

Radiofrequency ablation for total Barrett's eradication: a description of the endoscopic technique, its clinical results and future prospects

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Stepwise circumferential and focal radiofrequency ablation using the HALO system is a novel and promising ablative modality for Barrett's esophagus. Primary circumferential ablation is performed using a balloon-based bipolar electrode, while secondary treatment of residual Barrett's epithelium is performed using an endoscope-mounted bipolar electrode on an articulated platform. It has been used as a single-modality treatment or in combination with other therapies. Recent studies suggest that this ablation technique

is highly effective in removing Barrett's mucosa and its associated dysplasia without the known drawbacks of photodynamic therapy or argon plasma coagulation, such as esophageal stenosis and subsquamous foci of intestinal metaplasia (also known as "buried Barrett").

In this review paper we will explain the technical background of radiofrequency ablation using the HALO system, give a summary of its current status, and speculate on possible future applica-

Introduction

Because of the morbidity and mortality that may be associated with esophagectomy, less invasive endoscopic treatment modalities have emerged to treat high-grade dysplasia (HGD) and intramucosal cancer (IMC) in Barrett's esophagus. Endoscopic resection of focal lesions permits histological correlation, enabling optimal patient selection [1]. Patients with submucosally invading lesions should be referred for surgery because they have a 15%–30% risk of having positive local lymph nodes, whereas this risk is minimal in patients with IMC [2,3]. Endoscopic resection, however, only removes a focal area from the Barrett's esophagus, leaving the patient at risk of metachronous lesions during follow-up [4]. To prevent this, endoscopic resection has been combined with ablative therapy, such as photodynamic therapy (PDT) or argon plasma coagulation (APC), to remove residual (dysplastic) Barrett's mucosa [5–9]. PDT and APC, however, have significant shortcomings. First, they often do not result in complete ablation of the whole Barrett's esophagus [5–9]. Second, studies have shown that oncogenetic alterations, as present in Barrett's esophagus prior to ablation, can still be found in areas of residual Barrett's esophagus and these may be associated with recurrence of neoplasia [10]. Third, foci of intestinal metaplasia

may be hidden underneath the neosquamous mucosa after treatment (this is also known as "buried Barrett"), and some fear that these areas may progress to cancer without being detected endoscopically due to their hidden nature [11,12]. Lastly, PDT and APC are associated with complications, of which esophageal stenosis is the most relevant [5–9].

Stepwise circumferential and focal radiofrequency ablation (RFA) using the HALO system is a relatively new endoscopic treatment modality for Barrett's esophagus [13–15]. Recent studies suggest that this ablation technique is highly effective in removing Barrett's mucosa and associated dysplasia without the aforementioned drawbacks of other ablation techniques [16–22]. In this review we will explain the technical background of RFA, give a summary of its current status, and speculate on possible future applications.

Technical background

The HALO system comprises two distinct ablation systems: the HALO³⁶⁰ system for primary circumferential RFA and the HALO⁹⁰ system for secondary focal RFA or primarily as treatment for short-segment Barrett's esophagus.



Fig. 1 The HALO system for stepwise circumferential and focal radiofrequency ablation (RFA). Upper left: The HALO³⁶⁰ generator with integrated pressure:volume system, used to inflate the sizing and ablation catheters, to calculate esophageal inner diameter, and to deliver radiofrequency energy to the ablation catheter. Upper right: The HALO³⁶⁰⁺ ablation catheter. Lower left: The HALO⁹⁰ energy generator for delivery of radiofrequency energy. Lower right: The HALO⁹⁰ catheter fitted on the tip of an endoscope, without impairing the endoscopic view or function. Reproduced with permission from www.endosurgery.eu.

Prior to circumferential RFA, a sizing catheter with a 4-cm-long noncompliant balloon at its distal end is used to measure the inner esophageal diameter. Upon activation via a foot switch, the sizing balloon is inflated by the HALO³⁶⁰ energy generator, and the mean esophageal inner diameter is automatically calculated for the entire length of the 4-cm-long balloon.

The HALO³⁶⁰⁺ ablation catheter holds a balloon at its distal end, with a 3-cm-long bipolar electrode on its outer surface (Fig. 1).

The HALO³⁶⁰⁺ ablation balloon is available in five outer diameters (22, 25, 28, 31, and 34 mm). The ablation catheter is inflated via a foot switch, and upon activation RF energy is delivered to the electrode. Extensive dosimetry studies have shown that for circumferential ablation two applications of RF energy at 10 or 12 J/cm² and 40 W/cm² are the most effective regimens to ablate the full thickness of the epithelium [13–15].

Focal RFA of Barrett's esophagus may be conducted with the HALO⁹⁰ system, which consists of an endoscope-mounted ablation catheter and an energy generator similar to the HALO³⁶⁰

generator, but without the pressure:volume system (Fig. 1). The electrode surface is 20 mm long and 13 mm wide, allowing selective focal ablation. Currently, a “double × double” 12- or 15-J/cm² and 40-W/cm² ablation regimen is advised to achieve effective eradication of intestinal metaplasia.

