Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial *

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Bibliography
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Background and study aims: The AIM-II Trial included patients with nondysplastic Barrett's esophagus (NDBE) treated with radiofrequency ablation (RFA). Complete eradication of NDBE (complete response-intestinal metaplasia [CR-IM]) was achieved in 98.4% of patients at 2.5 years. We report the proportion of patients demonstrating CR-IM at 5-year follow-up.

Patients and methods: Prospective, multicenter US trial (NCT00489268). After endoscopic RFA of NDBE up to 6 cm, patients with CR-IM at 2.5 years were eligible for longer-term follow-up. At 5 years, we obtained four-quadrant biopsies from every 1 cm of the original extent of Barrett's esophagus. All specimens were reviewed by one expert gastrointestinal pathologist, followed by focal RFA and repeat biopsy if NDBE was identified. Primary outcomes were (i) proportion of patients demonstrating CR-IM at 5-year biopsy, and (ii) proportion of patients demonstrating CR-IM at 5-year biopsy or after the single-session focal RFA.

Results: Of 60 eligible patients, 50 consented to participate. Of 1473 esophageal specimens obtained at 5 years 85% contained lamina propria or deeper tissue (per patient, mean 30 [13], standard deviation [SD] 13). CR-IM was demonstrated in 92% (46/50) of patients, while 8% (4/50) had focal NDBE; focal RFA converted all these to CR-IM. There were no buried glands, dysplasia, strictures, or serious adverse events. Kaplan-Meier CR-IM survival analysis showed probability of maintaining CR-IM for at least 4 years after first durable CR-IM was 0.91 (95% confidence interval [CI] 0.77–0.97) and mean duration of CR-IM was 4.22 years (standard error [SE] 0.12).

Conclusions: In patients with NDBE treated with RFA, CR-IM was demonstrated in the majority of patients (92%) at 5-year follow-up, biopsy depth was adequate to detect recurrence, and all failures (4/4, 100%) were converted to CR-IM with single-session focal RFA.

Introduction

Barrett's esophagus occurs as a result of chronic injury to the esophageal epithelium by reflux of gastroduodenal contents associated with gastroesophageal reflux disease (GERD) [1,2]. A diagnosis of Barrett's esophagus is suspected upon discovery of salmon-colored epithelium in the esophagus and is confirmed by mucosal biopsy that demonstrates intestinal epithelium containing goblet cells, referred to as intestinal metaplasia [3]. Barrett's esophagus is categorized endoscopically by length and histologically according to the absence or presence/severity of dysplastic cellular changes: nondysplastic, low grade dysplasia (LGD), or high grade dysplasia (HGD). These morphological categories represent surrogate markers of increasing risk of developing esophageal adenocarcinoma (EAC). Hence, medical society guidelines have commonly recommended a strategy of surveillance endoscopy with biopsy for patients with nondysplastic and LGD Barrett's esophagus, to: (i) detect neoplastic progression prior to EAC, or (ii) detect EAC at a treatable stage [3–7].

A surveillance strategy for nondysplastic and LGD Barrett's esophagus has many recognized limitations: biopsy sampling errors, lack of compliance with surveillance protocols, cost, cost-utility considerations, and failure to avert EAC in many cases. Therefore, endoscopic therapies intended to completely remove or ablate the nondysplastic and LGD Barrett's esophagus epithelium have been evaluated as alternative strategies [8–13]. In a multicenter study, the AIM-II Trial, we have evaluated endoscopic radiofrequency ablation

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(RFA) for patients with nondysplastic Barrett's esophagus (NDBE), and have previously reported complete eradication of NDBE (all esophageal biopsies negative for intestinal metaplasia, termed complete response-intestinal metaplasia [CR-IM]) in 98.4% of patients at 2.5-year follow-up [14]. To assess the longer-term durability of complete reversion to a squamous epithelium after ablation, we performed endoscopy and biopsy at 5-year follow-up in patients from the trial who had shown CR-IM at 2.5 years.

Patients and methods

This is a report of the 5-year outcomes of a prospective cohort study (ClinicalTrials.gov identifier NCT00489268) conducted at eight US centers between May 2004 and November 2009. Five of the study centers were tertiary referral academic teaching hospitals, while three were large community practices with the experience and staffing for conducting clinical trials. The institutional review board at each site approved the study protocol and the form provided for informed consent from patients. All the study participants gave their informed consent.

Patients

In Phase I of this study (from study entry to 2.5-year follow-up), eligibility criteria included age 18 – 75 years and presence of NDBE (2 – 6 cm). All patients underwent confirmatory endoscopy with biopsies from the esophageal body within 6 months of enrollment for corroboration that the morphological grade of Barrett's esophagus was not worse than nondysplastic. Exclusion criteria were: esophageal stricture or varices, active esophagitis, previous ablation, previous endoscopic resection, previous radiation therapy to the esophagus, any history of esophageal dysplasia or malignancy, or presence of an implanted electrical device.
Patients were provided with antisecretory medication; oral esomeprazole (AstraZeneca LP, Wilmington, Delaware, USA) was used during the first 2.5 years of the study, at 40 mg per day with dose escalation to 40 mg twice a day for 1 month after ablation.
In Phase II of this study (2.5 years to 5 years), attempts were made to contact all 60 patients who met eligibility criteria for the 5-year biopsy. Antisecretory medication type and dosage were decided at the discretion of the investigator. Patients were provided with oral esomeprazole 40 mg twice per day for 2 months prior to the 5-year visit to minimize inflammation at the time of endoscopy with biopsy.

Study devices

In Phase I of the study, endoscopic circumferential RFA was performed with the HALO^{360} system (BÂRRX Medical, Inc., Sunnyvale, California, USA) comprising a sizing balloon, a balloon-based ablation catheter and an energy generator. Endoscopic focal RFA was done using the HALO^{90} system, comprising an electrode array fitted to the distal end of an endoscope.

Patient flow

At the beginning of the study (Phase I), we enrolled 70 patients who met all the inclusion criteria for the study and to whom none of the exclusion criteria applied (**Fig. 1**).
After circumferential RFA, a complete response for intestinal metaplasia (CR-IM), defined as all esophageal biopsies being negative for intestinal metaplasia, was seen in 48 of 69 patients (70%) at 1-year follow-up. After 1-year follow-up, patients with persistent Barrett's esophagus or an irregular squamocolumnar junction received focal RFA. As a result, CR-IM was found in 60 of 61 patients (98%) at 2.5-year follow-up. In the present trial (phase II), patients with CR-IM at the 2.5-year follow-up were eligible for 5-year endoscopic biopsy to assess the durability of reversion to a squamous epithelium. **Fig. 2** shows a series of endoscopic images from representative patients at various time points in the study.

