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Radiofrequency Ablation in Barrett's Esophagus with Dysplasia

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ABSTRACT

BACKGROUND

Barrett's esophagus, a condition of intestinal metaplasia of the esophagus, is associated with an increased risk of esophageal adenocarcinoma. We assessed whether endoscopic radiofrequency ablation could eradicate dysplastic Barrett's esophagus and decrease the rate of neoplastic progression.

METHODS

In a multicenter, sham-controlled trial, we randomly assigned 127 patients with dysplastic Barrett's esophagus in a 2:1 ratio to receive either radiofrequency ablation (ablation group) or a sham procedure (control group). Randomization was stratified according to the grade of dysplasia and the length of Barrett's esophagus. Primary outcomes at 12 months included the complete eradication of dysplasia and intestinal metaplasia.

RESULTS

In the intention-to-treat analyses, among patients with low-grade dysplasia, complete eradication of dysplasia occurred in 90.5% of those in the ablation group, as compared with 22.7% of those in the control group ($P<0.001$). Among patients with high-grade dysplasia, complete eradication occurred in 81.0% of those in the ablation group, as compared with 19.0% of those in the control group ($P<0.001$). Overall, 77.4% of patients in the ablation group had complete eradication of intestinal metaplasia, as compared with 2.3% of those in the control group ($P<0.001$). Patients in the ablation group had less disease progression (3.6% vs. 16.3%, $P=0.03$) and fewer cancers (1.2% vs. 9.3%, $P=0.045$). Patients reported having more chest pain after the ablation procedure than after the sham procedure. In the ablation group, one patient had upper gastrointestinal hemorrhage, and five patients (6.0%) had esophageal stricture.

CONCLUSIONS

In patients with dysplastic Barrett's esophagus, radiofrequency ablation was associated with a high rate of complete eradication of both dysplasia and intestinal metaplasia and a reduced risk of disease progression. (ClinicalTrials.gov number, NCT00282672.)

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Barrett's esophagus is defined as metaplasia of the esophageal epithelium, with normal squamous epithelium replaced by columnar epithelium containing goblet cells, also known as intestinal metaplasia (Fig. 1A).[1] This change is associated with gastroesophageal reflux disease.[2] Approximately 10% of patients with chronic reflux have Barrett's esophagus,[3,4] and the prevalence of the condition in a recent population study was 1.6%.[5] The condition is associated with an increased risk of esophageal adenocarcinoma.[6,7] The incidence of this once rare cancer has increased by more than 500% since the 1970s.[8] The cancer remains highly lethal, with a 5-year survival rate of less than 15%.[9]

Barrett's esophagus with no histologic evidence of cellular atypia is classified as nondysplastic intestinal metaplasia. However, intestinal metaplasia cells may develop progressively more abnormal features, ranging from low-grade dysplasia to high-grade dysplasia. Longitudinal studies have shown that most cases of Barrett's esophagus do not progress beyond nondysplastic intestinal metaplasia or transient low-grade dysplasia.[10,11] However, in cases of progression to high-grade dysplasia, the risk of esophageal cancer may be more than 10% per patient-year.[12-14] The optimal care of patients with dysplastic Barrett's esophagus is unclear.

We performed a multicenter, randomized trial of endoscopic radiofrequency ablative therapy versus a sham procedure. Both study groups underwent intensive endoscopic surveillance to monitor progression of the disease and response to therapy.

METHODS

STUDY DESIGN

At 19 sites in the United States, we recruited patients who were between 18 and 80 years of age and who had endoscopically evident, non-nodular, dysplastic Barrett's esophagus of no more than 8 cm in length. For patients with high-grade dysplasia, we additionally required negative results on endoscopic ultrasonography for lymphadenopathy and esophageal-wall abnormalities within 12 months before enrollment. Previous endoscopic mucosal resection was permissible 8 weeks or more before study entry if subsequent endoscopy showed non-nodular dysplasia. Exclusion criteria were pregnancy, active esophagitis or stricture precluding passage of the endoscope, a history of esophageal cancer, esophageal varices, uncontrolled coagulopathy, or a life expectancy of less than 2 years, as judged by the site investigator. Cancer risks and conventional treatment options (including esophagectomy in patients with high-grade dysplasia) were reviewed with all patients, who provided written informed consent.

Patients were randomly assigned in a 2:1 ratio to receive either radiofrequency ablation (ablation group) or a sham endoscopic procedure (control group). Randomization was stratified according to the grade of dysplasia (low-grade or high-grade) and the length of Barrett's esophagus (<4 cm or 4 to 8 cm), as viewed on endoscopy. All patients underwent upper endoscopy, esophageal intubation with a study catheter, measurement of the esophageal inner diameter,[15] and periprocedural assignment to a study group with the use of a computer-generated block-randomization sequence. Among patients in the ablation group, the entire segment of Barrett's esophagus was ablated. Among those in the control group, the study catheter was removed and the procedure was terminated.

