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ORIGINAL ARTICLE

Cryotherapy and Radiofrequency Ablation for Eradication of Barrett's Esophagus with Dysplasia or Intramucosal Cancer

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Abstract

Background and Aims Endoscopic ablation therapy has become the mainstay of treatment of Barrett's associated dysplasia and intramucosal cancer (IMC). The widely available techniques for ablation are radiofrequency ablation (RFA) and cryotherapy. Our aim was to compare eradication rates of metaplasia and dysplasia with both these modalities.

Patients and Methods Retrospective review of prospectively collected database of patients who underwent endoscopic therapy for Barrett's dysplasia or IMC from 2006 to 2011 was performed. Demographic features, comorbidities, and endoscopic data including length of Barrett's segment, hiatal hernia size, interventions during the endoscopy and histological results were reviewed.

Results Among 154 patients included, 73 patients were in the RFA and 81 patients were in the cryotherapy group. There was complete eradication of intestinal metaplasia (CE-IM) in 81 (52.6%), complete eradication of dysplasia (CE-D) in 133 (86.4%), and persistent dysplasia or cancer in 19 patients (12.3%). Compared to RFA, cryotherapy patients were found to be older and less likely to have undergone endoscopic mucosal resection. On multivariate analysis, patients who underwent RFA had a threefold higher odds of having CE-IM than those who underwent cryotherapy (odds ratio [OR] 2.9, 95% confidence interval [CI] 1.4–6.0, $p = 0.004$), but CE-D were similar between the two groups (OR 1.7, 95% CI 0.66–4.3, $p = 0.28$).

Conclusions Endoscopic therapy is highly effective in eradication of Barrett's associated neoplasia. Patients who underwent cryotherapy were equally likely to achieve CE-D but not CE-IM than patients who underwent RFA. Patient characteristics and preferences may effect choice of treatment selection and outcomes.

Keywords Barrett's esophagus · Dysplasia · Endoscopy · Ablation · Cryotherapy

Introduction

Barrett's esophagus (BE) is a well-recognized risk factor for esophageal adenocarcinoma (EAC), and the incidence of both BE and EAC has increased dramatically in the western hemisphere over the past several decades [1]. Development of EAC from BE usually involves progression through a sequence of increasing dysplasia manifested as low-grade dysplasia (LGD), high-grade dysplasia (HGD), intramucosal carcinoma (IMC), and finally invasive cancer [2]. Over the past few decades, a number of endoscopic modalities including endoscopic mucosal resection (EMR), cryotherapy, and radiofrequency ablation (RFA) have been employed for the treatment of dysplastic BE and IMC. Due to their proven efficacy and lower rate of adverse events over surgery, endoscopic ablative therapies are currently the standard of

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care and are recommended as the preferred treatment over esophagectomy for BE with HGD and IMC [3].

RFA involves direct application of rapid pulses of radiofrequency energy to the esophageal mucosa resulting in a uniform depth of ablation. This leads to complete eradication of intestinal metaplasia (CE-IM) or neoplasia which is replaced over time by new squamous epithelium [4]. Complete eradication rates of dysplasia (CE-D) as high as 90% have been described with RFA, and response is durable for up to five years [5].On the other hand, cryotherapy employs cycles of rapid freezing and slow thawing which destroys the tissue. It is performed using low-pressure liquid nitrogen or carbon dioxide delivered to the esophageal mucosa using spray catheters [6]. CE-D rates ranging between 80 and 88% have been reported with cryotherapy [7–9].However, recurrences of BE have been reported after both RFA and cryotherapy, necessitating the need for continued surveillance and long-term follow-up with either treatment modality [10–12].

Currently, there is paucity of data comparing these two modalities for the treatment of dysplastic BE and IMC. The aims of our study were: (1) to assess and compare the rates of CE-IM and CE-D of dysplastic BE and IMC with RFA and cryotherapy, and to (2) to identify factors associated with incomplete or absent response, and (3) to determine differences in the subsets of patients who are treated with each of these modalities.

