Advances in endoscopic resection and radiofrequency ablation of early esophageal neoplasia
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Radiofrequency ablation and endoscopic resection in a single session for Barrett’s esophagus containing early neoplasia: a feasibility study


ABSTRACT

Background Endoscopic resection (ER) followed by radiofrequency ablation (RFA) after 6 weeks is safe and effective for eradication of Barrett’s esophagus (BE) with high-grade dysplasia (HGD) and early cancer (EC). ER-related scarring after widespread ER may hamper circumferential balloon-based RFA (c-RFA). C-RFA immediately followed by ER in the same session could avoid the impact of scarring on c-RFA and reduce laceration and stenosis risk. Aim: assess the feasibility of ER immediately after c-RFA.

Methods Patients with BE ≥ 3 cm and ≥ 1 visible lesion (HGD/EC) were included. Visible lesions were marked with cautery. C-RFA (12 J/cm²) was delivered using 2 applications and a cleaning step, followed by resection of the delineated area. Outcome measures: BE surface regression at 3 months; need for subsequent c-RFA; complications; quality of ER-specimens.

Results 24 patients (20M, mean age 68 ± 12 years, median BE length C6M8) underwent single session c-RFA+ER with median 4 (IQR2-6) ER-specimens (18EC/6HGD). Complications included 1 perforation, 4 bleedings, and 5 stenoses. All were managed endoscopically. ER-specimens allowed for assessment of neoplasia depth, differentiation, lymphatic/vascular invasion. Median BE surface regression at 3 months was 95%. No patient required a second c-RFA-procedure. 40% of patients required repeat ER for visible lesions. CR-neoplasia and CR-IM were achieved in 100% and 95%.

Conclusions C-RFA followed by ER in the same session is feasible, but technically demanding and associated with a substantial rate of complications and repeat ER. This approach should be reserved for selected cases in expert centers. ER followed by RFA after 6-8 weeks should remain the standard approach for combined ER and RFA.
INTRODUCTION

For patients with Barrett’s esophagus (BE) containing high-grade dysplasia (HGD) or mucosal cancer endoscopic therapy is considered the treatment of choice.

Endoscopic resection (ER) is performed to remove focal lesions in BE. Histological evaluation of the ER specimen allows for optimal patient selection: patients with HGD or early cancer (EC) limited to the mucosa are eligible for endoscopic treatment, while patients with carcinoma invading deep in the submucosa or beyond are referred for surgical esophagectomy. After focal ER the remaining BE is still at risk for malignant transformation, therefore, it is advisable to completely eradicate all BE epithelium once focal early neoplasia has developed.1-3

The combined approach of focal ER followed by stepwise circumferential and focal radiofrequency ablation (RFA) of the remaining flat BE has shown to be safe and effective for patients with HGD/EC in BE, with rates of complete response for early neoplasia and IM of 81-100%.4-9 Circumferential balloon-based RFA (c-RFA) is the preferred primary RFA modality after ER, since it allows for circumferential ablation of the whole longitudinal extent of the BE. However, superficial lacerations at the level of the ER scar have been observed during c-RFA in patients who had undergone a more extensive ER.

Esophageal scarring and narrowing after a more extensive ER may result in non-uniform electrode contact and superficial laceration. Recent studies have therefore restricted the maximum extent of ER prior to RFA to <50% of the circumference and <2cm in longitudinal length.5-7 Nevertheless, in some patients a larger area has to be resected for removal of all visible lesions. Ideally, ER and RFA should be performed in a single session, prior to the development of scar tissue during the healing process. However, when RFA is performed immediately after ER, the ER-wound (which is as deep as the submucosal layer) will be ablated, which may hold a risk for severe stenosis or even perforation.

We hypothesized that single session c-RFA of the whole BE including visible abnormalities, followed by ER of the ablated yet still visible lesion, may preserve the diagnostic and therapeutic purpose of ER, and enables performing c-RFA on a non-scarred esophagus.

The aim of our study was to assess the feasibility of performing c-RFA immediately followed by ER in the same treatment session in patients with BE containing HGD and/or EC.

PATIENTS AND METHODS

Study setting

This study was performed in a tertiary referral center for patients with early neoplasia of the upper gastrointestinal tract with a high level of expertise in the endoscopic imaging, endoscopic treatment, and histopathology of early Barrett’s neoplasia.

