Endoscopic management of Barrett’s esophagus with dysplasia

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REMISSION OF BARRETT’S ESOPHAGUS WITH EARLY NEOPLASIA 5 YEARS AFTER RADIOFREQUENCY ABLATION WITH ENDOSCOPIC RESECTION: A NETHERLANDS COHORT STUDY


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BACKGROUND & AIMS: Radiofrequency ablation (RFA) with or without endoscopic resection, effectively eradicates Barrett’s esophagus (BE) containing high-grade intraepithelial neoplasia and/or early-stage cancer. We followed patients who received RFA for BE containing high-grade intraepithelial neoplasia and/or early-stage cancer for 5 years to determine the durability of treatment response.

METHODS: We followed 54 patients with BE (2-12 cm), previously enrolled in 4 consecutive cohort studies in which they underwent focal endoscopic resection in case of visible lesions (n=40, 72%), followed by serial RFA every 3 months. Patients underwent high-resolution endoscopy with narrow-band imaging at 6 and 12 months after treatment and then annually for 5 years (median, 61 months; interquartile range, 53-65 months); random biopsy samples were collected from neosquamous epithelium and gastric cardia. After 5 years, endoscopic ultrasound and endoscopic resection of neosquamous epithelium were performed. Outcomes included sustained complete remission of neoplasia or intestinal metaplasia (IM), IM in gastric cardia, or buried glands in neosquamous epithelium.

RESULTS: After 5 years, Kaplan-Meier analysis showed sustained complete remission of neoplasia and intestinal metaplasia in 90% of patients; neoplasia recurred in 3 patients and was managed endoscopically. Focal IM in the cardia was found in 19 of 54 patients (35%), in 53 of 1,143 gastric cardia biopsies (4.6%). The incidence of IM of the cardia did not increase over time; and IM was diagnosed based on only a single biopsy in 89% of patients. Buried glands were detected in 3 of 3,543 neosquamous epithelium biopsies (0.08%, from 3 patients). No endoscopic resection samples had buried glands.

CONCLUSIONS: Among patients who have undergone RFA, with or without endoscopic resection for neoplastic BE, 90% remain in remission at 5-year follow-up, with all recurrences managed endoscopically. This treatment approach is therefore an effective and durable alternative to esophagectomy. (trialregister.nl, NTR2998)
INTRODUCTION

Barrett’s esophagus (BE) is a pre-malignant condition in which the normal squamous lining of the esophagus has been replaced by columnar epithelium containing intestinal metaplasia (IM). Malignant degeneration of BE is gradual: from non-dysplastic IM, to low-grade intraepithelial neoplasia (LGIN), high-grade intraepithelial neoplasia (HGIN), and eventually progressing into invasive cancer.\textsuperscript{1,2} Patients with non-dysplastic IM or LGIN undergo regular endoscopic surveillance.\textsuperscript{2} Patients with HGIN or early-stage cancer limited to the mucosa can be treated endoscopically, whereas more advanced cancers require surgical treatment.\textsuperscript{3-6}

For focal lesions, endoscopic resection is the treatment of choice. However, after focal endoscopic resection, the residual Barrett segment remains at risk for malignant progression. Because the risk of developing metachronous lesions is estimated at 30% within 3 years, eradication of any residual BE is recommended.\textsuperscript{6-8} Radiofrequency ablation (RFA) is characterized by controlled and uniform delivery of radiofrequency energy. This technique has been shown to be safe and effective in eradicating non-dysplastic BE and BE containing LGIN or HGIN.\textsuperscript{9,10} The combination of endoscopic resection and RFA has also been shown successful for treatment of mucosal abnormalities and early-stage cancer. With this treatment approach, not only neoplasia is effectively removed, but the entire BE segment is successfully eradicated in 77-100% of patients.\textsuperscript{11-14}