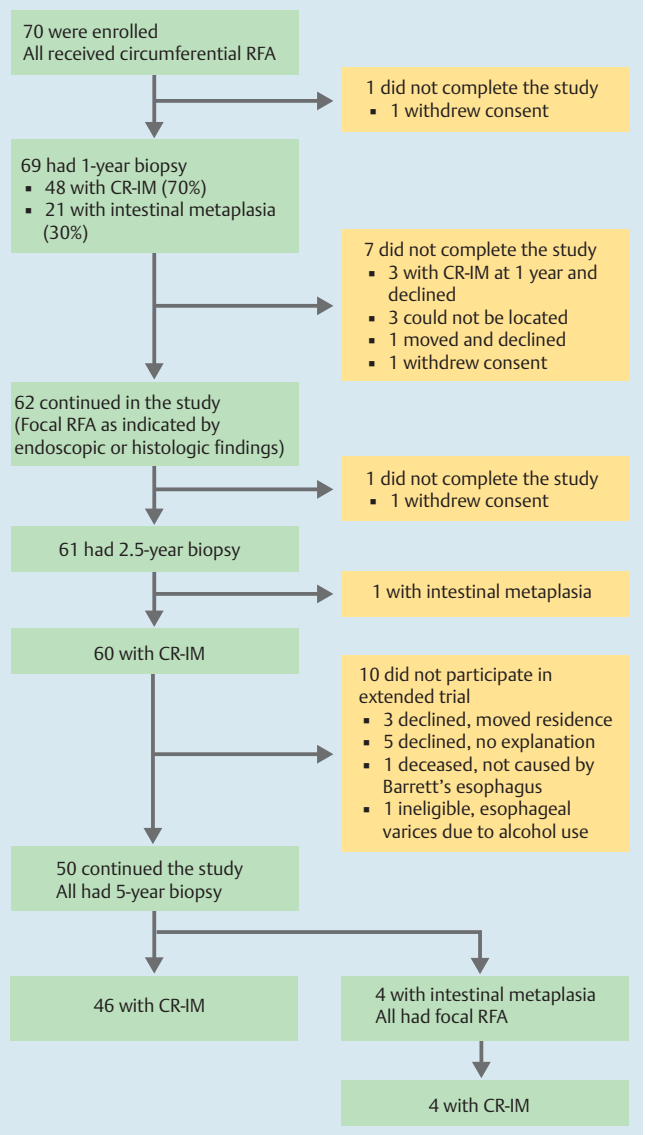

Fig. 1 AIM-II Trial: enrollment and follow-up of all patients from inception of trial. Among the 60 patients eligible for the 5-year follow-up phase based on complete response of intestinal metaplasia (CR-IM) status at 2.5 years, 50 (83%) patients elected to participate. RFA, radiofrequency ablation.

5-year endoscopy with biopsy visit

Radial Jaw-4 2.8-mm forceps (Boston Scientific Corp, Natick, Massachusetts, USA) were provided at each site for obtaining biopsies at the 5-year visit. Investigators were permitted, at their discretion, to use other large-jaw forceps including the Olympus Endojaw 220 FE 2.8-mm forceps and the Olympus FB-13K 3.7-mm forceps (Olympus America, Center Valley, Pennsylvania, USA). Biopsy specimens were obtained using these types of biopsy forceps, with tissue samples taken from four quadrants per

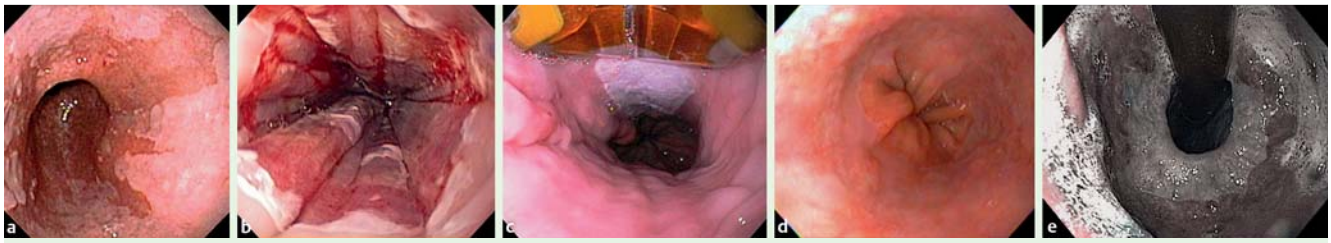

Fig. 2 Endoscopic images from representative study patients. **a** A 6-cm length of Barrett's esophagus without dysplasia at baseline. **b** Appearance immediately following circumferential ablation. **c** Focal radiofrequency device mounted on the tip of the gastroscope, with ablation zone seen distally. Ablation was done for residual intestinal metaplasia after 1-year follow-up. **d** Endoscopy demonstrating no Barrett's esophagus at 2.5 years with all biopsies negative for intestinal metaplasia. **e** Retroflexed view of gastroesophageal junction in patient at 5-year follow-up, showing neosquamous epithelium extending to the cardia. The esophagus was normal on endoscopy, with all biopsies negative for intestinal metaplasia.

level, beginning at the top of the gastric folds and moving proximally in 1-cm increments to encompass the entire baseline extent of Barrett's esophagus. Additionally, directed biopsy specimens were obtained from any areas that appeared abnormal. Biopsies distal to the top of the gastric folds were not mandated in this trial nor were they included in the analysis if obtained. All biopsy specimens from one level or one focal area were submitted in one jar containing formalin and labelled with the location of the biopsy as well as study subject identifier codes.

The study protocol did not mandate a specific type of endoscopic technique or type of endoscopic equipment for the 5-year endoscopy with biopsy visit. Investigators indicated on each case report form whether or not the following techniques were used: (i) Lugol chromoendoscopy, (ii) high-definition endoscopy, or (iii) electronic imaging, such as narrow band imaging (NBI).

Central pathology interpretation and processing

Study specimens were sent in a standardized kit to a central pathology laboratory (Gastrointestinal Pathology, LLC, Memphis, Tennessee, USA). The formalin-fixed specimens from each container were embedded in paraffin (one block per jar), affixed to slides, and stained with hematoxylin and eosin. One slide represented each level or focal area sampled.

A board-certified pathologist (P.J.D.) specializing in gastrointestinal pathology evaluated each specimen on each slide and categorized each according to tissue type (intestinal metaplasia versus squamous), dysplasia or cancer in intestinal metaplasia if present, and biopsy depth. Depth was defined as the deepest tissue layer present in each specimen: epithelium, lamina propria, muscularis mucosae, or submucosa. Biopsy specimens were considered to contain subepithelial structures if they contained lamina propria, muscularis mucosae, or submucosa. Each biopsy specimen was also evaluated for the presence of buried glandular mucosa, defined as "any specialized columnar epithelium covered by a layer of squamous epithelium with no communication with the surface" [15]. Finally, each tissue block was evaluated for the presence of inflammation. All data were entered into a standardized pathology case report form.