Patients and Methods

Study Subjects

After obtaining approval from the institutional review board, retrospective review of a prospectively maintained database of BE patients who had undergone endoscopic therapy for dysplastic BE or IMC from 2006 to 2011 at our institution was performed. Patients who had undergone either RFA or cryotherapy with at least one surveillance endoscopy after treatment were included. Patients who underwent endoscopic mucosal resection (EMR) only, or who were still actively undergoing treatment at the time of the study were excluded.

Information abstracted included demographic features [age, body mass index (BMI), race, and gender], medical history (alcohol use, smoking, diabetes, hypertension, and hyperlipidemia), medication use (aspirin, nonsteroidal anti-inflammatory drugs, acid suppression agents, lipid lowering agents, anti-hypertensive agents), and surgical history of fundoplication. Endoscopic data including length of Barrett's segment, hiatal hernia size, and number of endoscopies, interventions during the endoscopy and biopsy results were also reviewed and abstracted.

Outcomes

The primary outcome of the study was CE-D which was defined as eradication of all dysplasia with or without persistent non-dysplastic intestinal metaplasia. The secondary outcome of the study was CE-IM which was defined as the absence of all intestinal metaplasia and dysplasia on a surveillance endoscopy after endoscopic eradication therapy (EET). Follow-up was defined as duration between the first treatment session to the last surveillance or treatment endoscopy.

Treatment Protocol

Patients with dysplastic BE or IMC referred for possible EET were evaluated prior to procedures regarding the risks, benefits, and alternatives. The pathology slides were reviewed by an expert gastrointestinal pathologist and confirmed by a second pathologist prior to any intervention. All patients were started on twice daily proton pump inhibitor therapy.

Detailed examination was performed with high-definition white light endoscopy and narrow band imaging. Endoscopic ultrasound and four quadrant biopsies were performed at the endoscopist's discretion. Nodular mucosa was resected with band ligation endoscopic mucosal resection (EMR) when possible (Duette®, Cook Medical, Bloomington, IN) followed by ablation of remaining BE segment. Cryotherapy was used in patients where nodular mucosa was not amenable to EMR due to fibrosis. Cryotherapy was also preferred in patients taking anticoagulation medications to avoid the risk of bleeding with EMR and in patients with bleeding diathesis. In few instances for small areas of residual BE, other modalities such as argon plasma coagulation (APC) and banding were used.

Initial RFA was performed with the Halo 360 ® (Medtronics, Minneapolis, Minnesota, USA) if the BE segment length was ≥ 3 cm. The procedure involved measuring the diameter of esophagus at different levels using a sizing balloon. *N*-acetyl cysteine was applied to clear mucus. Then, the appropriate sized RFA balloon was passed over guide wire. RFA energy was applied at 12 J/cm^2 every 3-cm intervals with slight overlap under endoscopic guidance. The white coagulated tissue was scraped with a friction-fit cap mounted on the endoscope. Then second series of ablation was similarly completed. Follow-up treatments were performed with Halo-90 device. Energy was applied twice, then coagulated tissue was scraped off, and the whole sequence was repeated [5].

Cryotherapy involved passage of a cryospray catheter passed through the biopsy channel of endoscope which

delivered liquid nitrogen at − 196 °C and decompression tube with side holes for active venting of the stomach and esophagus (Generation 2 device, CSA Medical, Baltimore, MD). A hemi-circumferential 2–3 cm area was considered a treatment site. Initially, each site was frozen for two to three cycles of 20 s each with at least 45 s between freezes to allow tissue thawing [7]. Of note, carbon dioxide-based cryotherapy was not used in this study.

Follow-Up Protocol

All patients were brought back every 2–3 months for repeat treatments until endoscopic and histological eradication of BE or until the treatment was stopped due to progression or other clinical reasons based on patient and clinician preference. Once endoscopically visible BE was eliminated, four quadrant biopsies were obtained at every 1-cm interval along the original length of Barrett's segment to confirm histological eradication. Following the completion of treatment, patients came back for surveillance endoscopy and biopsies every 3–6 months for a year and then yearly thereafter. Recurrence is defined as endoscopically visible or histological BE after achieving CE-IM. Mortality if any and cause of mortality were ascertained by chart review.

