Endoscopic management of Barrett’s esophagus with dysplasia

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CIRCUMFERENTIAL BALLOON-BASED RADIOFREQUENCY ABLATION OF BARRETT’S ESOPHAGUS WITH DYSPLASIA CAN BE SIMPLIFIED, YET EFFICACY MAINTAINED, BY OMITTING THE CLEANING PHASE


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ABSTRACT

BACKGROUND & AIMS: The current procedure for circumferential balloon-based radiofrequency ablation (c-RFA) for the removal of dysplastic Barrett’s esophagus (BE) is labor intensive, comprising 2 ablation passes with a cleaning step to remove debris from the ablation zone and electrode. We compared the safety and efficacy of 3 different c-RFA ablation regimens.

METHODS: We performed a prospective trial of consecutive patients with flat-type BE with high-grade dysplasia. Fifty-seven patients (45 men; age, 64 ± 15 y; 28 with prior endoscopic resection) were assigned randomly to groups that underwent c-RFA with a double application of RFA (12 J/cm²). The standard group received c-RFA, with device removal and cleaning, followed by c-RFA; the simple-with-cleaning group underwent c-RFA, with device cleaning without removal, followed by c-RFA; and the simple-no-cleaning group received 2 applications of c-RFA, and the device was not removed or cleaned. The primary outcome was surface regression of BE 3 months later, graded by 2 blinded expert endoscopists. Calculated sample size was 57 patients, based on a non-inferiority design.

RESULTS: Median BE surface regression at 3 months was 83% in the standard group, 78% in the simple-with-cleaning group, and 88% in the simple-no-cleaning group (P= .14). RF ablation time was 20 minutes (interquartile range [IQR], 18-25 min) for the standard group, 13 minutes (IQR, 11-15 min) for the simple-with-cleaning group, and 5 minutes (IQR, 5-9 min) for the simple-no-cleaning group (P<.01). The median number of introductions (RFA devices/endoscope) for the standard group was 7, vs 4 for the simple groups (P<.01).

CONCLUSIONS: This randomized, prospective study suggests that c-RFA is easier and faster, but equally safe and effective, when the cleaning phase between ablations is omitted or simplified. (trialregister.nl, NTR 2495)
Radiofrequency ablation (RFA) with or without prior endoscopic resection (ER) is an accepted modality for the endoscopic treatment of Barrett’s esophagus (BE) containing early neoplasia, resulting in complete histologic eradication of early neoplasia and intestinal metaplasia in 77%-100% of patients.\(^1\)\(^-\)\(^5\) For initial circumferential RFA (c-RFA), the HALO\(^{360}\) (BARI\(X\) Medical, Inc, Sunnyvale, CA) balloon catheter is available. Subsequent focal RFA of remaining areas of BE is performed with the smaller HALO\(^{90}\) electrode. Complete removal of Barrett’s epithelium generally is achieved after a median of 3 RFA sessions. Currently, the advised treatment regimen for c-RFA procedures comprises 2 ablation passes with cleaning of both the ablation zone and the ablation balloon after the first ablation pass. This regimen therefore requires multiple introductions and removals of the endoscope, sizing catheter, and ablation balloons, which is labor intensive, time consuming and uncomfortable for the patient. The procedure might be simplified by omitting acetylcysteine spraying for mucolysis, not removing the ablation balloon between ablation passes, and no cleaning of the ablation zone. We hypothesized that a simplified c-RFA procedure would result 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 c-RFA regimen with 2 simplified balloon-based ablation regimens in a randomized trial.

**INTRODUCTION**

**PATIENTS AND METHODS**

**PATIENT SELECTION** Patients were eligible when they met the following criteria: scheduled for HALO\(^{360}\) ablation for BE with flat low-grade dysplasia, high-grade dysplasia, or for remaining BE after prior ER of lesions containing early neoplasia; at least one high resolution (HR) imaging endoscopy with biopsy specimens from 4 quadrants of every 2cm BE (4Q/2cm) before RFA; in case of a prior ER: no tumor positive vertical resection margins, no deep submucosal invasion (≥ T1sm2), no G3/G4 cancer, no lymphatic/vascular invasion; review of ER specimens and biopsy specimens by a local expert pathologist; and written informed consent.

**RADIOFREQUENCY ABLATION** RFA was performed using the HALO system, consisting of the HALO\(^{360}\) balloon catheter for circumferential ablation and the HALO\(^{90}\) catheter for focal ablation of BE areas of 2 cm or less.

