Advances in endoscopic resection and radiofrequency ablation of early esophageal neoplasia
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A simplified regimen for focal radiofrequency ablation of Barrett’s mucosa using the HALO\textsuperscript{90} System: a randomized multicenter trial comparing two ablation regimens


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ABSTRACT

Background: The currently recommended regimen for focal radiofrequency ablation (RFA) of Barrett’s esophagus (BE) comprises two applications of energy, cleaning of the device and ablation zone, and two additional applications of energy. A simplified regimen may be of clinical utility, if it is faster, easier and equally safe and effective.

Objective: compare the efficacy of two focal RFA regimens.

Setting: Three tertiary referral centers. Patients: Consecutive patients scheduled for focal RFA of BE were enrolled having flat type BE with ≥2 BE islands or mosaic groups of islands.

Interventions: BE areas were paired: one area was randomized to the ‘standard’ regimen (2x15J/cm²-clean-2x15J/cm²) or ‘simplified’ regimen (3x15J/cm²-no clean), allocating the second area automatically to the other regimen. The % surface area regression of each area was scored at 2 months by the endoscopist (blinded).

Outcome measure: proportion of completely removed BE areas at 2 months. Calculated sample size was 46 pairs of BE areas using a non-inferiority design. Non-inferiority was defined as <20% difference in the paired proportions.

Results: Forty-five equivalent pairs of BE areas were included in 41 patients. The proportion of completely removed BE areas at 2 months after focal-RFA was 30/45 (67%) for standard and 33/45 (73%) for simplified. Non-inferiority was demonstrated by a 7% difference (95%CI -10.6 to +20.9). Limitations: tertiary referral centers.

Conclusions: The results of this multicenter randomized trial suggest that a simplified 3x15J/cm² focal ablation regimen is not inferior to the standard regimen, regarding the endoscopic removal of residual Barrett’s islands.
INTRODUCTION

Endoscopic therapy is the treatment of choice for patients with Barrett’s esophagus (BE) containing high-grade dysplasia (HGD) or early carcinoma. Currently, the best available treatment approach is a combination of endoscopic resection (ER) of visible lesions followed by endoscopic ablation of the residual flat BE using radiofrequency ablation (RFA).\textsuperscript{1-4}

Radiofrequency ablation (RFA) is a recently introduced endoscopic treatment modality for the complete removal of Barrett’s esophagus (BE) with or without dysplasia. Several large scale multicenter studies have shown that RFA is safe and effective with reported rates of complete histological removal of BE and dysplasia in 77-100% of patients.\textsuperscript{3-7}

RFA can be performed with a balloon-based ablation catheter for circumferential ablation (HALO\textsuperscript{360+}-catheter) or a focal ablation device that is attached to the tip of the endoscope (HALO\textsuperscript{90}-catheter) for ablation of smaller areas of residual BE, such as remaining BE islands, small BE tongues, or an irregular Z-line. Generally, patients require about three RFA sessions to achieve histological eradication of dysplastic BE, usually one circumferential and two focal RFA sessions, performed with 2-3 month-intervals.\textsuperscript{3,7} The advised ablation regimen for both circumferential balloon-based as focal HALO\textsuperscript{90} ablation consists of two ablation passes in the same endoscopic session, with a cleaning step in between ablation passes to remove debris from the surface of the ablation zone and electrode.\textsuperscript{8} Although focal ablation with the HALO\textsuperscript{90}-catheter is relatively easy to perform, cleaning of the ablation zone, and removing, cleaning and reintroducing the HALO\textsuperscript{90}-catheter are impractical, time consuming, and uncomfortable to the patient. In this study, we evaluated a simplified HALO\textsuperscript{90}-ablation regimen in which cleaning of the ablation zone is abandoned, thereby reducing the number of introductions with the endoscope and the HALO\textsuperscript{90}-ablation device. We hypothesized that this simplified HALO\textsuperscript{90}-ablation procedure results in an easier and faster ablation procedure with fewer introductions, while maintaining efficacy and safety. The study aim was to compare the safety and efficacy of the current ‘standard’ HALO\textsuperscript{90}-ablation regimen versus a ‘simplified’ HALO\textsuperscript{90}-ablation regimen in a randomized trial using a non-inferiority design.

