Advances in endoscopic resection and radiofrequency ablation of early esophageal neoplasia
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Radiofrequency ablation for the endoscopic eradication of esophageal squamous high-grade intraepithelial neoplasia and mucosal squamous cell carcinoma


Chapter 7

ABSTRACT

Background: Radiofrequency ablation (RFA) with or without prior endoscopic resection (ER) safely and effectively removes early neoplasia in Barrett’s esophagus. We speculated that this approach might also be suited for early squamous neoplasia of the esophagus.

Objective: to assess our initial experiences with RFA for high-grade intraepithelial neoplasia (HGIN) and esophageal squamous cell cancer (ESCC) limited to the mucosa.

Design: Prospective case series.

Setting: Tertiary center. Patients: Patients with ≥1 unstained lesion (USL) of the esophagus using Lugol’s chromoendoscopy and squamous HGIN/ESCC upon biopsy were included.

Interventions: In case of non-flat USL’s, ER was performed for staging and to render the mucosa flat. After ER and subsequent circumferential RFA, chromoendoscopy was repeated every 3 months with focal RFA of residual USLs. Follow-up chromoendoscopy was repeated at 6 months and annually thereafter. Main

Outcome measures: Complete histological response for any squamous intraepithelial neoplasia or ESCC (CR-neoplasia).

Results: Thirteen patients (10HGIN/3ESCC) were included. After ER in 9 patients, the median extent of USLs was 4cm and 50% of circumference. All 13 patients achieved CR-neoplasia after a median of 2 RFA (IQR 1-3) sessions. RFA-related complications included 2 mucosal lacerations (at ER-scar) and 1 intramural hematoma, none requiring therapy. ER/RFA-related complications were 3 stenoses. Dilation resulted in perforation in 1 patient (managed with a covered stent). There were no recurrences (median follow-up 17 months (IQR 11-22). LIMITATION: small case series.

Conclusions: This study suggests that RFA with or without prior ER for esophageal squamous HGIN and mucosal ESCC is feasible and effective.
INTRODUCTION

Esophageal squamous cell carcinoma (ESCC) is the sixth most common cancer worldwide, with a poor five-year survival rate of only 10-15%. The incidence of ESCC varies, with a relatively low incidence in Western Europe and the United States and a high incidence in China, Iran, and India.\(^1,2\)

For squamous high-grade intraepithelial neoplasia (HGIN) and ESCC with a maximum infiltration depth of the lamina propria (T1\(_{m2}\)), the risk for lymph node metastasis is less than 5%.\(^3-6\) Therefore, endoscopic eradication is a viable option with lower morbidity and mortality as opposed to esophagectomy in these patients.\(^7-10\) Lesions infiltrating into the muscularis mucosae (T1\(_{m3}\)), or the superficial submucosa (T1\(_{sm1}\)) are considered borderline lesions with a higher risk for lymph node metastasis, and the choice between endoscopic and surgical treatment should be considered for each of these patients individually. For ESCC infiltrating deep into the submucosa or beyond (≥T1\(_{sm2}\)), surgical esophagectomy is indicated. Endoscopic resection (ER) is the cornerstone of endoscopic treatment since it effectively removes the lesion and provides a specimen for histological staging.\(^11-14\)

Squamous lesions >2-cm generally require piecemeal ER or endoscopic submucosal dissection (ESD) for complete removal.\(^13-17\) These procedures require a high level of endoscopic expertise, which is not widely available in many countries.\(^18,19\) In addition, piecemeal ER or ESD are associated with a risk for bleeding and perforation and when 50-75% of the circumference is resected an esophageal stenosis will occur in the majority of patients.\(^14,15,20\)

Radiofrequency ablation (RFA) is a novel endoscopic ablation technique, which may overcome these disadvantages of widespread ER and ESD. RFA ensures a controlled superficial ablation of 0.5-1mm, thereby avoiding stenosis due to deep submucosal damage. Prior to RFA, focal non-flat lesions need to be removed to render the mucosa flat and suitable for RFA, but also to allow for histological staging of the lesion. Several studies have shown that RFA with or without prior ER of focal lesions is safe and highly effective in the management of patients with early neoplasia in Barrett’s esophagus (BE). Complete eradication of early neoplasia and residual dysplastic BE is achieved in 96-100% of patients, with a very low rate of esophageal stenosis (<5%).\(^21-23\)

