

Comparison of the effects of radiofrequency ablation versus endoscopic surveillance on neoplastic progression among patients with Barrett esophagus and low-grade dysplasia: A randomized, clinical trial

K. Nadine Phoa (MD)¹; Frederike G.I. van Vilsteren (MD)¹; Bas L.A.M. Weusten (MD)², Raf Bisschops (MD)³, Erik J. Schoon (MD)⁴, Krish Ragunath (MD)⁵, Grant Fullarton (MD)⁶, Massimiliano Di Pietro (MD)⁷, Narayanasamy Ravi (MD)⁸, Mike Visser (MD)⁹, G. Johan Offerhaus (MD)⁹, Cees A. Seldenrijk (MD)¹⁰, Sybren L. Meijer (MD)⁹, Fiebo J.W. ten Kate (MD)⁹, Jan G.P. Tijssen (PhD)¹¹, Jacques J.G.H.M. Bergman (MD)¹

¹ Department of Gastroenterology, Academic Medical Center – University of Amsterdam, Amsterdam, The Netherlands

² Department of Gastroenterology, St Antonius Hospital, Nieuwegein, The Netherlands

³ Department of Gastroenterology, University Hospital Leuven, Leuven, Belgium

⁴ Department of Gastroenterology, Catharina Hospital, Eindhoven, The Netherlands

⁵ Department of Gastroenterology, Queens Medical Center, Nottingham, United Kingdom

⁶ Department of Surgical Gastroenterology, Glasgow Royal Infirmary, Glasgow, United Kingdom

⁷ Medical Research Council, Cancer Unit, Addenbrookes Hospital, Cambridge, United Kingdom

⁸ Department of Clinical Medicine & Gastroenterology, St James's Hospital, Dublin, Ireland

⁹ Department of Pathology, Academic Medical Center – University of Amsterdam, Amsterdam, The Netherlands

¹⁰ Department of Pathology, St Antonius Hospital, Nieuwegein, The Netherlands

¹¹ Department of Cardiology, Academic Medical Center – University of Amsterdam, Amsterdam, The Netherlands

Corresponding author:

Jacques Bergman, MD PhD, Professor of Gastrointestinal Endoscopy

Department of Gastroenterology and Hepatology

Academic Medical Center Amsterdam

Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

Email: j.j.bergman@amc.uva.nl

Phone number: +31-20-5663556

Word count (text only): 3451 words

Date of revision: 6 February 2014

Abstract

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: We investigated 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 and conducted between June 2007 and June 2011. Patient follow-up ended May 2013.

Interventions: Eligible patients were randomly assigned 1:1 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: 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: 68 patients were randomized to ablation and 68 to control. The planned enrollment was 126. Ablation reduced the risk of progression to high-grade dysplasia or adenocarcinoma by 25.0% (1.5% vs. 26.5%, 95% CI: 14.1-35.9; $p < 0.001$) and the risk of progression to adenocarcinoma by 7.3 (1.5% vs. 8.8%, 95% CI 0.0-14.7; $p = 0.026$). Complete eradication of dysplasia and intestinal metaplasia occurred in 92.6% and 88.2% of patients in the ablation group, respectively, compared to 27.9% and 0.0% of patients in the control group, respectively ($p < 0.001$). Treatment-related adverse events occurred in 19.1% of ablation patients ($p < 0.001$). The most common adverse event was stricture, occurring in eight ablation patients (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 a randomized trial of patients with Barrett esophagus with a confirmed diagnosis of low-grade dysplasia, radiofrequency ablation resulted in a reduced risk of neoplastic progression over 3 years of follow-up.

Trial Registration: trialregister.nl Identifier: NTR 1198

Funding: Dutch Digestive Diseases Foundation, Covidien GI Solutions (formerly BÂRRX Medical).