Statistical Analysis

Data are presented as mean ± SD, median [25th, 75th percentiles] or *n* (%). A univariable analysis was performed to assess differences between the treatment groups. Analysis of variance (ANOVA) or the nonparametric Kruskal–Wallis test was used to assess differences in continuous or ordinal variables, and Pearson's Chi-square test or Fisher's exact test was used for categorical factors. Univariable and multivariable logistic regression analyses were performed to assess factors associated with the 2 outcomes of interest: (1) CE-IM and (2) CE-D. An automated stepwise variable selection method performed on 1000 bootstrap samples was used to choose the final multivariable models; treatment type and time from baseline to last endoscopy were forced into the models, and other baseline variables except race and BMI (because of missing value) were considered for inclusion. Variables with inclusion rates of at least 40% were included in the final models. All analyses were performed using SAS version 9.2 software (The SAS Institute, Cary, NC).

Results

A total of 234 patients underwent endoscopic therapy during the period of study. Of these, 60 patients underwent neither RFA nor cryotherapy and 20 patients were still actively undergoing treatment at the end of study period and hence were excluded from the analysis. The remaining 154 patients were included in the study. Overall, 133 (86.4%) patients achieved CE-D and 81 (52.6%) patients achieved CE-IM. Persistence or progression of dysplasia despite endoscopic ablative treatment was seen in 19 (12.3%) patients (Fig. 1). Two patients discontinued treatment and were lost to follow up.

Cryotherapy was used in instances when RFA was not feasible due to uneven surface (nodular BE segment, $n = 16$) or proximal esophageal strictures precluding passage of RFA catheter ($n = 2$) and in an IMC in proximal esophagus when EMR could not be done. It was also used in patients with bleeding diathesis (cirrhosis, $n = 7$, thrombocytopenia in one patient) or on blood thinners (Coumadin, $n = 8$, clopidogrel, $n = 11$, aspirin, $n = 36$). It was used as salvage therapy when patients failed other ablative therapies such as RFA ($n = 7$), failed photodynamic therapy ($n = 1$), failed APC ($n = 1$). Finally, cryotherapy was performed in 20 patients due to their preference and in 5 patients with severe chronic obstructive pulmonary disease and IMC as they were high risk for esophagectomy.

Differences in RFA and Cryotherapy

Of the total 154 patients, 73 patients underwent RFA and 81 patients underwent cryotherapy. Differences in demographics and clinical characteristics between the two groups are given in Table 1. Patients in the cryotherapy group were older (69.8 ± 10.7 vs. 66.4 ± 9.5 years; $p = 0.041$) and were less likely to consume alcohol (32 vs. 55%; $p = 0.004$) than those in the RFA group. There were no significant differences in the demographic features, comorbidities, use of acid suppression agents or endoscopic findings including length of BE, size of hiatal hernia and histological findings on baseline biopsy between

