ORIGINAL ARTICLE

Multimodality endoscopic eradication for neoplastic Barrett oesophagus: results of an European multicentre study (EURO-II)

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ABSTRACT

Objective Focal endoscopic resection (ER) followed by radiofrequency ablation (RFA) safely and effectively eradicates Barrett's oesophagus (BO) containing high-grade dysplasia (HGD) and/or early cancer (EC) in smaller studies with limited follow-up. Herein, we report long-term outcomes of combined ER and RFA for BO (HGD and/or EC) from a single-arm multicentre interventional study.

Design In 13 European centres, patients with BO≤12 cm with HGD and/or EC on 2 separate endoscopies were eligible for inclusion. Visible lesions (<2 cm length; <50% circumference) were removed with ER, followed by serial RFA every 3 months (max 5 sessions). Follow-up endoscopy was scheduled at 6 months after the first negative post-treatment endoscopic control and annually thereafter. Outcomes: complete eradication of neoplasia (CE-neo) and intestinal metaplasia (CE-IM); durability of CE-neo and CE-IM (once achieved) during follow-up. Biopsy and resection specimens underwent centralised pathology review.

Results 132 patients with median BO length C3M6 were included. After entry-ER in 119 patients (90%) and a median of 3 RFA (IQR 3–4) treatments, CE-neo was achieved in 121/132 (92%) and CE-IM in 115/132 patients (87%), per intention-to-treat analysis. Per-protocol analysis, CE-neo and CE-IM were achieved in 98% and 93%, respectively. After a median of 27 months following the first negative post-treatment endoscopic control, neoplasia and IM recurred in 4% and 8%, respectively. Mild-to-moderate adverse events occurred in 25 patients (19%); all managed conservatively or endoscopically.

Conclusions In patients with early Barrett's neoplasia, intensive multimodality endotherapy consisting of ER combined with RFA is safe and highly effective, and the treatment effect appears to be durable during mid-term follow-up.

Trial registration number NTR 1211, http://www.trialregister.nl.

Significance of this study

What is already known on this subject?

- In single-centre studies, the combined use of endoscopic resection (ER) and radiofrequency ablation (RFA) is shown to be safe and effective for eradication of early Barrett's neoplasia, but multicentre studies with longer follow-up have not yet been reported.

What are the new findings?

- In this multicentre study conducted at expert centres, focal ER followed by RFA is safe and highly effective for eradication of early Barrett's neoplasia as well as complete removal of the entire Barrett's segment (success rates approximate 90%).
- During a median follow-up of 27 months, recurrence of neoplasia or visible Barrett's mucosa was rare (<10%).

How might it impact on clinical practice in the foreseeable future?

- The combined endoscopic approach of focal ER followed by RFA should be the preferred management strategy for patients with early Barrett's neoplasia in centres specialised in these techniques.
- In trained endoscopists a high procedural success of this combination therapy can be achieved.

INTRODUCTION

Barrett's oesophagus (BO) is an important risk factor for the development of oesophageal adenocarcinoma, a cancer with a markedly rising incidence in the Western world.[1] Malignant degeneration of BO is typically stepwise and gradual: from non-dysplastic intestinal metaplasia (IM), to low-grade dysplasia (LGD), high-grade dysplasia (HGD) and eventually invasive cancer.[2 3] Patients with BO containing HGD and/or early cancer (EC) may be treated by endoscopic means, given their low risk of local lymph node involvement, whereas patients with more advanced cancers (invading the submucosa >500 µ; ≥T1sm1) should be offered surgery.[4–9]

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Endoscopic therapy consists of endoscopic resection (ER) of visible lesions providing histological assessment and ablation of any residual BO regardless of dysplasia grade.[7 10 11] This combined approach has been shown to be superior to stepwise complete ER of the entire Barrett mucosa (neoplastic and non-neoplastic) in a recent randomised trial with regards to complications while achieving similar procedural success.[12]

The combined use of ER and radiofrequency ablation (RFA) for treatment of mucosal abnormalities and EC has also been studied by other groups, yet these studies are limited by either patient numbers, single-centre setting, retrospective design and/or relatively short duration of follow-up.[13–19] The aim of this prospective international multicentre study was to evaluate whether the procedural success of RFA combined with *limited* ER for visible abnormalities reported in our previous trials can be confirmed in a multicentre setting, and to report long-term treatment outcomes of this approach.