PATIENTS AND METHODS

The inception cohort of this study consisted of patients that underwent RFA treatment for the complete removal of BE in one of three tertiary referral centers. The indication for RFA was the complete removal of all BE with or without a prior ER of a focal lesion containing HGD or early cancer.\textsuperscript{9}

Radiofrequency ablation

RFA was performed using the HALO system (by BÂRRX/Covidien Medical Inc, Sunnyvale, CA, USA). The HALO system is based on the use of bipolar electrodes and a preset radiofrequency (RF) energy density to ensure a uniform ablation depth of 0.5-1mm. For
initial circumferential ablation, the HALO\textsuperscript{360}-balloon-catheter was used, as described elsewhere.\textsuperscript{3,8} For subsequent focal ablation of BE areas or islands smaller than 2cm in longitudinal length, and ≤50% of the circumference, the HALO\textsuperscript{90}-catheter was used, which consists of a cap-based electrode of 20mm x 13mm that is attached on the tip of the endoscope (Figure 1).\textsuperscript{3,8} RFA was repeated every 2-3 months with a maximum of 5 RFA sessions (≤2 HALO\textsuperscript{360}), until complete endoscopic and histological removal of all BE was achieved. Endoscopic work-up, and pre- and post-procedural care of the RFA procedures have been previously described.\textsuperscript{3,8}

![Figure 1: HALO\textsuperscript{90}-device for radiofrequency ablation (RFA). The HALO\textsuperscript{90}-device is used for secondary RFA of residual Barrett’s epithelium after initial circumferential ablation using the HALO\textsuperscript{360} system, or for primary RFA. The HALO\textsuperscript{90}-device is fitted on the tip of the endoscope and consists of a bipolar electrode array (20 mm x 13 mm) on an articulated platform, for optimal contact with the esophageal wall. The use of a bipolar electrode and a generator that delivers a fixed amount of RF energy results in uniform, controlled ablation with an ablation depth of ~0.5mm (permission for use from Covidien, GI Solutions (formerly BÅRRX Medical)).](image)

**Selection criteria**

Patients were eligible if they met the following criteria: scheduled for a first, second or third HALO\textsuperscript{90}-procedure for BE with or without dysplasia; absence of endoscopically visible active inflammation in the treatment zone; absence of esophageal stenosis (esophageal diameter <18mm) preventing introduction of the endoscope and/or the HALO\textsuperscript{90}-catheter; no previous randomization of BE areas for the purpose of this study; written informed consent.

‘BE areas’ had to meet the following criteria: presence of ≥2 BE islands with a size of ≥2mm, or clusters of BE islands, with a total surface area smaller than 2 adjacent HALO\textsuperscript{90}-applications and <50% of the circumference; a distance of >20mm or >33% of the circumference in between BE areas (to prevent overlap of two ablation zones treated with different RFA regimens); a distance of >10mm from the neosquamocolumnar junction (to prevent that ablation of the neosquamocolumnar junction would interfere with the allocated RFA regimen). BE islands that were elevated or contained endoscopic visible abnormalities suspicious for carcinoma were not eligible.
HALO\textsuperscript{90,-regimens}

During high resolution (HR) endoscopy with white light (WL) and narrow band imaging (NBI) or Fuji Intelligent Chromo Endoscopy (FICE), the BE was flushed with the mucolytic agent acetylcysteine (1\%) followed by flushing with tap water. The BE was inspected to exclude the presence of visible lesions, and stenosis. The number, size (maximum diameter) and localization (insertion depth of the endoscope, and the circumferential position in the endoscopic view) of all BE islands and tongues were registered and documented on still images (WL + NBI/FICE).