Wordcount: 340 (max.350)

Introduction

In the last three decades, the incidence of esophageal adenocarcinoma has increased six-fold, making it the most rapidly rising cancer in the Western world.¹ Esophageal adenocarcinoma originates from Barrett esophagus, a metaplastic change in the epithelium of the esophagus caused by gastro-esophageal 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 to estimates between 1.7%-5.6% in the US. Incidence rates vary between 23.1-32.7 per 100,000 person-years.²⁻⁶ Malignant degeneration is thought to occur in a step-wise fashion from non-dysplastic intestinal metaplasia, to low- then high-grade dysplasia, and eventually adenocarcinoma.^{7,8} Patients with Barrett esophagus undergo endoscopic surveillance or treatment, depending on the presence and grade of dysplasia.⁸

Radiofrequency ablation is an established endoscopic technique for eradication of Barrett esophagus which has been investigated in a variety of study designs (including two randomized trials), and settings (US and EU, tertiary academic centers, community referral centers).⁹⁻¹³ 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.⁹⁻¹³ As a result, radiofrequency ablation is considered standard of care for patients with high-grade dysplasia, as well as for residual Barrett tissue after endoscopic resection of early cancer.¹⁴ To date, no trial has 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.^{8,15-17} 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.¹⁸ A recent study, however, indicated that progression to high-grade dysplasia or adenocarcinoma occurs at a rate of 13.4% per patient year in this patient population, provided that the baseline diagnosis has been confirmed by expert pathologists.¹⁹ Given this significant risk of progression,, endoscopic treatment in this patient population may be justified . This is a clinically important question since 25-40% of Barrett esophagus patients are diagnosed with low-grade dysplasia at some point during follow-up.¹⁸

We conducted a multicenter randomized, trial, the SURF study (Surveillance vs. Radiofrequency), 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 (NTR1198, www.trialregister.nl). 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 at $t=0.5$ and $t=0.75$, with a nominal cut-off value of $p<0.0031$ 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 the expert central pathology panel (FtK, MV, KS, JO, SM). Exclusion criteria were prior endoscopic treatment for Barrett esophagus, history of high-grade dysplasia or adenocarcinoma, active secondary malignancy, estimated life-expectancy <2 years (according to the enrolling physician), and age <18 years or >85 years.

All patients required a baseline qualifying endoscopy <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/2cm) and from any visible abnormalities. Visible abnormalities were defined as any mucosal irregularity or discoloration within the a 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 one month after randomization, patients assigned to ablation were treated with a circumferential device (HALO³⁶⁰ system) or a focal device (HALO⁹⁰) (Covidien GI Solutions (formerly BÂRRX Medical), Sunnyvale, CA, USA) according to extent of disease and investigator preference (**Figure 1A-1E**).^{20,21} Subsequent ablation sessions occurred every 3 months, until complete endoscopic and histological eradication of Barrett esophagus (**Figure 1F**), or a maximum of 2 circumferential and a maximum of 3 focal sessions. At each ablation session, the squamocolumnar 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 ≤4 Barrett esophagus islands, ≤5mm) was allowed per protocol.¹⁰ All procedures were performed on an outpatient basis using midazolam plus fentanyl/pethidine, or propofol.

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 obtained every 2-cm of the original extent of the Barrett esophagus, starting one cm proximal to the top of the gastric folds. In addition 4 biopsies were obtained from the gastric cardia, <5-mm distal to the neo-squamocolumnar junction.

During the trial, ablation patients received double-dose proton pump inhibition as maintenance therapy. A H2-receptor antagonist and sucralfate suspension was added for 2 weeks after each therapeutic endoscopy.

Control

Patients assigned to control 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 biopsies were obtained from every 2-cm 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 nine 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.²² In cases of post-randomization biopsies 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 occurrence of high-grade dysplasia or adenocarcinoma (*i.e.*, neoplastic progression) at any time during the 3 years following randomization. Secondary outcomes were: complete histological eradication of dysplasia (*i.e.* absence of dysplasia of any grade in all biopsies obtained at the first follow-up endoscopy) and intestinal metaplasia (*i.e.* absence of intestinal metaplasia in all biopsies obtained at the first follow-up endoscopy), and adverse events. Patients who met the primary outcome were considered failures 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.

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.^{20,21,23} 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 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 two-tailed p-value <0.0440 was considered to indicate statistical significance.

Categorical variables were compared using the Fisher's exact test. Continuous variables are presented as means (\pm SD) and were compared using Student's t-test in case of a normal distribution, or presented as median (IQR) and compared using the Mann-Whitney U test in case of a 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 $p < 0.10$ the criterion level for selection. For data analysis the SPSS statistical software package (SPSS 20.0.1, IBM Corp., Armonk, NY, USA) 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 re-assessment of pre-randomization histology and/or endoscopy demonstrated study exclusion criteria (**Figure 2**). The remaining 136 patients (68 ablation, 68 control) were included in the modified-intention-to-treat population. The two 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 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 pre-planned O'Brien-Fleming method demonstrated superiority. The steering committee subsequently closed the trial on May 8th, 2013. At that time, all patients were followed for at least 24 months, with a median follow-up of 36 months and an interquartile range varying from 30 to 36 months.