For both HALO ablation devices, a HALO^{360/90} energy generator automatically delivers RF energy to the electrode upon activation via a foot switch. Due to the combination of high-power density and a preset energy density, ablation results in uniform tissue penetration depth (1000 μm) that is not operator-dependent. RFA using the HALO system therefore results in controlled destruction of the columnar epithelial layer, the lamina propria, and part of the lamina muscularis mucosae, while the submucosa typically remains uninjured [13–15].

The HALO³⁶⁰ and HALO⁹⁰ ablation procedures

Stepwise circumferential and focal ablation of a Barrett's esophagus generally starts with a circumferential ablation procedure using the HALO³⁶⁰ system (Fig. 2), which comprises the following steps:

1. Recording esophageal landmarks. After spraying the esophageal wall with acetylcysteine (1%) and flushing it with plain water to remove excessive mucus, the top of the gastric folds and the furthest proximal extent of the Barrett's esophagus (including isles) are recorded for reference during the sizing and ablation procedure. Then a stiff guide wire (e.g., Amplatz extra stiff 0.035-inch; Cook Europe, Bjaeverskov, Denmark) or metal wire is introduced and the endoscope is removed.

2. Sizing inner esophageal diameter. The sizing procedure is generally performed as a “blind” procedure using the 1-cm scale on the catheter shaft for reference. However, in special cases (e.g., localized narrowing) endoscopic visual control may be useful to ensure that sizing is performed at the required level. The measurement cycle is started with the catheter positioned 5 cm above the furthest proximal extent of the Barrett's esophagus (the distal end of the balloon is then located 1 cm above any Barrett's mucosa), and measurement is repeated for every centimeter of the targeted portion of the esophagus, advancing the balloon distally in 1-cm linear increments.

3. Selecting the appropriate HALO³⁶⁰⁺ ablation catheter. On the basis of the inner esophageal diameter measurements an appropriate HALO³⁶⁰⁺ ablation catheter is selected, which is smaller

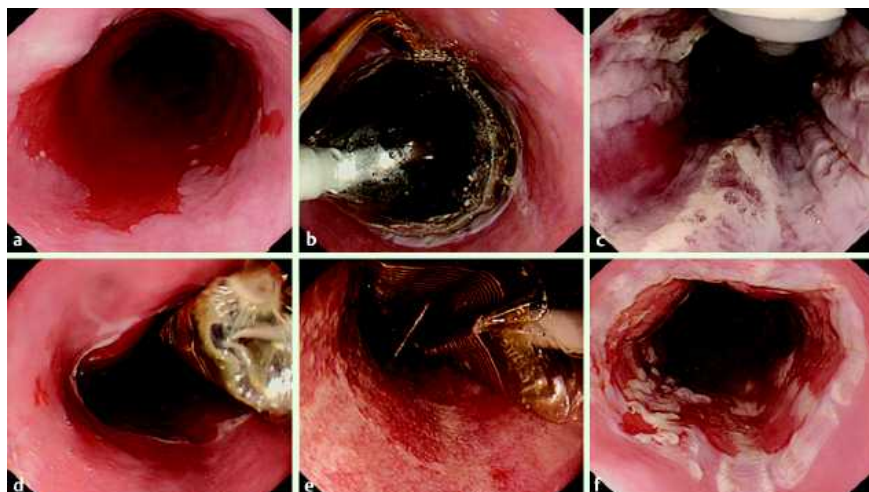


Fig. 2 Endoscopic appearance of a circumferential ablation procedure using the HALO³⁶⁰ system. **a** C8M9 Barrett's esophagus with high-grade dysplasia (HGD). **b** The HALO³⁶⁰⁺ catheter is introduced and inflated at the upper end of the Barrett's segment. **c** After the first application of energy the whitish coagulum resulting from the ablation shows after the catheter is deflated and advanced distally. **d** After ablation of the whole Barrett's segment and cleaning of the electrode and ablation zone, the catheter is reintroduced for a second ablation pass. **e** The second ablation pass results in a tan-colored ablation zone. **f** Treatment effect after two circumferential ablation passes. Reproduced with permission from www.endosurgery.eu.