MATERIALS AND METHODS

Study setting

The study was planned as a quasiexperimental, single-arm, interventional trial. Patients were included between September 2007 and February 2010 at 13 European centres having a tertiary referral function for the endoscopic management of early Barrett's neoplasia. To ensure standardisation of the RFA technique, the principal investigator (PI) of each centre received hands-on training at the coordinating study site (Academic Medical Centre (AMC), Amsterdam, the Netherlands), and the first three to four RFA procedures were supervised on-site by the principal investigator of this study (JJGHMB). To ensure protocol compliance and high-quality data, a study coordinator from AMC attended all RFA procedures and the first follow-up visit for each patient.

Patient selection

Patients were eligible if they were 18–85 years of age, had a BO segment measuring 2–12 cm, histological confirmation of HGD and/or EC on two separate endoscopies <6 months prior to inclusion, and no signs of metastatic disease on endoscopic ultrasound and CT (required only in case of EC). Any visible abnormality was removed by ER, prior to initial RFA. Visible abnormalities were defined as any mucosal irregularity or discolouration within the BO. Based on prior experiences,[15] the maximum extent of ER was limited to 2 cm in length and 50% of the circumference. Patients were excluded if the ER specimen showed cancer at the vertical (deep) resection margin, invasion >T1sm1, poorly differentiated or undifferentiated cancer, or lymphatic or vascular invasion. In addition, oesophageal stenosis preventing passage of a therapeutic endoscope, persistent visible lesions or cancer in biopsies obtained during two mandatory mapping endoscopies performed after ER and pre-RFA, were exclusion criteria. No monitoring of completeness of inclusion of eligible patients was available.

Treatment and follow-up protocol

At baseline, all visible abnormalities (<2 cm, <50% of circumference) were removed by a single ER for histological staging. ER was performed using the ER-cap technique (Olympus, Hamburg, Germany), multiband mucosectomy (Duette, Cook Endoscopy, Limerick, Ireland) or Euroligator (Mandel+Rupp, Erkrath, Germany). After two mapping endoscopies and at least 6 weeks after ER, the first RFA treatment was performed using either the HALO^{360} system for circumferential ablation, or the HALO^{90} system for focal ablation, as described in detail previously.[13–15] The neosquamocolumnar junction (neo-SCJ) at the upper end of the gastric folds was treated circumferentially with HALO^{90} ablation at every focal RFA session. RFA treatment was performed every 3 months until visible clearance of BO was achieved, with a maximum of two circumferential and three focal ablations. ER was performed for any visible lesions detected at any scheduled RFA session. Any residual BO persisting after the maximum number of RFA sessions was removed in a single 'escape' ER session (for areas >5 mm), treated with a maximum of two argon plasma coagulation (APC) sessions in case of areas <5 mm, or kept under endoscopic surveillance, at the discretion of the investigator. Escape treatment was performed in immediate conjunction to the RFA-treatment phase using the same 3-month intervals; as per study definition it was not allowed during follow-up. Therapeutic sessions were scheduled at 3-month intervals until visible clearance of all Barrett's mucosa had been achieved. At that time four-quadrant biopsies for histological correlation were obtained immediately distal (<5 mm) to the neo-SCJ (gastric cardia) and from every 2 cm encompassing the original extent of the BO segment (neosquamous epithelium). If histological eradication of all IM was confirmed the treatment phase was considered to be completed and the patient then entered the follow-up phase with endoscopic follow-up at 6 months and annually thereafter. Any recurrent HGD/EC diagnosed during follow-up required central pathology review and was treated according to the discretion of the local principal investigator. No treatment was allowed for recurrent BO without HGD/EC during follow-up.

During the entire study period, all patients were prescribed high-dose proton-pump inhibitor therapy twice daily, supplemented with a H2-receptor antagonist at bedtime and sucralfate suspension after every meal for 2 weeks after each therapeutic endoscopy.

Outcome parameters

Primary outcome parameters:

- Complete eradication of neoplasia (CE-neo), defined as absence of HGD and EC in all biopsies obtained at the first endoscopy with complete endoscopic clearance of BO or from residual BO after the maximum number of endoscopic treatment sessions had been performed. Complete eradication of IM (CE-IM), defined as absence of IM, in all oesophageal biopsies obtained at the first endoscopy with complete endoscopic clearance of BO.

