

## Original Investigation

# Radiofrequency Ablation vs Endoscopic Surveillance for Patients With Barrett Esophagus and Low-Grade Dysplasia

## A Randomized Clinical Trial

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**IMPORTANCE** Barrett esophagus containing low-grade dysplasia is associated with an increased risk of developing esophageal adenocarcinoma, a cancer with a rapidly increasing incidence in the western world.

**OBJECTIVE** To investigate whether endoscopic radiofrequency ablation could decrease the rate of neoplastic progression.

**DESIGN, SETTING, AND PARTICIPANTS** Multicenter randomized clinical trial that enrolled 136 patients with a confirmed diagnosis of Barrett esophagus containing low-grade dysplasia at 9 European sites between June 2007 and June 2011. Patient follow-up ended May 2013.

**INTERVENTIONS** Eligible patients were randomly assigned in a 1:1 ratio to either endoscopic treatment with radiofrequency ablation (ablation) or endoscopic surveillance (control). Ablation was performed with the balloon device for circumferential ablation of the esophagus or the focal device for targeted ablation, with a maximum of 5 sessions allowed.

**MAIN OUTCOMES AND MEASURES** The primary outcome was neoplastic progression to high-grade dysplasia or adenocarcinoma during a 3-year follow-up since randomization. Secondary outcomes were complete eradication of dysplasia and intestinal metaplasia and adverse events.

**RESULTS** Sixty-eight patients were randomized to receive ablation and 68 to receive control. Ablation reduced the risk of progression to high-grade dysplasia or adenocarcinoma by 25.0% (1.5% for ablation vs 26.5% for control; 95% CI, 14.1%-35.9%;  $P < .001$ ) and the risk of progression to adenocarcinoma by 7.4% (1.5% for ablation vs 8.8% for control; 95% CI, 0%-14.7%;  $P = .03$ ). Among patients in the ablation group, complete eradication occurred in 92.6% for dysplasia and 88.2% for intestinal metaplasia compared with 27.9% for dysplasia and 0.0% for intestinal metaplasia among patients in the control group ( $P < .001$ ). Treatment-related adverse events occurred in 19.1% of patients receiving ablation ( $P < .001$ ). The most common adverse event was stricture, occurring in 8 patients receiving ablation (11.8%), all resolved by endoscopic dilation (median, 1 session). The data and safety monitoring board recommended early termination of the trial due to superiority of ablation for the primary outcome and the potential for patient safety issues if the trial continued.

**CONCLUSIONS AND RELEVANCE** In this randomized trial of patients with Barrett esophagus and a confirmed diagnosis of low-grade dysplasia, radiofrequency ablation resulted in a reduced risk of neoplastic progression over 3 years of follow-up.

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In the last 3 decades, the incidence of esophageal adenocarcinoma has increased 6-fold, making it the most rapidly increasing cancer in the western world.<sup>1</sup> Esophageal adenocarcinoma originates from Barrett esophagus, a metaplastic change in the epithelium of the esophagus caused by gastroesophageal reflux disease. The histological landmark of Barrett esophagus is the presence of intestinal metaplasia. General population data are scarce, but the prevalence of Barrett esophagus is estimated to be 1.6% in Europe compared with estimates between 1.7% and 5.6% in the United States. Incidence rates vary between 23.1 and 32.7 per 100 000 person-years.<sup>2-6</sup> Malignant degeneration is thought to occur in a stepwise fashion from nondysplastic intestinal metaplasia, to low-grade then high-grade dysplasia, and eventually adenocarcinoma.<sup>7,8</sup> Patients with Barrett esophagus undergo endoscopic surveillance or treatment, depending on the presence and grade of dysplasia.<sup>8</sup>

Radiofrequency ablation is an established endoscopic technique for the eradication of Barrett esophagus, which has been investigated in a variety of study designs (including 2 randomized trials) and settings (United States and Europe, tertiary academic centers, community referral centers).<sup>9-13</sup> Radiofrequency ablation is associated with an acceptable safety profile, high rates of complete eradication of dysplasia and intestinal metaplasia, durability of effect, and a significant relative risk reduction for neoplastic progression.<sup>9-13</sup> As a result, radiofrequency ablation is considered a standard of care for patients with high-grade dysplasia, as well as for residual Barrett tissue after endoscopic resection of early cancer.<sup>14</sup> To our knowledge, no trial has ever evaluated the effect of radiofrequency ablation on the risk of neoplastic progression in patients with Barrett esophagus containing low-grade dysplasia. Most guidelines advise endoscopic surveillance (every 6 to 12 months) to monitor for neoplastic progression in this patient population.<sup>8,15-17</sup> There are, however, uncertainties related to the diagnosis and natural course of low-grade dysplasia: whereas some patients may progress to high-grade dysplasia or adenocarcinoma, others may remain stable or may not even have their diagnosis reproduced over time.<sup>18</sup> A recent study, however, indicated that progression to high-grade dysplasia or adenocarcinoma occurs at a rate of 13.4% per person-year in this patient population, provided that the baseline diagnosis has been confirmed by expert pathologists.<sup>19</sup> Given this significant risk of progression, endoscopic treatment in this patient population may be justified. This is a clinically important question because 25% to 40% of patients with Barrett esophagus are diagnosed with low-grade dysplasia at some point during follow-up.<sup>18</sup>

We conducted a multicenter randomized trial, the Surveillance vs Radiofrequency Ablation (SURF) study, comparing radiofrequency ablation with endoscopic surveillance in patients with Barrett esophagus and a confirmed diagnosis of low-grade dysplasia. In both groups, we assessed the rate of progression to high-grade dysplasia and adenocarcinoma.

