Endoscopic eradication of Barrett's oesophagus with early neoplasia
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Citation for published version (APA):
Eradication of Barrett’s oesophagus with early neoplasia by radiofrequency ablation, with or without endoscopic resection

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ABSTRACT

Background: Radiofrequency ablation is safe and effective for complete eradication of non-dysplastic Barrett’s oesophagus (BO). Aim was to report the combined results of two published and two ongoing studies on radiofrequency ablation of BO with early neoplasia, as presented at SSAT presidential plenary session DDW 2008.

Methods: Enrolled patients had BO ≤12 cm with early neoplasia. Visible lesions were endoscopically resected. A balloon-based catheter was used for circumferential ablation and an endoscope-based catheter for focal ablation. Ablation was repeated every 2 months until all Barrett’s epithelium was endoscopically and histologically eradicated.

Results: Forty-four patients were included (35 men, median age 68 years, median BO 7 cm). Thirty-one patients first underwent endoscopic resection (early cancer [n=16], high-grade dysplasia [n=12], low-grade dysplasia [n=3]). Worst histology remaining after resection was high-grade dysplasia (n=12) or no (n=2) dysplasia. After ablation, complete histological eradication of all dysplasia and intestinal metaplasia was achieved in 43 patients (98%). Complications following ablation: mucosal laceration at resection site (n=3) and transient dysphagia (n=4). After 21 months follow-up (IQR 10-27), no dysplasia had recurred.

Conclusions: Radiofrequency ablation, with or without prior endoscopic resection for visible abnormalities, is effective and safe in eradicating BO and associated neoplasia.
oncogenetic abnormalities as present in the pre-treatment BO are absent in the regenerated neosquamous epithelium after RFA, and the functional integrity of the oesophagus is not affected by RFA. In this paper we will present the results reported in Abstract 215, that was selected for oral presentation during the SSAT presidential plenary A session, at the Digestive Disease Week 2008, San Diego, CA, U.S. We will review our results, as available up until November 30, 2007, of stepwise circumferential and focal ablation in 44 patients with Barrett’s oesophagus and HGD/EC who were consecutively treated in four different, IRB-approved, study protocols at the Academic Medical Center, Amsterdam, the Netherlands.

MATERIALS AND METHODS

Patient selection

Starting July 2005, patients between 18 and 85 years old, were consecutively included in a series of IRB-approved clinical protocols evaluating the effect of RF ablation on BO with early neoplasia, and conducted at the Academic Medical Center, Amsterdam, the Netherlands. Patients were eligible if they had endoscopically visible BO (≤12 cm) with HGD or EC diagnosed at two separate endoscopies by an experienced gastrointestinal pathologist (FK). Any visible endoscopic abnormalities, or EC without a clear lesion detected by biopsies, were removed with ER prior to ablation, per the protocol. In case of prior ER, histological evaluation of the specimen could not show vertical resection margins positive for cancer (R+), deep submucosal invading cancer (T1sm1), poorly or undifferentiated cancer (G3, G4), or presence of lymphatic/vascular invasion (V+). Patients with oesophageal stenosis at baseline and patients with invasive cancer in biopsies obtained after ER but prior to RF ablation were also excluded. Our four serial and unique study protocols were as follows:

1. The first prospective study on circumferential RF ablation of HGD/EC in patients with a median BO segment of 5 cm (IQR 5-7) using the HALO³⁶⁰ ablation catheter, with prior en-bloc ER of visible lesions and EC. Halfway through this study, the focal HALO³⁶⁰ ablation device became available.

2. The second prospective study on RF ablation for the treatment of HGD and EC in patients with a median BO length of 7 cm (IQR 6-5-8) had a study protocol similar to the first study. Based on the experiences from the first trial, however, the protocol for this second trial had been optimized by thorough cleaning of the ablation zone and electrode surface in between ablation cycles, and the focal HALO³⁶⁰ device was available from the start of the study. In addition, also patients with prior piecemeal ER of visible lesions were included.

