Endoscopic eradication of Barrett's oesophagus with early neoplasia

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

Stepwise circumferential and focal radiofrequency ablation using the HALO system is a novel and promising ablative modality for Barrett’s oesophagus. 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 oesophageal stenosis and subsquamous foci of intestinal metaplasia (a.k.a. “buried Barrett’s”). 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 applications.

INTRODUCTION

Given the morbidity and mortality that may be associated with oesophagectomy, less invasive endoscopic treatment modalities have emerged to treat high-grade dysplasia (HGD) and intramucosal cancer (IMC) in Barrett’s oesophagus (BO). Endoscopic resection (ER) of focal lesions allows for histological correlation enabling optimal patient selection.1 Patients with submucosal invading lesions should be referred for surgery because they have a 15-30% risk of positive local lymph nodes whereas this risk is minimal in patients with IMC.2,3 ER, however, only removes a focal area from the BO keeping the patient at risk for metachronous lesions during follow-up.4 To prevent this, ER 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 BO.9 Second, studies have shown that oncogenetic alterations, as present in BO prior to ablation, can still be found in areas of residual BO and these may be associated with recurrence of neoplasia.10 Third, foci of intestinal metaplasia (IM) may be hidden underneath the neosquamous mucosa after treatment (a.k.a. “buried Barrett’s”) 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 oesophageal stenosis is the most relevant.5-9

Step-wise circumferential and focal radiofrequency ablation (RFA) using the HALO system is a relatively new endoscopic treatment modality for BO.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 BO. Prior to circumferential RFA, a sizing catheter with a 4-cm long non-compliant balloon at its distal end is used for measuring the inner oesophageal diameter. Upon activation via a foot-switch the sizing balloon is inflated by the HALO360 energy generator, and the mean oesophageal 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 bi-polar electrode on its outer surface (Fig. 1). The HALO360+ ablation balloon is available in five outer diameters (22, 25, 28, 31 and 34 mm). Via a foot-switch the ablation catheter is inflated 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 BO may be conducted with the HALO90 system that 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
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mm wide, allowing for selective focal ablation. Currently, a “double x double” 12 or 15 J/cm² and 40 W/cm² ablation regimen is advised to reach effective eradication of IM. For both HALO ablation devices, a HALO²⁶⁰° energy generator automatically delivers RF energy to the electrode upon activation via a footswitch. Due to the combination of high-power density, and a preset energy density, ablation results in uniform tissue penetration depth (~1,000 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 muscularis mucosae, while the submucosa typically remains uninjured.¹³⁻¹⁵.

The HALO³⁶⁰° and HALO⁹⁰° ablation procedures
Stepwise circumferential and focal ablation of a BE, generally starts with a circumferential ablation procedure using the HALO³⁶⁰° system (Fig. 2), which comprises the following steps:

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

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

3) Selecting the appropriate HALO³⁶⁰° ablation catheter:
Based on the oesophageal inner diameter measurements an appropriate HALO³⁶⁰°-ablation catheter is selected, which is smaller than the smallest measured diameter. In patients who underwent prior ER the ablation catheter should be selected conservatively.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 one cm above the maximum proximal extent of the BO. The balloon is inflated, and via a footswitch the electrode is then activated. Moving from proximally to distally the balloon is repositioned, allowing a small overlap with the previous ablation zone of 5-10 mm, until the entire BO has been ablated.

5) Cleaning procedure in between ablation cycles:
After the first ablation pass the ablation catheter is removed and the electrode surface is cleaned from coagulum with a 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, UK) 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 BO is ablated a second time.

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Figure 1. The HALO system for stepwise circumferential and focal RFA.
Upper left: The HALO³⁶⁰° generator with integrated pressure:volume system, used to inflate the sizing and ablation catheters, to calculate oesophageal inner diameter, and to deliver radiofrequency energy to the ablation catheter. Upper right: The HALO³⁶⁰° ablation catheter. Lower left: The HALO²⁶⁰° energy generator for delivery of radiofrequency energy. Lower right: The HALO²⁶⁰° catheter fitted on the tip of an endoscope, without impairing the endoscopic view or function.
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Figure 2. Endoscopic appearance of a circumferential ablation procedure using the HALO360 system.
A: C6M7 BO with 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.

A minimum of eight weeks after the first circumferential ablation treatment, patients are re-scheduled. In case of residual circumferential BO >2 cm or multiple isles or tongues, patients are treated with a second circumferential ablation. In case of an irregular Z-line, small tongues, circumferential extent <2 cm, or diffuse isles, patients 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 introducing the HALO90 catheter may prove difficult. In those cases 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 into the proximal oesophagus (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. While keeping the electrode into place it is 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 IM at the gastro-oesophageal junction.