**HALO\(^{360}\) REGIMENS** Before ablation, the esophagus was evaluated using HR white light (WL) endoscopy and narrow band imaging (NBI) or Fuji Intelligent Chromo Endoscopy (FICE). The extent of columnar-lined esophagus was documented according to the C&M classification and the number and localization of BE islands were registered.\(^6\) Still images (WL+NBI/FICE) were made of every 1-2 cm of the BE segment while pulling back from the top of the gastric folds. Patients subsequently were randomized to 1 of 3 c-RFA ablation regimens (Table 1).
STANDARD CIRCUMFERENTIAL RADIOFREQUENCY ABLATION REGIMEN  The BE was flushed with acetylcysteine (1%) for mucolysis followed by flushing with tap water. A guidewire was introduced and the endoscope was removed, followed by the introduction of a sizing balloon over the guidewire. Sizing of the esophageal inner diameter was performed and an appropriately sized ablation balloon was selected. The BE was ablated from proximal to distal (12 J/cm²), allowing for a small overlap of less than 1 cm between ablation zones. After removal of the ablation catheter and endoscope, the endoscope was reintroduced with a flexible distal attachment cap (MB0-046; Olympus, Tokyo, Japan). The necrotic debris was gently pushed off the ablation zone with the rim of the cap and by applying suctioning. Any remaining debris was removed by forcefully flushing water using a high-pressure pistol with water through a spray catheter. The surface of the ablation balloon was cleaned outside the patient using water and gauze. Subsequently, the guidewire was inserted, the endoscope was removed, followed by reintroduction of the ablation catheter and endoscope, and a second ablation was performed (12 J/cm²).

SIMPLE-WITH-CLEANING CIRCUMFERENTIAL RADIOFREQUENCY ABLATION REGIMEN  The BE segment was flushed with tap water before sizing. The distal cap was placed on the tip of the endoscope before ablation. After the first ablation (12 J/cm²) the ablation balloon was not removed but advanced distally into the stomach. The ablation zone was cleaned using the distal cap (not with the high pressure pistol and spray catheter) alongside the shaft of the ablation balloon. Subsequently, a second ablation pass (12 J/cm²) was performed.

SIMPLE-NO-CLEANING CIRCUMFERENTIAL RADIOFREQUENCY ABLATION REGIMEN  The BE segment was flushed with tap water before sizing. After the first ablation of the most proximal zone, a second ablation was performed immediately (2x12 J/cm²) in the same zone without a cleaning step. After deflation, the balloon was advanced distally to ablate subsequent zones with a double ablation in an identical way.

Patients completed questionnaires concerning treatment-related symptoms (chest pain, difficulty swallowing, pain during swallowing, throat pain, and abdominal pain using a 10-point scale, resulting in a scale of 0-50 for severity) at baseline, before c-RFA; day 0 after c-RFA, after recovery from sedative medication before leaving the hospital; day 1 after c-RFA; and at day 10 after c-RFA, blinded to the administered regimen.
SUBSEQUENT TREATMENT AND FOLLOW-UP  Follow-up HR-WL endoscopy with NBI/FICE was performed after 3 months, and the outcome measures were scored at that time. Still images (WL+NBI/FICE) were made for every 1-2 cm of the BE segment from distal to proximal. RFA was repeated with 2- to 3-month intervals until complete endoscopic removal of all BE was achieved. In case of remaining BE after 5 RFA sessions (≤2 c-RFA), an escape ER was performed. After complete endoscopic and histologic removal of BE, patients were scheduled for follow-up endoscopy with NBI/FICE and 4Q/2cm biopsy at 6 months, and annually thereafter.

PRIMARY OUTCOME AFTER A SINGLE HALO\textsuperscript{360} TREATMENT SESSION  The primary outcome was the percentage of endoscopically visual surface regression of BE epithelium at 3 months. This composite end point was defined by the mean percentage of BE surface regression of 2 endoscopists who independently and in retrospect scored the BE regression percentage. Two endoscopists blindly reviewed endoscopic images of every 1-2 cm of the original BE segment captured immediately before the initial HALO\textsuperscript{360} procedure and during follow-up endoscopy after 3 months. In case the BE surface regression percentage differed by 30% or more between both endoscopists, a new score was established during a consensus meeting. The endoscopists indicated if the endoscopic images were representative with regard to the quality and quantity (images per 1-2 cm of BE), scored as good, moderate, or poor. For cases scored as poor by either one of the endoscopists, the surface area regression as assessed in real time during the 3-month follow-up endoscopy was used for analysis.

