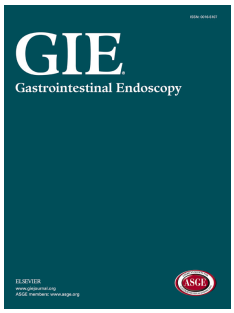

Radiofrequency ablation for low-grade dysplasia in Barrett's esophagus: long-term outcome of a randomized trial

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Radiofrequency ablation for low-grade dysplasia in Barrett's esophagus: long-term outcome of a randomized trial

Short title: RFA for low-grade Barrett's dysplasia

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R.E. Pouw: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; *E. Klaver:* study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript *K.N. Phoa:* study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; *F.G. van Vilsteren:* study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; *B.L. Weusten:* acquisition of data; critical revision of the manuscript for important intellectual content; *R. Bisschops:* acquisition of data; critical revision of the manuscript for important intellectual content; *E.J. Schoon:* acquisition of data; critical revision of the manuscript for important intellectual content; *O. Pech:* acquisition of data; critical revision of the manuscript for important intellectual content; *H. Manner:* acquisition of data; critical revision of the manuscript for important intellectual content; *K. Ragunath:* acquisition of data; critical revision of the manuscript for important intellectual content; *Jacobo Ortiz:* acquisition of data; critical revision of the manuscript for important intellectual content; *G. Fullarton:* acquisition of data; critical revision of the manuscript for important intellectual content; *M. Di Pietro:* acquisition of data; critical revision of the manuscript for important intellectual content; *W. Januszewicz:* acquisition of data; critical revision of the manuscript for important intellectual content; *D. O'Toole:* acquisition of data; critical revision of the manuscript for important intellectual content; *J.J. Bergman:* study concept and design; acquisition of data; critical revision of the manuscript for important intellectual content; study supervision.

ABSTRACT

Background and Aims: A prior randomized study (Surveillance versus Radiofrequency Ablation study [SURF study]) demonstrated that radiofrequency ablation (RFA) of Barrett's esophagus (BE) with confirmed low-grade dysplasia (LGD) significantly reduces the risk of esophageal adenocarcinoma. Our aim was to report the long-term outcomes of this study.

Methods: The SURF study randomized BE patients with confirmed LGD to RFA or surveillance. For this retrospective cohort study, all endoscopic and histological data acquired after end of the SURF study in May 2013 until December 2017 were collected. The main outcome was rate of progression to HGD/cancer. All 136 patients randomized to RFA (n=68) or surveillance (n=68) in the SURF study were included. After closure of the SURF study, 15 surveillance patients underwent RFA based on the patient's preference and the outcomes of the study.

Results: With 40 (IQR 12-51) additional months, the total median follow-up from randomization to last endoscopy was 73 (IQR 46-85) months. HGD/cancer was diagnosed in 1 patient in the RFA group (1.5%) and 23 in the surveillance group (33.8%) (p 0.000), resulting in an absolute risk reduction of 32.4% (95% CI, 22.4%-44.2%) with a number needed to treat of 3.1 (95% CI, 2.3-4.5). Seventy-five out of 83 patients (90%; 95% CI, 82.1%-95.0%) treated with RFA for BE reached complete clearance of BE and dysplasia. BE recurred in 7 out of 75 patients (9%; 95% CI, 4.6%-18.0%) mostly minute islands or tongues, LGD in 3 out of 75 (4%; 95% CI, 1.4%-11.1%).

Conclusions: RFA of BE with confirmed LGD significantly reduces risk of malignant progression, with sustained clearance of BE in 91% and LGD in 96% of patients, after a median follow-up of 73 months.

Keywords: Barrett's esophagus; low-grade dysplasia; radiofrequency ablation; surveillance.

