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

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Stepwise radical endoscopic resection versus radiofrequency ablation for Barrett’s esophagus with high-grade dysplasia or early cancer: a multicenter randomized trial

ABSTRACT

**Objective:** After focal endoscopic resection (ER) of high-grade dysplasia (HGD) or early cancer (EC) in Barrett’s esophagus (BE), eradication of all remaining BE reduces the recurrence risk. The aim of this study was to compare safety of stepwise radical ER (SRER) versus focal ER followed by radiofrequency ablation (RFA) for complete eradication of BE containing HGD/EC.

**Design:** Multicenter randomized clinical trial. **Setting:** Tertiary centers. **Patients:** Patients with BE ≤5cm containing HGD/EC were randomized to SRER or ER/RFA.

**Interventions:** SRER patients underwent piecemeal ER of 50% of BE followed by serial ER. ER/RFA patients underwent focal ER for visible lesions followed by serial RFA. Follow-up endoscopy with biopsies (4-quadrant/2cmBE) was performed at 6 and 12 months and then annually.

**Main outcome measures:** Stenosis rate; Complications; Complete histological response for neoplasia (CR-neoplasia); Complete histological response for intestinal metaplasia (CR-IM).

**Results:** CR-neoplasia was achieved in 25/25 (100%) SRER and 21/22 (96%) ER/RFA patients. CR-IM was achieved in 23 (92%) SRER and 21 (96%) ER/RFA patients. The stenosis rate was significantly higher in SRER (88%) versus ER/RFA (14%; p<0.001), resulting in more therapeutic sessions in SRER (6 versus 3; p<0.001) due to dilations. After median 24 months follow-up, 1 SRER patient had recurrence of EC, requiring ER.

**Conclusions:** In patients with BE ≤5cm containing HGD/EC, SRER and ER/RFA achieved comparably high rates of CR-IM and CR-neoplasia. However, SRER was associated with a higher number of complications and therapeutic sessions. For these patients a combined endoscopic approach of focal ER followed by RFA may thus be preferred over SRER.
INTRODUCTION

In Barrett’s esophagus (BE), the normal squamous esophageal epithelium has been replaced by a columnar epithelium containing specialized intestinal metaplasia (IM), as a result of chronic gastroesophageal reflux.\(^1\) BE is an important risk factor for the development of esophageal adenocarcinoma, a cancer with a rapidly rising incidence in the western world.\(^2\) High-grade dysplasia (HGD) and early cancer (EC) limited to the mucosa in BE can be effectively treated by endoscopic means, without the need for surgery. Endoscopic resection (ER) is the basis of endoscopic treatment. ER allows for removal of focal lesions within the BE and provides a specimen for histological evaluation which is imperative for optimal patient management: patients with HGD/EC can be managed endoscopically given their low risk of local lymph node involvement, whereas patients with lesions invading deep into the submucosa should be considered for esophagectomy and lymph node dissection.\(^3\) However, after focal ER alone, up to 30% of patients will develop metachronous lesions in the residual BE segment during follow-up.\(^4-6\) Therefore, complete eradication of the residual BE is recommended.\(^7-9\) Currently, the two most promising strategies for complete BE eradication are stepwise radical endoscopic resection (SRER) and radiofrequency ablation (RFA).

SRER is a technique in which the complete BE segment is removed in consecutive ER sessions. Retrieval of the entire BE segment for histological assessment is ideal, as it may permit referral to surgery for advanced lesions. Single center studies have shown excellent results of SRER for HGD/EC with eradication of all neoplasia (CR-neoplasia) in 76-100% and complete eradication of all intestinal metaplasia (CR-IM) in 68-100%.\(^10-15\) An important limitation of SRER is the rate of complications, such as esophageal stenosis requiring dilation which occurs in up to 56% of cases.\(^10-15\)

RFA is a new technique for endoscopic eradication of BE that is characterized by controlled and uniform thermal ablation. Several studies have shown that RFA, with and without prior ER, is an effective treatment for HGD/EC with eradication of all neoplasia in 81-100% and complete removal of IM in 74-100%.\(^16-20\) RFA has demonstrated a favorable safety profile with esophageal stenosis occurring in only 0-6% of cases.\(^16-20\) RFA, however, does not yield a histological specimen, therefore it is imperative that all visible abnormalities are removed by focal ER prior to RFA to guarantee optimal staging and to ensure that RFA is applied to flat mucosa only.\(^9\)

The aim of this prospective randomized clinical trial was to compare the safety and efficacy of endoscopic treatment of BE (≤5cm) containing HGD/EC using either SRER or RFA after focal ER of visible abnormalities.