Salvage focal ablation

Patients in whom intestinal metaplasia was detected at the 5-year follow-up underwent endoscopy with focal RFA 1 month later, followed by repeat biopsy 2 months after RFA to assess histological response. Treatment settings were 12 J/cm^2 and 40 W/cm^2. Areas positive for intestinal metaplasia at 5-year biopsy were targeted, along with the region of the top of the gastric folds. Each location was treated twice successively, followed by cleaning of the coagulum from the treated area and electrode, followed by treatment of each location twice again.

Outcome measures

The primary study outcomes were defined a priori as: (i) the proportion of patients with CR-IM at the 5-year biopsy visit, and (ii) the proportion of patients demonstrating CR-IM at the 5-year biopsy visit or at the biopsy visit after single-session salvage focal RFA.

Secondary outcomes were defined a priori as: (i) proportion of 5-year failures converted to CR-IM after single-session salvage focal RFA; (ii) biopsy depth; (iii) prevalence of buried glandular mucosa; (iv) prevalence of dysplasia; (v) Kaplan-Meier CR-IM survival analysis; and (vi) adverse events.

All adverse events and serious adverse events were recorded on a standardized case report form. Specifically, a stricture in this study was defined a priori as any narrowing of the esophageal lumen in the area of treatment causing symptoms or requiring dilation. All case report forms at each site were monitored throughout the study period and queries issued in cases of noncompliance.

Statistical analysis

Data analysis was performed using SAS software, version 9 (SAS Institute, Cary, North Carolina, USA). The study population for the primary analysis included all eligible patients who gave their informed consent for the 5-year follow-up. Baseline patient data for the eligible patient group were assessed to detect differences between participants and decliners. Biopsy sample characteristics were compared for patients with CR-IM at 5 years vs. those with failure at 5 years, as well as for those with failure at 5 years vs. post-salvage RFA after 5 years. Fisher's exact test was used to compare categorical variables. For continuous variables, a *t* test was used for variables which did not display non-normality for either treatment group (Shapiro-Wilk *P* value > 0.05) and the Mann-Whitney test was used otherwise. All tests were two-sided and *P* values less than 0.05 were considered statistically significant.

In participants, the durability of CR-IM was assessed using the Kaplan-Meier survival curve with 95 % confidence intervals (CIs) generated using Greenwood's formula for computing standard errors. In this analysis, "time-zero" (start of CR-IM period for the survival analysis calculation) was the first durable CR-IM after enrollment (defined as either the 2.5-year time point or an earlier time point at which the first of two consecutive study biopsy sessions demonstrated CR-IM [6 or 12 months]). Since all participants in this phase of the study had CR-IM at 2.5 years, time-zero was therefore either the 6-month, 12-month, or 2.5-year follow-

Table 1 Radiofrequency ablation of nondysplastic Barrett's esophagus. Patient demographic data at 5-year follow-up.

Parameter	All those eligible for 5-year follow-up	Participating patients	Patients declining participation
Number of patients	60	50	10
Gender, male/female	44 / 16	37 / 13	7 / 3
Ethnicity			
White	42 (70 %)	36 (72 %)	6 (60.0 %)
Black	2 (3 %)	1 (2 %)	1 (10.0 %)
Hispanic/Latino	16 (27 %)	13 (26 %)	3 (30.0 %)
Baseline data			
Age, years			
Mean (SD)	55.8 (11.1)	54.3 (10.8)*	63.6 (9.8)*
Range	26 – 79	26 – 72	48 – 79
Body weight, mean (SD), lbs	177.8 (38.8)	177.6 (38.0)	179.0 (44.8)
History of GERD, n (%)	60 (100 %)	50 (100 %)	10 (100.0 %)
Barrett esophagus length, mean (SD), cm	3.2 (1.3)	3.1 (1.3)	3.7 (1.4)
Hiatal hernia			
Present/Absent, n/n	50 / 10	43 / 7	7 / 3
Length, mean (SD), cm	2.5 (1.1)	2.6 (1.2)	1.9 (0.7)
RFA treatments in prior study phase, mean (SD), n			
Total	3.4 (1.0)	3.4 (0.9)	3.3 (1.1)
Circumferential	1.6 (0.5)	1.5 (0.5)	1.6 (0.5)
Focal	1.8 (0.7)	1.9 (0.7)	1.7 (0.7)

SD, standard deviation; GERD, gastroesophageal reflux disease
*$P < 0.05$, patients who participated vs. those who declined participation

Table 2 Biopsy characteristics at 5-year follow-up after radiofrequency ablation (RFA) of nondysplastic Barrett's esophagus. Data are shown for all participants, for those with persisting complete response of intestinal metaplasia (CR-IM), for those with treatment failure, and following salvage RFA for those with treatment failure.

Parameter	5-year biopsy			Following salvage RFA
	All participants	CR-IM	Treatment failures	
Number of patients	50	46	4	4
Total biopsy specimens, n	1473	1347	126	112
Specimens per patient, mean (SD), n	30 (13)	29 (13)	32 (17)	28 (17)
Specimens with lamina propria or deeper				
Total, n	1255	1145	110	99
Proportion, %	85 %	85 %	87 %	88 %
Number per patient, mean (SD), n	25 (10)	25 (10)	28 (15)	24 (11)
Proportion per patient, mean (SD), %	87 % (11 %)	87 % (11 %)	88 % (5 %)	94 % (13 %)
Specimens containing buried glandular mucosa, n	0	0	0	0
Specimens with dysplasia or cancer	0	0	0	0

No significant differences for any variables

up visit (endoscopy with biopsy) for all patients. For the purpose of this survival analysis, where patients were found to have recurrent intestinal metaplasia after 2.5 years it was assumed that for half the elapsed time between endoscopies their status had been CR-IM and for the other half intestinal metaplasia had been present.

Results

For this 5-year follow-up of the AIM-II trial there were 60 eligible patients from eight US centers, of whom 50 (83 %) were willing to participate and gave signed consent for the extended follow-up described in the approved protocol (**Fig. 1**). The baseline patient characteristics of the eligible (n = 60), participant (n = 50), and declining (n = 10) subgroups are shown in **Table 1**. Comparing baseline characteristics of participants (n = 50) versus decliners (n = 10), only entry age was different between the groups, with participants being younger than decliners ($P < 0.05$).

At the 5-year biopsy visit, the mean (SD) number of biopsies obtained per patient was 30 (13) comprising a total of 1473 biopsies (**Table 2**).