Initial dose-escalation studies in patients undergoing esophagectomy showed that RFA is feasible in the normal squamous mucosa.\(^24,25\) Thus far, clinical evidence on the efficacy of RFA for early squamous neoplasia is limited.\(^26\) Based on this limited experience in squamous disease and the excellent efficacy and safety profile of RFA in BE, and the extended experience with RFA for patients with early BE neoplasia of both study centers, we hypothesized that RFA might also be effective for early squamous neoplasia of the esophagus. The aim of this study was to report our initial experiences with RFA with or without prior ER for esophageal squamous HGIN and early mucosal ESCC.
PATIENTS AND METHODS

Selection criteria
Patients were included if they underwent RFA for esophageal early squamous neoplasia between March 2007 and December 2009 at two collaborating tertiary referral centers. All procedures relating to this collaboration were prospectively registered. Selection criteria were: 1) $\geq 1$ unstained lesion (USL) in the esophagus upon high resolution endoscopy (HRE) with Lugol’s staining; 2) squamous HGIN or mucosal ESCC upon biopsy of $\geq 1$ USLs; 3) completely flat (type 0-IIb), slightly elevated (less than a single jaw of a biopsy forceps (1.2mm); type 0-IIa), or slightly depressed (less than half the height of a single jaw of a biopsy forceps; type 0-IIc) USLs, according to the Paris classification of the endoscopic appearance of early gastrointestinal neoplasia; 4) in the case of a type 0-IIa/IIc lesion, ER $\geq 8$ weeks prior to RFA; 5) ER specimens demonstrating $\leq T1m3$, negative deep resection margins, G1-G2 tumor differentiation, no lymphatic/vascular invasive growth, and 6) $\leq T1m2$ immediately prior to RFA 7) no metastasis on endoscopic ultrasonography (EUS) and computed tomography (CT) scanning of thorax and abdomen (in case of ESCC); and 8) informed consent.

Endoscopic work-up and staging
Patients underwent at least one HRE with Lugol’s staining (1-3%) and narrow band imaging (Olympus GIF-Q160, GIF-Q260FZ, GIF-H260Z, Olympus, Hamburg, Germany). Targeted biopsies were obtained of all visible abnormalities and USLs. The macroscopic type of lesions was classified according to the Paris classification. EUS was performed to exclude deep tumor infiltration and regional lymph node involvement. Suspicious lymph nodes were sampled by fine needle aspiration (FNA). Patients with ESCC also underwent a CT scan of thorax and abdomen.

Endoscopic resection
Patients with non-flat components of any USL (type 0-II-a or 0-II-c) underwent ER with the ER-cap technique or multiband mucosectomy (MBM) to render the mucosa flat for subsequent RFA, and to enable histological evaluation of the most suspicious part of the USL. For lesions with suspicion of submucosal invasion as deemed by the endoscopist, the ER-cap technique with submucosal lifting was preferred. Two months after ER, patients underwent HRE with Lugol’s staining and biopsies to determine eligibility for subsequent RFA.

Radiofrequency ablation
During HRE with Lugol’s staining immediately prior to RFA, the location and size of the USLs were registered. The area from 1cm proximal to 1cm distal to the USL-bearing segment of the esophagus was defined as the treatment area (TA) and marked with argon plasma coagulation or by taking 1-2 biopsies. RFA was performed using the HALO system (BÁRRX Medical, Sunnyvale, CA, USA). Primary RFA was performed with circumferential balloon-
based RFA, however if the inner esophageal diameter was <18mm due to ER-scarring, or the USL was <2cm and <50% of the esophageal circumference, primary focal RFA was performed. Circumferential balloon-based RFA was performed using the HALO^360- catheter with a 12J/cm^2-clean-12J/cm^2 regimen.\(^{30}\) For focal ablation of small remaining USLs (<2cm) we used the HALO^90-catheter, a smaller electrode mounted on the tip of the endoscope. Focal ablation was performed using a 2x15J/cm^2-clean-2x15J/cm^2 regimen.\(^{30}\) Dosimetry for RFA was modified during the study period (see Results section).