PATIENTS AND METHODS

Selection criteria

Patients were eligible if they met the following criteria: 1) age between 18 and 85 years; 2) BE length ≤5cm; 3) HGD and/or EC in BE in specimens obtained at 2 separate
endoscopies; 4) no signs of deep submucosal invasion, regional lymph node involvement, or distant metastases on endoscopic ultrasonography (EUS) and computed tomography (CT) of thorax and abdomen (in case of EC); 5) no prior endoscopic treatment of BE other than a single prior ER for staging; 6) in case of a prior diagnostic ER, specimens with a negative deep resection margin, no deep submucosal invasion (≥T1sm2), no lymphatic/vascular invasive growth and no poorly or undifferentiated cancer (G3-G4); 7) written informed consent.

Endoscopic work-up and staging

Pre-assessment consisted of two high-resolution endoscopies (GIF-Q160/GIF-Q260FZ/GIF-H180, Olympus, Hamburg, Germany) with targeted biopsies of visible lesions and four-quadrant biopsies from every 1-2cm of the Barrett’s segment. Esophageal landmarks were recorded according to the Prague C&M-classification. Visible lesions were classified using the Paris Classification. EUS was performed for T- and N-staging, and suspicious lymph nodes were sampled by fine needle aspiration (FNA). In case of carcinoma, a CT-scan of thorax and abdomen was made for M-staging. Only patients with lesions that were deemed ‘suspicious for submucosal invasion’ by the endoscopist based on the macroscopic appearance, underwent a focal staging ER prior to randomization. In all other patients with visible lesions, ER was performed after randomization: in the SRER arm the lesion was removed together with the first 50% of the BE segment in the same session (to minimize the number of ER sessions and to avoid a more difficult ER at a later stage due to scarring at the site of the lesion), whereas in the RFA arm only a focal ER of the lesion was performed for staging and to render the mucosa flat prior to RFA.

Endoscopic resection

In both study groups, the ER-cap technique and the multiband mucosectomy technique (MBM) were used as described previously. Additionally, the use of the ‘simple snare’ technique was allowed.

Stepwise radical endoscopic resection (SRER)

In SRER, the Barrett’s segment was removed in consecutive sessions at 6-8 week intervals, with a maximum of 4 sessions, inclusive of the baseline ER (where applicable). In the initial SRER session, piecemeal ER of 50% of the circumference of the entire Barrett’s segment was performed, inclusive of the visible abnormality if not yet removed in a diagnostic ER session. For short segment BE (C≤1,M≤3), SRER in a single session was allowed. In case small bridges of residual BE were left in situ between ER wounds, these were preferably removed with additional ER, but argon plasma coagulation (APC) of tissue bridges during SRER was allowed as well (60-80 Watt for Erbe ICC200; 30-40 Watt for Erbe Vio; APC-probe 2200A, Erbe Elektromedizin GmbH, Tübingen, Germany).

If visible Barrett’s mucosa was present after the maximum allowable SRER sessions, patients underwent escape treatment with RFA. Escape treatment with APC or hot biopsy
forceps for areas of residual BE (<5 mm) was allowed to avoid an additional ER or RFA, or when ER was not possible.

**Radiofrequency ablation (RFA)**

Patients randomized to RFA underwent focal ER of visible abnormalities followed by RFA after 6-8 weeks, when the residual BE contained utmost HGD upon biopsy. RFA was performed using the HALO system (BÂRRX Medical, Sunnyvale, CA, USA) as previously described. Primary circumferential ablation was performed using the HALO-balloon-catheter, with a double RFA delivery (12J/cm², 40Watt/cm²) and a cleaning step in between two ablation passes to remove coagulum from the ablation zone and electrode surface. At subsequent RFA sessions, the HALO-device was used for focal ablation of residual Barrett’s tongues and islands <2cm in length, and to circumferentially ablate the squamocolumnar junction (‘Z-line’) at the gastric folds. The HALO-catheter consists of a small electrode that is fixed to the tip of the endoscope. Focal RFA was delivered twice to each area (15J/cm², 40Watt/cm²), followed by a cleaning step and a second ablation pass, again delivering RFA twice.

