Simplified versus standard regimen for focal radiofrequency ablation of dysplastic Barrett's oesophagus: a multicentre randomised controlled trial

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Summary

Background For focal radiofrequency ablation of Barrett's oesophagus, a simplified regimen (3x15 J/cm², without cleaning) has proven to be as effective as the standard regimen (2x15 J/cm², followed by cleaning, followed by 2x15 J/cm²). However, this simplified regimen seemed to be associated with a higher stenosis rate. Therefore, we lowered the radiofrequency energy and hypothesised that this new simplified regimen would be as effective and safe as the standard regimen.

Methods This randomised non-inferiority trial included patients with dysplastic Barrett's oesophagus or residual Barrett's oesophagus after endoscopic resection or circumferential radiofrequency ablation, in five European tertiary referral centres. Patients were randomly assigned (1:1) to the new simplified regimen (3x12 J/cm², without cleaning) or the standard regimen, with variable block sizes of four, six, and eight patients, stratified by participating hospital. Focal radiofrequency ablation was done every 3 months, up to a maximum of three treatments, until all Barrett's oesophagus was eradicated. The primary outcome was complete endoscopic and histological regression of dysplasia and intestinal metaplasia after two focal radiofrequency ablation treatments, assessed in the intention-to-treat population. Non-inferiority was assessed on the basis of the difference between groups in the median percentage of Barrett's oesophagus surface regression, with a non-inferiority margin of -15%. This study is registered with www.trialregister.nl, number NTR4994, and is completed.

Findings Between March 25, 2015, and July 25, 2016, 84 patients were randomly assigned to treatment: 44 to receive the simplified regimen and 40 to receive the standard regimen. One patient assigned to the simplified regimen and four assigned to the standard regimen were excluded because they were found not to be eligible; therefore the final intention-to-treat population consisted of 43 patients in the simplified ablation group and 36 in the standard ablation group. Complete endoscopic and histological regression of dysplasia and intestinal metaplasia after two focal radiofrequency ablation treatments was achieved in 32 (74%, 95% CI 59-87) patients treated with the simplified protocol, versus 30 (83%, 95% CI 67-94) patients treated with the standard protocol ($p=0.34$). Median Barrett's oesophagus surface regression after two focal radiofrequency ablation sessions was 98% (IQR 95-100) in the simplified regimen group and 100% (97-100) in the standard regimen group. The difference between medians was 2% (95% CI -0.562 to 3.162); thus the simplified regimen was deemed non-inferior to the standard regimen. Stenoses requiring dilatation were observed in four (9%) of 43 patients in the simplified regimen group and four (11%) of 36 in the standard regimen group. Post-procedural bleeding requiring repeat endoscopy occurred in one (2%) patient in the simplified ablation group and three (8%) patients in the standard ablation group. One patient (2%) in the simplified treatment group died 36 days after the second radiofrequency ablation procedure, due to an unknown cause.

Interpretation Based on the results of this study, we conclude that the simplified regimen is the preferred regimen for focal radiofrequency ablation of Barrett's oesophagus.

Introduction

Radiofrequency ablation is an established endoscopic ablation technique for eradication of dysplastic Barrett's oesophagus. For treatment of Barrett's oesophagus of less than 3 cm in length, residual islands, tongues, or ablation of the squamocolumnar junction after initial circumferential radiofrequency ablation, a catheter-based

focal ablation catheter (Barrx 90 [GI solutions Covidien/Medtronic; Sunnyvale, CA, USA]) is available. The advised ablation regimen in Europe for focal radiofrequency ablation of Barrett's oesophagus consists of two double ablations at 15 J/cm² with a cleaning phase in between. These energy settings were derived from clinical dose escalation studies conducted at the Academic Medical Center (AMC; Amsterdam, Netherlands) in 2007.^{1, 2} However, most US centres use a regimen with two ablations at 12 J/cm² with a cleaning phase in between, which originates from a randomised controlled trial in the USA (AIM-dysplasia study).³ The AIM-dysplasia study was initiated while the dosimetry studies were ongoing at the AMC. As a result, the first dose-escalation from 2x12 J/cm² to 2x2x12 J/cm², which was evaluated at the AMC, was included in the AIM-dysplasia trial protocol, but the second step-up from 12 J/cm² to 15 J/cm² was not. Since then, all radiofrequency ablation studies from the USA have used a 2 x 2 x 12 J/cm² ablation protocol, while all European radiofrequency ablation studies have used 2x2x15 J/cm².

