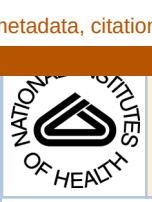

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Durability of Radiofrequency Ablation in Barrett's Esophagus with Dysplasia

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Disclosure

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Abstract

Background & Aims—Radiofrequency ablation (RFA) can eradicate dysplasia and intestinal metaplasia in patients with dysplastic Barrett's esophagus (BE), and reduce rates of esophageal adenocarcinoma. We assessed long-term rates of eradication, durability of neosquamous epithelium, disease progression, and safety of RFA in patients with dysplastic BE.

Methods—We performed a randomized trial of 127 subjects with dysplastic BE; after cross-over subjects were included 119 received RFA. Subjects were followed for a mean time of 3.05 years; the study was extended to 5 years for patients with eradication of intestinal metaplasia at 2 years. Outcomes included eradication of dysplasia or intestinal metaplasia after 2 and 3 years, durability of response, disease progression, and adverse events.

Results—After 2 years, 101/106 patients had complete eradication of all dysplasia (95%) and 99/106 had eradication of intestinal metaplasia (93%). After 2 years, among subjects with initial low-grade dysplasia, all dysplasia was eradicated in 51/52 (98%) and intestinal metaplasia was eradicated in 51/52 (98%); among subjects with initial high-grade dysplasia, all dysplasia was eradicated in 50/54 (93%) and intestinal metaplasia was eradicated in 48/54 (89%). After 3 years, dysplasia was eradicated in 55/56 of subjects (98%) and intestinal metaplasia was eradicated in 51/56 (91%). Kaplan-Meier analysis showed that dysplasia remained eradicated in >85% of patients and intestinal metaplasia in >75%, without maintenance RFA. Serious adverse events occurred in 4/119 subjects (3.4%); the rate of stricture was 7.6%. The rate of esophageal adenocarcinoma was 1/181 pt-yrs (0.55%/pt-yr); there was no cancer-related morbidity or mortality. The annual rate of any neoplastic progression was 1/73 pt-yrs (1.37%/pt-yr).

Conclusion—In subjects with dysplastic BE, RFA therapy has an acceptable safety profile, is durable, and is associated with a low rate of disease progression, for up to 3 years.

Keywords

esophagus; cancer; prevention; endoscopic therapy

Several treatment options are available for the care of subjects with dysplastic Barrett's esophagus (BE), including intensive endoscopic surveillance, esophagectomy, endoscopic mucosal resection (EMR), and endoscopic ablative therapy.[1] The choice between these modalities is made with consideration of the severity of dysplasia (low-grade dysplasia (LGD) vs. high-grade dysplasia (HGD)), the patient co-morbidities, the available physician

expertise in providing the treatments, and other factors.[2, 3] A paucity of literature guides the choice in selection of the most effective therapy for dysplastic BE.

Recently, several groups have reported their experience with endoscopic ablative therapy using radiofrequency ablation (RFA) for dysplastic BE.[4–7] These reports generally demonstrate high rates of complete eradication of dysplasia (CE-D) and intestinal metaplasia (CE-IM) and reduction in neoplastic progression, with few serious adverse events. Despite these promising outcomes, the longer term durability of these mucosal changes is less well-understood, and most of these studies are either cross-sectional or have relatively short periods of follow-up.

The AIM Dysplasia trial is a multi-center, randomized, sham-controlled trial comparing RFA plus endoscopic surveillance to endoscopic surveillance alone for the treatment of dysplastic BE. The 1 year outcomes of this trial demonstrated CE-D in 85.7% by intention-to-treat analysis (92.3% per protocol), CE-IM in 77.4% of subjects by intention-to-treat analysis (83.3% per protocol), and decreased rates of disease progression and cancer incidence in the treated groups.[7] Subjects initially randomized to the sham group were offered cross-over to active treatment (RFA) after 1 year. All subjects were followed for 2 years after initial RFA. Subjects who achieved CE-IM at 2-year follow-up (or who were salvaged with a single additional RFA treatment after failing to achieve CE-IM at 2 years) were eligible to enter a trial extension, an additional 3 year period of enrollment and endoscopic observation with biopsy to assess the durability of the neosquamous epithelium after RFA and longer term outcomes such as neoplastic progression. The current report describes the two- and three-year outcomes of the trial.