RFA was repeated every 2-3 months until complete endoscopic eradication of BE. In case BE persisted after 4 RFA sessions (≤2 HALO procedures), escape ER was performed using the MBM technique. For minute islands of unsuspicious BE (<5 mm) hot biopsy forceps treatment was allowed when this avoided an additional RFA session or escape ER.

**Pre- and post-procedural care**

All endoscopic procedures were performed on an outpatient basis using conscious sedation with midazolam and fentanyl, or pethidine, or monitored anesthesia with propofol. After endoscopic treatment, patients were observed in the endoscopy unit for 4 hours before being discharged to home with detailed instructions. During the study period, patients were administered esomeprazole 40 mg po BID, with addition of ranitidine 300 mg at bedtime and sucralfate suspension 5 mL (200mg/mL) QID for 14 days after every treatment session. Patients were allowed to take acetaminophen 500 mg (max. 3g per day) for post-procedural pain, or diclofenac suppositories 100 mg (max. 200mg per day) if not responding to acetaminophen.

**Follow-up**

After visible eradication of all BE was achieved, biopsies were taken from every 4-quadrant/2cm of the neosquamous epithelium throughout the original BE segment and immediately distal (<5mm) to the neo-Z-line. When histological assessment of the biopsies showed complete eradication of IM (CR-IM), patients were scheduled for follow-up high resolution endoscopy with NBI and 4-quadrant/2cm biopsies at 6 months, 12 months and annually thereafter. Standard EUS was performed at 12 months of follow-up to exclude local lymph node metastasis. The duration of follow-up was defined as the time between the first treatment session and the most recent follow-up endoscopy.
Histological evaluation

All biopsies and ER-specimens were routinely processed and were evaluated by a gastrointestinal pathologist. For the purpose of this study, all pre-treatment biopsies, ER-specimens, and biopsies obtained at the first follow-up endoscopy were reviewed by a local expert pathologist at each center with extensive experience in Barrett’s neoplasia. The study pathologists were blinded to study group assignment. Biopsies were assessed for presence of IM and grade of dysplasia using the revised Vienna classification (IM without dysplasia, indefinite for dysplasia (ID), LGD, HGD or cancer). ER specimens were evaluated for infiltration depth, vertical resection margins, tumor differentiation or grade of dysplasia, and lymphatic/vascular invasive growth. During follow-up, biopsies of neosquamous epithelium were assessed for the presence of IM at or below the surface (subsquamous intestinal metaplasia or buried Barrett’s).

Outcome parameters

Based on previous studies we expected that SRER and ER/RFA would be equally effective in the removal of neoplasia and IM, yet that SRER would result in a higher rate of esophageal stenosis as compared to RFA. Primary outcome parameter was the rate of symptomatic esophageal stenosis. Secondary outcome parameters were:

1. Complete response for neoplasia (CR-neoplasia), defined as absence of any neoplasia, including LGD and ID in all biopsies obtained at the first follow-up endoscopy;
2. Complete response for IM (CR-IM), defined as absence of IM in all biopsies, including biopsies obtained immediately distal to the neo-Z-line obtained at the first follow-up endoscopy;
3. Rate of complications other than stenosis;
4. Number of treatment sessions required to achieve CR-neoplasia and CR-IM inclusive of escape treatment and treatment for complications;
5. Proportion of patients with CR-neoplasia at the last follow-up endoscopy;
6. Proportion of patients with CR-IM at the last follow-up endoscopy;
7. Need for additional treatment for recurrent neoplasia during follow-up.

To classify stenosis and other complications, the following definitions were used: ‘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 treatment including dilation; ‘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.

Ethical considerations, sample size and statistics

The study protocol was approved by the local medical ethics committee of each study center (NTR1337, www.trialregister.nl). Written informed consent was obtained from all
participants. Patients were randomized in each center according to a computer-generated randomization sequence per center, which was concealed from the researchers who screened and enrolled patients by the use of sequentially numbered, sealed opaque envelopes. All procedures were attended by a study monitor (C.S.) who prospectively collected all relevant data on standardized case record forms, and data was entered into a dedicated database.