3. The first, ongoing, European multicenter trial to evaluate the safety and efficacy of RF ablation in patients with a Barrett’s segment up to 12 cm long, with early neoplasia, with or without prior ER.

4. An ongoing prospective randomized multicenter trial comparing SRER and RF ablation for the eradication of dysplasia and IM in patients with a BO ≤5 cm containing early neoplasia.

Endoscopic procedures and medication

All endoscopic procedures were performed on an outpatient basis using intravenous conscious sedation comprised of midazolam and/or fentanyl. After the procedure, patients were clinically observed for 2-4 hours before they were discharged. All patients were prescribed high-dose proton pump inhibitors (i.e., esomeprazole 40 mg bid) as a maintenance dosage during the entire study period. Sucralfate suspension 5 mL (200 mg/mL) qid and ranitidine 300 mg before bedtime were prescribed for two weeks after each therapeutic endoscopy. In case of post-procedural discomfort, patients were allowed to take acetaminophen 500 mg (max. 6/24 h), and if this did not suffice diclofenac suppositories 100 mg bid were permitted.

Endoscopic ablation systems (Chapter 5 Fig. 1)

Both ablation systems that were used (HALO Ablation Systems, BÂRRX Medical Inc., Sunnyvale, California, U.S.) have 510(k) clearance by the Food and Drug Administration in the U.S. and the CE Mark for Europe for the treatment of Barrett’s oesophagus. The HALO Ablation system comprises two distinct ablation systems: the HALO³⁶⁰ system for primary circumferential ablation and the HALO⁹⁰ system for secondary focal ablation. The HALO³⁶⁰ system includes an energy generator, ablation catheters, and sizing catheters. The HALO³⁶⁰ energy generator delivers radiofrequency (RF) energy to the electrode, and has an integrated pressure-volume system to inflate the sizing balloon and automatically measure the inner oesophageal diameter. The sizing balloon catheter consists of a 4-cm non-compliant balloon that is used for measuring the inner oesophageal diameter of the targeted portion of the oesophagus, prior to circumferential ablation. The sizing catheter is introduced over a guide-wire and it balloon is inflated in an automated manner to 4 psi (0.28 atm). Based on the baseline balloon volume, the volume needed to inflate the balloon to 4 psi, the mean oesophageal inner diameter is calculated. Measurement is repeated moving distally, for every centimeter of the targeted oesophagus, until an increase in diameter indicates the transition to the stomach or hiatal hernia. The HALO⁹⁰ ablation catheter has a balloon at its distal end that is completely encircled by 60 electrode rings that alternate in polarity, over a length of 3 cm. The HALO⁹⁰ ablation balloon is available in five outer diameters sizes (2, 25, 28, 31 and 34 mm). Extensive dosimetry studies in the porcine oesophagus and human oesophagus prior to surgical oesophagectomy have shown that for circumferential ablation two applications of RF energy at 10 - 12 J/cm² and 40 W/cm² is the most effective regimen to ablate the full thickness of the epithelial layer, without injuring the submucosa. Focal ablation of residual BO tissue was performed with the HALO⁹⁰ system. The HALO⁹⁰ system consists of the focal ablation catheter and an energy generator. The bipolar electrode array of the HALO⁹⁰ catheter is 20 mm long and 13 mm wide and is mounted on an articulated platform that can be attached to the tip of an endoscope with a flexible strap. The electrode array geometry and spacing is identical to that of the balloon-based electrode.

Endoscopic work-up

Prior to ablation, all patients underwent at least two high-resolution endoscopies with narrow band imaging [NBI] (GIF-Q240Z, Lucera 260 system, Olympus, Tokyo, Japan or GIF-H180, Excera II-system and a high-definition monitor, Olympus Europe, Hamburg, Germany) to...
thoroughly inspect the BO segment by an expert endoscopist. The maximum length of the
chorneal and contiguous Barrett’s epithelium was recorded according to the Prague
classification system. The maximum proximal extent of the Barrett’s mucosa (circumferential and contiguous Barrett’s epithelium was recorded according to the Prague
technique. Two months after the last treatment session, the endoscopic eradication of IM
lesions and lymph node involvement, all patients underwent endoscopic ultrasound (EUS)
in conjunction with an Aloka SSD-5000 ProSound processor (Aloka, Meerbusch, Germany).
In addition, computed tomography (CT) scanning of thorax and upper 1/3rd of the abdomen
was performed in all patients with EC, to detect any metastatic disease.