SECONDARY OUTCOMEs AFTER A SINGLE HALO\textsuperscript{360} TREATMENT SESSION  The secondary outcomes after a single HALO\textsuperscript{360} treatment session were as follows: duration of the HALO\textsuperscript{360} ablation procedure; the number of introductions of the ablation balloon and endoscope; patient discomfort after HALO\textsuperscript{360} treatment; and complications of the initial HALO\textsuperscript{360} procedure.\textsuperscript{7} The secondary outcomes after completion of the treatment protocol were as follows: complete response for early neoplasia (CR-neoplasia), which consisted of absence of early neoplasia and dysplasia in biopsy specimens (4Q/2cm) of neosquamous epithelium and just below the neosquamocolumnar junction; and complete response for intestinal metaplasia (CR-IM), which consisted of the absence of IM in biopsy specimens (4Q/2cm) of neosquamous epithelium and just below the neosquamocolumnar junction.

HISTOLOGY  ER specimens and biopsy specimens obtained before randomization, during treatment, and during follow up evaluation were assessed by a local expert pathologist at each center.\textsuperscript{8} ER specimens were assessed for tumor infiltration depth (T1sm2 defined as submucosal tumor infiltration depth ≥500 μm), differentiation, vasoinvasive tumor growth, and vertical resection margins (and lateral resection margins in case of en bloc resection). Biopsies obtained from neosquamous epithelium additionally were assessed for the presence of subsquamous IM (buried Barrett’s).

ETHICS AND STATISTICS  This study was approved by the medical ethics committees of the 3 study centers (www.trialregister.nl, Nederlands Trial Register 2495). All patients provided signed informed consent. Randomization was performed dur-
ing endoscopy using sealed opaque envelopes by a study monitor who attended the endoscopic procedures. The sample size calculation was based on existing data on the Barrett's surface regression percentage at 3 months after initial c-RFA.\textsuperscript{1,4,5} We assumed that a difference of 20% or more in the BE surface regression percentage among treatment arms would be of clinical relevance. To reject the hypothesis that the simple regimens are inferior to the standard regimen, a total of 57 patients (19 per group, 10% drop-out rate) were required, with non-inferiority defined as less than 20% difference in BE regression percentage after initial c-RFA between the simple regimens versus the standard regimen (1-sided, \( P=0.025 \), 80% Power). The authors had access to the data and reviewed and approved the final manuscript. Data analysis was performed using the SPSS statistical software package (version 16.0.2, SPSS, Inc, Chicago, IL) and the Confidence Interval Analysis (CIA) package (CIA Version 2.2.0, London, UK). nQuery Adviser (Version 7; Statistical solutions Ltd, Cork, Ireland) was used for sample size calculation. The Fisher exact test, the Mann-Whitney U test, and the Kruskal-Wallis test were used when appropriate. Differences were considered statistically significant if the \( P \) value was .05 or less.

\section*{RESULTS}

\textbf{PATIENTS} This randomized trial was performed in 3 collaborating tertiary referral centers in the Netherlands. Between December 2008 and April 2011, there were 76 patients screened (Supplementary Figure 1). Nineteen patients were not eligible for the study for the following reasons: focal RFA was indicated at the initial RFA session (n=9), esophageal stenosis (n=8), or no consent was obtained (n=2). Fifty-seven patients were included, 19 in each randomization arm (Supplementary Figure 1). Baseline characteristics were similar among the 3 groups (Table 2).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure1.png}
\caption{Patient flow chart. CR-IM, complete response for intestinal metaplasia; CR-N, complete response for neoplasia; HGD, high-grade dysplasia; Z-line, squamocolumnar junction.}
\end{figure}
PERCENTAGE OF BARRETT’S ESOPHAGUS SURFACE REGRESSION AFTER CIRCUMFERENTIAL RADIOFREQUENCY ABLATION 

Of the 57 included patients, 56 patients were available for assessment of the primary outcome at 3 months after c-RFA (Figures 1 and 2, Table 3). One patient died of unrelated disease (myocardial infarction) 8 weeks after c-RFA.