Sample size calculations were based on the assumption that SRER would result in a higher esophageal stenosis rate compared to RFA. No differences in CR-neoplasia, CR-IM, or severe complications were expected based on previous studies. To confirm the hypothesis that SRER results in a significantly higher stenosis rate, with estimated stenosis rates of 52% for SRER and 4% for RFA, 22 patients were needed in each arm, accounting for a dropout rate of 10%, resulting in a total study population of 44 patients (alpha= 0.05, beta= 0.10, two-sided testing).

Data analysis was performed using SPSS statistical software package (SPSS Inc.16.0.2, Chicago, IL, USA). Mean (±SD) was used for normal distribution and median (inter-quartile range, IQR) was used for skewed distribution. Fisher exact test and Mann-Whitney U test were used to compare groups when appropriate. Differences were considered statistically significant if \( p \leq 0.05 \). To calculate confidence intervals the Confidence Interval Analysis (CIA) package was used (CIA Version 2.2.0, London, UK). For sample size calculation and random sequence generation nQuery Adviser (Version 7, Cork, Ireland) was used.

**RESULTS**

**Patients**

Between April 2006 and April 2008, 55 patients with HGD/EC in a BE segment \( \leq 5 \)cm underwent endoscopic work-up and staging for eligibility in the Academic Medical Center (Amsterdam, Netherlands), Sint Antonius Hospital (Nieuwegein, Netherlands) and University Medical Center Hamburg-Eppendorf (Hamburg, Germany) (Figure 1).

Staging ER was performed prior to randomization in 30 of 55 patients. Eight patients were not eligible for study for the following reasons: non-lifting of the lesion (n=2), no residual IM after ER (n=2), lymphatic tumor invasion in the ER specimen (n=1), residual carcinoma after two ERs (n=1), tumor at the deep margin (n=1) and acute ER-related esophageal perforation (n=1). In two patients EUS-guided FNA of local lymph nodes was performed, and malignancy was excluded. Therefore, 47 of 55 screened patients fulfilled all study criteria after work-up and staging and were randomized to SRER (n=25) or RFA (n=22) (Figure 1). Baseline characteristics of patients in both groups were similar (Table 1).
Complete remission of neoplasia and IM

CR-neoplasia was reached in all 25 patients (100%) after SRER and in 21 of 22 patients (96%) after ER/RFA (Figure 1, Table 2). CR-IM was achieved in 23 of 25 patients (92%) after SRER and 21 of 22 patients (96%) after ER/RFA (Figure 2-3).

The single ER/RFA patient who failed to achieve CR-neoplasia and CR-IM underwent esophagectomy to treat persistent HGD. The choice for surgery over escape ER was due to the fact that previous ER made it impossible to perform additional ER. The surgical resection specimen showed residual HGD, while 20 lymph nodes were negative for malignancy. Two SRER patients failed to achieve CR-IM: one patient had a small rim of visible BE without

**Figure 1:** Patient enrolment and outcomes of patients treated with stepwise radical endoscopic resection (SRER) or endoscopic resection (ER) followed by radiofrequency ablation (RFA). HGD=high-grade dysplasia, EC= early cancer, BE= Barrett’s esophagus, ER= endoscopic resection, SRER= stepwise radical endoscopic resection, ER= endoscopic resection, RFA= radiofrequency ablation, CR-N= complete response for neoplasia, CR-IM= complete response for intestinal metaplasia.
Stepwise radical endoscopic resection versus RFA

dysplasia after 2 SRER sessions, but because of post-ER stricturing and poor healing after previous treatment no further treatment was performed, and one patient had persistent IM at the neo-Z-line without visible BE after two SRER sessions and RFA.