Eligible BE areas were numbered sequentially from distal to proximal. Area 1 was randomized and treated first, and area 2 was automatically allocated to the other ablation regimen, thus forming a pair. The ‘standard’ regimen (‘double-double-15’) consisted of a double application of RF energy at 15J/cm\textsuperscript{2}, cleaning of the debris from the ablation zone and cleaning of the HALO\textsuperscript{90,-electrode outside of the patient}, followed by another double ablation at 15 J/cm\textsuperscript{2}. The ‘simplified’ regimen (‘triple-15’) consisted of three consecutive ablations at 15J/cm\textsuperscript{2} without cleaning of the ablation zone or HALO\textsuperscript{90,-electrode}. A maximum of two pairs were randomized. Prior to switching over to the other ablation regimen, the surface of the ablation electrode was cleaned outside of the patient. In case BE areas were localized close to each other, 1-2mm sized endoscopic tattoos were placed to enable localization of both areas at 2 months (Endo Spot, GI Supply, Camp Hill, Pennsylvania, USA). After focal ablation of the included BE areas according to the allocated regimens, all other remaining BE including the neosquamocolumnar junction were treated with the standard regimen for focal RFA.

Scoring of outcome parameters during follow-up endoscopy at 2 months

Patients were scheduled for HR endoscopy with NBI/FICE after 2 months, and outcome parameters were scored at that time. Endoscopists were provided with information on the localization of included areas, the number and size of BE islands per area at baseline, and were allowed to review endoscopic images from baseline, however, they were blinded for the administered HALO\textsuperscript{90,-treatment regimen}. After thorough inspection, still images were made of any residual columnar epithelium (WL + NBI/FICE) at included BE areas, and the endoscopist scored the outcome parameters per included BE area after the endoscopy.

Outcome parameters at 2 months

*Primary outcome parameter:* complete endoscopic eradication of the BE area, defined as absence of any endoscopically visible columnar epithelium as judged by the endoscopist.

*Secondary outcome parameter:* surface regression of the BE area as compared to baseline, defined as the percentage of surface regression of endoscopically visible columnar epithelium observed by the endoscopist.

Follow-up protocol

When endoscopic BE eradication was achieved, 4Q/2cm random biopsies were obtained of the neosquamous epithelium of the original BE and immediately distal (<5 mm) to
the neosquamocolumnar junction (neo-Z-line). If histological assessment of the biopsies confirmed complete response for early neoplasia (CR-neoplasia) and intestinal metaplasia (CR-IM), patients were scheduled for HR endoscopy with NBI/FICE and 4Q/2cm biopsies at 6 months, and annually thereafter.

**Ethics and statistics**

The study was approved by the medical ethics committees of all study centers (NTR 2510, www.trialregister.nl). Written informed consent was obtained from all participants. Randomization was performed by a study monitor according to a computer-generated random order in sealed opaque envelopes during baseline endoscopy. The study monitor attended the baseline endoscopy and follow-up endoscopy at 2 months for prospective data registration using standardized case record forms.

The sample size was based on the assumption that a difference of 20% or more in the proportions of completely eradicated BE areas in both arms would be of clinically relevance. To reject the hypothesis that the simplified regimen is inferior to the standard regimen, 46 pairs of BE areas were required, with non-inferiority defined as <20% difference in the paired proportions of completely eradicated BE areas (one-sided, p=0.025, 80% power, 10% drop-out). For sample size calculation and random sequence generation nQuery Adviser (Version 7, Cork, Ireland) was used. Data analysis was performed using SPSS statistical software package (SPSS Inc.16.0.2, Chicago, IL, USA). For descriptive statistics, mean (±SD) was used for parametric distribution and median (inter-quartile range, IQR) was used for non-parametric distribution. To compare groups, McNemar’s test for paired data was used. Fisher exact test and Mann-Whitney U test were used when appropriate. Differences were considered statistically significant if \( p \leq 0.05 \). To calculate confidence intervals, the Confidence Interval Analysis package was used (CIA 2.2.0, London, UK).

**RESULTS**

**Patients**

This study was performed in three tertiary referral centers for the endoscopic treatment of early neoplasia in the upper gastrointestinal tract in the Netherlands: Academic Medical Center, Amsterdam; Sint Antonius Hospital, Nieuwegein; and Catharina Hospital, Eindhoven. In total 89 patients were screened for the study of whom 48 did not meet the inclusion criteria (too small islands, too close to each other or the Z-line within 10-mm distance (n=20), no remaining islands (n=11), only a single island (n=11), esophageal stenosis (n=2), need for circumferential balloon-based RFA for remaining BE (n=2), visible lesion requiring ER (n=1), no consent (n=1)). Forty-one patients were included (29 male, median age 63±11 years with a median BE length prior to any treatment of C5M7 (IQR:2-9;M5-10) (Table 1, Figure 2).