Patients were considered as a failure for CE-neo if (A) residual BO persisted after completing the treatment protocol, including—when necessary—a single escape ER or a maximum of two escape APC treatments (for diminutive islands only), and (B) this residual BO contained either HGD or EC.

Patients were considered as a failure for CE-IM if (A) residual BO persisted after completing the treatment protocol, including—when necessary—a single escape ER or a maximum of two escape APC treatments (for diminutive islands only) and (B) this residual BO contained IM.

Secondary outcome parameters:

- Durability of eradication of neoplasia and IM during follow-up, with follow-up defined as the interval between the first negative control endoscopy with biopsy and the last follow-up endoscopy.
- Adverse events, defined as 'acute' (during procedure), 'early' (0–48 h) and 'late' (>48 h). Adverse events were graded as 'mild' (unplanned hospital admission, hospitalisation <3 days, haemoglobin drop <3 g, no transfusion), 'moderate' (4–10 days hospitalisation, <4 units blood transfusion,

repeat endoscopic intervention, radiological intervention), 'severe' (hospitalisation >10 days, intensive care unit (ICU) admission, need for surgery, >4 units blood transfusion, in the case of stenosis: >5 dilatations, stent placement or incision therapy) or 'fatal' (death attributable to procedure <30 days or longer with continuous hospitalisation).[20 21]

Histological analysis

At each study site, histological evaluation was performed by a local expert pathologist, followed by central expert pathology review of all ER specimens, pre-RFA workup biopsies, and biopsies from the first follow-up endoscopy. In case of discrepancies between local and central expert interpretations, review by a third central expert pathologist was performed to reach consensus. ER specimens were evaluated for neoplasia according to the WHO classification,[22] tumour infiltration depth, differentiation grade, presence of lymphatic or vascular invasion and completeness of resection at the vertical (deep) margin. Biopsies were evaluated for presence of IM and neoplasia, as well as the presence of buried Barrett's glands in those biopsies from neosquamous mucosa. Cases of post-treatment biopsies locally read as HGD or EC required confirmation by central pathology review.

Statistical analysis

Statistical analysis was performed with the IBM SPSS 20.0 statistical software package (SPSS, Chicago, USA). Mean (±SD) was used in case of a normal distribution of variables and median (IQR 25–75%) was used for variables with a skewed distribution. To assess the durability of CE-neo and CE-IM, survival analysis using Kaplan-Meier estimation was performed. Patients who discontinued follow-up due to unrelated death or comorbidity were censored at the date of their last follow-up endoscopy.

RESULTS

Patients

In 132 included patients endoscopic therapy was pursued, table 1 shows the baseline characteristics of these patients. ER was performed in 119 patients (90%). Figure 1 details the flow of patients throughout the study.

Table 1 Baseline characteristics of included patients*

	n=132
Male: Female	107:25
Mean age—years (±SD)	65±14
Median BO length—cm (IQR)	C3M6 (C1–7, M4–9)
ER prior to RFA	119 (90%)
ER technique	
ER-cap technique	52 (44%)
Ligate-and-cut technique	67 (56%)
Resection	
En bloc resection	63 (53%)
Piecemeal resection	56 (47%)
Median nr resected pieces (IQR)	2 (2–4)
Worst histology ER-specimens	
Non-dysplastic IM	3
Low-grade dysplasia	7
High-grade dysplasia	31
Mucosal cancer	76
Submucosal cancer	2
Worst histology post-ER/pre-RFA biopsies	
Non-dysplastic IM	51
Low-grade dysplasia	45
High-grade dysplasia	36

*All of the included patients had had high-grade dysplasia and/or cancer on at least two occasions before inclusion.
BO, Barrett's oesophagus; ER, endoscopic resection; IM, intestinal metaplasia; nr, number; RFA, radiofrequency ablation.