The median BE surface regression at 3 months was 83% (interquartile range [IQR], 70-93) with the standard c-RFA regimen; 78% (IQR, 55-88) with the simple-with-cleaning c-RFA regimen; and 88% (IQR, 79-97) with the simple-no-cleaning c-RFA regimen. The simple-no-cleaning regimen was non-inferior to standard c-RFA, with a difference of 4.8% (95% confidence interval, -5.0 to +15.0). When comparing the simple-with-cleaning regimen with the standard regimen (difference 7.5%; 95% confidence interval, -20.0 to +7.0), non-inferiority could not be concluded.

A median of 9 (IQR 7-12) endoscopic images was available per pre- and post c-RFA endoscopy. The median difference in BE regression percentage between the real-time score and the mean score of the 2 scoring endoscopists was 2.5% (IQR, 5%-10%). For 6 patients the BE surface regression percentage was established in a consensus meeting. For 1 patient, images were scored as poor for representativeness, therefore the real-time score was used.

Table 2: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Standard n=19</th>
<th>Simple-with-cleaning n=19</th>
<th>Simple-no-cleaning n=19</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: female</td>
<td>15 M / 4 F</td>
<td>16 M / 3 F</td>
<td>14 M / 5 F</td>
<td>.73</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>61 ± 12</td>
<td>59 ± 14</td>
<td>62 ± 18</td>
<td>.77</td>
</tr>
<tr>
<td>Median Barrett’s length, cm</td>
<td>(IQR, C1-8, M4-10)</td>
<td>(IQR, C0-4, M3-6)</td>
<td>(IQR, C1-4, M3-7)</td>
<td>.38</td>
</tr>
<tr>
<td>Most advanced histology</td>
<td>8 EC, 9 HGD, 2 LGD</td>
<td>9 EC, 7 HGD, 3 LGD</td>
<td>5 EC, 11 HGD, 3 LGD</td>
<td>.50</td>
</tr>
<tr>
<td>Endoscopic resection before randomization</td>
<td>9/19</td>
<td>10/19</td>
<td>9/19</td>
<td>.93</td>
</tr>
<tr>
<td>Histology before radiofrequency ablation (biopsies)</td>
<td>9 HGD, 10 LGD/IM</td>
<td>12 HGD, 7 LGD/IM</td>
<td>10 HGD, 9 LGD/IM</td>
<td>.62</td>
</tr>
</tbody>
</table>

C, circumferential; EC, early cancer; HGD, high grade dysplasia; LGD, low grade dysplasia; M, maximal.
Figure 1: A: Baseline C4M6 Barrett’s esophagus containing high grade dysplasia. B: Simple-no-cleaning regimen for circumferential ablation; C: There is 88% BE surface regression at 3 months; focal ablation. D: Complete response for neoplasia/intestinal metaplasia after 4 RFA sessions.

Figure 2: A and B: Baseline C3M10 Barrett’s esophagus after ER (T1m3 carcinoma) treated with the simple-with-cleaning regimen for circumferential radiofrequency ablation; HALO360 balloon placed in the stomach during cleaning of the ablation zone. C: There is 83% Barrett’s surface regression at 3 months; focal ablation. D: Complete response for neoplasia/intestinal metaplasia after 4 RFA sessions.
Table 3: Treatment outcomes

<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>Standard (n=19)</th>
<th>Simple-with-cleaning (n=19)</th>
<th>Simple-no-cleaning (n=18)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrett’s surface regression at 3 months, median (IQR)</td>
<td>83% (70-93)</td>
<td>78% (55-88)</td>
<td>88% (79-97)</td>
<td>.14</td>
</tr>
<tr>
<td>Difference in Barrett’s surface regressions at 3 months among regimens [95% confidence interval]</td>
<td>simple-with-cleaning vs standard:</td>
<td>simple-no-cleaning vs standard:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-7.5% (-20.0 to 7.0)</td>
<td>+4.8% (-5.0 to 15.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary outcome:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications during circumferential balloon-based radiofrequency ablation</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>.60</td>
</tr>
<tr>
<td>Total procedure duration, median (IQR)</td>
<td>39 min (30-46 min)</td>
<td>32 min (23-40 min)</td>
<td>25 min (15-28 min)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Ablation time, median (IQR)</td>
<td>20 min (18-25 min)</td>
<td>13 min (11-15 min)</td>
<td>5 min (5-9 min)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Number of introductions, median (IQR)</td>
<td>7 (7-7)</td>
<td>4 (4-5)</td>
<td>4 (4-5)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Need for surgery, n</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Complete response for neoplasia (patients)</td>
<td>100% (19/19)</td>
<td>95% (18/19)</td>
<td>100% (18/18)</td>
<td>.87</td>
</tr>
<tr>
<td>Complete response for intestinal metaplasia (patients)</td>
<td>90% (17/19)</td>
<td>84% (16/19)</td>
<td>89% (16/18)</td>
<td>.37</td>
</tr>
<tr>
<td>Radiofrequency ablation sessions, median (IQR)</td>
<td>3 (2-3)</td>
<td>3 (2-4)</td>
<td>3 (2-3)</td>
<td>.72</td>
</tr>
</tbody>
</table>
PROCEDURE DURATION AND NUMBER OF INTRODUCTIONS The duration of the c-RFA procedure measured from the introduction of the HALO® balloon until removal of the endoscope at the end of the procedure was 20 minutes (IQR, 18–25) using the standard regimen vs 13 minutes (IQR, 11–15) using the simple-with-cleaning regimen vs 5 minutes (IQR, 5–9) using the simple-no-cleaning regimen (P < .01). The median number of introductions of the endoscope or ablation balloon device was 7 using the standard regimen vs 4 in both simplified regimens (P < .01).

