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Eradication of Barrett Esophagus 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 nondysplastic Barrett esophagus (BE). The aim was to report the combined results of two published and two ongoing studies on radiofrequency ablation of BE with early neoplasia, as presented at SSAT presidential plenary session DDW 2008.
Methods Enrolled patients had BE ≤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 the entire Barrett epithelium was endoscopically and histologically eradicated.
Results Forty-four patients were included (35 men, median age 68 years, median BE 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 (n=32), low-grade (n=10), 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 were mucosal laceration at resection site (n=3) and transient dysphagia (n=4). After 21 months of follow-up (interquartile range 10–27), no dysplasia had recurred.
Conclusions Radiofrequency ablation, with or without prior endoscopic resection for visible abnormalities, is effective and safe in eradicating BE and associated neoplasia.

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Introduction

Barrett esophagus (BE) is a condition characterized by a change of the normal squamous esophageal lining into a columnar epithelium containing specialized intestinal metaplasia (IM), due to longstanding exposure to gastroesophageal refluxate.[1,2] BE is the best-recognized risk factor for the development of esophageal adenocarcinoma, and patients diagnosed with nondysplastic BE are, therefore, advised to undergo endoscopic surveillance with biopsies every 1 to 3 years.[3] By histological evaluation of these biopsies, malignant progression to low-grade dysplasia (LGD), high-grade dysplasia (HGD), or early cancer (EC) may be detected.[1,2] Early neoplasia (i.e., HGD and/or EC) can be treated by surgical esophagectomy. Given the morbidity and mortality that may be associated with esophagectomy, less invasive endoscopic alternatives have been considered. Endoscopic resection (ER) is the cornerstone of endoscopic therapy, since it provides a relatively large tissue specimen for histopathological evaluation, enabling proper selection of patients for subsequent endoscopic versus surgical therapy.[4–6] Selected patients with HGD or EC limited to the mucosal layer (T1m) have a minimal risk of lymphatic involvement, and ER in these patients has been reported to have a 5-year disease-specific survival of 95%.[5] Patients with submucosal invading lesions (T1sm), however, have a 15–30% risk of lymphatic involvement, warranting surgical esophagectomy with resection of surrounding lymph nodes.[7,8]

After focal ER of HGD/EC, the residual BE still holds the potential of malignant degeneration, and metachronous lesions occur in 30% of patients.[9] Additional treatment of the residual BE after focal ER is therefore advocated, and different treatment modalities have been proposed for this end. The residual BE may be completely removed with stepwise radical endoscopic resection (SRER).[10–12] This approach allows for histopathological evaluation of the entire BE segment and removes all oncogenetic alterations that are present in the pretreatment BE.[13] SRER, however, is technically demanding, only amendable for patients with a BE <5 cm, and has a significant stricture rate.[10–12] Ablating the residual BE with argon plasma coagulation (APC) or photodynamic therapy (PDT) has also been described, but these techniques do not always result in complete eradication of all Barrett epithelium, preexisting oncogenetic alterations may still be found in residual areas of BE, and both techniques are associated with issues of variable ablation depth and safety.[14–19] Furthermore, after APC and PDT, areas of IM may become hidden underneath the newly formed squamous epithelium after ablation (a.k.a., "buried Barrett"), and some fear that these buried glands may progress to dysplasia and adenocarcinoma without being detected endoscopically.[20,21] Stepwise circumferential and focal radiofrequency ablation (RFA) using the HALO system is a novel and promising ablative modality. Primary circumferential ablation is performed using a balloon-based bipolar electrode, while secondary treatment of residual BE is performed using an endoscope-mounted bipolar electrode on an articulated platform. Studies involving circumferential ablation were initially conducted in the porcine animal model and in humans prior to esophagectomy in order to determine dosing and technique parameters.[22–24] Subsequently, RFA has been proven safe and effective for the eradication of dysplasia and IM in a number of clinical trials involving patients without dysplasia, with LGD or HGD, and after ER of EC and visible lesions.[25–27] In addition, no buried Barrett glands have been found in over 4,000 neosquamous biopsies obtained during follow-up,[25–27] oncogenetic abnormalities as present in the pretreatment BE are absent in the regenerated neosquamous epithelium after RFA,[28] and the functional integrity of the esophagus is not affected by RFA.[29] In this paper, we will present the results reported in Abstract 215, which was selected for oral presentation during the SSAT presidential plenary A session, at the Digestive Disease Week 2008, San Diego, CA, USA.[30] We will review our results, as available up until November 30, 2007, of stepwise circumferential and focal ablation in 44 patients with BE 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 RFA on BE with early neoplasia, and conducted at the Academic Medical Center, Amsterdam, the Netherlands. Patients were eligible if they had endoscopically visible BE (≤12 cm) with HGD or EC diagnosed at two separate endoscopies by an experienced gastrointestinal pathologist (FtK). Any visible endoscopic abnormalities, or EC without a clear lesion detected by biopsies, were removed with ER prior to ablation, as 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 undiffer-

