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

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Endoscopic radiofrequency ablation combined with endoscopic resection for early neoplasia in Barrett’s esophagus longer than 10 cm

ABSTRACT

Background: Radiofrequency ablation (RFA) is safe and effective for eradicating Barrett’s esophagus (BE) and BE associated early neoplasia. Most RFA studies have limited the baseline length of BE (<10cm) and therefore little is known about RFA for longer BE.

Objective: To assess safety and efficacy of RFA with or without prior endoscopic resection (ER) for BE ≥10cm containing neoplasia.

Design: Prospective trial.

Patients: Consecutive patients with BE ≥10cm with early neoplasia. Interventions: Focal ER for visible abnormalities, followed by a maximum of 2 circumferential and 3 focal RFA procedures every 2-3 months until complete remission.

Main outcome measurements: Complete remission, defined as endoscopic resolution of BE and no intestinal metaplasia (CR-IM) or neoplasia (CR-neoplasia) in biopsies.

Results: Of the 26 patients included, 18 underwent ER for visible abnormalities prior to RFA. The ER specimen showed early cancer in 11, high-grade intraepithelial neoplasia (HGIN) in 6 and low-grade intraepithelial neoplasia (LGIN) in 1. The worst residual histology, pre-RFA and after any ER, was HGIN in 16 and LGIN in 10 patients. CR-neoplasia and CR-IM was achieved in 83% (95%CI 63-95%) and 79% (95%CI 58-93%) respectively. None of the patients showed ‘fatal’ or ‘severe’ complications, 15% (95%CI 4-35%) showed ‘moderate’ complications. During a mean follow-up of 29 (±9.1) months no neoplasia recurred.

Limitations: Tertiary center, short follow-up.

Conclusions: ER for visible abnormalities followed by RFA of residual BE is a safe and effective treatment for BE ≥10cm containing neoplasia with a low chance of recurrence of neoplasia or BE during follow-up.
INTRODUCTION

Barrett’s esophagus (BE) is a pre-malignant condition characterized by the presence of a columnar lined distal esophagus containing intestinal metaplasia (IM) upon biopsy.\(^1\) BE is caused by chronic gastroesophageal reflux and found in 8% of patients undergoing endoscopy for reflux symptoms.\(^2\) BE can undergo a multi-step transition from low-grade intraepithelial neoplasia (LGIN) to high-grade intraepithelial neoplasia (HGIN) to invasive adenocarcinoma.\(^3\) HGIN and mucosal cancer in BE have a low risk of lymph node metastases and can therefore be treated endoscopically by endoscopic resection techniques, endoscopic ablative techniques, or a combination thereof. Endoscopic resection techniques allow for histological evaluation of the resected specimen which is the only reliable way to exclude patients with submucosal invading cancers from further endoscopic treatment.\(^4\) After focal removal of endoscopically visible abnormalities, the remaining BE generally contains residual HGIN or LGIN and recurrences occur in 19-30% of cases.\(^5-7\) Therefore, ablation of the remaining BE has been advocated and recent studies suggest that this reduces the chances of recurrent neoplasia elsewhere in the BE during follow-up.\(^7\)

Radiofrequency ablation (RFA) is one of the most promising ablative techniques for BE. The technique uses a bipolar electrode that is available as a balloon based device for primary circumferential ablation or as a cap based device that can be mounted on the tip of the endoscope for focal ablation.

RFA has been proven to be safe and effective for the removal of IM and neoplasia in BE in a wide range of clinical studies including 2 randomized trials.\(^8-15\) In addition, studies have shown that the regenerated neosquamous epithelium after RFA is free of the oncogenetic abnormalities as present in the BE prior to RFA and that subsquamous foci of IM (a.k.a. buried Barrett’s) are rare.\(^16\) Furthermore, RFA preserves the diameter, compliance and motility of the esophagus and is associated with a low rate of stenosis.\(^17\)

From other endoscopic therapies it is known that safety and efficacy may depend on the length of the Barrett’s segments treated: after radical mucosectomy and after photodynamic therapy (PDT), stenosis rates for example increase with the BE length treated.\(^18,19\) In addition, also the rate of complete removal of the whole Barrett’s segment is found to decrease with the length of the BE.\(^20\) For these reasons endoscopic therapy is thought to be more difficult in longer Barrett’s segments. Most studies on the use of ablation techniques for BE have therefore restricted the baseline BE length to less than 10cm.