Table 1: Baseline patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>SRER (n=25)</th>
<th>ER+RFA (n=22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: female</td>
<td>21:04</td>
<td>19:03</td>
<td>1.00</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>68 (R 45-88)</td>
<td>69 (R 55-73)</td>
<td>0.97</td>
</tr>
<tr>
<td>Median BE (cm)</td>
<td>C2M4</td>
<td>C2M4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(IQR C1-3; M2-5)</td>
<td>(IQR C1-3; M2-5)</td>
<td></td>
</tr>
<tr>
<td>Visible lesion prior to treatment</td>
<td>17/25 (68%)</td>
<td>18/22 (82%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Lesion type prior to treatment (Paris classification)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-IIa</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>0-IIa-c</td>
<td>4 / 0-IIc: 1</td>
<td>0-IIa-c: 9</td>
<td></td>
</tr>
<tr>
<td>0-IIa+I</td>
<td>2 / 0-Is: 1</td>
<td>0-IIa+I: 3</td>
<td></td>
</tr>
<tr>
<td>Staging ER prior randomization</td>
<td>10</td>
<td>12*</td>
<td>0.39</td>
</tr>
<tr>
<td>ER after randomization</td>
<td>15</td>
<td>6*</td>
<td>0.04</td>
</tr>
<tr>
<td>Worst diagnosis histology of biopsies or ER specimens</td>
<td>13 EC / 12 HGD</td>
<td>15 EC / 7 HGD</td>
<td>0.37</td>
</tr>
</tbody>
</table>

SRER = stepwise radical endoscopic resection, ER = endoscopic resection, RFA = radiofrequency ablation, R = range, BE = Barrett’s esophagus, C = length of circumferential BE, M = maximal BE length, IQR = interquartile range, EC = early cancer, HGD = high-grade dysplasia. *Of the 22 patients in the RFA arm, 12 underwent a diagnostic ER for staging purposes and were then randomized to the RFA-arm, 6 other patients with visible lesions underwent ER after they were randomized to RFA. Four patients in the RFA-arm did not show visible abnormalities and underwent RFA monotherapy.

Figure 2: Stepwise radical endoscopic resection (SRER) for Barrett’s esophagus (BE) containing early neoplasia: A: Lesion in BE (C<1M3); B: Lesion with narrow band imaging (NBI); C: ER in 3 pieces (T1m3 adenocarcinoma); D: Healed resection wound; E: Remaining BE is removed with ER after they were randomized to RFA. Four patients in the RFA-arm did not show visible abnormalities and underwent RFA monotherapy.
Esophageal stenosis:

Symptomatic esophageal stenosis occurred in 22 of 25 (88%) SRER patients versus 3 of 21 (14%) RFA patients (RR=6.2 (95%CI 2-18; p<0.001) (Table 2). All RFA patients who developed stenosis had undergone ER of relatively large lesions prior to RFA, with stenosis developing at the ER sites. In the SRER group, 5 stenoses were graded as severe complications; all other stenoses were graded as moderate complications. Most stenoses resolved upon balloon or bougie dilation, while 1 patient required incision therapy in addition to dilation. The median number of dilations was 4 (range 1-19, IQR 2-5) for post-SRER stenoses and 3 (range 1-4) for post-ER/RFA stenoses (p=0.39).

Acute complications (Table 2): There was one severe acute complication in the SRER arm: a perforation occurred during ER, which was treated non-surgically with a covered stent. After stent removal and healing, SRER treatment was continued. Additionally, in the SRER arm, 5 mild acute bleedings occurred and were treated endoscopically by hot biopsy forceps, adrenaline injection and/or clip placement. Acute complications in the ER/
Stepwise radical endoscopic resection versus RFA

RFA arm were mild and included 2 bleedings immediately after ER treated endoscopically with a clip and APC, and 1 superficial mucosal laceration during RFA that required no intervention, but prevented a second ablation pass.

Early complications: There was one bleeding in the SRER arm, graded as a ‘moderate’ complication, in a patient presenting with hematemesis within 24 hours after ER due to an arterial bleeding from the resection wound that was treated by placement of a clip. After blood transfusion (Hb level drop from 7 to 5.2mmol/L, 2 units of packed red blood cells (RBCs) transfused) the patient was discharged.

Late complications other than stenosis: There was one delayed bleeding after RFA, graded as a ‘moderate’ complication. This patient developed melena after re-initiating oral anticoagulation therapy (acenocoumarol) for atrial fibrillation two weeks after focal RFA. Upper endoscopy showed a visible vessel in the treatment area, which was injected with adrenaline (1:10,000) and coagulated using bipolar electrocoagulation. The patient underwent blood transfusion (baseline Hb level unknown, Hb level after bleeding 5.7mmol/L, 2 units of packed RBCs transfused) the patient was discharged.