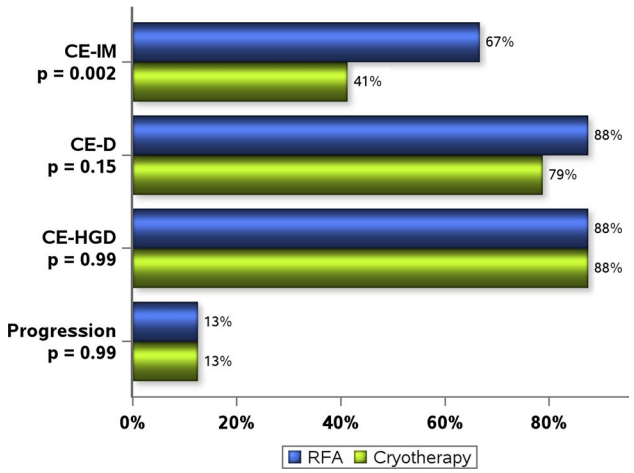

Fig. 1 Eradication rates of RFA and cryotherapy

Table 1 Demographic and clinical characteristics

Factor	RFA	Cryotherapy	*p*-value
Age (years)	66.4 ± 9.5	69.8 ± 10.7	0.041[a]
Male	66 (90.4)	65 (80.2)	0.077[c]
Caucasian	66 (94.3)	66 (97.1)	0.68[b]
Smoking			0.84[c]
Non-smoker	34 (47.2)	40 (50.0)	
Ex-smoker	32 (44.4)	32 (40.0)	
Current smoker	6 (8.3)	8 (10.0)	
Current alcohol use	39 (54.9)	25 (31.6)	0.004[c]
Alcohol use			0.016[c]
Never	31 (43.7)	51 (64.6)	
Mild	31 (43.7)	23 (29.1)	
Moderate	8 (11.3)	2 (2.5)	
Ex-alcohol use	1 (1.4)	3 (3.8)	
Body mass index	31.7 ± 7.3	30.1 ± 6.3	0.18[a]
Aspirin	33 (45.2)	37 (45.7)	0.95[c]
NSAIDs	8 (11.0)	6 (7.4)	0.44[c]
Statins	40 (54.8)	43 (53.1)	0.83[c]
Proton pump inhibitors	72 (98.6)	81 (100.0)	0.47[b]
H2 blockers	1 (1.4)	1 (1.2)	0.99[b]
Hypertension	39 (53.4)	48 (59.3)	0.47[c]
Diabetes	12 (16.4)	16 (19.8)	0.59[c]
Hyperlipidemia	41 (56.2)	35 (43.2)	0.11[c]
History of fundoplication	3 (4.1)	2 (2.5)	0.67[b]
C length of Barrett's in cm	3.38 ± 3.2	3.9 ± 2.8	0.56[a]
M length of Barrett's in cm	5.2 ± 3.2	5.2 ± 3.4	0.95[a]
Length of hiatal hernia in cm	2.9 ± 1.9	3.2 ± 1.8	0.23[a]
Nodularity prior to ablation	38 (52.1)	25 (30.9)	0.008[c]
Nodularity during ablation	29 (39.7)	24 (29.6)	0.19[c]
Baseline biopsy			0.16[c]
Low-grade dysplasia	13 (17.8)	11 (13.6)	
High-grade dysplasia	50 (68.5)	49 (60.5)	
Intramucosal cancer	10 (13.7)	21 (25.9)	

Statistics presented as mean ± SD or *n* (column %)

Data not available for all subjects. Missing values: race = 16, smoking = 2, current alcohol use = 4, alcohol use = 4, BMI = 20

p-values: [a]ANOVA, [b]Fisher's exact test, [c]Pearson's Chi-square test

the two groups. Ten patients underwent RFA after initial cryotherapy. Nine had CE-IM and one progressed and underwent esophagectomy.

Patients who had undergone cryotherapy were as expected less likely to have had EMR and more likely to have had focal touch-up ablation with APC for limited areas of persistent BE mucosa (ERBE, Marietta, GA) (Table 2). One patient died in RFA group from EAC. In the cryotherapy group, EAC was cause of the death in 4 out of 8 patients. On univariable analysis, patients in the RFA group were more likely to achieve CE-IM (66.7 vs. 41.3%; $p = 0.002$) than patients in cryotherapy group. However, there was no difference in rates of CE-D between the two groups (87.5 vs. 78.9%, $p = 0.15$).

To exclude the effect of nodularity, a subgroup analysis is performed for patients with flat BE (Table 3). There were a greater proportion of women in cryotherapy group compared to RFA group. There were no cases of IMC in RFA group and 11 cases of IMC in cryotherapy group. CE-IM and CE-D were higher in RFA group compared to cryotherapy group (CE-IM 67.6 vs. 37.5%, $p = 0.006$, CE-D 94.1 vs. 75%, $p = 0.021$). Next, IMC cases were excluded and outcomes in flat dysplasia were compared with RFA ($n = 35$) versus cryotherapy ($n = 45$). CE-IM remained higher in RFA group (67.6 vs. 37.7%, $p = 0.085$); however, CE-D was comparable (94.1% in RFA group versus 88.8% in cryotherapy group, $p = 0.41$).