Regarding the first primary outcome, 92 % (46 / 50) of patients showed CR-IM at the 5-year biopsy visit. Four patients (8 %) had intestinal metaplasia at 5 years (**Fig. 3**).

In these four patients, a mean (SD) of 32 (17) esophageal specimens were obtained from each patient; one patient had three specimens positive for intestinal metaplasia and three patients each had one such specimen. Five of the 6 specimens positive for intestinal metaplasia were located within 1 cm of the squamocolumnar junction near the top of the gastric folds. These four patients received a single session of focal RFA 1 month after biopsy and all (4 / 4, 100 %) were found to have CR-IM status upon subsequent biopsy at 2 months after RFA. Therefore, regarding the sec-

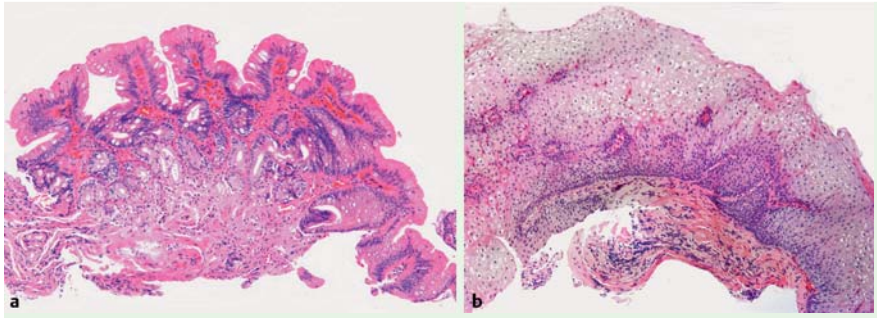

Fig. 3 Photomicrographs of esophageal biopsy specimens obtained from a patient with intestinal metaplasia at 5-year follow-up after radiofrequency ablation (RFA), i. e. treatment failure with regard to primary outcome (both images hematoxylin and eosin [H&E]; original magnification × 200). **a** Intestinal metaplasia seen in a biopsy obtained in the distal esophagus at the top of the gastric folds. Biopsy depth extends to the muscularis mucosae and intestinal metaplasia is present at the surface layer. **b** Esophageal biopsy 2 months after single-session focal RFA at 5 years for the residual intestinal metaplasia. Neosquamous epithelium is completely re-established and there was no evidence of intestinal metaplasia in any of 30 biopsies. The biopsy depth extends to the muscularis mucosae and shows completely squamous epithelium.

ond primary outcome, all patients (50/50, 100%) were in CR-IM at either the 5-year biopsy visit or after a single salvage focal ablation after the 5-year biopsy visit.

In the biopsies obtained at the 5-year visit, subepithelial structures were present in 85% of the specimens (**Fig. 4**).

In the four patients with intestinal metaplasia at 5-year biopsy, the mean (SD) number of biopsies per patient obtained 2 months after salvage RFA was 28 (17) (total 112 biopsies), with subepithelium present in 88% of these specimens. No evidence of buried glandular mucosa or dysplasia was detected on any 5-year biopsy or post-salvage biopsy.

At the 5-year visit, the Radial Jaw-4 2.8-mm biopsy forceps was used in 72% of patients (36/50), the Olympus Endojaw 220-FE 2.8-mm forceps in 26% (13/50), and the Olympus FB-13K 3.7-mm device in 2% (1/50). There was no difference in biopsy specimen depth according to type of biopsy forceps used.

At the 5-year follow-up biopsies investigators used high-definition endoscopy in 35/50 of patients (70%) and electronic imaging (such as NBI) in 17/50 (34%). None used Lugol chromoendoscopy. High-definition endoscopy was used in 32/46 (70%) of the CR-IM patients and 3/4 (75%) of those with intestinal metaplasia. Corresponding values for electronic imaging were 16/46 (35%) and 1/4 (25%).

The Kaplan-Meier survival curve for the secondary outcome of CR-IM survival is shown in **Fig. 5**.

All participants (n = 50) are represented in this analysis. The probability of maintaining CR-IM for at least 4 years after the first durable CR-IM was 0.91 (95% confidence interval [CI] 0.77 – 0.97). The mean (standard error [SE]) duration of CR-IM in participants was 4.22 (0.12) years. Included in this survival analysis is one patient with CR-IM status at 5 years, but who had an off-protocol biopsy between the 2.5- and 5-year study visits that detected nondysplastic intestinal metaplasia in one specimen; this was followed by focal ablation. Although the biopsy was obtained outside of the study protocol and the histological findings were not reviewed by the study pathologist, treatment is considered to have failed in the survival analysis. However it is not considered to have failed with regard to the study's primary end point (CR-IM at 5 years). Of note, amongst the remaining 49 patients, 33 also had a nonprotocol endoscopy with biopsy procedures as part of standard care during the interval between 2.5 and 5 years with none having intestinal metaplasia in esophageal biopsies and none undergoing ablation in the esophagus.

At the 5-year biopsy visit, 45 patients reported taking oral esomeprazole 40 mg twice per day, 3 patients oral omeprazole 40 mg twice per day, 1 patient oral lansoprazole 30 mg per day, and 1 patient no antisecretory medication. Of the 50 patients, three (6%) had either grade A (n = 1) or grade B (n = 2) erosive esophagitis (Los Angeles Classification) at the 5-year visit, while the remainder had no signs of erosive esophagitis. All three patients with erosive esophagitis were taking oral esomeprazole 40 mg twice per day. None of the four patients subsequently noted to have intestinal metaplasia at 5-year biopsy had erosive esophagitis during that visit.

There were no differences in baseline demographic data or Barrett's esophagus characteristics between patients with CR-IM status or treatment failure at 5 years. In addition, there was no difference between these groups in the mean (SD) number of biopsies collected (29 [13] vs. 32 [17]) or in the percentage per patient of biopsy specimens containing subepithelium (87% vs. 88%). Similarly in the treatment failure group, comparing the 5-year biopsy visit with the follow-up biopsy visit 2 months after salvage focal RFA, there was no difference between the mean number of biopsies per patient (32 [17] vs. 28 [17]) or the proportion per patient of biopsies containing subepithelium (88% vs. 94%) (**Table 2**).

No strictures were noted at any follow-up endoscopy. One patient reported a globus sensation 1 week after salvage focal ablation, which resolved without intervention. There were no other adverse events.

