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Detection of Intestinal Metaplasia After Successful Eradication of Barrett's Esophagus with Radiofrequency Ablation

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Abstract

Background—Radiofrequency ablation (RFA) is an effective means of eradicating Barrett's esophagus (BE), both with and without associated dysplasia. Several studies have documented high initial success rates with RFA. However, there is limited data on IM detection rates after eradication.

Aims—To determine the rate of detection of intestinal metaplasia (IM) after successful eradication of Barrett's esophagus.

Methods—BE patients with and without dysplasia who had undergone RFA were retrospectively identified. Only those who had complete eradication as documented on the initial post-ablation endoscopy, and had minimum two surveillance endoscopies, were included in the analyses. Clinical, demographic, and endoscopic data were collected. Cumulative incidence of IM detection was calculated by the Kaplan–Meier method.

Results—Forty-seven patients underwent RFA and had complete eradication of Barrett's epithelium. The majority of patients were male (76.6%), and the mean age was 64.2 years. The cumulative incidence of newly detected IM at 1 year was 25.9% (95% CI 15.1–42.1%). Dysplasia

was detected at the time of recurrence in four patients, and all cases were detected at the GE junction in the absence of visible BE. Patients with recurrent IM had longer baseline segments of BE (median, 4 cm vs. 2 cm, $p = 0.03$).

Conclusions—The rate of detection of new IM is high in patients who have undergone successful eradication of BE by RFA. Additionally, dysplasia can recur at the GE junction in the absence of visible BE. Future studies are warranted to identify those patients at increased risk for the development of recurrent intestinal metaplasia.

Keywords

Barrett's esophagus; Endoscopy; Therapy; Recurrence

Introduction

Barrett's esophagus (BE) is characterized by a metaplastic change from the normal squamous epithelium to intestinal columnar epithelium with goblet cells in the distal esophagus. It affects approximately 5–15% of those with gastro-esophageal reflux disease (GERD) and is prevalent in an estimated 1–5% of the population [1–4]. BE is likely the obligate precursor for the development of esophageal adenocarcinoma (EAC). In Barrett's patients without evidence of dysplasia (non-dysplastic Barrett's esophagus; NDBE), the rate of progression to EAC is estimated at 0.5% per year [5]. However, the risk of EAC increases in the setting of low-grade (LGD) and high-grade dysplasia (HGD) to approximately 1–5% and 5–15% per year, respectively [4].

Endoscopic ablation therapy is frequently performed in patients with Barrett's esophagus, both with and without dysplasia, in the hopes of reducing the risk of progression to EAC. Radiofrequency ablation (RFA) is one such therapy that can effectively eradicate Barrett's mucosa. In a recent randomized, sham-controlled trial of patients with LGD and HGD, 90.5% of treated patients had complete eradication of any dysplasia, and 77.4% of those ablated had no IM on any biopsies 1 year after entering the study [6]. In this particular study, the protocol specified post-ablation surveillance endoscopies every 3 months in the first year after ablation was completed, with subsequent endoscopies spaced at greater intervals. However, there is limited published data on durability of response to treatment to guide recommendations with regard to appropriate post-ablation surveillance intervals.

We therefore decided to perform a retrospective review of our single-center cohort of patients with BE who had undergone radiofrequency ablation. We aimed to determine the incidence of detection of IM in patients who had achieved successful initial complete eradication of all Barrett's esophagus.

Methods

We performed a retrospective analysis of patients with Barrett's esophagus who underwent radiofrequency ablation at Columbia University Medical Center (New York, NY) between 2006 and 2009. The electronic medical records were reviewed to identify potentially eligible patients. This strategy was combined with a search of the electronic endoscopy reporting system (ProVation® MD; ProVation® Medical, Minneapolis, MN) using Current Procedural Terminology (CPT) codes 43228 and 43258. Endoscopy and pathology reports were then manually reviewed to confirm that patients had at baseline histologically confirmed BE and had subsequently undergone RFA. RFA was performed with a combination of the BÂRRX Halo³⁶⁰ and/or Halo⁹⁰ devices (BÂRRX Medical, Inc.), used at the discretion of the individual endoscopist.

A total of 257 unique patients underwent RFA for Barrett's esophagus during the study period. Analyses were restricted to those patients who had undergone consecutive RFA sessions until there was no visible Barrett's esophagus. Inclusion criteria were as follows: (1) successful initial eradication of all intestinal metaplasia (IM), defined as the absence of IM on biopsies from the first post-ablation EGD in patients treated with RFA; and (2) a minimum of two post-ablation surveillance endoscopies. Patients who were enrolled in a clinical trial of radiofrequency ablation (AIM Dysplasia Trial; $n = 13$) were excluded from the analyses, as post-ablation biopsies were not taken below the neo-squamocolumnar junction in that study.