Ablation with the Barrx 90 catheter is relatively easy to perform. However, cleaning the ablation zone and removal of the catheter to clean the electrode, followed by reintroduction for the second ablation pass, is time consuming and may be uncomfortable for the patient. A recent randomised study by our group showed that a

simplified regimen (3 x15 J/cm² without cleaning) was

as effective as the standard regimen (2 x15 J/cm², followed by cleaning, followed by 2 x 15 J/cm²) for eradication of Barrett's oesophagus islands.⁴ However, in a retrospective series, we observed a relatively high stenosis rate (11%) when this regimen was applied to the whole Barrett's oesophagus segment, including circumferential ablation of the squamocolumnar

junction.⁵ Reducing the energy settings to 12 J/cm² when using the simplified regimen might be the best compromise between efficacy and an acceptable stenosis percentage.

The aim of this study was to compare the efficacy and safety of a new simplified regimen with the standard regimen for focal radiofrequency ablation treatment of Barrett's oesophagus in a randomised setting.

Methods

Study design and participants

This randomised controlled trial was done in five tertiary referral centres for the treatment of Barrett's oesophagus and related neoplasia in the Netherlands and Belgium: the Academic Medical Center, Amsterdam, Netherlands; St Antonius Hospital, Nieuwegein, Netherlands; Erasmus Medical Center, Rotterdam, Netherlands; Catharina Hospital, Eindhoven, Netherlands; and the University Hospital Gasthuisberg, Leuven, Belgium

(appendix p 1). See Online for appendix

Patients aged 18–85 years were eligible if there was presence of a treatment-naïve short segment Barrett's oesophagus eligible for treatment with the Barrx 90 device, or in the case of residual Barrett's oesophagus after initial (one or two sessions) circumferential radiofrequency ablation treatment, endoscopic resection, or a combination thereof. Baseline diagnosis before any treatment had to be Barrett's oesophagus with low-grade dysplasia, high-grade dysplasia, or cancer, confirmed by an expert pathologist in the field of gastrointestinal pathology. If patients had cancer or visible abnormalities, an endoscopic resection was required.

Exclusion criteria were presence of an oesophageal stenosis preventing passage of an endoscope or prior dilation because of a stenosis, oesophageal varices, uncorrectable haemostatic disorders, or use of anti-coagulant therapy that could not be discontinued before radiofrequency ablation. Patients who had undergone previous endoscopic resection were excluded if the resected specimen showed a tumour-positive <resection margin (R1 resection), invasion into the <submucosa (>500 µm), poorly or undifferentiated cancer, presence of lymphovascular invasion, or (for biopsies after endoscopic resection and before radiofrequency ablation) invasive cancer.

The study protocol was approved by the Medical Ethics Committees of all five participating hospitals. All patients gave signed informed consent before participation in the study.

Randomisation and masking

Patients were randomly assigned (1:1) to either the new simplified regimen or the standard regimen during the first focal ablation procedure, using online randomisation software (ProMISE). Randomisation consisted of variable block sizes of four, six, and eight patients, stratified by participating hospital. Randomisation was performed by a study nurse or PhD candidate. The allocated radiofrequency ablation regimen was not concealed for endoscopists, data collectors, or patients. The two endoscopists who scored the percentage of Barrett's oesophagus surface regression after two focal radiofrequency ablation treatments were blinded for the regimen used and the centre where the patient was treated.

Procedures

All procedures were done on an outpatient basis under conscious sedation using midazolam or monitored anaesthesia using propofol. Upper endoscopy was done using high-resolution endoscopes with white-light endoscopy and virtual chromoendoscopy (narrow-band imaging, Fuji Intelligent Chromo Endoscopy, or iSCAN). After careful inspection of the Barrett's oesophagus mucosa for the presence of visible lesions or stenosis, the patient was randomly assigned to one of the two ablation regimens. The Barrx 90 device was used for focal radiofrequency ablation treatment. During each focal radiofrequency ablation treatment, the oesophagogastric junction was ablated circumferentially, irrespective of its endoscopic appearance.

For the standard ablation regimen, two ablations with

15 J/cm² were performed. Thereafter, the coagulum

was removed using the distal rim of the Barrx 90 catheter or forceful spraying of water through a spraying catheter, or both. The Barrx 90 electrode was then cleaned outside the patient, and subsequently the endoscope was reintroduced. All ablation zones were then treated with another two ablations at 15 J/cm² (appendix p 1). For the simplified regimen, three

successive ablations at 12 J/cm² were performed while

keeping the catheter in place, without cleaning of the ablated area and electrode in between ablations (appendix p 2).

Additional focal radiofrequency ablation sessions were performed after 3 months until all Barrett's oesophagus was endoscopically eradicated. A maximum of three focal radiofrequency ablation treatments was allowed. After three focal radiofrequency ablation treatments, escape endoscopic resection was performed if there was residual Barrett's oesophagus larger than 5 mm in diameter. For Barrett's oesophagus areas smaller than 5 mm, argon plasma coagulation was performed at 40 W. Argon plasma coagulation was also allowed after two focal radiofrequency ablation treatments.