Discussion

Esophageal mucosa demonstrating glandular epithelium with goblet cells defines the entity Barrett's esophagus [3]. The morphological categories in Barrett's esophagus of nondysplastic tissue, LGD, and HGD are surrogate markers of increasing risk for incident EAC, although genetic alterations enabling neoplastic behavior and progression are present in NDBE prior to development of a dysplasia phenotype [16 – 20]. While nondysplastic tissue is associated with the lowest risk for EAC of the nondysplastic/LGD/HGD categories (0.5% – 0.6% incidence per patient year of follow-up; 5% – 8% lifetime risk), its detection prompts the initiation of a surveillance endoscopy and biopsy regimen intended to detect neoplastic progression [21 – 24]. Recognized limitations of

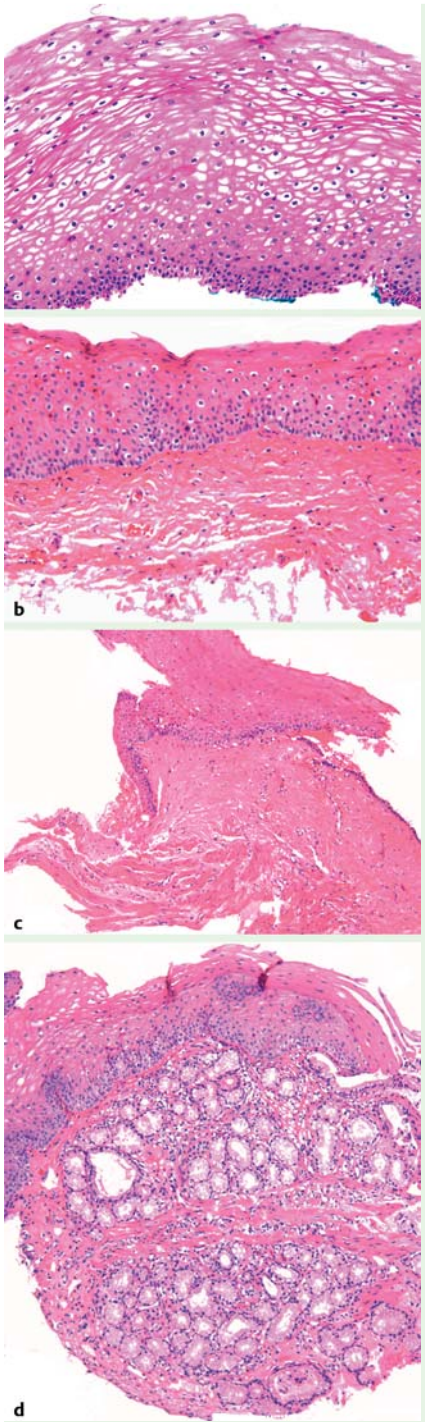

Fig. 4 Photomicrographs of esophageal biopsy specimens obtained from a patient deemed to have complete response-intestinal metaplasia (CR-IM) at 5 years (hematoxylin and eosin [H&E]; original magnification ×200). Depth of specimen categorized as: **a** full epithelium; **b** lamina propria; **c** muscularis mucosae; **d** submucosa.

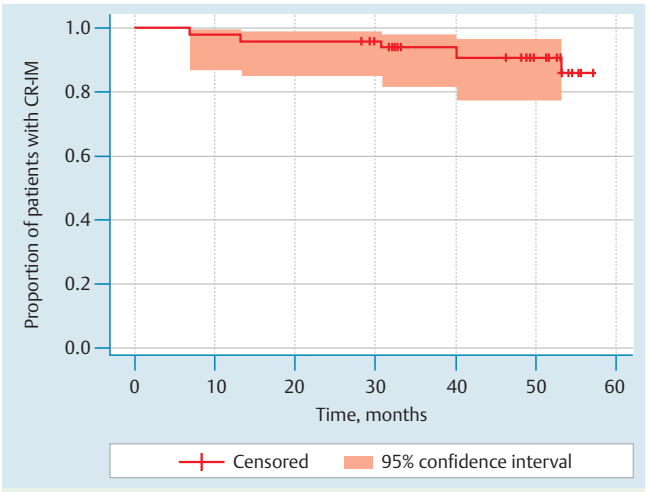

Fig. 5 Kaplan-Meier survival curve for duration of complete response of intestinal metaplasia (CR-IM). All participants (n = 50) are represented in this analysis. The probability of maintaining CR-IM for at least 4 years after first durable CR-IM is 0.91 (95 %CI 0.77 – 0.97). The mean duration of CR-IM in participants was 4.22 years (standard error [SE] 012).

a surveillance strategy include biopsy sampling error, lack of compliance with surveillance protocols, cost, cost-utility issues, and failure to avert EAC in many cases [8 – 13]. An ideal management paradigm for an nondysplastic population in the future might be to risk-stratify patients by assaying for a genotype associated with propensity for neoplastic progression, and then to eradicate the NDBE in those patients at highest risk, with surveillance or no action in those patients at lower or zero risk. The ability to risk-stratify a Barrett's esophagus population according to genotype has proven elusive, and is not yet possible.

More, however, is now known regarding the safety and short- to intermediate-term efficacy of a number of endoscopic techniques used to eradicate the Barrett's esophagus epithelium. We previously reported the 1- and 2.5-year safety and efficacy outcomes of the AIM-II trial, which applied endoscopic RFA in patients with up to 6 cm of NDBE. Circumferential ablation achieved CR-IM in 70 % of patients at 1-year follow-up [25]. Thereafter, focal ablation of residual intestinal metaplasia achieved CR-IM in 98 % of these patients at 2.5-year follow-up [14]. There were no strictures, neoplastic progression, buried glands, or serious adverse events. Others studies of RFA applied in nondysplastic, LGD, and HGD Barrett's esophagus populations, including a randomized, sham-controlled multicenter trial, report similarly high rates of CR-IM (or complete response for dysplasia) with acceptable safety profiles [26 – 40].

Since Barrett's esophagus is a chronic disease state with long-term implications for neoplastic progression, information on longer-term outcomes regarding the durability of CR-IM after RFA are essential to assess the utility of this strategy. In this long-term follow-up of patients from the AIM-II trial, we conducted endoscopy and biopsy at 5-year follow-up and found that in 92 % of patients (46/50) CR-IM was maintained. We utilized the more objective measurement of histological findings rather than endoscopic observation. A Kaplan-Meier survival curve showed the probability of maintaining CR-IM for at least 4 years after first durable CR-IM was 0.91 (95 %CI 0.77 – 0.97), while the mean (SE) duration of CR-IM was 4.22 (0.12) years. Recurrent NDBE was identified in four patients at 5 years (8 %) in 6/128 esophageal specimens, most of which were located within 1 cm of the top of the gastric folds. These patients underwent single-session focal RFA and all showed CR-IM thereafter. No dysplasia, stricture, serious adverse event, or buried glandular mucosa was noted. Assessment of the depth of esophageal biopsy specimens showed that 85 % of the 1473 esophageal biopsy specimens contained lamina propria or deeper structures, a depth considered adequate for detection of buried glandular mucosa. Our 5-year data with RFA can be compared with long-term outcomes of other ablative modalities. A technical review by Wani et al. reported recurrence rates of up to 68 % in patients with NDBE treated with argon plasma coagulation (APC) [41,42] . While long-term data for multipolar electrocoagulation (MPEC) are limited, one case series described recurrence at 2-year follow-up in 27 %

of patients with baseline nondysplastic or LGD Barrett's esophagus [43]. In the PHOBAR trial, which evaluated the safety, efficacy and durability of photodynamic therapy in patients with HGD in Barrett's esophagus, there was a 48% probability of maintaining complete eradication of HGD at 5 years [44].