Patients in the ablation group could receive up to four ablation sessions, performed at baseline and at 2, 4, and 9 months. Patients with low-grade dysplasia underwent biopsy procedures at 6 and 12 months; those with high-grade dysplasia underwent such procedures at 3, 6, 9, and 12 months. Endoscopic biopsies were performed with maximum-capacity or jumbo forceps in four quadrants every 1 cm throughout the original length of Barrett's esophagus; in addition, directed biopsies were performed at sites with any visible abnormalities. After completion of all 12-month assessments, patients in the control group were offered open-label radiofrequency ablation. All patients received 40 mg of esomeprazole (which was provided by AstraZeneca) twice daily throughout the trial.

The protocol was approved by the ethics committee at each study center. The trial was performed in accordance with the provisions of the Declaration of Helsinki. An independent data and safety monitoring committee monitored the trial. The academic investigators collected data at each study site, and the sponsor, BÂRRX Medical, managed the database. At the completion of the study, the database was transferred to the authors and the independent study statistician with concealment of study-group assignments. The statistician and the lead academic author analyzed

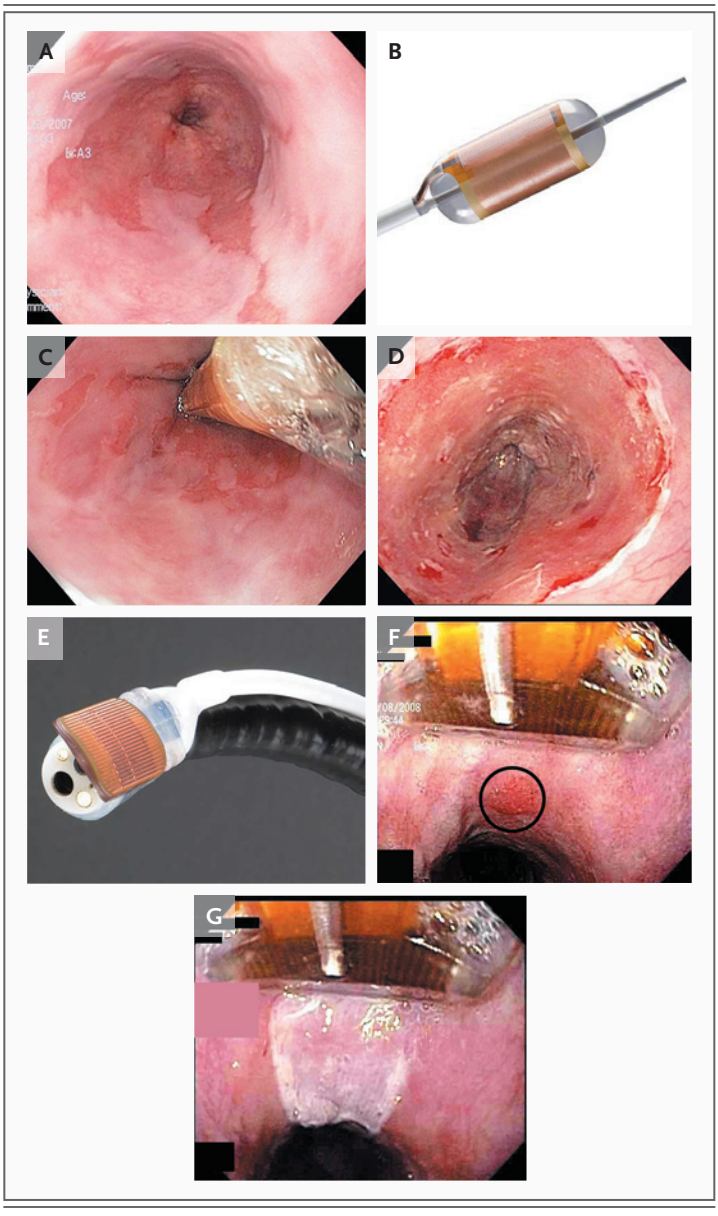

Figure 1. Radiofrequency Ablation in the Treatment of Barrett's Esophagus.

In Panel A, an endoscopic photograph shows the distal esophagus in a patient with Barrett's esophagus, taken from the midesophagus toward the gastroesophageal junction. The pale mucosa in the foreground is normal squamous epithelium, whereas the salmon-colored tissue is the Barrett's tissue. In Panel B, a circumferential radiofrequency-ablation balloon is inflated to demonstrate the bipolar electrode array. The balloon is covered by a 3-cm-long bipolar electrode array with 60 tightly spaced electrodes encircling it. In Panel C, a deflated radiofrequency-ablation balloon is positioned in a segment of Barrett's esophagus to be treated. Once the balloon is inflated, it will be used to treat the Barrett's tissue that comes into contact with the electrode. In Panel D, the immediate treatment effect after circumferential ablation is shown, with all epithelium within the treatment zone removed. In Panel E, a focal radiofrequency-ablation device is shown on the distal end of the endoscope. The upper surface (20 mm by 13 mm) contains the electrode array. When the endoscope is deflected upward, the platform pivots, bringing the electrode into apposition with the epithelium. This device has the same electrode spacing and delivers the same energy density and power density as the circumferential device. In Panel F, an endoscopic photograph shows a small residual island of Barrett's tissue (circled) 2 months after primary circumferential ablation, with the majority of tissue having reverted to neosquamous epithelium. In Panel G, the same small residual island is visible immediately after application of focal radiofrequency ablation. The residual island is now encompassed in a rectangular area of white coagulum.

the data and vouch for the completeness and accuracy of the analyses.