Number of treatment sessions

SRER-patients: For SRER, the MBM technique (n=12), ER-cap technique (n=8) or MBM and ER-cap (n=5) were used. In 7 patients, SRER was performed in a single session. A median of 5 (IQR 2-7) resections was performed per session. Per patient, a total median number of 10 (IQR 6-13) resection specimens were removed. In 3 SRER patients (3/25, 12%), APC

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**Table 2:** Outcome parameters and characteristics of endoscopic treatment.

<table>
<thead>
<tr>
<th></th>
<th>SRER (n=25)</th>
<th>ER+RFA (n=22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR-neoplasia</td>
<td>25/25 (100%)</td>
<td>21/22 (96%)</td>
<td>0.47</td>
</tr>
<tr>
<td>(95%CI 86-100%)</td>
<td>(95%CI 77-100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR-IM</td>
<td>23/25 (92%)</td>
<td>21/22 (96%)</td>
<td>1.00</td>
</tr>
<tr>
<td>(95%CI 74-99%)</td>
<td>(95%CI 77-100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe complications</td>
<td>6 (1 acute perforation, 5 stenoses)</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Moderate complications</td>
<td>18 (1 early bleeding, 17 stenoses)</td>
<td>4 (1 late bleeding, 3 stenoses)</td>
<td>0.00</td>
</tr>
<tr>
<td>Mild complications</td>
<td>5 (5 acute bleedings)</td>
<td>3 (2 acute bleedings, 1 acute non-transmural laceration)</td>
<td>0.71</td>
</tr>
<tr>
<td>Sessions SRER / ER + RFA (median)</td>
<td>2 (IQR 1-3)</td>
<td>3 (IQR 3-4)</td>
<td>0.07</td>
</tr>
<tr>
<td>Escape treatment</td>
<td>8/25 (32%)</td>
<td>4/21 (19%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Dilation sessions (median)</td>
<td>4 (R 1-19)</td>
<td>3 (R 1-4)</td>
<td>0.39</td>
</tr>
<tr>
<td>Total no therapeutic sessions (median)</td>
<td>6 (R 1-20, IQR 3-9)</td>
<td>3 (R 1-8, IQR 3-4)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

SRER= stepwise radical endoscopic resection, ER= endoscopic resection, RFA= radiofrequency ablation, CR= complete response, CI= confidence interval, IM= intestinal metaplasia, IQR= interquartile range, R= range, no= number.
was used to treat residual BE tissue bridges between resection wounds. Escape treatment to reach CR-neoplasia and CR-IM was required in 8 patients (8/25, 32%): RFA for residual BE because post-SRER scarring and stenosis impeded further ER (n=5); APC for residual BE because stricturing did not allow for passage of an ER-cap or HALO\textsuperscript{90}-catheter (n=1) or APC for ablation of tiny islands <5mm (n=2).

ER/RFA-patients: Prior to RFA 18/22 patients underwent ER of a visible lesion with the ER-cap technique (n=11), the MBM-technique (n=6) or the simple snare technique (n=1). Escape treatment to reach CR-neoplasia and CR-IM was performed in 4 patients (4/21, 19%): hot biopsy forceps to remove a BE island (<2mm, n=2); ER for residual visible BE (n=1): histology showed no IM or dysplasia; and ER plus APC (n=1) for an elevated island of BE: histology showed a radically removed T1sm1 cancer.

The median number of therapeutic sessions to achieve CR-neoplasia and CR-IM was not significantly different in both groups (SRER 2 (IQR 1-3) versus RFA 3 (IQR 3-4); p=0.07). However, due to stenosis requiring dilations, the total number of endoscopic interventions patient was significantly higher in SRER (6 (IQR 3-9) versus 3 (IQR 3-4); p<0.001). The median duration of the treatment period was not significantly different between SRER and RFA (5 (IQR 3-13) versus 8 (IQR 5-10) months respectively; p=0.26).