For all post-ablation surveillance endoscopies, narrow band imaging was used for all cases to evaluate for the presence of intestinal metaplasia and/or dysplasia. High-definition upper endoscopes (Olympus GIF-H180) were used when available. At least four random biopsies were taken from the gastro-esophageal junction (just distal to the neo-squamocolumnar junction) in addition to targeted biopsies of any areas suspicious for Barrett's esophagus. As per clinical practice in our group, subjects were scheduled for post-ablation surveillance exams every 3 months for the first year, and then every 6–12 months thereafter. All patients were prescribed twice-daily proton pump inhibitors during the treatment and follow-up periods.

Data were recorded with regard to basic demographic information (age, sex, and race), baseline BE length, highest degree of dysplasia prior to ablation, and history of prior endoscopic therapy for BE, including endoscopic mucosal resection (EMR) or unsuccessful endoscopic ablation therapy with other modalities.

The primary endpoint of this study was the detection of IM on surveillance biopsies. If IM was detected, the presence or absence of dysplasia was documented and the endoscopic location of the recurrence was noted. Clinical follow-up data were recorded when available.

Categorical variables were analyzed using Fisher's exact tests, and continuous variables were analyzed using Wilcoxon rank-sum tests. Life tables were generated to determine cumulative incidence of detection of IM and 95% confidence intervals. The Kaplan–Meier method was used to generate curves for cumulative incidence of IM detection, with patients censored at the time of the last recorded endoscopy. All statistical analyses were performed using Stata 11.0 (StataCorp, College Station, TX).

This study was approved by the Columbia University Institutional Review Board.

Results

A total of 47 patients were identified who had undergone RFA for histologically confirmed BE, had no IM detected on the first post-ablation endoscopy, and had a minimum of two post-RFA surveillance exams. The basic demographics and baseline Barrett's characteristics are displayed in Table 1. The median post-ablation follow-up interval was 13.3 months (range 5–38 months), with a median of two follow-up surveillance endoscopies (range 2–5).

Fifteen patients (31.9%) had IM detected at some point during the post-ablation surveillance period (Table 2). At 1 year, the cumulative incidence of IM was 25.9% (95% CI 15.1–42.1%; Fig. 1). The median time to detection of IM in these 15 patients was 9 months. Four patients had dysplasia detected: two patients with HGD and two with LGD. In one of the patients with HGD, this represented a progression from LGD pre-ablation. All cases of dysplasia were detected at the GE junction, in the absence of visible BE. No EAC was detected in any of the patients.

Patients with IM detected during post-ablation surveillance had longer Barrett's segments at baseline than those without IM detected (median, 4 cm vs. 2 cm; $p = 0.03$). There were no other significant differences between those with and without IM detection after successful initial eradication of BE. Among the 22 patients previously treated, 14 had EMR alone, one had APC alone, and seven had both EMR and APC. Prior endoscopic treatment was not significantly associated with detection of IM post-ablation.

Among the 15 patients with IM detected during follow-up, 11 (73%) had IM at the gastroesophageal junction and four (27%) had IM detected as an island within neosquamous epithelium. The clinical characteristics and outcomes of these 15 patients are shown in Table 2.

Discussion

Among Barrett's esophagus patients who underwent radiofrequency ablation and had complete eradication, the 1-year cumulative incidence of detection of intestinal metaplasia in this cohort was 25%. This figure suggests that, even if an initial post-eradication endoscopy fails to demonstrate IM, frequent surveillance is still indicated within the first year. Longer baseline length of BE was the only pre-treatment factor associated with detection of IM post-ablation. Reasons for this are unclear, although perhaps these patients have more severe reflux or even a genetic predisposition to the development of BE.

It is unclear whether "new" IM detected during follow-up represented de novo intestinal metaplasia, or whether the initial post-eradication endoscopy simply failed to detect existing IM due to sampling error. In the presence of endoscopically suspected Barrett's esophagus, multiple random biopsies often fail to detect intestinal metaplasia. In a study of 296 endoscopies performed in patients with endoscopically suspected BE, IM was detected in only 68% of cases when 5–8 biopsies were taken [7]. However, if IM detected after BE eradication is in fact new IM, then BE patients post-ablation may represent an excellent model with which we can gain a better understanding of the origins of BE.

The rate of IM detection post-ablation in our series was distinctly higher than that reported in a small series by Gondrie et al. [8]. In that study of 12 patients who underwent radiofrequency ablation and had complete eradication of Barrett's mucosa, no new intestinal metaplasia was detected after a median follow-up period of 14 months. In a separate study of non-dysplastic patients who were treated with radiofrequency ablation, intestinal metaplasia was present in 30% of subjects 1 year after ablation [9]. It was not reported how many of the patients had absence of IM on the initial post-ablation endoscopy followed by the detection of IM on a subsequent exam. In the long-term follow-up analyses restricted to subjects with no IM after 2.5 years, the cumulative incidence of recurrent IM was 9%, suggesting that new IM can develop several years after complete eradication of BE [10]. In recent data presented in abstract form of 40 BE patients treated predominantly with cryoablation therapy, 30% developed recurrent intestinal metaplasia [11]. Data from the AIM Dysplasia Trial presented in abstract form suggests that recurrence of IM can occur beyond 1 year after ablation, albeit at a low rate [12]. In this clinical trial of RFA for Barrett's esophagus with low- or high-grade dysplasia, 4.8% of patients with no IM at 1 year developed new IM between years 1 and 2. An important difference to note is that, in the AIM Dysplasia trial, biopsies were taken from just proximal to the squamocolumnar junction but not from the GE junction itself. The majority of cases from the current study with new IM were detected at the GE junction, and it is therefore unclear how our results might compare to those of the AIM Dysplasia trial.