Patients treated with ablation were less likely, compared to control, to progress to high-grade dysplasia or adenocarcinoma (1.5% vs. 26.5%, $p < 0.001$) and less likely to progress to adenocarcinoma (1.5% vs. 8.8%, $p = 0.026$) (**Table 2**). Ablation reduced the risk of progression to high-grade dysplasia or adenocarcinoma by 25.0% (95% CI 14.1-35.9), with a number needed to treat 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 a number needed to treat of 13.6 (95% CI 6.8- ∞).

The ablation group had one patient that progressed (adenocarcinoma). This patient was treated with endoscopic resection, and achieved complete eradication of dysplasia. The control group had 18 patients that progressed (12 high-grade dysplasia, 6 adenocarcinoma). One control patient with adenocarcinoma underwent esophagectomy for poorly differentiated submucosal carcinoma. No residual cancer or positive lymph nodes were detected and the patient remains free of disease after 37 months of follow-up. Of the remaining 17 control patient progressors, fifteen (10 high-grade dysplasia, 5 mucosal adenocarcinoma) underwent endoscopic resection ($n=9$, median 4 resections, range 1-14) and/or radiofrequency ablation ($n=15$). Eleven of fifteen achieved complete eradication

of dysplasia and intestinal metaplasia, while four are still under treatment. The remaining two progressors (2 high-grade dysplasia) opted for endoscopic surveillance.

Complete eradication of dysplasia and intestinal metaplasia occurred in 92.6% (63/68) and 88.2% (60/68) of ablation patients, respectively. During the follow-up phase of the trial, complete eradication of dysplasia was maintained in 62 of 63 (98.4%) ablation patients. 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 71%, 95%CI 59-82; $p < 0.001$). Complete eradication of intestinal metaplasia was maintained in 54 of 60 ablation patients (90.0%), compared with 0 of 68 control patients (0%) (risk difference, 90%, 95% CI 82-98; $p < 0.001$). All recurrences in the ablation group were small islands or tongues < 10 -mm (**Table 2**).

Ablation patients underwent 211 ablation sessions (median 3 per patient) and 208 endoscopic biopsy sessions (median 3 per patient, median 37 biopsies per patient). Escape endoscopic resection and argon plasma coagulation was used in 5 (7.4%) and 12 (17.6%) ablation patients, respectively. Control patients underwent 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 four days after ablation, treated to resolution with analgesics. A second patient experienced bleeding 7 days after endoscopic resection 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 three patients (no intervention required, procedure completed). One patient reported retrosternal pain three weeks after focal ablation. Endoscopy was normal and the pain resolved with analgesics. Eight patients (11.8%) developed esophageal stricture requiring dilation (median 1 dilation, IQR 1-2). There were no adverse events in control patients (risk difference 19%, 95% CI (9.7%-28.4%; $p < 0.001$).

Multivariable analysis (Model-fit significance 0.001, Nagelkerke R^2 0.35) demonstrated that the number of years since the diagnosis of Barrett esophagus (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 (data not shown).

Discussion

In this randomized trial of ablation vs. surveillance in patients with Barrett esophagus with 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% ($p < 0.001$), an absolute risk reduction of 25.0% (95% CI 14.1-35.9) corresponding to a number needed to treat of 4.0. In addition, ablation reduced the risk of progression to adenocarcinoma, from 8.8% to 1.5% ($p = 0.026$), an absolute risk reduction of 7.4% (95% CI 0.0-14.7), corresponding to a number needed to treat of 13.6. Of patients who underwent ablation, 92.6% achieved complete eradication of dysplasia, versus 27.9% in controls. Complete eradication of intestinal metaplasia was achieved in 88.2% of patients, versus 0.0% in controls. Follow-up after ablation showed that eradication of dysplasia and intestinal metaplasia persisted in the majority of patients. These results comport with those of previous prospective studies of ablation for HGD and adenocarcinoma in Barrett esophagus.^{9,12,24}

This trial was terminated early, upon recommendation of the Data and Safety Monitoring Board, due to superiority of ablation for the primary endpoint 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-years 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 subjects with Barrett esophagus and confirmed low-grade dysplasia. Given the high rate of malignant degeneration in our control group, and the relatively low number needed to treat to avert a single progression, as well as the acceptable safety profile, a paradigm shift to earlier endoscopic intervention in this patient population deserves consideration.

