Endoscopic eradication of Barrett's oesophagus with early neoplasia
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Radiofrequency ablation combined with endoscopic resection, for eradication of Barrett’s oesophagus containing early neoplasia in 132 patients: results of a European multicentre study (EURO-II)
ABSTRACT

Objectives:
Barrett’s oesophagus (BO) containing high-grade intraepithelial neoplasia (HGIN) or early cancer (EC), can be treated by radiofrequency ablation (RFA) with prior endoscopic resection (ER) in case of focal lesions, as demonstrated by a number of relatively small-sized, single-centre studies. Patients with high-grade intraepithelial neoplasia (HGIN) or early cancer (EC), may be treated endoscopically given a low risk of lymph node metastasis, but more advanced cancers are indications for surgery. The cornerstone of endoscopic treatment for early Barrett’s neoplasia is endoscopic resection (ER), which allows for removal of visible lesions and accurate histological assessment of infiltration depth, differentiation grade and lymph-vascular invasion. 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, the residual Barrett’s segment can be eradicated by radiofrequency ablation (RFA). This endoscopic ablation technique has been shown to be successful in eradicating non-dysplastic Barrett’s mucosa and BO containing low-grade intraepithelial neoplasia (LGIN) and HGIN. The combination of ER and RFA for mucosal abnormalities and early cancer (EC) has also been proven safe and effective in a number of relatively small sized studies.

We performed a multicentre trial in 13 European centres, to evaluate the efficacy and safety of RFA, combined with ER for visible lesions, in patients with BO containing HGIN or EC.

MATERIALS AND METHODS

Study Design
This prospective cohort trial was conducted at thirteen tertiary-care medical centres in Europe, with expertise in detection and treatment of early Barrett’s neoplasia. To ensure standardization of the technique, the principal investigator of each center received hands-on training in RFA at the coordinating study centre (JBe). In addition, a coordinating study team attended all RFA procedures and the first follow-up visit for each patient at all sites, to maximize protocol compliance. Data was collected during procedures on standardized case record forms and entered in a central database.

Patient selection
Patients were eligible if they were 18-85 years of age, with histological confirmation of HGIN or EC at two separate endoscopies within 6 months prior to inclusion, in a maximum Barrett’s segment measuring 2 to 12 cm in length. During work-up, there could be no signs of metastasis on endoscopic ultrasound (EUS) or computed tomography, the latter was only mandatory in patients with EC. Any visible mucosal irregularities needed to be removed by ER, limited to 2 cm in length and 50% of the circumference, prior to the initial RFA treatment. Patients were excluded if the ER-specimen showed cancer at the vertical resection margin, invasion ≤T1sm1, poorly or undifferentiated cancer, or lymph-vascular invasion. In addition, oesophageal stenosis preventing passage of a 11.3 mm endoscope and/or persistent visible lesions or cancer in four-quadrant/2 cm biopsies obtained during 2 mapping endoscopies performed after ER and pre-RFA, were criteria for exclusion from this study.
Treatment protocol

At baseline, all mucosal irregularities were removed by ER to allow for histological staging. ER was performed using the ER-cap technique (Olympus, Hamburg, Germany), multiband mucosectomy (Duette®, Cook Endoscopy, Limerick, Ireland) or the Euroligator (Mandel+Rupp, Erkrath, Germany). Based on prior experiences, the extent of ER allowed for inclusion in this study, was limited to 2 cm in length and 50% of the circumference to prevent complications at subsequent RFA treatment, due to post-ER stricturing. A minimum of 6 weeks after any ER, the first RFA treatment was performed using either the HALO360 system for circumferential ablation, or the HALO90 system for focal ablation, as described in detail previously.12-14 The gastro-oesophageal junction was treated circumferentially with HALO90 ablation at least once. RFA treatment was performed at 0-3-6-9-12 months, with a maximum of 2 circumferential and 3 focal RFA treatments. ‘Escape’ ER as part of the treatment protocol was performed for any visible lesions detected prior to any of the scheduled RFA treatments, or for residual neoplasia persisting after the maximum number of RFA sessions. Any residual non-dysplastic Barrett’s epithelium persisting after the maximum number of allowed RFA sessions was recorded, and at the discretion of the responsible endoscopist either removed by escape-ER, biopsied and treated with APC only in case of areas <5 mm, or kept under endoscopic surveillance.