Primary and secondary outcomes

CE-neo and IM

Treatment was discontinued in 8 of 132 patients (6%) after a median of two (IQR 1–4) RFA sessions, for reasons including: non-oesophageal tumour detected (n=3); withdrawal of consent (n=3); or lost to follow-up (n=2). Of these, two patients had follow-up at 13 months and 18 months, respectively, with no neoplastic progression, while the remaining six had no follow-up. By intention-to-treat analysis (considering all eight patients who discontinued treatment as failures), CE-neo and IM was achieved in 121/132 (92%, 95% CI 83% to 93%) and 115/132 (87%, 95% CI 80% to 92%) patients, respectively. By per-protocol (PP) analysis (censoring for unrelated dropouts instead of considering them as failures), CE-neo and CE-IM were reached in 121/124 (98%, 95% CI 93% to 99%) and 115/124 (93%, 95% CI 87% to 96%) patients, respectively. The 121 patients with CE-neo constituted the CE-neo follow-up group; the 115 patients with CE-IM constituted the CE-IM follow-up group (the CE-neo follow-up group included 6 cases with complete neoplasia eradication but incomplete Barrett's oesophagus (BO) ablation).

Patients underwent a median of one (IQR 1–2) circumferential and two (IQR 2–3) focal RFA sessions. In six patients, ER was performed for visible lesions detected at one of the RFA sessions during the treatment phase. Of these, one patient was noted to have submucosal cancer (T1sm1G2), and underwent oesophagectomy (16 lymph nodes negative for metastasis, 12 months disease free FU).

After completing the maximum allowed number of RFA sessions, per-protocol escape therapy (ER for residual BO>5 mm and APC for residual BO<5 mm) for removal of small areas of residual Barrett's mucosa was performed in 24 patients (18%): 9 patients underwent escape-ER (for residual BO>5 mm), and of these, one patient was noted to have a submucosal cancer (T1sm1G1). This patient was considered unfit for surgery and underwent additional endoscopic treatment (see treatment failures below). The remaining 15 patients received APC for diminutive (<5 mm) residual BO islands. The median total number of treatment sessions (baseline ER, RFA, escape) for the entire cohort was four (IQR 4–5). The median treatment time (including any escape treatment was 12 months (IQR 9–19 months).

CE-neo failed in three patients. One patient (baseline C7M9 with HGD) underwent ER of a visible lesion after the fourth ablation session, which showed a submucosal cancer (T1sm1G2). This patient underwent surgery as mentioned above. Two other patients (baseline C6M7 with HGD and C10M10 with EC) had residual neoplastic BO after the maximum of five RFA sessions and escape treatment. Both patients were considered unfit for surgery, and underwent additional endoscopic treatment until CE-neo was achieved. Complete eradication of IM after RFA and per-protocol escape therapy failed in nine patients: three aforementioned CE-neo failures, three patients who had little or no conversion to squamous mucosa and three patients who required additional off-protocol endoscopic treatment after completing the maximum number of treatment sessions.