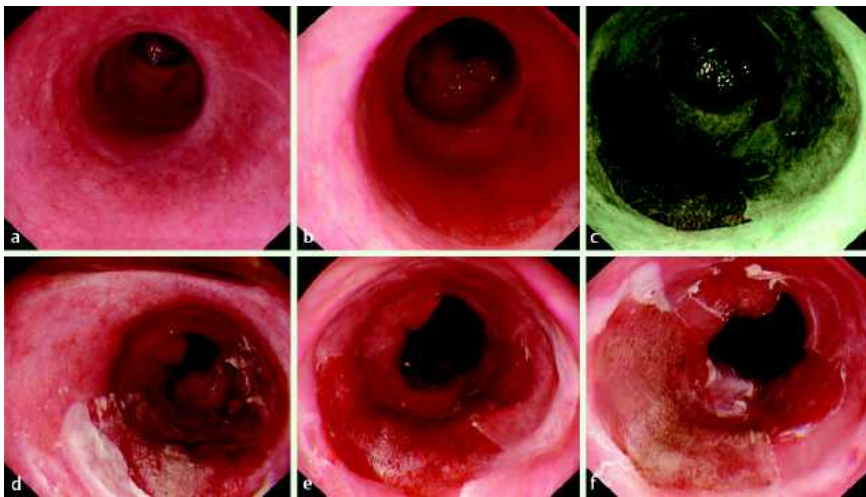


Fig. 3 Endoscopic appearance of a focal ablation procedure using the HALO⁹⁰ system. **a** Antegrade view of an initial C6M7 Barrett's esophagus 6 weeks after primary circumferential ablation. **b** Residual isles of Barrett's mucosa; **c** Corresponding image with narrow-band imaging (NBI). **d** Ablation effect immediately after ablation with the HALO⁹⁰ system; the distal end of the catheter is visible at the 12 o'clock position in the endoscopic field. **e** Endoscopic appearance after the first ablation pass (2 ×, 15 J/cm²) and cleaning of the ablation zones. **f** After the second ablation pass (2 × 2, 15 J/cm²) the ablation zones have a tan-colored appearance. Reproduced with permission from www.endosurgery.eu.

than the smallest measured diameter. In patients who have undergone prior endoscopic resection the ablation catheter should be selected conservatively (see below under “Unanswered questions and directions for future research”) [23].

4. First circumferential ablation pass. The HALO³⁶⁰⁺ catheter is introduced, followed by the endoscope. Under endoscopic visualization the proximal margin of the electrode is placed 1 cm above the furthest proximal extent of the Barrett's esophagus. The balloon is inflated, and the electrode is then activated via a foot switch. Moving from proximal to distal the balloon is repositioned, allowing a small overlap of 5–10 mm with the previous ablation zone, until the entire Barrett's esophagus has been ablated.

5. Cleaning procedure between ablation cycles. After the first ablation pass the ablation catheter is removed and the electrode surface is cleaned of coagulum with wet gauze. A soft distal attachment cap (e.g., model MB-046; Olympus, Tokyo, Japan) is fitted on the tip of the endoscope, and the soft extending rim of the cap can be used to slough off the coagulum from the ablation zone (▶ Fig. 2). Additional forceful spraying of plain water through a spraying catheter using a high-pressure pistol (e.g., Alliance; Boston Scientific, Limerick, Ireland) can be used to “blast” off residual coagulum. Although the extensive cleaning procedure requires extra procedure time, it has been proven to increase the efficacy of the first ablation session from 90% surface regression to 95% [21, 22, 24].

6. Second ablation pass. After the cleaning procedure, the entire Barrett's esophagus is ablated a second time.

A minimum of 8 weeks after the first circumferential ablation treatment, patients are rescheduled to undergo a second ablation. Patients with residual circumferential Barrett's esophagus greater than 2 cm in size and/or multiple isles or tongues are treated with a second circumferential ablation. Patients with an irregular Z-line, small tongues, circumferential extent below 2 cm, or diffuse isles are treated with focal ablation using the HALO⁹⁰ system (▶ Fig. 3), following the steps below:

1. Introduction of the HALO90 catheter. The HALO⁹⁰ electrode is fitted on the tip of the endoscope and positioned at the 12 o'clock position in the endoscopic video image. When the laryngeal cavity is visualized the tip of the endoscope is deflected slightly downward, allowing the leading edge of the catheter to be passed behind the arytenoids. The patient is asked to swallow and the endoscope is gently advanced. In about 8% of cases in-

roducing the HALO⁹⁰ catheter may prove difficult. In such cases the presence of a Zenker diverticulum should be excluded, and a biopsy forceps, a guide wire, or a spraying catheter may be used as a guide to enter the proximal esophagus (▶ Fig. 4).

2. First ablation pass. Residual Barrett's epithelium is positioned at the 12 o'clock position in the endoscopic video image. The electrode is brought into close contact with the mucosa, deflected upward, and activated, then kept in place and immediately activated again, resulting in a “double” application of energy. Ablation of the entire Z-line with the HALO⁹⁰ device is recommended, to ensure eradication of intestinal metaplasia at the gastroesophageal junction.

3. Cleaning procedure. After all residual Barrett's esophagus has been ablated, the coagulum is carefully pushed off the esophageal wall with the leading edge of the electrode, followed by cleaning of the electrode outside the patient and cleaning of the ablation zone with forceful spraying of water as described above.

4. Second ablation pass. Using the ablation zones from the first ablation pass for orientation, all ablated areas are treated with a double application of energy again.

Ablation can be repeated every 2–3 months, until all Barrett's esophagus has been eradicated visually and the eradication confirmed histologically. Most patients will need one circumferential ablation session and one or two focal ablation sessions for all dysplasia and intestinal metaplasia to be eradicated.