## Methods

### Study Design and Patients

The trial was conducted at 9 Barrett treatment centers in Europe. The institutional review board at each center approved

the study protocol. Written informed consent was obtained from all study patients. Prior to the start of the trial, all of the investigators received hands-on training in ablation at the coordinating study site by the principal investigator of the trial. An independent data and safety monitoring board (DSMB) monitored the trial with standardized adverse event reporting procedures and interim analyses were performed at 50% and 75% follow-up time, with a nominal cutoff *P* value of less than .0031 based on the O'Brien-Fleming method. Independent study monitors attended all study procedures and verified all recorded data.

Eligible patients had undergone upper endoscopy and biopsy within the previous 18 months demonstrating Barrett esophagus containing low-grade dysplasia. The local pathologist's diagnosis was confirmed by our expert central pathology panel. Exclusion criteria were prior endoscopic treatment for Barrett esophagus, history of high-grade dysplasia or adenocarcinoma, active secondary malignancy, estimated life expectancy less than 2 years (according to the enrolling physician), and age of 18 years or younger or 85 years and older.

All patients required a baseline qualifying endoscopy less than 6 months prior to randomization to exclude visible abnormalities, high-grade dysplasia, or adenocarcinoma, which was performed using high-resolution endoscopy with biopsies obtained according to the Seattle protocol (4-quadrant biopsies/2-cm intervals) and from any visible abnormalities. Visible abnormalities were defined as any mucosal irregularity or discoloration within the Barrett esophagus.

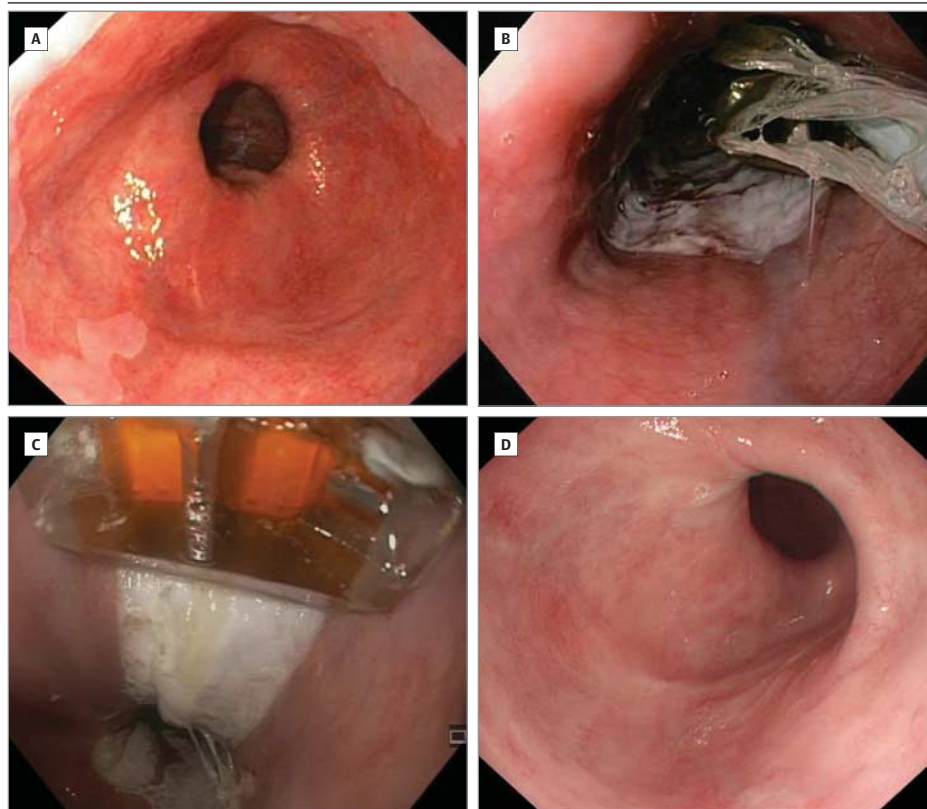
### Randomization

Patients were randomly assigned in a 1:1 ratio to receive either endoscopic radiofrequency ablation (ablation) or endoscopic surveillance (control). The randomization sequence was concealed from trial staff, who screened eligible patients. After informed consent had been obtained, assignment was made by the central study monitor using sequentially numbered, sealed opaque envelopes and conveyed to the site by telephone.