PRIMARY AND SECONDARY OUTCOMES

There were three primary outcome variables: the proportion of patients with low-grade dysplasia who had complete eradication of dysplasia at 12 months, the proportion of patients with high-grade dysplasia who had complete eradication of dysplasia at 12 months, and the proportion of all patients who had complete eradication of intestinal metaplasia at 12 months.

Secondary outcome variables included the proportion of patients who had progression of dysplasia, including progression of low-grade dysplasia to high-grade dysplasia or to esophageal cancer and progression of high-grade dysplasia to esophageal cancer; the proportion of biopsy samples from each study group that were free of intestinal metaplasia at 12 months, stratified according to dysplasia grade; the discomfort level of patients, as assessed with the use of a 14-day diary of daily symptoms, scored on a 100-point visual-analogue scale; and the proportion of patients who reported adverse events.

ENDOSCOPIC INTERVENTION

Patients who were assigned to receive radiofrequency ablation were treated with a circumferential ablation device (HALO^{360}, BÂRRX Medical) (Fig. 1B, 1C, and 1D). The ablation catheter incorporated a cylindrical balloon that was inflated, bringing the electrodes into contact with the esophageal lining. A preset amount of energy was then delivered (12 J and 40 W per square centimeter). For Barrett's esophagus segments that were more

A video showing radiofrequency ablation is available at NEJM.org

than 3 cm in length, the catheter was repositioned, and the remaining Barrett's esophagus was ablated in 3-cm increments. The catheter was withdrawn, coagulative debris was cleaned from the ablation zone and electrodes, and the abnormal tissue was again ablated (for details, see the video in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Patients who received radiofrequency ablation and had residual Barrett's esophagus at subsequent visits were treated with a focal ablation device (HALO^{90}) (Fig. 1E, 1F, and 1G). Ablation was applied to the residual Barrett's esophagus twice, followed by removal of coagulum from the treatment area and the electrodes. Two additional treatments were then delivered, totaling four applications per session.

HISTOLOGIC ANALYSIS

Samples from eligible patients with a diagnosis of dysplastic Barrett's esophagus underwent review by a study pathologist at a central laboratory. If the readings were concordant, the patient was deemed to be eligible for the study and was assigned an entry grade of dysplasia. If the readings were discordant, a second masked review was performed, with assignment by concordance.

At follow-up biopsy sessions, tissues were fixed in formalin, stained with hematoxylin and eosin, and interpreted by pathologists at the central laboratory with the use of standardized criteria.[16] Each biopsy specimen was assessed for tissue type and the presence or absence of subsquamous intestinal metaplasia, defined as intestinal metaplasia beneath a layer of squamous epithelium. Each biopsy specimen containing intestinal metaplasia was assessed for the worst histologic grade in the sample (nondysplastic intestinal metaplasia, indefinite for dysplasia, low-grade dysplasia, high-grade dysplasia, or cancer). All samples with dysplasia underwent a confirmatory masked review by a second pathologist and, in cases of disagreement, a third review with assignment by concordance. The worst histologic grade that was identified was the overall histologic grade for that session.

STATISTICAL ANALYSIS

Power calculations were performed for the primary outcome variables with the use of estimates from cohort studies of ablative therapy and reports of the natural history of dysplastic Barrett's esophagus. We assumed that 30% of the patients in the control group would have no dysplasia at 1 year and that 5% would have no intestinal metaplasia. The study was designed to have statistical power of no less than 80% to detect a difference of 50% in the proportion of patients with complete eradication of dysplasia and a difference of 45% in the proportion of patients with complete eradication of intestinal metaplasia between the ablation group and the control group on the basis of a two-sided test with a significance level of 0.05. Calculations allowed for a dropout rate of 15 to 20%.

The study population for the primary intention-to-treat analysis included all patients who underwent randomization. In this analysis, patients who were lost to follow-up were regarded as having had a failure of treatment for the primary outcome. A secondary per-protocol analysis was performed in patients who completed the 12-month visit. Fisher's exact test and Student's t-test were used to compare baseline variables. Fisher's exact test was used to assess differences between the two study groups in eradication of dysplasia and intestinal metaplasia at 12 months. Because of a non-normal distribution, chest-pain scores were compared with the use of the Wilcoxon rank-sum test, and medians were reported.