Feasibility of single session RFA and ER
Selection criteria
Patients were eligible if they met the following criteria: 1) age between 18 and 85 years; 2) BE ≥3cm containing HGD and/or cancer in biopsies; 3) endoscopic visible abnormality Type 0-I, 0-IIa, 0-IIc or combinations thereof; 4) no signs of regional lymph node involvement or distant metastases on endoscopic ultrasonography (EUS) and computed tomography (CT) (in case of cancer); 5) no previous endoscopic treatment for dysplasia or cancer in BE; 6) no esophageal stenosis preventing passage of a therapeutic endoscope with an ER-cap; 7) no endoscopic signs of esophageal varices; 8) written informed consent.

Patients were excluded from further endoscopic treatment after single session RFA+ER if ER specimens showed poorly differentiated cancer, lymphatic/vascular invasion, deep submucosal infiltration (≥T1sm2) or a positive vertical resection margin. In selected patients, who were unfit for surgery, endoscopic treatment was continued despite such findings.

Endoscopic work-up and staging
Pre-assessment consisted of at least one high-resolution endoscopy with narrow band imaging (NBI) (Olympus GIF-H260Z/H180/FQ260Z, Olympus, Hamburg, Germany) with targeted biopsies of visible lesions and four-quadrant biopsies from every 2cm (4Q/2cm) of the BE. Esophageal landmarks were recorded according to the Prague C&M-classification. For T- and N-staging, EUS was performed, and suspicious lymph nodes were sampled with fine needle aspiration (FNA). CT-scan of thorax and abdomen was performed for M-staging in case of cancer.

Single session ER and RFA session
All visible lesions were delineated by placing clearly visible coagulation markers (APC 40Watt forced coagulation, effect 3, Erbe Vio, APC-probe 2200A, Tübingen, Germany) 1-2 mm outside the lesion. Subsequently, C-RFA was performed using the HALO360+-balloon-catheter (BÄRRX Medical, Sunnyvale, CA, USA), which is equipped with a cylindrical electrode array of 3cm in length. C-RFA (energy density 12J/cm², power 40Watt/cm²) was performed under endoscopic visualization, followed by cleaning of the ablation zone with a distal attachment cap (MB0-046; Olympus, Tokyo, Japan) and forcefully spraying of water using a spraying catheter (PV-5-1; Olympus, Tokyo, Japan) and a high-pressure pistol (Alliance; Boston Scientific, Limerick, Ireland). After cleaning the debris from the electrode surface, the balloon was reintroduced and the treatment area was ablated again. ER of the delineated visible abnormalities was performed after c-RFA using the coagulation markers as guidance. The first 12 consecutive patients were treated with the multiband mucosectomy (MBM) technique, whereas the next 12 patients were treated with the ER-cap technique.

Pre- and postprocedural care protocols are described elsewhere.

Subsequent treatment and follow-up
Patients were scheduled for subsequent endoscopy at 3 months, and BE surface regression was scored at that time. RFA was repeated every 2-3 months as described previously.
Repeat ER was allowed to remove remaining BE epithelium after a maximum of 5 RFA (≤2 c-RFA) sessions, or for visible lesions identified during the treatment phase. When complete histological removal of BE was achieved, patients were scheduled for follow-up endoscopy with NBI and 4Q/2cm biopsies of nequamous epithelium and <5mm below the squamocolumnar junction at 6 and 12 months and annually thereafter.

**Histological evaluation**

All ER specimens and biopsies were routinely processed and assessed by a local expert pathologist. The revised Vienna classification was used for histological grading. ER specimens were evaluated for infiltration depth, vertical resection margins, tumor differentiation or grade of dysplasia, and lymphatic/vascular invasive growth. For the purpose of the study, ER-specimens were reviewed independently by two expert pathologists (FtK, MV). The maximal depth of mechanical and thermal damage due to RFA was scored for the epithelial, mucosal and submucosal layer. Biopsies of neosquamous epithelium were assessed for subsquamous IM (buried Barrett’s).