INTRODUCTION

Barrett's esophagus (BE) is a precursor lesion for esophageal adenocarcinoma, a disease with increasing incidence and poor 5-year survival (1, 2). Progression to cancer in BE patients is believed to occur in a stepwise manner from nondysplastic intestinal metaplasia (IM) to low-grade dysplasia (LGD), high-grade dysplasia (HGD), and eventually invasive cancer (3). To detect cancer at a curable stage, regular endoscopic surveillance with biopsies is advised for known BE patients. The presence and grade of dysplasia found during surveillance determine further management. Current (inter-) national guidelines advise endoscopic treatment for BE with HGD or early stage cancer using endoscopic resection (ER), radiofrequency ablation (RFA), or a combination thereof. Patients with nondysplastic BE will receive regular endoscopic surveillance with biopsies at intervals guided by the length of the BE segment (4-7).

Over the past years, a shift has occurred in the management of BE patients with LGD. As an alternative to endoscopic surveillance, prophylactic treatment of the BE with RFA is now recommended to be considered by most guidelines (4, 8, 9). This recommendation is strongly based on the outcomes of the Surveillance Versus Radiofrequency Ablation (SURF) study (10). This prospective randomized trial was conducted between 2007 and 2013 and compared RFA with endoscopic surveillance in patients with BE and LGD confirmed by an expert pathology panel (10). The primary outcome was progression to HGD and/or cancer. A 25% absolute risk reduction in neoplastic progression over 3 years of follow-up was seen in the RFA group compared with the surveillance group (1.5% vs 26.5%, p<.001). Because of the superiority of RFA, the SURF study was stopped prematurely. The aim of this study was to describe the long-term follow-up results of the SURF study.

METHODS

Study setting and patients

This is a retrospective cohort study of all 136 patients included in the SURF study (trialregister.nl identifier NTR1198) (10). Patients were considered eligible for randomization in the SURF study if they had BE with at least one diagnosis of LGD confirmed by an expert central pathology panel, within 18 months before randomization. Exclusion criteria included previous endoscopic treatment for BE, history of HGD or esophageal adenocarcinoma, active secondary malignancy, estimated life expectancy less than 2 years, and age of 18 years or younger or 85 years or older. The study was conducted in 8 hospitals in 5 countries in Europe. For the SURF study, 68 patients were randomized to RFA treatment and 68 patients to endoscopic surveillance. The RFA treatment protocol has been described in detail in the SURF study (10). At the end of the SURF study, it was up to the discretion of the endoscopist and preference of the patients in the surveillance arm, whether RFA was performed. After RFA treatment, the first follow-up endoscopy was scheduled 3 months after the last therapeutic endoscopy, and subsequent follow-up endoscopies were performed annually thereafter. Biopsy specimens just distal to the neosquamocolumnar junction and from 4 quadrants every 2 cm of the original BE length were obtained during follow-up in the SURF protocol; after this, biopsies after RFA were not required if no visible BE mucosa was seen. For this study, data from all endoscopies and correlating histology performed after end of the SURF study in May 2013 up to December 2017 were retrieved and entered in a dedicated database.

Outcomes

The primary outcome was rate of progression to HGD and/or cancer in patients randomized to RFA and patients randomized to endoscopic surveillance. Progression was defined as a diagnosis of HGD or cancer in biopsies or ER specimens, assessed by an expert pathologist. Patients were followed from the time of randomization till last follow-up endoscopy. Patients were censored from the analysis at the point where follow-up was discontinued, in case of unrelated death and for surveillance patients when they were treated with ablation for BE with LGD after end of the SURF study.

Secondary outcomes included:

1. Recurrence of BE, dysplasia, and focal IM distal to a normal-appearing neosquamocolumnar junction among patients who achieved complete clearance of IM with LGD (CIM) by RFA treatment. Recurrence of BE was defined as endoscopically visible Barrett's mucosa, also when no biopsy specimens were obtained to confirm presence of IM. IM found in biopsy specimens obtained from a normal-appearing neosquamocolumnar junction was not considered a recurrence of BE. CIM was defined as a single endoscopy without endoscopic evidence of Barrett's mucosa and without IM or dysplasia in biopsy specimens obtained just distal to the neosquamocolumnar junction after RFA treatment.

2. Regression of LGD in the surveillance group without any ablative treatment, defined as no more LGD in biopsy specimens obtained according to Seattle protocol at any follow-up endoscopy after randomization in the SURF study.

