Endoscopic eradication of Barrett's oesophagus with early neoplasia

Pouw, R.E.

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Efficacy of radiofrequency ablation combined with endoscopic resection for Barrett’s oesophagus with early neoplasia
INTRODUCTION
Barrett’s oesophagus (BO), defined as a columnar-lined oesophagus and biopsy demonstrating specialized intestinal metaplasia (IM), is the most important risk factor for the development of esophageal adenocarcinoma. Patients with known BO undergo endoscopic surveillance to detect neoplasia (i.e. high-grade intraepithelial neoplasia (HGIN) or early cancer (EC)) at a curable stage. Patients with HGIN or with EC confined to the mucosa (T1m) may be treated endoscopically due to low risk for lymph node metastasis at time of diagnosis, but more advanced cancers are surgical indications. The cornerstone of endoscopic treatment of early BO neoplasia is endoscopic resection (ER), which allows for removal of visible lesions and assessment of tumour infiltration depth and differentiation. After focal ER, however, the residual Barrett’s mucosa remains at risk for malignant transformation and cancer recurrences are found in 30% of patients during follow-up. To prevent such metachronous lesions, endoscopic approaches have been studied in an attempt to eradicate the residual Barrett’s mucosa, e.g. radical ER, photodynamic therapy (PDT), and argon plasma coagulation (APC). These treatment options, however, do not always result in complete clearance of IM and associated intraepithelial neoplasia and are limited by other shortcomings such as oesophageal stenosis, photosensitivity, and subsquamous foci of IM, a.k.a. “buried Barrett’s”. A newer endoscopic ablative technique is radiofrequency ablation (RFA), which has promising safety and efficacy results published for non-dysplastic BO, low-grade intraepithelial neoplasia (LGIN), and HGIN. Single-centre studies have effectively combined focal ER of visible lesions with RFA for residual Barrett’s mucosa in patients with HGIN and EC. The aim of the present study was to further evaluate the safety and efficacy of this combined modality approach in BO patients with HGIN or EC in a European multicentre setting.

MATERIALS AND METHODS
Study Design
This is a prospective cohort trial conducted at three tertiary-care medical centres in Europe. The ethical committee of each institution reviewed and approved the protocol and the patient informed consent form. The trial was registered at www.trialregister.nl (NTR1434). A central study coordinator monitored all procedures and entered data into a central database. Patients were eligible if they met all inclusion criteria: age 18–85 years; BO length ≤12 cm; HGIN or EC in BO segment on two endoscopies in prior 6 months; visible lesions removed with ER prior to RFA; no signs of metastasis on endoscopic ultrasonography (EUS) or CT-scan. Patients were excluded if they met any exclusion criterion: pre-RFA ER with cancer at the vertical resection margin, >T1sm invasion, poor differentiation or worse, or angiolymphatic invasion; oesophageal stenosis preventing passage of 11.3 mm endoscope; persistent visible lesions after ER and pre-RFA; invasive cancer on biopsies after ER and pre-RFA. To ascertain eligibility, patients underwent two high-resolution endoscopies with documentation of BO landmarks according to the Prague classification system. If in the case of visible lesions, these were removed with ER followed by two additional endoscopies with 4-quadrant 1 cm
biopsies to exclude residual cancer and residual non-flat lesions. EUS was performed in all patients to rule out exclusionary lesions. In the case of cancer on biopsy or ER, a CT-scan of thorax and upper 1/3 of the abdomen was performed to rule-out metastatic disease.

**Endoscopic interventions**

All procedures were performed on an outpatient basis using intravenous midazolam, fentanyl, pethidine, propofol, or a combination thereof. All patients were prescribed high-dose proton pump inhibitor therapy (esomeprazole 40 mg BID) during the entire study period, supplemented with sucralfate suspension 5 mL (200 mg/mL) QID and ranitidine 300 mg before bedtime for two weeks after any therapeutic endoscopy. ER of any non-flat lesions was performed using the ER-cap technique, the multiband mucosectomy (MBM) technique or endoscopic submucosal dissection, at the discretion of the physician.