### Ablation

Within 1 month after randomization, patients assigned to ablation were treated with a circumferential device (HALO<sup>360+</sup> system) or a focal device (HALO<sup>90</sup>; both from Covidien GI Solutions [formerly BARRX Medical]) according to extent of disease and investigator preference (Figure 1A-1C).<sup>20,21</sup> Subsequent ablation sessions occurred every 3 months, until complete endoscopic and histological eradication of Barrett esophagus (Figure 1D) or a maximum of 2 circumferential and 3 focal sessions. At each ablation session, the gastroesophageal junction was ablated circumferentially, irrespective of its endoscopic appearance. If residual columnar epithelium persisted after the maximum allowable number of ablations, a single session of endoscopic resection or argon plasma coagulation (for  $\leq 4$  Barrett esophagus islands,  $\leq 5$  mm in size) was allowed per protocol.<sup>10</sup> All procedures were performed on an outpatient basis using midazolam plus fentanyl, midazolam plus pethidine, or propofol.

Figure 1. Endoscopic Images From Patients With Barrett Esophagus and Low-Grade Dysplasia From Baseline Endoscopy and During and After Radiofrequency Ablation



A, Endoscopic image showing the distal esophagus at the baseline endoscopy, looking toward the gastroesophageal junction. The Barrett epithelium is characterized by its salmon-colored appearance on endoscopy compared with the pale appearance of the normal squamous mucosa. B, A deflated circumferential radiofrequency ablation balloon (extending from the device on the right) is positioned in the segment of Barrett esophagus. The immediate treatment effect of the circumferential ablation can be seen as the whitish discoloration. C, The focal radiofrequency ablation device visible at the top of the image is used for targeted ablation of a small area. The immediate treatment effect is visible as whitish discoloration in the middle and at the bottom of the image of residual Barrett epithelium. D, Endoscopic photograph showing the distal esophagus after complete eradication of all Barrett epithelium. Images are not from the same patient.

The first follow-up endoscopy was scheduled 3 months after the last therapeutic endoscopy. Subsequent follow-up endoscopies were performed annually thereafter until 3 years after randomization (2 years after completion of ablation). At each follow-up endoscopy, 4-quadrant biopsies were performed at every 2-cm interval of the original extent of the Barrett esophagus, starting at 1 cm proximal to the top of the gastric folds. In addition 4 biopsy samples were obtained from the gastric cardia, less than 5 mm distal to the neosquamocolumnar junction.

During the trial, the ablation group received double-dose proton pump inhibition as maintenance therapy. A histamine ( $H_2$ ) receptor antagonist and sucralfate suspension were added for 2 weeks after each therapeutic endoscopy.

### Control

Patients assigned to the control group underwent high-resolution endoscopy at 6 and 12 months after the baseline qualifying endoscopy and annually thereafter until 3 years after randomization. At each follow-up endoscopy, 4-quadrant biopsy samples were obtained from every 2-cm interval of Barrett epithelium. If histology showed either low-grade dysplasia or no dysplasia, patients were scheduled for follow-up according to the study protocol.

### Histologic Analysis

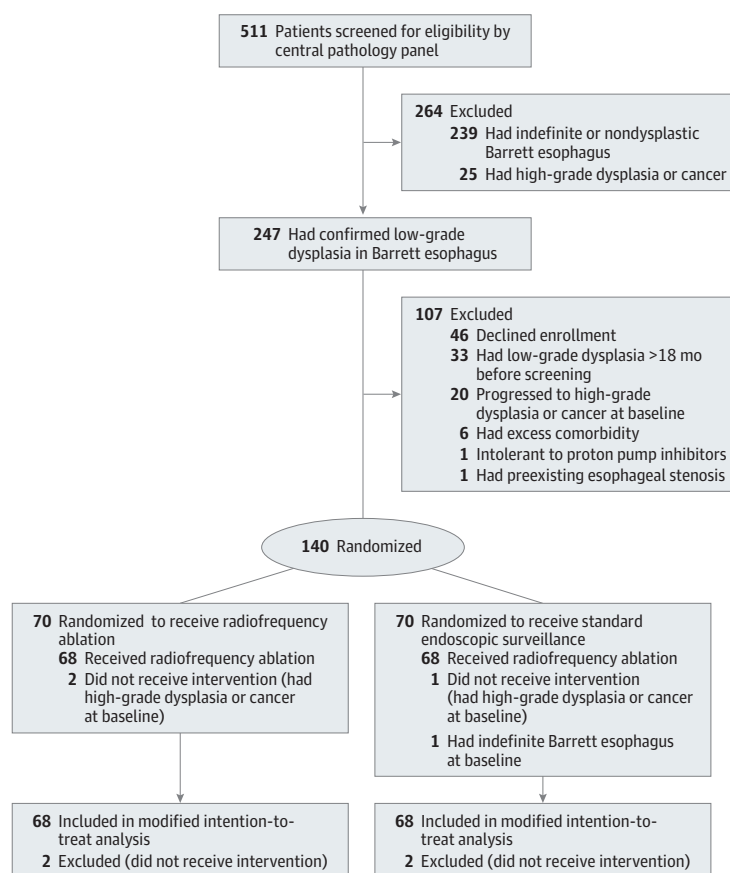
Follow-up esophageal biopsy specimens were processed and locally evaluated at each of the 9 participating centers. Each

specimen was assessed for the presence of intestinal metaplasia (as the histological feature of residual Barrett esophagus) and grade of dysplasia according to the Vienna classification.<sup>22</sup> In cases of postrandomization biopsy specimens locally read as high-grade dysplasia or adenocarcinoma, confirmation of this primary outcome required agreement by 2 pathologists from the central expert pathologist panel. The central pathologist was not informed on the exposure status of the patient. In case of discordance, a third central expert pathologist interpretation was employed as a tiebreaker or the panel reviewed the slides mutually and reached a consensus diagnosis.