Post-treatment care

Proper acid suppressant therapy is very important after RFA, to minimize patient discomfort and to allow the esophagus to heal optimally and regenerate with squamous epithelium. Patients should be prescribed high-dose proton-pump inhibitors as maintenance medication. Additional H₂-receptor antagonists and sucralfate can be prescribed; there is, however, no scientific evidence that this improves healing. After RFA, patients are advised to adhere to a liquid diet for 24 hours; then they may gradually expand to a soft and then normal diet at their own discretion. Patients may experience symptoms of chest discomfort, sore throat, difficulty or pain with swallowing, and/or nausea; these usually improve each day. Proposed analgesic measures are viscous lidocaine, liquid acetaminophen with or without codeine, and antiemetic medication. If necessary, patients may use acetaminophen suppositories. Use of nonsteroidal anti-inflam-

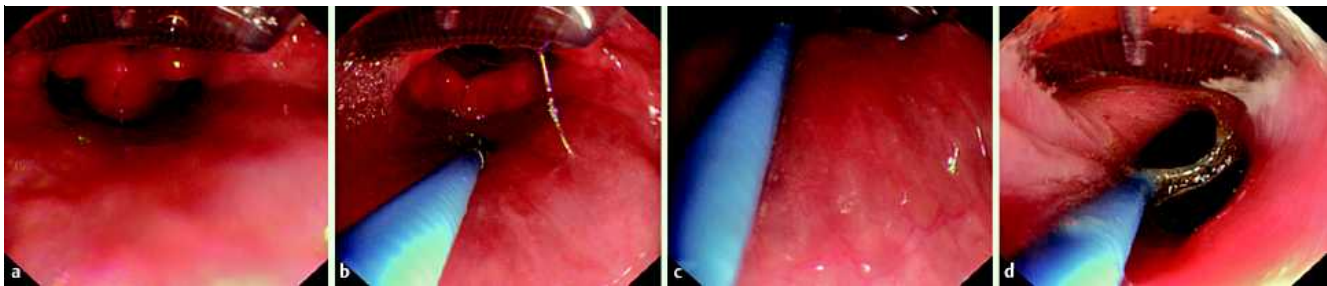


Fig. 4 Difficult introduction of the HALO⁹⁰ catheter may be facilitated by using a biopsy forceps or spraying catheter as a guide to enter into the proximal esophagus, as is demonstrated in this sequence. **a** Leading edge of the HALO cap is visible just proximal to the arytenoids. **b** A biopsy forceps is blindly advanced behind the arytenoids into the proximal esophagus.

c The endoscope is angulated downward, causing the leading edge of the HALO⁹⁰ catheter to touch the shaft of the biopsy forceps. **d** After gently advancing the endoscope, using the biopsy forceps for guidance, the proximal esophagus is entered. Reproduced with permission from www.endosurgery.eu.



Fig. 5 Follow-up endoscopy after RFA. **a** On high-resolution endoscopy with white light, no evident residual Barrett's mucosa is observed in this patient treated with RFA. **b, c** Upon inspection with NBI, however, two minute isles of Barrett's mucosa are detected. Reproduced with permission from www.endosurgery.eu.

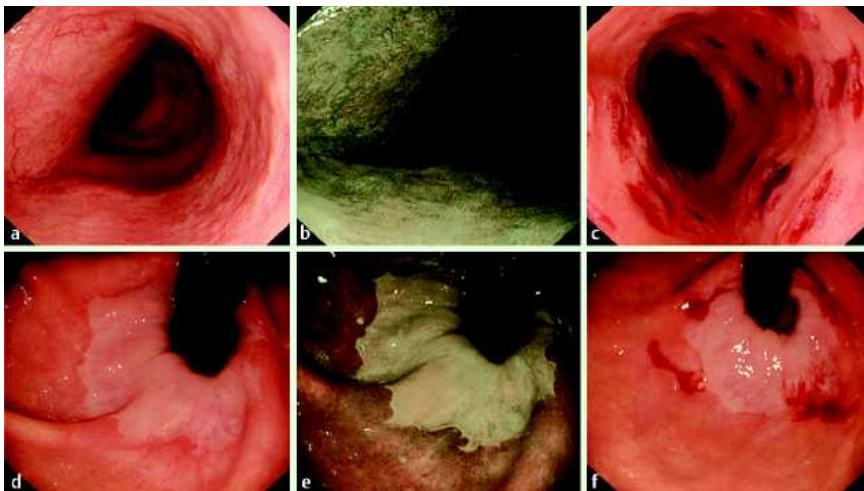


Fig. 6 Follow-up endoscopy with biopsies after eradication of a long-segment Barrett's esophagus with RFA. **a** High-resolution white light image of an initial C9M10 Barrett's segment, completely regenerated with neosquamous epithelium after successful treatment with RFA. **b** Corresponding NBI view. **c** Four-quadrant biopsies are obtained for every 1–2 cm over the entire length of the initial Barrett's segment. **d** A normal-appearing neosquamocolumnar junction. **e** Corresponding NBI view. **f** To histologically confirm the absence of intestinal metaplasia, four-quadrant biopsies are obtained 5 mm distal to the neosquamocolumnar junction. Reproduced with permission from www.endosurgery.eu.

matory drugs is not advisable. Some patients may have severe chest pain and fever; observation and conservative management with an optimal antisecretory and analgetic regimen usually suffices in these cases.