PATIENT DISCOMFORT At baseline before c-RFA, the overall patient discomfort was 0 (IQR, 0–2) on a scale of 0 to 50 points for the severity of treatment-related symptoms (Supplementary Table 1). At day 0 after c-RFA, more symptoms were reported with a median severity of 6 (IQR, 0–13). At day 1 after c-RFA, this increased to a median severity of 9 (IQR, 3–15). At day 10, 55% of patients were free of symptoms and 73% of patients had resumed normal daily activities. No differences were found among the 3 regimens.

Supplementary Table 1: Patient discomfort relating to circumferential balloon-based RFA using 3 different ablation regimens, based on questionnaires concerning treatment-related symptoms, that were completed a several time points before and after c-RFA

<table>
<thead>
<tr>
<th>Ablation regimen</th>
<th>Overall n=57</th>
<th>Standard n=19</th>
<th>Simple-with-cleaning n=19</th>
<th>Simple-no-cleaning n=19</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 0, at baseline</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Severity of symptoms, median (IQR)*</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
<td>0 (0-3)</td>
<td>0 (0-2)</td>
<td>.48</td>
</tr>
<tr>
<td><strong>Day 0, after c-RFA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of symptoms, median (IQR)</td>
<td>6 (0-13)</td>
<td>3 (0-9)</td>
<td>6 (4-15)</td>
<td>5 (0-13)</td>
<td>.26</td>
</tr>
<tr>
<td><strong>Day 1, after c-RFA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of symptoms, median (IQR)</td>
<td>9 (3-15)</td>
<td>14 (9-12)</td>
<td>5 (3-21)</td>
<td>7 (4-9)</td>
<td>.06</td>
</tr>
<tr>
<td><strong>Day 10, after c-RFA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of pain medication during 10 d (patients)</td>
<td>68% (28/41)</td>
<td>69% (9/13)</td>
<td>77% (10/13)</td>
<td>60% (9/15)</td>
<td>.64</td>
</tr>
<tr>
<td>Symptom free (patients)</td>
<td>55% (21/38)</td>
<td>75% (9/12)</td>
<td>50% (6/12)</td>
<td>43% (6/14)</td>
<td>.24</td>
</tr>
<tr>
<td>Returned to normal activities (patients)</td>
<td>73% (27/37)</td>
<td>80% (8/10)</td>
<td>62% (8/13)</td>
<td>79% (11/14)</td>
<td>.52</td>
</tr>
</tbody>
</table>

*Symptoms were scored using questionnaires concerning treatment-related symptoms (chest pain; difficulty swallowing; pain during swallowing; throat pain; abdominal pain), using a 10-point scale, resulting in a scale of 0-50 points for severity of symptoms. Questionnaires were completed at baseline before c-RFA; day 0 after c-RFA (after recovery from sedative medication before leaving the hospital); day 1 after c-RFA; and day 10 after c-RFA.

COMPLICATIONS Two mild acute complications occurred during the c-RFA procedure: 2 asymptomatic superficial lacerations occurred during the sizing procedure. In both patients c-RFA was postponed for 1–2 months. No problems were encountered at the subsequent c-RFA.