Methods

Study Design

Participants were recruited at 19 U.S. sites. Subjects were aged 18–80, and had endoscopically evident, non-nodular, dysplastic BE ≤8 cm in length confirmed by a central pathology laboratory. For subjects with HGD, we additionally required an endoscopic ultrasound negative for lymphadenopathy or esophageal wall abnormalities within 12 months of enrollment. Previous EMR was permissible ≥8 weeks prior to entry, provided that subsequent endoscopy demonstrated non-nodular dysplasia. Exclusion criteria included pregnancy, active esophagitis or stricture, history of esophageal malignancy, varices, uncontrolled coagulopathy, or life expectancy of <2 years, as judged by the investigator. Subjects' cancer risk and conventional treatment options (including esophagectomy in subjects with HGD) were reviewed with all participants, and subjects provided written informed consent. Further details of patient selection have been published previously.[7]

Subjects were randomly assigned in a 2:1 ratio to receive either RFA or a sham endoscopic procedure (SHAM). Randomization was stratified by grade of dysplasia (LGD vs. HGD) at study entry and endoscopic length of BE (<4 cm vs. 4–8 cm). All underwent upper endoscopy, esophageal intubation with a study catheter, measurement of the esophageal inner diameter,[8] and in-room assignment of treatment group (RFA vs. SHAM) using a computer-generated block randomization sequence. In subjects assigned to RFA, the entire BE segment was ablated circumferentially. In SHAM, the study catheter was removed and procedure terminated.

RFA subjects could receive up to four RFA sessions in the first year, performed at 0, 2, 4, and 9 months and based on interval biopsy results, and one RFA session in the second year (15 months). The month 15 treatment was mandatory for patients who failed to achieve CE-IM at 1 year, but could also be optionally delivered based on endoscopist preference (for

instance, mild irregularity of the Z line), and was not driven by histologic biopsy results from previous sessions.

The treatment protocol has been described previously.[7] An initial treatment was performed with a HALO^{360} device, the circumferential balloon catheter, with settings of 12 J/cm^2 and 300 Watts (BÂRRX Medical, Inc., Sunnyvale, CA, USA). Any necessary follow-up treatments of residual BE were performed with a HALO^{90} device, an electrode array mounted on an articulated platform, affixed to the tip of the endoscope. Subjects underwent endoscopy with biopsy at 6 and 12 months (LGD arm), or 3, 6, 9 and 12 months (HGD arm). Endoscopic biopsies were performed with maximum-capacity or jumbo forceps in 4 quadrants every 1 cm throughout the original length of BE, with the most distal biopsies 3–5 mm above the gastric folds, plus directed biopsies of any visible abnormalities. After completion of the 12 month assessment, subjects in the sham arm were offered cross-over to active (RFA) treatment. All subjects were followed for 2 years after initial RFA therapy, with endoscopy and biopsy intervals as above, based on study entry pathology. Because subjects initially assigned to SHAM spent 12 months without ablative therapy, the earliest time 0 endoscopy in the SHAM group occurred after the patient had been in the study for at least 13 months.

Subjects demonstrating CE-IM at 2 years were eligible for participation in a 3 year study extension. The purpose of this extension was to assess the longterm durability of changes induced by RFA, and outcomes associated with treatment. Subjects who did not achieve CE-IM at 2 years were offered a single salvage RFA treatment at that time with repeat biopsy 2 months later. Those with CE-IM at repeat biopsy were then eligible for the study extension. The study extension provided for three additional years of follow-up for these subjects (to a total of 5 years), with annual surveillance endoscopies with biopsies identical in methodology to the primary protocol. All subjects in the trial extension were maintained on esomeprazole 40 mg twice daily.

The protocols for both the parent trial and the extension were approved by all institutions' ethics committees, and the trial was performed in accordance with the Declaration of Helsinki. An independent data and safety monitoring committee monitored the trial. Data were collected by the academic sites, and the database managed by the sponsor. The database was transferred to the authors and the independent study statistician (JAG) for analysis. Analysis was performed by the statistician and the primary author, who vouch for the data and the analysis. The first draft of the manuscript was written by the primary author, who subsequently incorporated edits from the other authors.

Outcomes

The outcomes assessed included treatment success, defined as the proportion of subjects who demonstrated CE-D and CE-IM (separately reported). Because ablative therapy might be used as either a chronic suppressive therapy for dysplastic BE, allowing for recurrent "touch-up" therapy of any recurrent BE, or as a single series of applications with no further maintenance therapy after achieving CE, we calculated treatment success in two ways:

1. Proportion of subjects demonstrating CE-D and CE-IM at the 2 and 3 year biopsy sessions, allowing interim focal touch-up RFA treatment as indicated for histological evidence of interval recurrence. In this analysis, time 0 is considered the first RFA treatment, and all enrolled subjects are included, and,
2. Proportion of subjects attaining, then maintaining CE-D and CE-IM, where any recurrent dysplasia or IM, respectively, after initial CE at 1 year or later was considered a failure of therapy for that outcome, even if the subject could again attain CE-D or CE-IM with an additional focal RFA treatment. In this durability

analysis, time 0 is considered the first histological analysis at 12 months or greater demonstrating CE-D or CE-IM (ie, the start of the intervention-free period), and only subjects attaining one or both of these endpoints (n=110 for CE-D, n=108 for CE-IM) appear in the survival analyses.

