Advances in endoscopic resection and radiofrequency ablation of early esophageal neoplasia
van Vilsteren, F.G.I.

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Simplifying circumferential balloon-based radiofrequency ablation of Barrett’s esophagus containing dysplasia: randomized trial comparing three ablation regimens


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Chapter 8

ABSTRACT

Background and aims: The current regimen of circumferential balloon-based radiofrequency ablation (c-RFA) for the removal of dysplastic Barrett’s esophagus (BE) is labor-intensive, consisting of two ablation passes with a cleaning step to remove ablation debris from the ablation zone and electrode. We aimed to compare the safety and efficacy of three c-RFA ablation regimens.

Methods: Consecutive BE patients scheduled for c-RFA for flat-type BE containing ≤ high-grade dysplasia were enrolled. c-RFA consisted of a double RFA application (12 J/cm²) in all regimens: ‘standard’: c-RFA, remove device, clean, c-RFA; ‘simple-with-cleaning’: c-RFA, clean without removing device, c-RFA; ‘simple-no-cleaning’: 2 applications of c-RFA, no removal of device, no cleaning. Primary outcome: BE surface regression (%) at 3 months, graded by 2 expert endoscopists, blinded to the allocated regimen. Sample size: 57 patients, non-inferiority design, with a difference in BE regression ≥20% considered as clinically relevant.

Results: 57 patients (45M, 64±15yrs, BE C3M5) were randomized, 28 had had prior endoscopic resection. Median BE surface regression at 3 months was 83% with ‘standard’; 78% with ‘simple-with-cleaning’; and 88% with ‘simple-no-cleaning’ (p=0.14). RF ablation time was 20min (IQR18-25) using ‘standard’ vs. 13min (IQR11-15) using ‘simple-with-cleaning’ vs 5min (IQR5-9) using ‘simple-no-cleaning’ (p<0.01). Median number of introductions (RFA devices/endoscope) using ‘standard’ was 7 vs. 4 in both simplified regimens (p<0.01).

Conclusions: This randomized study suggests that c-RFA can be made easier and faster without sacrificing safety or efficacy, by omitting or simplifying the cleaning phase in between ablations.
INTRODUCTION

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 histological eradication of early neoplasia and intestinal metaplasia in 77 to 100% of patients.\textsuperscript{1-5} For initial circumferential RFA (c-RFA), the HALO\textsuperscript{360}-balloon catheter is available. Subsequent focal RFA of remaining areas of BE is performed with the smaller HALO\textsuperscript{90}-electrode. Complete removal of Barrett's epithelium is generally achieved after a median of three RFA sessions. Currently, the advised treatment regimen for c-RFA procedures comprises two 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 to the patient. The procedure might be simplified by omitting acetylcysteine spraying for mucolysis, not removing the ablation balloon in 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 to two 'simplified' balloon-based ablation regimens in a randomized trial.

PATIENTS AND METHODS

Patient selection

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

Radiofrequency ablation

RFA was performed using the HALO system (by BÂRRX Medical Inc, Sunnyvale, CA, USA), consisting of the HALO\textsuperscript{360}-balloon-catheter for circumferential ablation and the HALO\textsuperscript{90}-catheter for focal ablation of BE areas \(\leq 2\)cm.

HALO\textsuperscript{360}-regimens

Prior to 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.\textsuperscript{6} Still images (WL+NBI/FICE) were made of every 1-2cm of the BE segment while pulling back from the top of the gastric
folds. Patients were subsequently randomized to one of three c-RFA ablation regimens (Table 1).

‘Standard’ c-RFA regimen: The BE was flushed with acetylcysteine (1%) for mucolysis followed by flushing with tap water. A guide wire was introduced and the endoscope was removed, followed by the introduction of a sizing balloon over the guide wire. 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 <1cm 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 a gauze. Subsequently, the guide wire was inserted, the endoscope removed, followed by reintroduction of the ablation catheter and endoscope, and a second ablation (12 J/cm²).