Endoscopic resection procedures
All visible lesions and EC were removed with endoscopic resection (ER) prior to ablation. The objective of the ER was twofold. Firstly, ER allowed for histological evaluation and staging, enabling optimal selection of patients eligible for endoscopic treatment. Secondly, ER of visible lesions ensured that the subsequent ablation could be performed on an endoscopically flat mucosa. ER was performed using the ER-cap technique (Olympus GmbH, Hamburg, Germany) after submucosal lifting, or the multi-band mucosectomy (MBM) technique (DuetteTM, Cook Endoscopy, Limerick, Ireland). Lesions with a diameter <2 cm were resected en-bloc, larger lesions were resected in multiple pieces (piecemeal procedure). All resected specimens were retrieved, pinned down on paraffin, and fixed in formalin for histopathological evaluation.

Endoscopic ablation procedures
For primary circumferential ablation the oesophageal wall was sprayed with acetylcysteine (1%) and flushed with plain water, to remove excessive mucous. After recording the oesophageal landmarks (i.e., top gastric folds, maximum extent of BO) the endoscope was removed, leaving a guide-wire (Amplatz extra stiff 0.035”, Cook, Denmark, Europe) behind. A sizing balloon was introduced and the inner oesophageal diameter was measured for every centimeter of the targeted BO segment, moving from proximally to distally. Based on the measurements, an ablation catheter with an appropriate outer diameter was selected. The ablation catheter was introduced over the guide-wire, followed by the endoscope to allow the ablation procedure to be performed under endoscopic guidance. The electrode was placed one centimeter above the maximum proximal extent of the BO, the balloon was inflated and the electrode activated (12 J/cm², 40 W/cm²). This resulted in a 3-cm long, circumferentially ablated segment. Depending on the length of the BO segment, the ablation catheter was advanced and, allowing an overlap of 5-10 mm, repositioned distal to the first ablation zone. Ablation was repeated until the entire length of the BO segment had received one application of energy. Then, the ablation zone and electrode surface were}

cleaned. In the first eleven patients cleaning was performed by advancing the ablation balloon into the stomach where it was inflated, and flushed with water through the endoscope to rinse off excessive coagulum. The ablation zone was also rinsed with water through the spraying channel of the endoscope. For the next 12 patients, the ablation catheter was removed and the electrode surface was cleaned outside the patient. The ablation zone was more rigorously cleaned compared to the first trial, by forcefully spraying water through a spraying catheter using a pressure pistol (Alliance™, Boston Scientific, Limerick, Ireland, UK). In the following patients cleaning was optimized by the use of a soft distal attachment cap fitted on the tip of the endoscope that was used to slough off most of the coagulum from the ablation zone, prior to forceful rinsing with water through a spraying catheter. After the cleaning procedure, the entire ablation zone was ablated a second time, using the same energy settings. For secondary focal ablation with the HALO™ system, the mucosa was sprayed with acetylcysteine (1%) and flushed with plain water. The HALO™ electrode was fitted on the tip of the endoscope, introduced, and used for targeted ablation of residual Barrett’s epithelium. The squamocolumnar junction was routinely ablated when the HALO™ electrode was introduced to ablate residual isles or tongues. The HALO™ system only became available at the end of the first trial, and the energy settings were escalated from 2x 12 J/cm² to 2x2x 12 J/cm² and eventually to 2x2x 15 J/cm² at 40 W/cm². All areas were ablated with cleaning of the electrode and ablation zone in between ablation cycles, as previously described for the circumferential ablation procedure.