We also assessed disease progression, defined as any patient with LGD histology at study entry demonstrating HGD or EAC at any follow-up, or any patient with HGD histology at study entry demonstrating EAC at any follow-up. Additionally, we assessed the rate of serious adverse events, defined as any untoward medical event that resulted in death, was life-threatening, required hospitalization or prolongation of ongoing hospitalization, or resulted in persistent/significant incapacity. Stricture rate, defined as an endoscopically-identified narrowing of the esophageal lumen, with or without accompanying dysphagia, was calculated on a per-patient and per-procedure basis.

Histological Analysis

The histological analysis of subjects on study entry has been previously described.[7] Esophageal biopsy specimens for eligible subjects having a home institution diagnosis of dysplastic BE underwent review by the expert central pathology laboratory. If the grade of dysplasia reading for the specimens between home institution and central laboratory were concordant, the subject was eligible and assigned an entry grade of dysplasia (LGD or HGD). If discordant, a second masked review was performed by the central laboratory, with assignment by concordance.

At follow-up endoscopic biopsy sessions, tissue biopsies were fixed in formalin and sent to the central pathology laboratory for standardized processing, and interpreted by the central laboratory expert pathologists using standardized criteria.[9] Each biopsy specimen was assessed for tissue type and subsquamous IM, defined as IM beneath a layer of squamous epithelium. Each biopsy containing IM was assessed for the worst histological grade. Any biopsy containing dysplasia on first reading underwent a confirmatory masked review by a second pathologist, and, in cases of disagreement, a third review with assignment by concordance. The worst histological grade present was the overall histological grade for that session.

Statistical Analysis

Power calculations have been previously described relating to the study's primary 1-year endpoints. Two methods were used to calculate the proportion of RFA subjects with CE-D and CE-IM. To assess the proportion of subjects free of disease at a given time point, and allowing interim touch-up therapy with RFA, the number of subjects with CE-D and CE-IM was divided by the total number of RFA subjects reaching the time point. To assess the durability of CE-D and CE-IM and considering any interim treatment after achieving complete eradication as a failure for the outcome, survival analysis using Kaplan-Meier estimation was performed. To compare demographic and disease-specific features of those attaining CE-D and CE-IM to those who did not, Fisher's exact test was used for categorical data and Student's t test was used for continuous data. Logistic regression was used to control for potential confounders and assess for predictors of response to therapy. For all outcomes, a two-sided p value <0.05 was considered statistically significant. All analyses were performed using SAS software, version 9 (SAS Institute, Cary, NC).

Results

Enrollment and Characteristics of Subjects Undergoing Treatment

Of 755 subjects screened, 127 (64 LGD, 63 HGD) were randomized (84 RFA, 43 SHAM) and 117 (78 RFA, 39 SHAM) completed 1-year follow-up, as reported previously.[7] After reaching the 1 year primary endpoint, 35 of 39 subjects from SHAM were eligible for cross-over to RFA treatment and all elected to receive treatment. The remaining 4 of 39 developed EAC prior to the 1 year primary outcome and were not eligible for cross-over. In all, 119 subjects underwent RFA in this trial (84 RFA at study outset plus 35 SHAM crossed over to RFA after 1 year), representing the safety and efficacy cohort for this report (58 LGD, 61 HGD) (table 1). All available subjects (n=106) have now reached the 2 year follow-up mark (52 LGD, 54 HGD). Thirteen of the 119 subjects have left the cohort before the year 2 time point, for reasons including: patient/physician preference (n=5); unrelated, life-limiting, co-morbid conditions (n=3); patient relocation/unreachable (n=3); and death from an unrelated cause (n=2; ocular melanoma and gunshot wound). Six of the remaining 106 subjects were ineligible for the study extension, due to lack of CE-IM at the year 2 time-point. Of the 100 subjects eligible for the study extension, to date, 56 subjects have completed year 3 follow-up (32 LGD and 24 HGD), with the remainder not yet completing the year 3 time-point. The mean period of follow-up from first RFA treatment in the cohort is 3.05 years (standard deviation 1.08 years), and the median is 3.34 years (interquartile range, 2.35 years to 3.88 years). Figure 1 details the flow and accountability of all subjects through the study.