3. Outcomes of patients with progression to HGD/cancer at any point during the SURF study.

Statistical analysis

Statistical analysis was performed using a statistical software package (Statistical Package for the Social Sciences 24; SPSS Inc, Chicago, Ill, USA). Descriptive statistics were described using median with interquartile range (IQR) for variables with a skewed distribution. Proportional event rates during follow-up were assessed by Kaplan Meier estimate and compared using a log-rank test.
All authors had access to the study data and reviewed and approved the final manuscript.
The medical ethics review committee of the Academic Medical Center Amsterdam waived the need for ethical approval.

RESULTS

A total of 136 patients was included in the original SURF study, of which 68 were randomized to RFA

treatment and 68 to endoscopic surveillance. Demographic and disease-specific characterisics are presented in the SURF study (10). In May 2013 the SURF study was prematurely closed based on a significant difference ($p < 0.001$) in progression to HGD/cancer in the RFA group (1 patient, 1.5%) compared with the surveillance group (18 patients, 26.5%) (10). This study adds an additional median follow-up of 40 (IQR 12-51) months, resulting in a total median follow-up of 73 (IQR, 46-85) months from randomization to last follow-up endoscopy. In the initial surveillance group, a total of 401 endoscopies was performed from randomization until progression or the last follow-up endoscopy, including the RFA endoscopies underwent by the 15 patients that switched. In the RFA group a total of 641 endoscopies was performed from randomization until progression or the last endoscopy.

Figure 1 depicts the flow of patients during and after the closure of the SURF study. In the surveillance group, 15 patients were treated with RFA for BE with persisting LGD after the study was closed. In the remaining patients surveillance was discontinued in 9 patients at some point due to comorbidity (n=3)/death (n=4), patient's preference (n=1) and unknown reason (n=1). In the RFA group, follow-up was discontinued in 12 patients at some point due to comorbidity(n=2)/death (n=3), old age (n=5), or patient's preference (n=2).

Progression to HGD/cancer

Figure 2 shows a Kaplan Meier survival curve depicting progression-free survival for HGD and cancer in the RFA group and surveillance group from start of randomization, censoring those patients in whom follow-up was discontinued and surveillance patients treated with ablation after ending of the SURF study. In the RFA group, apart from to the patient with progression to cancer during the SURF study, no additional patients showed progression at further follow-up. In addition to the 18 surveillance patients in the SURF study, 5 more patients showed progression to HGD (n=4) or intramucosal cancer (n=1). Overall, progression to HGD/cancer was seen in 1 patient (1/68, 1.5%) in

the RFA group (cancer, T1a) and in 23 patients (23/68, 33.8%) in the surveillance group (HGD, 16; T1a cancer, 6; T1b cancer, 1) (p 0.000). This resulted in an absolute risk reduction of 32.4% (95% CI, 22.4%-44.2%) with a number needed to treat of 3.1 (95% CI, 2.3-4.5). Progression to cancer was seen in 1.5% of the patients in the ablation group and 10.3% in the surveillance group, reducing the risk of progression the adenocarcinoma by 8.8% (95% CI, 4.1%-17.9%).

Recurrence rate

In addition to the 68 patients in the RFA group of the SURF study, 15 patients from the surveillance group were treated with RFA for BE with LGD after closure of the SURF study. CIM was achieved in 75 out of 83 patients (90%; 95% CI, 82.1%-95.0%). During a median follow-up of 63 months (IQR, 44-79) from last treatment, among the patients who had achieved CIM, recurrence of visible Barrett's mucosa was observed in 7 out of 75 patients (9.3%; 95% CI, 4.6%-18.0%). In 5 of these 7 cases, histological confirmation of IM was obtained by biopsy specimens. In 2 out of 7 cases, no biopsy specimens were obtained, but immediate additional treatment was performed. All BE recurrences were small islands or tongues of less than 10 mm, except for 1 patient in whom a C<1M2 BE segment with reflux esophagitis grade C was diagnosed upon endoscopy 86 months after the last RFA treatment. Recurrence of LGD was found in 3 of these (3/75, 4%; 95% CI, 1.4%-11.1%), successfully treated by ER (n= 1) and APC (n= 1) or left untreated (n= 1).