entiated cancer (G3, G4), or presence of lymphatic/vascular invasion (V+). Patients with esophageal 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 RFA of HGD/EC in patients with a median BE segment of 5 cm [interquartile range (IQR) 5–7] using the HALO^{360} ablation catheter, with prior en-bloc ER of visible lesions and EC. Halfway through this study, the focal HALO^{90} ablation device became available.[26]
2. The second prospective study on RFA for the treatment of HGD and EC in patients with a median BE 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 HALO^{90} device was available from the start of the study. In addition, patients with prior piecemeal ER of visible lesions were also included.[27]
3. The first ongoing European multicenter trial to evaluate the safety and efficacy of RFA in patients with a Barrett segment up to 12 cm long, with early neoplasia, with or without prior ER.[31]
4. An ongoing prospective randomized multicenter trial comparing SRER and RFA for the eradication of dysplasia and IM in patients with a BE <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 h 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 2 weeks after each therapeutic endoscopy. In case of postprocedural 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

Both ablation systems that were used (HALO Ablation Systems, BÂRRX Medical, Sunnyvale, CA, USA) have 510(k) clearance by the Food and Drug Administration in the USA and the CE Mark for Europe for the treatment of BE. The HALO ablation system comprises two distinct ablation systems: the HALO^{360} system for primary circumferential ablation and the HALO^{90} system for secondary focal ablation. The HALO^{360} system includes an energy generator, ablation catheters, and sizing catheters. The HALO^{360} 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 esophageal diameter. The sizing balloon catheter consists of a 4-cm noncompliant balloon that is used for measuring the inner esophageal diameter of the targeted portion of the esophagus, prior to circumferential ablation. The sizing catheter is introduced over a guide-wire and its balloon is inflated in an automated manner to 4 psi (0.28 atm). Based on the baseline balloon volume–geometry and the volume needed to inflate the balloon to 4 psi, the mean esophageal inner diameter is calculated. Measurement is repeated moving distally, for every centimeter of the targeted esophagus, until an increase in diameter indicates the transition to the stomach or hiatal hernia. The HALO^{360} 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 HALO^{360} ablation balloon is available in five outer diameter sizes (22, 25, 28, 31, and 34 mm). Extensive dosimetry studies in the porcine esophagus and human esophagus prior to surgical esophagectomy have shown that, for circumferential ablation, two applications of RF energy at 10–12 J/cm^2 and 40 W/cm^2 is the most effective regimen to ablate the full thickness of the epithelial layer, without injuring the submucosa. Focal ablation of residual BE tissue was performed with the HALO^{90} system. The HALO^{90} system consists of the focal ablation catheter and an energy generator. The bipolar electrode array of the HALO^{90} 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 are identical to those of the balloon-based electrode (Fig. 1).

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 have the BE segment thoroughly inspected by an expert endoscopist. The maximum length of the circumferential and contiguous Barrett epithelium was recorded according to the Prague classification system.[32] The maximum proximal extent of the Barrett mucosa (i.e., isles) was additionally documented, as isolated islands are not categorized in the Prague system.

Figure 1 The HALO ablation system used for circumferential and focal RFA of BE. *Left*: The HALO^{360} generator and HALO^{360} ablation catheter used for primary circumferential ablation. *Right*: The HALO^{90} ablation catheter fitted on the tip of an endoscope, for secondary focal ablation.

