE prior to CEIM consistently associates with post-treatment outcomes (Table 1). Data derived from the AIM Dysplasia Trial illustrate this finding. These investigators documented incidence rates for any recurrence of 10.8 per 100 PY (95% CI 8.7–15.0/100 PY), 8.3 per 100 PY (95% CI 4.9–14.0/100 PY), and 13.5 per 100 PY (95% CI 8.8–20.7/100 PY) for all baseline histologic grades, baseline LGD, and baseline HGD, respectively [22•]. When considering dysplastic recurrence specifically, similar findings were reported. Here, an overall rate of dysplastic recurrence of 5.2 per 100 PY (95% CI 3.3–8.2/100 PY) was documented. The rates of dysplastic recurrence among patients with baseline LGD and HGD were 3.3 per 100 PY (95% CI 1.5–7.2/100 PY) and 7.3 per 100 PY (95% CI 4.2–12.5/100 PY). Increasingly severe pretreatment histologic grade was also associated with overall recurrence rates in data from the US RFA Patient Registry [11]. Yearly recurrence rates were 7% for patients with baseline non-dysplastic BE, 11% for patients with baseline LGD, 10% for patients with baseline HGD, 12% for patients with baseline IMC, and 19% for patients with baseline EAC.

Risk for histologic progression and esophageal adenocarcinoma following endoscopic eradication therapy

In the setting of BE with CEIM, histologic disease progression denotes the recurrence of BE with a histologic grade more advanced than that found prior to treatment. This finding occurs infrequently. As noted in the previously described US RFA Registry study, recurrent disease with histologic progression occurred in 6% (20/334) of cases with recurrent disease, and 1.2% of the total number of patients treated [11]. Histologic progression was also rare in the BETRNet Consortium study. These investigators found a single (1/37) recurrent case with progression. In this case, the patient, who had HGD at baseline, progressed to IMC [12].

An additional study analyzing data from the US RFA Registry estimated the incidence of EAC following RFA in a cohort of 4698 patients [31•]. Of these 4698 patients, 3946 (84%) with CEIM were followed for on average for 2.7 ±1.6 years. There were 100 (2%) with diagnoses of EAC. A slight majority (54 patients) was IMC with the rest being invasive EAC (46 patients). Through the follow-up period described in this paper, 9/157 (0.6%) deaths were attributed to EAC.

A systematic review collated the risk for EAC following EET [14]. Of 1000 relapses included within this systematic review, 54/1000 (5.4%) contained EAC. It is worth noting that 25/39 studies included within the systematic review solely assessed RFA. The remainder examined stepwise complete endoscopic mucosal resection, and as such, the aforementioned estimate of 5.4% derives from both procedure types.

Risk of recurrent intestinal metaplasia or Barrett's-associated neoplasia as a function of time following EET

The risk of recurrent IM and BE with dysplasia likely varies with time from initial ablative therapy, though papers variably report this association. For instance, a retrospective cohort study examined time to recurrence of disease following CEIM with RFA in 218 patients [21]. For these 218 patients, 24% had recurrence of IM or Barrett's-associated neoplasia in 540.6 PY of follow-up time. The mean time to recurrence was 1.88 years (SD±1.42), with an average of 2.32 surveillance endoscopies (SD±1.35) prior to recurrence, and an incidence rate of 9.6% per year. From this analysis, the authors concluded that the rate of recurrence and proportion of patients with recurrence were constant over time. Other data [12, 22•] suggest that the rate of recurrent IM and dysplastic BE differs with increasing time from ablation. In a study utilizing data from the AIM Dysplasia Trial [22•], recurrent disease was overwhelmingly found in the first year or surveillance (e.g., 24 of 35 recurrences). A survival analysis [12] similarly found that the incidence of recurrent disease in year 1 was 20% and only 33% by year 2. It is unclear whether these differences reflect underlying differences between the patient populations, or perhaps a type 2 error due to inadequate patient numbers in some trials.