The ablation systems used in this trial have 510(k) clearance by the Food and Drug Administration in the U.S.A. and the CE Mark for Europe for the treatment of BO (BÂRRX Medical Inc., Sunnyvale, California, U.S.A.). For circumferential RFA, a sizing catheter was introduced over a guide-wire to measure the inner oesophageal diameter of the oesophagus. A HALO™ ablation catheter of appropriate outer diameter was introduced over the guide-wire followed by the endoscope in a side-by-side manner. The electrode was positioned 1 cm above the proximal extent of the BO, the balloon inflated, and energy delivered (12 J/cm², 40 W/cm²) resulting in circumferential ablation of a 3 cm segment. The ablation catheter was repositioned distal to the prior ablation zone, allowing minimal overlap, and ablation was repeated until the entire BO was ablated. The ablation catheter was removed to clean the electrode surface, while a soft distal attachment cap (Model MB-046, Olympus, Tokyo, Japan) was mounted on the endoscope and used to clean the ablation zone. Residual debris was then removed by forceful spraying of water through a spraying catheter with a pressure pistol (Alliance™, Boston Scientific, Limerick, Ireland, U.K.). After cleaning, the ablation catheter was re-introduced and the BO segment was treated a second time. For secondary focal ablation, each island or tongue of residual Barrett’s mucosa was aligned with the focal HALO™ catheter, the endoscope deflected to bring the electrode into contact, and RF energy delivered twice in succession (15 J/cm², 40 W/cm²). All areas were cleaned by pushing the coagulum off with the leading edge of the device. The electrode was removed to clean its surface, and then reintroduced to re-treat all areas twice more in succession. In all patients, the gastro-oesophageal junction was treated circumferentially with the HALO™ catheter at least once (2x2 15 J/cm²), to ensure eradication of IM at this level.

**Patient Flow**

Baseline visible lesions were removed by ER, followed by primary RFA at least 6 weeks after the ER and within 3 months after the last biopsy session. Additional RFA sessions were thereafter scheduled every 8 weeks until complete endoscopic eradication was achieved. A maximum of 2 circumferential and 3 focal RFA sessions was allowed. Any residual Barrett’s epithelium persisting after the maximum number of allowable RFA sessions was removed with a focal ER as escape therapy. Two months after the last treatment session, the original extent of BO was biopsied every 1 cm, including immediately (<5 mm) distal to the neo-squamocolumnar junction. If patients had reached complete resolution of intestinal metaplasia and complete resolution of neoplasia, they were scheduled for follow-up endoscopy and four-quadrant biopsies at 6 and 12 months after the last treatment session, and annually thereafter (Fig. 1).

**Figure 1. Flow-chart of the study protocol.**

Outcome variables
The primary endpoints were histology-based (biopsies obtained 2 months after last therapeutic intervention). A complete response was defined as all biopsies negative for IM (CR-IM) and neoplasia (CR-neoplasia), separately reported. Secondary endpoints: disease progression, adverse events, and durability of CR-IM and CR-neoplasia at last biopsy available.

Histological Analysis
All ER specimens and biopsies from baseline and follow-up were evaluated by the central study pathologist (FK), an expert in gastrointestinal pathology. ER specimens were evaluated for neoplasia according to the WHO classification, tumour infiltration depth, differentiation, presence of lymphatic or vascular infiltration and completeness of resection at the vertical margin. Biopsies were evaluated for presence of IM, LGIN, HGIN and EC, and follow-up biopsies from neo-squamous epithelium were evaluated for the presence of subsquamous areas of IM.

Statistical analysis
Statistical analysis was performed with SPSS 16.0.2 Software for Windows. For descriptive statistics mean (± standard deviation (SD)) was used in case of a normal distribution of variables, and median (interquartile range [IQR]) was used for variables with a skewed distribution. Where appropriate, the student t test and the Mann-Whitney test were used.

RESULTS
Enrolment and baseline characteristics
Twenty-four patients were included, 20 men, mean age 65±9.8 years, median BO length C6M8 [IQR C2-9, M4-10]. Twenty patients had a hiatal hernia [median 2 cm [IQR 2-3]]. Sixteen patients had a baseline diagnosis of cancer; eight patients had HGIN as the worst histological finding at two work-up endoscopies.

Baseline Endoscopic Resection
Twenty-three patients (96%) underwent a total of 25 ER sessions prior to RFA [2 patients had 2 ER sessions]. Of the 25 ER sessions, 12 were performed with the ER-cap technique, 12 with the MBM technique and 1 with endoscopic submucosal dissection. The worst histological grade based on ER was EC in 16 patients [T1m2, n=8; T1m3, n=6; T1sm1, n=2] and HGIN in 7 patients. The worst grade of residual intraepithelial neoplasia in biopsies obtained from the remaining BO during at least two high-resolution endoscopies after any ER, was HGIN in 10 patients [in the absence of any visible lesions], LGIN in 11 patients, and three patients had IM without neoplasia.