Less is known about the longer-term durability of this approach. Several factors can influence the persistence of neosquamous epithelium after complete eradication of BE and neoplasia. For example, the presence of ongoing reflux exposure can play a role in recurrent disease given the role of reflux in the pathogenesis of BE.\textsuperscript{15} Permanent eradication of neoplasia and IM would justify a prolonged surveillance interval, a less rigorous biopsy protocol, or even omitting surveillance endoscopies at all. Although several groups have reported promising outcomes of RFA treatment for neoplastic BE, most of these studies lack systematic long-term follow-up.\textsuperscript{9, 10, 16, 17}

To assess the durability of post-RFA epithelium in a large prospective cohort of patients treated for BE with HGIN and/or early-stage cancer, we have systematically followed patients for 5 years after the initial RFA. This follow-up study is characterized by regular high-resolution endoscopy with extensive biopsy sampling and centralized pathology review completed by endoscopic ultrasound (EUS) and endoscopic resection of neosquamous epithelium.
PATIENT SELECTION  Patients were initially included if they had endoscopically visible BE with histology proven HGIN and/or early-stage cancer, demonstrated on at least two separate endoscopies. Patients were treated per one of the following study protocols (Table 1):

1. The first pilot study (AMC-I) on circumferential RFA using the HALO®360 ablation device, with earlier en-bloc endoscopic resection allowed, of HGIN and/or early-stage cancer in patients with BE segment between 2 and 10 cm. 11
2. The second prospective study (AMC-II) on RFA, with earlier piecemeal endoscopic resection allowed, for treatment of HGIN and/or early-stage cancer in patients with a BE segment between 2 and 10 cm, using both the HALO®360 and the HALO<sup>90</sup> ablation device from the start of the study. 12
3. The first European multicenter trial (EURO-I) evaluating the efficacy and safety of RFA, with or without endoscopic resection, in patients with a BE segment <12 cm. 13
4. A prospective randomized multicenter trial (AMC-IV) comparing stepwise radical endoscopic resection with RFA for the eradication of neoplasia and IM in patients with a BE segment <5 cm. 14

For this study, all 55 patients who were initially treated at the Academic Medical Center were included.

Table 1: Overview of referenced treatment protocols, from which patients were derived for evaluation of 5-year results after RFA.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients included</th>
<th>Eligible patients for 5-year study</th>
<th>BE-length in centimeters</th>
<th>Endoscopic resection-technique</th>
<th>Circumferential RFA</th>
<th>Focal RFA</th>
<th>Median reported FU in months</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMC-I</td>
<td>(n = 69) 11</td>
<td>11</td>
<td>2-10</td>
<td>En-bloc resection only</td>
<td>All patients underwent 2 circumferential sessions with the 2x12J/cm² regimen</td>
<td>Became available halfway through the study</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>The ablation zone was cleaned superficially between ablation cycles</td>
<td>Used in a dose-escalation manner at subsequent treatment sessions: 2x12J/cm²; 2x2x12J/cm²; 2x2x15J/cm²</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Used in case of an irregular appearance of the SCJ, residual BE islands or tongues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMC-II</td>
<td>(n = 55)* 12</td>
<td>12</td>
<td>2-10</td>
<td>Piecemeal resection allowed</td>
<td>2x12J/cm² regimen</td>
<td>2x2x12J/cm² or 2x2x15J/cm² regimen</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thorough cleansing of ablation zone and electrode surface between ablation cycles</td>
<td>Used in case of an irregular appearance of the SCJ, residual BE islands or tongues</td>
<td></td>
</tr>
<tr>
<td>EURO-I</td>
<td>(n = 24) 24</td>
<td>14*</td>
<td>&lt; 12</td>
<td>Piecemeal resection allowed</td>
<td>2x12J/cm² regimen</td>
<td>2x2x15J/cm² regimen</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thorough cleansing of ablation zone and electrode surface between ablation cycles</td>
<td>Used in case of residual BE islands or tongues</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Routine circumferential treatment of SCJ mandated to ensure eradication of IM at this level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMC-IV</td>
<td>(n = 18*) 22</td>
<td>18</td>
<td>&lt; 5</td>
<td>Piecemeal resection allowed</td>
<td>2x12J/cm² regimen</td>
<td>2x2x15J/cm² regimen</td>
<td>24</td>
</tr>
<tr>
<td>RFA arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thorough cleansing of ablation zone and electrode surface between ablation cycles</td>
<td>Used in case of residual BE islands or tongues</td>
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<td></td>
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<td></td>
<td>Routine circumferential treatment of SCJ mandated to ensure eradication of IM at this level</td>
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</table>