In the intention-to-treat population, we calculated how many patients would need to be treated to prevent one outcome failure, according to the variable being assessed. Logistic regression was used to control for other risk factors and assess for predictors of response to therapy. To account for correlation in cases in which there were repeated measures from the same patient, generalized estimating equations were used. For all outcomes, a two-sided P value of less than 0.05 was considered to indicate statistical significance, and no adjustments were made for multiple comparisons. All analyses were performed with the use of SAS software, version 9.0 (SAS Institute).

RESULTS

PATIENTS

Of the 755 patients screened, 191 fulfilled study criteria and provided histologic specimens for review (Fig. 2). Of these patients, 127 underwent randomization; 64 were deemed to have low-grade dysplasia, and 63 were deemed to have high-grade dysplasia. Of the total group, 84 were assigned to

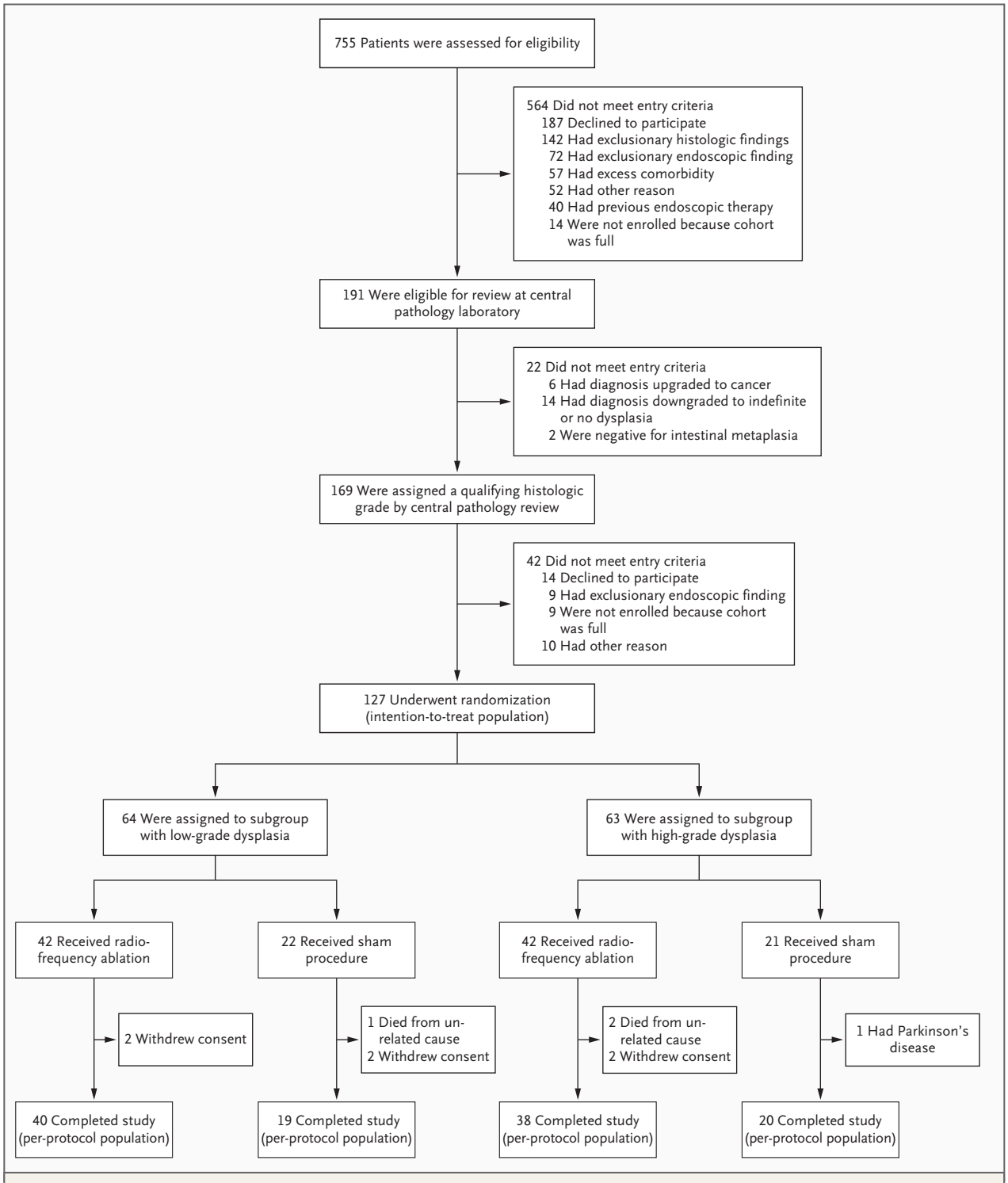

Figure 2. Enrollment and Outcomes.