After the initial RFA session, endoscopy with Lugol's was repeated at 2-3 months intervals to visualize, biopsy and ablate (focal RFA) residual USLs. If no USLs were present, the TA was biopsied (≥2 biopsies/2cm of TA).

**Pre- and post-procedural care**

Endoscopic procedures were performed on an outpatient basis using sedation with midazolam, fentanyl, pethidine, or monitored anesthesia care with propofol.\(^{31}\) After endoscopic treatment, patients were observed for 4 hours, and then discharged with specific instructions. Patients were provided with esomeprazole 40mg po BID and sucralfate suspension 5mL (200mg/mL) QID for 14 days after ER/RFA. Acetaminophen 500mg (max. 3g/day), diclofenac suppositories 100mg (max. 200mg/day), or liquid lidocaine 20mg/mL (5-10mL/4 hours) were advised for post-procedural pain.

**Follow up**

If HRE with Lugol's staining yielded no further USLs and biopsies showed absence of squamous intraepithelial neoplasia or ESCC, patients underwent follow-up HRE with Lugol's staining, narrow band imaging and biopsies (2 specimens/2cm treatment area) at 6 months and annually thereafter. In case of prior ESCC, follow-up endoscopy was combined with EUS to exclude lymph node metastasis.

**Histological evaluation**

All biopsies and ER-specimens were reviewed by experienced pathologists, using the World Health Organization classification, defined as: no intraepithelial neoplasia, indefinite for intraepithelial neoplasia, low-grade intraepithelial neoplasia, high-grade intraepithelial neoplasia (HGIN; T1m1), carcinoma (ESCC).\(^{32}\) ESCC infiltrating into lamina propria was classified as T1m2; ESCC infiltrating into the muscularis mucosae as T1m3; and ESCC infiltrating the superficial, middle, and deep thirds of the submucosa was classified as T1sm1, T1sm2, and T1sm3, respectively. ER-specimens were assessed for infiltration depth, radical resection (vertical resection margin), grade, tumor differentiation, and lymphatic/vascular invasive tumor growth.
Chapter 7

Endpoints

Primary outcome parameter:
1. Complete response for neoplasia (CR-neoplasia), defined as absence of low-grade intraepithelial neoplasia, HGIN and ESCC in all biopsies from the treatment area at two months after the last treatment session.

Table 1: Patient characteristics and endoscopic treatment of 13 patients with early squamous neoplasia of the esophagus that underwent endoscopic treatment with radiofrequency ablation (RFA) with or without prior endoscopic resection (ER).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Risk factors for ESCC</th>
<th>Indication for upper endoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>48</td>
<td>Fanconi anemia</td>
<td>Screening for liver transplantation</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>58</td>
<td>Smoking; alcohol abuse</td>
<td>Loss of appetite, heartburn</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>72</td>
<td>Smoking</td>
<td>Dysphagia</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>56</td>
<td>Swallowing caustic agent (dichloroethane); alcohol abuse; ex-smoking</td>
<td>Surveillance endoscopy Barrett’s esophagus</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>77</td>
<td>-</td>
<td>Dyspepsia</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>67</td>
<td>Radiotherapy for hypopharyngeal carcinoma</td>
<td>Control endoscopy after hypopharyngeal carcinoma</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>64</td>
<td>-</td>
<td>Dyspepsia; abdominal pain</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>62</td>
<td>Smoking</td>
<td>Dyspepsia</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>56</td>
<td>Smoking; ex-alcohol abuse</td>
<td>Retrosternal pain during eating</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>59</td>
<td>-</td>
<td>Odynofagie</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>74</td>
<td>Ex-smoking</td>
<td>Dysphagia</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>69</td>
<td>-</td>
<td>Pyrosis</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>73</td>
<td>-</td>
<td>Pyrosis</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5F/8M</td>
<td>65 (IQR 58-73)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ESCC= esophageal squamous cell cancer, ER=endoscopic resection, no.= number, RFA= radiofrequency ablation, USLs= unstained lesions, cm= centimeter, F= female, M= male, IQR= interquartile range, R= range, MBM= multiband mucosectomy, HGIN= high grade intraepithelial neoplasia, ∞ alcohol abuse: >4 units/day.
Secondary outcome parameters:
1. Complications of RFA, defined as: ‘acute’: during the procedure; ‘early’: ≤48 hours; ‘late’: >48 hours, graded as ‘mild’: non-transmural laceration >1cm, unscheduled hospital admission for observation, hospitalization ≤3 days, hemoglobin drop <3g, no need for transfusion; ‘moderate’: hospitalization 4-10 days, <4 units blood transfusion, need for repeat endoscopic intervention including dilation; ‘severe’: hospitalization >10 days, ICU admission, need for surgery, ≥4 units blood transfusion, or >5 dilations for stenosis, stent placement or incision therapy; ‘fatal’: death attributable to procedure <30 days or longer in case of continuous hospitalization;33
2. Number of RFA treatment sessions required to reach CR-neoplasia;
3. Sustained remission for neoplasia during follow-up.