**Primary outcome variables**

1. BE surface regression (%) at 3 months, estimated by the endoscopist during follow-up endoscopy at 3 months;
2. Proportion of patients requiring an additional c-RFA after the primary c-RFA session;
3. Complications of single session RFA+ER

Complications were defined as: ‘acute’: during the procedure; ‘early’: ≤48 hours; ‘late’: >48 hours, graded as ‘mild’: unscheduled hospital admission, hospitalization <3 days, hemoglobin drop <3g/dL, no need for transfusion; ‘moderate’: hospitalization 4-10 days, ≤4 units blood transfusion, need for repeat endoscopic intervention, radiological intervention; ‘severe’: hospitalization >10 days, ICU admission, need for surgery, >4 units blood transfusion, or in case of stenosis: >5 dilations, stent placement or incision therapy; ‘fatal’: death attributable to procedure <30 days or longer with continuous hospitalization. Only events requiring any intervention were scored.

**Secondary outcome variables**

1. Feasibility of the histological assessment of ER specimens including infiltration depth, differentiation, lymphatic/vascular invasive tumor growth, and resection margins;
2. Complete response for neoplasia (CR-neoplasia) of the treatment protocol;
3. Complete response for IM (CR-IM) of the treatment protocol;

CR-IM and CR-neoplasia were defined as absence of IM and neoplasia respectively in all biopsies, including biopsies (4Q/2cm) of the original BE extent and immediately distal (<5mm) to the neo-Z-line obtained at the first follow-up endoscopy.

**Ethics, sample size and statistics**

This feasibility study was approved by the local medical ethics committee (NTR 2542, www.trialregister.nl). Of all patients, written informed consent was obtained. We aimed
at inclusion of 24 consecutive patients, allowing for comparison with prospective studies on ER and RFA with a comparable sample size. No official sample size calculations were performed. Intention-to-treat (ITT) and per protocol (PP) analysis were performed for the outcomes measures when applicable. In the ITT analysis, all patients who discontinued endoscopic treatment or died were considered a failure. In the PP analysis, patients who did not finish the treatment protocol due to unrelated death or disease were censored. Patients that were referred for curative surgical resection based on initial ER specimens were excluded from the PP analysis.

SPSS statistical software (SPSS Inc.16.0.2, Chicago, IL, USA) and Confidence Interval Analysis software were used for data analysis (CIA Version 2.2.0, London, UK). Mean (±SD) was used for normal distribution and median (inter-quartile range, IQR) for skewed distribution.

RESULTS

Patients

Between December 2008 and June 2010, 24 consecutive patients were included (Figure 1). There were 20 males with a mean age of 68 years (±12) (Table 1). The median BE

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Figure 1 Patient flow chart of 24 patients with Barrett’s esophagus and a visible lesion containing high grade dysplasia or early carcinoma who were treated with radiofrequency ablation and endoscopic resection in a single treatment session. RFA= radiofrequency ablation, ER= endoscopic resection, HGD= high-grade dysplasia, EC= early cancer, CR-neoplasia= complete response for neoplasia, IM= intestinal metaplasia, ITT= intention to treat, PP= per protocol.
length was C6M8 (IQR3-9, M6-10) and the maximal diameter of the lesions was 3cm (IQR1-4). During work-up 3 patients underwent EUS-guided FNA of local lymph nodes, showing no malignancy.

**Endoscopic treatment with single session RFA and ER**

ER proved to be feasible despite the preceding ablation. In all patients the coagulation markers still were adequately visible after the RFA (Figure 2; Table 2). A median of 4 (IQR2-6) resections was performed. The most advanced histological diagnosis of all biopsies and ER specimens was HGD in 6 patients and EC in 18 patients, including 5 patients with superficial submucosal invasion (T1sm1). The median procedure time of the single session RFA+ER session was 75 (IQR50-111) minutes, including inspection time, placement of coagulation markers, RFA procedure (median 21 minutes) and ER (median 30 minutes).

**Efficacy of single session RFA and ER**

Three months after the single session RFA+ER session, the median BE surface regression in 21 available patients was 95% (IQR90-95). None of the patients required a second circumferential balloon-based RFA session (Table 2).

In three patients, endoscopic treatment was discontinued after single session RFA+ER. Two patients were sent for surgical esophagectomy because the ER specimens showed a poorly differentiated T1sm1 carcinoma with a tumor positive vertical resection margin. A third patient suffered from progressive dementia, and it was decided to cease endoscopic treatment and follow-up; ER specimens showed HGD with negative vertical resection margins.