A subgroup analysis performed within the cryotherapy group to assess eradication rates in patients who underwent cryotherapy due to endoscopist/personal preference ($n = 20$) versus those with other indications ($n = 60$) showed higher eradication rates in the former group (CE-IM 50 vs. 38.3%, $p = 0.36$, CE-D 85 vs. 76.7%, $p = 0.43$).

Factors Associated with CE-IM

We studied the factors associated with CE-IM (Table 4). On univariable analysis, younger age, baseline biopsy and mode of treatment were found to be significantly associated with a higher likelihood of CE-IM. After adjusting for age, length of BE, baseline biopsy, and time to last endoscopy, patients who received RFA were almost 3 times more likely to achieve CE-IM (OR2.9 (95% CI 1.4, 6) $p = 0.004$) compared to cryotherapy. In addition, patients who had HGD on baseline biopsy were 3 times more likely to have CE-IM (OR 3.1 (1.2, 8.5) $p = 0.024$).

Factors Associated with CE-D

On analysis of factors associated with CE-D, current alcohol use, absence of IMC on baseline endoscopy and longer time from baseline to last endoscopy were found to be significantly associated with CE-D (Table 5). There was no evidence to suggest that type of ablative treatment was associated with CE-D (OR 1.7, 95% CI 0.66–4.3, $p = 0.28$).

Discussion

Over the past decade, endoscopic ablation techniques including RFA and cryotherapy have emerged as effective and safe modalities for the treatment of dysplastic BE and IMC. Because of their safety, efficacy and better tolerance than esophagectomy, these modalities are increasingly being employed for the management of HGD and

Table 2 Treatment outcomes

Factor	RFA ($n=73$)	Cryotherapy ($n=81$)	p-value
Treatment duration (months)	4.6 [2.0, 10.1]	3.5 [1.4, 9.1]	0.43[a]
No. of treatment sessions	3.0 [2.0, 3.0]	3.0 [2.0, 5.0]	0.24[a]
Any EMR	49 (67.1)	35 (43.2)	0.003[b]
Timing of EMR	24 (32.9)	46 (56.8)	0.021[b]
Never			
Prior to ablative therapy only	20 (27.4)	11 (13.6)	
During ablative therapy only	11 (15.1)	10 (12.3)	
Both prior and during ablative therapy	18 (24.7)	14 (17.3)	
Any APC/banding	1 (1.4)	12 (14.8)	0.003[b]
Follow-up (months)	25.1 [13.0, 38.5]	31.8 [12.6, 50.7]	0.15[a]
Treatment outcome*			
Complete eradication of metaplasia	48 (66.7)	33 (41.3)	0.002[b]
Complete eradication of dysplasia	63 (87.5)	63 (78.8)	0.15[b]
Progression/failed EET	9 (12.5)	10 (12.5)	0.99[b]
If eradication, disease recurrence	7 (11.1)	9 (14.3)	0.59[b]
Deceased	1 (1.4)	8 (10.8)	0.034[c]
Death due to esophageal cancer	1 (1.4)	4 (5.4)	0.37[c]

EET endoscopic eradication therapy

P-values: [a]Kruskal–Wallis test, [b]Pearson's Chi-square test, [c]Fisher's exact test

*Two subjects discontinued treatment and treatment outcome is not determined for them. Statistics presented as Median [P25, P75] or *n* (column %)

IMC in BE. Through this study, we attempted to determine the efficacy of RFA and cryotherapy in the treatment of dysplastic BE and IMC with RFA. Our study found that overall endoscopic therapy was highly effective in the eradication of dysplasia with a high success rate. Patients who underwent RFA were more likely to achieve CE-IM than patients who underwent cryotherapy. In spite of differences in patient characteristics, CE-D rates were comparable between both groups. Although overall mortality was noted to be higher in the cryotherapy group (10.8 vs. 1.4%, $p=0.034$), esophageal cancer-related mortality was similar among the two groups (5.4 vs. 1.4%, $p=0.37$).