3) Cleaning procedure:
After all residual BO has been ablated, the coagulum is carefully pushed off the oesophageal 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 BO has been eradicated visually, and then confirmed histologically. Most patients will need one circumferential ablation session and 1-2 focal ablation sessions to eradicate all dysplasia and IM.

Figure 3. Endoscopic appearance of a focal ablation procedure using the HALO90 system.
A: Antegrade view of a C6M7 BO 6 weeks after primary circumferential ablation. B: Residual isles of Barrett’s mucosa. C: Corresponding image with NBI. D: Ablation effect immediately after HALO90 ablation (distal end of the catheter visible at 12 o’clock). E: Endoscopic appearance after the first ablation pass (2x15 J/cm²) and cleaning of the ablation zones. F: After the second ablation pass (2x2 15 J/cm²) the ablation zones have a tan-colored appearance.

Figure 4. Difficult introduction of the HALO90 catheter may be facilitated by using a biopsy forceps.
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 oesophagus. C: The endoscope is angled downward, causing the leading edge of the HALO90 catheter to touch the biopsy forceps. D: After gently advancing the endoscope, using the biopsy forceps for guidance, the proximal oesophagus is entered.
Post-treatment care
After RFA proper acid suppressant therapy is very important to minimize patient discomfort, and to allow the oesophagus 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 that they may gradually expand to a soft and normal diet to their own discretion. Patients may experience symptoms of chest discomfort, sore throat, difficulty or pain with swallowing and/or nausea, which usually improve each day. Proposed analgesic measurements are viscous lidocain, liquid acetaminophen with or without codeine, and anti-emetic medication. If necessary, patients may use acetaminophen suppositories. Use of NSAIDs is not advisable. Some patients may present with severe chest pain and fever, observation and conservative management with an optimal anti-secretory 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 examined 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 IM (Fig. 5). A strict biopsy protocol should be applied with 4 quadrant biopsies immediately distal (<5 mm) to the neosquamoscolnlar 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 two and six months after the last treatment and then annually.

Position of RFA for Barrett’s eradication
RFA after ER of visible lesions containing IMC or HGD:
Patients with visible abnormalities in a BO containing IMC or HGD may be treated with RFA, but only after ER of the IMC or visible lesion. First, ER allows for optimal histopathological staging of a lesion, enabling selection of patients with IMC and a low risk of lymph node involvement, 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 BO may prevent development of IMC. Proper selection of these patients is, however, of the utmost importance. Patients should have no visible lesions: these require ER for optimal staging and treatment. We have also required absence of cancer in biopsies (4Q/1-2cm) obtained during at least 2 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 LGD in BO is a controversial issue. Recent publications, however, have shown that after a consensus diagnosis of LGD, patients are indeed at an increased risk of malignant degeneration, suggesting that eradication of all BO at risk may prevent development of cancer.25 Recent US studies on the use of RFA for LGD have shown excellent
efficacy and safety profile, which have led several centers to accepting LGD as an indication for RFA treatment. In Europe, LGD is currently only treated with RFA in clinical trials. These differences are mainly driven by cultural approaches, and 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 enlighten what approach is preferable in these patients.

**RFA for non-dysplastic BO:**
The risk of progression to cancer in patients with non-dysplastic BO 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 BO, there are still some unclear issues that need to be studied further, especially relating to its long-term efficacy. Treatment of patients with non-dysplastic BO with RFA is, therefore, still controversial. Since the risk of progression to cancer in patients with non-dysplastic BO is small, randomized trials to evaluate if RFA reduces the risk of developing cancer are difficult to perform given the required sample size. Hopes are set for future development of biological markers for risk-stratification to decide which patients with non-dysplastic BO are at risk for malignant progression and would benefit from RFA.

**Overview of clinical trials**
After initial dosimetry studies in the porcine oesophagus and human oesophagus prior to oesophagectomy, a number of prospective clinical studies were initiated to evaluate the safety and efficacy of RFA in the whole spectrum of BO patients: non-dysplastic BO, LGD, HGD, and IMC. In the AIM-trial reported by Sharma et al. 102 patients with non-dysplastic BE 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 and safety of circumferential ablation by one application of RF energy ranging from 6-12 J/cm². There were no dose-related adverse events, and for the second phase of the trial (AIM-III), the effectiveness phase (n=70), two applications of 10 J/cm² were delivered for circumferential ablation. In the AIM-II trial complete eradication of IM at 12 months was achieved in 48/70 subjects (70%), using only the HALO™ system for circumferential ablation. The HALO™ device for focal ablation became available halfway during the first human trials. Fleischer et al. described the use of the HALO™ device for additional ablation in patients from the AIM-II trial with residual BO. At 30 months follow-up this resulted in complete clearance of IM in 97% of patients by intention to treat analysis. None of the patients from the AIM-trial presented with oesophageal stenosis, and no buried Barrett’s glands were found in any of the >4000 neosquamous biopsies obtained during follow-up.