Durability of the post-ablation neo-squamous epithelium in patients treated with cryotherapy

Cryotherapy, utilizing liquid nitrogen or carbon dioxide, is an alternative EET for BE. This method consists of the application of a cryogen (e.g., liquid nitrogen, nitrous oxide, or carbon dioxide) through a low-pressure catheter directly upon affected tissue. Though RFA represents an effective means of producing CEIM, treatment-related strictures occur in approximately 5% of patients [32]. Cryoablation, as opposed to RFA, leaves the tissue architecture of the superficial squamous layers relatively intact and may result in a decreased rate of treatment-related stenosis. Additionally, some data suggest that patients treated with cryotherapy may suffer less post-procedural pain [33].

Data from a single-center retrospective cohort study reported outcomes following liquid nitrogen spray cryoablation at 3 and 5 years [34•]. This study describes a cohort of 50 patients with HGD followed for 3 years and 40 patients followed up to 5 years following therapy. The authors report 98% (49/50) with complete eradication of HGD, 90% (45/50) with complete eradication of dysplasia, and 60% (30/50) with CEIM initially. In the 45 patients with initial complete eradication of dysplasia, 11/45 (24%) were found to have recurrent dysplasia at 3 years. For the 30 patients with initial CEIM, 12/30 (40%) had recurrent IM at 3 years. Following 5 years in the 40 patients, the authors documented that the durability of complete eradication of HGD was 96%, the durability of complete eradication of dysplasia was 92%, and the durability of CEIM was 81%. Overall, there were two cases of EAC with no reported deaths.

This data must be considered in light of the much larger body of literature pertinent to the utilization of RFA for BE. The role of cryotherapy in the treatment of dysplastic BE remains to be fully elucidated and ultimately may require head-to-head trials with RFA.

Surveillance endoscopy intervals following the complete eradication of intestinal metaplasia

Current recommendations for surveillance endoscopy following the complete eradication of intestinal metaplasia

At present, consensus guideline recommendations endorse indefinite surveillance at intervals determined by the highest pretreatment histologic grade preceding CEIM [1•]. The data supporting these guidelines derive largely from cohort studies and expert opinion [13, 20]. Current recommendations include surveillance endoscopy every 3 months in the first year following CEIM for patients with baseline HGD or IMC. This is followed by every 6 months in the second year and additional surveillance endoscopy yearly. For patients with LGD at baseline, recommendations include surveillance every 6 months in the first year after CEIM followed by annual assessment [1•].

Surveillance intervals following complete eradication of intestinal metaplasia as informed by new data on the durability of the post-ablation esophagus

Though effective in producing low rates of unresectable EAC following CEIM [35], current consensus recommendations [1•] are likely too aggressive. This supposition makes intuitive sense given that post-ablation recommendations mirror identically the intervals recommended for patients who have not undergone treatment. RFA lowers incident cancer risk, so surveillance protocols should reflect this decreased risk with less intense surveillance. Data from the AIM Dysplasia Trial, US RFA Registry, and UK National Halo Registry (UK NHR) were utilized to propose new surveillance intervals following CEIM [15•, 22•].

An analysis of data from these two registries allowed investigators to build and validate models to predict the risk of neoplasia (e.g., LGD, HGD, or EAC in

Table 2. Recommended time after complete eradication of intestinal metaplasia to perform surveillance endoscopy based on new data. From Cotton CC, Haidry R, Thrift AP, et al. Development of Evidence-Based Surveillance Intervals After Radiofrequency Ablation of Barrett's Esophagus. *Gastroenterology*. 2018;155(2):316–326.e6. Table 2. Used with permission from Elsevier

Risk category	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Low-grade dysplasia	1 years	3 years	>5 years[a]	a	a	a	a	a
High-grade dysplasia or adenocarcinoma in situ	3 months	6 months	1 year	2 years	3 years	4 years	5 years	>5 years[a]

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

Table 3. Comparing the number of surveillance endoscopies that would be performed in the US Radiofrequency Ablation Registry and the UK National Halo Registry Under Current Surveillance Regimens and Newly Proposed Regimens. From Cotton CC, Haidry R, Thrift AP, et al. Development of Evidence-Based Surveillance Intervals After Radiofrequency Ablation of Barrett's Esophagus. *Gastroenterology*. 2018;155(2):316–326.e6. Table 3. Used with permission from Elsevier