In our study, 87.5% of the patients in the RFA group achieved CE-D, which was overall similar to the rate of around 90% previously described in the literature [13, 14]. Similarly, the rate of CE-D with cryotherapy in our study was 79%, which was in line with the previously described rates of 81–88% [7–9]. However, the CE-IM rate of 66.7% for the RFA group and 41.3% for the cryotherapy group in our study was lower than the previously described rate of 78–88% and 53–65%, respectively [7–9, 13, 14]. This may perhaps be due to the earlier time frame when the study was conducted (2006–2011) when EET was just becoming the norm. Supporting this theory is the data from UK registry which show improvement in CE-IM and CE-D from early period (2008–2010) to later period (2011–2013). CE-D and CE-IM improved significantly between the former and later time periods, from 77 and 56% to 92 and 83%, respectively ($p<0.0001$) [15].

Our study has several important clinical implications. Firstly, our findings suggest that RFA and cryotherapy are effective for the treatment of dysplastic BE. These findings support the use of cryotherapy in appropriately selected patients, especially those with nodular mucosa, with life-threatening comorbidities and/or in the setting of anticoagulation medication use. In these settings, cryotherapy provides similar efficacy to RFA. However, cryotherapy as an initial or primary modality for the ablation of flat dysplastic BE was inferior to RFA. It should be noted that among patients with flat BE, there were several patients with IMC (19%) in cryotherapy group as opposed to none in RFA group. Current guidelines from all 3 major gastrointestinal societies in the US recommend RFA as the modality of choice for the treatment of dysplastic BE [3, 6, 16]. In comparison, only one of the three guidelines currently mentions cryotherapy as a treatment options without any recommendations for or against its use at this time [6].

Secondly, we found that higher CE-IM rates were observed in patients undergoing RFA as compared to cryotherapy. In fact, the odds of achieving CE-IM were three-fold higher with use of RFA than with cryotherapy after controlling for baseline dysplasia. This may be explained by potential differences in patient selection between the 2 modalities, given the retrospective nature of this study

Table 3 Demographic and clinical characteristics of flat Barrett's esophagus subgroup

Factor	RFA ($n=35$)	Cryotherapy ($n=56$)	p-value
Age (years)	66.6 ± 7.5	69.2 ± 10.8	0.21[a]
Male gender	34 (97.1)	41 (73.2)	0.004[c]
Caucasian race*	32 (97.0)	45 (95.7)	0.99[b]
Smoking*			0.54[c]
Non-smoker	20 (57.1)	25 (45.5)	
Ex-smoker	13 (37.1)	25 (45.5)	
Current smoker	2 (5.7)	5 (9.1)	
Current alcohol use*	21 (60.0)	16 (29.6)	0.005[c]
Alcohol use*			0.005[b]
Never	13 (37.1)	36 (66.7)	
Mild	17 (48.6)	16 (29.6)	
Moderate	4 (11.4)	0 (0.0)	
Ex-alcohol use	1 (2.9)	2 (3.7)	
Body mass index (BMI)*	30.2 ± 6.1	30.0 ± 6.8	0.90[a]
Aspirin	16 (45.7)	22 (39.3)	0.55[c]
NSAIDs	6 (17.1)	5 (8.9)	0.24[c]
Statins	18 (51.4)	25 (44.6)	0.53[c]
Proton pump inhibitors	34 (97.1)	56 (100.0)	0.38[b]
H2 blockers	0 (0.0)	1 (1.8)	0.99[b]
Hypertension	18 (51.4)	29 (51.8)	0.97[c]
Diabetes	5 (14.3)	10 (17.9)	0.66[c]
Hyperlipidemia	16 (45.7)	22 (39.3)	0.55[c]
Length of Barrett's segment (cm)	5.6 ± 3.0	5.2 ± 3.1	0.55[a]
Length of hiatal hernia (cm)	3.2 ± 1.5	3.3 ± 1.6	0.80[a]
Index biopsy			0.020[c]
Low-grade dysplasia	8 (22.9)	10 (17.9)	
High-grade dysplasia	27 (77.1)	35 (62.5)	
Intramucosal cancer	0 (0.0)	11 (19.6)	