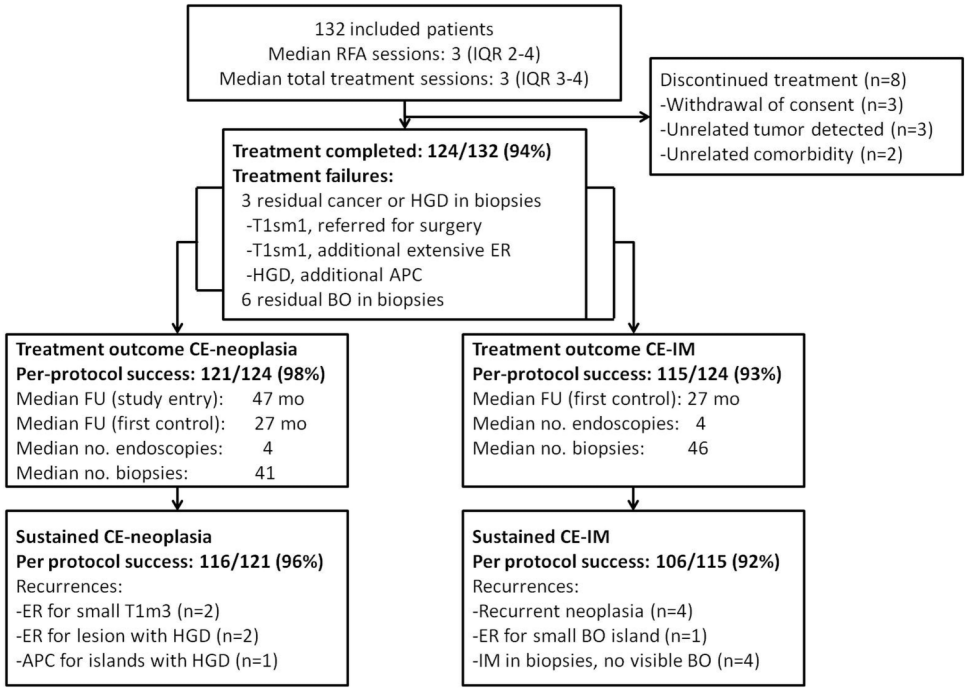


Figure 1 Treatment and outcomes. APC, argon plasma coagulation; BO, Barrett's oesophagus; CE, complete eradication; ER, endoscopic resection; FU, follow-up; HGD, high-grade dysplasia; IM, intestinal metaplasia; RFA, radiofrequency ablation.

Durability of response during follow-up

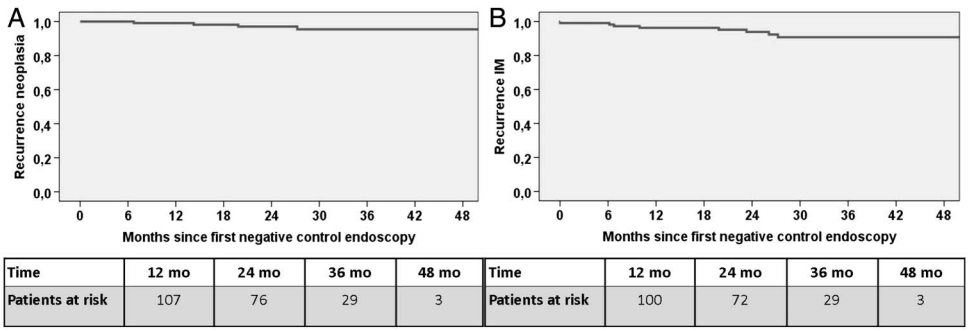
Figure 2A shows the cumulative rate of recurrence of neoplasia during a median of 27 months (IQR 20–35 months) of follow-up since the first negative control endoscopy of the 121 patients who achieved CE-neo after treatment. Patients underwent a median of 4 endoscopies (IQR 3–5), with a median of 41 biopsies (IQR 25–60).

At 36 months (reached by 25% of patients in follow-up) 95% of patients remained free of neoplasia. In five patients (4%) recurrence of HGD/mucosal cancer was observed, which was successfully treated endoscopically to CE-neo. Of the 121 patients who entered follow-up after CE-neo was established, CE-neo was maintained in 116 patients (96%, 95% CI 90% to 98%).

Figure 2B shows the cumulative rate of recurrence of IM during a median of 27 months (IQR 20–36 months) since the first negative control endoscopy of the 115 patients who achieved CE-IM after treatment. At 24 months (reached by 60% of patients in follow-up) 90% of patients remained free of IM. Four patients were treated for recurrent neoplasia (see above), five patients with recurrent IM in biopsies were treated with ER for a BO island (n=1), or kept under surveillance because there was no BO visible on endoscopy (n=4). Of the 115 patients who entered follow-up after CE-IM was established, CE-IM was maintained in 106 patients (92%, 95% CI 86% to 96%).

During follow-up non-neoplastic focal IM was diagnosed in biopsies from a normal appearing neo-SCJ in 28 of 115 patients (24%, 95% CI 17% to 33%). In 24 of these patients (86%), this was detected at a single FU-endoscopy, and could not be reproduced during subsequent FU (median 4 FU endoscopies, median 14 biopsies). In four patients focal IM was found twice during follow-up, no patient required re-treatment. No increase in the incidence of focal IM in the cardia was observed over time.

Buried glands were detected in 1 of 115 patients (1%, 95% CI 0% to 5%), in 1 of 4174 neosquamous biopsies obtained



Time	12 mo	24 mo	36 mo	48 mo
Patients at risk	107	76	29	3

Time	12 mo	24 mo	36 mo	48 mo
Patients at risk	100	72	29	3

Figure 2 Kaplan-Meier curves representing the estimated 48 months cumulative incidence rates of recurrence of neoplasia, after complete eradication of neoplasia is established in 122 patients (A); and of recurrence of intestinal metaplasia (IM), after complete eradication of intestinal metaplasia is established in 115 patients (B). Any recurrence was considered a failure for recurrence-free survival, even though complete eradication was re-established after endoscopic treatment.

during follow-up. This patient was initially treated successfully for C4M5 BO with HGD. After repeated detailed endoscopic inspection with narrow-band imaging no visible Barrett's mucosa was seen, however in a biopsy from the same area buried glands were confirmed again. The whole circumferential extent of the original BO was therefore treated once again with the HALO^{360}-device (2×12 J/cm^2). During subsequent 54 months follow-up, with 3 ER specimens obtained at 3 separate endoscopies from the healed area and 55 neosquamous biopsies, no buried glands were detected.