Surveillance risk group	Patients in surveillance	Endoscopies under current recommendations	Endoscopies under proposed recommendation	Actual reduction in stratum %	Total reduction for population (%)
US Radiofrequency Ablation Registry					
2: Low-grade dysplasia	658	3948	1316	67	38
3: High-grade dysplasia or intramucosal adercarcinoma	767	6903	5369	22	
UK National Halo Registry					
2: Low-grade dysplasia	83	498	166	67	29
3: High-grade dysplasia or intramucosal adercarcinoma	290	2610	2030	22	

the esophagus or cardia) after CEIM by RFA [15•]. Using their model to predict histologic recurrence of neoplasia, they found that HGD and IMC overlapped in the estimated risk of recurrence. This was also true for patients with baseline non-dysplastic BE and indeterminate for dysplasia. Annual rates of recurrence with neoplasia was 0.19% (95% CI 0.09–0.40) in those with pre-CEIM non-dysplastic BE and indeterminate for dysplasia, 1.98% (95% CI 1.34–2.93) in those with pre-CEIM LGD, and 5.93% (95% CI 4.77–7.36) in patients with pre-CEIM HGD or IMC. The investigators subsequently choose 2.9% as the rate of neoplastic recurrence per surveillance endoscopy to produce an estimated rate of invasive EAC of 0.1%. This level of risk was chosen in light of the complication rate associated with endoscopic surveillance. Their analysis allowed them to propose surveillance endoscopy at 1 and 3 years after CEIM for patients with baseline LGD. For patients with baseline HGD or IMC, suggested surveillance endoscopy intervals of 3 months, 6 months, and annually to 5 years were proposed. Given limitations in their data, recommendations could not be extrapolated beyond the fifth year (Table 2). These attenuated surveillance intervals should provide a low constant rate of incident recurrence with neoplasia, while accomplishing a sizable reduction in the overall number of upper endoscopies necessary to survey post-ablation populations, when compared with current recommendations (Table 3).

Management of recurrent Barrett's esophagus following the complete eradication of intestinal metaplasia

Following CEIM, recurrent IM and BE with dysplasia may be treated with further EET [13, 22•, 23, 25]. In a 2017 study, second CEIM was obtained in 58% of subjects with recurrence of IM or Barrett's-associated neoplasia. It is worth noting that 37% of the patients with recurrent disease were still completing EET when the paper was published. As such, the success of EET in this setting was likely under reported. Of the 30 patients achieving second CEIM, a third recurrence was found in 13%. However, a minority (4%) of patients in this study ultimately failed endoscopic re-treatment and progressed to EAC [21].

Novel imaging and sampling modalities in the surveillance of Barrett's esophagus patients obtaining complete eradication of intestinal metaplasia

Random biopsies of the esophagus can miss areas of dysplasia or IMC as a consequence of sampling error [1•, 36–38]. Careful endoscopic examination and advanced imaging and sampling technologies, including volumetric laser endomicroscopy (VLE) and wide-area trans-epithelial sampling (WATS), represent potential solutions to this problem.

At present, careful endoscopic examination of the esophageal mucosa under high-resolution white light endoscopy following CEIM represents the standard

of care for detection of residual or recurrent BE. Careful examination of both the tubular esophagus, in the region of the prior BE segment, and the GEJ junction in both antegrade and retrograde views is essential [1•]. Most studies suggest obtaining four-quadrant biopsies through the previous area of BE as well as obtaining targeted biopsies of abnormal areas [1•]. A substantial proportion of patients treated in the community setting, however, do not undergo adequate biopsies during surveillance examinations compromising dysplasia detection [39].

Recent data documented that recurrent IM is most common at or near the gastroesophageal junction. Recurrent disease within the tubular esophagus greater than a centimeter proximal to the gastroesophageal junction generally recurs with visible abnormalities, not as an incidental finding on surveillance biopsies [35]. Additionally, recurrence of disease within the cardia is common, and biopsies should be obtained from this anatomic location. Recurrence within the cardia, though, also tends to occur within 1 cm of the gastroesophageal junction [21].