Visible lesions were classified in concordance with the Paris classification; type 0-I being polypoid, type 0-IIa slightly elevated, type 0-IIb flat, type 0-IIc depressed, and type 0-III excavated.[33] Biopsies were obtained from all visible lesions detected upon white light endoscopy or by advanced imaging techniques (NBI, autofluorescent imaging), and random four-quadrant biopsies were taken every 1–2 cm of the whole BE segment. To assess infiltration depth of lesions and lymph node involvement, all patients underwent endoscopic ultrasound (EUS) using electronic radial endoscopes (GF-UE160, Olympus GmbH, Hamburg, Germany) in conjunction with an Aloka SSD-5000 ProSound processor (Aloka, Meerbusch, Germany). In addition, computed tomography scanning of thorax and upper one-third of the abdomen was performed in all patients with EC to detect any metastatic disease.

ER Procedures

All visible lesions and EC were removed with 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) after submucosal lifting, or the multiband mucosectomy (MBM) technique (Duette™, 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 esophageal wall was sprayed with acetylcysteine (1%) and flushed with plain water to remove excessive mucous. After recording the esophageal landmarks (i.e., top gastric folds, maximum extent of BE), the endoscope was removed, leaving a guide-wire (Amplatz extra stiff 0.035 in., Cook, Denmark, Europe) behind. A sizing balloon was introduced and the inner esophageal diameter was measured for every centimeter of the targeted BE segment, moving 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 1 cm above the maximum proximal extent of the BE, the balloon was inflated, and the electrode was activated (12 J/cm^2, 40 W/cm^2). This resulted in a 3-cm-long, circumferentially ablated segment. Depending on the length of the BE 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 BE segment had received one application of energy. Then, the ablation zone and electrode surface were cleaned. In the first 11 patients,[26] 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,[27] 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^{90} system, the mucosa was sprayed with acetylcysteine (1%) and flushed with plain water. The HALO^{90} electrode was fitted on the tip of the endoscope, introduced, and used for targeted ablation

of residual Barrett epithelium. The squamocolumnar junction was routinely ablated when the HALO^{90} electrode was introduced to ablate residual isles or tongues. The HALO^{90} system only became available at the end of the first trial, and the energy settings were escalated from 2×12 to 2×2×12 J/cm^2 and, eventually, to 2×2×15 J/cm^2 at 40 W/cm^2. All areas were ablated with cleaning of the electrode and ablated area in between ablation cycles, as previously described for the circumferential ablation procedure.

Treatment Protocol

After a minimum of 6 weeks after any ER, patients were treated with primary circumferential ablation using the HALO^{360} system. After 6 to 8 weeks, patients were scheduled for endoscopy to assess the treatment effect. Depending on the extent of residual BE, patients underwent a second HALO^{360} procedure, or secondary focal ablation using the HALO^{90} system. In the first study protocol, all patients were treated with a second circumferential ablation using the HALO^{360} system, regardless of the extent of the residual BE, since the HALO^{90} system for focal ablation was only introduced halfway through the study.[26] Additional ablation was repeated every 6–8 weeks, and a maximum number of two circumferential and three focal ablation sessions were allowed to achieve complete eradication of all IM. 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 neosquamocolumnar junction and every 1–2 cm from the neosquamous epithelium over the full length of the initial BE segment.

Follow-up

Patients were scheduled for follow-up endoscopy 2, 6, and 12 months after the last treatment session and then annually. High-resolution endoscopes with narrow-band imaging facilities were used to thoroughly inspect the esophagus for recurrence of IM, and four-quadrant biopsies were obtained for every 1–2 cm of the neosquamous epithelium over the original BE length and immediately distal to the neosquamocolumnar 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 (FtK). The ER specimens were evaluated for the presence of dysplasia according to the revised Vienna classification,[34] tumor infiltration depth, tumor 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 30 November 2007: 35 men, median age 68 (IQR 57–75) years, median Barrett length C5M7 (IQR C2–7, M4–9). Eleven patients were included in the first published trial on RFA,[26] 12 patients in the second published trial,[27] nine patients in the ongoing European multicenter trial,[31] and 12 patients were randomized to RFA in the ongoing randomized trial comparing RFA 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 submucosal lifting and 17 with the multiband mucosectomy technique. There were 16 en-bloc and 20 piecemeal resections, with a median of two pieces per resection (IQR 2–3). The worst histological grade per patient found in the ER specimens was EC in 16 patients, all radically resected at the deep resection margin, HGD in 12 patients, and LGD in three patients. The worst histological grade of the BE after any ER, but prior to the first ablation procedure, was HGD in 32 patients, LGD in 10 patients, and residual nondysplastic IM in two patients.