Of the 127 patients in the study, 6 patients who received radiofrequency ablation and 4 who received a sham procedure (7.9% of the total) discontinued the study prematurely (P=0.23). There were three deaths that were unrelated to esophageal neoplasia during follow-up: two in the ablation group and one in the control group. A total of 11 patients had a history of endoscopic mucosal resection (7 in the ablation group and 4 in the control group).

Table 1. Baseline Characteristics of the Patients, According to Grade of Dysplasia.*

Variable	High-Grade Dysplasia (N=63)		Low-Grade Dysplasia (N=64)	
	Radiofrequency Ablation (N=42)	Sham Procedure (N=21)	Radiofrequency Ablation (N=42)	Sham Procedure (N=22)
Age — yr				
Mean	65.9±1.4	67.3±1.8	66.3±1.4	64.6±1.9
Range	49–80	54–80	41–79	45–78
Sex — no. (%)				
Female	5 (12)	0	9 (21)	3 (14)
Male	37 (88)	21 (100)	33 (79)	19 (86)
Race or ethnic group — no. (%)†				
White	38 (90)	21 (100)	40 (95)	22 (100)
Black	2 (5)	0	1 (2)	0
Latino	2 (5)	0	1 (2)	0
Body-mass index				
Mean	27.8±0.7	31.7±1.3‡	29.2±0.8	30.9±1.2
Range	21.3–38.3	23.4–46.8	18.9–44.0	21.5–41.3
Length of Barrett's esophagus — cm				
Mean	5.3±0.3	5.3±0.5	4.6±0.4	4.6±0.5
Range	1.0–8.0	1.0–8.0	0.5–8.0	0.5–8.0
Subsquamous intestinal metaplasia — no. (%)	10 (24)	3 (14)	11 (26)	8 (36)
Multifocal dysplasia — no. (%)	33 (79)	18 (86)	32 (76)	13 (59)
Time since diagnosis of Barrett's esophagus — yr				
Mean	4.7±0.6	4.2±1.4	5.8±0.7	5.2±1.0
Range	0.2–13.9	0.1–27.0	0.2–22.9	0.2–15.9
Time since diagnosis of dysplasia — yr				
Mean	2.1±0.4	1.3±0.6	2.2±0.5	2.4±0.6
Range	0.1–12.4	0.1–12.2	0.1–11.9	0.1–9.4
Current use of aspirin or NSAID — no. (%)	18 (43)	12 (57)	20 (48)	7 (32)

* Plus–minus values are means ±SE. The body-mass index is the weight in kilograms divided by the square of the height in meters. Percentages may not total 100 because of rounding. NSAID denotes nonsteroidal antiinflammatory drug.
† Race or ethnic group was self-reported.
‡ P<0.05 for the comparison between the ablation group and the control group among patients with high-grade dysplasia.

the ablation group and 43 to the control group. The baseline characteristics of the patients in the two study groups, as stratified according to the level of dysplasia, did not differ significantly, except for an elevated body-mass index (BMI) among patients with high-grade dysplasia in the control group (Table 1).

PRIMARY AND SECONDARY OUTCOMES

Regardless of the level of dysplasia, patients who received radiofrequency ablation were significantly more likely than those in the control group to achieve complete eradication of dysplasia (Fig. 3 and Table 2). Among patients with low-grade dysplasia, complete eradication of dysplasia occurred in 90.5% of the patients assigned to the ablation group, as compared with 22.7% of those assigned to the control group (P<0.001). Among patients with high-grade dysplasia, complete eradication of dysplasia occurred in 81.0% of the patients assigned to the ablation group, as compared with 19.0% of those assigned to the control group (P<0.001). Among all patients regardless of the grade of dysplasia, complete eradication of all in-

testinal metaplasia occurred in 77.4% of the patients assigned to the ablation group, as compared with 2.3% of those assigned to the control group (P<0.001).

Among patients in the ablation group, the rate of complete eradication of intestinal metaplasia among patients with high-grade dysplasia (73.8%) was similar to that among those with low-grade dysplasia (81.0%, P=0.44). Logistic-regression modeling using study group, age, BMI, length of Barrett's esophagus, and time since the diagnosis of Barrett's esophagus as predictor variables and the three primary outcome variables as response variables showed that the strong relationship between study-group assignment and eradication of dysplasia and intestinal metaplasia was not attenuated by adjustment for other risk factors (P<0.001 for study-group assignment in all three models) (for details, see the Supplementary Appendix).