Adverse events

No clinically relevant complications occurred in relation to any of the ER procedures. Adverse events related to RFA are summarised in table 2.

DISCUSSION

This is the largest prospective multicentre study to date on ER followed by RFA for early Barrett's neoplasia, with a median follow-up reported of almost 2.5 years after the end of therapy and almost 4 years after study entry. Treatment consisted of several sessions of resection and ablation (including limited application of APC) and took a median of 12 months. The overall results demonstrate the procedural success of this combined treatment approach for eradication of neoplasia and IM. In our treatment protocol, ER had an indispensable role as it allowed for removal and accurate histological staging of neoplastic lesions, which ensured optimal patient selection and rendered the mucosa flat for subsequent RFA. Furthermore, if neoplasia developed during the ablation phase or persisted after ablation, additional ER proved a safe escape modality for diagnosis and treatment.

Based on adverse events that occurred in the EURO-I trial, a pilot trial in three European centres in which 24 patients were enrolled,[15] in the present trial the extent of ER prior to RFA was limited to 2 cm in length and 50% of the circumference of the oesophagus. Limiting ER seems effective in preventing potential RFA complications after a prior ER, as minor mucosal lacerations after RFA occurred in only 8% of patients in this study, compared with 21% in the EURO-I study. Complications related to treatment were observed in 26 patients (20%) in this study, all were graded mild or moderate. All complications were managed conservatively or endoscopically, without complication related mortality. Oesophageal stenosis was observed in eight patients (6%); all could be dilated with a minimum of endoscopic dilatation sessions. The combination of limited ER and RFA is therefore a relatively safe approach.

CE-neo and CE-IM after RFA has previously been reported in 77–98% of patients in cohort studies from USA and the UK.[19 23–25] Our eradication rates for neoplasia (intention to treat (ITT) 92%, per protocol 98%) and IM (ITT 87%, PP 93%) lie at the upper end of this spectrum.[19 25] Our high rates of complete eradication may reflect the rigorous quality control in this study: only expert centres were selected to participate in the trial, all investigators had previously received hands-on training at the coordinating site and were supervised on-site to ensure adherence to the treatment protocol. An important difference with RFA studies from USA is that we incorporated circumferential HALO^{90} treatment of the neo-SCJ during each focal ablation procedure, to ensure optimal treatment of this area.[23 26 27] In addition, our standardised treatment protocol allowed for additional RFA or escape treatment at a low threshold, until all Barrett's mucosa was visibly eradicated. All of our patients received aggressive acid suppression after each treatment procedure. Finally, systematic follow-up endoscopies were performed using a rigorous biopsy protocol.

Poor response to endoscopic treatment (ie, failure to reach CE-neo and/or CE-IM) occurred in a small subset of our patients. Neoplastic progression occurred in two of these patients who failed to achieve CE-neo. In both of these patients, ER showed submucosal (T1sm1) carcinoma, and one of the patients underwent surgery. This progression rate to invasive disease is much lower than reported in a recent UK cohort,[19] mainly because we insisted on complete removal of all visible abnormalities by ER prior to RFA, and absence of cancer on two separate mapping endoscopies prior to RFA. Baseline ER was performed in 90% of patients in our study, as compared with only 49% of patients in the UK cohort. This stresses the importance of careful inspection of Barrett's mucosa prior to any RFA session, with a low threshold for performing a diagnostic ER to avoid disease progression. Importantly, neither escape ER nor escalation to surgical therapy was impaired by previous endoscopic treatment.