* Of the 69 patients included, 55 underwent treatment at a single center (Academic Medical Center Amsterdam), and were invited for the 5-year study.
TREATMENT PROTOCOL A detailed description of the treatment protocol is beyond the scope of this paper as both the endoscopic resection and RFA procedure have been described previously. Briefly, after a minimum interval of 6 weeks after endoscopic resection for endoscopically visible abnormalities, patients were treated with primary circumferential ablation using the HALO® system (BARRX Medical Inc., Sunnyvale, CA). Subsequently, patients underwent a series of circumferential or focal RFA procedures (HALO® and HALO®, BARRX Medical Inc.) at 3-months intervals, depending on the extent of residual BE. RFA treatment was performed until complete histological and endoscopic eradication was achieved. In case Barrett’s mucosa persisted after 5 ablation sessions, escape endoscopic resection was performed using the multiband mucosectomy technique (Duette, Cook Endoscopy, Limerick, Ireland).

FOLLOW-UP AFTER TREATMENT Two months after the last treatment session patients underwent endoscopy to confirm complete response; defined as endoscopically normal-appearing neosquamous epithelium on high-resolution endoscopy (HRE) and narrow-band imaging (NBI). Four-quadrant biopsies were obtained from every 2 cm of neosquamous epithelium, starting 10 mm above the neo-squamocolumnar junction (neo-SCJ), encompassing the entire length of the baseline BE. In addition the gastric cardia was sampled by obtaining 4 random biopsies immediately distal (<5 mm) to the neo-SCJ (Figure 1C). Subsequent follow-up endoscopies were scheduled 6 and 12 months after the last treatment session, and annually thereafter.

Esomeprazole 40 mg twice a day was prescribed as a maintenance drug during the treatment and follow-up phase. Additionally, ranitidine 300 mg at bedtime and 5 ml sucralfate suspension (200 mg/ml) 4 times a day were prescribed for a period of 2 weeks after each endoscopic treatment procedure.

Figure 1. Retrograde view of a normal appearing neo-squamocolumnar junction after earlier RFA. In 1 of 4 biopsies focal IM was detected. (A) White-light; (B) Narrow-band imaging; (C) Directly after obtaining gastric cardia follow-up biopsies.

FIVE-YEAR FOLLOW-UP VISIT AS PART OF THIS STUDY Detailed endoscopic inspection of the esophagus was performed with HRE and NBI, with specific attention paid to the appearance of the neo-SCJ. Per-protocol biopsy sampling of neosquamous epithelium and gastric cardia was performed using a standard or Radial Jaw-4 2.8-mm forceps (Boston Scientific Corp, Natick, MA). A random en-bloc endoscopic resection specimen from neosquamous epithelium (>10 mm above the
neo-SCJ) was obtained using the multiband mucosectomy technique for adequate detection of buried Barrett’s glands. Documented still images of preceding endoscopies were used to determine the extent of the original Barrett segment, and to select a neosquamous epithelium site that was separate from any baseline/escape endoscopic resection. Subsequently all patients underwent EUS using electronic radial endoscopes (GF-UE160; Olympus GmbH, Hamburg, Germany) in conjunction with an Aloka Alpha-10 ProSound processor (Aloka, Meerbusch, Germany), if necessary, completed by fine-needle aspiration, to exclude any abnormal regional lymph nodes, subsquamous growth or invasive growth of recurrent neoplasia.