### Outcome Measures

The primary outcome was the occurrence of high-grade dysplasia or adenocarcinoma (ie, neoplastic progression) at any time during the 3 years following randomization. Secondary outcomes included complete histological eradication of dysplasia (ie, absence of dysplasia of any grade in all samples obtained at the first follow-up endoscopy) and intestinal metaplasia (ie, absence of intestinal metaplasia in all samples obtained at the first follow-up endoscopy), and adverse events. Patients who met the primary outcome were considered to have failure for the secondary outcome of complete eradication. Patients who met the primary outcome were treated at investigator's discretion, per standards for high-grade dysplasia and adenocarcinoma at that institution.

Figure 2. Enrollment and Outcomes



### Statistical Analysis

We estimated that ablation would produce a 90% relative risk reduction for progression to high-grade dysplasia or adenocarcinoma, using prior studies of the outcomes of ablation.<sup>20,21,23</sup> We assumed that 14% of control and 1% of ablation patients would develop high-grade dysplasia or adenocarcinoma during the 3-year follow-up. We projected that with a sample size of 120 patients, the study would have at least 80% statistical power to detect the hypothesized differences in the primary outcome variable between the groups. Based on an anticipated 5% dropout rate, we sought to enroll 126 patients.

The modified intention-to-treat population included all randomized patients meeting all study criteria. The time to progression was calculated from the date of randomization until the endoscopy date on which high-grade dysplasia or adenocarcinoma was first detected. The proportional event rates during follow-up were compared by Kaplan-Meier analysis and log-rank test. Risk differences were calculated as the difference in the proportional event rates during follow-up. Number needed to treat (NNT) was calculated as 1 divided by the risk difference. For the primary outcome (in view of the use of the O'Brien-Fleming rule), a 2-tailed *P* value less than .0440 was considered significant.

Categorical variables were compared using the Fisher exact test. Continuous variables are presented as mean (standard deviation) and were compared using the *t* test for nor-

mal distribution or presented as median (interquartile range [IQR]) and compared using the Mann-Whitney *U* test for skewed distribution. We conducted subgroup analyses for risk factors of progression and absence of low-grade dysplasia during follow-up by means of logistic regression. In the multivariable regression model, baseline variables were identified with a forward stepwise selection strategy using the likelihood ratio statistic, with a *P* value less than .10 as the criterion level for selection. For data analysis the SPSS statistical software package (SPSS 20.0.1, IBM Corp) was used.

### Results

Patients were enrolled between June 2007 and June 2011 in 9 centers from 5 European countries. Of 511 patients screened, 140 were included and randomized (Figure 2). Four patients (2 ablation, 2 control) were excluded from analysis because of inadvertent randomization, after reassessment of prerandomization histology, endoscopy, or both demonstrated study exclusion criteria (Figure 2). The remaining 136 patients (68 ablation, 68 control) were included in the modified intention-to-treat population. The 2 groups were similar in their baseline characteristics (Table 1).

Upon review of the second planned interim analysis in April 2013, the DSMB recommended early termination of the trial

due to the superiority of ablation for the primary outcome and the potential for patient safety issues if the trial continued. The stopping rule was followed by the DSMB after the preplanned O'Brien-Fleming method demonstrated superiority. The steering committee subsequently closed the trial on May 8, 2013. At that time, all patients were followed-up for at least 24 months, with a median follow-up of 36 months (IQR, 30-36).

Patients in the ablation group were less likely than the control group to progress to high-grade dysplasia or adenocarcinoma (1.5% ablation group [n = 1] vs 26.5% control group [n = 18], *P* < .001) and less likely to progress to adenocarcinoma (1.5% ablation group [n = 1] vs 8.8% control group [n = 6], *P* = .03) (Table 2). Ablation reduced the risk of progression to high-grade dysplasia or adenocarcinoma by 25.0% (95% CI, 14.1%-35.9%), with an NNT of 4.0 (95% CI, 2.8-7.1) (Figure 3). Ablation reduced the risk of progression to adenocarcinoma by 7.4% (95% CI, 0.0%-14.7%), with an NNT of 13.6 (95% CI, 6.8-∞).

The ablation group had 1 patient who progressed to adenocarcinoma. This patient was treated with endoscopic resection and achieved complete eradication of dysplasia. The control group had 18 patients who progressed (12 high-grade dysplasia, 6 adenocarcinoma). One patient in the control group with adenocarcinoma underwent esophagectomy for poorly differentiated submucosal carcinoma. No residual cancer or positive lymph nodes were detected and the patient remained free of disease after 37 months of follow-up. Of the remaining 17 progressors in the control group, 15 patients (10 high-grade dysplasia, 5 mucosal adenocarcinoma) underwent endoscopic resection plus radiofrequency ablation (n = 9; median [range], 4 resections [1-14]), or radiofrequency ablation (n = 6). Of these 15 patients, 11 patients achieved complete eradication of dysplasia and intestinal metaplasia and 4 are still being treated for high-grade dysplasia or carcinoma. The remaining 2 progressors (2 high-grade dysplasia) opted for endoscopic surveillance.