In 16 out of 75 patients (21%; 95% CI, 13.6%-31.9%) who were treated successfully with RFA, focal IM was found just below a normal-appearing neosquamocolumnar junction. This was reproduced in only 5 patients.

Regression of LGD

In the original SURF study, 19 out of 68 patients (28%) in the surveillance group did not show any dysplasia during the scheduled 3-year follow-up period with 4 endoscopies. In 3 out of 19 patients,

surveillance was discontinued after the SURF study. During additional follow-up, LGD was diagnosed again in 6 out of 16 patients of whom one progressed to HGD. In 10 out of 16 patients no more LGD was detected during further surveillance. These patients all had multifocal LGD, except one. The 6 patients with a recurring LGD diagnosis also all had multifocal LGD.

Outcomes of patients with progression to HGD/cancer

A total of 24 patients showed progression to HGD (n= 16) or adenocarcinoma (n= 8). One patient in the surveillance group underwent esophagectomy after an endoscopic resection of a poorly differentiated submucosal carcinoma, without residual cancer or positive lymph nodes in the esophagectomy specimen. Of the remaining 23 progressors, 11 were treated with ER and RFA and 12 with RFA monotherapy. Complete clearance of neoplasia was reached in all 23 out of 23 (100%) patients treated endoscopically and CIM was reached in 20 out of 23 (87%; 95% CI, 67.9%-95.5%). During a median follow-up of 37 months (IQR 12-61) with a median number of 3 endoscopies (IQR 1-6) per patient, 2 patients had a recurrence of Barrett's mucosa (2/23, 9%). One patient was treated successfully with endoscopic resection for nondysplastic Barrett's mucosa. The other patient had recurrence of Barrett's mucosa harboring an early cancer (1/23, 4%), which was successfully treated by endoscopic resection.

DISCUSSION

In 2014 Phoa et al[10] published the results of a randomized trial demonstrating that RFA treatment decreases the risk of progression to HGD/cancer in BE patients with confirmed LGD by 25% (SURF study). The current study describes the long-term follow-up results of this randomized trial, which was important in accepting RFA treatment as an alternative to surveillance for BE with LGD in current guidelines. This study adds an additional median follow-up of 40 (IQR 12-51) months, resulting in a total median follow-up of 73 (IQR 46-85) months. Next to the patient in the RFA group who

progressed to cancer during the SURF study, no additional patients in the RFA group showed progression during further follow-up. In the surveillance group, where 18 patients already showed malignant progression during the SURF study, another 5 patients progressed to HGD (n=4) or cancer (n=1). RFA treatment reduced the absolute risk of progression by 32.4% (95% CI, 22.4%-44.2%) with a number needed to treat of 3.1 (95% CI, 2.3-4.5) and a relative risk reduction of 95.7% (95% CI, 68.7%-99.4%). Furthermore, RFA treatment was effective with complete clearance of all BE and dysplasia in 90% of patients, which proved to be durable in >95% during a median follow-up of 63 months. The results of this follow-up study, therefore, endorse the results of the earlier SURF study and confirm that RFA can be considered in patients with confirmed LGD, given the significant reduced risk of malignant progression, the low NNT, and the relatively low risk of adverse events. On the other hand, one could argue that strict surveillance remains a legitimate strategy because all patients except one could be treated endoscopically and no unresectable cancer was demonstrated. It should be taken into account, however, that these patients were surveyed mainly within a strict study protocol and in clinical practice, progression might be detected at a later stage. Nevertheless, the advantages of RFA treatment in patients with confirmed LGD should be balanced against patients preference, comorbidity, and life expectancy.