The aim of this study, therefore, was to assess the safety and efficacy of RFA with or without prior ER for BE of ≥10cm containing early neoplasia.
METHODS

Patient selection

Patients were consecutively included from January 2006 till November 2008. They were treated at two tertiary referral centers in the Netherlands: the Academic Medical Center in Amsterdam and the Sint Antonius hospital in Nieuwegein.

Patients were eligible if they met all the following inclusion criteria: age $\geq 18$ year; maximum BE length $\geq 10cm$; presence of LGIN, HGIN or early cancer (EC) (defined as $\leq$T1sm1 infiltration with good or moderate differentiation and no lymphatic/vascular invasive growth) confirmed by study pathologist (FTK, MV or CS) at two endoscopic procedures; no signs of metastasis on endoscopic ultrasound (in case of HGIN and EC) or CT-scan (in case of EC). Patients were excluded if they had any of the following exclusion criteria: previous treatment with PDT or argon plasma coagulation (APC); prior ER larger than 3cm in length or extending over more than 50% of the circumference; ER specimen showing cancer at the vertical (deep) resection margin, $>T1sm1$ invasion, poor tumor differentiation, or lymphatic/vascular invasive growth; persistent visible abnormalities after ER or invasive cancer in mapping biopsies (post-ER) prior to RFA.

The current study enrolled some patients who were included in other published or ongoing trials from our group as well as patients who were treated outside of these trials, mainly because of the length of their BE (Table 1). Patients who were not previously consented as part of prior IRB-approved trials provided informed consent for participation in this study.

Endoscopic work-up prior to RFA

Patients underwent two high-resolution endoscopies of the BE with biopsies from all visible abnormalities (i.e. any nodule, flat lesion or mucosal irregularity, no matter how subtle) and random 4 quadrant biopsies every 2cm. All lesions suspicious for EC were endoscopically resected, to remove and stage these lesions prior to RFA. ER was performed under conscious sedation as an out-patient procedure either with the ER-cap technique (after submucosal lifting), or the multi-band mucosectomy (MBM) technique. Depending on the size, lesions were resected en-bloc or in multiple pieces (piecemeal procedure). All resected specimens were retrieved, pinned down on paraffin with the

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**Table 1. Patients of current study participating in other trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Baseline pathology</th>
<th>BE inclusion length</th>
<th>Number of pts BE $\geq 10cm$ included in this study</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMC-II*</td>
<td>Single center prospective study</td>
<td>HGIN/EC</td>
<td>2-10cm</td>
<td>2</td>
</tr>
<tr>
<td>EURO-I*</td>
<td>Multi center prospective study</td>
<td>HGIN/EC</td>
<td>$\leq 12cm$</td>
<td>8</td>
</tr>
<tr>
<td>EURO-II*</td>
<td>Multi center prospective study</td>
<td>HGIN/EC</td>
<td>$\leq 12cm$</td>
<td>5</td>
</tr>
<tr>
<td>SURF*</td>
<td>Multi center randomized controlled trial</td>
<td>LGIN</td>
<td>No restrictions</td>
<td>4</td>
</tr>
<tr>
<td>None</td>
<td>Prospective registration</td>
<td>HGIN/EC</td>
<td>No restrictions</td>
<td>7</td>
</tr>
</tbody>
</table>

HGIN high-grade intraepithelial neoplasia; EC early cancer; LGIN low-grade intraepithelial neoplasia; BE Barrett’s esophagus. * Ongoing trails
mucosal side up, and fixed in formalin for histological evaluation. No attempts were made to reconstruct the piecemeal resections.

After ER the residual BE was mapped twice to exclude residual lesions and residual cancer in the flat mucosa.

**RFA system and endoscopic procedure**

The RFA system and endoscopic procedure have been described previously. In short, RFA procedures were performed as out-patient procedures under conscious sedation with midazolam and fentanyl or pethidine. Patients were discharged after 2-4 hours of observation.

Circumferential RFA was performed with the balloon based HALO system (BÂRRX Medical Inc., Sunnyvale, California, USA). The BE was ablated at 12J/cm$^2$ under endoscopic control. Two ablation passes of the BE were performed with cleaning of the ablation after the first pass.