All patients received high-dose proton pump inhibitor (40 mg twice daily) during the entire treatment phase, with the addition of a histamine-2-receptor antagonist at bedtime for 14 days after each treatment, and (in most cases) sucralfate suspension 3–4 times a day. Choice of proton-pump inhibitor varied by centre and patient, although most patients were prescribed esomeprazole. For post-treatment pain, patients were allowed to take oral paracetamol or diclofenac suppositories if the pain did not respond to paracetamol.

Patients were asked to complete questionnaires about treatment-related symptoms, including pain in the throat, difficulty swallowing, pain during swallowing, pain in the treatment area, and abdominal pain. The severity of pain was recorded for each component using a 10-point scale, resulting in a 0–50 points scale in total. Symptoms were assessed before radiofrequency ablation treatment, immediately afterwards, and 2 days after treatment.

If all Barrett's oesophagus was endoscopically eradicated, biopsies were taken immediately distal (<5 mm) to the neosquamocolumnar junction and from four quadrants every 2 cm of the neosquamous epithelium over the length of the original Barrett's oesophagus segment. When histopathological assessment confirmed the absence of intestinal metaplasia and dysplasia, patients were scheduled for follow-up endoscopy at regular time intervals, depending on the worst histology before radiofrequency ablation.

Biopsies were evaluated for the presence of intestinal metaplasia or dysplasia according to the revised Vienna classification; biopsies from the neosquamous epithelium were assessed for the presence of subsquamous intestinal metaplasia (ie, buried Barrett's oesophagus).

The regression percentage was scored by two endoscopists with experience in radiofrequency ablation treatment of Barrett's oesophagus (BW and RP), who were blinded to the regimen used. The regression percentage was scored as an absolute number, using photos obtained before the first radiofrequency ablation treatment and at endoscopy roughly 3 months after the second radiofrequency ablation treatment. Photos were taken as standard of care in the participating Barrett's oesophagus expert centres, but this was not done in a standardised way. For cases with a discrepancy in Barrett's oesophagus regression percentage of more than 30% between endoscopists, a telephone consensus meeting took place.

Outcomes

The primary outcome was complete eradication of dysplasia or intestinal metaplasia after two focal radiofrequency ablation treatments assessed in the intention-to-treat (ITT) population. Complete eradication was defined as absence of dysplasia and intestinal metaplasia

in all biopsies taken during the first follow-up endoscopy during which complete endoscopic eradication of Barrett's oesophagus was observed. If patients had endoscopically visible Barrett's oesophagus after two focal radiofrequency ablation treatments and required additional radiofrequency ablation treatment, no biopsies were obtained and patients were considered to not have achieved complete eradication of dysplasia or intestinal metaplasia after two focal radiofrequency ablation treatments.

In a post-hoc analysis, we analysed the percentage of Barrett's oesophagus surface regression after two focal radiofrequency ablation treatments. We also did a further post-hoc analysis of percentage of Barrett's oesophagus surface regression after two focal radiofrequency ablation treatments, as scored in real time by the treating endoscopist, who was not blinded to the allocated ablation regimen.

The secondary outcomes were: complete eradication of dysplasia or intestinal metaplasia after three focal radiofrequency ablation treatments, with or without escape treatment; total number of focal radiofrequency ablation treatments required to achieve complete eradication of dysplasia or intestinal metaplasia; rate of oesophageal stenosis requiring dilatation; overall complications requiring admission or unplanned endoscopy; median procedure time; and post-procedural pain, measured on a 0-50 points scale for the severity of symptoms related to radiofrequency ablation treatment. Overall complications requiring admission or unplanned endoscopy were defined as acute if they occurred during the procedure; early if they occurred less than 48 h after the procedure; and late if they occurred more than 48 h after the procedure. Complications requiring admission or unplanned endoscopy were defined as mild if there was unscheduled hospital admission, admission was less than 3 days, there was a haemoglobin drop of less than 3 g/dL, and there was no need for transfusion; moderate if hospital admission was for 4-10 days, the patient required transfusion of fewer than 4 units of blood, or there was a need for repeat endoscopic treatment, including dilation; and severe if hospital stay was for more than 10 days, intensive care unit admission was required, surgery was needed, 4 or more units were required for blood transfusion, or, in the case of stenosis, more than five dilatations, stent placement, or incision therapy were needed; and fatal if death was attributable to the procedure and occurred within 30 days of the procedure, or longer with continuous hospitalisation. Only events requiring any intervention were scored.⁷