‘Simple-with-cleaning’ c-RFA regimen: The BE segment was flushed with tap water prior to sizing. The distal cap was placed on the tip of the endoscope prior to 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’ c-RFA regimen: The BE segment was flushed with tap water prior to sizing. After the first ablation of the most proximal zone, immediately a second ablation was performed (2x12 J/cm²) of 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 swallowing, throat pain, abdominal pain using a 10-point scale, resulting in a 0-50 points scale for severity) ‘at baseline’ prior to c-RFA; ‘day-0 post c-RFA’

### Table 1: Three regimens for circumferential balloon-based radiofrequency ablation (12 J/cm²).

<table>
<thead>
<tr>
<th>Ablation regimen</th>
<th>‘Standard’</th>
<th>‘Simple-with-cleaning’</th>
<th>‘Simple-no-cleaning’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spraying with acetylcysteine prior to ablation</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cleaning of the debris from the ablation balloon outside of the patient after the first ablation pass</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cleaning of the debris from the ablation zone after the first ablation pass</td>
<td>Yes</td>
<td>Yes (distal attachment cap, high pressure pistol, spray catheter)</td>
<td>No (distal attachment cap only)</td>
</tr>
<tr>
<td>Minimum number of introductions of endoscope and balloon catheters</td>
<td>7</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
after recovery from sedative medication prior to leaving the hospital; ‘day-1 post c-RFA’; and at ‘day-10 post 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 1-2cm of the BE segment from distal to proximal. RFA was repeated with 2-3 months intervals until complete endoscopic removal of all BE was achieved. In case of remaining BE after 5 RFA sessions (≤2 c-RFA) escape ER was performed. After complete endoscopic and histological removal of BE, patients were scheduled for follow-up endoscopy with NBI/FICE and 4Q/2cm biopsies at 6 months, and annually thereafter.

**Primary outcome after a single HALO\textsuperscript{360}-treatment session**

Percentage of endoscopically visual surface regression of BE epithelium at 3 months.

This composite endpoint was defined by the mean percentage of BE surface regression of two endoscopists who independently and in retrospect scored the BE regression percentage. Two endoscopists blindly reviewed endoscopic images of every 1-2cm of the original BE segment captured immediately prior the initial HALO\textsuperscript{360}-procedure and during follow-up endoscopy after 3 months. In case the BE surface regression percentage differed ≥30% between both endoscopists, a new score was established during a consensus meeting. The endoscopists indicated if the endoscopic images were representative with regards to the quality and quantity (images per 1-2cm 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 months follow-up endoscopy was used for analysis.

**Secondary outcomes after a single HALO\textsuperscript{360}-treatment session**

- Duration of the HALO\textsuperscript{360}-ablation-procedure;
- Number of introductions of the ablation-balloon and endoscope;
- Patient discomfort after HALO\textsuperscript{360}-treatment;
- Complications of the initial HALO\textsuperscript{360}-procedure.\textsuperscript{7}

**Secondary outcomes after completion of the treatment protocol:**

- Complete response for early neoplasia (CR-neoplasia): absence of early neoplasia and dysplasia in biopsies (4Q/2cm) of neosquamous epithelium and just below the neosquamocolumnar junction;
- CR-IM: absence of IM in biopsies (4Q/2cm) of neosquamous epithelium and just below the neosquamocolumnar junction.

**Histology**

ER specimens and biopsies obtained prior to randomization, during treatment and during follow up 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 ≥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 were additionally assessed for the presence of subsquamous IM (buried Barrett’s).

Ethics and statistics

This study was approved by the medical ethics committees of the three study centers (www.trialregister.nl, NTR 2495). All patients signed informed consent. Randomization was performed during 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. 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) were required, with non-inferiority defined as <20% difference in BE regression percentage after initial c-RFA between the simple regimens versus the standard regimen (one-sided, p=0.025, 80% Power). Data analysis was performed using SPSS statistical software package (SPSS Inc.16.0.2, Chicago, IL, USA) and the Confidence Interval Analysis package (CIA Version 2.2.0, London, UK). nQuery Adviser (Version 7, Cork, Ireland) was used for sample size calculation. Fisher exact test, Mann-Whitney U test, and Kruskal Wallis test were used when appropriate. Differences were considered statistically significant if p≤0.05.

RESULTS

Patients

This randomized trial was performed in three collaborating tertiary referral centers: Academic Medical Center, Amsterdam, St Antonius Hospital Nieuwegein, and Catharina Hospital Eindhoven, the Netherlands. Between December 2008 until April 2011, 76 patients were screened (Figure 1). Nineteen patients were not eligible for study: focal RFA was indicated at the initial RFA session (n=9), esophageal stenosis (n=8), or no consent obtained (n=2). A total of 57 patients was included, 19 in each randomization arm (Figure 1). Baseline characteristics were similar among the three groups (Table 2).