**Table 1** Baseline patient characteristics.

<table>
<thead>
<tr>
<th>Patients (n=24)</th>
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<tbody>
<tr>
<td>Male: female</td>
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<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Median BE (cm)</td>
</tr>
<tr>
<td>Most advanced pre-treatment histology</td>
</tr>
<tr>
<td>Lesion type (Paris classification)</td>
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<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Multiple lesions (2 or 3)</td>
</tr>
<tr>
<td>Lesion size: largest diameter (cm)</td>
</tr>
</tbody>
</table>

n=number, MBM=multiband mucosectomy technique, ER=endoscopic resection, BE=Barrett’s esophagus, C=length of circumferential BE, M=maximal BE length, IQR=interquartile range, EC=early cancer, HGD=high grade dysplasia, pts=patients.
There were no severe complications, but 10 moderate complications occurred in 8 patients (Table 2).

One patient had an esophageal perforation during an ER-cap procedure after RFA which could be effectively closed endoscopically with the ‘over-the-scope clip’ (OTSC, Ovesco Endoscopy, Tübingen, Germany). Oral contrast series showed no leakage and oral intake was restarted on day 2 followed by discharge on day 3. At three months, the

Figure 2 Endoscopic images of a patient with a Barrett’s esophagus (BE) containing early neoplasia treated with radiofrequency ablation (RFA) and endoscopic resection (ER) in a single treatment session. A: C9M11 BE with a 4 cm lesion; B: Corresponding image with narrow band imaging (NBI); C: Lesion delineated by coagulation markers; D: Coagulation markers remain visible after circumferential balloon-based RFA; E: Overview of the ablated BE segment; F: ER using multiband mucosectomy in 3 pieces (T1m2 adenocarcinoma); G/H: Two small remaining BE islands after 3 months; H: Corresponding image with NBI; I: Focal RFA of BE islands and the gastroesophageal junction using the HALO90 catheter; J: Normal gastroesophageal junction 2 months after focal RFA; K: Corresponding image with NBI; L: Complete endoscopic and histological removal of BE.
Table 2  Outcome parameters and treatment characteristics of endoscopic treatment with radiofrequency ablation immediately followed by endoscopic resection in the same session for early neoplasia in Barrett’s esophagus.

<table>
<thead>
<tr>
<th>Outcome/characteristic</th>
<th>Patients (n=24)</th>
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</thead>
<tbody>
<tr>
<td>Total RFA+ER session time (minutes, median)</td>
<td>75 (IQR 50-111)</td>
</tr>
<tr>
<td>RFA procedure time (minutes, median)</td>
<td>21 (IQR 17-25)</td>
</tr>
<tr>
<td>ER procedure time (minutes, median)</td>
<td>30 (IQR 21-54)</td>
</tr>
<tr>
<td>Number of ER specimens per patient</td>
<td>4 (IQR 2-6)</td>
</tr>
<tr>
<td>Patients with ER specimens adequate for histological assessment, n (%)</td>
<td>24 (100%)</td>
</tr>
<tr>
<td>Worst diagnosis histology of biopsies and ER specimens</td>
<td>18 EC / 6 HGD</td>
</tr>
<tr>
<td>Regression rate of BE epithelium at 3 months (median)</td>
<td>95% (IQR 90-55)</td>
</tr>
<tr>
<td>Second circumferential balloon-based RFA</td>
<td>0</td>
</tr>
<tr>
<td>Severe complications</td>
<td>0</td>
</tr>
<tr>
<td>Moderate complications</td>
<td>10 in 8 pts</td>
</tr>
<tr>
<td>(1 esophageal perforation, 4 bleedings, 5 symptomatic stenoses)</td>
<td></td>
</tr>
<tr>
<td>Mild complications</td>
<td>0</td>
</tr>
<tr>
<td>All complications</td>
<td>10 in 8 pts</td>
</tr>
</tbody>
</table>

n= number, RFA= radiofrequency ablation, ER= endoscopic resection, IQR= interquartile range, EC= early cancer, HGD= high grade dysplasia.

patient remained free of symptoms. No follow-up endoscopy or subsequent treatment was performed, because of a progressive dementia (see above). We were, therefore, not able to assess if the OTSC hampered subsequent endoscopic treatment.