Advanced modalities, such as VLE and WATS, may better identify residual IM and neoplasia after ablation and increase diagnostic yields for recurrent disease relative to random biopsies [40]. Data exist for both VLE [41] and WATS [42, 43], but these findings require further confirmation.

Chemopreventive strategies for patients following esophageal ablation

The efficacy of chemopreventive medications for the prevention of recurrent IM or dysplastic BE following CEIM remains unknown. However, poor reflux control in this setting is believed to increase the risk for recurrent disease [14]. Current consensus recommendations promote control of reflux symptoms as well as the prevention or healing of reflux esophagitis [1•]. Typical recommendations include twice daily PPI in this cohort. Though not assessed in the setting of CEIM, data from a recent RCT suggest that high-dose PPI, over standard dosing, may safely improve outcomes in patients with BE [44•]. Performance of pH testing while on PPI is reasonable to assess treatment efficacy in patients desiring discontinuation of these medications [45]. Though data specifically addressing this question remain sparse, a standardized reflux management protocol for patients obtaining CEIM may provide improved durability of the neo-squamous esophagus when compared with historical controls [17•].

Prior studies associate the use of non-steroidal anti-inflammatory drugs (NSAIDs) with a reduction in risk for EAC in the general population [46, 47]. Moreover, though again assessed in a patient population naïve to BE treatment, aspirin in combination with high-dose PPI may reduce the time to progression in BE. However, this finding was non-significant [44•]. Given the relatively low risk of EAC following CEIM, the bleeding risk associated with NSAIDs/aspirin may very well exceed the use of these medications as a chemopreventive strategy in this setting [1•].

Conclusion

In most cases, EET is the preferred treatment strategy for patients with BE and early neoplastic changes. These modalities are effective with an acceptable side effect profile. Mounting data describe the durability of CEIM in the post-ablation esophagus. Dysplastic BE and EAC post-CEIM are rare, though recurrent IM following EET is relatively common. Recent studies underscore this finding and suggest that current surveillance intervals following CEIM are too aggressive. Future investigation will better determine the length of time for which surveillance is indicated post-CEIM, the efficacy of chemopreventive strategies in preventing recurrent disease, and the utility of advanced technologies during surveillance to reduce sampling error.

Funding

This research was supported by NIH Award K24DK100548 (NJS).

Compliance with Ethical Standards

Conflict of Interest
Nicholas Shaheen reports grants from Medtronic, CSA Medical, C2 Therapeutics, CDx Medical, and Interpace Diagnostics and personal fees from Pfizer and Boston Scientific.
Craig Reed declares no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance

1.• Shaheen NJ, Falk GW, Iyer PG, Gerson L. ACG clinical guideline: diagnosis and Management of Barrett's esophagus. Am J Gastroenterol. 2015;108(8):1238–4.
This paper contains current consensus guidelines for the management of Barrett's esophagus.
2. Ronkainen J, Aro P, Storskrubb T, Johansson S–E, Lind T, Bolling–Sternevald E, et al. Prevalence of Barrett's esophagus in the general population: an endoscopic study. Gastroenterology. 2005;129(6):1825–31.
3. Zagari RM, Fuccio L, Wallander M-A, Johansson S, Fiocca R, Casanova S, et al. Gastro-oesophageal reflux symptoms, oesophagitis and Barrett's oesophagus in the general population: the Loiano-Monghidoro study. Gut. 2008;57(10):1354–9.
4. Johansson J, Håkansson H-O, Mellblom L, Kempas A, Johansson KE, Granath F, et al. Prevalence of precancerous and other metaplasia in the distal oesophagus and gastro-oesophageal junction. Scand J Gastroenterol. 2005;40(8):893–902.
5. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63(1):11–30.
6. Basu KK, Pick B, Bale R, West KP, de Caestecker JS. Efficacy and one year follow up of argon plasma coagulation therapy for ablation of Barrett's oesophagus: factors determining persistence and recurrence of Barrett's epithelium. Gut. 2002;51(6):776–80.
7. Shaheen NJ, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, et al. Radiofrequency ablation