Of note, no control patient demonstrated unresectable cancer or cancer-related death. While 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, one of our control patients did require esophagectomy for development of advanced stage disease. Outside of a rigorous study protocol, neoplastic progression in subjects 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 patient year of follow-up) comports with rates from studies requiring expert GI pathologist confirmation.^{7,13,17} The observed progression rate in our control group, however, contrasts with lower rates from other studies (1.4%- 1.83% per patient year) with no expert confirmation of baseline diagnosis or poor interobserver agreement.¹⁵⁻¹⁷ After expert pathology review, 50-85% of patients initially diagnosed with low-grade dysplasia may be down-staged to non-dysplastic Barrett's with an associated lower risk of neoplastic progression.^{19,25} Expert pathology review by a panel of experienced pathologists with an acceptable inter-observer agreement (kappa 0.50 for our panel¹⁹) is therefore important to accurately ascertain patient risk for progression and determining which patients would benefit from treatment vs. surveillance.

Of note, 28% of controls had no dysplasia detected during follow-up. This proportion is similar to the randomized trial by Shaheen *et al.* where 26% of low-grade controls did not show dysplasia at 12 months follow-up.¹² Ideally, ablation should be avoided in these patients, given their lower risk of progression and the associated risks and costs of treatment, however we don't know in advance which patients will fail to demonstrate LGD 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 to patients with only focal dysplasia (spatial distribution).²⁶ Second, low-grade dysplasia on multiple endoscopies likely increases the risk of progression compared to a single endoscopy diagnosis (temporal distribution).²⁷ In our study, 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 patients 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 median 1 dilation. This is higher than the 5% pooled estimate of a recent meta-analysis, however this analysis was limited by heterogeneity of the included studies of which half were retrospective studies.²⁸ 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 AIM Dysplasia trial was 2.6.¹²

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 work-up, treatment and follow-up of Barrett esophagus with dysplasia should be restricted to centers with extensive expertise in this field. Second, our primary endpoint was progression to a combined endpoint of high-grade dysplasia or adenocarcinoma and our trial was underpowered for a “cancer-related death” endpoint. However, progression to high-grade dysplasia/adenocarcinoma is the most clinically relevant and appropriate endpoint, as both are presently considered indications for endoscopic treatment. Third, a confirmed diagnosis of low-grade dysplasia at one 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.

Conclusions

In this multicenter, randomized trial of radiofrequency ablation versus surveillance in patients with a 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.

Wordcount: 3451 (max. 3000)

Author Contributions

Dr Bergman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

van Vilsteren, Weusten, Bisschops, Schoon, Rangunath and Bergman designed the study. Phoa, van Vilsteren, Weusten, Bisschops, Schoon, Rangunath, Di Pietro, Ravi, Visser, Offerhaus, Seldenrijk, Meijer, ten Kate, and Bergman did the data collection, analysis and interpretation. Phoa, Tijssen and Bergman did the statistical analysis and interpretation of statistical data. Phoa, Tijssen and Bergman wrote the paper and created the figures. All authors reviewed the drafts of the paper and gave final approval of the version to be published.

SURF study group

Steering committee: Bergman (principal investigator) and Tijssen. Writing committee: Phoa, Tijssen and Bergman. Data safety monitoring board: NJ Shaheen (chair, gastroenterologist), M Vieth (pathologist) and J Rubenstein (gastroenterologist). Study investigators: The Netherlands: Weusten, St Antonius Ziekenhuis, Nieuwegein; Schoon, Catharina Ziekenhuis, Eindhoven; Bergman, Academisch Medisch Centrum Amsterdam, Amsterdam. Belgium: Bisschops, UZ Gasthuisberg, Leuven. United Kingdom: Rangunath, Queens Medical Center, Nottingham; Fullarton, Royal Infirmary, Glasgow; Di Pietro and R Fitzgerald, Addenbrookes Hospital, Cambridge. Ireland: Ravi and D O'Toole, St James's Hospital, Dublin. Germany: Pech, Dr. Horst-Schmidt Kliniken, Wiesbaden. Study pathologists: The Netherlands: Visser, Offerhaus, ten Kate and Meijer, Academisch Medisch Centrum Amsterdam, Amsterdam; Seldenrijk, St Antonius Ziekenhuis, Nieuwegein.