Treatment protocol
After a minimum of six weeks after any ER, patients were treated with primary circumferential ablation using the HALO™ system. After six to eight weeks patients were scheduled for endoscopy to assess the treatment effect. Depending on the extent of residual BO, patients underwent a second HALO™ procedure, or secondary focal ablation using the HALO™ system. In the first study protocol all patients were treated with a second circumferential ablation using the HALO™ system, regardless of the extent of the residual BO, since the HALO™ system for focal ablation was only introduced halfway through the study. Additional ablation was repeated every 6-8 weeks and a maximum number of 2 circumferential and 3 focal ablation sessions were allowed to achieve complete eradication of all intestinal metaplasia. Persisting IM after the maximum number of ablations could be endoscopically resected using the MBM technique. Two months after the last treatment session, the endoscopic eradication of IM was assessed during endoscopy using high-resolution endoscopes with Lugol’s staining [2%] or narrow-band imaging. To assess the histological clearance of IM, biopsies were obtained from four quadrants just distal to the neo-squamocolumnar junction, and every 1-2 cm from the neosquamous epithelium over the full length of the initial BO segment.

Follow-up
Patients were scheduled for follow-up endoscopy two, six and twelve months after the last treatment session, and then annually. High-resolution endoscopes with narrow-band imaging facilities were used to thoroughly inspect the oesophagus for recurrence of IM.
and 4 quadrant biopsies were obtained for every 1-2 cm of the neosquamous epithelium over the original BO length, and immediately distal to the neo-squamocolumnar junction. Patients initially treated for EC underwent EUS every 12 months to exclude the presence of lymph node metastases.

Histopathological review
All biopsies and ER specimens were embedded in paraffin, mounted on glass slides and routinely stained with hemotoxylin and eosin. For the purpose of the described studies, all slides were reviewed by an expert GI-pathologist (FK). The ER specimens were evaluated for the presence of dysplasia according to the revised Vienna classification, tumour infiltration depth, tumour differentiation grade, presence of lymphatic or vascular infiltration, and the radicality of the resection at the deep resection margins. Biopsies were evaluated for the presence of IM, LGD, HGD or EC and in case of neosquamous biopsies the presence of glandular mucosa underneath the neosquamous epithelium was assessed.

Ethical considerations and statistical analysis
The Medical Ethics Committee at our institute approved all aforementioned study protocols, and written informed consent was obtained from all included patients. Statistical analysis was performed with SPSS 12.0.1 Software for Windows. For descriptive statistics mean (± SD) was used in case of a normal distribution of variables, and median (IQR) was used for variables with a skewed distribution. Where appropriate, the student t-test and the Mann-Whitney test were used.

RESULTS
Patients
A total of 44 patients was enrolled in the different study protocols, and all had finished treatment by November 30, 2007: 35 men, median age 68 (IQR 57-75) years, median Barrett’s length C5M7 (IQR C2-7, M4-9). Eleven patients were included in the first published trial on RF ablation, 12 patients in the second published trial, 9 patients in the ongoing European multicenter trial, and 12 patients were randomized to RF ablation in the ongoing randomized trial comparing RF ablation with SRER. A total of 36 ER procedures were performed in 31 patients prior to ablation. Nineteen were performed with the ER-cap technique after peroral ER, whereas 17 were performed after a peroral transmural approach. RF ablation was used in 31 patients prior to ablation. Nineteen were performed with the ER-cap technique after peroral ER, whereas 17 were performed after a peroral transmural approach. RF ablation, 12 patients in the second published trial, 9 patients in the ongoing European multicenter trial, and 12 patients were randomized to RF ablation in the ongoing randomized trial comparing RF ablation with SRER. A total of 36 ER procedures were performed in 31 patients prior to ablation. Nineteen were performed with the ER-cap technique after peroral ER, whereas 17 were performed after a peroral transmural approach.