in Barrett's esophagus with dysplasia. N Engl J Med. 2009;360(22):2277–88.
8. Okoro NI, Tomizawa Y, Dunagan KT, Lutzke LS, Wang KK, Prasad GA. Safety of prior endoscopic mucosal resection in patients receiving radiofrequency ablation of Barrett's esophagus. Clin Gastroenterol Hepatol. 2012;10(2):150–4.
9. Bulsiewicz WJ, Kim HP, Dellon ES, Cotton CC, Pasricha S, Madanick RD, et al. Safety and efficacy of endoscopic mucosal therapy with radiofrequency ablation for patients with neoplastic barrett's esophagus. Clin Gastroenterol Hepatol. 2013;11(6):636–42.
10. Sharma VK, Jae Kim H, Das A, Wells CD, Nguyen CC, Fleischer DE. Circumferential and focal ablation of Barrett's esophagus containing dysplasia. Am J Gastroenterol. 2009;104(2):310–7.
11. Pasricha S, Bulsiewicz WJ, Hathorn KE, Komanduri S, Muthusamy VR, Rothstein RI, et al. Durability and predictors of successful radiofrequency ablation for Barrett's esophagus. Clin Gastroenterol Hepatol. 2014;12(11):1840–1847.e1.
12. Gupta M, Iyer PG, Lutzke L, Gorospe EC, Abrams JA, Falk GW, et al. Recurrence of esophageal intestinal metaplasia after endoscopic mucosal resection and radiofrequency ablation of Barrett's esophagus: results from a US multicenter consortium. Gastroenterology. 2013;145(1):79–86.
13. Phoa KN, Pouw RE, Van Vilsteren FGI, et al. Remission of Barrett's esophagus with early neoplasia 5 years after radiofrequency ablation with endoscopic resection: a Netherlands cohort study. Gastroenterology. 2013;145(1):96–104.
14. Fuji-Lau L, Cinnor B, Shaheen N, et al. Recurrence of intestinal metaplasia and early neoplasia after endoscopic eradication therapy for Barrett's esophagus: a systematic review and meta-analysis. Endosc Int Open. 2017;5(6):E430–49.
15.• Cotton CC, Haidry R, Thrift AP, Lovat L, Shaheen NJ. Development of evidence-based surveillance intervals after radiofrequency ablation of Barrett's esophagus. Gastroenterology. 2018;155(2):316–326.e.

This study analyzed data from the US RFA and UK NHR to produce new recommendations for surveillance intervals in patients with BE and CEIM. They propose surveillance at 1 and 3 years after CEIM for LGD and surveillance at 0.25, 0.5, and 1 year after CEIM for HGD.

16. Yasuda K, Choi SE, Nishioka NS, Rattner DW, Puricelli WP, Tramontano AC, et al. Incidence and predictors of adenocarcinoma following endoscopic ablation of Barrett's esophagus. Dig Dis Sci. 2014;59(7):1560–6.
17.• Komanduri S, Kahrilas PJ, Krishnan K, McGorisk T, Bidari K, Grande D, et al. Recurrence of Barrett's esophagus is rare following endoscopic eradication therapy coupled with effective reflux control. Am J Gastroenterol. 2017;112(4):556–66

The authors underscore the importance of reflux control in patients with BE who completed EET.

18. Titi M, Overhiser A, Ulusarac O, Falk GW, Chak A, Wang K, et al. Development of subsquamous high-grade dysplasia and adenocarcinoma after successful radiofrequency ablation of Barrett's esophagus. Gastroenterology. 2012;143(3):564–6.
19. Anders M, Bähr C, El-Masry MA, et al. Long-term recurrence of neoplasia and Barrett's epithelium after complete endoscopic resection. Gut. 2014;63(10):1535–43.
20. Orman ES, Kim HP, Bulsiewicz WJ, Cotton CC, Dellon ES, Spacek MB, et al. Intestinal metaplasia recurs infrequently in patients successfully treated for Barrett's esophagus with radiofrequency ablation. Am J Gastroenterol. 2013;108(2):187–95.
21. Guthikonda A, Cotton CC, Madanick RD, Spacek MB, Moist SE, Ferrell K, et al. Clinical outcomes following recurrence of intestinal metaplasia after successful treatment of Barrett's esophagus with radiofrequency ablation. Am J Gastroenterol. 2017;112(1):87–94.
22.• Cotton CC, Wolf WA, Overholt BF, Li N, Lightdale CJ, Wolfsen HC, et al. Late recurrence of Barrett's esophagus after complete eradication of intestinal metaplasia is rare: final report from ablation in intestinal metaplasia containing dysplasia trial. Gastroenterology. 2017;153(3):681–8

Here, the authors assessed data from the AIM Dypsplasia Trial to examine the proportion of patients with recurrence over time. This data suggest that the recurrent disease occurs disproportionately in the first year following CEIM.