Conflicts of interest

Dr. Bergman reports grants from Dutch Digestive Disease Foundation, grants and non-financial support from Covidien GI solutions (formerly BÂRRX Medical), during the conduct of the study; personal fees from Covidien GI solutions (formerly BÂRRX Medical), grants from Covidien GI solutions (formerly BÂRRX Medical), outside the submitted work; Dr. Bisschops reports grants from Fund for Scientific research Flanders (FWO), during the conduct of the study; personal fees from Covidien GI solutions (formerly BÂRRX Medical), outside the submitted work; Dr. Fullarton reports personal fees from Covidien GI solutions (formerly BÂRRX Medical), outside the submitted work;. Dr. Phoa reports grants from Dutch Digestive Diseases Foundation (MLDS), non-financial support from Covidien GI solutions (formerly BÂRRX Medical), during the conduct of the study; personal fees from Covidien GI solutions (formerly BÂRRX Medical), outside the submitted work;

Dr. Di Pietro reports educational grants from Covidien GI solutions (formerly BÂRRX Medical), outside the submitted work; Dr. Rangunath reports non-financial support from Covidien GI solutions (formerly BÂRRX Medical), during the conduct of the study; grants, personal fees and non-financial support from Covidien GI solutions (formerly BÂRRX Medical), outside the submitted work; Dr. Schoon reports grants from Astra-Zeneca, personal fees from BEST-academia, during the conduct of the study; Dr. van Vilsteren reports grants from Dutch Digestive Diseases Foundation (MLDS), non-financial support from Covidien GI solutions (formerly BÂRRX Medical), during the conduct of the study. Dr. Meijer, Dr. Ten Kate, Dr. Offerhaus Dr. Ravi, Dr. Seldenrijk, Dr. Tijssen, Dr. Visser, Dr. Weusten reported no conflicts.

Funding/Support

This work was supported, in part, by Covidien GI Solutions, (formerly BÂRRX Medical), Sunnyvale, CA, USA and by a grant from the Dutch Digestive Diseases Foundation (MLDS grant: WO 07-60).

Role of the funding source

This was an investigator initiated trial supported by grants from the Dutch Digestive Diseases Foundation and Covidien GI Solutions, (formerly BÂRRX Medical), Sunnyvale, California, USA. These organizations were not involved in study design, data collection/entry, analysis, interpretation, writing or submission of the report. Covidien GI Solutions provided ablation devices and access to a central electronic data management system. Approval of the manuscript and the decision to submit the manuscript for publication was made by the steering committee.

Additional Contributions

We thank research fellows Roos E Pouw, MD; Lorenza Alvarez Herrero, MD and Wouter L Curvers, MD, Academic Medical Center Amsterdam for their help in setting up this trial, and research nurses Carine M Sondermeijer, BSc; Wilda D Rosmolen, MSc; Brenda Elzer, MSc and Ineke Verhulst, Academic Medical Center Amsterdam; Kim van der Meulen, St Antonius Hospital Nieuwegein; Mirjam van Loon, Catharina Hospital Eindhoven and Hilde Willekens, University Hospital Leuven for their professional research support, no compensation for their work was provided. We thank Oliver Pech, MD, Dr. Horst-Schmidt Kliniken, Wiesbaden for his contribution in setting up this trial in Germany, who was compensated by Covidien GI solutions for IRB approval. We thank Martin Houben, MD, Hagaziekenhuis, Den Haag; Ed Schenk, MD, Isala klinieken, Zwolle; Arnoud van Oijen, MD, Medisch Centrum Alkmaar, Alkmaar; Antonius HJ Naber, MD, and Jan MH van den Brande, MD, Tergooziekenhuizen, Hilversum; Jeroen J Kolkman, MD, Medisch Spectrum Twente, Enschede;

Lubbertus C Baak, Onze Lieve Vrouwe Gasthuis, Amsterdam; Pieter Scholten, MD, St Lucas Andreas Ziekenhuis, Amsterdam; Clarisse Böhmer, MD, Spaarne Ziekenhuis, Hoofddorp; Rosalie C Mallant-Hent, MD, Flevoziekenhuis, Almere, The Netherlands for helping to make the SURF trial possible, no compensation for their work was provided. We thank the Fund for Scientific Research of Flanders for supporting the SURF trial in Belgium by providing a research grant to Dr. Bisschops. We thank all patients for participating in this trial.