Once CE-neo and CE-IM was established, it was maintained in the majority of patients (96% and 92%, respectively). All recurrences of neoplasia in this study were detected at an early stage, and all were managed endoscopically. The recurrence rate of neoplasia appears to be very low and in line with other publications assessing the durability of neosquamous epithelium after RFA for neoplastic BO. A randomised trial on RFA for patients with LGD or HGD, recently reported the 2-year and 3-year follow-up results. Patients randomised to control were offered RFA treatment after 1 year. For the patients with HGD, CE-neo was demonstrated in 95% of 54 available patients at 2-year follow-up, allowing interim focal touch-up RFA. At 3 years, CE-neo was 96% in 24 available patients.[28] In a prospective study following 54 patients who underwent RFA with or without ER for early BO neoplasia, sustained CE-neo and CE-IM was 94% at 5-year follow-up.[29] In general, the present data comport well with these two recent studies, reporting sustained eradication rates of neoplasia and IM.

Table 2 Related adverse events in 26 patients occurring during or after RFA treatment

Adverse event	Adverse event rate % (n)	Classification
Acute*		
Superficial mucosal laceration	8 (11)	Mild (11×)
Bleeding	1 (1)	Mild (1×)
Early (<48 h)		
Fever resulting in hospital admission	1 (1)	Mild (1×)
Fainting	1 (1)	Mild (1×)
Late (>48 h)		
Oesophageal stenosis†	6 (8)	Moderate (8×)
Haematemesis‡	1 (1)	Moderate (1×)
Food bolus§	1 (1)	Moderate (1×)
Melena¶	1 (1)	Mild (1×)
Total	19 (25)	–

*None of the acute complications required endoscopic intervention.
†Oesophageal stenosis required a median of 1 (IQR 1–2) endoscopic dilations.
‡Haematemesis occurred 2 weeks after focal RFA requiring hospitalisation and repeat endoscopy, in a patient on warfarin.
§Food bolus occurred in an inflamed oesophagus 7 days after focal RFA requiring repeat endoscopy, without the need for subsequent dilatations.
¶Melena was self-reported and could not be objectified.
RFA, radiofrequency ablation.

Two neoplastic recurrences in this study were detected at the neo-SCJ. This is in concordance with previous studies, in which recurrent neoplasia mainly occurred in the cardia, months to years after complete eradication of BO.[12 20 30 31] To minimise the risk of recurrences, effective treatment at this level is imperative. In this study, most patients underwent multiple ablations of this area, since focal ablation of visible BO was always combined with circumferential treatment of the neo-SCJ with the focal RFA device. To assess if all Barrett's mucosa has been completely eradicated, biopsies obtained immediately distal to the neo-SCJ were used as an objective end point, as endoscopic differentiation between gastric mucosa and IM is unreliable.[32] One may argue that in patients who have undergone endoscopic therapy for BO neoplasia, subsequent detection of IM of the cardia may reflect insufficient treatment of that area, truly recurrent disease, or an irrelevant normal finding. In our study, focal IM of the cardia was detected in 24% of patients, but in the vast majority of cases this finding was incidental and could not be reproduced during further follow-up. If focal IM of the cardia would reflect residual disease, one would expect to find this more than once in the same patient. If focal IM in this area results from ongoing reflux after treatment, we would expect an increased incidence over time. Studies have shown that focal IM in this area often follows a benign course, with no increased incidence over time or reproducible detection during follow-up.[26 29] Furthermore, focal IM is found in up to 25% of the normal population, and this is generally not considered a premalignant condition.[33 34] In those studies, generally less than four biopsies were obtained at a single time point. In our study a median of 14 cardia biopsies were obtained at a median of four FU endoscopies. Our data further support the notion that focal IM of the cardia after RFA is of limited clinical relevance, and suggest that this is not related to residual or recurrent BO.[29]

After endoscopic eradication of Barrett's mucosa, there is a generally held concern that occult buried Barrett's glands may develop underneath neosquamous epithelium and thus may progress to a malignant stage while remaining endoscopically invisible. However, in reports of more than 700 patients treated with RFA the rate of buried glands appears almost negligible.[23 25 26 35–37] Studies have shown that biopsy depth of treated and untreated squamous epithelium is similar, hence neosquamous biopsies are of adequate depth to evaluate the presence of buried glands.[38–40] In our study all of our patients were subjected to a stringent biopsy protocol during follow-up, and we found buried glands in only one patient who was successfully re-treated with RFA. These results add to the evidence that the presence of buried glands in normal appearing post-RFA epithelium is rare.