Number of treatment sessions
Patients underwent a median of 1 (IQR 1-1) primary circumferential and 1 (IQR 1-2) secondary focal RFA sessions. Escape ER was necessary in 1 patient to remove a resistant 8 mm Barrett’s island (LGIN). Escape ER was necessary in a second patient to remove 4 small BO foci (IM, no neoplasia) due to difficulty in introducing the focal RFA device. Overall, patients required a median number of 3 (IQR 3-4) therapeutic interventions (including any ER before and after RFA), during a median period of 6.4 (IQR 5.5-11.3) months.

Primary Outcome Variables
Eradication of intraepithelial neoplasia and IM
In 20/21 patients with residual LGIN/HGIN in their BO after ER and prior to ablation, CR-neoplasia was achieved with RFA (95%). Escape ER for an 8mm island of LGIN resulted in CR-neoplasia in all 21 patients (100%). CR-IM was achieved with RFA in 21/24 patients (88%). After escape ER in two patients [see above], CR-IM was reached in 23/24 patients (96%). The failure (n=1) had a C10M10 non-neoplastic Barrett’s segment after ER of a T1m2 carcinoma at baseline, and did not regenerate neosquamous epithelium readily after RFA. Thus, he was removed from the trial.

Secondary Outcome Variables
Progression
During follow-up, there were no new cancers and no histological progression of disease.

Adverse events
ER related complications:
One severe complication, an oesophageal perforation, occurred after baseline ER (cap technique), treated non-surgically with clips and a covered stent. This patient underwent a second ER session 3 months after the perforation and went on to have RFA 2 months after the second ER, without further complication, and is now CR-IM at 2, 6 and 12 months. RFA related complications: No severe complications occurred after RFA. Two complications (8%) were graded as being of moderate severity since they required additional endoscopic procedures: one patient presented with melena 2 weeks after focal ablation. Upon endoscopic inspection, no active bleeding was observed, but two visible vessels in the ablated area were preventively clipped. A second patient developed dysphagia after the first RFA. He had undergone widespread ER prior to RFA and had a mucosal laceration after circumferential RFA. The stenosis was resolved with 5 endoscopic dilatation sessions, after which ablation treatment could be resumed. Mucosal laceration was observed in five patients (21%) after circumferential RFA, all occurring within the mucosal scar region of a prior ER (Fig. 2). All patients remained asymptomatic and no therapeutic interventions were required. These lacerations were therefore graded as mild complications.

Durability of complete response
After a median follow-up of 22 (IQR 17.2-23.8) months after the last treatment, and a median of 3 (IQR 3-4) follow-up endoscopies per patient, no recurrence of neoplasia was observed. Long-term complete response for IM was maintained in 20/24 included patients (83%). In one patient with baseline C9M10 and CR-neoplasia and CR-IM at 2 months, a tiny (0.5x3 mm) glandular island with IM upon biopsy was found at 6 months follow-up endoscopy (Fig. 3). The island was located distal to a reflux stenosis and was only detected after inspection with NBI. In 2 patients at 6 months, focal non-neoplastic IM was found in one biopsy each, obtained distal to the gastro-oesophageal junction. In neither patient was this finding reproduced at 12 months. No buried Barrett’s was found in a total of 1,201 neosquamous biopsies obtained during follow-up.
Figure 2. Endoscopic images of circumferential RFA, complicated by non-transmural mucosal laceration.

A: C11M12 BO. B: At 32 cm from the incisors a suspicious lesion was observed. C: The lesion was removed in 2 pieces. Histology showed HGIN. D: Prior to circumferential RFA oesophageal scarring was observed at the resection site. E, F: During circumferential RFA, inflation of the balloon catheter caused non-transmural mucosal laceration, due to overstretching at the level of the ER scar. G: Three months after primary RFA, two residual Barrett’s islands were detected with NBI. H: The islands were treated with focal RFA. I-L: Two months after the last ablation, complete endoscopic eradication of neoplasia and IM was reached and the oesophagus was covered with normal appearing neosquamous epithelium, as seen with white light endoscopy and NBI.

Figure 3. Endoscopic images of a small island of glandular mucosa detected during follow-up.