Figure 1. Radiofrequency ablation treatment in a patient with Barrett esophagus and low-grade dysplasia

An endoscopic image shows the distal esophagus at the baseline endoscopy, looking toward the gastro-esophageal junction (A). A deflated circumferential radiofrequency ablation balloon is positioned in the segment of Barrett esophagus. The immediate treatment effect of the circumferential ablation can be seen (B). The focal radiofrequency ablation device is used for targeted ablation of a small area of residual Barrett epithelium (C). An endoscopic photograph shows the distal esophagus after complete eradication of all Barrett epithelium (D). Shown images do not correspond to the same patient.

Figure 2. Enrollment and outcomes.

BQE denotes baseline qualifying endoscopy; FU denotes follow-up; HGD denotes high-grade dysplasia; LGD denotes low-grade dysplasia; NDBE denotes non-dysplastic Barrett esophagus.

Figure 3. Occurrence of progression to high-grade dysplasia or adenocarcinoma.

Shown is the rate of progression to high-grade dysplasia or cancer, in the two study groups. Using log-rank testing there was a significant difference ($p < 0.001$) between the two groups.

Table 1. Demographic and disease-specific characteristics of enrolled patients.*

Characteristic	Ablation (n=68)	Control (n=68)
Age – yr	63±10	63±9
Male sex – no. (%)	55 (81)	61 (90)
Whiterace or ethnic group – no. (%) †	66 (97)	66 (97)
Body Mass Index ‡	26.8±3.7	27.9±4.8
Circumferential Barrett esophagus – cm ¶/¥	2 (0-6)	2 (1-4)
Maximum Barrett esophagus – cm ¶/¥	4 (2-8)	4 (3-6)
Time since diagnosis of Barrett esophagus – yr ¶	5 (2-10)	7 (3-11)
Time since diagnosis of dysplasia – yr ¶	1 (0-5)	2 (0-5)
Barrett surveillance endoscopies prior to baseline – no. ¶	5 (3-8)	5 (3-7)
Barrett surveillance endoscopies with dysplasia prior to baseline – no. ¶	2 (1-4)	2 (1-3)
Reported history of gastro-esophageal reflux disease – no. (%) †	62 (91)	65 (96)
Reported use of proton-pump inhibitor – no. (%) †	68 (100)	67 (99)
Use of proton-pump inhibitors – yr ¶	8 (5-14)	9 (4-14)

* Plus-minus values are means±SD and were compared using independent T-test. Categorical data were compared using Fisher’s Exact test. There were no significant differences between the two study groups.

† Race or ethnic group, history of reflux disease and use of proton-pump inhibitors were self reported.

‡ The body mass-index is the weight in kilograms divided by the square of the height in meters.

¶ Data are shown as median (IQR) and were compared using Mann-Whitney U test. There were no significant differences between the two study groups.

¥ The circumferential and maximum Barrett extent were measured according to the Prague C&M classification.²⁹

Table 2. Primary and secondary efficacy outcomes.

Efficacy outcomes	Ablation (n=68)	Control (n=68)	Risk difference	95% confidence interval	P value*
	Patients with Event <i>no. (%)</i>	Patients with Event <i>no. (%)</i>	%	%	
Progression to high-grade dysplasia or cancer	1 (1.5)	18 (26.5)	25.0	14.1-35.9	<0.001
Progression to cancer	1 (1.5)	6 (8.8)	7.3	0.0-14.7	0.026
Complete eradication of dysplasia at the end of endoscopic treatment	63/68 (92.6)‡	--	--	--	n.a.
Complete eradication of IM at the end of endoscopic treatment	60/68 (88.2)‡	--	--	--	n.a.
Complete eradication of dysplasia during follow-up [¶]	62/63 (98.4)‡	19/68 (27.9)	70.5	59.4-81.6	<0.001
Complete eradication of IM during follow-up [¶]	54/60 (90.0)‡	0/68 (0.0)	90.0	82.4-97.6	<0.001

* Two-sided p-values were derived using log-rank testing on Kaplan-Meier estimates.