Statistical analysis

The sample size calculation for this study was based on percentage of surface regression of Barrett's oesophagus after two focal radiofrequency ablation sessions, which was estimated to be 96% based on previous studies with the standard radiofrequency ablation regimen.¹⁰ However, mistakes were made while calculating the required sample size for this study (see Discussion). First, the percentage of surface regression was not included as an endpoint in the original study protocol. Second, the sample size calculation used to demonstrate non-inferiority with a non-inferiority margin of -15% (one-sided α 0.025, power 90%) used a binary variable, whereas percentage of surface regression is a continuous variable. The calculated sample size of 72 patients (36 per group) was therefore not correct and the study might be underpowered to demonstrate non-inferiority of the simplified regimen. Therefore, we included 95% CIs for all outcomes to put our results into context.

Data analysis was performed using SPSS (version 23). For descriptive statistics, the mean (SD) was used for normally distributed variables, and the median (IQR)

was used for variables with a skewed distribution. Categorical variables were compared using the χ^2 or

Fisher's exact test. Continuous variables were compared using the t test for normal distribution or the Mann-Whitney U test for skewed distribution. Differences were considered significant if the p value was 0.05 or less. This study is registered with www.trialregister.nl, number NTR4994.

The trial protocol is available online.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 25, 2015, and July 25, 2016, 84 patients were included. After randomisation, five patients were found to be ineligible, were unable to undergo ablation, or were excluded due to technical issues and were therefore not included in the final analysis (figure). Five patients. Of the 79 patients who were included in the final intention-to-treat analysis, 43 were randomised to the simplified treatment group, and 36 to the standard treatment group. Patients had a median Barrett's oesophagus length of 20 cm. Before radiofrequency ablation treatment, 35 (44%) of 79 patients underwent an endoscopic resection because of a visible lesion (15 [42%] in the standard treatment group vs 20 [47%] in the simplified treatment group). 34 (43%) of 79 patients underwent primary circumferential radiofrequency ablation treatment before inclusion in the study (14 [39%] in the standard treatment group vs 20 [47%] in the simplified treatment group). Worst documented histology, based on either biopsies or resection specimen, was low-grade dysplasia in 23 (29%), high-grade dysplasia in 39 (49%), and early cancer in 17 (22%) patients. Baseline characteristics are shown in table 1. Two patients treated with the simplified protocol for focal radiofrequency ablation treatment did not finish treatment: one patient because of death 36 days after the second radiofrequency ablation treatment, and one because of psychological problems after a complicated treatment course (this patient achieved complete eradication of dysplasia but not of intestinal metaplasia). Both of these patients were included in the intention-to-treat analysis.

After two focal radiofrequency ablation treatments, median Barrett's oesophagus surface regression was 100% (IQR 97-100) with the standard protocol, compared with a median of 98% (95-100) following the simplified regimen ($p=0.13$). The difference between medians was 2% (-0.562 to 3.162). Since the lower limit of the 95% CI was above the non-inferiority

margin of 15%, non-inferiority was concluded (table 2).

When using the real-time regression score of the treating endoscopist, median Barrett's oesophagus surface regression was 100% (IQR 99-100) following two focal radiofrequency ablation treatments using the standard regimen, as well as following treatment with the simplified regimen (100%, 99-100; $p=0.43$; table 2).

In the intention-to-treat analysis, complete eradication of dysplasia after three focal radiofrequency ablation treatments, including escape treatment, was achieved in 42 (98%; 95% CI 88-100) of 43 patients using the simplified regimen, and in all 36 (100%; 90-100) patients using the standard regimen ($p=1$).

Complete eradication of dysplasia and intestinal metaplasia was achieved in 36 (84%; 95% CI 69-93) of 43 patients using the simplified regimen, and in 33 (92%; 78-98) of 36 patients using the standard regimen ($p=0.33$; table 2). Eight of ten patients with residual intestinal metaplasia had no visible residual Barrett's oesophagus mucosa, but only focal intestinal metaplasia in biopsies obtained just distal to a normal-appearing oesophagogastric junction. No additional radiofrequency ablation of the oesophagogastric junction was performed in these eight patients because: they had either already been treated with the maximum of three radiofrequency ablation sessions ($n=5$); because of comorbidity and old age ($n=1$); because of the presence of a stenosis ($n=1$); or patient preference ($n=1$). The other two patients with residual intestinal metaplasia did not finish the treatment.

In the intention-to-treat analysis, complete eradication of dysplasia or intestinal metaplasia after two focal ablation sessions was achieved in 32 (74%; 95% CI 59-87) of 43 patients treated with the simplified protocol, versus 30 (83%; 67-94) of 36 patients treated with the standard protocol ($p=0.34$; table 2). All other patients required additional treatment for residual Barrett's mucosa.