Prior to RFA, 28 patients underwent ER of focal lesions. Initial circumferential balloon-based RFA was performed in 39 of 41 patients, whereas 2 patients underwent initial focal RFA. Primary focal RFA was performed for the removal of a residual Barrett’s tongue of
Table 1: Baseline characteristics of 41 patients with dysplastic Barrett’s esophagus treated with endoscopic radiofrequency ablation, and in whom pairs of Barrett’s areas were randomized to two different focal radiofrequency ablation regimes.

<table>
<thead>
<tr>
<th></th>
<th>n= 41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: female</td>
<td>29:12:00</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>63 (±11)</td>
</tr>
<tr>
<td>Median BE length (cm) prior to RFA</td>
<td>C5M7 (C2-9; M5-10)</td>
</tr>
<tr>
<td>Most advanced histology overall (biopsies or ER specimens)</td>
<td>Carcinoma 22, HGD 12, LGD 5, NDBE 2</td>
</tr>
<tr>
<td>ER prior to randomization</td>
<td>28</td>
</tr>
<tr>
<td>Histology prior to any RFA (biopsies)</td>
<td>HGD 20, LGD 12, NDBE 9</td>
</tr>
</tbody>
</table>

BE= Barrett’s esophagus, C=circumferential BE length, M= maximal BE length, RFA= radiofrequency ablation, ER= endoscopic resection, HGD= high-grade dysplasia, LGD= low-grade dysplasia, NDBE= non dysplastic Barrett’s epithelium.

Figure 2: Patient inclusion and outcomes of patients with dysplastic Barrett’s esophagus treated with endoscopic radiofrequency ablation, in whom pairs of Barrett’s areas were randomized to two different focal radiofrequency ablation regimes. RFA= radiofrequency ablation, BE= Barrett’s esophagus, HGD= high-grade dysplasia, ER= endoscopic resection, CR-N= complete response for neoplasia, CR-IM= complete response for intestinal metaplasia.
3 cm in one patient; and for optimal electrode contact in another patient with reflux-related scarring in a C3M6 BE. Patients were included during the first focal RFA session in 34 cases, while in 7 others this was the second (n=5) or third (n=2) focal RFA session. The most advanced histology (biopsies or ER specimens) overall was carcinoma in 22, HGD in 12 and LGD in 5 and non-dysplastic BE in 2 patients. Two patients with non-dysplastic BE underwent RFA treatment (long segment BE of C9M10 in a 39-year-old male, and a C7M8 BE in a 64-year-old female with two first degree relatives with esophageal adenocarcinoma). Prior to any RFA, the most advanced histology (biopsies) was HGD in 20, LGD in 12 and non-dysplastic BE in 9 patients.

**HALO\(^{90}\)-procedure**

In total 92 BE areas (46 pairs) were randomized to the standard or simplified regimen. One patient with one pair of BE areas was excluded from analysis because the second area was accidently ablated with the wrong regimen, leaving 45 pairs for the final analysis (Table 2). Of 41 patients, there were 36 patients with a single pair of BE areas (2 BE areas per patient) and 5 patients with two pairs of BE areas (4 BE areas per patient). BE areas contained one (n=54, median size 10mm (IQR 6-15)) or multiple islands (n=38) (Figure 3). In 3 cases BE areas were marked with an endoscopic tattoo (Figure 4). Baseline characteristics were similar in both groups (Table 2). There were no acute or severe complications. Two patients, both treated with an extensive ER prior to balloon-based RFA, developed a symptomatic stenosis after a second focal RFA procedure. Symptoms resolved after endoscopic dilation.

| Table 2: Baseline characteristics of 45 pairs of Barrett’s areas that were randomized to two different treatment regimens (‘Standard’ or ‘Simplified’) for focal radiofrequency ablation. |
|--------------------|-----------------|-----------------|-----------------|-----------------|
| Overall (n=45)     | Standard (n=45) | Simplified (n=45) | p-value         |
| Single island: multiple BE islands per area | 54:36:00 | 26:19:00 | 28:17:00 | 0.77\(\times\) |
| Islands per BE area in case of multiple islands (median, R) | 2 (2-10) | 2 (2-5) | 2 (2-10) | 0.79\(\Delta\) |
| Size of single BE islands (median, IQR) | 10 mm (6-15) | 10 mm (5-16) | 10 mm (7-10) | 0.60\(\Delta\) |

BE= Barrett’s esophagus, R= range, IQR= interquartile range, \(\times\)Mc Nemar test, \(\Delta\)Wilcoxon Signed Ranks test.