Durability of Neosquamous Epithelium

At 2-year follow-up, in the overall cohort, 101/106 (95%) of subjects had CE-D and 99/106 (93%) had CE-IM. Outcomes according to study entry grade show that CE-D and CE-IM were achieved in 51/52 (98%) and 51/52 (98%) of LGD subjects, and 50/54 (93%) and 48/54 (89%) of HGD subjects, respectively (table 2). Focal RFA was used in 65 of 119 (55%) subjects after the 1 year primary endpoint, but only 25 of 65 treatments (38%) were indicated based on prior biopsy results while 40 of 65 (62%) were performed at the endoscopist's discretion as described previously (month 15, non-histology-based endoscopy session). Although subjects withdrew consent for continued participation for a variety of reasons as noted above, in the most stringent analysis, if we include any subject who ever received any RFA and left the trial before the 2 year endpoint as a failure (n=13), the response rates were 101/119 (85%) CE-D and 99/119 (83%) CE-IM. At 3-year follow-up, 55/56 (98%) of available subjects had CE-D and 51/56 (91%) of available subjects had CE-IM.

For subjects attaining CE-D or CE-IM at 1 year or later, an analysis of durability was performed using Kaplan-Meier estimation as noted above. Figure 2 demonstrates the durability of CE-D in the 110/119 subjects who attained CE-D at or after the 12 month endpoint, considering any recurrent dysplasia as a failure even if subsequent RFA resulted in reestablishment of CE-D. Greater than 85% of HGD patients and 90% of LGD patients remained free of dysplasia at a mean follow-up of greater than 3 years with no additional therapy. Figure 3 demonstrates the durability of CE-IM in the 108/119 subjects who attained CE-IM at or after the 12 month endpoint, again considering any recurrent IM as a failure even if subsequent RFA resulted in reestablishment of CE-IM. Greater than 75% of HGD patients and LGD patients remained free of IM, again with follow-up of greater than 3 years, with no additional therapy.

Among subjects who attained CE-IM, but then experienced recurrence of IM at or after the 1 year follow-up (n=14), the surface area of recurrence was minimal. In 7 of 14 subjects, recurrent IM was detected in subjects felt to have an endoscopically "normal appearing z-

line" (n=4) or an "irregular z-line" (n=3). In the remaining 7 subjects, 3 were noted endoscopically to have an isolated island of BE ≤2 cm in diameter, and 4 had a tongue of BE ≤2 cm. Within subjects with recurrence of IM, a mean of 37.2 biopsy specimens were obtained per patient during the endoscopy session at which recurrent BE was noted. Of these 37.2 biopsies per patient, 1.4 biopsies (3.8%) per patient demonstrated IM, with the remainder demonstrating normal tissue. In 11 of these 14 subjects, the grade of dysplasia at the time of recurrence was at or below study entry grade. Of the 14 subjects with histological recurrence of BE after RFA, 4 subjects (28.5%) demonstrated sub-squamous intestinal metaplasia (SSIM) equating to a total year 2 SSIM prevalence of 4/106 (3.8%) in the cohort, compared to the baseline prevalence of SSIM at study entry (pre-RFA) of 25.2%. Two of the 4 subjects with SSIM had this finding only in biopsies taken from the top of the gastric folds, and, in the other 2, one biopsy each, from 2 and 6 cm above the top of the gastric folds, respectively, demonstrated SSIM. In 2 of the 4 subjects with SSIM, the endoscopic appearance was normal. The remaining two subjects with SSIM were noted endoscopically to have a 5 mm tongue of BE and an irregular Z line, respectively. With further RFA therapy, 8 of the 14 patients with recurrent IM re-attained CE-IM, with none requiring more than a single additional treatment to re-attain CE-IM. In 5/14 cases, the physician or patient elected to have no further RFA treatment, and in a single case, the treatment was ongoing at the time of this analysis.

Disease Progression

Five of 119 subjects (4.2%) who received any RFA as part of this trial have experienced disease progression, as defined above. In an overall observation period of 363 years, this corresponds to an annual rate of overall disease progression of 1/73 patient-years, or 1.37% per patient per year, and an annual rate of progression to EAC of 1/181 patient-years, or 0.55% per patient per year. Stratified by baseline histology at study entry, for subjects enrolled with LGD, the annual rate of overall disease progression was 1/49 patient-years, or 2.04% per patient per year, and the annual rate of progression to EAC was 1/197 patient-years, or 0.51% per patient per year. Among subjects enrolled with HGD, the annual rate of overall disease progression was 1/166 patient-years, or 0.60% per patient per year, and the annual rate of progression to EAC was 1/166 patient-years, or 0.60% per patient per year. Because we allowed cross-over to active treatment at 1 year, a comparator group to RFA is no longer available. However, the annual progression rate in the SHAM cohort for this study was 16.3%.