Escape treatment was performed in 16 (37% CI 23-53) of 43 patients in the simplified treatment group and eight (22%; CI 10-39) of 36 patients in the standard treatment group ($p=0.15$). Escape treatment consisted of argon plasma coagulation in 21 (88%) patients (15 of 16 in the simplified group, six of eight in the standard group), escape endoscopic resection in two (8%) patients in the standard group, or combination in one (4%) patient in the simplified group. Endoscopic resection specimens showed squamous epithelium without intestinal metaplasia ($n=1$ in the simplified group), intestinal metaplasia without dysplasia ($n=1$ in the standard group), and T1m2 cancer (ie, mucosal cancer infiltrating the lamina propria; $n=1$ in the standard group). The T1m2 lesion developed in a patient initially diagnosed with high-grade dysplasia without a visible lesion; however, after one radiofrequency ablation session, a visible lesion (Paris classification type 0-IIb) was detected and curatively removed. Buried Barrett's oesophagus under the neosquamous epithelium was found in one (1%) patient in the simplified treatment group.

A median of 2 (IQR 1-2) focal radiofrequency ablation treatment sessions was required to achieve complete eradication of all Barrett's epithelium for both regimens. Oesophageal stenosis requiring dilation therapy developed in four (9%; 95% CI 2-5-22.1) of 43 patients after focal radiofrequency ablation treatment using the simplified regimen, and four (11%; 95% CI 3-1-26.1) of 36 patients using the standard regimen ($p=1$). A median of 2 (IQR 1-3) dilation sessions were required to resolve the stenoses (2.5 [IQR 2.0-3.0] in the simplified treatment group vs 1.5 [1.0-2.0] in the standard treatment group; $p=0.23$).

Complications leading to additional endoscopy or hospital admission were observed in seven patients in the simplified group and in six in the standard group ($p=0.25$; table 3). Five of these complications were graded as severe (two in the simplified group vs three in the standard group; $p=0.36$). Four patients experienced bleeding a median of 9 (IQR 7-12) days after radiofrequency ablation treatment, three of whom were treated with the standard regimen. These patients underwent an upper endoscopy with injection of adrenaline ($n=2$), adrenaline and clips ($n=1$), or no intervention ($n=1$). All four patients were admitted to the hospital for 4 days. One patient treated with the simplified regimen developed a stenosis after the first focal radiofrequency ablation treatment. This patient subsequently developed dysphagia requiring dilation therapy. During the second dilatation in a community hospital not participating in this study, a perforation developed, which was treated by the placement of a stent and intravenous antibiotics. This patient was admitted to hospital for 5 days, and 7 days after leaving hospital was readmitted for 9 days because of pain complaints due to stent placement. 4 weeks after the perforation occurred, the stent was removed. Residual Barrett's oesophagus was treated with additional radiofrequency ablation. Following this radiofrequency ablation treatment, a few Barrett's oesophagus islands of 3 mm in diameter were observed. Biopsies showed Barrett's oesophagus without dysplasia. However, the patient refused to undergo another gastroscopy due to psychological complaints that developed after the perforation; this patient therefore failed to achieve complete eradication of intestinal metaplasia. An endoscopy was performed in one patient because of dysphagia, but no stenosis was seen. One patient in the simplified regimen group died at home due to an unknown cause, 36 days after the second focal radiofrequency ablation treatment.

Median procedure time of the simplified regimen was 13 min (IQR 10-17), compared with 20 min (16-24) for the standard regimen ($p<0.0001$; difference in medians 7, 95% CI 5-9). Median ablation time, measured from introduction until removal of the Bam 90 device, was 7 min (IQR 5-9) for the simplified regimen and 13 min (IQR 10-16) for the standard regimen ($p<0.0001$, difference in medians 6; 95% CI 4-8).

Before focal radiofrequency ablation, overall patient discomfort was 0 (IQR 0-0) on a 0-50 points scale for the severity of symptoms related to radiofrequency ablation treatment (table 4). Directly after radiofrequency ablation, 38% of patients reported pain, with an overall discomfort of 4 (2-6). At day 2 after radiofrequency ablation, 70% of patients reported discomfort, these patients had a median score of 4 (3-6), and 48 (61%) of 79 patients took analgesics to relieve the symptoms (paracetamol in most patients). 24 (30%) patients were free of symptoms at day 2. No significant differences in post-procedural pain were found between the two regimens.

At the end of the treatment period, after finishing radiofrequency ablation treatment and escape treatment if necessary,

complete eradication of dysplasia was achieved in 42 (98%) patients in the simplified treatment group and in 36 (100%) of patients in the standard group; complete eradication of intestinal metaplasia was noted in 36 (84%) and 33 (92%), respectively.