Several cost-utility models indicate that endoscopic ablation is a cost-effective strategy for Barrett's esophagus with nondysplastic tissue, LGD, and HGD. The cost-utility evidence is strongest for the highest risk lesions, i.e., LGD/HGD, with ablation being preferred or dominant to other strategies. Specifically regarding no dysplasia, however, Inadomi et al. reported that ablation is the preferred strategy for Barrett's with no dysplasia if a permanent CR-IM is achieved in 40% of patients and surveillance discontinued after CR-IM. This model's threshold for cost–effectiveness represents a lower CR-IM (40%) than reported in published trials of RFA, yet sets a high threshold for the durability of CR-IM and requires cessation of surveillance in CR-IM patients, a step that may not be acceptable to patients or physicians. However, the next most preferred strategy from this model (over that of surveillance) is ablation in which CR-IM is achieved in 40% and surveillance is, in fact, continued in all patients [45]. In a separate model, Das et al. found that, if CR-IM was achieved in 50% of patients, RFA yielded the most quality-adjusted life-years (QALYs) when compared with strategies of no intervention (natural history) and management following current American College of Gastroenterology surveillance guidelines [46]. Both of these models indicate that durability of CR-IM after ablation of NDBE has an important influence on the cost-utility of the strategy. The persistence of CR-IM in 92% of NDBE patients at 5-year follow-up in the present study, as well as the successful re-establishment of CR-IM in all patients with treatment failure by single-session focal RFA after 5 years, is promising in that it permits us to apply these models for the first time in clinical practice and to consider RFA as a viable alternative to surveillance alone for NDBE.

As Barrett's esophagus is a surrogate marker identifying risk for neoplasia progression and EAC incidence, therapeutic management strategies should be designed to avert these outcomes. In a meta-analysis, Wani et al. reported that the incidence of EAC in an observed NDBE population was 0.598% per patient per year of follow-up, while the incidence of EAC in ablated NDBE populations (regardless of CR-IM outcome) was 0.163% [21]. In this analysis, ablation affords an absolute risk reduction (ARR) of 0.435% per patient per year of follow-up in patients with NDBE, demonstrating that ablation does avert EAC for this population. Using these data for NDBE, the number needed to treat (NNT) to avoid one EAC over a 1-year period is 230 (1/ARR), while the NNT to avoid one EAC over 5 years is 46. Sharma et al. found that nondysplastic tissue progresses to HGD at a rate of 0.9% per patient per year of follow-up [22]. Using the natural history progression rates from Wani et al. and Sharma et al. for NDBE to EAC (0.6%) and HGD (0.9%), we might have expected seven cases of EAC or HGD in this trial over the 5-year study period (if the patients were observed and not treated), rather than the absence of HGD or EAC cases that was noted.

Buried glandular mucosa is an important consideration in the management of Barrett's esophagus. This entity is present in a significant proportion of ablation-naïve Barrett's esophagus patients (25%–39%), as well as in post-PDT (51%) and post-APC (44%) patients [26,42,47,48]. In the present study, we collected 1473 esophageal biopsies at 5-year follow-up and 3930 biopsies at earlier visits and found no evidence of buried glandular mucosa. Others have reported similarly low rates of this finding after RFA. Shaheen et al. found that 25% of LGD and HGD patients had buried glands prior to RFA, while at 1-year buried glands were present in 5% of RFA patients and 40% of sham patients [26]. In our study, and in the randomized controlled trial of Shaheen et al., post-RFA biopsy specimens contained lamina propria or deeper structures in 85% and 79% of cases, respectively, suggesting that biopsy depth after RFA is adequate for detection of buried glandular mucosa and that occult buried glandular mucosa after RFA is unlikely [49].

Strengths of this study include the prospective, multicenter design, long duration of follow-up, large number of biopsy specimens obtained, standardized biopsy sampling protocol, use of large-jaw biopsy forceps, use of a single expert gastrointestinal pathologist for histological interpretation, objective histological outcomes, and use of complete histological response as the primary outcome.

This study has some possible limitations:

- Regarding patient attrition, the original patient group comprised 70 patients, whereas 69 and 61 patients were available for evaluation at 1 and 2.5 years, respectively. There were 60 eligible patients for the present study (those with CR-IM at 2.5 years), while 50 (83%) provided consent and participated. Nonparticipants were older than participants. If, because of age or other unmeasured factors, nonparticipants were three times more likely to have treatment failure (a very conservative estimate given that age was not associated with response to therapy in this study), our 5-year CR-IM outcome would drop nominally from 92% (46/50) to 82% (49/60). Therefore, it is unlikely that attrition significantly impacted our primary findings.
- One patient with CR-IM at 5 years had an off-protocol biopsy between the 2.5-year and 5-year study visits that showed nondysplastic intestinal metaplasia in one specimen obtained from the region of the gastric folds and the patient was treated with focal ablation. Although the biopsy was obtained outside of the protocol and not reviewed histologically by the study pathologist, to present the data transparently and as conservatively as possible, this patient was considered to have treatment failure in the Kaplan-Meier CR-IM survival analysis. No other patients underwent ablation between 2.5 and 5 years. If we considered this single patient as having treatment failure for the primary analysis, the 5-year CR-IM would drop nominally from 92% (46/50) to 90% (45/50).
- Another possible limitation of this study relates to the Kaplan-Meier CR-IM durability analysis and our methodology for assignment of a "time zero" for durable CR-IM for each patient. After the 1-year follow-up, focal RFA was applied at 2-month intervals (maximum of 3 sessions) in patients with intestinal metaplasia (1-year failure) as well as in patients with an irregular squamocolumnar junction (without confirmation of intestinal metaplasia) with the aim of optimizing efficacy outcomes at the 2.5-year follow-up. If some of the focal RFA sessions in patients without confirmation of intestinal metaplasia actually ablated minute residual foci of intestinal metaplasia, then it is possible that our durability analysis overestimated the true duration of CR-IM in these patients by setting the "time zero" point too early. While we do not believe that this would significantly affect the durability curve, an optimal study design might have required histological confirmation of intestinal metaplasia prior to any focal ablation after the 1-year follow-up.