Three subjects had progression from LGD to HGD, one from HGD to EAC, and one from LGD to EAC. For the 3 subjects that progressed from LGD to HGD, all were originally randomized to RFA. Two remained in the study after detection of HGD and continued to receive RFA. One achieved CE-D and CE-IM at 2 and 3 years while the other achieved CE-D and CE-IM at 2 years, then withdrew consent. The third of these subjects had EMR of the focal HGD and elected not to continue in the study. The 1 subject who progressed from HGD to EAC has been previously described,[7] and was originally randomized to RFA. In this subject, focal intramucosal EAC was noted in a small nodule 3 months after primary RFA, focal EMR was used to remove the nodule, and the subject then underwent subsequent RFA. This subject was CE-D at 1 year, then CE-D and CE-IM at 2 and 3 years. The 1 subject who progressed from LGD to EAC was initially assigned to SHAM and completed 12 month follow-up with evidence of persistent multi-focal LGD. The subject crossed over to active therapy, was treated with 3 sessions of RFA (one circumferential, and 2 focal), demonstrated CE-IM at 12 months, but 6 months later was noted to have intramucosal EAC located 1 cm proximal to the top of the gastric folds, which was treated curatively with EMR. No disease progression-related morbidity or mortality has occurred in the study.

Safety and Tolerability

To date, four serious adverse events have occurred in the 119 subjects (3.4%), designated by the investigator as possibly or probably associated with the study procedure. The events included: one upper GI hemorrhage in a subject that was receiving dual anti-platelet therapy with aspirin and clopidogrel for heart disease, and whose bleeding was treated endoscopically; one overnight hospitalization for new-onset chest pain 8 days after primary RFA; and two overnight hospitalizations for chest discomfort and nausea immediately following RFA. No perforations or procedure-related deaths occurred. Among the 119 subjects receiving any RFA, 9 developed esophageal stricturing (7.6% of subjects, 1.8% of procedures), defined as endoscopically-identified narrowing with or without dysphagia. All were successfully dilated to endoscopic resolution (mean 2.8 sessions).

Predictors of Response to Therapy

We assessed age, race, sex, BMI, initial degree of dysplasia, previous EMR, ASA/NSAID use, hiatal hernia size, BE length and duration of BE diagnosis as predictors of incomplete eradication of IM at the 2 year time-point. While subjects attaining CE-IM were, on average, younger, more likely to be ASA/NSAID users, and more likely to have LGD than HGD, none of these predictors was statistically significant in either bivariate analysis or logistical regression (full models not shown).

Discussion

Endoscopic therapy of dysplastic Barrett's esophagus with RFA has demonstrated a high rate of CE-D and CE-IM, with an acceptable side effect profile.[4, 7] The most important remaining issues in this field are the durability of the treatment effect and the longer term outcomes of therapy. Since durability of treatment effect is a determinant of the cost-effectiveness of the procedure,[10] and because subjects with recurrent BE after RFA are presumably at continued risk for developing EAC, it is vital to know whether the neosquamous epithelium present after RFA is durable.

Our study demonstrates that the majority of subjects treated with RFA demonstrate CE-D and CE-IM at 2 and 3 year follow-up. In subjects who achieved CE-IM in this study and then subsequently demonstrated recurrent disease, the amount of recurrent disease always involved a minute proportion of the original BE surface area and the grade of recurrent disease was at or below study entry grade in most patients. Half of recurrences (7/14) occurred in subjects felt endoscopically to have either a normal or irregular Z line (without tongues >5 mm in length). Whether some or all of these recurrences might have been averted by mandating routine circumferential treatment of the Z line in the absence of endoscopic evidence of BE is unknown.

Five of the 119 subjects (4.2%) who received RFA therapy as part of this trial did demonstrate disease progression, representing an annual rate of progression of 1 case per 73 patient years (1.37%). While this annual rate is sizably lower than the 1-year progression rate in the SHAM group (1 case per 6 patient years, 16.3%), it points out the need for meticulous endoscopic monitoring of this high-risk population. Given the low number of progressors in this trial, the progression rates we report must be viewed as imprecise. Therefore, we are unable to comment on whether successful ablation (CE-IM after RFA) might allow a lengthening of the currently recommended surveillance intervals for dysplastic BE. However, if larger studies confirm the low rate of progression of treated subjects demonstrated here, our current endoscopic surveillance protocols may be unnecessarily aggressive for a successfully treated patient.