If endoscopic eradication of all visible Barrett’s mucosa was reached, biopsies for histological correlation were obtained immediately distal (<5 mm) to the neo-squamous columnar junction, and from four-quadrants every 2 cm of the original extent of the BO segment. Additional follow-up was then performed 6 and 12 months after the last treatment session, and annually thereafter. During the entire study period, all patients were prescribed high-dose proton pump inhibitor therapy, supplemented with an H2-receptorantagonist and sucralfate suspension for two weeks after each therapeutic endoscopy.

Outcome parameters

Primary outcome parameters:
- Histological eradication of neoplasia, defined as all biopsies negative for neoplasia, 12 months after the first RFA treatment.
- Histological eradication of IM 12 months, defined as all biopsies negative for IM, 12 months after the first RFA treatment.

Secondary outcome parameters:
- Adverse events, defined as ‘acute’ (during procedure), ‘early’ (0-48hrs) and ‘late’ (>48hrs). Adverse events were only recorded if they were clinically significant and graded as ‘mild’ (unplanned hospital admission, hospitalization <3 days, hemoglobin drop <3g/dl, no transfusion), ‘moderate’ (4-10 days hospitalization, <4 units blood transfusion, need for repeat endoscopic intervention, radiologic intervention), ‘severe’ (hospitalization >10 days, ICU admission, need for surgery, > 4 units blood transfusion, in the case of stenosis: >5 dilatations, stent placement or incision therapy) or ‘fatal’ (death attributable to procedure <30 days or longer with continuous hospitalization).
- Durability of eradication of neoplasia during follow-up.
- Durability of eradication of IM during follow-up.

Histological analysis

At each centre histological evaluation was performed by a local expert pathologist, followed by central pathology review of all ER specimens, work-up biopsies, and biopsies from the first follow-up endoscopy, at the coordinating study site. In case of discrepancies, revision by a second expert pathologist was performed to reach consensus. ER specimens were evaluated for neoplasia according to the WHO classification,15 tumour infiltration depth, differentiation grade, presence of lymph-vascular invasion and radiality of resection at the vertical margin. Biopsies were evaluated for presence of IM and neoplasia, and for the presence of subsquamous areas of IM in biopsies from neosquamous mucosa.

Statistical analysis

Statistical analysis was performed with SPSS Statistics 17.0 Software for Macintosh. For descriptive statistics mean ± standard deviation (SD) was used in case of a normal distribution of variables, and median (interquartile range (IQR)) in case of a skewed distribution.

Ethical considerations

The ethical committee of each institution reviewed and approved the protocol and the patient informed consent form. All patients signed an informed written consent form prior to inclusion. The trial was registered at www.trialregister.nl (NTR1211).

RESULTS

Patients

A total of 132 patients was included, 107 men, mean age 65 ±14 years, with a median BO length of C3 (IQR 1-7) M4 (IQR 4-9). In 119 patients ER was performed, using the ER-cap technique with submucosal lifting (n=52) or a ligate-and-cut technique (n=67). En-bloc resection was performed in 63 patients (52%) and piecemeal resection in 57 patients (48 %) with a median of 2 pieces (IQR 2-4) per session. Worst pathology in the resected specimens was EC (n=78), HGIN (n=31), LGIN (n=7) or no-dysplasia (n=3). Prior to RFA, the worst histological grade in the residual Barrett’s segment was HGIN (n=36), LGIN (n=45) or no-dysplasia (n=51).