Percentage of BE surface regression after c-RFA

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

The median BE surface regression at 3 months was 83% (IQR 70-93) with the standard c-RFA regimen; 78% (IQR 55-88) with the simple-with-cleaning c-RFA regimen; and 88%
Simplified circumferential balloon-based RFA

(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%CI -5.0-+15.0]). When comparing the simple-with-cleaning regimen to the standard regimen (difference -7.5% [95%CI -20.0-+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 two scoring endoscopists was 2.5% (IQR -5-10%). Of 6 patients the BE surface regression percentage was established in a consensus meeting. Of 1 patient, images scored ‘poor’ for representativeness, therefore the real time score was used.
Chapter 8

Procedure duration and number of introductions

The duration of the c-RFA procedure measured from introduction of the HALO$^{360}$-balloon until removal of the endoscope at the end of the procedure was 20 minutes (IQR 18-25) using the standard regimen versus 13 minutes (IQR11-15) using the simple-with-cleaning regimen versus 5 minutes (IQR 5-9) using the simple-no-cleaning regimen (p<0.01). The median number of introductions of the endoscope or ablation balloon-device was 7 using the standard regimen versus 4 in both simplified regimens (p<0.01).

Patient discomfort

At baseline prior to c-RFA, overall patient discomfort was 0 (IQR 0-2) on a 0-50 points scale for the severity of treatment-related symptoms (Supplements, Table S1). 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 three regimens.

Figure 2: A: Baseline C4M6 Barrett’s esophagus containing high-grade dysplasia. B: simple-no-cleaning regimen for circumferential radiofrequency ablation. C: 88% BE surface regression at 3 months; focal ablation. D: complete response for neoplasia and intestinal metaplasia after 4 RFA sessions.
Figure 3: A-B: Baseline C3M10 Barrett’s esophagus after ER (T1m3 carcinoma) treated with the simple-with-cleaning regimen for circumferential radiofrequency ablation; HALO\textsuperscript{360} balloon placed in the stomach during cleaning of the ablation zone. C: 83% Barrett’s surface regression at 3 months; focal ablation. D: complete response for neoplasia and intestinal metaplasia after 4 RFA sessions.

Complications
Two mild acute complications occurred during the c-RFA procedure: two 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 three complications occurred. One late bleeding occurred in a patient who presented with haematemesis (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. Another patient was hospitalized for one night because of pain after focal RFA. A third patient who had a pre-existing esophageal narrowing prior to endoscopic treatment developed a symptomatic stenosis after a second c-RFA procure, resolving upon 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 55/56 patients (98%) and 49/56 patients (88%),
respectively in a median of 3 (IQR 2-3) RFA sessions (Table 3). There were no differences among the three ablation regimens.

One patient failed CR-neoplasia. This patient was referred for esophagectomy because of <25% surface regression with poor healing and persisting HGD after two 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 three of these patients, RFA treatment was discontinued. One patient with a C4M9 BE demonstrated only 40% BE surface regression after two 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 due to severe reflux and poor healing of the esophagus, which precluded further ablation during several occasions. Three others had residual IM in biopsies from an irregular neo-Z-line at two occasions.

Table 3: Treatment outcomes.

<table>
<thead>
<tr>
<th></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>Primary outcome:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>0.14</td>
</tr>
<tr>
<td>Difference in Barrett’s surface regressions at 3 months among regimens [95% CI]</td>
<td>‘simple-with-cleaning’ vs ‘standard’: -7.5% [95%CI -20.0-+7.0]</td>
<td>‘simple-no-cleaning’ vs ‘standard’: +4.8% [95%CI -5.0-15.0]</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>0.60</td>
</tr>
<tr>
<td>Total procedure duration (median/IQR)</td>
<td>39 min (30-46)</td>
<td>32 min (23-40)</td>
<td>25 min (15-28)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Ablation time (median/IQR)</td>
<td>20 min (18-25)</td>
<td>13 min (11-15)</td>
<td>5 min (5-9)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Number of introductions</td>
<td>7 (7-7)</td>
<td>4 (4-5)</td>
<td>4 (4-5)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Need for surgery</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Complete response for neoplasia (pts)</td>
<td>100% (19/19)</td>
<td>95% (18/19)</td>
<td>100% (18/18)</td>
<td>0.87</td>
</tr>
<tr>
<td>Complete response for intestinal metaplasia pts)</td>
<td>90% (17/19)</td>
<td>84% (16/19)</td>
<td>89% (16/18)</td>
<td>0.37</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>0.72</td>
</tr>
</tbody>
</table>

IQR= interquartile range, CI= confidence interval, min= minutes, pts= patients
Supplements, Table S1: Patient discomfort relating to circumferential balloon-based radiofrequency ablation (c-RFA) using three different ablation regimens, based on questionnaires concerning treatment related symptoms, that were completed at several times points pre- and post c-RFA.