The present study reports the longest duration of follow-up of subjects undergoing RFA for dysplastic BE. Because subjects with dysplastic BE are at highest risk for progression to cancer, such data are essential to understand the value of ablative therapy in the setting of BE. Other strengths of our study include compulsive and complete accounting for all subjects, expert histological analysis of biopsy samples by a central laboratory, *a priori* protocols for endoscopic treatment, and standardized biopsy procedures with a large number of samples taken. Limitations include the potential for underestimation of residual or recurrent disease due to SSIM. Random biopsies may miss small areas of SSIM, or biopsies may not sample deeply enough to detect residual columnar tissue. Another potential effect of sampling error in this study is that some subjects designated as recurrent BE may have instead had incomplete initial eradication, with false negative histology documenting disease eradication. In such subjects, the apparent recurrent IM would rather truly be failure of the initial therapy. Also, we reported 2 year outcomes based on the 106 of 119 patients that were available for endoscopic biopsy, which could artificially elevate the rate of CE-D and CE-IM if subjects withdrawing consent were more likely to have failed therapy. Therefore, we have additionally reported the most conservative possible response rates considering these 13 patients lost to follow-up patients as failures in the 2 year outcomes, and response rates remained acceptable [101/119 (85%) CE-D and 99/119 (83%) CE-IM]. Also, we allowed subjects into the extension phase of the study only if CE-IM was attained at 2-year follow-up or if a single session of salvage therapy with RFA after a 2-year failure achieved CE-IM. While we felt it was not ethical to continue study participation in subjects who had not responded to therapy by that time, this decision has the effect of artificially elevating our 3 year response rates as calculated by simple proportions, since 2-year failures are no longer in the cohort. The Kaplan-Meier curve is, however, unaffected by this potential bias, since any subject that did not qualify for the study extension would have reached the censoring event for that analysis (and been considered a failure in the survival analysis). Another limitation is that the study sites for this trial are experienced in the care of subjects with dysplastic BE, following rigorous, *a priori* study protocols. Whether these results can be generalized to community practice settings is unknown. Lastly, because we allowed crossover from the sham arm to RFA, we no longer have a comparison group. While such a group would be beneficial, the ethical issues involved in retaining a sham arm long-term given the risk for disease progression were untenable.

These data add to a small, but growing, body of literature reporting the longterm outcomes and durability of the reversion to squamous epithelium induced after RFA therapy. Fleischer et al recently reported the five year results of their trial for subjects with non-dysplastic BE.[11] After primary circumferential RFA followed by touch-up focal RFA, this study demonstrated CE-IM in 98% of evaluable patients at 2.5 year follow-up. In an extension of their trial that did not allow for interval touch-up therapy after 2.5 years, 92% of evaluable patients remained CE-IM at 5-year follow-up, suggesting that the reversion to neosquamous epithelium after RFA is durable in non-dysplastic BE. In the 4 subjects who demonstrated recurrent BE at 5 years, the magnitude of recurrence was minimal and a single additional RFA resulted in subsequent CE-IM.

Pouw et al. reported 44 patients with BE containing HGD and or early cancer using EMR as a diagnostic staging tool at baseline in most, followed by step-wise RFA. After a median of 21 months follow-up (IQR 10–27), CE-D and CE-IM were achieved in 43 of 44 patients (98%) with no cases of recurrence after CE.[12] In a retrospective study, Ganz and colleagues reported on 92 subjects with BE and HGD undergoing RFA. At an average 12 months follow-up, CE-D and CE-IM were achieved in 80% and 54%, respectively. Most patients in this trial had a single circumferential ablation and no patient had focal ablation due to its lack of availability.[13] Lyday et al reported their experience with 429 subjects undergoing RFA for BE in community practices. Of the 27 subjects in this group with dysplasia who

were treated and followed for at least one year, all 27 were CE-D at a mean follow-up of 20 months, and 77% were CE-IM.[4] In a multi-center prospective trial, Pouw et al. applied RFA for patients with BE containing HGD and/or early cancer. At 22 months median follow-up in 23 patients, CE-D and CE-IM were achieved at 95% and 88% of patients, respectively. A single salvage EMR in 2 patients elevated the responses rates to 100% CE-D and 96% CE-IM. Once CE-IM was achieved, no patients demonstrated recurrence.[14] Sharma, et al. treated patients with LGD (n=10) with RFA.[15] At 2-year follow-up, CR-D and CE-IM were 100% and 90%, respectively. In a larger trial, Sharma et al. evaluated RFA in 63 patients with dysplastic BE (39 LGD, 24 HGD). At a median follow-up of 2 years, CE-D and CE-IM were achieved in 95% and 87% of LGD patients and 79% and 67% of HGD patients, respectively. No patient demonstrated neoplastic progression, stricture, or buried glands.[16] In a randomized controlled trial, Van Vilsteren, et al. compared RFA to EMR in patients with up to 5 cm of BE containing HGD and or early cancer. At 24 months follow-up, similar outcomes for CE were seen in each group: 100% CE-D and 92% CE-IM in the EMR group, and 96% CE-D and 96% CE-IM in the RFA group. The stenosis rate in the EMR group was significantly higher than that of the RFA group (88% vs. 14%, $p<0.001$), and there was one perforation in the EMR group.[17]