Primary endpoints

During the treatment period 6/132 patients (5%) dropped out from the study (withdrawal of consent, n=3; second primary cancer, n=3). By August 2011, eight patients had not yet reached the 12-month endpoint. According to intention-to-treat analysis, all 6 dropouts were considered as failures for eradication of neoplasia. After a median of 1 (IQR 1-2) HALO360 ablation and 2 (IQR 1-3) HALO90 ablations, eradication of neoplasia and IM at 12 months was reached in 115/124 (92%) and 105/124 (84%) patients, respectively. After additional escape ER, as part of the treatment protocol, to remove residual columnar mucosa after the maximum number of RFA sessions (no dysplasia, n=3; LGIN, n=1), and for visible lesions popping-up during the treatment period (HGIN, n=1; EC, n=1), eradication of neoplasia and IM was reached in 117/124 (94%) and 111/124 (90%) patients, respectively.
In a per-protocol analysis (i.e., censoring the 6 patients as unrelated drop outs instead of blindly labeling them as failures), eradication of neoplasia and IM at 12 months was reached in 117/118 (99%) and 111/118 (94%) patients, respectively.

Secondary endpoints

**Durability of response during follow-up**

After a median follow-up of 21 months (IQR 15-27), recurrence of neoplasia was found in 2 patients (1.5%). The first patient had a C1M2 BO, successfully treated by en-bloc resection for mucosal cancer, followed by two focal RFA sessions for residual BO with HGIn. After two follow-up endoscopies without any endoscopic or histological signs of recurrence of neoplasia or IM, a small visible lesion with HGIn was detected at the neosquamocolumnar junction, 24 months after the last RFA session. The lesion was removed en-bloc by MBM, and histological evaluation showed a small focus of radically removed HGIn and IM. The second case was a patient with a C5M7 BO treated by en-bloc resection for mucosal cancer, followed by RFA for residual BO with HGIn. He required two circumferential and three focal ablation sessions with poor healing in between the treatment sessions but finally achieved CR-neo and CR-IM. During the first follow-up endoscopy, a small island of columnar mucosa was detected and removed by biopsy, showing LGIN. At the second endoscopy no columnar mucosa was detected yet a grade B reflux oesophagitis hampered optimal inspection. At 12 months HGIn was detected in a biopsy from the same island that was thought to have been removed by biopsy before. This area was subsequently effectively treated with ER. In 4 patients (4%), a small endoscopically visible area of columnar epithelium with IM upon biopsy recurred. In 9 patients (8%), non-dysplastic IM was diagnosed in a single biopsy from a normal appearing neosquamocolumnar junction, during a single follow-up endoscopy. In 1 patient (1%) buried Barrett’s was detected. This patient was treated successfully for C4M5 BO with HGIn. During the first follow-up endoscopy, buried glands were diagnosed in a neosquamous biopsy from the middle part of the initial BO. Repeated detailed endoscopic inspection did not reveal any visible Barrett’s mucosa. However, a biopsy from the same area again confirmed the presence of substomas IM. The area with the buried Barrett’s was therefore treated anew with balloon-based circumferential RFA (2x 12 J/cm²). Two, six and 18 months after the repeat RFA treatment, a total of 16 biopsies and 3 ER specimens from the healed area did not show any signs of submucosal glands.

**Adverse events**

No clinically relevant complications occurred during or immediately after any of the ER procedures. Acute complications during RFA consisted of mucosal laceration in 8/122 patients (7%) undergoing HALO™ ablation, none of which required endoscopic intervention was necessary. One early complication (1%) was observed after RFA: fever resulting in prolonged hospital admission, graded as a mild complication. Late complications of treatment were seen in 9/132 patients (7%). Two late complications were graded as mild: non-objectified melena (n=1), and fainting after all three RFA sessions (n=1). Seven late complications were graded as moderately severe: hematemesis two weeks after HALO™ ablation requiring repeat endoscopy (n=1), and oesophageal stenosis requiring a median of 1 (IQR 1-2) endoscopic dilatation (n=6). Of the patients who developed oesophageal stenosis, 3 underwent en-bloc ER prior to RFA, and 3 underwent piecemeal ER with 2 resections. In 7/132 patients (5%) a non-treatment related adverse event occurred during the treatment phase: pancreatitis (n=1), or coronary heart disease (n=6).