For the ablation group, complete eradication of dysplasia (92.6%; 63 of 68 patients) and intestinal metaplasia (88.2%; 60 of 68 patients) occurred. During the follow-up phase of the trial, complete eradication of dysplasia was maintained in 62 of 63

Table 1. Demographic and Disease-Specific Characteristics of Enrolled Patients<sup>a</sup>

Characteristic	Ablation Group (n = 68)	Control Group (n = 68)
Age, mean (SD), y	63 (10)	63 (9)
Men, No. (%)	55 (81)	61 (90)
White race/ethnicity, No. reported (%) <sup>b</sup>	66 (97)	66 (97)
BMI, mean (SD)	26.8 (3.7)	27.9 (4.8)
Clinical characteristics, median (IQR)		
Circumferential Barrett esophagus, cm <sup>c,d</sup>	2 (0-6)	2 (1-4)
Maximum Barrett esophagus, cm <sup>c,d</sup>	4 (2-8)	4 (3-6)
Time since diagnosis of Barrett esophagus, y <sup>c</sup>	5 (2-10)	7 (3-11)
Time since diagnosis of dysplasia, y <sup>c</sup>	1 (0-5)	2 (0-5)
Barrett surveillance endoscopies prior to baseline, No. <sup>c</sup>	5 (3-8)	5 (3-7)
Barrett surveillance endoscopies with dysplasia prior to baseline, No. <sup>c</sup>	2 (1-4)	2 (1-3)
Reported history of gastroesophageal reflux disease, No. (%) <sup>b</sup>	62 (91)	65 (96)
Reported use of proton pump inhibitor, No. (%) <sup>b</sup>	68 (100)	67 (99)
Use of proton pump inhibitors, y <sup>c</sup>	8 (5-14)	9 (4-14)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range.

<sup>a</sup> Mean (SD) was compared using independent *t* test. Categorical data were compared using Fisher exact test. There were no significant differences between the 2 study groups.

<sup>b</sup> Race or ethnic group, history of reflux disease, and use of proton pump inhibitors were self-reported.

<sup>c</sup> Data were compared using Mann-Whitney *U* test. There were no significant differences between the 2 study groups.

<sup>d</sup> The circumferential and maximum Barrett extent were measured according to the Prague C&M classification.<sup>24</sup>

Table 2. Primary and Secondary Efficacy Outcomes

Efficacy Outcomes	No. of Patients (%)		Risk Difference, % (95% CI)	<i>P</i> Value
	Ablation Group (n = 68)	Control Group (n = 68)		
Progression to high-grade dysplasia or cancer	1 (1.5)	18 (26.5)	25.0 (14.1-35.9)	<.001 <sup>a</sup>
Progression to cancer	1 (1.5)	6 (8.8)	7.4 (0.0-14.7)	.03 <sup>a</sup>
Complete eradication of dysplasia at the end of endoscopic treatment	63/68 (92.6) <sup>b</sup>			NA
Complete eradication of IM at the end of endoscopic treatment	60/68 (88.2) <sup>b</sup>			NA
Complete eradication of dysplasia during follow-up, No. of events/total patients (%) <sup>c</sup>	62/63 (98.4) <sup>b</sup>	19/68 (27.9)	70.5 (59.4-81.6)	<.001
Complete eradication of IM during follow-up, No. of events/total patients (%) <sup>c</sup>	54/60 (90.0) <sup>b</sup>	0/68 (0.0)	90.0 (82.4-97.6)	<.001

Abbreviations: IM, intestinal metaplasia; NA, not applicable.

<sup>a</sup> Two-sided *P* values were derived using log-rank testing on Kaplan-Meier estimates.

<sup>b</sup> Including 1 patient who died of metastasized lung carcinoma after the second ablation treatment and 1 patient who had esophageal adenocarcinoma diagnosed after the fourth ablation session as failures for complete eradication of dysplasia and intestinal metaplasia.

<sup>c</sup> At any follow-up, if endoscopy biopsies showed intestinal metaplasia or low-grade dysplasia, this was considered a failure for persistence of complete eradication during follow-up.

(98.4%) patients receiving ablation. In the control group, low-grade dysplasia was not detected during the follow-up period in 19 of 68 patients, resulting in complete eradication of dysplasia of 27.9% (risk difference, 70.5% [95% CI, 59.4%-81.6%];  $P < .001$ ). Complete eradication of intestinal metaplasia was maintained in 54 of 60 patients (90.0%) receiving ablation compared with 0 of 68 patients receiving control (risk difference, 90% [95% CI, 82.4%-97.6%];  $P < .001$ ). All recurrences in the ablation group were small islands or tongues less than 10 mm (Table 2).