<table>
<thead>
<tr>
<th>Contra-indications for surgery</th>
<th>ER technique (no. of ER specimens)</th>
<th>Histology ER</th>
<th>Most advanced histology prior to RFA</th>
<th>Circumferential extent of USLs prior to RFA (%)</th>
<th>Length of USLs prior to RFA (cm)</th>
<th>RFA sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>ER-cap (1); MBM (2)</td>
<td>HGIN</td>
<td>HGIN</td>
<td>75</td>
<td>9</td>
<td>2 (2x HALO360)</td>
</tr>
<tr>
<td>No</td>
<td>-</td>
<td>-</td>
<td>HGIN</td>
<td>50</td>
<td>2</td>
<td>2 (HALO360, HALO90)</td>
</tr>
<tr>
<td>Yes</td>
<td>MBM (1)</td>
<td>HGIN</td>
<td>HGIN</td>
<td>50</td>
<td>3</td>
<td>1 (HALO360)</td>
</tr>
<tr>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>HGIN</td>
<td>50</td>
<td>10</td>
<td>3 (1x HALO360, 2x HALO90)</td>
</tr>
<tr>
<td>No</td>
<td>MBM (1)</td>
<td>HGIN</td>
<td>HGIN</td>
<td>25</td>
<td>5</td>
<td>3 (1x HALO360, 2x HALO90)</td>
</tr>
<tr>
<td>No: refused surgery</td>
<td>MBM (1)</td>
<td>HGIN</td>
<td>HGIN</td>
<td>100</td>
<td>7</td>
<td>4 (2x HALO360, 2x HALO90)</td>
</tr>
<tr>
<td>Yes</td>
<td>ER-cap (1)</td>
<td>HGIN</td>
<td>ESCC</td>
<td>75</td>
<td>3</td>
<td>1 (HALO90)</td>
</tr>
<tr>
<td>No</td>
<td>-</td>
<td>-</td>
<td>HGIN</td>
<td>25</td>
<td>6</td>
<td>2 (HALO360, HALO90)</td>
</tr>
<tr>
<td>Yes</td>
<td>ER-cap (1); ER-cap (2)</td>
<td>HGIN</td>
<td>ESCC</td>
<td>10</td>
<td>0.5</td>
<td>1 (HALO90)</td>
</tr>
<tr>
<td>No</td>
<td>ER-cap (3)</td>
<td>HGIN</td>
<td>HGIN</td>
<td>75</td>
<td>4</td>
<td>1 (HALO90)</td>
</tr>
<tr>
<td>No</td>
<td>MBM (2)</td>
<td>HGIN</td>
<td>HGIN</td>
<td>25</td>
<td>1</td>
<td>1 (HALO90)</td>
</tr>
<tr>
<td>6/13 contra-indications for surgery</td>
<td>9 ER / 4 no ER</td>
<td>7 HGIN/ 2 ESCC</td>
<td>12 HGIN/ 1 ESCC</td>
<td>Median 50 (IQR 25-75)</td>
<td>Median 4 (IQR 3-8)</td>
<td>Median 2 (IQR 1-3)</td>
</tr>
</tbody>
</table>
Ethics and statistical analysis

No IRB approval was requested since treatment was performed on a case by case basis. RFA with or without ER was only considered for individual patients with contraindications for surgery and in whom other alternative therapies were deemed much less favorable by a multidisciplinary oncology team. The HALO systems are FDA and CE cleared and all patients gave informed consent after they were thoroughly informed on the use of RFA and alternative treatment options.