‡ Including one patient who died of metastasised lung carcinoma after the second ablation treatment and one patient who had esophageal adenocarcinoma diagnosed after the fourth ablation session as failures for complete eradication of dysplasia and intestinal metaplasia.

¶ If, at any follow-up endoscopy biopsies showed intestinal metaplasia or low-grade dysplasia, this was considered a failure for persistence of complete eradication during follow-up.

Table 3. Univariable and multivariable analysis of predictors of progression in the control group.

Variable	Univariable analysis		Multivariable analysis	
	Odds Ratio (95% CI)	p value	Odds Ratio (95% CI)	p value
Age - yr	0.94 (0.88-1.00)	0.06	0.92 (0.85-1.00)	0.05
Body Mass Index	1.06 (0.94-1.18)	0.36		
Circumferential Barrett esophagus - cm	1.12 (0.93-1.34)	0.25	1.35 (1.04-1.76)	0.03
Maximum Barrett esophagus - cm	1.05 (0.86-1.28)	0.63		
Time since diagnosis of Barrett esophagus - yr	0.88 (0.77-0.99)	0.04	0.84 (0.72-0.98)	0.02
Time since diagnosis of dysplasia - yr	1.00 (0.97-1.03)	0.86		
Barrett surveillance endoscopies prior to baseline - no	0.97 (0.78-1.20)	0.77		
Barrett surveillance endoscopies with dysplasia prior to baseline - no	1.24 (0.94-1.63)	0.12	1.44 (1.03-2.03)	0.03
Use of proton-pump inhibitors - yr	0.96 (0.91-1.05)	0.49		

References

1. 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):142–6. doi:10.1093/jnci/dji024.
2. Ronkainen J, Aro P, Storskrubb T, et al. Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology.* 2005;129(6):1825–31. doi:10.1053/j.gastro.2005.08.053.
3. 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):572–7. doi:10.1007/s10620-008-0395-7.
4. 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):451–7. doi:10.1111/j.1442-2050.2010.01054.x.
5. 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):1062–6. doi:10.1136/gut.2004.063685.
6. 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):516–24. doi:10.1111/j.1572-0241.2007.01599.x.
7. Shaheen NJ, Richter JE. Barrett's oesophagus. *Lancet.* 2009;373(9666):850–61. doi:10.1016/S0140-6736(09)60487-6.
8. Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology.* 2011;140(3):1084–91. doi:10.1053/j.gastro.2011.01.030.
9. 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. doi:10.1053/j.gastro.2013.03.046.
10. 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):765–73. doi:10.1136/gut.2010.229310.
11. 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):23–9. doi:10.1016/j.cgh.2009.07.003.
12. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med.* 2009;360(22):2277–88. doi:10.1056/NEJMoa0808145.

13. 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):781–9. doi:10.1055/s-0030-1255779.
14. Bennett C, Vakil 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):336–46. doi:10.1053/j.gastro.2012.04.032.
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):1179–86, 1186.e1. doi:10.1053/j.gastro.2011.06.055.
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):1375–83. doi:10.1056/NEJMoa1103042.
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):1049–57. doi:10.1093/jnci/djr203.
18. Vieth M. Low-grade dysplasia in Barrett's esophagus - an innocent bystander? *Contra. Endoscopy*. 2007;39(7):647–649. doi:10.1055/s.
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):1523–30. doi:10.1038/ajg.2010.171.
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):359–69.
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):370–9.
22. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut*. 2000;47(2):251–5.
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):185–95. doi:10.1016/j.gie.2006.09.033.
24. 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. doi:10.1016/j.gie.2011.03.1243.
25. 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):682–8. doi:10.1080/00365520601075803.

26. 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):483–93; quiz 694. doi:10.1111/j.1572-0241.2007.01073.x.
27. Hur C, Choi SE, Rubenstein JH, et al. The cost effectiveness of radiofrequency ablation for Barrett's esophagus. *Gastroenterology*. 2012;143(3):567–75. doi:10.1053/j.gastro.2012.05.010.
28. 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):1245–55. doi:10.1016/j.cgh.2013.03.039.
29. 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):1392–9. doi:10.1053/j.gastro.2006.08.032.