Eradication of Dysplasia and IM

Complete histological eradication of dysplasia and complete endoscopic and histological clearance of IM was achieved in

43 patients (98%), after a median of one (IQR 1–2) circumferential ablation, two (IQR 1–2) focal ablation sessions, and escape ER in three patients (Fig. 2). 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 two 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 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 esophageal perforation. The perforation was treated conservatively by placement of clips (resolution clips, Boston Scientific), and a covered esophageal stent (Esophageal Choo Stent, Fujinon Medical Holland B.V., Veenendaal, the Netherlands). In addition, the patient received immediate intravenous administration of antibiotics and acid suppressant therapy, an esophageal tube for suction and nil per mouth. He remained asymptomatic and no signs of leakage were seen on contrast swallowing examination. After 2 months, the defect had completely healed and treatment could be resumed. After initial circumferential ablation, a nontransmural laceration was

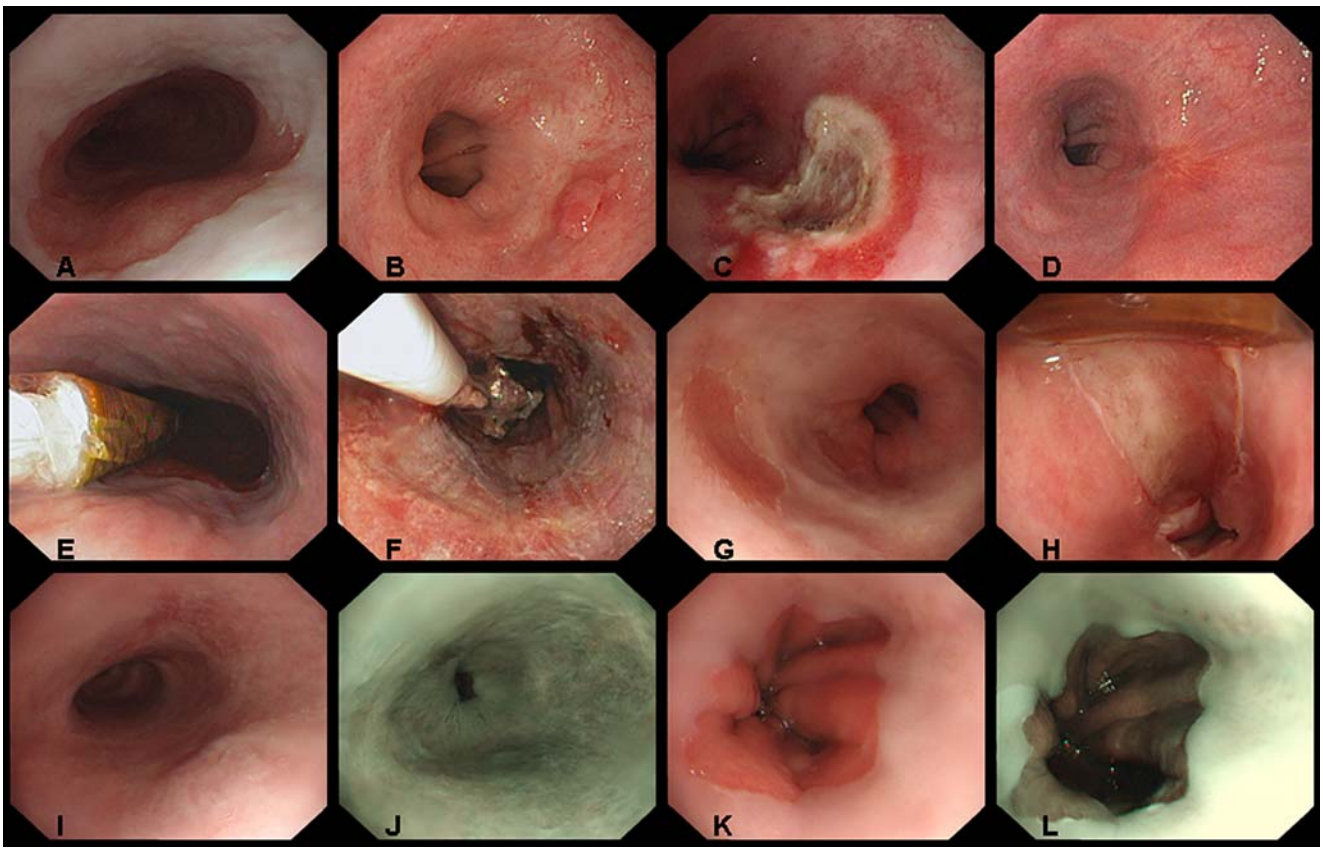

Figure 2 Endoscopic treatment of a C8M9 BE with HGD and a visible lesion treated with a combination of ER and RFA using the HALO system. **A** Antegrade view on a C8M9 BE. **B** View on a 0-I–IIa lesion at the 5 o'clock position. **C** View on the resection wound. The specimen showed a submucosal cancer with radical vertical and lateral resection margins. **D** Same area 6 weeks after the ER. The wound has healed completely with scarring. **E** HALO^{360} ablation balloon positioned 1 cm above the maximum extent of the BE. **F** Ablation effect after cleaning off the coagulum. **G** Residual isle of Barrett mucosa remaining 6 weeks after prior circumferential ablation. **H** Effect immediately after ablation with the focal ablation device. **I** Complete removal of he whole Barrett segment mucosa after one ER and two ablation sessions. **J** Corresponding image with NBI. **K** neosquamocolumnar junction after treatment. **L** Corresponding image with NBI.

observed in three patients (7%). All patients remained asymptomatic and no therapeutic interventions were required. The lacerations all occurred at the level of the ER scar in patients were an ablation catheter with a relatively large diameter was selected in relation to the esophageal inner diameter and who had undergone prior ER with a median extent of 33% of the circumference and 2.5 cm in length. Four patients (9%) developed dysphagia after ablation that could be resolved with a median of three (IQR 1–5) endoscopic dilatations. These patients all had prior widespread ER [median of three (IQR 1–5) pieces per procedure, 50% of the circumference and 2 cm in length], two had undergone two ER sessions, and one patient had a narrow esophagus at baseline. No lacerations or stenoses were observed in patients after ablative therapy if they had not had prior ER. Four patients (9%) were hospitalized after primary circumferential ablation for observation of fever (n=1), chest pain (n=2), and superficial mucosal laceration at a previous ER site followed by a negative contrast study (n=1). After conservative treatment and analgesics, all were discharged after 24–48 h.