**DISCUSSION**

This multicentre trial of 132 patients in 13 European centres was initiated as a continuation on the EURO-I study, a pilot trial in 3 European centres in which 24 patients were enrolled. In this study, eradication of neoplasia and IM was reached in 92% and 84% of patients, respectively. In our analysis we considered all dropouts due to unrelated causes as failures ("intention-to-treat analysis"). After additional escape ER, eradication of neoplasia and IM was achieved in 94% and 90% of patients. According to per-protocol analysis (excluding drop-outs from the analysis), complete eradication of neoplasia and IM was reached in 99% and 94% of patients, respectively. These per-protocol results are almost identical to the eradication rates for neoplasia and IM of 100% and 96% in the EURO-I study. The results of this study add to the convincing evidence that ER for visible lesions combined with RFA for residual Barrett’s mucosa, should be preferred over surgery for BO with early neoplasia. In this study, ER had an indispensable role in this treatment approach: it allowed for removal and accurate histological staging of neoplastic lesions, which ensured optimal patient selection and rendered the mucosa flat for subsequent effective ablation with RFA. Furthermore, ER proved to be a safe and effective escape treatment in case neoplasia developed during the ablation phase or persisted after ablation. This is a unique feature of RFA since other ablation techniques generally result in significant esophageal scarring making additional ER often impossible. Based on experiences from the EURO-I study, the extent of ER prior to RFA was limited to 2 cm in length and 50% of the circumference in order to prevent more complicated RFA procedures due to post-ER scarring. Mucosal laceration after HALO™ ablation occurred in 7% of patients, which was much lower than the 21% in the EURO-I study, in which the limitation of ER extent was only introduced halfway through the study. Limiting ER therefore seems effective in preventing potential RFA complications after a prior ER. Due to these strict selection criteria, however, the results of this study may not be applicable for patients who require more widespread ER. In these patients complications such as mucosal laceration or oesophageal stricturing may occur more frequently than described in this study. In patients with widespread lesions, the ER should, however, still be performed for complete removal of all irregular mucosa. Post-ER scarring can then best be resolved by oesophageal dilatation up to at least 18 mm followed by circumferential RFA at a later stage. Mild complications related to treatment were observed in 2% of patients (fever which prolonged hospital admission, anamnestic melena and fainting after RFA). Moderate complications were observed in 7% of patients, of which 5% were oesophageal stenoses. All these strictures could be dilated with a minimum of endoscopic dilatation sessions. None of the >500 treatment sessions in this study were associated with severe complications, and there were no treatment related deaths. The combination of limited ER and RFA was therefore very safe, and all complications could be managed either conservatively or endoscopically. Our study had a median follow-up of 21 months (IQR 15-27), during which recurrence
of neoplasia was observed in 1.5% of patients. Both recurrences were detected during endoscopic follow-up and could be removed by additional ER. In comparison to recurrences observed after ER monotherapy (25-33% within 5 years)\cite{18,19} the recurrence rate found in this study appears favorable and in line with other approaches that aim at completely eradicating the whole BO such as stepwise ER of the complete BO (2% recurrence during median follow-up of 32 months).\cite{20} A recent randomized trial comparing stepwise ER with ER+RFA found that both approaches were highly effective in eradicating neoplasia (100% vs 96%) and preventing recurrences (4% vs. 0% during 22 months follow-up).\cite{21} Stepwise ER, however, was associated with a 88% oesophageal stenosis rate and required double the number of treatment sessions. Given the relative simplicity of ER+RFA and the fact that this is also effective for longer segments of BO, this approach should be preferred.\cite{22} The two recurrences of neoplasia in this study were both detected at the neosquamousmucular junction. This is in concordance with two recent studies on SRER and RFA, in which recurrence of neoplasia also mainly occurred at this level.\cite{23,24} Other groups have also reported on the issue of neoplasia developing in the cardia months to years after complete removal of BO.