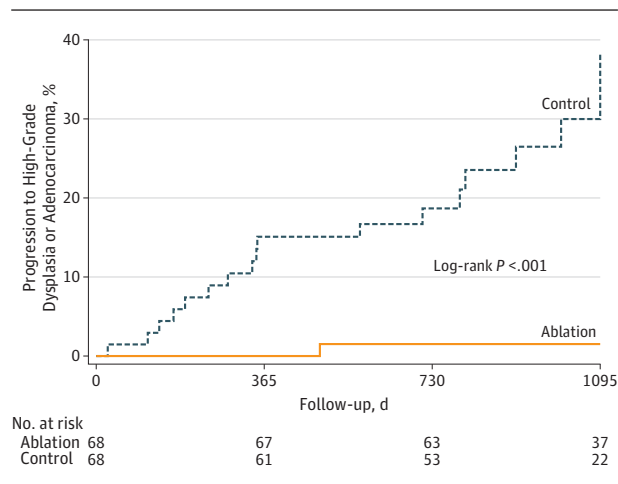
The ablation group underwent a total of 211 ablation sessions (median, 3 per patient) and 208 endoscopic biopsy sessions (median, 3 per patient; median, 37 biopsies per patient). Escape endoscopic resection was used in 5 ablation patients (7.4%) and argon plasma coagulation in 12 ablation patients (17.6%). The control group underwent a total of 227 endoscopy and biopsy sessions (median, 3 per patient; median, 32 biopsies per patient).

There were 3 serious adverse events in 2 ablation patients. One patient was hospitalized for abdominal pain 4 days after ablation, treated to resolution with analgesics. A second patient experienced bleeding 7 days after endoscopic resec-

tion for a visible lesion (low-grade dysplasia) prior to the first ablation. Later, this same patient was dilated for stricture and developed fever and chills. No perforation was noted and the patient was hospitalized and treated with antibiotics. There were 12 adverse events in 12 ablation patients. During ablation, a small mucosal laceration was noted in 3 patients (no intervention required, procedure completed). One patient reported retrosternal pain 3 weeks after focal ablation. Endoscopy findings were normal and the pain resolved with analgesics. Eight patients (11.8%) developed esophageal stricture requiring dilation (median, 1 dilation [IQR, 1-2]). In total, 13 ablation patients had an event (1 patient had both a serious adverse event and an adverse event), there were no adverse events in control patients (risk difference, 19.1% [95% CI, 9.7%-28.4%];  $P < .001$ ).

Multivariable analysis demonstrated that the number of years since the diagnosis of Barrett esophagus (odds ratio [OR], 0.84 [95% CI, 0.72-0.98]), the number of endoscopies with dysplasia prior to inclusion (OR, 1.44 [95% CI, 1.03-2.03]), and circumferential Barrett esophagus length in centimeters (OR, 1.35 [95% CI, 1.04-1.76]) were independent predictors of progression in the control group (Table 3). Multivariable analysis could not identify significant predictors for absence of low-grade dysplasia during surveillance in the control group.

Figure 3. Occurrence of Progression to High-Grade Dysplasia or Adenocarcinoma



## Discussion

In this randomized trial of ablation vs surveillance in patients with Barrett esophagus and a confirmed diagnosis of low-grade dysplasia, ablation reduced the risk of progression to high-grade dysplasia or adenocarcinoma from 26.5% to 1.5%, corresponding to an NNT of 4.0. In addition, ablation reduced the risk of progression to adenocarcinoma, from 8.8% to 1.5%, an absolute risk reduction of 7.4%, corresponding to an NNT of 13.6. Furthermore, complete eradication of dysplasia and intestinal metaplasia occurred and persisted in the majority of patients in the ablation group. These results comport with those of previous prospective studies of ablation for high-grade dysplasia and adenocarcinoma in Barrett esophagus.<sup>9,12,25</sup>

Table 3. Univariable and Multivariable Analysis of Predictors of Progression in the Control Group

Variable	Univariable Analysis, OR (95% CI)	P Value	Multivariable Analysis, OR (95% CI)	P Value
Age, per y	0.94 (0.88-1.00)	.06	0.92 (0.85-1.00)	.05
BMI, per unit	1.06 (0.94-1.18)	.36		
Circumferential Barrett esophagus, per cm	1.12 (0.93-1.34)	.25	1.35 (1.04-1.76)	.03
Maximum Barrett esophagus, per cm	1.05 (0.86-1.28)	.63		
Time since diagnosis of Barrett esophagus, per y	0.88 (0.77-0.99)	.04	0.84 (0.72-0.98)	.02
Time since diagnosis of dysplasia, per y	1.00 (0.97-1.03)	.86		
Barrett surveillance endoscopies prior to baseline, per endoscopy	0.97 (0.78-1.20)	.77		
Barrett surveillance endoscopies with dysplasia prior to baseline, per endoscopy	1.24 (0.94-1.63)	.12	1.44 (1.03-2.03)	.03
Use of proton pump inhibitors, per y of use	0.96 (0.91-1.05)	.49		

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); OR, odds ratio.

This trial was terminated early, upon recommendation of the DSMB, due to superiority of ablation for the primary end point and concerns about patient safety should the trial continue. Early termination did not affect patient enrollment and only led to shortening of the follow-up from the intended 3 years to 2 years in 40% of patients. In the remaining patients, 3-year follow-up was achieved. Given the minimal loss of longitudinal data, the profound differences between the groups in disease progression made it unjustified to continue the trial for an additional year.