Follow-up

During a median follow-up of 21 (10–27) months, no recurrence of dysplasia was observed. In one patient, a 1-mm BE island was identified 16 months after the last treatment, located at the upper end of the initial C9M10 Barrett segment; none of the other 43 patients showed endoscopic signs of BE during follow-up. Five patients had focal IM detected in biopsies obtained immediately distal to an endoscopically normal appearing neosquamocolumnar junction at a single follow-up endoscopy. In 1,475 biopsies obtained from neosquamous epithelium, only one (0.07%) showed buried glandular mucosa.

Discussion

This manuscript reviews our interim results of RFA for BE with early neoplasia from four different study protocols at the Academic Medical Center, Amsterdam, the Netherlands, and was written to accompany our oral presentation during the SSAT presidential plenary A session, at the Digestive Disease Week 2008.[30] A total of 44 consecutive patients with BE containing HGD and/or EC had finished treatment by November 30, 2007. Of these, 23 patients were treated in the first two pilot studies worldwide to evaluate the use of stepwise circumferential and focal ablation of BE with HGD/EC after prior ER of any visible abnormalities and EC.[26,27] The other 21 patients were included for the first European multicenter study on RFA of BE up to 12 cm containing HGD/EC,[31] or in an ongoing study comparing SRER with RFA in patients with early neoplasia in BE<5 cm. In all four studies, it was protocolized that any visible lesions and EC had to be removed with ER prior to ablation to enable histological evaluation for accurate staging of the infiltration depth and tumor differentiation and to ensure that subsequent RFA could be performed on an endoscopically flat mucosa. In the first study, six of the 11 patients had undergone an en-bloc resection of a visible lesion. No significant esophageal 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 esophageal 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^{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 esophageal inner diameter measurements. No esophageal stenoses were observed in patients without a prior ER who were exclusively treated with ablation therapy. These results are in concordance with the USA multicenter ablation of IM study, where no strictures were reported in 100 patients treated with RFA.[25] The absence of submucosal scarring as a result of RFA was also illustrated by our ability, in three patients, to remove focal areas of persistent Barrett 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 1,475 biopsies obtained from neosquamous epithelium during follow-up, only one biopsy showed focal IM hidden underneath the newly formed squamous epithelium. This biopsy was obtained at the upper end of an initial C9M10 Barrett 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 eight 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, suggests that the biopsy with buried IM may have sampled this minute isle tangentially, rather than sampling truly buried Barrett glands. Although this hypothesis cannot be confirmed, the 0.07% of subsquamous IM still compares