OUTCOMES  Primary outcome parameters were sustained complete histological remission of HGIN/early-stage cancer (CR-neoplasia) and sustained complete histological remission of IM (CR-IM).

Secondary outcome parameters were presence of IM in biopsies obtained <5mm distal to neo-SCJ (gastric cardia); presence of buried Barrett’s glands in neosquamous epithelium biopsies/endoscopic resection specimens; and presence of abnormalities on EUS.

HISTOPATHOLOGICAL EVALUATION  All biopsy and endoscopic resection specimens obtained during follow-up and at the 5-year visit were routinely processed and reviewed by an expert gastrointestinal pathologist. In case of IM, neoplasia or buried Barrett’s glands, biopsies were reviewed by 2 expert GI pathologists. Four-quadrant biopsies from one level were fixed in formalin in one jar, resulting in one paraffin-embedded block per level, cut into 5-μm-thick sections and routinely stained with H&E. Endoscopic resection specimens were sectioned in 2-mm slices, embedded in paraffin, and a minimum of 4 serial cuts per slice were mounted on glass slides for standard H&E staining.

Biopsies and endoscopic resection specimens were assessed for the presence of IM at or below the surface (buried Barrett’s glands), and grade of dysplasia according to the Vienna classification. Endoscopic resection specimens were evaluated for depth, defined as the deepest layer of tissue present in each specimen: epithelium, lamina propria, muscularis mucosa, or submucosa. We did not systematically review the depth of biopsies, as this was performed in a previous study by our group.

ETHICS AND STATISTICAL ANALYSIS  The initial study protocols and the study extension for the 5-year visit were approved by the medical ethics committee of the AMC (NTR2938, http://www.trialregister.nl/). Renewed written informed consent was obtained from patients who participated in the study extension. All authors had access to the study data and approved the final version of the manuscript. Data were analyzed using the IBM SPSS 19.0.0.1 statistical software package (SPSS Inc., Chicago, IL). Mean (±SD) was used in case of a normal distribution of variables and median (interquartile range, 25%-75%) was used for variables with a skewed distribution. To assess the durability of CR-neoplasia and CR-IM, survival analysis using Kaplan-Meier estimation was performed.
PATIENT CHARACTERISTICS AND INITIAL TREATMENT  Fifty-five patients (45 men) with a mean age of 65 years (±9.6 years) were included, with a median BE length of C4M5 cm (IQR, 1-7 to M4-8). Forty patients (72%) underwent endoscopic resection of visible abnormalities before the first RFA treatment. After RFA treatment, CR-neoplasia/CR-IM was achieved in 54 of 55 (98%) patients. One patient underwent surgery for persisting HGIN, as scarring after previous endoscopic resection treatment made it impossible to perform escape endoscopic resection, and this patient was excluded from further analysis in this study. Therefore, 54 patients entered the follow-up protocol.

SUSTAINED COMPLETE REMISSION OF NEOPLASIA AND IM

Overall cohort  Median follow-up (FU) from first treatment session until last follow-up endoscopy of all 54 patients was 61 months (IQR, 53-65 months; range, 16-86 months), with a median of 6 endoscopies (IQR, 5-6 endoscopies). Eight patients discontinued follow-up because of unrelated death (cardiac cause n=3, pancreatic cancer, bowel ischemia), comorbidity (prostate cancer, cerebrovascular disease), or emigration. Median follow-up of these 8 patients was 36 months (IQR, 26-46 months; range, 16-54 months); all were CR-neoplasia/CR-IM at their last endoscopy. Figure 2 details the flow and accountability of patients throughout the study period.