Our data suggest that endoscopic ablative therapy is a superior management strategy to endoscopic surveillance in patients with Barrett esophagus and confirmed low-grade dysplasia. Given the high rate of malignant degeneration in our control group, and the relatively low NNT to avert a single progression, as well as the acceptable safety profile, a shift to earlier endoscopic intervention in this patient population deserves consideration.

Of note, no control patient demonstrated unresectable cancer or cancer-related death. Although the lack of cancer-associated mortality might suggest that endoscopic surveillance remains an appropriate management strategy for low-grade dysplasia, we would advise caution with this interpretation. Our patients were maintained in a trial setting, and despite rigorous monitoring at expert centers, 1 of our control patients did require esophagectomy for the development of advanced-stage disease. Outside of a rigorous study protocol, neoplastic progression in patients undergoing endoscopic surveillance might be detected at a later stage. If so, the neoplasia might not be amenable to endoscopic therapy, and henceforth be associated with higher rates of surgery, unresectable disease, and cancer-related death.

A wide range of neoplastic progression rates have been reported for Barrett esophagus with low-grade dysplasia. The observed rate of progression in our control group (26.5% overall; 11.8% per person-year of follow-up) comports with rates from studies requiring expert gastrointestinal pathologist confirmation.<sup>7,13,17</sup> The observed progression rate in our control group, however, contrasts with lower rates from other studies (1.4%-1.83% per person-year) with no expert confirmation of baseline diagnosis or poor interobserver agreement.<sup>15-17</sup> After expert pathology review, 50% to 85% of patients initially diagnosed with low-grade dysplasia may be downstaged to nondysplastic Barrett esophagus with an associated lower risk of neoplastic progression.<sup>19,26</sup> Expert pathology review by a panel of experienced pathologists with an acceptable interobserver agreement ( $\kappa$  0.50 for our panel<sup>19</sup>) is therefore important to accurately ascertain patient risk for progression and determining which patients would benefit from treatment vs surveillance.

Of note, 28% of the control group had no dysplasia detected during follow-up. This proportion is similar to the randomized trial by Shaheen and coauthors<sup>12</sup> in which 26% of low-grade controls did not show dysplasia at 12 months follow-up. Ideally, ablation should be avoided in these patients, given their lower risk of progression and the associated risks and costs of treatment; however, we do not know in advance which patients will fail to demonstrate low-grade dysplasia over time.

In our trial, histological confirmation of low-grade dysplasia by an expert pathologist was the most important selection criterion. Risk of progression may, however, depend on additional factors. Patients harboring multifocal dysplasia in their Barrett esophagus segment likely carry an increased risk for progression compared with patients with only focal dysplasia (spatial distribution).<sup>27</sup> Second, low-grade dysplasia on multiple endoscopies likely increases the risk of progression compared with a single endoscopy diagnosis (temporal distribution).<sup>28</sup> In our trial, a single confirmed diagnosis of low-grade dysplasia sufficed for enrollment, yet the number of endoscopies with dysplasia prior to inclusion was an independent predictor for progression in the multivariable analysis. Insisting that a confirmed diagnosis of low-grade dysplasia is reproduced over time may therefore improve the selection of patients for ablation. Adequate endoscopic inspection is, however, required to avoid that patient's progress to advanced neoplasia during this lag time: 14% of patients were excluded because high-grade dysplasia or adenocarcinoma was diagnosed at the baseline qualifying endoscopy, and 10 of our 19 progressors were diagnosed within 12 months follow-up.

Ablation treatment was generally safe with esophageal stricture being the most common complication (11.8%), requiring a median of 1 dilation. This is higher than the 5% pooled estimate of a recent meta-analysis; however, this analysis was limited by the heterogeneity of the included studies of which half were retrospective studies.<sup>29</sup> Although we found a higher stricture rate in our trial, our strictures were generally mild in nature, given the low average number of required dilations. In comparison, the average number of required dilations for stricture after ablation in the Ablation of Intestinal Metaplasia Containing Dysplasia (AIM Dysplasia) trial was 2.6.<sup>12</sup>

Strengths of our study include a small proportion of patients lost to follow-up, centralized expert pathology review, rigorous quality control, expert center participation, hands-on training for investigators, and procedure supervision by study coordinators. Limitations of our study include exclusive participation of expert referral centers, which may render these results less generalizable to general practice. In our opinion endoscopic workup, treatment, and follow-up of Barrett esophagus with dysplasia should be restricted to centers with extensive expertise in this field. Second, our primary end point was progression to a combined end point of high-grade dysplasia or adenocarcinoma, and our trial was underpowered for a "cancer-related death" end point. However, progression to high-grade dysplasia or adenocarcinoma is the most clinically relevant and appropriate end point, as both are presently considered indications for endoscopic treatment. Third, a confirmed diagnosis of low-grade dysplasia at 1 endoscopy session sufficed for inclusion in the study. Fourth, we allowed endoscopic rescue therapy in a small number of patients for diminutive residual Barrett tissue.