A, B: C9M10 BO with proximal reflux stenosis, containing diffuse HGIN after ER for early cancer. C: Residual Barrett’s mucosa was completely converted to neosquamous mucosa by 1 circumferential and 1 focal RFA. No recurrence of neoplasia or IM was found at two months follow-up. E, F: At 6 months follow-up NBI revealed a tiny island of columnar epithelium just distal to the reflux stenosis and biopsy showed IM.
DISCUSSION

There is no generally accepted management strategy for patients with early neoplasia in BO. However, studies in which focal ER for neoplasia was followed by surveillance of residual BO have reported a 20–30% rate of metachronous lesions,\textsuperscript{2,3} whereas studies in which the whole BO was eradicated after focal ER only reported recurrence in up to 6% of patients.\textsuperscript{2,4,5} Based on these data, we believe that combining ER with complete ablation of residual Barrett’s mucosa is the preferable treatment approach, and in this first multicenter European trial we therefore evaluated RFA in conjunction with ER for the treatment of BO containing neoplasia and early cancer. The primary endpoint of complete eradication of all residual neoplasia after ER was achieved in 21 of 21 patients (CR-neoplasia 100%). The primary endpoint of complete eradication of all residual IM after ER was achieved in 23 of 24 patients (CR-IM 96%). These results comport with those from two recently published, single-centre studies in which RFA was used in conjunction with ER for HGIN and EC to achieve 100% CR-IM and 100% CR-neoplasia.\textsuperscript{24,25} These favourable outcomes collectively endorse a central role for RFA in the treatment of patients with flat-type neoplasia in a BO. All but one patient in this study underwent baseline ER for visible lesions. This emphasizes that in our opinion ER should be performed not only for nodules, but for any mucosal irregularity or area with suspicious glandular patterns no matter how subtle, even if prior biopsies do not show cancer but HGIN or lower. Not only is baseline ER important to render the mucosa flat for subsequent ablation, but it provides an adequate specimen for histopathological analysis and has been shown to change the histological diagnosis on the basis of prior biopsies in 49% of patients.\textsuperscript{24} Such a rigorous baseline evaluation is of the utmost importance to enable selection of patients who are eligible for further endoscopic treatment with RFA, i.e. patients without deep submucosal invading cancer (T1sm1), or poorly differentiated cancer, versus those that require surgical intervention. In the case of minimal submucosal infiltration (T1sm1), recent studies have suggested that the risk of lymph node metastasis is very low.\textsuperscript{6,7} Two patients had minimal submucosal invasion diagnosed in the ER specimen. Due to the absence of other risk factors for lymph node metastasis (poor differentiation grade, irradical resection, lymphatic/vascular infiltration), surgical as well as endoscopic treatment options were elaborately discussed with the patients, and both decided to be treated endoscopically within the study protocol.

In a prior clinical study,\textsuperscript{26} we allowed only single-piece baseline ER prior to RFA. In a subsequent study,\textsuperscript{27} we relaxed this restriction to allow multiple piece ER (median 2 specimens [IQR 2–3]) prior to RFA. No mucosal lacerations occurred and a stricture occurred in only one patient after 2 ER sessions and RFA. In the present study, based partially on prior results, we did not initially restrict the extent of baseline ER. During the first half of this study, we noted 5 mucosal laceration events within the ER scar zone during circumferential RFA and one stenosis; and we related this to extensive baseline ER and scarring. None of the lacerations required intervention or caused complaints and, therefore, they were regarded as mild complications. However, since lacerations may provoke severe bleeding or oesophageal perforation, the investigator group added a restriction to the baseline extent of ER (max. 50% of circumference, 2 cm length, and 1 session). We also used a more conservative approach in selecting an ablation catheter balloon size, erring on the small size. After this modification, no further lacerations or stenoses were observed. One patient was removed from the trial and considered a failure due to poor healing of the oesophagus after circumferential RFA. Atbaseline, the patient had an EC resected with ER, leaving a residual C10M10 Barrett’s segment with no neoplasia. The patient had previously undergone a Nissen fundoplication and post-operative 24 pH-metry was normal off proton-pump inhibitor. Yet, despite a maximum acid suppressant regimen [esomeprazole 80 mg BID, ranitidine 300 mg AN, sucralfate 5 ml QID] the oesophagus failed to readily regenerate with neosquamous epithelium. It is unclear what factors were at play in this particular patient’s poor healing, but it highlights the fact that tailored management may be necessary in some cases.