Eradication of dysplasia and intestinal metaplasia (Fig. 1)
Complete histological eradication of dysplasia and complete endoscopic and histological clearance of IM was achieved in 43 patients (98%), after a median of 1 (IQR 1-2) circumferential ablation, 2 (IQR 1-2) focal ablation sessions, and escape ER in 3 patients. These three patients had small areas of residual columnar epithelium that persisted after the maximum number of allowed ablation sessions. These areas were resected using the MBM technique, and showed LGD (n=2) and HGD (n=1) upon histological evaluation. In one patient the proposed treatment protocol failed (2%). After 2 ER sessions, one circumferential and two focal ablations, a persisting area of suspicious looking columnar epithelium was observed and resected en-bloc using the MBM technique. Histology showed a T1sm1 adenocarcinoma, radically resected at the deep resection margins (R0). Two months after the escape ER, however, a suspicious 5-mm isle was identified. Additional resection of this area failed due to scarring resulting from the prior ER sessions. Since the patient strongly opposed against surgical treatment, the area was ablated with APC (forced coagulation 60 W, gas flow 1.6 L/min, ERBE Vio System, Erbe Elektromedizin GmbH, Tübingen, Germany). Two subsequent follow-up endoscopies with extensive biopsies and EUS showed no signs of recurrent dysplasia or IM.