favorably to the 53% rate of buried glands reported after other ablation techniques.[14–21] Our findings were in concordance with the absence of buried glands in 3,007 neosquamous biopsies after RF ablation in the 100 patients described by Sharma et al.[25] Further studies on the adequacy of biopsies from the neosquamous epithelium after RFA should, however, clarify this issue further. Ablation at the GE-junction using the HALO^{360} catheter may be difficult, since the often tortuous course of the distal esophagus and widening into a hiatal hernia, present in most BE patients, may impede good circumferential contact of the electrode with the mucosa at this level. In addition, endoscopically differentiating cardia mucosa from Barrett mucosa at the top of the gastric folds after ablation treatment may be difficult. Therefore, all patients were treated with ablation of the GE-junction using the HALO^{90} catheter. The HALO^{90} device allows for targeted, focal ablation and was used to completely ablate the full circumference of the GE-junction to ensure that there was no small rim of residual Barrett 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 neosquamocolumnar 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 squamocolumnar junction and is not considered a premalignant condition in those cases.[35] 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 IM. Although the median BE 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^{90} 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 BE, whereas in the second trial, the HALO^{90} 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/cm^2, to two times two ablations at 12 J/cm^2 ("double-double"), to double-double 15 J/cm^2 when the device became available during the first trial. In the second trial, the double-double 12 J/cm^2 dose was used initially, but in four patients, a step-up to double-double 15 J/cm^2 ablation was required to eradicate all IM. Since this "double-double 15 J/cm^2" 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^{360} 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, while the ablation zone was thoroughly cleaned by suctioning off the debris and high-pressure rinsing with water through 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).[36] We think that, although it requires additional procedure minutes, meticulous cleaning of the electrode and ablation zone after the first pass improves the efficacy of RFA and should always be performed. The thorough cleaning protocol has, therefore, been incorporated in current trials.

Conclusion

Stepwise circumferential and focal RFA of Barrett epithelium with HGD or EC, with or without prior ER of focal lesions, is highly effective in achieving complete eradication of dysplasia and IM, without any serious adverse events. This novel treatment modality, therefore, appears to be a favorable alternative to esophagectomy, radical ER, APC, or PDT.

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Discussion

Eradication of Barrett Esophagus with Early Neoplasia by Radiofrequency Ablation, With or Without Endoscopic Resection

Jeffrey H. Peters, M.D. (Rochester, NY)

Members and guests, I believe we have just heard what I would call a paradigm changing paper. The search for a treatment for the epithelial changes of Barrett's, as opposed to the reflux related disease, has been ongoing for more than two decades. Drug therapy, surgery, a multitude of ablation technologies, thermal energy, laser, photodynamic therapy, all of these have fallen well short of the safety and effectiveness necessary for everyday clinical use. Radiofrequency ablation, however, seems poised to change this paradigm.

The authors have reported successful endoscopic mucosal resection followed by RF ablation in a relatively large cohort of patients with Barrett's and high grade dysplasia and/or early neoplasia. Successful eradication, as you heard, occurred in 43 of the 44 patients. There are a few caveats, however, that deserve highlighting. Firstly, remember, this is not a trial of RF ablation alone. Three quarters of the patients had mucosal resection prior to the RF; also, a very careful patient selection protocol was necessary to exclude those with submucosal cancer, a key issue; and finally, the longevity of the ablation is unknown at present. On the other hand, ablation was highly effective, successful, and was not associated with the development of strictures or buried submucosal glands.

This technology, this study, and others like presented at this meeting. Are changing the treatment paradigm of dysplastic Barrett's esophagus and early cancer. This is an excellent and well done study from one of the world's best units treating early esophageal neoplasia.

Jacques, I have a few brief questions for you. Firstly, visible lesions were key to the EMR technique. Most visible lesions are submucosal. You excluded all submucosal lesions. This suggests to me a very highly select patient population. Further, you didn't mention whether you had any patients with cancer on their biopsy that did not have visible lesions and what you would do under those circumstances. Surely you encountered such patients. Would you suggest how to approach these?

Second, ablation at the gastroesophageal junction may be an Achilles' heel of this technology. Reading the manuscript, Jacques has chosen to ignore biopsies right at the top of the stomach in the efficacy assessment. I would like for you to comment on this issue.