Focal RFA was performed with the cap based HALO system (BÂRRX Medical Inc., Sunnyvale, California, USA) for treatment of residual BE after circumferential RFA. Areas were ablated twice using the “double-double” 15J/cm$^2$ regimen (i.e. two ablation passes consisting of two consecutive ablations with 15J/cm$^2$ each, with cleaning of the ablated area after the first pass), which is in accordance to our initial experience with the focal ablation device and all our published and ongoing studies. In all focal RFA sessions the area of the neosquamocolumnar junction at the upper end of the gastric folds was ablated, irrespective of its endoscopic appearance.

After each RFA procedure patients were treated for a period of 2 weeks with ranitidine 300mg at bedtime and 5 ml sulcralfate suspension (200mg/ml) qid in addition to the maintenance medication of esomeprazole 40 mg bid.

**Treatment protocol and follow-up**

In case of prior ER, the first circumferential RFA of the whole Barrett’s segment was performed at least 6 weeks after ER. Subsequent RFA sessions were scheduled every 2-3 months until complete eradication of all visible BE was achieved. Patients underwent a maximum of 2 circumferential and 3 focal ablations. In case of residual BE after the maximum number of RFA sessions an ER was performed as “escape” procedure (Figure 1). Once complete remission of all visible BE was achieved and complete histological clearance of dysplasia and IM was documented (or 2-3 months after the “escape” procedure), patients were followed with high resolution endoscopies with narrow-band imaging at 3, 6 and 12 months and annually thereafter. At these follow-up endoscopies four quadrant biopsies were obtained immediately distal (<5mm) to the neosquamocolumnar junction and from the neosquamous epithelium at 2cm intervals.

**Histology**

All ER specimens and biopsies were routinely processed and stained with hematoxylin and eosin and assessed by two study pathologist (FTK, MV or CS). The ER specimens
and biopsies were evaluated for presence of neoplasia and cancer according to the WHO classification. In the case of cancer in the ER specimens, tumor infiltration depth, tumor differentiation grade, presence of lymphatic/vascular invasive growth and radicality of the vertical resection margins were documented. Biopsies of the neosquamous epithelium were also evaluated for the presence of subsquamous foci of IM.

**Outcome parameters**

Primary endpoints were:

1. Complete removal of neoplasia (CR-neoplasia), defined as absence of LGIN, HGIN and EC from all biopsies obtained during the first follow-up endoscopy.
2. Complete removal of intestinal metaplasia (CR-IM), defined as endoscopic resolution of all BE and no evidence of IM in any of the biopsies obtained during the first follow-up endoscopy (including the biopsies from the neosquamocolumnar junction and from the neosquamous mucosa).

Secondary endpoints were:

1. Recurrence of neoplasia during follow-up.
2. Recurrence of BE during follow-up (either endoscopic or histological).
3. Complication rate of ER and RFA.
Severity of the complications was graded as follows: ‘mild’ (unplanned hospital admission, hospitalization ≤3 days, clinical significant bleeding with haemoglobin drop <3g and no need for transfusion), ‘moderate’ (4-10 days hospitalization, ≤4 units blood transfusion, need for repeat endoscopic intervention, radiologic intervention), ‘severe’ (hospitalization >10 days, ICU admission, need for surgery, >4 units blood transfusion, in the case of stenosis: >5 endoscopic dilatations, stent placement or incision therapy) or ‘fatal’ (death attributable to procedure <30 days or longer with continuous hospitalization).\textsuperscript{22}

**Statistics**

Statistical analysis was performed with a statistical software package (Statistical Package for the Social Sciences 14.0.2; SPSS Inc, Chicago, IL, USA). Data with a normal distribution were described with the mean and standard deviation whereas data with a skewed distribution were described by the median and interquartile ranges (IQR) or ranges. Confidence intervals of the proportions were calculated with the Confidence Interval Analysis package.\textsuperscript{23}