Follow-up regimen

Two to three months after the last treatment the absence of residual Barrett's epithelium is verified by endoscopic inspection. The use of high-resolution endoscopes with Lugol's staining (2%) or, preferably, NBI is important to detect even small areas of residual intestinal metaplasia (● Fig. 5).

A strict biopsy protocol should be applied with four-quadrant biopsies immediately distal (<5 mm) to the neosquamocolumnar junction and every 1–2 cm of the neosquamous epithelium (● Fig. 6).

Since no long-term follow-up data after RFA are available thus far, it is recommended to schedule patients for follow-up endoscopy 2 and 6 months after the last treatment and then annually.

Role of RFA in Barrett's eradication

▼ RFA after endoscopic resection of visible lesions containing IMC or HGD

Patients with visible abnormalities in a Barrett's esophagus containing IMC or HGD may be treated with RFA, but only after endoscopic resection of the IMC or visible lesion (● Fig. 7).

First, endoscopic resection permits optimal histopathological staging of a lesion, enabling patients with IMC and a low risk of lymph node involvement to be selected for endoscopic treatment [1,21,22]. Second, RFA should be performed on an endoscopically flat mucosa to ensure that the uniform ablation depth, as uniquely effected by the HALO system, truly reaches as deep as the muscularis mucosae.

RFA for flat HGD

Barrett's patients with HGD seem to be ideal candidates for RFA, since eradication of their dysplastic Barrett's esophagus may prevent development of IMC. Proper selection of these patients is, however, of the utmost importance. Patients should have no visible lesions: these require endoscopic resection for optimal

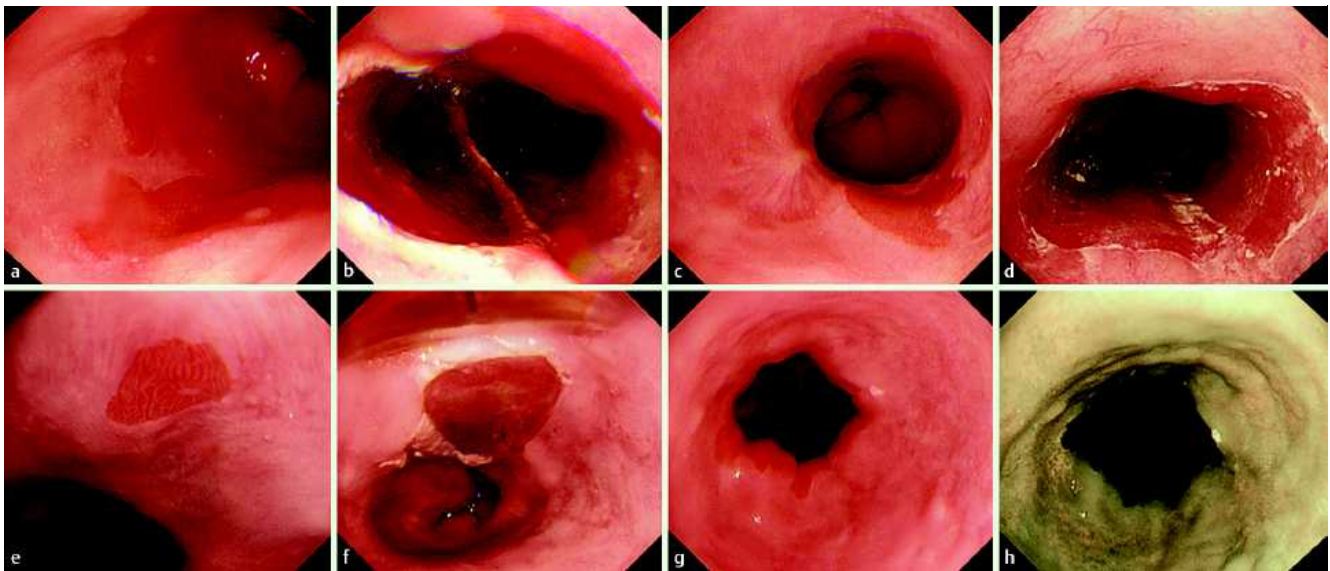


Fig. 7 Endoscopic images of a C3M5 Barrett's esophagus with HGD and a visible lesion treated with a combination of endoscopic resection and RFA. **a** Antegrade view on a C3M5 Barrett's esophagus, with a flat-type lesion at the 6–7 o'clock position. **b** View of the resection wound. The specimen showed HGD. **c** Same area 6 weeks after the endoscopic resection. The wound has healed completely with scarring. **d** Ablation effect after primary

circumferential ablation using the HALO³⁶⁰ system ($2 \times, 12 \text{ J/cm}^2$); **e** Residual isle of Barrett's mucosa remaining 6 weeks after circumferential ablation. **f** Effect immediately after ablation with the focal ablation device ($2 \times 2, 15 \text{ J/cm}^2$). **g** Complete removal of the whole Barrett's segment. **h** Corresponding NBI image. Reproduced with permission from www.endo-surgery.eu.

staging and treatment. We have also required absence of cancer in biopsies (4-quadrant/1–2 cm) obtained during at least two high-resolution work-up endoscopies within 2 months prior to RFA, and no studies have yet evaluated the use of RFA for flat IMC.