Strengths of this study include the baseline training of participating centres: hands-on training at the coordinating site (AMC) was organised for all participating endoscopists at the start of this study. Furthermore, the first three to four RFA procedures were supervised on-site by the principal investigator of this study, and all RFA sessions and the first follow-up visit were attended by a coordinating study team that ensured prospective registration of data, standardisation of technique throughout the study, and compliance to the treatment and follow-up protocol. All patients underwent thorough endoscopic workup with at least two high-resolution endoscopies, and histological review of pretreatment biopsies and all ER specimens was performed at the AMC. Lastly, the European multicentre setting enabled inclusion of a large number of patients with a widespread demographic background.

We included a seemingly low number of patients per centre, which may raise the question of selection bias and extrinsic validity of the study. We believe that during the accrual period (which ranged from 6 months to 23 months in the different centres) a limited number of patients were missed who fulfilled the selection criteria for inclusion. However, since most centres did not prospectively register their ER procedures we are not informed on how many patients with early BO neoplasia are candidates for the limited ER plus RFA approach as described in our series. Based on experiences in the Netherlands and Belgium, we believe that 75% of patients can be treated with this approach. It should be noted that for patients who require more widespread ER the results of this study may not be applicable. For such patients there are several endoscopic treatment approaches available. In a previous study we have evaluated the use of circumferential RFA followed by ER within the same treatment session.[41] This approach is technically feasible but demanding and is associated with a substantial rate of complications and repeat ER. Based on these results, we would advocate reserving this 'single-step' approach for highly selected individuals only, especially in case of large lesions or pre-existing oesophageal stenosis. A second option is stepwise radical ER, in which the whole BO segment is removed in subsequent ER sessions.[20] Despite the excellent eradication rates achieved with this technique, stepwise radical ER is associated with high rates of stenosis, bleeding and perforation compared with ER plus RFA.[12] For the majority of patients, therefore, focal ER should be performed for complete removal of all visible abnormalities. Post-ER scarring should then be resolved by oesophageal dilatation, followed by RFA at a later stage. One limitation of this study is that ER procedures were not attended by a member of the coordinating study team. Registration of ER procedures and extent of ER may therefore have been less accurate than registration of all RFA procedures. Second, we allowed endoscopic rescue therapy in 18% of patients after RFA. Most escape treatments were APC touch-ups of diminutive, flat and non-suspicious Barrett's areas (<5 mm). APC is a cheap and widely used ablation technique which has proven successful in eradication of BO, but can be quite time-consuming for ablation of a larger area of Barrett's mucosa as it is performed spot by spot.[42] We believe that APC can be used complementary to the ER plus RFA treatment protocol, for final patching up of small areas of BO. Continuation of treatment until all Barrett's mucosa is eradicated visibly and histologically should be pursued to ensure low recurrence rates of neoplasia during follow-up. Lastly, all patients underwent endoscopic workup and treatment at centres with extensive expertise in the management of neoplastic BO. Therefore the results of this study cannot automatically be extrapolated to general practice. In our opinion however, it is imperative to centralise endoscopic management of patients with Barrett's neoplasia in dedicated centres with multidisciplinary experience in this field (ie, experience in endoscopic detection and treatment, adequate case volume, expert GI-pathology, access to oesophageal surgery), to ensure the procedural success rate as reported in the current study.

CONCLUSION

This is the largest prospective multicentre study to date on limited ER followed by RFA for early Barrett's neoplasia. ER followed by RFA was shown to be safe and effective, and was durable during medium-term follow-up. The main adverse event was stricture occurrence in 6% of patients, which resolved with dilatation. Our results underline that the combined approach of

ER followed by RFA, when performed by trained endoscopists, should be the first choice for treatment of carefully selected patients with early BO neoplasia.

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Contributors REP and JJGHMB: conception and design. KNP, REP, RB, OP, KR, BLAMW, BS, BR, AM, HM, EJS, LG, JM, CAS, MV, TL, SS, FJtK, CE, HN and JJGHMB: acquisition of data. KNP, REP, CAS, MV, FJtK and JJGHMB: analysis and interpretation of data. KNP, REP and JJGHMB: drafting of the manuscript. All authors: critical revision and final approval of the manuscript.

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Patient consent Obtained.

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