Four bleedings (‘early’ n=1, ‘late’ n=3) occurred after combined RFA+ER. One patient had haematemesis (Hb drop from 8.9 to 7.6mmol/L, no anticoagulant therapy) <24h after RFA+ER; the patient underwent a subsequent endoscopy during which an oozing visible vessel in the resection wound was coagulated with a coagrasper. One patient developed haematemeses (no Hb drop, calcium carbasalate therapy) 2 months after RFA+ER. At endoscopy an erosive esophagitis was seen, related to replacing esomeprazole by ranitidine therapy by the general practitioner. One patient had melena (no Hb drop, acenocoumarol therapy) 2 weeks after RFA+ER. At endoscopy, a visible vessel in the treatment area was clipped. One patient had melena (Hb drop from 9.9 to 7.4mmol/L, calcium carbasalate therapy) 2 weeks after RFA+ER, spontaneously resolving after 3 days. Upper endoscopy showed diffuse superficial ulcerations related to RFA+ER treatment.

Five symptomatic stenoses occurred. Three patients developed dysphagia after the initial RFA+ER: two of these had been treated with a widespread ER (six-piece resection of 75% of the circumference of 2cm in length; 11-piece resection of 75% of the circumference of 4cm in length); another patient had a pre-existing reflux stenosis. A fourth patient with a pre-existent narrow esophagus developed dysphagia after one focal ablation session. The fifth patient developed a symptomatic stenosis after focal ablation and a repeat ER. All stenoses resolved upon a median of 2 (R1-2) dilation sessions.
Histological evaluation

In all ER specimens all histological characteristics relevant for staging could be adequately assessed despite RFA prior to ER (Figure 3). Visible thermal and mechanical damage (necrotic debris, loss of cellular architecture, loss of nuclei) was limited to the epithelial layer and the lamina propria in 95 of 103 ER specimens (92%), while in 8 ER specimens (8%) focal thermal damage to the superficial muscularis mucosa was observed. ER specimens reached as deep as the submucosal layer in 100 of 103 specimens (97%).

Complete response for neoplasia and IM

Of the 24 patients who underwent single session RFA+ER, 21 patients underwent additional focal RFA sessions, whereas in 3 patients endoscopic treatment was ceased (surgery n=2, progressive dementia n=1). One of 21 patients died from unrelated cardiac disease three months after a single HALO$^{90}$ session.

CR-neoplasia was achieved in all remaining 20 patients after a median of 2 focal HALO$^{90}$ RFA sessions (Figure 1, Table 3). CR-IM was achieved in 19 of 20 patients. The

Figure 3 Photomicrograph of ER specimens of Barrett’s esophagus containing early neoplasia with an ablated surface after treatment with balloon-based RFA (2x 12 J/cm² and a cleaning step). The epithelial layer is absent or demonstrates thermal and mechanical damage (necrotic debris, loss of cellular architecture, loss of nuclei), however the lamina propria, muscularis mucosae and submucosal layer are present for assessment of infiltration depth, vertical resection margins and tumor characteristics. In A, C and D, black arrows indicate the transition between completely necrotic cells (pink areas, marked with *) and a thermally damaged deeper layer that will become necrotic with more delay due to RFA-induced damage, yet that can still be fully evaluated histologically. A: H&E, 40x T1m3 carcinoma; B: H&E, 20x, HGD; C: H&E, 20x, T1m3 carcinoma; D: H&E, 20x, T1m3 carcinoma.
patient who failed to reach CR-IM had complete endoscopic removal of a C1M6 BE yet a single focus of buried Barrett’s was detected in one biopsy of neosquamous epithelium obtained during the first follow-up endoscopy. The patient subsequently died from an unrelated cause before an additional follow-up procedure could be performed.

We performed an intention-to-treat (ITT) analysis where we considered all patients who died (n=1) or discontinued the endoscopic treatment protocol (n=3) as failures, including 2 patients who were sent for curative surgery based on the results of their ER specimens. On an ITT basis, therefore, CR-neoplasia was achieved in 20/24 patients (83%) and CR-IM was achieved in 19/24 patients (79%). In the per protocol analysis, patients who died or discontinued treatment for unrelated causes were censored, and patients who were sent for curative surgery based on the ER specimens were excluded. According to the per protocol analysis, therefore, CR-neoplasia and CR-IM were achieved in 20/20 (100%) and 19/20 (95%) of patients, respectively.

During the treatment phase, 8 of 20 patients (40%) underwent a total of 9 repeat ERs for removal of visible lesions (Table 3). The visible lesions that required repeat ER were located at the edge of the prior ER scar (n=4) or within a radius of 2cm of the prior ER scar (n=4). ER specimens showed non-dysplastic Barrett’s epithelium (n=1), indefinite for dysplasia (n=1), HGD (n=2) and T1m2/3 carcinoma (n=5).