- The study had no concurrent control arm, although the objective histological end points mitigate the likelihood of bias due to lack of controls at 5 years.
- There was no standardized post 2.5-year antisecretory medication regimen. Up to 2.5 years, all patients were provided with oral esomeprazole 40 mg per day (with escalation to twice per day for 1 month post-RFA). The inability to assess adequacy of acid suppression and compliance with medication during the post 2.5-year period, however, limits our ability to draw conclusions about the role of these factors in disease recurrence or persistent cure. However, given the high degree of maintenance of CR-IM at 5 years, despite the heterogeneity of antisecretory regimens in the post 2.5-year follow-up period, it is unlikely that the composition of the antisecretory regimen is an important predictor of CR-IM durability.
- There is an inherent lack of precision in identifying the precise location of the distal terminus of the esophagus and in accurately distinguishing this from the proximal extent of the stomach. This may be important regarding accurate assessment of the presence or absence of intestinal metaplasia in the esophagus after ablative therapy. Our biopsy methodology in this trial used the top of the gastric folds as the landmark for the distal terminus of the esophagus, and we obtained biopsies from this location (and proximally at 1-cm intervals) in all patients at all follow-up visits. It is possible that this methodology could: (i) overestimate the presence of intestinal metaplasia if these distal biopsies were actually from the untreated gastric cardia and if they contained intestinal metaplasia (a common finding); or (ii) underestimate the presence of intestinal metaplasia if the location of the gastric folds was located too proximally, as we would miss sampling a portion of the distal, previously treated esophagus. The importance of thoroughly assessing the distal esophagus is emphasized by our finding that 5/6 biopsy specimens positive for intestinal metaplasia in the patients with treatment failure were located within 1 cm of the top of the gastric folds.
- The interval of 2 months from salvage RFA to subsequent biopsy to assess CR-IM after salvage was short. It is possible that after salvage RFA occult intestinal metaplasia was present that would have been detected after additional time or with further biopsy sessions. However, this only affected four patients (8%) and the salvage outcome was not used for calculation of the main study end point, that of CR-IM at 5 years.
- A final possible limitation is that biopsy forceps were not standardized for all cases, with the Radial Jaw-4 2.8-mm forceps employed in two-thirds of the biopsy visits and the Endojaw 220 FE 2.8-mm or Olympus FB-13K 3.7-mm forceps used in one-third. However biopsy depth did not differ according to forceps type, so this is unlikely to be a confounding variable.

In summary, this is the first report of 5-year CR-IM outcomes related to RFA for Barrett's esophagus. In our patients from the AIM-II Trial who had NDBE treated previously with RFA, CR-IM persisted in the majority of patients (92%) at 5-year follow-up, the biopsy depth was adequate to detect recurrence, and all treatment failures were converted to CR-IM with single-session focal RFA (4/4, 100%). Kaplan-Meier survival analysis of CR-IM durability demonstrated that the probability of maintaining CR-IM for at least 4 years is 0.91 (95%CI 0.77 – 0.97) and mean (SE) duration of CR-IM is 4.22 (0.12) years. There were no buried glands, dysplasia, strictures or serious adverse events. These long-term data have important implications for the clinical management of patients with NDBE and perhaps also those with LGD/HGD. If early recurrence of Barrett's esophagus had been common in these patients, the value of this therapeutic intervention for Barrett's esophagus (specifically, nondysplastic) would be called into doubt. Our report of CR-IM at 5 years in the context of the many other studies reporting favorable outcomes related to the safety, efficacy, cost-utility, and reduction in neoplastic progression lend further credence for a role of RFA in the treatment of NDBE.

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References

1 *Haggitt RC.* Barrett's esophagus: pathogenesis, dysplasia, and adenocarcinoma. Hum Pathol 1994; 25: 982 – 993
2 *Winters C Jr., Spurling TJ, Chobanian SJ et al.* Barrett's esophagus: a prevalent, occult complication of gastroesophageal reflux disease. Gastroenterology 1987; 92: 118 – 124
3 *Wang KK, Sampliner RE.* Updated Guidelines 2008 for the diagnosis, surveillance and therapy of barrett's esophagus. Am J Gastroenterol 2008; 103: 788 – 797
4 *Sharma P, McQuaid K, Dent J et al.* A critical review of the diagnosis and management of Barrett's esophagus: the AGA Chicago Workshop. Gastroenterology 2004; 127: 310 – 330
5 *Watson A, Heading RC, Shepherd NA.* Guidelines for the diagnosis and management of Barrett's columnar-lined oesophagus: a report of the Working Party of the British Society of Gastroenterology. London: British Society of Gastroenterology, 2005
6 *Boyer J, Laugier R, Chemali M et al.* French Society of Digestive Endoscopy SFED guideline: monitoring of patients with Barrett's esophagus. Endoscopy 2007; 39: 840 – 842
7 *Society for Surgery of the Alimentary Tract.* SSAT patient care guidelines. Management of Barrett's esophagus. J Gastrointest Surg 2007; 11: 1213 – 1215
8 *Inadomi JM.* Surveillance in Barrett's esophagus: a failed premise. Keio J Med 2009; 58: 12 – 18
9 *Shaheen NJ, Provenzale D, Sandler RS.* Upper endoscopy as a screening and surveillance tool in esophageal adenocarcinoma: a review of the evidence. Am J Gastroenterol 2002; 97: 1319 – 1327
10 *Montgomery E, Bronner MP, Goldblum JR et al.* Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation. Hum Pathol 2001; 32: 368 – 378