**RESULTS**

**Patients**

Between January 2006 and October 2008 26 consecutive patients (21 males, mean age 66±10.6 years) were included in this study. Patient characteristics are described in Table 2. Median BE length was C9M11 (IQR C8-10, M10-12). None of the patients showed signs of active reflux disease, yet thirteen patients (50%) were found to have a reflux stenosis at the proximal end of their Barrett’s segment. These stenoses were generally asymptomatic and allowed passage of the therapeutic endoscopes. In 3 patients, however, endoscopic

<table>
<thead>
<tr>
<th>Table 2. Patient characteristics.</th>
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<tbody>
<tr>
<td>Patients</td>
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<tr>
<td>Age</td>
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<tr>
<td>Gender</td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td>Barrett’s length</td>
</tr>
<tr>
<td>C</td>
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<tr>
<td>M</td>
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<tr>
<td>Overall worst histology</td>
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<tr>
<td>EC</td>
</tr>
<tr>
<td>HGIN</td>
</tr>
<tr>
<td>LGIN</td>
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<tr>
<td>ER prior to RFA</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Histology flat mucosa</td>
</tr>
<tr>
<td>HGIN</td>
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<tr>
<td>LGIN</td>
</tr>
</tbody>
</table>

C circumferential extent; M maximum extent; EC early cancer; HGIN high-grade intraepithelial neoplasia; LGIN low-grade intraepithelial neoplasia; ER endoscopic resection; RFA radio-frequency ablation.
bougienage of the reflux stenosis was required prior to treatment to facilitate the introduction of an ER cap and RFA catheters.

Eighteen patients underwent an ER of visible abnormalities prior to RFA. The ER cap technique was used in 5 and MBM in 13 patients.

The ER specimens showed early cancer in 11 patients (intramucosal (n=10) sm1 (n=1), all with good or moderate differentiation and no lymphatic/vascular invasive growth), HGIN in 6 patients, and LGIN in 1. Prior to RFA, and after ER if applicable, all patients had flat mucosa without visible abnormalities with random mapping biopsies showing HGIN in 16 and LGIN in 10 patients.

**Primary outcomes: eradication of early cancer, neoplasia and intestinal metaplasia**

In 2 patients (8%), the treatment protocol was discontinued due to unrelated co-morbidity (psychiatric disorder and lung cancer). In both, at the last endoscopy before

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**Figure 2:** Enrollment and outcomes. Pts patients; BE Barrett’s esophagus; EC early cancer; HGIN high-grade intraepithelial neoplasia; LGIN low-grade intraepithelial neoplasia; ER endoscopic resection; RFA radiofrequency ablation; CR-neoplasia complete removal of neoplasia; CR-IM complete removal of endoscopically visible BE and histological intestinal metaplasia; IM intestinal metaplasia; FU follow-up.
discontinuation, endoscopic regression of BE was 99% without histological information available. These patients were excluded from analysis of the primary endpoints.

Complete histological eradication of neoplasia, CR-neoplasia, was achieved in 20 of the 24 patients: 83% (95%CI 63-95%). Complete endoscopic and histological eradication of IM, CR-IM, was achieved in 19 of the 24 patients, 79% (95%CI 58-93%) (Figure 2 and 3).

In 4 patients (15% [95%CI 4-35 %]), the RFA treatment was discontinued after 1-3 sessions because of a poor healing and no or almost no regeneration of neosquamous mucosa (Figure 4). These patients were therefore considered as failures for the primary endpoints of the study (CR-neoplasia and CR-IM).

Patients achieved CR-neoplasia and CR-IM after a median of 1 (IQR 1-2) circumferential and 2 (IQR 1-3) focal ablations. Three patients underwent an escape ER for persisting Barrett’s islands after the maximum RFA treatments. Another two patients were treated with APC after RFA: in one patient for a small persisting BE island (1x2mm) which in the opinion of the endoscopist did not justify ER; in the other patient APC was performed for small (<5mm) remaining Barrett’s islands after 2 circumferential RFA sessions, because the focal RFA catheter could not pass the reflux stenosis despite dilatation.