The clinical significance of new IM at the GE junction in the post-ablation setting is unclear. In untreated patients who have IM at the GE junction in the absence of endoscopically suspected BE, the cancer risk is generally assumed to be significantly lower than in patients with BE. However, the rate of metachronous disease is high in BE patients with prior advanced neoplasia [13], and new IM at the GE junction in these patients may have a high risk of neoplastic progression. We found a 1 year cumulative incidence of dysplasia of 8%. It should be noted that all cases of recurrent dysplasia developed at the GE junction, in the absence of any visible BE. Whether IM detected at the GE junction after ablation represents recurrent IM or simply IM missed previously due to sampling error may be irrelevant from a clinical perspective. Our data suggest that the GE junction post-ablation should be considered an area at risk for the development of dysplasia and potentially adenocarcinoma. Possible solutions to prevent de novo IM may include repeat ablation at the GE junction or extension of treatment 1–2 cm distal to the top of the gastric folds.

The strengths of the current study include restriction of analyses to patients in whom the initial post-eradication endoscopy did not demonstrate intestinal metaplasia. This was done to exclude patients with incomplete eradication. Biopsies were taken on all patients at the GE junction (just distal to the neo-squamocolumnar junction), and irrespective of the presence of any endoscopically suspected Barrett's esophagus.

The number of patients with follow-up beyond 1 year was too few to draw firm conclusions with regard to rates of detection of IM at later time points post-ablation. While we restricted analyses to patients in whom no IM was detected on the initial post-ablation endoscopy, it is possible that small areas of IM were present at the GE junction and simply missed due to sampling error. Intestinal meta-plasia at the GE junction can be difficult to recognize visually, even with the use of high-definition white light endoscopy and narrow band imaging. Additional limitations to the current study include the relatively small sample size as well as the retrospective design.

The results of the present study suggest that the rate of detection of intestinal metaplasia after successful eradication of Barrett's esophagus may be higher than previously suspected. These data support the practice of frequent surveillance exams within the first year, especially in patients with a history of high-grade dysplasia or adenocarcinoma. The findings need to be confirmed in a larger series of patients who have undergone RFA for Barrett's esophagus. The risk of neoplastic progression of new IM at the GE junction is still unknown. However, all of the cases of recurrent dysplasia in this cohort developed at the GE junction, in the absence of visible BE. It is also important to determine whether the rates of IM detection vary by history of prior dysplasia or cancer. Additionally, future studies should be aimed at the identification of biomarkers from both pre-treatment and post-treatment biopsies in order to predict which patients are likely to develop recurrence.

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Fig. 1.
Cumulative incidence of intestinal metaplasia in patients who had undergone radiofrequency ablation for Barrett's esophagus with complete eradication

Table 1

Demographics and clinical characteristics of Barrett's esophagus patients who had initially successful eradication after radiofrequency ablation

	n	%
Total	47	100%
Male sex	36	76.6%
Mean age, years (SD)	64.2	(9.8)
Median BE length, cm (IQR)	2	(1–4)
Previous endoscopic treatment	22	46.8%
Pre-treatment histology		
No dysplasia	5	10.6%
Low-grade dysplasia	6	12.8%
High-grade dysplasia	33	70.2%
Adenocarcinoma	3	6.4%

Table 2

Endoscopic and pathologic characteristics of 15 patients with intestinal metaplasia detected on surveillance after initial successful eradication of Barrett's esophagus

Patient	Histology		Site of recurrence	Clinical follow-up
	Baseline	Recurrence		
1	LGD	HGD	GE junction	Retreated with EMR and RFA successfully (no subsequent IM)
2	HGD	NDBE	GE junction	Retreated with RFA successfully
3	HGD	NDBE	Island	No follow-up to date
4	HGD	HGD	GE junction	No follow-up to date
5	HGD	NDBE	Island	No IM detected on subsequent endoscopies
6	HGD	NDBE	Island	Retreated with RFA; no further follow-up to date
7	LGD	LGD	GE junction	Retreated with RFA successfully
8	HGD	NDBE	GE junction	Continued surveillance with intermittently detected IM
9	HGD	NDBE	Island	Retreated with RFA; no further follow-up to date
10	HGD	NDBE	GE junction	No IM detected on subsequent endoscopies
11	HGD	NDBE	GE junction	Retreated with RFA; no further follow-up to date
12	HGD	NDBE	GE junction	Retreated with EMR and RFA with intermittently detected IM
13	HGD	LGD	GE Junction	Retreated with RFA; no further follow-up to date
14	NDBE	NDBE	GE junction	No follow-up to date
15	HGD	NDBE	GE junction	Continued endoscopic surveillance; progressed to LGD