23. Gaddam S, Singh M, Balasubramanian G, Thota P, Gupta N, Wani S, et al. Persistence of nondysplastic Barrett's esophagus identifies patients at lower risk for esophageal adenocarcinoma: results from a large multicenter cohort. Gastroenterology. 2013;145(3):548–53.
24. Lee JK, Cameron RG, Binmoeller KF, Shah JN, Shergill A, Garcia-Kennedy R, et al. Recurrence of subsquamous dysplasia and carcinoma after successful endoscopic and radiofrequency ablation therapy for dysplastic Barrett's esophagus. Endoscopy. 2013;45(7):571–4.
25. Haidry RJ, Dunn JM, Butt MA, Burnell MG, Gupta A, Green S, et al. Radiofrequency ablation and endoscopic mucosal resection for dysplastic Barrett's esophagus and early esophageal adenocarcinoma: outcomes of the UK national halo RFA registry. Gastroenterology. 2013;145(1):87–95.
26. Gray NA, Odze RD, Spechler SJ. Buried metaplasia after endoscopic ablation of Barrett's esophagus: a systematic review. Am J Gastroenterol. 2011;106(11):1899–908 quiz 1909.
27. Zhou C, Tsai TH, Lee HC, Kirtane T, Figueiredo M, Tao YK, et al. Characterization of buried glands before and after radiofrequency ablation by using 3-dimensional optical coherence tomography (with videos). Gastrointest Endosc. 2012;76(1):32–40.
28. Phoa KN, van Vilsteren FGI, Weusten BLAM, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia. Jama. 2014;311(12):1209, 1217.
29. Overholt BF, Lightdale CJ, Wang KK, Canto MI, Burdick S, Haggitt RC, et al. Photodynamic therapy with

porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: international, partially blinded, randomized phase III trial. Gastrointest Endosc. 2005;62(4):488–98.
30. Krishnamoorthi R, Singh S, Ragunathan K, Katzka DA, Wang KK, Iyer PG. Risk of recurrence of Barrett's esophagus after successful endoscopic therapy. Gastrointest Endosc. 2016;83(6):1090–106.
31.• Wolf WA, Pasricha S, Cotton C, Li N, Triadafilopoulos G, Muthusamy VR, et al. Incidence of esophageal adenocarcinoma and causes of mortality after radiofrequency ablation of Barrett's esophagus. Gastroenterology. 2015;149(7):1752–6.
Results from this paper underscore that the incidence of EAC following RFA is low. Among patients undergoing RFA for BE, less than 1% died from EAC.
32. Shaheen NJ, Overholt BF, Sampliner RE, Wolfsen HC, Wang KK, Fleischer DE, et al. Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. Gastroenterology. 2011;141(2):460–8.
33. Solomon SS, Kothari S, Smallfield GB, et al. Liquid nitrogen spray cryotherapy is associated with less postprocedural pain than radiofrequency ablation in Barrett's esophagus: a multicenter prospective study. J Clin Gastroenterol 2018 Jan 18 [Epub ahead of print].
34.• Ramay F, Cui Q, Breenwald B. Outcomes after liquid nitrogen spray cryotherapy in Barrett's esophagus-associated high-grade dysplasia and intramucosal adenocarcinoma: 5-year follow-up. Gastrointest Endosc. 2017;86(4):626–32
This paper describes the known long-term durability of cryotherapy for the management of BE.
35. Cotton CC, Wolf WA, Pasricha S, Li N, Madanick RD, Spacek MB, et al. Recurrent intestinal metaplasia after radiofrequency ablation for Barrett's esophagus: endoscopic findings and anatomic location. Gastrointest Endosc. 2015;81(6):1362–9.
36. Evans JA, Early DS, Fukami N, Ben-Menachem T, Chandrasekhara V, Chathadi KV, et al. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. Gastrointest Endosc. 2012;76(6):1087–94.
37. Cameron J, Carpenter H. Barrett's esophagus, high-grade dysplasia, and early adenocarcinoma: a pathological study. Am J Gastroenterol. 1997;92(4):586–91.
38. Pohl J, Pech O, May A, Manner H, Fissler-Eckhoff A, Ell C. Incidence of macroscopically occult neoplasias in Barrett's esophagus: are random biopsies dispensable in the era of advanced endoscopic imaging? Am J Gastroenterol. 2010;105(11):2350–6.
39. Abrams JA, Kapel RC, Lindberg GM, Saboorian MH, Genta RM, Neugut AI, et al. Adherence to biopsy guidelines for Barrett's esophagus surveillance in the community setting in the United States. Clin Gastroenterol Hepatol. 2009;7(7):736–42.
40. Thosani N, Abu Dayyeh BK, Sharma P, Aslanian HR, Enestvedt BK, Komanduri S, et al. ASGE Technology Committee systematic review and meta-analysis assessing the ASGE Preservation and Incorporation of Valuable Endoscopic Innovations thresholds for adopting real-time imaging-assisted endoscopic targeted biopsy during endoscopic surveillance. Gastrointest Endosc. 2016;83(4):684–98 e7.
41. Trindade AJ, Inamdar S, Sejpal DV, Rishi A, Sultan K. Targeting neoplasia using volumetric laser endomicroscopy with laser marking. Endoscopy. 2017;49:E54–5.
42. Anandasabapathy S, Sontag S, Graham DY, Frist S, Bratton J, Harpaz N, et al. Computer-assisted brush-biopsy analysis for the detection of dysplasia in a high-risk Barrett's esophagus surveillance population. Dig Dis Sci. 2011;56(3):761–6.
43. Johanson JF, Frakes J, Eisen D. Computer-assisted analysis of abrasive transepithelial brush biopsies increases the effectiveness of esophageal screening: a multicenter prospective clinical trial by the endocdx collaborative group. Dig Dis Sci. 2011;56(3):767–72.
44.• Jankowski JAZ, de Caestecker J, Love SB, et al. Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial. Lancet. 2018;392(10145):400–8
Though not in a post-abliation cohort, this study provide clinical trial data describing the efficacy of aspirin and proton pump inhibitors for improving outcomes in Barrett's esophagus. The results suggest that high-dose proton pump inhibitors and aspirin may improve outcomes.
45. Shafa S, Shaheen NJ. How I approach it: care of the post-ablation Barrett's esophagus patient. Am J Gastroenterol. 2017;112(10):1487–90. https://doi.org/10.1038/ajg.2017.291.
46. Zhang S, Zhang X-Q, Ding X-W, Yang RK, Huang SL, Kastelein F, et al. Cyclooxygenase inhibitors use is associated with reduced risk of esophageal adenocarcinoma in patients with Barrett's esophagus: a meta-analysis. Br J Cancer. 2014;110(9):2378–88.
47. Liao LM, Vaughan TL, Corley DA, Cook MB, Casson AG, Kamangar F, et al. Nonsteroidal anti-inflammatory drug use reduces risk of adenocarcinomas of the esophagus and esophagogastric junction in a pooled analysis. Gastroenterology. 2012;142(3):442–52.
48. Small AJ, Sutherland SE, Hightower JS, et al. Comparative risk of recurrence of dysplasia and carcinoma after endoluminal eradication therapy of high-grade dysplasia versus intramucosal carcinoma in Barrett's esophagus. Gastrointest Endosc. 2015;81(5):1156–66.
49. Pouw RE, Wirths K, Eisendrath P, et al. Efficacy of radiofrequency ablation combined with endoscopic resection for Barrett's esophagus with early neoplasia. Clin Gastroenterol Hepatol. 2010;8(1):23–9.

Publisher's Note