Discussion

In this randomised trial we showed that a simplified regimen (3x12 J/ cm², without cleaning) was non-inferior to the standard regimen (2x15 J/cm², followed by cleaning, followed by 2x15 J/cm²) for focal radiofrequency ablation treatment of dysplastic Barrett's oesophagus.

Two flaws in the design of this study came to our attention only after finishing the trial. First, our sample size calculation was based on Barrett's oesophagus surface regression after two focal radiofrequency ablation sessions, but this parameter was accidentally not included as an endpoint in the original study protocol. This endpoint was evaluated at the end of the study and added as a post-hoc analysis. Second, for our sample size calculation we aimed to calculate the number of patients required to demonstrate non-inferiority of the simplified regimen compared with the standard regimen. For this, we used the percentage of surface regression of Barrett's oesophagus after two focal radiofrequency ablation sessions as the relevant outcome, and we defined non-inferiority as 15% difference in Barrett's oesophagus surface regression after two focal radiofrequency ablation sessions. Based on prior studies we know that Barrett's oesophagus surface regression after two focal radiofrequency ablation sessions is 96% in most patients. We set a 15% difference as the non-inferiority margin, since regression of 80% or less would probably need significant additional radiofrequency ablation treatment, whereas patients with more than 80% Barrett's oesophagus surface regression could be treated with argon plasma coagulation or escape endoscopic resection. However, Barrett's oesophagus surface regression is a continuous outcome and the sample size formula we used was based on binary outcomes, which in hindsight was incorrect. However, the results of our study showed a 95% CI between means of 0.562 and 3.162, and the lower limit of this 95% CI was well above the predefined non-inferiority margin of 15%. These results, in our opinion,

demonstrate non-inferiority of the simple regimen compared with the standard regimen and we felt it would be artificial to perform a post-hoc sample size calculation.

In addition to Barrett's oesophagus surface regression after two focal radiofrequency ablation sessions, other important outcomes of this study were complete eradication of dysplasia or intestinal metaplasia after two focal radiofrequency ablation sessions. In the majority of radiofrequency ablation studies, most patients require two focal radiofrequency ablation sessions to achieve complete eradication of dysplasia or intestinal metaplasia.^{1,7,12} A significant difference in the number of patients requiring additional radiofrequency ablation after two treatment sessions would therefore be clinically relevant. Since no significant difference in the percentage of patients achieving complete eradication of dysplasia or intestinal metaplasia was found after two sessions, the simplified and standard regimen appeared to be equally effective.

The rates of complete eradication of dysplasia or intestinal metaplasia after two focal radiofrequency ablation sessions reported in this study (74% for the simple regimen and 83% for the standard regimen), should not be compared with eradication rates mentioned in other publications on radiofrequency ablation, since these generally only report eradication rates at the end of the treatment period. Additionally, since we did not obtain biopsies before additional ablation, the rate of complete eradication of dysplasia or intestinal metaplasia after two focal radiofrequency ablation sessions might even be higher than that reported in this study.

After finishing radiofrequency ablation treatment and escape treatment if necessary, complete eradication of dysplasia was achieved in 98% of patients in the simplified treatment group and in 100% of patients in the standard treatment group in the intention-to-treat analysis and complete eradication of intestinal metaplasia and dysplasia was achieved in 84% and 92%, respectively. These results are similar to the results of a large European multicentre study (EURO-II study), in which complete eradication of dysplasia was achieved in 92% of patients and complete eradication of intestinal metaplasia in 87% of patients. Four of the centres participating in this randomised trial were also part of the EURO-II study, in which the standard regimen for focal radiofrequency ablation treatment was used.¹²

Complete eradication of intestinal metaplasia was not achieved after two or three focal radiofrequency ablation sessions in ten patients. In eight of these patients, there was no visible Barrett's oesophagus mucosa, but persistent intestinal metaplasia was detected in biopsies obtained just below the neosquamocolumnar junction. However, the clinical relevance of intestinal metaplasia in a normal-appearing neosquamocolumnar junction during endoscopy could be questioned. Intestinal metaplasia in the cardia is found in up to 25% of the healthy population, and several studies have shown that focal intestinal metaplasia of the cardia often follows a benign course.¹³⁻¹⁵ The follow-up of this study is too short to report on the long-term outcomes of these eight patients. Occult intestinal metaplasia in the neosquamous epithelium was found in one (1%) patient. The general fear is that buried Barrett's oesophagus might progress to dysplasia or cancer while remaining endoscopically invisible. However, the incidence of buried Barrett's oesophagus after radiofrequency ablation is reported to be very rare, and our results are in line with