Statistics presented as mean ± SD or n (column %)

NSAID nonsteroidal anti-inflammatory drugs, *RFA* radiofrequency ablation

p-values: [a]ANOVA, [b]Fisher's exact test, [c]Pearson's Chi-square test

*Data not available for all subjects. Missing values: race = 11, smoking = 1, current alcohol use = 2, alcohol use = 2, BMI = 13

and the treatment modality being influenced by physician and patient preference. Even though we did not observe significant differences in demographics and clinical characteristics between the two groups, anatomical differences such as nodular surface or tortuosity of the esophagus may have made it challenging to achieve circumferential treatment with cryotherapy. Additionally, more patients in the RFA group underwent EMR than cryotherapy group. This may have also partly contributed to the higher CE-IM rates in this group and reflects the avoidance of EMR-associated risks of perforation in patients with life-threatening comorbidities and bleeding in those on anticoagulation medications. It is unclear whether this difference in CE-IM rates translates into any differences in the rates of long-term adverse outcomes. In our cohort of patients, there were no statistically significant differences in the dysplasia recurrence rate or esophageal cancer-related mortality rate between the two groups.

It is worthwhile to note that EET often involves a combination of various techniques irrespective of the initial modality selected. As seen in our study, EMR is attempted initially if nodularity is seen in BE segment. This is followed by ablation of residual BE. If there is little or no response to the selected modality, then an alternative ablative technique is frequently used.

The strengths of our study include a large sample of patients undergoing real-world experience with both RFA and cryotherapy. All biopsies with dysplasia in our study were confirmed by a second gastrointestinal pathologist. Additionally, the study population was very similar to that seen in routine clinical practice in the western hemisphere making the results generalizable to other patients.

Table 4 Analysis of factors associated with complete eradication of metaplasia in Barrett's esophagus

Factor	Unadjusted analysis		Adjusted analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (1 year increment)	0.96 (0.93, 1.00)	0.025	0.97 (0.94, 1.01)	0.13
Male versus female	1.05 (0.43, 2.6)	0.91	–	–
Caucasian race	1.2 (0.24, 6.4)	0.8	–	–
Smoking				
Ex-smoker versus non-smoker	0.93 (0.47, 1.8)	0.82	–	–
Current smoker versus non-smoker	1.4 (0.43, 4.8)	0.56	–	–
Current alcohol use	1.8 (0.93, 3.5)	0.081	–	–
Body mass index	1.03 (0.98, 1.09)	0.22	–	–
Aspirin	0.71 (0.37, 1.3)	0.29	–	–
Nonsteroidal anti-inflammatory drugs	3.6 (0.95, 13.3)	0.059	–	–
Statins	1.2 (0.64, 2.3)	0.55	–	–
Proton pump inhibitors	0.37 (0.00, 7.1)	0.67	–	–
H2 blockers	0.17 (0.00, 2.1)	0.35	–	–
Hypertension	0.63 (0.33, 1.2)	0.16	–	–
Diabetes	0.71 (0.31, 1.6)	0.42	–	–
Hyperlipidemia	1.5 (0.77, 2.8)	0.25	–	–
History of fundoplication	0.57 (0.09, 3.5)	0.55	–	–
Length of Barrett's segment in cm	0.93 (0.84, 1.03)	0.15	0.91 (0.81, 1.02)	0.1
Size of hiatal hernia in cm	0.87 (0.72, 1.04)	0.13	–	–
Baseline biopsy				
High-grade versus low-grade dysplasia	2.6 (1.01, 6.5)	0.048	3.1 (1.2, 8.5)	0.024
Cancer versus low-grade dysplasia	0.86 (0.28, 2.6)	0.78	1.2 (0.36, 4.0)	0.77
RFA versus cryotherapy	2.8 (1.5, 5.5)	0.002	2.9 (1.4, 6.0)	0.004
Num. of treatment sessions	0.98 (0.85, 1.1)	0.82	–	–
Months from baseline to last endoscopy (1 month increment)	1.01 (0.99, 1.02)	0.21	1.01 (1.00, 1.03)	0.17