Figure 2. Flow diagram of patients progressing through the treatment and follow-up phase of the trial.
Overall, of 54 patients who initially reached CR-neoplasia and CR-IM after treatment, 51 patients (94%; 95% CI: 84.9-98.1) demonstrated sustained CR-neoplasia and CR-IM during follow-up. In 3 patients, abnormalities were observed at HRE. In a 71-year-old patient with baseline C7M7 BE with early-stage cancer and multifocal HGIN, a small area with columnar mucosa with LGIN was discovered at the 5-year visit. At previous endoscopies, the same area was seen and interpreted as reflux esophagitis, located close to the scar of a previous endoscopic resection. After diagnostic biopsy, the area was not rediscovered at subsequent endoscopy, however, prophylactic argon plasma coagulation was applied at the previously affected area. Eighteen months after argon plasma coagulation, no endoscopic or histological evidence of residual BE was found. In an 81-year-old patient with baseline C2M4 BE with early-stage cancer and residual BE with HGIN, a lesion containing carcinoma was observed during the fifth endoscopy at 52 months in his referral center. During workup at our site, a 6-mm lesion was seen and radically removed en-bloc by endoscopic resection-cap technique. Histological evaluation showed a radically resected mucosal cancer without evidence of lymph-vascular invasion. No endoscopic or histological evidence of neoplasia or IM was found at 3 and 9 months after endoscopic resection. Finally, a 62-year-old patient with baseline C0M2 BE with early-stage cancer and HGIN, underwent 5 follow-up endoscopies without endoscopic or histological signs of recurrence of neoplasia or IM. At the 5-year visit, an elevated Barrett’s island containing carcinoma was discovered 2 cm above the neo-SCJ (Figure 3). EUS did not show any signs of subsquamous growth and the lesion was radically removed en bloc by endoscopic resection-cap technique. Histological evaluation showed a radically resected mucosal cancer without evidence of lymph-vascular invasion.

Figure 3. Endoscopic resection for recurrent mucosal (T1m2) carcinoma at 5-year follow-up. (A)/(B) Detection of an elevated Barrett’s island 2cm above the neo-SCJ, on white-light and NBI. (C) Delineation and (D), (E) resection of the lesion. (F) Neo-SCJ, without visible residual BE or abnormalities 3 months after endoscopic resection.
Three months after endoscopic resection, no endoscopic or histological evidence of neoplasia or IM was found. Figure 4 shows the recurrence-free survival curve of the entire cohort of 54 patients since complete remission of neoplasia and IM was established. In this analysis, all patients who discontinued follow-up were censored from the date of their last follow-up endoscopy. Ninety percent of patients remained free of neoplasia 5 years after initial CR-neoplasia and CR-IM.

5-year follow-up cohort In total, 46 patients were followed for at least 5 years. Forty patients underwent a dedicated 5-year visit at our center, 6 patients did not give informed consent and underwent scheduled standard endoscopic follow-up at their referral center; all were CR-neoplasia and CR-IM at last endoscopy. All 46 patients were followed for a median of 62 (IQR, 57-67) months, with 6 (IQR 5-6) endoscopies. In this cohort of patients, sustained CR-neoplasia and CR-IM were maintained in 43 of 46 patients (93%; 95% CI: 82.5-97.8).

PRESENCE OF IM IN GASTRIC CARDIA BIOPSIES Gastric cardia biopsies were obtained at a median of 5 (IQR 5-6) follow-up endoscopies, with a median of 20 (IQR 15-26) biopsies per patient. In 19 of 54 patients (35%, 95% CI: 23.8-48.5), focal IM was found in gastric cardia biopsies obtained during any follow-up endoscopy. In 17 of 19 patients (89%), this finding was not reproduced at subsequent endoscopies (median, 2; IQR 1-4), median follow-up 25 (IQR, 12-47) months, and median of 8 (IQR, 4-12) cardia biopsies). Focal IM in the cardia was diagnosed on 2 separate occasions in only 2 patients. All patients with focal IM of the cardia had a normal endoscopic appearance of the neo-SCJ (Figure 1), and none of these patients underwent retreatment. In total, 53 of 1,143 (4.6%, 95% CI: 3.6-6.0) gastric cardia biopsies obtained during follow-up were found positive for focal IM.
Figure 5. Proportion of patients (%) with focal intestinal metaplasia (IM) of the gastric cardia at each follow-up, in relation to the number of patients visiting. There is no increased incidence observed over time. Of 19 patients with focal IM, this finding was not reproduced during subsequent endoscopies in 89% of cases.