\cite{25,26} To minimize the risk of recurrences, eradication of all IM at this level should therefore be optimized. Effective ablation of the gastro-oesophageal junction using the HALO\textsuperscript{90} catheter is difficult, given the often tortuous anatomy and presence of a hiatal hernia in most BO patients. In our opinion, the entire circumference of the gastro-oesophageal junction should be treated with the HALO\textsuperscript{90} device at least once during the treatment period. In this study, most patients even underwent multiple HALO\textsuperscript{90} ablations of this area since focal ablation of visible BO remnants was always combined with circumferential HALO\textsuperscript{90} treatment of the cardia. This is an important difference with RFA studies from the US in which circumferential HALO\textsuperscript{90} ablation of the cardia was not incorporated in treatment protocols.\cite{27,28,29} Since endoscopic differentiation between gastric mucosa and IM is almost impossible, it is difficult to assess if all Barrett’s mucosa has been eradicated. We have therefore used the histological eradication of IM in biopsies obtained immediately distal (<5 mm) to the neosquamousmucular junction as an objective endpoint for effective treatment at this level. After eradication of BO, this area should be thoroughly inspected during follow-up endoscopies, as well as biopsied, to detect recurrence of neoplasia at a curable stage. The downside of this approach, however, is that this may lead to the detection of non-dysplastic IM in a normal appearing gastro-oesophageal junction, often as a single-biopsy-single endoscopy finding.\cite{30} One may argue that in patients with an initial diagnosis of early neoplasia in their BO, such a finding of IM reflects insufficient treatment or recurrence of their underlying disease. However, in patients with a normal appearing squamousmucular junction, focal IM is found in 25% of patients, and this is not considered a premalignant condition in those cases.\cite{31} The presence of buried Barrett’s has been reported in about 53% of patients treated with argon plasma coagulation or photodynamic therapy.\cite{32,33} The 1% of submucous IM found in this study may therefore be considered very low, especially given the stringent biopsy protocol used during follow-up endoscopies. According to protocol, biopsies from neosquamous epithelium were only obtained after inspection with NBI, FICE or I-Scan, to prevent a histological finding of buried Barrett’s due to artifacts resulting from accidental biopsying residual columnar mucosa. Since buried Barrett’s in normal appearing neosquamous mucosa after RFA are very rare, one may question if extensive biopsies from the neosquamous mucosa will remain necessary after thorough inspection with white light endoscopy and NBI, FICE or I-Scan. Strengths of this study are the baseline training of participating centres, quality control, stringent endoscopic work-up, central pathology review, and the prospective, European multicenter set-up. Training at the start of the study was organized for all endoscopists participating in this study. They received hands-on training at the coordinating study site, and the first three RFA procedures at each center were supervised on-site by the principal investigator. All treatment sessions as well as the first follow-up endoscopy were attended on site by a coordinating study team who ensured prospective registration of data, and standardization of the technique throughout the study. All patients underwent thorough endoscopic work-up with at least 2 high-resolution endoscopies, and histological revision of all ER specimens and pre-treatment biopsies was performed at the coordinating study site. Lastly, the European multicenter setting enabled inclusion of a large number of patients with a different demographic background, which increased the generalizability of this study. Limitations of the study are that patients underwent endoscopic work-up and treatment at centres with extensive expertise in management of Barrett’s neoplasia. Results from this study should therefore be extrapolated to general practice with care. However, one may question if future Barrett’s management should not be centralized in such dedicated centres, to maintain the safety and efficacy results reported for endoscopic treatment. In addition, ER was not required to be performed as part of the study protocol, and ER procedures were therefore not attended by one of the study coordinators. Registration of ER procedures and extent of ER may therefore have been less accurate than registration of the RFA procedures. This is the largest European multicentre trial on the efficacy and safety of RFA, with or without ER for mucosal irregularities, for patients with early neoplasia in BO. Results show that if performed by trained endoscopists, in carefully selected patients, a combined treatment approach of RFA and RFA is highly effective and safe.
REFERENCES