After the c-RFA procedure 3 complications occurred. One late bleeding occurred in a patient who presented with hematemesis (hemoglobin level unchanged, no blood transfusion, no anticoagulant use) 2 weeks after the first focal RFA treatment. During upper endoscopy, a visible vessel in the treatment area was coagulated with a Gold-probe (Boston Scientific, Natick, MA). Another patient was hospitalized for 1 night because of pain after focal RFA. A third patient who had a pre-existing esophageal narrowing before endoscopic treatment developed a symptomatic stenosis after a second c-RFA procure, resolving after 1 dilation.
SUBSEQUENT TREATMENT  All 56 available patients underwent subsequent RFA sessions after initial c-RFA. Overall, CR-neoplasia and CR-IM was achieved in 55 of 56 patients (98%) and 49 of 56 patients (88%), respectively, in a median of 3 (IQR, 2-3) RFA sessions (Table 3). There were no differences among the 3 ablation regimens.

One patient failed CR-neoplasia. This patient was referred for esophagectomy because of less than 25% surface regression with poor healing and persisting high-grade dysplasia after 2 c-RFA sessions of a C13M14 BE after ER of a T1m2 carcinoma. The esophagectomy specimen showed a focus of T1m2 carcinoma and 30 lymph nodes were negative for carcinoma.

Six patients failed CR-IM. In 3 of these patients, RFA treatment was discontinued. One patient with a C4M9 BE showed only 40% BE surface regression after 2 c-RFA sessions. The BE showed poor healing and a lesion suspicious for neoplasia. An extensive escape ER was performed (T1m2 carcinoma) and CR-neoplasia was achieved. Another patient with a C11M13 BE showed 0% BE surface regression and reflux grade B after c-RFA. CR-neoplasia was achieved after ER of a visible lesion (T1m3 carcinoma). A third patient with a C3M4 BE failed CR-IM owing to severe reflux and poor healing of the esophagus, which precluded further ablation during several occasions. Three other patients had residual IM in biopsy specimens from an irregular neo-Z-line (new squamocolumnar junction) at 2 occasions.

DISCUSSION

This randomized multicenter trial suggests that omitting or simplifying the cleaning step between ablations can make circumferential balloon-based RFA easier and faster without sacrificing efficacy.

The combined approach of ER and RFA is currently considered the treatment of choice for patients with Barrett’s esophagus containing early neoplasia.9 The CR-neoplasia and CR-IM rates in the current study were 98% and 88%, respectively, which corresponds with the results of other studies.1,2,4,5,10,11 Recent data show sustained eradication of early neoplasia and IM in 96%-98% and 91%-100% of patients, respectively, after 3-5 years of follow-up evaluation.10,12 Currently, more than 1000 centers worldwide offer RFA treatment for BE, therefore, a simplified ablation regimen is of significant relevance. An easier ablation regimen serves the endoscopist, fewer introductions of devices may increase safety and diminish patient discomfort, and a reduced procedure time improves the cost-effectiveness of RFA.

In this randomized study with a non-inferiority design, the efficacy of the simple-no-cleaning regimen (ie, double application of 12 J/cm²), without cleaning of the ablation zone and ablation catheter between ablation passes, was comparable with the standard regimen. When comparing the efficacy of the simple-with-cleaning regimen with the standard c-RFA regimen, non-inferiority could not be concluded because the lower border of the 95% confidence interval included the predefined border of 20% Barrett’s surface regression that a priori was considered as a clinically relevant difference. In our opinion, however, it is justified to conclude that there are no important differences in efficacy between the 3 c-RFA regimens. It also is essential to realize that the final treatment outcome of RFA generally results from multiple RFA sessions. Small differences in the initial efficacy of c-RFA thus can be
compensated by one of the subsequent focal RFA sessions. For these reasons, and because the simple-no-cleaning regimen is by far the easiest and fastest of the 3 regimens tested, we considered this c-RFA regimen as the most suitable for clinical use. The simple-no-cleaning regimen had a significantly shorter RF ablation time, lasting only 5 vs 20 minutes for the standard regimen, respectively, and required only 4 introductions of the endoscope and RFA balloon vs 7 with the standard regimen.