During follow-up, two patients died from unrelated causes (cardiac failure, duodenal perforation). After a median follow-up of 19 (IQR 13-21) months after single session RFA+ER and 6 (IQR 3-12) months after the final treatment session all 18 patients had sustained CR-neoplasia and CR-IM.

DISCUSSION

This prospective study shows that endoscopic treatment with circumferential RFA immediately followed by focal ER in the same endoscopic session for patients with HGD or early carcinoma in BE is feasible: the regression percentage of the surface area of BE was high and no patient required a second circumferential RFA procedure. Therefore, the purpose to combine ER and RFA without being hampered by post-ER scarring was achieved.

Single session RFA and ER treatment may be a feasible alternative for selected patients who require an extensive ER (>50% of the circumference) to remove a widespread lesion or patients with a pre-existing esophageal narrowing, in whom single session c-RFA and ER may be the only option to safely apply c-RFA due to stenosis risk after extensive ER. Alternatives for patients with extensive neoplastic lesions in BE are stepwise radical endoscopic resection (SRER) and endoscopic submucosal dissection (ESD). In SRER, the complete BE segment is removed in consecutive ER sessions. However, this approach has the disadvantage of a high rate of stenosis. A recent randomized study comparing SRER with ER+RFA found an 88% of stenosis rate in the SRER arm compared to 15% in the combination arm.9,19,21-23 ESD allows for en bloc resection of large lesions in the esophagus, yet the experience with this technically demanding procedure is limited in the West.24,25 Furthermore, both SRER and ESD are associated with bleeding and esophageal
In this study, we aimed to develop a combined endoscopic approach with ER and RFA, which would also be suitable for patients with larger esophageal lesions. However, when we compare the results to the standard protocol of ER followed by RFA after 6-8 weeks, both the number of repeat ERs and the complication rate after RFA+ER appear higher in the current study.

In our study, 8 of 20 patients (40%) required an additional ER during the treatment phase to remove visible lesions that were observed at a later stage during the treatment phase. The high rate of repeat ER after serial RFA following single session RFA and ER makes the overall treatment protocol more technically challenging. Seven of the nine resected lesions contained HGD or cancer and all were observed at the edge of the initial ER site, or within 2cm thereof. Although it appeared that all coagulation markers remained clearly visible after RFA and were removed during the initial ER procedure, the rate of additional ER during the treatment phase may suggest that lesions were sometimes not removed completely. The higher rate of repeat ER during the treatment phase may also reflect a more complex disease at baseline in our study, given a larger size of lesions (median 3cm versus ≤2cm) and the larger proportion of carcinoma (75%) in our study as compared to other studies. Of note, repeat ER did not increase the number of complications or the

Table 3 Endoscopic treatment and follow-up after the combined RFA+ER treatment session for early neoplasia in Barrett’s esophagus.

<table>
<thead>
<tr>
<th>Subsequent treatment</th>
<th>Patients (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued treatment</td>
<td>2/24 (unrelated comorbidity or death)</td>
</tr>
<tr>
<td>Esophagectomy based on ER specimens</td>
<td>2/24 (curative surgery)</td>
</tr>
<tr>
<td>CR-neoplasia (ITT)</td>
<td>20/24 (83%) (95%CI 63-95%)</td>
</tr>
<tr>
<td>CR-IM (ITT)</td>
<td>19/24 (79%) (95%CI 58-93%)</td>
</tr>
<tr>
<td>CR-neoplasia (PP)</td>
<td>20/20 (100%) (95%CI 83-100%)</td>
</tr>
<tr>
<td>CR-IM (PP)</td>
<td>19/20 (95%) (95%CI 75-100%)</td>
</tr>
<tr>
<td>Subsequent RFA sessions (median)</td>
<td>2 (IQR 2-3)</td>
</tr>
<tr>
<td>Repeat ER</td>
<td>9 ER procedures in 8 patients</td>
</tr>
<tr>
<td>Escape treatment</td>
<td>APC in 4 patients (≤1mm BE islands n=3; 8mm BE island n=1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Patients (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued follow-up</td>
<td>2/20 (unrelated death)</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>19 (IQR 13-21)</td>
</tr>
<tr>
<td>Follow-up endoscopies (median)</td>
<td>1 (IQR 1-2)</td>
</tr>
<tr>
<td>Biopsies from neosquamous (total)</td>
<td>401 biopsies</td>
</tr>
<tr>
<td>Biopsies &lt;5mm distal of the neo-Z-line (total)</td>
<td>143 biopsies</td>
</tr>
<tr>
<td>Recurrent neoplasia</td>
<td>0</td>
</tr>
<tr>
<td>Visible BE</td>
<td>0</td>
</tr>
<tr>
<td>IM in biopsies in follow-up</td>
<td>0</td>
</tr>
<tr>
<td>- focal IM neo-Z-line</td>
<td>0</td>
</tr>
<tr>
<td>- buried Barrett’s glands</td>
<td>0</td>
</tr>
</tbody>
</table>