Two patients underwent a diagnostic ER during the treatment protocol of slightly elevated Barrett’s islands in order to avoid performing RFA on possibly invading cancers (thus not to supplement the efficacy of RFA). Histology of both ER specimens showed only LGIN.
Chapter 6

Secondary outcome: complications after ER and RFA

No ‘fatal’ or ‘severe’ complications occurred. Four patients (15% [95%CI 4-35%]) developed complications after ER or RFA, which were graded as ‘moderate’. One patient developed a delayed bleeding 6 days after ER. This patient received blood transfusion and was treated successfully with endoscopic hemostatic therapy (adrenaline injection, bipolar probe coagulation and clip placement). Two patients had an unplanned admission: one patient was admitted for observation after a superficial laceration which showed no transmural leakage on the swallowing contrast examination, this 80 year old patient, however, became deliriant and as a result the admission was prolonged; another patient was admitted 3 days after the RFA procedure because of pain, nausea and vomiting that resolved with conservative treatment. Since both admissions were >4 days these complications were graded as ‘moderate’. The fourth patient with a ‘moderate’ complication had a relative stenosis after ER and developed symptoms of dysphagia after RFA, which resolved after 2 dilatations.

Figure 4: Barrett’s esophagus with C10M11 length treated with endoscopic resection for a mucosal cancer and radiofrequency ablation for the remaining Barrett’s segment. Radiofrequency ablation failed to remove the Barrett’s segment. A, B and C: Barrett’s esophagus after endoscopic resection and before ablation. D, E and F: 3 months after the first ablation the esophagus had not completely healed with only limited regression into neosquamous mucosa. A second circumferential ablation was performed at a later stage G, H and I: again no significant visible response was seen after the second ablation. As a consequence ablations were stopped.
In 7 patients (27% [95% CI 12-48%]) a superficial laceration was observed during the circumferential ablation procedure. Six of these superficial lacerations remained asymptomatic, did not require intervention, and were therefore not considered to be a complication. However, one patient was admitted for observation (see above), since this was the first laceration we observed during our RFA experience. This patient, again, did not experience symptoms attributable to the laceration. Lacerations were located either at the level of the reflux stenosis (n=4) or at the level of the ER scar (n=3). In 4 of the 7 patients the laceration was noted after the first circumferential ablation pass and the second pass was either therefore not performed (n=1), modified by choosing a balloon with a smaller diameter (n=1), or by skipping the zone comprising the laceration during the second RFA pass (n=2). All patients were able to continue the RFA according to the protocol 2-3 months later.

**Secondary outcome: follow-up**

Patients that achieved CR-neoplasia and CR-IM were followed up for a mean duration of 29±9.1 months (21±11.7 months since last treatment session). None of the 20 patients developed neoplasia during follow-up, thus 100% (95% CI 82-100%) continued to be CR-neoplasia.

Two patients showed a small island of BE during follow-up. One patient showed a 3mm island 6 months after treatment located at the upper part of the initial Barrett’s segment immediately distal to a reflux stenosis that was likely to be overlooked initially. After removing this island with ER, this patient stayed CR-IM. Another patient showed a 1mm island 18 months after treatment located near the z-line and the island was treated with APC.

Focal IM below the neosquamocolumnar junction was found in 3 patients in a single biopsy obtained during follow-up. This finding was not reproduced in 33 follow-up biopsies obtained at the neosquamocolumnar junction in 6 procedures.

Of the 1,272 biopsies taken from neosquamous epithelium only 1 biopsy (2cm proximal to the neosquamocolumnar junction) showed focal subsquamous IM without neoplasia.

**DISCUSSION**

In this study 83% of the patients with a BE≥10cm containing early neoplasia were effectively treated by RFA preceded by ER for visible abnormalities when present. The treatment not only resulted in complete removal of all neoplasia but also in complete endoscopic and histological removal of the whole Barrett’s segments. There were no severe complications and remarkably these results were achieved using an apparently similar number of treatments as for BE<10cm.8-13,15

Our data are in accordance with the reported rates of complete remission of neoplasia and IM by Shaheen et al., even though longer Barrett’s segments were treated in our study.13 However, in contrast to the study of Shaheen et al. our treatment protocol permitted 2 instead of 1 circumferential ablations as well as an escape treatment with ER
after the maximum number of RFA treatments in the case of residual endoscopic BE. Thus our study shows similar complete remission rates of neoplasia and IM but with a more extensive treatment protocol. Compared to previous RFA studies from our own group in which we used the same protocol, the remission rates for BE ≥10cm were lower and did not reach the 95-100% complete remission of neoplasia and IM.\textsuperscript{9-12,15} This difference in remission rate was caused by 4 patients in whom we decided to discontinue treatment because of poor healing and no visible regression in the surface area of BE despite of medication compliance and increased esomeprazole dosage (80mg BID). We hypothesize that this reflects the severity of the underlying reflux disease in this selected group of BE patients. Nevertheless in the remaining patients, complete remission of neoplasia and IM was achieved with a median of 3 RFA treatments, which is similar to the 3-4 RFA treatments that have been reported for shorter Barrett’s segments.\textsuperscript{9-13,15}