For data analysis the SPSS statistical software package (SPSS Inc.16.0.2, Chicago, IL, USA) was used. For descriptive statistics, mean (±SD) was used for normal distribution and median (IQR or range) was used for skewed distribution. To compare groups Fisher’s exact test was used when appropriate. Differences were considered significant if \( p \leq 0.05 \).

RESULTS

Patients and endoscopic treatment

Thirteen patients (8 males) were included (median age of 65 years (IQR 58-73)). All 13 patients had a diagnosis that made them eligible for esophagectomy. All elected endoscopic therapy, after being informed about all therapeutic options. One patient refused surgery and 6 patients had significant contraindications for surgery (Table 1).

Nine patients underwent a total of 11 ER-sessions (ER-cap=6; MBM=5) prior to RFA to remove non-flat lesions, resulting in a median number of 1 (range 1-3) ER-specimens per patient. The most advanced histological diagnosis at baseline ER or biopsy was HGIN in 10 patients and mucosal carcinoma in 3 patients. During work-up, 2 of 13 patients underwent FNA of suspicious lymph nodes during EUS, and cytology was negative for malignancy in both. Immediately prior to RFA, the median length of the USL-bearing segment was 4cm (IQR 3-8) extending over a median of 50% (IQR 25-75%) of the inner circumference of the esophagus. The most advanced histological diagnosis immediately prior to RFA was HGIN in 12 patients and carcinoma (type 0-IIb) in 1 inoperable patient.

In 10 patients primary ablation was performed with the balloon-based HALO\(^{360}\)-system. In 3 patients primary focal HALO\(^{90}\)-ablation was used, because of a post-ER stenosis (n=1) or small size (≤1cm) of the USLs (n=2). In two patients, the USL-bearing segment was treated in two separate HALO\(^{360}\)-sessions: in one patient the procedure was discontinued and rescheduled due to patient tolerability and sedation issues; in another patient a mucosal laceration precluded a second ablation pass. In a total, 12 circumferential and 13 focal RFA-sessions were applied using various ablation-regimens (Table 2). During the study, several adjustments were made to the treatment protocol (Table 3).

Complete remission for squamous neoplasia

CR-neoplasia was achieved in all 13 patients after a median of 2 (IQR 1-3, range 1-4) RFA-sessions per patient (Figure 1, Tables 1 and 4).
Complications

There was one severe complication in a patient who developed an esophageal perforation after dilation of a stenosis (#9, Tables 1 and 4). This patient developed a relative narrowing of the esophagus after an en bloc ER. To avoid a possible laceration of the narrowed portion of the esophagus during balloon-based ablation, circumferentially HALO\textsuperscript{90} treatment at 3 adjacent levels (5-6cm) with the 2x15J/cm\textsuperscript{2}-clean-2x15J/cm\textsuperscript{2} regimen was performed. Twelve days after ablation, the patient developed a symptomatic stenosis and was dilated with Savary bougies to 13mm using the ‘rule of three’ according to current guidelines.\textsuperscript{34,35} Esophageal perforation and a mediastinal abscess were noted two days later and managed with a covered stent and percutaneous drainage. After removal of the stent, a newly formed stenosis was observed at the distal margin of the stented
area, that resolved after 12 dilation sessions with Savary bougies including intra-lesional corticosteroid injection and incisional therapy.

Two moderate complications, both strictures, occurred in two patients. The first patient (#1) underwent 2 ER sessions, resulting in a relative esophageal narrowing (inner diameter 16mm) prior to RFA. After 2 circumferential RFA-sessions (12J/cm²-clean-12J/cm²) for the proximal and distal part of the USL-bearing segment respectively, the patient developed dysphagia that resolved after 3 dilations. The second patient (#8) had an en bloc ER of a non-flat component in a circumferential USL and developed stenosis after the first

Figure 1: Endoscopic images of a patient with high-grade intraepithelial neoplasia of the squamous esophagus treated with radiofrequency ablation (RFA) preceded by endoscopic resection (ER). A-B: Squamous esophageal lesion extending over 7 cm of length after prior en bloc endoscopic resection of the most suspicious area; C: Lesion with narrow band imaging; D-E: Unstained lesion upon Lugol’s stain; F: Circumferential balloon-based RFA; G: Small remaining squamous lesion after circumferential RFA; H: corresponding image with Lugol’s stain; I: Focal RFA of the residual lesion using the HALO® catheter; J-K: Complete resolution of squamous neoplasia (K: distal part of the treatment area upon Lugol’s stain; L: proximal part of the treatment area upon Lugol’s stain).
circumferential RFA-session (1x12J/cm² regimen, no second ablation pass because of a mucosal laceration), requiring one dilation session to enable subsequent RFA.