The double application of RF energy used in the current c-RFA regimens is based on initial dosimetry studies in animals and in human patients before esophagectomy.13,14 These studies showed a dose-response relation between the number of RFA applications and the ablation depth, resulting in a higher rate of complete epithelial removal after a double RFA application vs a single application. In addition, a double RFA application ensures that missed areas during the first ablation pass are ablated during the second pass. The cleaning step with removal of the debris of the electrode and ablation zone between ablation passes was incorporated in the treatment protocol based on the theory that the debris after RFA would insulate ablated areas from further ablation injury, thus reducing the efficacy of RFA. Similarly, flushing with acetylcysteine was included, based on the hypothesis that mucus on the esophageal wall could insulate the mucosa from ablation injury. 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.4,5,15,16 However, these studies also incorporated other modifications to the ablation protocol: first, the ablation was performed under endoscopic visualization to optimize positioning of the balloon catheter, whereas previously this was performed blindly using the shaft of the balloon catheter as a reference. Second, a dose adjustment from 10 to 12 J/cm² for c-RFA was adopted by most centers at this time.2,4,5 Third, focal RFA for residual BE areas using the HALO90 device was introduced. Last, a learning effect in performing RFA may have played a role. Theoretically, the cleaning step may also be counterproductive: the ablated mucosa underneath the debris may become swollen and hyperemic as a result of the first ablation or as a result of manipulation by the cleaning process. The RF energy subsequently may not reach as deeply in the thickened mucosa, which may thus counterbalance the beneficial effect of removing the debris. This randomized study suggests that cleaning between ablation passes may not be as relevant as previously believed.

The simple-no-cleaning regimen is the most simple ablation regimen of 3 investigated in this study. Based on the results of this study, we have incorporated the simplified c-RFA regimen in our daily practice for uncomplicated c-RFA cases. In addition, we have included the simplified regimen in our RFA training programs (www.RFA-academia.eu).

The simple-no-cleaning regimen, however, may have some drawbacks compared with standard c-RFA. Theoretically, the simple-no-cleaning regimen may leave small skipped BE zones that are not ablated during c-RFA because the same zone is ablated twice, keeping the balloon virtually in the same position. In contrast, the standard c-RFA regimen consists of 2 separate ablation passes from proximal to distal; usually this results in successful ablation of skipped zones during the second ablation pass because the balloon will not be in the exact same level in the BE.

For patients with a more complex Barrett’s segment, in our opinion, the simple-no-cleaning regimen may be less appropriate. In patients with a relative stenosis, or a narrowing at the ER scar, the balloon may migrate during ablation, resulting in
skipped zones or zones with too much overlap that are ablated multiple times. The cleaning step of the standard regimen is a good way to assess the completeness of the first complete ablation pass, and allows for adjustment of the balloon position during the second ablation pass to treat skipped zones. Therefore, for patients with a complex or tortuous esophagus, we recommend the standard regimen for c-RFA.

Finally, theoretically, 2 immediate double ablations of the same zone, as applied in the simple-no-cleaning regimen, may result in heat stacking and cause deeper thermal damage than when the ablation zone has had time to cool down during a cleaning step. We did not observe any RFA-related stenoses in this study and this concern therefore remains theoretical.

A potential limitation of our study was the use of a surrogate primary end point. Our primary end point was the mean score of 2 expert endoscopists who blindly and independently scored the BE surface regression percentage at 3 months after c-RFA for each patient using endoscopic images. This approach ensured an unbiased BE surface regression percentage score. We assume that the BE surface regression percentage reflects the c-RFA efficacy the more directly than the rate of complete response of neoplasia and IM after multiple RFA sessions. In addition to a comparable rate of BE surface regression at 3 months after c-RFA of the simple-no-clean and standard c-RFA regimen, there was also no difference in CR-neoplasia and CR-IM rates or the number of RFA sessions, which highlights the clinical relevance of the study. Another limitation was the setting of 3 tertiary referral centers for the management of early Barrett’s neoplasia with experienced endoscopists and pathologists, making our results untranslatable to non-expert centers. However, we strongly encourage centralization of ER and RFA treatment for all patients with early Barrett’s neoplasia in expert centers. Other limitations concern the small sample size and short-term follow-up evaluation.

In conclusion, in this randomized multicenter trial we compared 3 ablation regimens for circumferential balloon-based RFA in the management of early Barrett’s neoplasia. We showed that the efficacy of a simplified regimen in which the cleaning step is completely abandoned is non-inferior to the standard regimen, and this regimen is twice as fast and requires significantly fewer introductions than the standard regimen. Therefore, we recommend the use of the simplified c-RFA regimen without cleaning step as a quick and easy alternative for patients with an uncomplicated Barrett’s esophagus without scarring and stenosis.