Finally, although your 98% success rate is spectacular, more widespread experiences suggest that it may not be quite this easy. Has your near uniform success continued as your experience has grown?

This is a wonderful contribution from the Amsterdam group and it is really a pleasure to see it presented here at the SSAT. Thank you for the honor of discussing it.

Jacques J. Bergman, M.D. (Amsterdam, Netherlands)

ell, thank you, Jeff, for those questions and those kind words. Coming back to your first question, are most visible lesions submucosal, the answer is no. The vast majority of visible lesions that we encounter are mucosal, but you bring up an important issue: we should simply teach our endoscopists how visual abnormalities look like so that they detect them at a stage that they are still mucosal. In our study, we excluded approximately 15% of our patients after EMR showed the resected lesion to be submucosal.

What do we do if we don't see visual abnormalities? I think that good endoscopic inspection is crucial before you decide that there is nothing there. We have a very low threshold of calling something a visual abnormality, and I would urge everybody who steps into this technique to do this. EMR is the crucial here: it is the final step in the diagnostic work-up and it is the first step in therapy. If you cannot do an EMR, you should not ablate. So if we didn't see any visual abnormalities, but as you said, it is only a quarter of our patient population, then that patient is eligible for immediate radiofrequency ablation.

The IM immediately distal to the neo Z line is a tough issue. We had that happen in five of our patients who during

follow up had IM detected in a single biopsy that was obtained immediately distal to the neo Z line. At subsequent follow up endoscopies, this was not reproduced. I think it is all reflecting sampling error. It will be very difficult to call an end point for absence of IM at the Z-line. What to do if you take biopsies at a certain point and you don't find it and you don't find it at the second or the third follow up and it the pops up at the fourth and the fifth and then again is absent at the sixth, how do we call this? This is one of the issues that I think we need to clarify if we define outcomes, and especially if we go into the long term follow up of these patients. You rightfully pointed out that we don't have long term follow up on these patients. We simply have to continue looking at these patients to prove that the complete removal of all Barrett's is indeed maintained. If we look at oncogenetic abnormalities, if we do brush cytology, if we do biopsies, then we see that the neo squamous epithelium really is "clean," in that sense.

Experience, how did it change during our consecutive studies? It maintained at the same level. We are presenting at this meeting the first results of the European multicenter study with three centers. The success rate for that was 96%. We are currently doing a multicenter study with 11 European centers, and we hope to present those data to you next year.

Stephen Attwood, M.D. (North Shields, UK)

Jacques, the real test of any new treatment is a randomized controlled trial. Can you randomize between EMR versus EMR and HALO, or can you randomize between surgical resection versus EMR and HALO, and what are the hurdles to setting up such a randomized trial?

Dr. Bergman: My presentation is competing with the presentation of the results of a randomized sham controlled study that is presented at the AGA plenary session. I think the main issue is if you want to do randomized studies, at least in the Netherlands, we have to do randomized studies comparing endoscopic treatment with another endoscopic treatment. Our Dutch guidelines state specifically that for the patient category that we included in this study, endoscopic treatment is the treatment of choice. So we could never do a randomized study with a surgical arm for this group. I know that in the U.K. there are thoughts about that, and of course, it will be the ultimate proof. In the Netherlands, we have moved beyond that. According to our guidelines, we don't need more proof to treat these patients endoscopically.

John G. Hunter, M.D. (Portland, OR)

As surgeons, we were very happy to be part of the randomized U.S. trial of radiofrequency ablation of HGD, which will be presented at the AGA. The proof of this therapy will be durability, and you have pointed out that 21 months is a little early to prove that the natural history of HGD has been changed by this therapy. The second proof is the elimination of sub-squamous glands, which have the potential to become malignant. In your salvage EMR cases, did you find sub-squamous glands beneath that beautiful neo-squamous epithelium?

Dr. Bergman: The first 23 patients that were in our studies, the first two studies that were published in Endoscopy this month, were all called back the last two months for an EMR of the neo squamous mucosa. So we EMR'd a part of their neo squamous mucosa out. Sixteen have been completed, and preliminary results don't show any submucosal or sub squamous IM in any of these. We took biopsies of the neo squamous mucosa and biopsies of untreated epithelium and, blinded, gave them to two expert pathologists asking them what is neo squamous and what is normal squamous. They cannot tell the difference.?