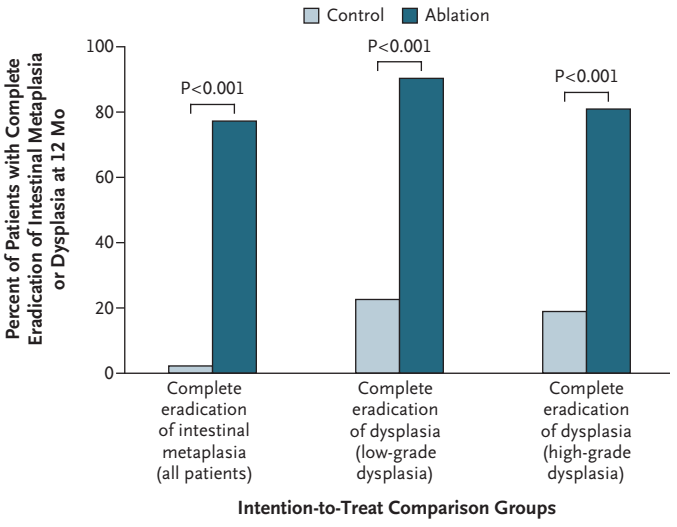

Figure 3. Primary Outcomes in the Intention-to-Treat Analysis.
The primary outcomes were complete histologic eradication of intestinal metaplasia in all patients and complete eradication of dysplasia in the subgroup with low-grade dysplasia and in the subgroup with high-grade dysplasia at 12 months.

DISEASE PROGRESSION

Patients who were assigned to the control group were more likely to have disease progression (16.3%) than were those in the ablation group (3.6%, P=0.03). Among patients with high-grade dysplasia, 19.0% of those in the control group had progression to esophageal cancer, as compared with 2.4% of those in the ablation group (P=0.04). Among all patients, esophageal cancer developed in significantly more patients in the control group than in the ablation group (9.3% vs. 1.2%, P=0.045). Of the four patients in the control group in whom esophageal cancer developed, two had intramucosal carcinoma, and two had T1 lesions; the single patient with esophageal cancer in the ablation group had intramucosal carcinoma.

SAFETY AND SIDE EFFECTS

A total of 298 treatments were performed in 84 patients in the ablation group (mean, 3.5 treatments per patient). All procedures were performed on an outpatient basis with the use of intravenous sedation (narcotic with benzodiazepine in 70% of procedures and propofol in 30%). Median procedure times were 36 minutes (interquartile range, 29 to 45) for circumferential radiofrequency ablation and 26 minutes (interquartile range, 19 to 40) for focal radiofrequency ablation.

Three serious adverse events possibly or probably associated with the study occurred in the ablation group and none in the control group (P=0.55). The events were one episode of upper gastrointestinal hemorrhage in a patient receiving antiplatelet therapy for heart disease, which was treated endoscopically; one overnight hospitalization for new-onset chest pain 8 days after radiofrequency ablation; and one overnight hospitalization for chest discomfort and nausea immediately after radiofrequency ablation. No perforations or procedure-related deaths occurred. Two extraesophageal incident cancers were diagnosed during follow-up (one gastric cancer in the ablation group and one ocular melanoma in the control group).

After the initial treatment, the degree of chest discomfort on day 1 was higher in the ablation group than in the control group (median, 23 vs. 0 on a 100-point visual-analogue scale; P<0.001). By day 8, the median chest-discomfort score had returned to 0. By comparison, because of the localized nature of focal ablation, the median day 1 score after subsequent focal radiofrequency ablation was 0.

Among patients in the ablation group, esophageal stricture (defined as endoscopically identified narrowing of the esophagus with or without dysphagia) developed in five patients (6.0%). All five patients underwent successful endoscopic dilatation (mean, 2.6 sessions).

BIOPSY ANALYSIS

From baseline to 12 months, 13,573 biopsy specimens were collected (9517 in the ablation group and 4056 in the control group). Among 1260 samples from patients with low-grade dysplasia in the ablation group, 1228 (97.5%) were free of intestinal metaplasia at 12 months, as compared with 313 of 550 samples (56.9%) in the control group (Table 2). Among 1464 samples from patients with high-grade dysplasia in the ablation group, 1442 (98.5%) were free of intestinal metaplasia at 12 months, as compared with 360 of 614 samples (58.6%) in the control group (P<0.001 for all pairwise comparisons after accounting for intrapatient correlation).

SUBSQUAMOUS INTESTINAL METAPLASIA

At baseline, 25.2% of the patients had evidence of subsquamous intestinal metaplasia (20.6% of those with high-grade dysplasia and 29.7% of those