the results of earlier studies.¹⁶⁻¹⁸

Our study did not show a significant difference in complication rate between treatment regimens. The number of stenoses was similar, as was the number of dilations required to resolve the stenoses. Although this study was not powered to look at differences in complications, these results might have implications for daily practice. The use of a simplified regimen has several advantages regarding the safety profile. Omitting the cleaning step is more practical for the endoscopist, shortens procedure time, and diminishes patient discomfort. Furthermore, the risk of damaging the hypopharynx with the endoscope-mounted Barrx 90 catheter during introduction decreases by 50% when using the simplified regimen since it only requires one introduction. Although trauma to the hypopharynx or oesophageal wall did not occur in this study, it has been described in up to 10% of patients during introduction of the endoscope.¹⁹ Furthermore, a significantly shorter procedure time for the simplified regimen might also result in fewer sedation-related risks. Our overall stenosis rate of 9% lies above the pooled estimate rate (6%) of a recent meta-analysis.²⁰ However, most of the included studies were retrospective nature and included a heterogeneous population. In studies performed by our group we found a stenosis rate ranging between 0% and 12%.^{1,7,12} Of note, three patients experienced bleeding after treatment with the standard regimen, compared with one patient after treatment with the simplified regimen. However, these numbers are too low to draw conclusions regarding a possible diminished risk of bleeding with the simplified regimen.

All focal radiofrequency ablation treatments in this study were performed using the Barrx 90 catheter. However, various differently sized focal radiofrequency ablation catheters are available—ie, the Barrx 90 Ultra device, the Barrx 60 device, and the charme! radiofrequency ablation device. Since most published studies on the safety and efficacy of radiofrequency ablation treatment for Barrett's oesophagus used the Barrx 90 device, the ablation regimen recommended for all focal radiofrequency ablation devices is based on previous experience with this device. For uniformity of focal radiofrequency ablation treatment, we advocate the use of the simple regimen studied in this randomised trial in combination with all focal radiofrequency ablation devices.

Strengths of our study include the randomised design, assessment of all histology specimens before focal radiofrequency ablation treatment by expert gastrointestinal pathologists, and the participation of five European centres with a tertiary referral function for Barrett's oesophagus neoplasia. Furthermore, we ablated the oesophagogastric junction in a circumferential manner during each focal radiofrequency ablation session. In combination with aggressive acid suppression therapy after each focal radiofrequency ablation treatment, we feel that this is the optimal treatment protocol for Barrett's oesophagus with dysplasia. Last, all patients underwent a rigorous biopsy protocol during the first follow-up endoscopy after radiofrequency ablation treatment: not only the area directly distal to the neosquamocolumnar junction was biopsied, but biopsies were also obtained every 2 cm of the neosquamous epithelium over the length of the original Barrett's oesophagus segment.

Several limitations of this study need to be acknowledged in addition to the sample size calculation. First, we evaluated only short-term efficacy, and therefore we cannot confirm whether the simplified regimen is as durable as the standard regimen used in previous studies.^{1,2} Indeed, a simplified regimen might imply some practical challenges such as avoiding too much overlap in treatment zones and avoiding missed areas that cannot be treated by the second pass in the standard regimen. Second, we included only patients in tertiary referral centres, and therefore results of this study might not be extrapolated to common practice. Third, escape therapy was performed for small Barrett's oesophagus areas by means of argon plasma coagulation or escape endoscopic resection in a considerable number of patients. However, this did not affect our primary outcome, since escape therapy was allowed only after two focal radiofrequency ablation treatments. Argon plasma coagulation is a commonly used, cheap, and effective ablation technique for the treatment of small Barrett's oesophagus areas.³ Of note, escape treatment with argon plasma coagulation for small Barrett's oesophagus islands (<5 mm) was applied in 16 (37%) patients in the simple treatment group versus eight (22%) patients in the standard treatment group. For comparison, escape treatment using argon plasma coagulation or endoscopic resection was applied in 18% of patients in the EURO-II study, in which the standard regimen for focal radiofrequency ablation was used.⁴ However, in the EURO-II study, escape treatment was allowed only after the maximum number of three focal radiofrequency ablation sessions had been applied, whereas escape treatment was allowed in our study for small Barrett's oesophagus islands remaining after two focal radiofrequency ablation treatments. Although not significantly different, the difference in number of patients requiring escape treatment between treatment regimens could be explained by the fact that, when using the standard regimen, small areas that might be missed during the first ablation pass are ablated during the second ablation pass. When using the simple regimen, the catheter is kept in place for the three ablations, and small areas of Barrett's oesophagus that are located just adjacent to the catheter can be missed.