In 9 patients (13.2%) of the surveillance group, follow-up was discontinued versus 12 patients (17.6%) of the RFA group. The main reason in both groups for discontinuation was comorbidity or death (unrelated to Barrett's esophagus). The mean age was 62 years for both groups as can be seen in the demographics stated in the SURF study. In both groups, the mean body mass index was above 25 (ablationgroup 26.8 vs control 27.9), suggesting a nonoptimal health status. In the RFA group 2, patients preferred to discontinue the follow-up opposed to 1 patient in the surveillance group, but because these numbers are very small, no conclusions can be drawn from this.

In the SURF study, 19 patients (28%) did not have their baseline LGD diagnosis reproduced during the four subsequent endoscopies in the surveillance arm of the SURF study. Concerns were raised that this implied that 28% of patients with a single diagnosis of LGD might be overtreated, because LGD was only a single finding. However, during further follow-up we found that a repeat diagnosis of LGD was confirmed in 6 patients, of which one progressed to HGD.

When looking at the temporal distribution of LGD diagnosis in the 23 patients who progressed, the diagnosis LGD was reproduced after the initial baseline diagnosis in 22 out of 23 (96%) patients. These results are in concordance with most guidelines that advise performing RFA treatment in patients with at least 2 diagnoses of LGD to minimize overtreatment.

In a study by Duits et al (11) , 255 patients with a baseline diagnosis of LGD had their baseline LGD biopsies and subsequent LGD diagnosis during follow-up reviewed by 3 expert pathologists. During a median follow-up of 42 months, 45 out of 255 patients (18%) developed HGD or cancer. Duits et al found that the risk of neoplastic progression significantly increased when LGD was diagnosed at 2 subsequent endoscopies (OR 9.28).

By applying RFA in patients with a repeat diagnosis of LGD, the benefit on the reduction of neoplastic progression would probably even be higher than demonstrated by the SURF study and our follow-up study, which also included patients with a single diagnosis of LGD.

Next to efficacy, safety is also a very important issue when offering prophylactic treatment. In the SURF study, there were 2 serious adverse events related to the RFA treatment. One patient was admitted 4 days after ablation because of pain requiring analgesics. The other patient, who also underwent ER for a visible lesion after RFA, was dilated for a stenosis and developed fever and chills for which he was admitted and treated with antibiotics. Furthermore, 8 patients developed an esophageal stricture requiring a median of 1 dilation (IQR 1-2) (10). These results are in accordance with other studies that reported that RFA treatment is a safe treatment with a relatively low risk of

adverse events. This is especially the case in patients without prior endoscopic resection, as is most often the case in BE patients with LGD (12-17). We did not report on adverse events of RFA treatment in the 15 patients treated after the end of the SURF study. We felt that given the extensive safety data on RFA that is already available, the retrospective information on adverse events in the 15 patients treated additionally in this study, was not very relevant.

Strengths of this study are the randomized design of the original SURF study, the long follow-up period, complete collection of all possible follow-up data and the fact that histology was assessed by pathologists with experience in the field of Barrett's dysplasia.

A limitation of this study is the fact that after closure of the SURF study, 15 patients in the surveillance group were treated with RFA, resulting in uneven groups when comparing long-term outcomes of surveillance versus RFA. In addition, the decision to treat these patients with RFA or offer further surveillance was based on characteristics that may have led to bias, considering that the patients less likely to show progression (eg, short segment Barrett's, no more LGD during follow-up, older age) were surveyed whereas patients more likely to progress were offered RFA. In all likelihood, the observed progression rate in the surveillance group would have been higher if these cases would not have been treated with RFA. Another limitation of this study is the fact that it was conducted in expert Barrett centers, so the results cannot be extrapolated to clinical practice in countries were treatment and surveillance of dysplasia in BE patients is not centralized in expert centers.

In conclusion, the results of our study endorse the results of the earlier SURF study and confirm that RFA significantly reduces the risk of malignant progression and should be considered in patients with confirmed LGD.

Legends

Figure 1. Flow chart illustrating flow of patients during and after closure of the SURF study.

Figure 2. Kaplan Meier survival curve showing progression free survival for high-grade dysplasia and/or adenocarcinoma in the surveillance and RFA groups, censoring patients in whom follow-up was discontinued, in case of unrelated death and in the surveillance group those patients treated with RFA after ending of the SURF study.