Adverse events
In five patients a complication occurred during ER (16%): there were four mild bleedings that could be easily managed with endoscopic hemostatic techniques, and there was one oesophageal perforation. The perforation was treated conservatively by placement of clips (resolution clips, Boston Scientific, Limerick, Ireland, UK), and a covered oesophageal stent
RF ablation could be performed on an endoscopically flat mucosa. In the first study, six of the eleven patients had undergone an end-bloc resection of a visible lesion. No significant oesophageal scarring was observed in these patients, and no complications such as mucosal injury or dysphagia occurred after ablation treatment. In the other three studies, patients with prior piecemeal ER or multiple ER sessions were included, and mucosal injuries \( n=3 \) and dysphagia \( n=4 \) were observed for the first time. The four patients presenting with dysphagia had all undergone widespread ER and/or were treated with a relatively large diameter ablation catheter compared to the measured oesophageal diameter. To prevent complications resulting from ER scarring, it is in our opinion that one should limit the extent of ER of visible lesions to 50% of the circumference and 2 cm in length. In addition, the HALO\textsuperscript{360} ablation catheter size should be selected conservatively in cases of prior ER, preferably one size smaller than the catheter that would be selected based on the oesophageal inner diameter measurements. No oesophageal stenoses were observed in patients without a prior ER who were exclusively treated with ablation therapy. These results are in concordance with the U.S. multicenter AIM-study (ablation of intestinal metaplasia), where no strictures were reported in 100 patients treated with RF ablation.\textsuperscript{25} The absence of submucosal scarring as a result of RF ablation was also illustrated by our ability, in 3 patients, to remove focal areas of persistent Barrett’s mucosa after multiple ablation sessions using the multiband mucosectomy technique, without the need for submucosal lifting in three patients. This is a significant advantage compared to other endoscopic ablation techniques, after which escape treatment using ER is usually difficult as a result of submucosal scarring. In the 1475 biopsies obtained from neosquamous epithelium during follow-up, only one biopsy showed focal intestinal metaplasia hidden underneath the newly formed squamous epithelium. This biopsy was obtained at the upper end of an initial C9M10 Barrett’s segment, at the same level where at a following endoscopy a small 1 mm isle was identified with narrow-band imaging that may have been left untreated and unobserved at the preceding endoscopies. The fact that no buried glands were found in 8 biopsies obtained at this level during other follow-up endoscopies, and the absence of any IM in an ER specimen to remove the 1 mm isle, suggest that the biopsy with buried IM may have sampled this minute isle tangentially, rather than sampling truly buried Barrett’s glands. Although this hypothesis cannot be confirmed, the 0.07% of submucous IM still compares favorably to the 53% rate of buried glands reported after other ablation techniques.\textsuperscript{16–22} Our findings were in concordance with the absence of buried glands in 3007 neosquamous biopsies after RF ablation in the 100 patients described by Sharma \textit{et al.}\textsuperscript{29} Further studies on the adequacy of biopsies from the neosquamous epithelium after RF ablation should, however, clarify this issue further. Ablation at the GO-junction using the HALO\textsuperscript{360} catheter may be difficult, since the often tortuous course of the distal oesophagus and widening into a hiatal hernia, present in most BO patients, may impede good circumferential contact of the electrode with the mucosa at this level. In addition, endoscopically differentiating cardia mucosa from Barrett’s mucosa at the top of the gastric folds after ablation treatment may be difficult. Therefore, all patients were treated with ablation of the GO-junction using the HALO\textsuperscript{360} catheter. The HALO\textsuperscript{360} device allows for targeted, focal ablation, and was used to completely ablate the full circumference of the GO-junction to ensure that there was no small rim of residual Barrett’s mucosa left untreated at the transition of the columnar
epithelium into the neosquamous epithelium. Despite this approach, focal IM was diagnosed in five patients (11%) in a single biopsy obtained just distal to a normal appearing neosquamous-columnar junction at a single follow-up endoscopy, not reproduced at following endoscopies. The clinical relevance of this finding may be debated. Since all patients had an initial diagnosis of HGD or EC, one may argue that finding residual IM in the cardia during follow-up means that the IM had not been completely eradicated and that the patients were not completely cured from their underlying disease. IM of the cardia, however, can be detected in up to 25% of patients with a normal appearing squamous-columnar junction and is not considered a premalignant condition in those cases.31 In addition, we think that the patchy nature of this finding, and the fact that all patients will remain under endoscopic follow-up given their initial diagnosis of HGD/EC, does not justify additional treatment. As described in the “Materials and Methods” section, the treatment protocol for the second trial was improved based on the experiences from the first trial. These improvements were reflected in the median number of treatment sessions required to achieve complete eradication of intestinal metaplasia. Although the median BO length was longer in the second trial (7 cm [IQR 6.5-8] vs. 5 cm [IQR 4-7]), the mean number of ablation sessions was lower (3.4 vs. 4.2 sessions). The three most significant changes in the protocol were as follows: firstly, the HALO® catheter for secondary focal ablation only became available halfway through the first trial. Most patients had by then already undergone a second circumferential ablation session, regardless of the amount of residual BO, whereas in the second trial the HALO® device could be used to treat isles or tongues persisting after the first circumferential ablation. Secondly, the energy settings used for focal ablation were escalated from two ablations at 12 J/cm², to two times two ablations at 12 J/cm² (“double-double”), to double-double 15 J/cm² when the device became available during the first trial. In the second trial, the double-double 12 J/cm² dose was used initially, but in four patients a step up to double-double 15 J/cm² ablation was required to eradicate all IM. Since this “double-double 15 J/cm²” approach proved effective without causing significant side-effects, this dose is currently used in the ongoing studies. Thirdly, in the first study the electrode surface of the HALO® catheter was cleaned by inflating the balloon in the stomach and flushing it with water prior to the second ablation pass, without significant cleaning of the ablation zone. In the second trial the electrode surface was cleaned with a wet gauze outside the patient, whilst the ablation zone was thoroughly cleaned by suctioning off the debris and high-pressure rinsing with water by a spraying catheter. The effect of this improved cleaning protocol was observed in the amount of surface regression after the primary circumferential ablation session; the median percentage of surface regression improved from 90% in the first trial to 99% in the second trial [p=0.035].34 We think that, although requiring additional procedure minutes, meticulous cleaning of the electrode and ablation zone after the first pass improves the efficacy of RF ablation and should always be performed. The thorough cleaning protocol has, therefore, been incorporated in current trials.

CONCLUSION

Stepwise circumferential and focal radiofrequency ablation of Barrett’s epithelium with high-grade dysplasia or early cancer, with or without prior endoscopic resection of focal lesions, is highly effective in achieving complete eradication of dysplasia and intestinal metaplasia, without any serious adverse events. This novel treatment modality, therefore, appears to be a favorable alternative to oesophagectomy, radical endoscopic resection, argon plasma coagulation or photodynamic therapy.

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