There were three mild complications. During circumferential balloon-based RFA, in two patients a mucosal laceration >1cm occurred at the level of the ER-scar. Another patient developed a submucosal hematoma during HALO⁹₀-treatment, while not using anticoagulants or platelet inhibiting medications. These complications were asymptomatic and required no intervention, however RFA-treatment was limited to a single ablation pass at that session (Table 2).

**Sustained remission of squamous neoplasia**

All 13 patients remained in CR-neoplasia (100%) during a median follow-up of 17 months since the first RFA session (IQR 11-22) and 3 (IQR 1-4) follow-up endoscopies with biopsies.
One patient died from an unrelated cause (hepatocellular carcinoma) 8 months after reaching CR-neoplasia with prior follow-up endoscopies showing sustained CR-neoplasia.

**DISCUSSION**

In this study of RFA with or without prior ER for esophageal squamous HGIN and mucosal ESCC, we achieved complete response of neoplasia in all 13 patients after a median of 2 ablation sessions and there were no recurrences during a median follow-up of 17 months. These results suggest that RFA with or without prior ER is a promising treatment modality for early squamous neoplasia of the esophagus (HGIN/mucosal ESCC).

Endoscopic resection (ER) is considered the cornerstone of endoscopic treatment since it effectively removes the lesion and provides a specimen for histological staging. Although, ER for esophageal early squamous neoplasia is mainly practiced in the East, two European studies have shown that focal ER is safe and effective for limited lesions containing squamous intraepithelial neoplasia or early ESCC, by achieving CR-neoplasia in >90% of patients.\textsuperscript{11,14} Although local recurrences were reported in 26% of the cases, all were managed with repeat ER. For ER of lesions >2cm, however, piecemeal ER or endoscopic submucosal dissection (ESD) is required. ESD may be preferred for larger lesions, since it enables en bloc resection of large lesions which reduces the recurrence rate as compared to piecemeal ER.\textsuperscript{16} Still, widespread ER and ESD have some disadvantages in common: 1) they are time consuming procedures that require a high level of endoscopic skills and experience; 2) they carry a significant risk for acute complications such as bleeding and perforation;\textsuperscript{17,19} 3) they are associated with esophageal stenosis when >50% of the circumference is resected;\textsuperscript{13,15,17,33,36} 4) they only remove the USL and leave the surrounding epithelium -which may still harbor oncogenetic alterations- untreated which may lead to regional recurrences, as may be reflected by the aforementioned recurrence rate of 26% after focal ER of squamous neoplasia.\textsuperscript{11,14}

In contrast, studies in early Barrett’s neoplasia demonstrate that RFA is associated with a low rate (<5%) of ablation-induced stenosis.\textsuperscript{21-23,37,38} Furthermore, the combined approach of focal ER and RFA is technically much easier to perform than widespread ER and ESD. Additionally, by performing primary balloon-based RFA, the epithelium surrounding the USL(s) is also treated, which may prevent the development of metachronous lesions. These theoretical advantages and the high success rate of this study suggest that the combined approach of focal ER followed by RFA may be a suitable alternative to widespread ER and ESD for flat-type early squamous neoplasia, especially in a setting where expertise in performing piecemeal ER or ESD is limited.