**Outcome parameters at two months follow-up**

At the two months follow-up endoscopy, the proportion of completely eradicated BE areas was 30/45 (67%) for the standard RFA regimen and 33/45 (73%) for the simplified regimen: a difference of 7% (95%CI -10.6% - 20.9%) (Table 3 + 4). The median surface regression for each BE areas at 2 months was 100% in both groups, whereas for not completely eradicated areas this was 78% (IQR50-90) for standard and 80% (IQR50-90) for simplified (p=1.0).
Figure 3: Endoscopic images of areas of Barrett’s epithelium that were randomized to the simplified or standard regimen for focal radiofrequency ablation (RFA) using the HALO™-device.

Figure 4: Focal radiofrequency ablation (RFA) of remaining Barrett’s epithelium (BE) after circumferential balloon-based RFA, in a patient with a baseline C7M9 Barrett’s esophagus (BE) containing a mucosal cancer that was removed with endoscopic resection. A: remaining BE after circumferential balloon-based RFA, B: narrow band imaging showing several BE islands; the encircled island was included in the study and treated with the standard regimen, C: corresponding image after placement of a tattoo for relocalization of the island, D: ablation of the randomized pair of BE areas using the standard and the simplified regimen in the same patient, E: circumferential ablation of the neosquamocolumnar junction, F: complete histological response for neoplasia and intestinal metaplasia.
Table 3: Rate of complete endoscopic removal of 45 pairs of Barrett’s areas randomized to two different treatment regimens (‘Standard’ or ‘Simplified’) for focal radiofrequency ablation.

<table>
<thead>
<tr>
<th></th>
<th>Simplified regimen (3x15 J/cm² without cleaning)</th>
<th>Standard regimen (2x2x15 J/cm² with cleaning)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete removed</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Not completely removed</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>

McNemar test of symmetry for paired data (p=0.58).

Table 4: Rate of complete endoscopic removal of 45 pairs of Barrett’s areas by using focal radiofrequency ablation after randomization to two different ablation regimens (‘Standard’ or ‘Simplified’).

<table>
<thead>
<tr>
<th></th>
<th>Standard (2x2x15 J/cm² with cleaning) (n=45)</th>
<th>Simplified (3x15 J/cm² without cleaning) (n=45)</th>
<th>p-value / CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Completely removed BE areas (IQR)</td>
<td>67% (n=30/45)</td>
<td>73% (n=33/45)</td>
<td>0.58∞</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median BE regression overall (IQR)</td>
<td>100% (90-100)</td>
<td>100% (99-100)</td>
<td>0.39∆</td>
</tr>
<tr>
<td>Median BE regression of not completely removed areas</td>
<td>78% (50-90)</td>
<td>80% (50-90)</td>
<td>1.00∆</td>
</tr>
</tbody>
</table>

CI= confidence interval, IQR= interquartile range, ∞Mc Nemar test, ∆Wilcoxon Signed Ranks test
**Non-inferiority was demonstrated if the 95%CI of the difference in proportions (paired) of completely removed BE areas of the simplified regimen was <20% worse than the standard regimen.

Subsequent treatment

Of 40 patients that were included in the study, CR-neoplasia and CR-IM were achieved in 100% and 93% (37/40) of patients respectively, in a median of 3 RFA sessions (IQR 2-4) overall during the endoscopic treatment period. In 6 patients, additional ER was performed after RFA to remove a focal lesion during the RFA treatment phase (n=3) or to remove persisting BE after 5 RFA sessions (n=3). ER specimens showed a T1m3 carcinoma in 1 patient, BE without dysplasia in 4 patients, and no IM in 1 patient. None of the focal lesions was localized at the BE areas that were included in this study. In 5 patients, additional argon plasma coagulation was used for ablation of tiny islands <2mm.