<table>
<thead>
<tr>
<th>Ablation regimen</th>
<th>Overall n=57</th>
<th>‘Standard’ n=19</th>
<th>‘Simple-and-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>
<td></td>
<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>0.48</td>
</tr>
<tr>
<td><strong>Day-0 post 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>0.26</td>
</tr>
<tr>
<td><strong>Day-1 post 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>0.06</td>
</tr>
<tr>
<td><strong>Day-10 post c-RFA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of pain medication during 10 days (pts)</td>
<td>68% (28/41)</td>
<td>69% (9/13)</td>
<td>77% (10/13)</td>
<td>60% (9/15)</td>
<td>0.64</td>
</tr>
<tr>
<td>Symptom free (pts)</td>
<td>55% (21/38)</td>
<td>75% (9/12)</td>
<td>50% (6/12)</td>
<td>43% (6/14)</td>
<td>0.24</td>
</tr>
<tr>
<td>Returned to normal activities (pts)</td>
<td>73% (27/37)</td>
<td>80% (8/10)</td>
<td>62% (8/13)</td>
<td>79% (11/14)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

IQR= interquartile range, R= range, pts= patients, c-RFA= circumferential balloon-based radiofrequency ablation. *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 0-50 point scale for severity of symptoms). Questionnaires were completed ‘at baseline’ prior to c-RFA; ‘day-0 post c-RFA’ after recovery from sedative medication prior to leaving the hospital; ‘day-1 post c-RFA’; and at ‘day-10 post c-RFA’.

**DISCUSSION**

This randomized multicenter trial suggests that omitting or simplifying the cleaning step in 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. The CR-neoplasia and CR-IM rates in the current study were 98% and 88%, respectively, which comports with the results of other studies. Recent data demonstrate sustained eradication of early neoplasia and IM in 96-98% and 91-100% of patients respectively, after 3-5 years follow-up. Currently, more than 1,000 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, i.e. double application of 12 J/cm², without cleaning of the ablation zone and ablation catheter in between ablation passes, was comparable to 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 which 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 three c-RFA regimens. It is also 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 can thus be compensated by one of the subsequent focal RFA sessions. For these reasons, and since the simple-no-cleaning regimen is by far the easiest and fastest of the three 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 minutes versus 20 minutes for the standard regimen respectively and required only 4 introductions of endoscope and RFA-balloon versus 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 prior to esophagectomy. These studies demonstrated 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 versus 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 in 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. However, these studies also incorporated other modifications to the ablation protocol: 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/cm² for c-RFA was adopted by most centers at this time. Third, focal RFA for residual BE areas using the HALO device was introduced. Lastly, 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 hyperaemic as a result of the first ablation or due to manipulation by the cleaning process. The RF energy may subsequently reach less deep in the thickened mucosa, which may thus counter balance the beneficial effect of removing the debris. This randomized study suggest that cleaning in between ablation passes may not be as relevant as previously thought.

The simple-no-cleaning regimen is the most simple ablation regimen of three 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 to standard c-RFA. Theoretically, the simple-no-cleaning regimen may leave small skipped BE zones that are not ablated during c-RFA, since the same zone is ablated twice keeping...
the balloon virtually in the same position. In contrast, the standard c-RFA regimen consists of two separate ablation passes from proximal to distal, usually this results in successful ablation of skipped zones during the second ablation pass, since 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 of assessing the completeness of the first complete ablation pass, and to allow 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, two 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 is the use of a surrogate primary endpoint. Our primary endpoint was the mean score of two 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-cleaning 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 is the setting of three tertiary referral centers for the management of early Barrett’s neoplasia with experienced endoscopists and pathologists, making our results not translatable 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.

In conclusion, in this randomized multicenter trial we compared three 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, but that this regimen is twice as fast and requires significantly less 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.
REFERENCES