In our series, we encountered one severe complication. This patient had a stenosis after ER that prevented using balloon-based ablation, and was therefore treated with focal RFA at 3 adjacent circumferential levels. In retrospect, the 2x15J/cm\(^2\)-clean-2x15J/cm\(^2\) regimen used in this patient is likely too aggressive, especially when used to treat the entire inner circumference of the esophagus at multiple overlapping levels. With our current knowledge, this patient should have been treated with careful stepwise dilation to enable primary balloon-based circumferential ablation. Furthermore, initial RFA dose-escalation
studies in animals and human patients prior to esophagectomy have shown that the RF energy density (J/cm\(^2\)) is linearly related to the depth of ablation, and that deeper ablation due to higher RF energy density is related to a higher stenosis rate.\(^{24,25,39}\) In addition, one of these studies demonstrated a relation between more frequent RF application and ablation depth.\(^{39}\) Based on these dose-escalation studies, and our case described above, for subsequent patients that required focal RFA, a 15J/cm\(^2\)-clean-15J/cm\(^2\) regimen or 3x12J/cm\(^2\)-no-clean regimen was applied. These adjusted regimens have the additional advantage of making focal ablation easier and faster. No stenoses developed after focal ablation with these adjusted HALO\(^{90}\)-regimens.

Other complications included two stenoses and two lacerations, all occurring in patients who underwent ER prior to RFA during balloon-based circumferential ablation. Studies in Barrett’s esophagus have demonstrated that stenosis may be avoided by limiting the ER-size prior to RFA, and that conservative selection of the ablation balloon diameter size reduces the risk for laceration.\(^{23,40}\) These concepts may be even more important for patients with early squamous neoplasia, who often have a narrowed esophagus with a reduced compliance. Yet, during ER the squamous mucosa is sucked into the cap more easily as compared to BE, resulting in large specimens. This is reflected by two of three patients that developed stenosis in our study, who already developed a relative esophageal narrowing after an en bloc resection. Therefore, for patients with early squamous neoplasia in particular, adherence to the rules of thumb of a limited ER-size and conservative catheter selection is advisable.

This study suggests that fewer ablation sessions and lower energy settings may be adequate to achieve CR-neoplasia in HGIN and early ESCC cases, as compared to Barrett’s esophagus cases. A median of 2 ablation sessions, and a single ablation session in 6 patients, were sufficient to achieve CR-neoplasia, versus a median of 3 ablation sessions to remove a complete BE containing early neoplasia.\(^{21-23}\) This difference may reflect a generally larger treatment surface in BE. In addition, Barrett’s patients may require more treatment sessions because the gastroesophageal junction with its folds and curves may be more difficult to ablate due to diminished electrode contact. Furthermore, BE contains goblet cells containing mucous, glandular structures with crypts, and a mucin layer which may absorb the RF energy and attenuate cell injury. By comparison, squamous epithelium has none of these features, and may be thinner with a lower density of blood vessels, which thus may incur cell injury with RFA at lower doses and/or fewer applications.

Limitations of this study include the small number of patients with limited follow-up which prohibit drawing firm conclusions on safety and long-term efficacy of this management strategy for this patient population. Despite the small sample size of selected patients, we argue that this initial experience provides important information on the feasibility of RFA as a novel treatment modality for early esophageal squamous neoplasia. Prospective multicenter trials are required to assess if our promising feasibility results are translatable to a wider and larger patient population. Another limitation was the fact that treatment was performed in expert centers by two expert-endoscopists in the field of early neoplasia of the upper gastrointestinal tract, making these results less translatable to the general gastroenterology practice. We recommend centralization of
endoscopic treatment of patients with early neoplasia in the esophagus in well-trained tertiary referral centers with well-trained endoscopists.

In our study we treated a heterogeneous cohort of patients in terms of histology, prior ER, varying ER extent, and RFA treatment regimen. Still, we made observations that are of significant value for further research on RFA for patients with early squamous neoplasia. We have optimized the energy settings, implemented tattoo placement, limited the baseline ER size, determined that primary circumferential balloon-based RFA is preferred as the first ablation modality, and reduced the concentration of Lugol’s solution for chromoendoscopy (Table 3). These findings were considered in the design of an ongoing prospective study in China to assess the feasibility of RFA in a much larger group of patients with more extensive squamous disease. In regions where ESCC has a high incidence, an easy-in-use technique with high efficacy and acceptable safety such as RFA is needed for patients with early flat-type squamous neoplasia. Future research should focus on further improvement of the treatment protocol: finding optimal energy settings and regimen, optimal use of focal and balloon-based circumferential RFA, and optimize the combined treatment of ER and RFA.
REFERENCES