RFA for LGD

The natural course of low-grade dysplasia (LGD) in Barrett's esophagus is a controversial issue. Recent publications, however, have shown that after a consensus diagnosis of LGD, patients are indeed at increased risk of malignant degeneration, suggesting that eradication of all at-risk Barrett's esophagus may prevent development of cancer [25]. Recent studies in the United States on the use of RFA for LGD have shown an excellent efficacy and safety profile [18–20], which has led several centers to accept LGD as an indication for RFA treatment. In Europe, LGD is currently treated with RFA only in clinical trials. These differences are mainly driven by cultural approaches; studies comparing the rate of cancer development in patients treated with RFA and patients undergoing surveillance, as well as future studies on molecular and oncogenic markers that may predict malignant progression, may shed more light on which approach is to be preferred in these patients.

RFA for nondysplastic Barrett's esophagus

The risk of progression to cancer in patients with nondysplastic Barrett's esophagus is small, and no objective markers are yet available to identify patients with an increased risk of developing cancer. Although RFA seems a very promising ablation modality for Barrett's esophagus, there are still some unclear issues that need to be studied further, especially relating to its long-term efficacy. Treatment of patients with nondysplastic Barrett's esophagus with RFA is therefore still controversial. Since the risk of progression to cancer in patients with nondysplastic Barrett's esophagus is small, randomized trials to evaluate whether RFA reduces the risk of developing cancer are difficult to perform giv-

en the required sample size. Hopes are set on the future development of biological markers for risk stratification to decide which patients with nondysplastic Barrett's esophagus are at risk of malignant progression and would benefit from RFA.

Overview of clinical trials

After initial dosimetry studies in the porcine esophagus and human esophagus prior to esophagectomy [13–15], a number of prospective clinical studies were initiated to evaluate the safety and efficacy of RFA in the whole spectrum of Barrett's esophagus patients: nondysplastic Barrett's esophagus [16,17], LGD [18–20], HGD [19–20], and IMC [21,2].

In the AIM trial reported by Sharma et al., 102 patients with nondysplastic Barrett's esophagus were included and treated with RFA. The first phase of the study (AIM-I) was a dosimetry phase ($n = 32$) to evaluate the dose–response relationship and safety of circumferential ablation by one application of RF energy ranging from 6 to 12 J/cm^2 . There were no dose-related adverse events, and for the second phase of the trial (AIM-II), the effectiveness phase ($n = 70$), two applications of 10 J/cm^2 were delivered for circumferential ablation [16]. In the AIM-II trial complete eradication of intestinal metaplasia at 12 months was achieved in 48 / 70 subjects (70%) using only the HALO³⁶⁰ system for circumferential ablation [16]. The HALO⁹⁰ device for focal ablation became available halfway during the first human trials. Fleischer et al. described the use of the HALO⁹⁰ device for additional ablation in patients from the AIM-II trial with residual Barrett's esophagus. At 30 months' follow-up this resulted in complete clearance of intestinal metaplasia in 97% of patients (intention-to-treat analysis) [17]. None of the patients from the AIM trial presented with esophageal stenosis, and no buried Barrett's glands were found in any of the more than 4000 neosquamous biopsies obtained during follow-up [16,17].

In a prospective trial by Sharma et al. that included 10 patients with confirmed LGD, RFA resulted in 100% clearance of dysplasia and 90% clearance of intestinal metaplasia at 2-year follow-up, again without any esophageal strictures or buried Barrett's glands [18]. In a prospective cohort of 63 patients with LGD (n = 39) and HGD (n = 24) at the Mayo Clinic with a median follow-up of 24 months, Sharma et al. reported an overall complete response for intestinal metaplasia of 79% and a complete response for dysplasia of 89%. For the LGD cohort, complete response was 87% for intestinal metaplasia and 95% for dysplasia. For the HGD cohort, complete response was 67% for intestinal metaplasia and 79% for dysplasia [19].

For ablation of Barrett's esophagus in patients with LGD or HGD, the strongest evidence that RFA reduces the risk of malignant progression comes from the randomized sham-controlled trial by Shaheen et al. that was conducted in 19 centers in the United States. Although it has not been completely published yet, the 1-year interim results of this high-profile quality study provide convincing evidence that RFA is effective in eradicating intestinal metaplasia and dysplasia in patients with LGD and with flat HGD. By intention-to-treat analysis, a total of 101 patients with HGD (n = 43) and LGD (n = 58) were included and randomized to RFA treatment or sham (2:1). At 12 months, 85% of patients treated with RFA had clearance of dysplasia (sham: 24%, $P < 0.001$), and 77% had clearance of intestinal metaplasia (sham: 0%, $P < 0.001$). In the sham arm, 18.9% of patients had progression of dysplasia: 3/19 from LGD to HGD and 4/18 from HGD to early cancer. In the RFA arm 4.7% of patients had progression of dysplasia: 2/39 from LGD to HGD and 1/25 from HGD to early cancer. Five patients presented with an esophageal stricture (6%); all of the strictures resolved with a mean of two endoscopic dilations. There were no related deaths or perforations [20].