During treatment of our patients we encountered several technical challenges that have not been reported in patients with shorter BE. First, half of the patients were found to have a relative reflux stenosis at the upper end of the BE. In some patients, prior dilatation of this stenosis was required to allow introduction of ER-cap and RFA catheters. In addition, reflux stenoses may have led to a conservative selection of the ablation balloon-catheter diameter. In theory, a conservative balloon choice may result in less contact between the electrode and the mucosa in the wider distal part of the esophagus, therefore resulting in a suboptimal treatment. A second difficulty encountered during RFA treatment of BE ≥10cm were non-transmural lacerations that were seen in 27% of the patients after circumferential ablation occurring at the reflux stenosis or previous ER site (i.e. the narrowest part of the esophagus). These lacerations were, however, asymptomatic and did not require intervention. When a laceration was noticed after the first pass, further RFA was modified or stopped during that session to prevent deeper laceration and further ablation of the deeper layers. Nevertheless, lacerations did not impede subsequent treatment 2-3 months later.

Only one patient (4%), who underwent previous ER, developed symptoms of dysphagia after RFA that resolved after two dilatations. Dysphagia was rare after RFA, unlike after other endoscopic treatment modalities, such as radical endoscopic resection and PDT which despite the fact that they are generally applied in shorter BE are associated with stenosis in more than 25% of the patients.\textsuperscript{15,18,19}

During follow-up, three patients were found to have focal IM below the neosquamo-columnar junction. IM was, however, only found in a single biopsy during one follow-up endoscopy and it was not reproduced during subsequent follow-up endoscopies. It might be that IM in this region is a physiological finding as others have reported that approximately 25% of the normal population shows IM in the biopsies of the cardia.\textsuperscript{24,25} On the other hand we can not completely exclude it to be remnants of persisting IM not found previously due to sampling error, or even being the start of more widespread new-onset intestinal metaplasia. Further follow-up is needed to elucidate the relevance of IM in the neo-z-line.

This study has some limitations that need to be addressed. First, it was performed in tertiary referral centers. Endoscopies were performed by experienced endoscopists in
the field of BE imaging and therapy and pathology was reviewed in consensus by expert gastro-intestinal pathologists. Second, the patients in this study are a highly selected group not frequently seen in common practice. The results may therefore not be generalized to centers with different set-up. Finally, the follow-up time is relatively short. Longer follow-up is needed to show if the complete remission will be sustained in this selected group of patients with probably more severe reflux disease. Nevertheless, previous studies in this field have reported neoplasia recurrence rates of approximately 19-30% during a median follow-up of 1.5-5 years with most of the recurrences developing within the first 15 months after treatment.\textsuperscript{5-7}

In our opinion, the treatment of the patients with BE \( \geq 10 \text{cm} \) should be performed in centers with experience in imaging and therapy of BE. It is not only essential to recognize all subtle abnormalities that may harbor cancer in such a long BE, but the treatment itself is also technically more demanding due to the reflux stenoses and the ER scars. In addition, the number of patients with no or poor regeneration of neosquamous epithelium after RFA is relatively high. Further research is necessary to predict which patients will not respond adequately to RFA, as well as which mechanisms underlie this lack of response.

In conclusion, RFA of Barrett’s segments \( \geq 10 \text{cm} \) seems to be more challenging: ablations were stopped in 15% due to poor healing and no regression which probably reflects the severity of the reflux disease in this selected group of patients. Nevertheless, the vast majority of this complex group of Barrett’s patients reached complete removal of neoplasia and complete reversal of the Barrett’s segment without severe complications and with a similar number of treatment sessions as reported for patients with a shorter Barrett’s segments.
REFERENCES