In 3 patients that failed CR-IM, focal IM was found at the Z-line in 2 patients, whereas in 1 patient a single focus of buried IM was detected in the proximal esophagus, which was not reproduced during follow-up.

DISCUSSION

RFA is an endoscopic ablation technique that has shown to be a safe and effective treatment modality for the histological eradication of dysplastic BE in 77-100% of patients.\textsuperscript{3-5,7 With}
more endoscopists having access to the technique and more patients being treated, it is of relevance to improve the practicality of the treatment, while preserving efficacy and safety.\textsuperscript{11,12}

In this randomized trial we compared two different treatment regimens for focal radiofrequency ablation of Barrett’s epithelium in patients with early BE neoplasia. We hypothesized that a new, simplified focal ablation regimen would result in an easier and faster focal ablation procedure with fewer introductions, while maintaining efficacy and safety.

In this study we used a non-inferiority design to evaluate if the simplified regimen has a comparable efficacy as the standard focal RFA treatment. Our results show that the proportion of completely eradicated BE areas was 67\% for the standard regimen and 73\% for the simplified regimen: a difference of 7\%. Because the lower border of the 95\% confidence interval of this difference does not exceed the predefined limit of -20\% (7\%; 95\%CI -10.6\% to +20.9\%) we conclude that the simplified regimen is not inferior to the standard regimen. Although in this study we were not able to separately compare the complication rate of both regimens, there were only two late complications, and no serious or acute complications occurred, which is in accordance with other RFA series.\textsuperscript{3,5}

The currently used double-double-15 J/cm\textsuperscript{2} regimen has its origin in initial balloon-based RFA dose-escalation studies in animals and human patients prior to esophagectomy, as well as subsequent clinical trials.\textsuperscript{1,2,5,13-16} These studies demonstrated a dose-response relation between the energy density (J/cm\textsuperscript{2}) and the number of RF energy applications versus the ablation depth.\textsuperscript{13,14,16} Cleaning of the debris from the ablation surface and electrode was first introduced for circumferential RFA, because the debris was thought to insulate ablated areas from further ablation damage. When the HALO\textsuperscript{90}-catheter came available, a similar ablation regimen as for circumferential RFA was applied for focal RFA. Subsequent dose-escalation from 2x12 J/cm\textsuperscript{2} to 2x2x12 J/cm\textsuperscript{2} to 2x2x15 J/cm\textsuperscript{2} suggested that a double-double-15 J/cm\textsuperscript{2} regimen was the most effective regimen.\textsuperscript{1,2} Improvement of the surface regression of Barrett’s epithelium and reduction of the number of RFA sessions was observed in uncontrolled cohort studies in which the cleaning step was implemented for circumferential balloon-based RFA.\textsuperscript{1,2,5,15} However, other modifications were made to the ablation protocol at the same time: the ablation was performed under endoscopic visualization to optimize positioning of the balloon-catheter, whereas at first this was performed blindly using the shaft of the balloon-catheter as a reference. Secondly, a dose adjustment from 10 to 12 J/cm\textsuperscript{2} for c-RFA was adopted by most centers at this time. Third, a learning effect in performing RFA may have played a role in the improved results. During the cleaning step, the mucosa may however become edematous, hyperemic, and thicker as a reaction to the ablation and the manipulation by pushing, spraying and sloughing off the debris. These effects might neutralize the beneficial effect of removing the debris. Therefore, we used a triple application instead of a double-double application of RFA based on the hypothesis that the cleaning step may neutralize or even decrease the efficacy, and to avoid the potential deeper damage of four RFA applications without cleaning step.
The simplified ablation regimen that we propose in this study has several advantages over the currently used ablation regimen, while the safety and efficacy of focal RFA is maintained. Only a single introduction of the HALO\textsuperscript{90}-catheter is required in the simplified ablation regimen, whereas two introductions of the endoscope and the HALO\textsuperscript{90} catheter are needed in the standard protocol.\textsuperscript{8} Apart from being more practical for the endoscopist, this likely reduces discomfort to the patient and makes the procedure safer, since each introduction can potentially harm the hypopharynx or esophageal wall. This is of relevance, since in an estimated 10% of the cases, based on our own clinical experiences, the introduction of the HALO\textsuperscript{90}-catheter into the esophagus is difficult. In most cases simple tricks suffice, such as asking the patient to swallow, or the introduction of a spraying catheter or biopsy forceps into the esophagus as a conduit. Incidentally, however, dilation of the upper esophageal sphincter with a controlled radial expansion balloon is required. In rare cases, also the removal of the HALO\textsuperscript{90}-catheter may be troublesome, when the HALO\textsuperscript{90}-electrode platform tilts downwards and becomes stuck distal to a stenosis or the upper esophageal sphincter. Especially in patients with a relative stenosis caused by scarring due to prior ER or reflux it may be complicated to introduce or remove the HALO\textsuperscript{90}-catheter. Therefore, this patient group in particular may benefit from an ablation regimen that requires only a single introduction of the HALO\textsuperscript{90}-catheter into the esophagus versus two introductions with the standard regimen. Currently, the smaller HALO\textsuperscript{60}-electrode (electrode surface 60% of the HALO\textsuperscript{90}) is also available for small residual BE islands and tongues, which is easier to introduce. Furthermore, the duration of focal RFA using the simplified regimen may be shorter, since the cleaning of the ablation surface with the cap-electrode and spraying catheter, and cleaning of the ablation surface and the RFA electrode outside of the patient is abandoned.