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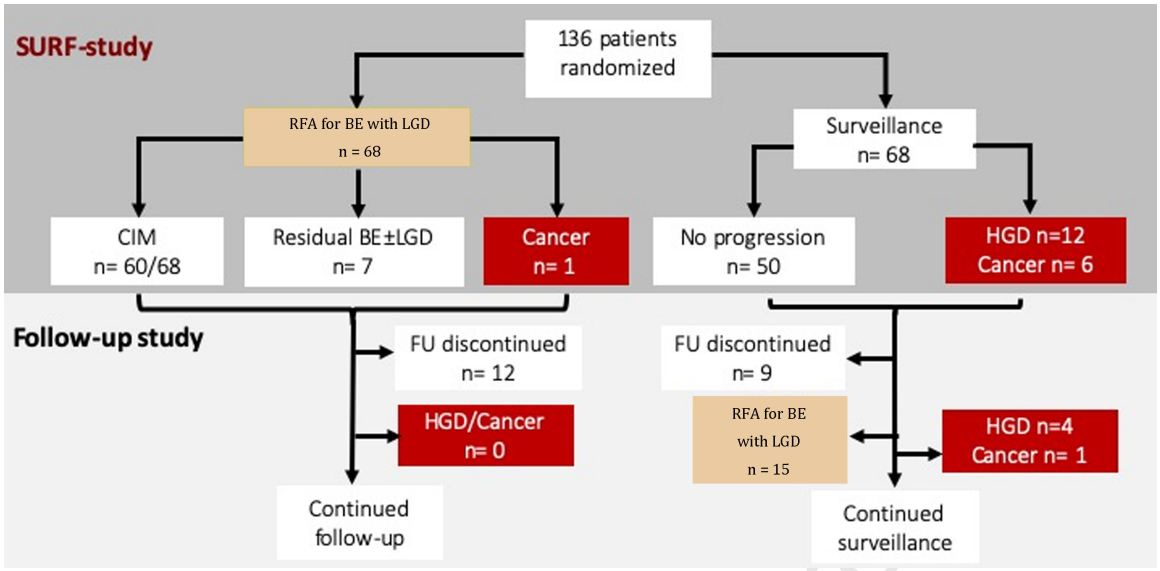

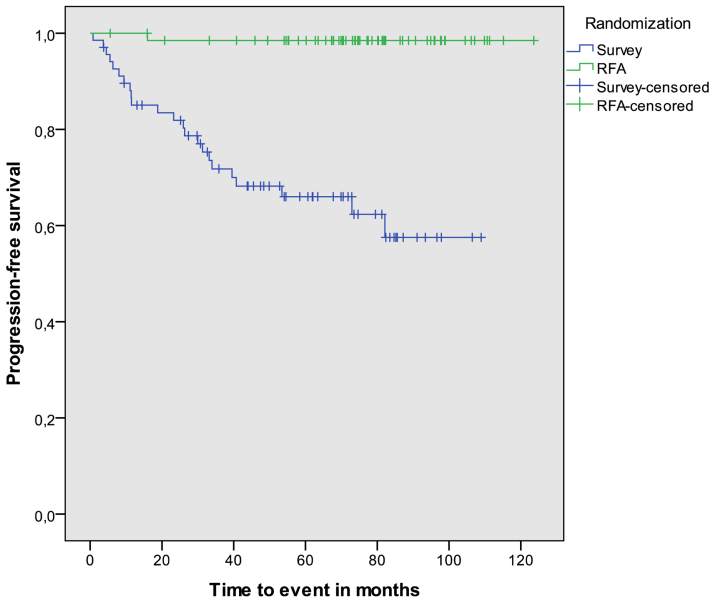

Abbreviations: Barrett's esophagus (BE), endoscopic resection (ER), high-grade dysplasia (HGD), interquartile range (IQR), intestinal metaplasia (IM), low-grade dysplasia (LGD), radiofrequency ablation (RFA)