In general, the above studies are in concordance with the present data, reporting high rates of CE-D and CE-IM at 1 and 2 years. The remaining variability in outcomes data in these studies may in part reflect the diverse patient populations in the studies, and the way that treatment failure was defined, as well as the relatively recent availability of a focal ablation device for treating the small area of residual BE after primary therapy or in cases of recurrence. Predictors of response to therapy would allow better patient selection. While our study did not demonstrate significant predictors at the 2 year time-point, it was not powered to do so, and larger studies will be necessary to define these variables.

All of the subjects in the present study have been maintained on high-dose proton pump inhibitor therapy with esomeprazole at 40 mg twice daily for the duration of the trial. While this therapy is generally well-tolerated, the optimal medical regimen longterm for the subject after successful ablative therapy is not known. While multiple observational studies suggest that longterm maintenance therapy with high-dose proton pump inhibitor may expose the subject to some increased risk of hip fracture,[18, 19] pneumonia[20, 21] or enteric infection,[22, 23] a substantial proportion of subjects with BE will not normalize esophageal acid exposures on once daily proton pump inhibitor therapy,[24, 25] and the threat of recurrent neoplasia in this high-risk group may warrant the higher doses of acid suppression. Further investigation will be necessary to better understand optimal maintenance therapy of this population.

In conclusion, follow-up of the subjects from the AIM Dysplasia trial to an average of 3.05 years demonstrates that a high percentage of subjects with both low-grade and high-grade dysplasia retain complete eradication of dysplasia and intestinal metaplasia after treatment. Most subjects with recurrence of disease could again attain complete eradication of intestinal metaplasia with further treatment. Progression of disease was rare in subjects who underwent RFA treatment, and the rate of progression to EAC in this dysplastic cohort was 0.55%. There was no procedure- or cancer-related mortality. The main adverse side effect was stricture occurrence, which occurred in 7.6% of subjects and was correctable with dilation. Further systematic, prospective follow-up of this cohort will allow additional assessment of long term outcomes of ablative therapy in dysplastic BE.

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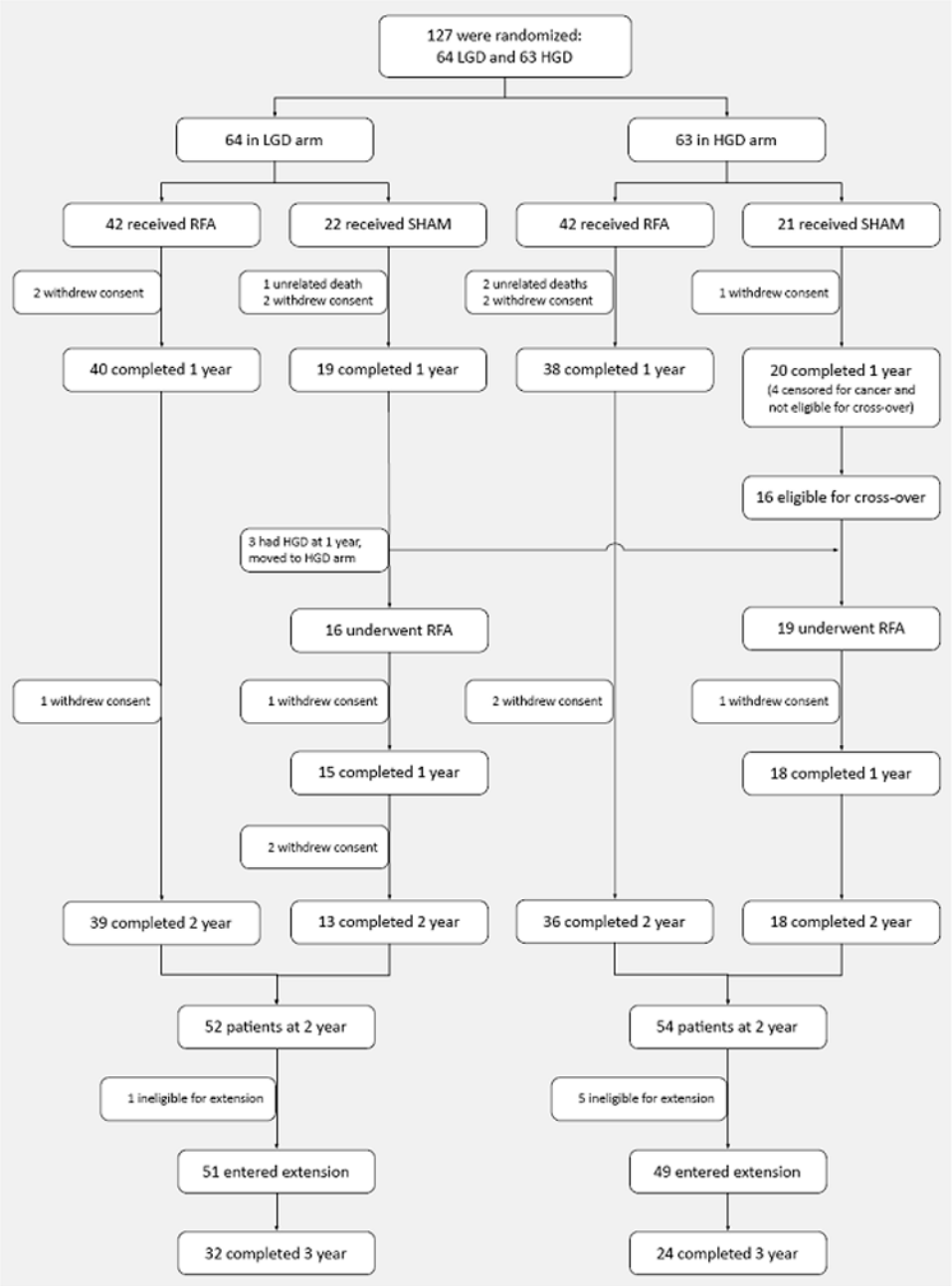