11 *Reid BJ, Haggitt RC, Rubin EC et al.* Observer variation in the diagnosis of dysplasia in Barrett's esophagus. Human Pathol 1988; 19: 166 – 178
12 *Alikhan M, Rex D, Khan A et al.* Variable pathologic interpretation of columnar lined esophagus by general pathologists in community practice. Gastrointest Endosc 1999; 50: 23 – 26
13 *Abrams JA, Kapel RC, Lindberg GM et al.* Adherence to biopsy guidelines for Barrett's esophagus surveillance in the community setting in the United States. Clin Gastroenterol Hepatol 2009; 7: 736 – 742
14 *Fleischer DE, Overholt BF, Sharma VK et al.* Endoscopic ablation of Barrett's esophagus: a multicenter study with 2.5-year follow-up. Gastrointest Endosc 2008; 68: 867 – 876
15 *Dulai GS, Jensen DM, Cortina G et al.* Randomized trial of argon plasma coagulation vs. multipolar electrocoagulation for ablation of Barrett's esophagus. Gastrointest Endosc 2005; 61: 232 – 240
16 *Fitzgerald RC.* Complex diseases in gastroenterology and hepatology: GERD, Barrett's, and esophageal adenocarcinoma. Clin Gastroenterol Hepatol 2005; 3: 529 – 537
17 *Rabinovitch PS, Longton G, Blount PL et al.* Predictors of progression in Barrett's esophagus III: baseline flow cytometric variables. Am J Gastroenterol 2001; 96: 3071 – 3083
18 *Reid BJ, Levine DS, Longton G et al.* Predictors of progression to cancer in Barrett's esophagus: baseline histology and flow cytometry identify low- and high-risk patient subsets. Am J Gastroenterol 2000; 95: 1669 – 1676
19 *Wijnhoven BP, Hussey DJ, Watson DI et al.* MicroRNA profiling of Barrett's oesophagus and oesophageal adenocarcinoma. Br J Surg 2010; 97: 853 – 861
20 *Huang Q, Hardie LJ.* Biomarkers in Barrett's oesophagus. Biochem Soc Trans 2010; 38: 343 – 347
21 *Wani S, Puli SR, Shaheen NJ et al.* Esophageal adenocarcinoma in Barrett's esophagus after endoscopic ablative therapy: a meta-analysis and systematic review. Am J Gastroenterol 2009; 104: 502 – 513
22 *Sharma P, Falk GW, Weston AP et al.* Dysplasia and cancer in a large multicenter cohort of patients with Barrett's esophagus. Clin Gastroenterol Hepatol 2006; 4: 566 – 572
23 *Shaheen NJ, Crosby MA, Bozymski EM, Sandler RS.* Is there publication bias in the reporting of cancer risk in Barrett's esophagus? Gastroenterology 2000; 119: 333 – 338
24 *Anderson LA, Murray LJ, Murphy SJ et al.* Mortality in Barrett's oesophagus: results from a population based study. Gut 2003; 52: 1081 – 1084
25 *Sharma VK, Wang KK, Overholt BF et al.* Balloon-based, circumferential, endoscopic radiofrequency ablation of Barrett's esophagus: 1-year follow-up of 100 patients. Gastrointest Endosc 2007; 65: 185 – 195
26 *Shaheen NJ, Sharma P, Overholt BF et al.* Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 2009; 360: 2277 – 2288
27 *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: 23 – 29
28 *Lyday WD, Corbett FS, Kuperman DA et al.* Radiofrequency ablation of Barrett's esophagus: outcomes of 429 patients from a multicenter community practice registry. Endoscopy 2010; 42: 272 – 278
29 *dos Santos RS, Bizekis C, Ebright M et al.* Radiofrequency ablation for Barrett's esophagus and low-grade dysplasia in combination with an antireflux procedure: a new paradigm. J Thorac Cardiovasc Surg 2010; 139: 713 – 716
30 *Velanovich V.* Endoscopic endoluminal radiofrequency ablation of Barrett's esophagus: initial results and lessons learned. Surg Endosc 2009; 23: 2175 – 2180
31 *Sharma VK, Kim HJ, Das A et al.* Circumferential and focal ablation of Barrett's esophagus containing dysplasia. Am J Gastroenterol 2009; 104: 310 – 317
32 *Eldaif SM, Lin E, Singh KA et al.* Radiofrequency ablation of Barrett's esophagus: short-term results. Ann Thorac Surg 2009; 87: 405 – 410
33 *Pouw RE, Gondrie JJ, Sondermeijer CM et al.* Eradication of Barrett esophagus with early neoplasia by radiofrequency ablation, with or without endoscopic resection. J Gastrointest Surg 2008; 12: 1627 – 1636
34 *Ganz RA, Overholt BF, Sharma VK et al.* Circumferential ablation of Barrett's esophagus that contains high-grade dysplasia: a U.S. multicenter registry. Gastrointest Endosc 2008; 68: 35 – 40
35 *Gondrie JJ, Pouw RE, Sondermeijer CM et al.* Stepwise circumferential and focal ablation of Barrett's esophagus with high-grade dysplasia: results of the first prospective series of 11 patients. Endoscopy 2008; 40: 359 – 369
36 *Gondrie JJ, Pouw RE, Sondermeijer CM et al.* Effective treatment of early Barrett's neoplasia with stepwise circumferential and focal ablation using the HALO system. Endoscopy 2008; 40: 370 – 379
37 *Sharma VK, Kim HJ, Das A et al.* A prospective pilot trial of ablation of Barrett's esophagus with low-grade dysplasia using stepwise circumferential and focal ablation (HALO system). Endoscopy 2008; 40: 380 – 387
38 *Hernandez JC, Reicher S, Chung D et al.* Pilot series of radiofrequency ablation of Barrett's esophagus with or without neoplasia. Endoscopy 2008; 40: 388 – 392
39 *Roorda AK, Marcus SN, Triadafilopoulos G.* Early experience with radiofrequency energy ablation for Barrett's esophagus with and without dysplasia. Dis Esophagus 2007; 20: 516 – 522
40 *Hubbard N, Velanovich V.* Endoscopic endolumenal radiofrequency ablation of Barrett's esophagus in patients with fundoplication. Surg Endosc 2007; 21: 625 – 628
41 *Wani S, Sayana H, Sharma P.* Endoscopic eradication of Barrett's esophagus. Gastrointest Endosc 2010; 71: 147 – 166
42 *Basu KK, Pick B, Bale R et al.* 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: 776 – 780
43 *Sharma P, Bhattacharyya A, Garewal HS et al.* Durability of new squamous epithelium after endoscopic reversal of Barrett's esophagus. Gastrointest Endosc 1999; 50: 159 – 164
44 *Overholt BF, Wang KK, Burdick JS et al.* Five-year safety and efficacy of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia. Gastrointest Endosc 2007; 66: 460 – 468
45 *Inadomi JM, Somsouk M, Madanick RD et al.* A cost-utility analysis of ablative therapy for Barrett's esophagus. Gastroenterology 2009; 136: 2101 – 2114
46 *Das A, Wells C, Kim HJ et al.* An economic analysis of endoscopic ablative therapy for management of nondysplastic Barrett's esophagus. Endoscopy 2009; 41: 400 – 408
47 *Ban S, Mino M, Nishioka NS et al.* Histopathologic aspects of photodynamic therapy for dysplasia and early adenocarcinoma arising in Barrett's esophagus. Am J Surg Pathol 2004; 28: 1466 – 1473
48 *Sharma P, Morales TG, Bhattacharyya A et al.* Squamous islands in Barrett's esophagus: what lies underneath? Am J Gastroenterol 1998; 93: 332 – 335
49 *Shaheen NJ, Goldblum JR, Sampliner RE et al.* Are biopsies after ablation for dysplastic Barrett's esophagus of adequate depth to detect glandular mucosa beneath the neosquamous epithelium? Comparative histopathological outcomes from a randomized, sham-controlled trial (AIM Dysplasia Trial). Gastroenterology 2008; 134: A – 724