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## Conclusions

In this multicenter, randomized trial of radiofrequency ablation vs surveillance in patients with Barrett esophagus and a

confirmed histological diagnosis of low-grade dysplasia, ablation substantially reduced the rate of neoplastic progression to high-grade dysplasia and adenocarcinoma over 3 years

of follow-up. Patients with a confirmed diagnosis of low-grade dysplasia should therefore be considered for ablation therapy.

#### ARTICLE INFORMATION

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#### REFERENCES

- Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst*. 2005;97(2):142-146.
- Ronkainen J, Aro P, Storskrubb T, et al. Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology*. 2005;129(6):1825-1831.
- Fan X, Snyder N. Prevalence of Barrett's esophagus in patients with or without GERD symptoms: role of race, age, and gender. *Dig Dis Sci*. 2009;54(3):572-577.
- Hayeck TJ, Kong CY, Spechler SJ, Gazelle GS, Hur C. The prevalence of Barrett's esophagus in the US: estimates from a simulation model confirmed by SEER data. *Dis Esophagus*. 2010;23(6):451-457.
- van Soest EM, Dieleman JP, Siersema PD, Sturkenboom MCJM, Kuipers EJ. Increasing incidence of Barrett's oesophagus in the general population. *Gut*. 2005;54(8):1062-1066.
- Musana AK, Resnick JM, Torbey CF, Mukesh BN, Greenlee RT. Barrett's esophagus: incidence and prevalence estimates in a rural Mid-Western population. *Am J Gastroenterol*. 2008;103(3):516-524.
- Shaheen NJ, Richter JE. Barrett's oesophagus. *Lancet*. 2009;373(9666):850-861.
- Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ; American Gastroenterological Association. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology*. 2011;140(3):1084-1091.
- Phoa KN, Pouw RE, van Vilsteren FGI, et al. Remission of Barrett's esophagus with early neoplasia 5 years after radiofrequency ablation with endoscopic resection: a Netherlands cohort study. *Gastroenterology*. 2013;145(1):96-104.
- van Vilsteren FGI, Pouw RE, Seewald S, et al. Stepwise radical endoscopic resection versus radiofrequency ablation for Barrett's oesophagus with high-grade dysplasia or early cancer: a multicentre randomised trial. *Gut*. 2011;60(6):765-773.
- Pouw RE, Wirths K, Eisendrath P, et al. Efficacy of radiofrequency ablation combined with endoscopic resection for Barrett's esophagus with early neoplasia. *Clin Gastroenterol Hepatol*. 2010;8(1):23-29.
- Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med*. 2009;360(22):2277-2288.
- Fleischer DE, Overholt BF, Sharma VK, et al. Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. *Endoscopy*. 2010;42(10):781-789.



14. Bennett C, Vakili N, Bergman J, et al. Consensus statements for management of Barrett's dysplasia and early-stage esophageal adenocarcinoma, based on a Delphi process. *Gastroenterology*. 2012;143(2):336-346.
15. Wani S, Falk GW, Post J, et al. Risk factors for progression of low-grade dysplasia in patients with Barrett's esophagus. *Gastroenterology*. 2011;141(4):1179-1186.
16. Hvid-Jensen F, Pedersen L, Drewes AM, Sørensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med*. 2011;365(15):1375-1383.
17. Bhat S, Coleman HG, Yousef F, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. *J Natl Cancer Inst*. 2011;103(13):1049-1057.
18. Vieth M. Low-grade dysplasia in Barrett's esophagus—an innocent bystander? *Endoscopy*. 2007;39(7):647-649.
19. Curvers WL, ten Kate FJ, Krishnadath KK, et al. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. *Am J Gastroenterol*. 2010;105(7):1523-1530.
20. Gondrie JJ, Pouw RE, Sondermeijer CMT, 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(5):359-369.
21. Gondrie JJ, Pouw RE, Sondermeijer CMT, et al. Effective treatment of early Barrett's neoplasia with stepwise circumferential and focal ablation using the HALO system. *Endoscopy*. 2008;40(5):370-379.
22. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut*. 2000;47(2):251-255.
23. 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(2):185-195.
24. Sharma P, Dent J, Armstrong D, et al. The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M criteria. *Gastroenterology*. 2006;131(5):1392-1399.
25. Pouw RE, van Vilsteren FGI, Peters FP, et al. Randomized trial on endoscopic resection-cap versus multiband mucosectomy for piecemeal endoscopic resection of early Barrett's neoplasia. *Gastrointest Endosc*. 2011;74(1):35-43.
26. Pech O, Vieth M, Schmitz D, et al. Conclusions from the histological diagnosis of low-grade intraepithelial neoplasia in Barrett's oesophagus. *Scand J Gastroenterol*. 2007;42(6):682-688.
27. Srivastava A, Hornick JL, Li X, et al. Extent of low-grade dysplasia is a risk factor for the development of esophageal adenocarcinoma in Barrett's esophagus. *Am J Gastroenterol*. 2007;102(3):483-493.
28. Hur C, Choi SE, Rubenstein JH, et al. The cost effectiveness of radiofrequency ablation for Barrett's esophagus. *Gastroenterology*. 2012;143(3):567-575.
29. Orman ES, Li N, Shaheen NJ. Efficacy and durability of radiofrequency ablation for Barrett's Esophagus: systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2013;11(10):1245-1255.