Figure 1.
Flow Diagram of Subjects progressing through the trial. Cross-over to active therapy is represented by the arrows leading from the sham arm to active treatment.

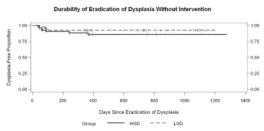

Figure 2.

Kaplan-Meier analysis of the durability of complete eradication of dysplasia. All subjects in this analysis achieved complete eradication of dysplasia at or after the 12 month endpoint (n=110), and time 0 for this analysis is the first finding of complete eradication of dysplasia at or after month 12. For purposes of this analysis, any recurrent dysplasia noted after initially achieving CE-D was considered a failure, even if such recurrence was followed by focal RFA and reestablishment of CE-D. HGD, High-grade dysplasia; LGD, Low-grade dysplasia.

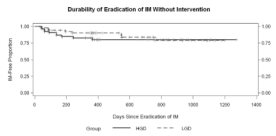

Figure 3.

Kaplan-Meier analysis of the durability of complete eradication of intestinal metaplasia. All subjects in this analysis achieved complete eradication of dysplasia at or after the 12 month endpoint (n=108), and time 0 for this analysis is the first finding of complete eradication of intestinal metaplasia at or after month 12. For purposes of this analysis, any recurrent intestinal metaplasia noted after initially achieving CE-IM was considered a failure, even if such recurrence was followed by focal RFA and reestablishment of CE-IM. HGD, High-grade dysplasia; LGD, Low-grade dysplasia; IM, intestinal metaplasia.

Table 1

Baseline Characteristics of Treated Patients

	LGD (n=58)	HGD (n=61)
Age – mean ± SD	65.5 ± 9.1	66.4 ± 8.8
Male – no. (%)	47 (81)	55 (90)
BMI – mean ± SD	29.9± 5.7	28.6 ± 4.9
AA/W/Latino (%)	1/56/1	2/57/2
Multifocal dysplasia no. (%)	40 (69)	50 (82)
Length of BE cm – Mean ± SD	4.5 ± 2.3	5.2 ± 2.1
Hiatal Hernia – no. (%)	51 (88)	58 (95)
Previous EMR – no. (%)	5 (9)	5 (8)
Years with BE – mean ± SD	5.8 ± 4.6	5.1 ± 5.1

Abbreviations: BE, Barrett's esophagus; HGD, high-grade dysplasia, LGD, low-grade dysplasia; BMI, body mass index; AA, African-American; W, White; EMR, endoscopic mucosal resection.

Table 2

Two- and Three-Year Outcomes of the AIM Dysplasia Trial.

	CE-IM (Entire Cohort) n (%)	CE-D (HGD Cohort) n (%)	CE-D (LGD Cohort) n (%)
Year 2	99/106 (93)	50/54 (95)	51/52 (98)
Year 3	51/56 (91)	23/24 (96)	32/32 (100)

CE-IM and CE-D, allowing for interim focal touch-up RFA.

CE-IM, complete eradication of intestinal metaplasia; CE-D, complete eradication of dysplasia; HGD, high-grade dysplasia; LGD, low-grade dysplasia