**Follow-up: persistence of CR-neoplasia and CR-IM**

Median follow-up from initial treatment to March 2010 was 24 months (IQR 18-29) overall, and median follow-up from the final treatment session to March 2010 was 18 months (IQR 11-23), with a median of 3 (IQR 3-4) follow-up endoscopies for both groups (Table 3). Forty-five patients (96%) remained under endoscopic follow-up. Two of 47 patients

<table>
<thead>
<tr>
<th>Table 3: Follow-up after endoscopic treatment.</th>
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<tbody>
<tr>
<td>SRER (n=25)</td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Lost to FU</td>
</tr>
<tr>
<td>Unrelated death</td>
</tr>
<tr>
<td>FU (months)</td>
</tr>
<tr>
<td>FU from final treatment session (months)</td>
</tr>
<tr>
<td>Follow-up endoscopies</td>
</tr>
<tr>
<td>Biopsies from neosquamous (median)</td>
</tr>
<tr>
<td>Biopsies from neo-Z-line (median)</td>
</tr>
<tr>
<td>Recurrent neoplasia</td>
</tr>
<tr>
<td>Visible BE</td>
</tr>
<tr>
<td>Repeated IM including at the last FU endoscopy</td>
</tr>
<tr>
<td>Single finding of focal IM at the neo-Z-line, not reproduced during FU</td>
</tr>
<tr>
<td>Single finding of buried Barrett’s glands, not reproduced during FU</td>
</tr>
<tr>
<td>IM at any time point during FU (total)</td>
</tr>
</tbody>
</table>

SRER= stepwise radical endoscopic resection, ER= endoscopic resection, RFA= radiofrequency ablation, FU= follow-up, IQR= interquartile range, Z-line= squamocolumnar juction, BE= Barrett’s esophagus, IM= intestinal metaplasia
were not available for endoscopic follow-up: one ER/RFA patient failed CR-neoplasia and underwent surgery; another ER/RFA patient died 4 months after reaching CR-neoplasia and CR-IM due to myocardial infarction (unrelated death).

In the SRER group, one patient (4%) was diagnosed with cancer at the neo-Z-line 16 months after SRER and was treated with ER. The resection specimen showed T1m3 carcinoma. Follow-up endoscopy after 4 months revealed no dysplasia or cancer. In the ER/RFA group, no recurrence of neoplasia was observed during follow-up.

None of the patients who reached CR-IM during the treatment phase showed endoscopic signs of recurrence of BE on any follow-up endoscopy. At the last follow-up endoscopy, histological signs of IM were found in 3 SRER and 2 RFA patients: all had repeated findings of IM at the neo-Z-line and were considered failures for CR-IM at the last follow-up endoscopy (p=1.00). Six other patients had a focal IM in a single biopsy during a single follow-up endoscopy without being reproduced at subsequent endoscopies, including 4 SRER patients (2 focal IM at the neo-Z-line, 2 buried BE glands in neosquamous biopsies) and 2 RFA patients (focal IM at the neo-Z-line). These 6 patients were not considered as failures for CR-IM at the last follow-up endoscopy.

DISCUSSION

This multicenter randomized trial showed that in patients with BE ≤5cm containing HGD or early cancer, both SRER and focal ER-plus-RFA are highly effective with high rates of CR-neoplasia and CR-IM. After a median follow-up of 24 months after initial treatment, recurrences of neoplasia or BE were rare for both groups. Regarding safety, SRER and RFA resulted in comparably low rates of acute complications, but SRER carried a significantly higher risk for the late complication of esophageal stenosis, resulting in more procedures per patient in the SRER group due to dilation sessions. In addition, significantly more complications were graded as ‘severe’ in the SRER-arm (1 perforation and 5 stenoses) with no severe complications in the ER/RFA-arm.

The most important finding of the study is a significantly higher stenosis rate of 88% in SRER compared to 14% after ER/RFA. Although all SRER stenoses were effectively treated with dilation, 5 of 22 SRER-stenoses were quite resistant to therapy (>5 dilatations and need for combination therapy). In addition, dilation of these stenoses may cause significant complications as illustrated by a recent multicenter SRER study that reported 2 perforations after dilation for a SRER-induced stenosis. More importantly, treatment of SRER-induced stenoses doubled the total number of endoscopic procedures in the SRER group compared to the ER/RFA group. In the ER/RFA group, the three patients with stenosis all had undergone widespread ER prior to RFA to remove all visible lesions. Studies of patients treated with RFA, not preceded by ER, have reported stenosis rates ≤6%. This suggests that ER, not RFA, was the primary cause of stenosis in these patients.