Gondrie et al. reported on a total of 23 patients with HGD and/or IMC, of whom 13 underwent endoscopic resection of IMC and visible lesions prior to RFA. After a median of 1.5 circumferential and 2.6 focal ablation sessions, and additional "escape" endoscopic resection in two patients, complete eradication of all dysplasia and intestinal metaplasia was achieved in all patients (100%). There were no adverse events, and no buried glandular mucosa in any of the 839 biopsies obtained during follow-up. Only one patient presented with dysphagia, which resolved after one endoscopic dilation [21,22]. An important observation from the studies by Gondrie et al. is the possibility of resecting areas of Barrett's mucosa that persist after multiple RFA sessions with the ligate-and-cut technique, without the need for submucosal lifting [21,22]. This may be a significant advantage compared to other endoscopic ablation techniques that typically result in submucosal scarring, which makes escape treatment with endoscopic resection complicated.

Compared to the 0%–56% stricture rate associated with other endoscopic ablation techniques [5–9], the minimal rate of esophageal stenosis reported in the trials discussed above is encouraging. A study by Beaumont et al., comparing measurements of esophageal inner diameter, motility, and compliance before RFA treatment and 2 months after the last ablation session, showed no significant differences, grounding the observation that RFA does not impair the functional integrity of the esophagus [26]. Gondrie et al. demonstrated that stepwise circumferential and focal ablation of Barrett's esophagus with HGD results in restoration of normal-appearing neosquamous mucosa without any of the oncogenetic abnormalities present

before treatment, using fluorescence in situ hybridization analyses of brush cytology specimens obtained from the Barrett's esophagus prior to ablation and from the neosquamous epithelium after RFA [27]. These important findings were confirmed by Finkelstein et al., suggesting that the neosquamous tissue holds no residual malignant potential [28].

Unanswered questions and directions for future research



Since RFA is a relatively new technique, there are some unanswered questions that hopefully will be answered by ongoing and future research.

First, since the HALO⁹⁰ technology only became available halfway through the first human trials, the optimal energy settings for the eradication of dysplasia and intestinal metaplasia have not been completely unraveled. Currently, different energy settings and ablation regimens are applied for focal ablation, e.g., "double × double" 12 J/cm² and "double × double" 15 J/cm² ablation. Furthermore, very small residual isles (< 2 mm) may just as well be targeted with APC, which may be quicker, cheaper, and equally effective for this indication as ablation with the HALO⁹⁰ system.

Second, although RFA may appear to be a very appealing new technique for Barrett's esophagus ablation, it has to be stressed that endoscopic resection remains the cornerstone of endoscopic treatment for HGD and IMC as was discussed above. Combining endoscopic resection of visible lesions with RFA of residual Barrett's esophagus, therefore, seems to be the ideal treatment modality for patients with early Barrett's esophagus neoplasia. Thus far, however, there are only limited data on the combination of endoscopic resection with RFA. In an evaluation by Pouw et al. circumferential RFA seemed safe if no prior endoscopic resection was performed. However, mucosal lacerations were observed in patients who had undergone prior endoscopic resection of more than 33% of the circumference and more than 2.5 cm in length, and who underwent ablation with a catheter that exceeded the smallest measured inner esophageal diameter. The few cases of esophageal stenosis after RFA all occurred in patients with endoscopic resection of more than 50% of the circumference and more than 2 cm in length [23]. On the basis of these observations, it is advisable to limit the extent of endoscopic resection to less than 50% of the circumference and less than 2 cm in length, and to select the ablation catheter conservatively (e.g., if the smallest measured diameter is 29 mm, a 28-mm balloon would be appropriate if there had been no prior endoscopic resection; prior endoscopic resection, however, would warrant the selection of a 25-mm balloon). It is expected that ongoing clinical studies will provide more information to optimize this promising combination of endoscopic resection with RFA.

Another area that requires further research is the optimal approach to RFA of the gastroesophageal junction. The often tortuous course of the distal esophagus and its widening into a hiatal hernia may make it difficult to bring the electrode of the HALO³⁶⁰⁺ catheter into good circumferential contact with the mucosa at the gastroesophageal junction. This may result in insufficient ablation of the Barrett's esophagus at this level, and given the difficulty of distinguishing Barrett's mucosa from gastric mucosa endoscopically, a rim of untreated Barrett's esopha-

gus may persist at the top of the gastric folds. To prevent this, we advise ablation of the full circumference of the gastroesophageal junction using the focal HALO⁹⁰ device. Histological confirmation is, however, mandatory to ensure complete clearance of intestinal metaplasia. Despite this approach, however, focal nondysplastic intestinal metaplasia can be detected in biopsies obtained immediately distal to the neosquamocolumnar junction. The clinical relevance of this finding remains unclear. One may argue that these patients, with an initial diagnosis of HGD or IMC, are still not completely cured of their underlying disease. Intestinal metaplasia of the cardia, however, is found in up to 25% of normal subjects and in these cases it is not considered a premalignant condition [29]. Nondysplastic intestinal metaplasia in biopsies distal to the neosquamocolumnar junction does not, therefore, require additional treatment, whereas intestinal metaplasia with LGD or HGD should be treated.