In conclusion, although this randomised controlled trial was not correctly powered to assess non-inferiority of a simplified regimen (3 x 12 J/cm², without cleaning) for focal radiofrequency ablation treatment versus the standard regimen (2 x 15 J/cm², followed by cleaning, followed by 2 x 15 J/cm²), the simplified protocol seemed to be non-inferior based on a post-hoc assessment of the percentage of Barrett's oesophagus surface regression after two focal radiofrequency ablation treatments. Since the procedure time was also significantly shorter and the simplified regimen was equally safe, the simplified regimen appears to be the preferred method for focal radiofrequency ablation.

Contributors

RP conceived and designed the study, acquired data, analysed and interpreted data, and critically revised the manuscript for important intellectual content. HK acquired data, drafted the manuscript, analysed and interpreted data, and did statistical analysis. RB, CS, AK, PD, AG, ES, WC, and JB acquired data and critically revised the manuscript for important intellectual content. BW conceived and designed the study, acquired data, critically revised the manuscript for important intellectual content, and supervised the study.

Declaration of interests

RB reports financial support for research from Fujifilm, Pentax, and Cook Medical, outside the submitted work; speaker's fee and consultancy for Medtronic, Pentax, and Fujifilm; and consultancy for Boston Scientific. ADK reports financial support for research from

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JJGHMB reports consultancy for Boston Scientific, Cook Medical, and Covidien/Medtronic. BLAMW reports financial support for research from C2Therapeutic and Covidien/Medtronic, outside the submitted work. All other authors declare no competing interests.

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	Standard regimen (n=36)	Simplified regimen (n=43)
Sex		
Male	30 (83%)	41 (95%)
Female	6 (17%)	2 (5%)
Median age (years)	66 (61–74)	64 (52–73)
Reported use of proton-pump inhibitors	36 (100%)	43 (100%)
Endoscopic resection before radiofrequency ablation	15 (42%)	20 (47%)
Worst documented histology before radiofrequency ablation*		
Low-grade dysplasia	12 (33%)	11 (26%)
High-grade dysplasia	17 (47%)	22 (51%)
Mucosal oesophageal adenocarcinoma	5 (14%)	9 (21%)
Submucosal oesophageal adenocarcinoma	2 (6%)	1 (2%)
Barrx 360 before radiofrequency ablation	14 (39%)	20 (47%)
Barrett's oesophagus length before focal radiofrequency ablation (cm)		
Circumferential	0 (0–0)	0 (0–0)
Maximum	2 (1–2)	1 (1–2)
Data are n (%) or median (IQR). *Based on endoscopic resection specimens and biopsies.		
Table 1: Baseline characteristics		

	Standard regimen (n=36)	Simplified regimen (n=43)	p value
Complete eradication of dysplasia and intestinal metaplasia after two focal radiofrequency ablation treatments	30 (83%)	32 (74%)	0.34
Barrett's oesophagus surface regression after two focal radiofrequency ablation treatments	100% (97-100)	98% (95-100)	0.13
Barrett's oesophagus surface regression after two focal radiofrequency ablation treatments (as scored real-time by the treating endoscopist)	100% (99-100)	100% (99-100)	0.43
Complete eradication of dysplasia and intestinal metaplasia after three focal radiofrequency ablation sessions, with or without escape treatment	33 (92%)	36 (84%)	0.33
Focal radiofrequency ablation treatment sessions needed to achieve complete eradication of dysplasia and intestinal metaplasia	2 (1-2)	2 (1-2)	0.5
Stenosis requiring dilation therapy	4 (11%)	4 (9%)	1
Complications requiring admission or unplanned endoscopy	7 (19%)	6 (14%)	0.25
Procedure time (min)	20 (16-24)	13 (10-17)	<0.0001

Data are n (%), median (IQR), or mean (SD).

Table 2: Primary and secondary outcomes

	Standard regimen (n=36)	Simplified regimen (n=43)
Bleeding	3 (8%)	1 (2%)
Stenosis	4 (11%)	3 (7%)
Dysphagia without presence of stenosis	0	1 (2%)
Stenosis, subsequently complicated by perforation due to dilatation	0	1 (2%)
No early or acute complications leading to unplanned endoscopy or admission were reported.		
Table 3: Late complications leading to unplanned endoscopy or admission		

	Overall (n=79)	Standard regimen (n=36)	Simplified regimen (n=43)
Baseline (day 0)			
Severity of symptoms	0 (0-0)	0 (0-0)	0 (0-0)
Day 0 after radiofrequency ablation			
Severity of symptoms	0 (0-3)	0 (0-2)	0 (0-3)
Day 2 after radiofrequency ablation			
Severity of symptoms	3 (0-5)	4 (0-6)	2 (0-5)
Use of pain medication during 2 days	48/79 (61%)	26/36 (72%)	22/43 (51%)
Scored on a scale of 0 to 50.			
Table 4: Patient discomfort			