Esophageal stenosis is a recognized complication of SRER of BE, varying from 2 to 56%. Compared to other series, the 88% stenosis rate after SRER in our study is quite high. An explanation may be that the three study centers prospectively screened all patients with BE ≤5cm with HGD/EC and offered participation to all eligible patients. In
contrast, other retrospective series may have included less complicated cases, e.g. with a shorter BE segment or BE mainly consisting of tongues. It has been shown that the stenosis rate after SRER increases with the length of the BE.\textsuperscript{33,34} We assume that our patient population had a relatively long circumferential extent (median C2M4, IQR C1-3, M2-5) which may account for the relatively high stenosis rate. Our rigorous follow-up in this prospective study may also have contributed to the observed stenosis rate, with all stenoses and dilations being fully recognized and transparently reported.

Although no significant differences were found in eradication rates of neoplasia and IM, we can not conclude that SRER and ER/RFA are equally effective: the current study was powered to evaluate the difference in symptomatic stenosis rate between both treatment modalities, based on previous experience of the study centers. Uncontrolled studies have reported success rates for CR-neoplasia of SRER and ER/RFA varying between 88-100\%.\textsuperscript{10-12,14-19,35} If a difference of more than 10\% in CR-neoplasia for one of both treatment modalities would be clinically relevant and assuming a 90\% success rate for both treatment modalities, 155 patients would have been necessary in each treatment arm to be able to prove equivalence or non-equivalence. Given the relative rareness of HGD/EC in BE this is an unrealistic number of patients for a randomized study in this field. In addition, it is debatable whether it would be ethical or clinically relevant to perform such a study, knowing that combined ER and RFA has an excellent success rate with a low risk for symptomatic stenosis.

In our study there was one recurrent carcinoma (4\%) in the SRER arm, located at the neo-Z-line of a patient that had focal IM detected at this site at a previous follow-up endoscopy. This is in agreement with a recent multicenter SRER study of 169 patients in which all recurrences of HGD/EC (2\%) were located at the neo-Z-line.\textsuperscript{33} This suggests that IM in the Z-line after SRER may be a relevant finding, and may predict recurrence of neoplasia. On the other hand, our patients underwent extensive biopsy sampling during follow-up (median 12 biopsies obtained from the neo-Z-line per patient). Mostly, focal IM was observed in a single biopsy during a single endoscopy and not reproduced during subsequent endoscopies. Studies have shown that IM of the cardia can be detected in biopsies of 25\% of the normal population, and these studies generally obtained less biopsies than were obtained during follow-up in our patients.\textsuperscript{36} More data are therefore needed to address the relevance of IM distal to the Z-line.

There are two additional arguments in favor of a strategy of focal ER followed by RFA rather than SRER for the complete removal of BE. First, we studied only those patients with $\text{BE} \leq 5\text{cm}$. If we had studied longer segments, it is possible that the SRER group would have encountered further complications and failures. In contrast, recent data have shown that RFA is also effective and safe in longer segment BE, even in patients with $\text{BE} \geq 10\text{cm}$.\textsuperscript{37} Secondly, combination treatment of ER and RFA is technically less demanding than SRER.

Our study protocol allowed for escape treatment to achieve complete BE eradication after SRER or ER/RFA. Since RFA does not result in significant scarring of the esophagus escape ER after RFA has been incorporated in the treatment algorithm in other studies.\textsuperscript{16,17,19} Accordingly, in other SRER studies, ablation therapy has been used to treat small areas of residual BE that can not be resected due to scarring after previous ERs.
Although it can be argued that escape treatment may influence the results, we feel that comparing SRER and ER/RFA inclusive of escape treatment in both treatment arms makes our results better translatable to clinical practice.

A limitation of this study concerns its external validity: treatment was carried out in centers with a tertiary referral function for endoscopic treatment of early Barrett’s neoplasia. Hence, patients were treated by highly experienced endoscopists in SRER and RFA treatment. The outcomes of our study may therefore not apply to the general practice. However, because of the low incidence of early Barrett’s neoplasia in the general population, it is desirable to centralize care for these patients in well-trained expert centers.

In summary, this randomized multicenter trial showed that SRER and focal ER plus RFA are highly effective in the treatment of patients with BE≤5cm containing early neoplasia. SRER, however, resulted in a significantly higher stenosis rate than ER/RFA, and consequently required a higher number of therapeutic sessions due to dilations. Therefore, for patients with BE containing early neoplasia, a combined approach of focal ER for visible lesions followed by RFA for complete eradication of the remaining BE may be preferred.
REFERENCES