Table 2. Primary and Secondary Outcomes at Follow-up.*

Outcome and Analysis	Radiofrequency Ablation	Sham Procedure	Relative Risk (95% CI)	P Value	No. Needed to Treat†
	no./total no. (%)				
Primary outcome					
Complete eradication of intestinal metaplasia (all patients)					
Intention-to-treat	65/84 (77)	1/43 (2)	33.3 (4.8–231.7)	<0.001	1.3
Per-protocol	65/78 (83)	1/39 (3)	32.5 (4.6–225.5)	<0.001	1.2
Complete eradication of dysplasia (low-grade dysplasia)					
Intention-to-treat	38/42 (90)	5/22 (23)	4.0 (1.8–10.7)	<0.001	1.5
Per-protocol	38/40 (95)	5/19 (26)	3.6 (1.7–7.7)	<0.001	1.5
Complete eradication of dysplasia (high-grade dysplasia)					
Intention-to-treat	34/42 (81)	4/21 (19)	4.2 (1.7–10.4)	<0.001	1.6
Per-protocol	34/38 (90)	4/20 (20)	4.5 (1.8–10.8)	<0.001	1.4
Secondary outcomes					
Complete eradication of intestinal metaplasia (high-grade dysplasia)					
Intention-to-treat	31/42 (74)	0/21	ND	<0.001	1.4
Per-protocol	31/38 (82)	0/20	ND	<0.001	1.2
Complete eradication of intestinal metaplasia (low-grade dysplasia)					
Intention-to-treat	34/42 (81)	1/22 (4)	17.8 (2.6–121.5)	<0.001	1.3
Per-protocol	34/40 (85)	1/19 (5)	16.1 (2.4–109.3)	<0.001	1.3
Complete eradication of dysplasia (all patients)					
Intention-to-treat	72/84 (86)	9/43 (21)	4.1 (2.3–7.4)	<0.001	1.5
Per-protocol	72/78 (92)	9/39 (23)	4.0 (2.2–7.1)	<0.001	1.4
Progression of dysplasia					
Any	3/84 (4)	7/43 (16)	0.2 (0.1–0.8)	0.03	7.9
Low-grade to high-grade	2/42 (5)	3/22 (14)	0.3 (0.1–1.9)	0.33	11.3
Low-grade to cancer	0/42	0/22	ND	ND	NA
High-grade to cancer	1/42 (2)	4/21 (19)	0.1 (0.01–1.0)	0.04	6.0
High-grade or low-grade to cancer	1/84 (1)	4/43 (9)	0.1 (0.01–1.1)	0.045	12.3
Biopsy specimen free of intestinal metaplasia at 12 mo					
All patients	2670/2724 (98)	673/1164 (58)	1.7 (1.6–1.8)	<0.001	NA
Low-grade-dysplasia subgroup	1228/1260 (98)	313/550 (57)	1.7 (1.6–1.8)	<0.001	NA
High-grade-dysplasia subgroup	1442/1464 (98)	360/614 (59)	1.7 (1.6–1.8)	<0.001	NA

Table 2. (Continued.)

Outcome and Analysis	Radiofrequency Ablation	Sham Procedure	Relative Risk (95% CI)	P Value	No. Needed to Treat†
	no./total no. (%)				
Secondary outcomes					
Chest-pain score on day 1‡					
All patients				<0.001	NA
No. of patients	81	40			
Median	23	0			
Interquartile range	0–51	0–0			
Low-grade dysplasia				<0.001	NA
No. of patients	40	20			
Median	26	0			
Interquartile range	4–48	0–0			
High-grade dysplasia				<0.001	NA
No. of patients	41	20			
Median	22	0			
Interquartile range	0–57	0–0			

* NA denotes not applicable, and ND not done.
† The number needed to treat refers to the number of patients who would need to be treated with radiofrequency ablation to prevent one outcome failure (the inverse of the absolute risk reduction).
‡ Chest pain was measured on a visual-analogue scale of 0 to 100, with higher scores indicating a greater severity of pain.

with low-grade dysplasia) (Table 1). At 12 months, subsquamous intestinal metaplasia occurred in 5.1% of the patients in the ablation group and in 40.0% of those in the control group (P<0.001).

PREDICTORS OF RESPONSE TO THERAPY

Bivariate analysis showed that patients in the ablation group who achieved complete eradication of intestinal metaplasia were on average younger, had shorter-length Barrett's esophagus, had a lower BMI, and had a shorter history of dysplasia than did those who did not have a complete response. However, in multivariate analysis, none of these factors reached statistical significance (for details, see the model in the Supplementary Appendix).

DISCUSSION

Despite the large number of patients with Barrett's esophagus and the remarkable increase in the incidence of esophageal adenocarcinoma in the past 30 years, the optimal management strategy for dysplastic Barrett's esophagus has not been defined. Although professional guidelines endorse various strategies,[17,18] the relative safety and efficacy of these interventions remain unclear. In uncontrolled studies, excellent results have been noted in patients with high-grade dysplasia who were treated with esophagectomy,[19] intensive endoscopic surveillance,[11] and ablative therapy.[20] Because of the morbidity and mortality associated with more invasive treatments, such as ablative therapy and surgery, a more conservative approach has been advocated by some investigators,[11] who recommend more invasive therapies only for patients with high-grade dysplasia that progresses to cancer.

In our study, we compared outcomes in patients treated with radiofrequency ablation with those in patients treated with a sham procedure, with all patients undergoing intensive endoscopic surveillance. Our data show that most patients who were treated with radiofrequency ablation had complete eradication of intestinal metaplasia and dysplasia and a decreased risk of disease progression at 12 months. Our a priori plan was to analyze the eradication of dysplasia, stratified according to the grade of dysplasia at baseline, on the basis of the hypothesis that high-grade dysplasia might be more difficult to eradicate than

low-grade dysplasia. However, we observed similar rates of complete eradication of dysplasia in both subgroups (90.5% in patients with low-grade dysplasia and 81.0% in those with high-grade dysplasia). These high rates of complete eradication were associated with a decreased incidence of progression of dysplasia and a decreased risk of esophageal cancer in the ablation group, as compared with the control group.