CI confidence interval, *NSAID* nonsteroidal anti-inflammatory drugs, *OR* odds ratio, *RFA* radiofrequency ablation

Our study has some limitations. This being a retrospective study, the patient assignment to each treatment arm was not randomized and was based on the patient or physicians' preference. This may have led to selection bias as discussed above with greater proportion of women and sicker patients in cryotherapy group compared to RFA group. A related point to consider is that since 2013, second-generation cryospray device has been replaced by third-generation True Freeze system. There have been numerous enhancements such as improved thermal and pressure control with less gas pressure in vivo, integrated pressure sensing capabilities to allow real-time pressure monitoring for improved control and safety while passive venting, two flow settings combined with active and passive venting options for increased procedure flexibility, uniform, non-pulsing flow for a consistent, touch-free delivery of cryogen to the ablation site, new stainless steel reinforced catheter enabling access to hard to treat areas and built-in active suction with high and low warnings. Whether this leads to improved eradication rates needs to be evaluated. Also, the study population included was being followed at a tertiary referral center. This might have introduced a referral bias. Balanced against this is the fact that procedures like RFA and cryotherapy are generally performed at tertiary referral centers, making it the only setting feasible for this study.

In conclusion, endoscopic therapy was overall highly effective in the eradication of dysplasia in BE. Patients who underwent cryotherapy were equally likely to achieve CE-D but not CE-IM than patients who underwent RFA. Based on these results, while RFA remains the preferred treatment of choice when feasible, cryotherapy can be considered in dysplastic BE or IMC with nodular mucosa when EMR is not feasible or in patients with life-threatening comorbidities or on anticoagulant medications. Prospective studies comparing RFA to newer cryotherapy devices are needed to define the optimal role for each modality.

Table 5 Analysis of factors associated with complete eradication of dysplasia in Barrett's esophagus

Factor	Unadjusted analysis		Adjusted analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (1 year increment)	0.96 (0.92, 1.01)	0.11	–	–
Male versus female gender	1.9 (0.68, 5.5)	0.22	–	–
Caucasian race	1.04 (0.12, 9.3)	0.97	–	–
Smoking				
Ex-smoker versus non-smoker	0.91 (0.37, 2.2)	0.85	–	–
Current smoker versus non-smoker	0.64 (0.15, 2.7)	0.55	–	–
Current alcohol use	3.0 (1.1, 8.0)	0.027	–	–
Body mass index	1.01 (0.94, 1.08)	0.82	–	–
Aspirin	2.0 (0.83, 5.0)	0.12	–	–
NSAIDs	6.8 (0.86, 883.1)	0.2	–	–
Statins	1.2 (0.50, 2.7)	0.71	–	–
Proton pump inhibitors	1.6 (0.01, 30.4)	0.84	–	–
H2 blockers	0.04 (0.00, 0.49)	0.089	–	–
Hypertension	0.50 (0.20, 1.2)	0.14	–	–
Diabetes	0.70 (0.25, 2.0)	0.5	–	–
Hyperlipidemia	1.7 (0.70, 3.9)	0.26	–	–
History of fundoplication	0.29 (0.05, 1.8)	0.19	–	–
Length of Barrett's segment (cm)	0.90 (0.80, 1.02)	0.092	–	–
Size of hiatal hernia (cm)	0.92 (0.73, 1.2)	0.46	–	–
Baseline biopsy				
Cancer versus dysplasia	0.21 (0.08, 0.52)	< 0.001	0.24 (0.09, 0.63)	0.004
RFA versus cryotherapy	1.9 (0.78, 4.6)	0.16	1.7 (0.66, 4.3)	0.28
Num. of treatment sessions	1.04 (0.85, 1.3)	0.72	–	–
Months from baseline to last endoscopy (1 month increment)	1.03 (1.00, 1.05)	0.031	1.03 (1.00, 1.05)	0.039

CI confidence interval, *NSAID* nonsteroidal anti-inflammatory drugs, *OR* odds ratio, *RFA* radiofrequency ablation

Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest.

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