A strength of our study was the randomization of pairs of islands within one patient, instead of randomizing individual patients. This ensured that both ablation regimens were performed and compared under equal circumstances, ruling out interpatient variation and interprocedure variation.

The most important limitation of our study is that we compared both ablation regimens exclusively for the treatment of BE islands, whereas in clinical practice, focal RFA is performed for larger BE areas, such as tongues and for the circumferential ablation of the gastroesophageal junction.\textsuperscript{8} Theoretically, areas with more exposure to reflux such as the gastroesophageal junction may respond differently to the two regimens. Additionally, in our study, each BE area was treated with a clean HALO\textsuperscript{90}-catheter. Hypothetically, the HALO\textsuperscript{90}-catheter may become more and more covered with debris after repeated RF applications, which may act as an isolation layer and reduce the efficacy of the ablation. Therefore, after a certain number of RF applications, it may be necessary to clean the debris of the HALO\textsuperscript{90}-electrode to keep the efficacy of the ablation optimal.

Another limitation of our study is that our study set-up did not allow for comparison of the duration of both regimens, since both regimens were applied during the same procedure. Further, we were not able to match islands of the exact same size. First, it would be difficult to find two equally sized BE areas within one patient. Secondly, it is currently not possible to quantify the exact surface of a BE island in mm\textsuperscript{2}. The randomized
design of our study, however, makes it unlikely that this has influenced the results. A further limitation is we have not used a histological endpoint. No biopsies were taken from the included areas prior to ablation to assess the presence of IM and dysplasia. Obtaining a biopsy would have changed the size of the BE island, and would therefore interfere with the results of the study. Since the baseline histology of each specific BE area was unknown, we were not able to compare histology before and after focal RFA per randomized BE area. It is, however, unknown if the grade of dysplasia of flat type BE islands is related to the success rate of RFA.6,7 Although we cannot guarantee an equal spread of dysplastic areas over both groups since we did not biopsy prior to RFA, our randomized study set-up makes any influences of this issue small.

In conclusion, in this study we have evaluated a simplified ablation regimen for focal RFA using the HALO90-catheter, by comparing it with the currently used focal ablation regimen in a randomized multicenter trial. The simplified regimen (3x15J/cm² without cleaning) has the advantages of requiring fewer introductions, and, theoretically, a shorter procedure time. Our findings suggest that the proposed simplified 3x15J/cm² focal ablation regimen is not inferior to the standard regimen for focal RFA of residual BE islands after circumferential RFA.

In future studies of focal RFA regimens, patients instead of Barrett’s areas should be randomized to the simplified or the standard RFA regimen, to allow for comparison of procedure time, safety, complete histological response rates for neoplasia and IM, and long-term follow-up.
REFERENCES