n= number, CR= complete response ITT= intention-to-treat analysis, CI= confidence interval, IM= intestinal metaplasia, PP= per protocol analysis, RFA= radiofrequency ablation, IQR= interquartile range, ER= endoscopic resection, APC= argon plasma coagulation, BE= Barrett’s esophagus, Z-line= squamocolumnar junction.
total number of treatment sessions, and all 8 patients who underwent repeat ER achieved CR-neoplasia and CR-IM. It does, however stress the importance of careful inspection of the residual BE during the treatment phase, with a low threshold to perform a diagnostic ER to avoid disease progression.

Performing ER immediately after RFA is more challenging than in the naive esophagus, because the endoscopic visibility is less in the ablated segment. Furthermore, it may be more difficult to suction the mucosa into the cap, which may result in smaller specimens, and to appreciate the submucosal lifting sign during ER-cap, because the mucosa may have become hyperemic and swollen due to RFA with a cleaning step.

Initially, in this feasibility study, the MBM-technique was used, which is faster and easier than ER-cap. Based on the promising results of the first 12 single session RFA+ER procedures using MBM, we assessed the feasibility of c-RFA followed by ER-cap in the next 12 patients. Although this study was not randomized, we found no differences in the rate of radical resection or perforation between single session RFA+ER with MBM or ER-cap (data not shown), which comports with the findings of a recent randomized trial comparing ER-cap versus MBM.17

ER is the first step in the endoscopic treatment of early Barrett’s neoplasia with a therapeutic as well as diagnostic intent. Based on the histology of the ER specimens, patients with unfavorable tumor characteristics or incomplete resection are referred for surgery, whereas others are selected for subsequent endoscopic treatment. In the combined use of ER and RFA, non-flat lesions or early cancer should always be removed with ER for staging purposes and to render the mucosa flat for effective RFA. In our study, after initial ER and RFA, a poorly differentiated submucosal carcinoma was detected in two patients, who subsequently underwent surgery without delay. Although single session RFA and ER may reduce the number of endoscopic procedures in some patients, on the other hand some may undergo an unnecessary RFA procedure with the inherent complication risk and discomfort.

The rate of complications in this study appears higher than reported in other studies on sequential ER and RFA (acute/early complications: 25% vs. 0-14%; stenosis 21% vs. 0-14%, respectively). The higher complication rate in our study may again reflect the more complex disease at baseline compared to our previous ER and RFA study protocols in which selection criteria encompassed a single lesions with a limited size (≤2cm in length and ≤50% of the circumference) and a BE ≤12cm, with no prior endoscopic dilatation for esophageal stenosis.

A limitation of this study was, that the technically demanding endoscopic procedures were performed by two experienced endoscopists (BW and JB) in a tertiary referral center for ER and RFA, and that ER specimens were assessed by experienced pathologists, therefore results may be different in other centers. However, we advocate that endoscopic treatment of early Barrett’s neoplasia should only be performed in tertiary centers by well-trained endoscopists, in collaboration with experienced pathologists. Other limitations concern the small sample size of selected patients with a limited duration of follow-up.

In conclusion, in this study we showed that circumferential balloon-based RFA followed by focal ER in the same endoscopic session is feasible for patients with HGD/EC in BE, in
the setting of a tertiary referral center. However, in our study, the number of complications was substantial and a relatively large number of patients required an additional ER session after *single session* RFA+ER to remove visible lesions. Therefore, *single session* RFA and ER should only be performed in expert centers and should be reserved for selected patients with large lesions or pre-existing esophageal stenosis, carefully weighing the advantages and disadvantages for each individual patient. For the majority of cases, however, ER followed by RFA after 6-8 weeks should remain the standard treatment protocol for the combined use of ER and RFA for early Barrett’s neoplasia.
REFERENCES