Our finding of a decreased incidence of cancer in the ablation group should be viewed with caution. Cancers occurred in only 5 patients (1 of 84 in the ablation group and 4 of 43 in the control group), so the shift of a single incident cancer would have resulted in a loss of statistical significance. Radiofrequency ablation was associated with a transient increase in chest pain, with a median resolution of pain by day 8, and a rate of serious adverse events that did not differ significantly from that in the control group.

In a study by Overholt and colleagues,[12,21] patients with high-grade dysplasia were randomly assigned to receive either photodynamic therapy or endoscopic surveillance, with the absence of high-grade dysplasia at any time during the 18-month follow-up as a primary outcome. The investigators observed no high-grade dysplasia in 77% of the patients receiving photodynamic therapy and in 39% of the patients in the control group, with a decreased risk of esophageal cancer in the photodynamic-therapy group. Among patients receiving such therapy, esophageal stricture developed in 36% of the patients, and 69% had a photosensitivity reaction to the chemosensitizing agent.

In our study, among patients with high-grade dysplasia, the 1-year incidence of esophageal cancer in the control group (19.0%) was higher than that reported in some previous studies.[11,13,22] There are several possible explanations for this difference. Our study incorporated a central pathology laboratory and required concurrence of two pathologists for entry. It is likely that this method resulted in the exclusion of patients with equivocal diagnoses of high-grade dysplasia, leaving a subgroup with more severe cellular atypia. A previous study with similar histologic requirements for entry likewise reported a high incidence of cancer.[12] In addition, our rigorous biopsy protocol probably provided more sensitive early detection of cancer than would standard-of-care endoscopy.[23] Finally, the patients in our study were referred to tertiary care centers and may have differed in substantial ways from patients with Barrett's esophagus in the community.

The strengths of our study include rigorous masking of study-group assignments, expert histologic analysis of biopsy samples, and a low, nondifferential loss to follow-up. Our study also had several limitations. We used eradication of intestinal metaplasia and dysplasia, along with neoplastic progression, as surrogate markers for death from cancer, even though long-term data demonstrating an association between eradication of intestinal metaplasia and a decreased risk of cancer are sparse.[21] Second, the study duration was 1 year. Although other data suggest that reversion to neosquamous epithelium after radiofrequency ablation is durable,[24] it is not clear whether the results of the study will persist. Third, because of stratified randomization according to the degree of dysplasia and our 2:1 ratio for assignment of patients to the ablation group and the control group, the number of patients in some groups was small. Fourth, since our study did not compare radiofrequency ablation with other interventions, such as photodynamic therapy and esophagectomy, we cannot determine which of these interventions is superior. Finally, whether our results can be generalized to community-practice settings is unknown.

The risk of subsquamous intestinal metaplasia after ablative therapy is a concern for all ablative techniques.[25] However, the malignant potential of subsquamous intestinal metaplasia is unknown. In our study, subsquamous intestinal metaplasia was quite common in patients (25.2%) before enrollment and, similar to previous reports,[20,26] was low after radiofrequency ablation (5.1%). Although our biopsy regimen was aggressive, it is possible that some patients had undetected subsquamous intestinal metaplasia.

Because we sought to define the efficacy of radiofrequency ablation for the spectrum of dysplasia, we enrolled patients with both low-grade dysplasia and high-grade dysplasia. However, the implications of these two diagnoses are markedly different. Low-grade dysplasia implies a risk of progression to cancer of less than 1% per patient-year,[10] whereas the risk associated with high-grade dysplasia may be higher by a factor of 10.[13,22] In making decisions about the management of precancerous conditions, clinicians, patients, and policymakers consider possible benefits and risks

of competing strategies. Because high-grade dysplasia has a more ominous natural history than low-grade dysplasia (or nondysplastic intestinal metaplasia), greater risks and costs are tolerable. For less severe disease, the safety profile and associated costs become increasingly important. Detailed consideration of these trade-offs is beyond the scope of this study. Regardless, both of the dysplasia subgroups showed high rates of reversion to squamous epithelium after radiofrequency ablation and reduced rates of disease progression with few serious adverse effects, suggesting that the application of ablative therapy in patients with low-grade dysplasia is worth further investigation and consideration.

In conclusion, in this multicenter, randomized, sham-controlled study of radiofrequency ablation in patients with dysplastic Barrett's esophagus, there was a high rate of complete eradication of dysplasia and intestinal metaplasia and decreased disease progression in patients in the ablation group, as compared with the control group.

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APPENDIX

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