Figure 5 shows the proportion of patients with focal IM in relation to the number of patients visiting at each follow-up time point. No increase in the incidence of IM in the cardia was observed over time.

At 5-year follow-up, a total of 178 random cardia biopsies were obtained in 44 of 46 patients (median, 4 biopsies). In 2 patients, the cardia was not biopsied due to simultaneous use of coumarines hampering extensive sampling. Focal IM was found in 3 of 44 patients (6.8%, 95% CI: 2.4-18.2), in only 1 biopsy each.

**Presence of Buried Barrett’s Glands** During the entire follow-up period, biopsies from neosquamous epithelium were obtained at a median of 6 (IQR, 5-6) follow-up endoscopies, with a median of 53 (IQR, 33-91) biopsies per patient, with a total of 3,543 biopsies obtained. Overall, buried Barrett’s glands were detected in 3 patients, in 3 of 3,543 biopsies (0.08%, 95% CI: 0.03-0.2); 2 biopsies had been obtained from small islands of columnar epithelium, 1 biopsy had been obtained just above the neo-SCJ. In none of the 3 patients were buried glands detected at subsequent endoscopies (median, 4 endoscopies; IQR, 2-6; median, 57 neosquamous epithelium biopsies; IQR, 34-101).

At 5-year follow-up, a median of 8 (IQR, 4-14) neosquamous epithelium biopsies was obtained per patient, and in 30 patients endoscopic resection of neosquamous epithelium was performed. Ten patients were considered not to be eligible for endoscopic resection, due to an original BE length <2cm (n=5), coumarine use (n=2), or recurrent disease which required treatment (n=3), and 6 patients did not give informed consent. No evidence of buried Barrett’s glands was detected in any of the 475 biopsies or the 30 endoscopic resection specimens, all endoscopic resection specimens contained at least lamina propria depth or deeper.
PRESENCE OF ABNORMALITIES ON EUS  In 40 patients who underwent EUS, this was negative for lymphadenopathy or esophageal-wall abnormalities. In 1 patient, fine-needle aspiration of an 8-mm, oval-shaped local lymph node was performed and malignancy was excluded.

DISCUSSION

In this prospective cohort of patients who reached complete remission of neoplasia and IM after endoscopic resection/RFA, sustained remission was observed in 93% of 46 patients (95% CI: 82.5-97.8) who were followed for at least 5 years. Overall, sustained remission was demonstrated in 94% of 54 patients (95% CI: 84.9-98.1) during a median follow-up of 5 years. All recurrences of neoplasia observed during this trial were detected at an early stage during endoscopic follow-up and could be managed endoscopically; all 3 patients were in complete remission for neoplasia and IM after a median of 9 months' follow-up. The Kaplan-Meier analysis also demonstrates a recurrence-free proportion of 90% of patients after 5 years of follow-up, considering the 3 patients with recurrent neoplasia as a failure for disease-free survival, even though complete remission of neoplasia was re-established after endoscopic treatment. The favorable long-term results of this study add to the evidence that RFA treatment, preceded by endoscopic resection for visible lesions, should be preferred over surgical resection for patients with BE containing HGIN and/or early-stage cancer. It does demonstrate, however, that long-term follow-up is required for these patients, because both cancer recurrences occurred after almost 5 years of follow-up. This study also demonstrates how small and subtle recurrences can be. In these cases, recurrent disease was most likely related to the multifocal diffuse HGIN as present before RFA. In such cases, even a minimal area of residual Barrett's might be at risk for malignant progression, and this emphasizes the importance of a dedicated treatment protocol and careful endoscopic inspection to ensure complete eradication of all Barrett's epithelium.