In three patients (83%) with complete eradication of IM and neoplasia, IM was found in biopsies during follow-up, which raises the question if endoscopic surveillance will remain necessary after complete eradication of IM and neoplasia has been reached. Currently, endoscopic follow-up after successful eradication BO by RFA is recommended at regular intervals based on baseline histological diagnosis, since no long-term follow-up data is as yet available. In 2/3 patients with IM during follow-up, focal non-dysplastic IM was found in a single biopsy just distal to the neo-squamocolumnar junction at a single follow-up endoscopy and in neither patient was this finding reproduced during following endoscopies. Since all patients had an initial diagnosis of HGIN/EC, one may argue that residual IM in the cardia reflects incomplete cure of the underlying disease. However, IM of the cardia can be detected in up to 25% of patients with a normal appearing squamocolumnar junction and is not considered premalignant in those cases.\textsuperscript{28} The clinical relevance of this finding is thus unclear, but in our opinion non-dysplastic IM in biopsies distal to the neoquamocolumnar junction does not require additional treatment, whereas IM with LGIN or HGIN should be treated. However, long-term follow-up data of these patients may clarify how focal IM in the cardia will behave after RFA. One patient had a 0.5x3 mm island of columnar epithelium detected, with IM upon biopsy, during follow-up endoscopy at 6 months, despite being CR-IM at 2 months. The island was only observed after inspection with NBI. We hypothesize that we missed this island visually on prior follow-up endoscopy due to its limited size and position just distal to a reflux stenosis. It is in our opinion therefore recommended to use high-resolution endoscopy, NBI, Lugol’s chromoendoscopy or comparable techniques during follow-up after RFA, to exclude the presence of residual BO tissue, especially small islands. As described in this manuscript, selection of patients for endoscopic treatment involves thorough endoscopic work-up, the possibility to safely perform ER, and accurate histological evaluation of tissue specimens for presence of risk factors for lymph node metastasis.\textsuperscript{29} Since all patients in this study underwent endoscopic work-up and RFA in specialized tertiary-care centres, the high reported safety and efficacy should be extrapolated to general practice with care. In our opinion, it may be advisable to centralize RFA of BO patients with HGIN/EC in centres with multidisciplinary experience in this field (i.e. expertise with endoscopic imaging and ER, access to oesophageal surgery, expert GI histopathology) and that have participated in dedicated RFA training courses at expert centres.

One strength of this study is the use of a single expert gastrointestinal pathologist for all specimen reviews. Other strengths include the multicentre design, use of baseline ER for imaging and ER, access to oesophageal surgery, expert GI histopathology) and that have participated in dedicated RFA training courses at expert centres.

Another limitation of this study is that we missed this island visually on prior follow-up endoscopy due to its limited size and position just distal to a reflux stenosis. It is in our opinion therefore recommended to use high-resolution endoscopy, NBI, Lugol’s chromoendoscopy or comparable techniques during follow-up after RFA, to exclude the presence of residual BO tissue, especially small islands. As described in this manuscript, selection of patients for endoscopic treatment involves thorough endoscopic work-up, the possibility to safely perform ER, and accurate histological evaluation of tissue specimens for presence of risk factors for lymph node metastasis. Since all patients in this study underwent endoscopic work-up and RFA in specialized tertiary-care centres, the high reported safety and efficacy should be extrapolated to general practice with care. In our opinion, it may be advisable to centralize RFA of BO patients with HGIN/EC in centres with multidisciplinary experience in this field (i.e. expertise with endoscopic imaging and ER, access to oesophageal surgery, expert GI histopathology) and that have participated in dedicated RFA training courses at expert centres.

One strength of this study is the use of a single expert gastrointestinal pathologist for all specimen reviews. Other strengths include the multicentre design, use of baseline ER for histological staging, post-ER and pre-RFA biopsy regimen to elucidate the post-ER diagnosis,
observation of all RFA procedures and primary endpoint biopsy procedures by the central study monitor to ensure protocol adherence, and patient follow-up that extends a median of 22 months beyond the last therapeutic intervention.

One weakness of this study is that many of the baseline ER procedures were performed prior to patient enrolment during confirmation of eligibility, and therefore were not supervised by the study coordinator. However, all centers used standardized techniques and data collection, and all ER specimens were reviewed by the study pathologist. Also, we allowed focal escape ER in certain rare circumstances, which could favourably bias our outcomes. Midway through the study we necessarily adjusted the extent of permissible baseline ER. This restriction appears to be associated with a lower risk of complications (namely, mucosal laceration), but more patients are needed to make this determination. Lastly, a relatively small number of patients was included in this study and treated in three expert centres. We have therefore initiated a second multicentre study in 12 European centres that uses the inclusion criteria defined in this study and aims at including a minimum of 100 patients. The results of this first European multicentre study demonstrate that patients with early neoplasia arising in BO can be effectively and safely treated with RFA, in combination with prior ER of visible lesions.

REFERENCES