Fourth, we would like to address the issue of “buried Barrett’s glands” after ablation. The clinical relevance of “buried Barrett” is still uncertain, but of concern is the possibility of occult malignant progression of the buried glands, as has been suggested by incidental reports of adenocarcinoma arising underneath neosquamous epithelium after ablation therapy [11,2]. Thus far, no truly buried Barrett’s has been detected in patients who have had complete eradication of all intestinal metaplasia after RFA. Since this finding is at variance with the rate of subsquamous intestinal metaplasia (0%–53%) found after other ablative techniques [5–8], some argue that the biopsies do not sample the neosquamous epithelium deep enough to reliably evaluate the presence of buried Barrett’s glands. Ongoing studies evaluating sampling depth and the presence of buried glands in biopsies and endoscopic resection specimens from neosquamous epithelium after RFA should cast more light on this issue. In this connection, the artifacts that may lead to a wrongful diagnosis of buried Barrett’s should also be addressed. Biopsies from neosquamous epithelium near the neosquamocolumnar junction may lead to sampling of the transition from neosquamous to columnar epithelium. This may lead to a histological finding of glandular mucosa underneath the neosquamous epithelium, which may mistakenly be interpreted as buried Barrett. The same holds when a biopsy is taken from what is presumed to be neosquamous epithelium, when in fact there is a small isle of intestinal metaplasia that was not detected endoscopically. Tangential sampling of the isle and tangential sectioning of the biopsy may then also result in an erroneous finding of buried Barrett. A diagnosis of buried Barrett’s glands should, therefore, only be made if the endoscopist is positive that there were no Barrett’s esophagus isles after detailed inspection with NBI, and if the biopsies are not obtained at the level of the neosquamocolumnar junction, as was the case in a case report of a single-patient, single-biopsy “buried gland” [30].

Fifth, it is questionable whether every endoscopist should be trained in RFA. Although this novel ablation technique is relatively easy to apply, RFA is just one aspect of the whole spectrum of endoscopic management of patients with Barrett’s esophagus. Selection of patients with a proper indication for RFA involves thorough endoscopic work-up, the possibility of performing endoscopic resection safely, and accurate histological evaluation of tissue specimens for the presence of risk factors for lymph node metastasis. We think it would be desirable if RFA were centralized in centers with multidisciplinary expertise in this field. To bring this in to being, appropriate training courses (see, e.g., www.endosurgery.eu), aimed at the whole spectrum of endo-

scopic management, are mandatory to maintain the status of endoscopic treatment as a valid and safe alternative to surgical treatment in the management of early Barrett’s neoplasia [31–33].

An important question that remains is where the neosquamous epithelium originates from. Different hypotheses have arisen over the past few years, involving outgrowth from existing pools of squamous cell progenitors, repopulation from adjacent areas with squamous epithelium, or multipotent progenitor cells [34–36]. To fully understand the process of squamous repopulation after RFA, further studies are required, since more insight in the source of the neosquamous epithelium may cast some light onto whether replacing Barrett’s esophagus with neosquamous epithelium by RFA does indeed reduce the risk of developing cancer.

Furthermore, identification of factors that are associated with a good or poor response after RFA may enable prediction of which patients will respond well and will only need one or two ablation sessions, and which will respond with poor healing and will need multiple treatment sessions. In those rare patients who respond poorly to RFA, measures that improve post-RFA healing would be valuable.

Other developments should be aimed at the use of imaging technology to inspect residual isles and the gastroesophageal junction, to assess whether these contain intestinal metaplasia and thus require immediate treatment during the same endoscopy session.

Summary



Current data suggest that RFA is an encouraging modality for eradication of Barrett’s esophagus, with many appealing aspects. RFA has been proven to be highly effective in eradicating intestinal metaplasia and its associated dysplasia; it has a low complication rate, preserves the functional integrity of the esophagus, and is relatively easy to apply; and the regenerating neosquamous epithelium is free of the pre-existing oncogenetic alterations. There are, however, still some unanswered questions concerning the optimal use of the HALO⁹⁰ catheter, the optimal combination of endoscopic resection with RFA, the presence of buried Barrett’s glands following RFA, and whether the effect is maintained on the long run. For patients with IMC and HGD, RFA appears to be a valid and less invasive alternative to PDT, APC, or esophagectomy, albeit after thorough endoscopic work-up and endoscopic resection of IMC and visible lesions. For patients with LGD or nondysplastic Barrett’s esophagus, RFA treatment is more debatable, but in our opinion is justified in selected cases. Further clinical studies, data from long-term follow-up after RFA, and development of biological markers to predict malignant progression of intestinal metaplasia, however, will elucidate the question of which patients should be treated with RFA for eradication of Barrett’s esophagus.

Competing interests: None

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