In our single-center study, patients were followed for 5 years according to a rigorous and unique follow-up protocol. All patients underwent HRE with NBI at predefined time points, and random biopsies were obtained from both neosquamous epithelium and gastric cardia, with a large amount of samples obtained. In order to optimize tissue sampling for detection of buried Barrett’s glands, an additional endoscopic resection specimen of neosquamous epithelium was obtained. EUS was scheduled in all patients to exclude extra-esophageal or intramural disease at 5-year follow-up. Other strengths of our study include accurate and complete accounting for all patients, with no cases lost to follow-up. Limitations of this study are that all patients were treated at a tertiary academic referral center with extensive expertise in the management of Barrett’s neoplasia. Therefore, the high reported sustained remission rate of neoplasia cannot automatically be extrapolated to general practice. In our opinion, however, it is imperative to centralize endoscopic management of patients with neoplastic BE in centers with multidisciplinary experience in this field (i.e. experience in endoscopic detection and treatment, adequate case-volume, expert gastrointestinal pathology, access to esophageal surgery), to ensure optimal treatment and follow-up.
The present study reports the longest duration of follow-up of patients undergoing RFA for BE containing HGIN and/or early-stage cancer and, therefore, has significant implications for management of patients with neoplastic BE. Our data also add to a number of publications assessing the durability of neosquamous epithelium after RFA for BE. Shaheen et al recently reported the 2 and 3-year results of the AIM Dysplasia Trial, for patients with LGIN or HGIN.\textsuperscript{17} Patients were randomized to RFA or sham treatment followed by endoscopic surveillance, and patients initially randomized to the sham group were offered cross over to RFA after 1 year. This study demonstrated CR-neoplasia in 95% and CR-IM in 93% of 106 available patients at 2-year follow-up, allowing interim focal touch-up RFA treatment. After 3 years, CR-neoplasia was demonstrated in 98% and CR-IM in 91% of 56 available patients undergoing the 3-year biopsy visit. Fleischer et al reported 5-year results of RFA for non-dysplastic BE.\textsuperscript{10} After demonstrating CR-IM in 98% of 61 patients at 2.5-year follow-up, the trial extension demonstrated CR-IM in 92% of 50 evaluable patients at 5-year follow-up, not allowing for any touch-up therapy. In general, the present data comport well with these 2 recent studies, reporting high sustained remission rates of neoplasia and IM.

In our study none of the recurrences of neoplasia occurred at the neo-SCJ, after complete eradication of BE. This is remarkable, given that previous studies have reported that recurrent neoplasia generally develops in the cardia.\textsuperscript{14, 21-23} To minimize the risk of these recurrences, we have strived to optimize treatment of the gastric cardia. An important difference with RFA studies from the United States is that we incorporated circumferential HALO$^{90}$ treatment of the neo-SCJ during all focal RFA sessions in our treatment protocols. HALO$^{360}$ ablation at this level is often insufficient due to poor contact between the electrode and the mucosa.\textsuperscript{9, 10, 16}

To assess if all Barrett’s mucosa has been eradicated effectively, biopsies obtained immediately distal to the neo-SCJ were used as an objective endpoint, as endoscopic differentiation between gastric mucosa and IM is nearly impossible.\textsuperscript{24} Given the increased risk of recurrences at this level, this area was biopsied intensively during follow-up. With a median of 20 gastric cardia biopsies per patient, the downside of this approach is that this might have led to detection and overestimation of non-dysplastic IM in a normal appearing neo-SCJ. The question is whether in patients with an initial diagnosis of neoplastic BE, detection of IM in this area reflects insufficient treatment, recurrence of disease, or an irrelevant normal finding. In our study, IM of the cardia was mostly observed in a single biopsy, this diagnosis was generally not reproduced during further follow-up, and there was no increased incidence over time. If IM of the cardia would reflect residual disease, one would expect to find IM more than once in a single patient. If IM of the cardia results from ongoing reflux after treatment, we would expect an increased incidence over time. It should be noted that all patients in this study received high-dose maintenance therapy with esomeprazole 40 mg twice a day. Studies have shown that IM of the cardia can be detected in biopsies of 25% of the normal population and this is generally not considered a premalignant condition.\textsuperscript{25-27} These studies generally obtained <4 biopsies at a single time point and, in our study, patients had a median of 20 biopsies taken during a 5-year period. The clinical relevance of focal IM of the cardia after RFA is therefore unknown, but our long-term data do not suggest that this is related to residual BE or recurrent disease.

After RFA treatment, there is a generally held fear that occult, buried Barrett’s glands underneath neosquamous epithelium can remain endoscopically invisible
while progressing to an advanced malignant stage. The presence of buried glands has been reported in up to half of patients treated with argon-plasma coagulation or photodynamic therapy. This is in contrast with the low rate of buried glands found post-RFA. In our study we did not find buried glands in any of the endoscopic resection specimens, and we found buried glands in only 3 neosquamous epithelium biopsies (n=3, 0.08% of biopsies). In retrospect, 2 biopsies were obtained from visible islands of columnar epithelium. A third biopsy was obtained just above the neo-SCJ. Autopsy studies have described a 4 to 8-mm overlap of squamous and cardiac mucosa at the squamocolumnar junction. Biopsies obtained close to the junction or accidental sampling of residual Barrett’s mucosa can lead to a false-positive histological diagnosis of buried glands, as was demonstrated previously. In addition, studies have shown that neosquamous biopsies post-RFA are of adequate depth to evaluate the presence of buried Barrett’s glands. Biopsy depth of treated and untreated squamous epithelium is similar, as the lamina propria is sampled in one third of biopsies regardless of epithelial type. Because this study and others demonstrate that the presence of buried glands in normal-appearing neosquamous epithelium after RFA is rare, one might question the need to obtain extensive biopsies from neosquamous mucosa during follow-up. We hypothesize that it is sufficient to perform high-resolution endoscopy with NBI, or comparable techniques, to enable careful inspection of the neo-SCJ and neosquamous mucosa. We believe that biopsies should be obtained immediately distal to the neo-SCJ, as this remains an area at risk, and endoscopy cannot reliably distinguish gastric mucosa from BE. As far as the neosquamous mucosa is concerned, it can be sufficient to obtain targeted biopsies only, in case of visible lesions or of areas of residual columnar mucosa upon meticulous endoscopic inspection.

CONCLUSION

This is the first prospective and systematic long-term follow-up study after RFA for patients with early neoplasia in BE, with or without prior endoscopic resection for focal lesions. Kaplan-Meier survival analysis demonstrates sustained remission of neoplasia and IM in 90% of patients after 5 years, without esophageal cancer-related mortality. Three cases of recurrent disease were all detected at an early stage and managed by endoscopic therapy. The favorable long-term outcomes validate this treatment approach as a safe and effective alternative to esophagectomy. Continued endoscopic surveillance with HRE and NBI remains necessary after treatment, combined with gastric cardia biopsies and targeted biopsies of subtle visible abnormalities in neosquamous epithelium. Extensive tissue sampling after RFA will lead to the occasional detection of focal IM of the cardia, which has a questionable clinical relevance. Biopsies and endoscopic resection specimens from neosquamous epithelium post-RFA rarely show buried Barrett’s glands, especially if biopsying residual BE islands or close to the SCJ is avoided. Additional follow-up studies are necessary to determine if endoscopic surveillance can be performed at longer time-intervals, or even omitted in certain patients.