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 IM at two-year follow-up, again without any oesophageal strictures or buried Barrett’s glands. 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 IM of 79% and complete response for dysplasia of 89%. For the LGD cohort, complete response for IM was 87% and 95% for dysplasia. For the HGD cohort, complete response for IM was 67% and 79% for dysplasia.

For ablation of BO 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 USA centers. 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 IM 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 IM (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 EC. In the RFA arm 4.7% of patients had progression of dysplasia: 2/39 from LGD to HGD and 1/25 from HGD to EC. Five patients presented with an oesophageal stricture (6%), all resolved with a mean of 2 endoscopic dilations. There were no related deaths or perforations. Gondrie et al. reported on a total of 23 patients with HGD and/or IMC, of which 13 underwent ER of IMC and visible lesions prior to RFA. After a median of 1.5 circumferential and 2.6 focal ablation sessions, and additional ‘escape’ ER in two patients, complete eradication of all dysplasia and IM was achieved in all patients (100%). There were no adverse events, or buried glandular mucoza in any of the 839 biopsies obtained during follow-up. Only one patient presented with dysphagia that resolved after one endoscopic dilatation. An important observation from the studies by Gondrie et al. is the possibility to resect areas of Barrett’s mucosa that persist after multiple RFA sessions with the ligate-and-cut technique, without the need for submucosal lifting.

This may be a significant advantage compared to other endoscopic ablation techniques that typically result in submucosal scarring, which makes escape treatment with ER complicated.

Compared to the 0-56% stricture rate associated with other endoscopic ablation techniques, the minimal rate of oesophageal stenosis reported in the trials discussed above, is encouraging. A study by Beaumont et al., comparing measurements of oesophageal 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 oesophagus.

Gondrie et al. demonstrated that stepwise circumferential and focal ablation of BE with HGD results in restoration of normal appearing neosquamous mucosa without any of the oncogenetic abnormalities as present before treatment, using fluorescence in situ hybridization analyses of brush cytology specimens obtained from the BO prior to ablation and from the neosquamous epithelium after RFA. These important findings were confirmed by Finkelstein et al., suggesting that the neosquamous tissue holds no residual malignant potential.

**Unanswered questions and directions for future research**
Since RFA is a relatively new technique, there are some unanswered questions that will hopefully be answered by ongoing and future research. First, since the HALO™ technology only became available halfway during the first human trials the optimal energy settings to eradicate dysplasia and IM have not been completely unraveled. Currently, different energy settings and ablation regimens are applied for focal ablation, e.g. “double x double” 12 J/cm²;
cm² and “double x 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, though RFA may appear to be a very appealing new technique for BE ablation, it has to be stressed that ER remains the cornerstone of endoscopic treatment for HGD and IMC as was discussed above. Combining ER of visible lesions with RFA of residual BO, therefore, seems to be the ideal treatment modality for patients with early BO neoplasia. Thus far, however, there is only limited data on the combination of ER with RFA. In an evaluation by Pouw et al. circumferential RFA seemed safe in case no prior ER was performed. However, mucosal lacerations were observed in patients who had prior ER >33% of the circumference and >2.5 cm in length, and who underwent ablation with a catheter that exceeded the smallest measured inner oesophageal diameter. The few cases of oesophageal stenosis after RFA all occurred in patients with ER >50% of the circumference and >2 cm in length. Based on these observations, it is advisable to limit the extent of ER to <50% of the circumference and <2 cm in length, and to conservatively select the ablation catheter (e.g. if the smallest measured diameter is 29 mm, a 28-mm balloon would be appropriate in case of no prior ER; prior ER, however, warrants the selection of a 25-mm balloon). It is expected that ongoing clinical studies will provide more information to optimize this promising combination of ER with RFA.

Another area that requires further research is the optimal approach to RFA of the gastro-oesophageal (GO) junction. The often tortuous course of the distal oesophagus and 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 GO-junction. This may result in insufficient ablation of the BO at this level and give the difficulty to endoscopically differentiate Barrett’s mucosa from gastric mucosa, a rim of untreated BE may persist at the top of the gastric folds. To prevent this, we advise to ablate the full circumference of the GE-junction using the focal HALO90 device. Histological confirmation is, however, mandatory to ensure complete clearance of IM. Despite this approach, however, focal non-dysplastic IM 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 from their underlying disease. IM of the cardia, however, is found in up to 25% of normal subjects and in those cases it is not considered a premalignant condition. Non-dysplastic IM in biopsies distal to the neosquamocolumnar junction does, therefore, not require additional treatment, whereas IM 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’s” 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. Thus far, no truly buried Barrett’s has been detected in patients that had complete eradication of all IM after RFA. Since this finding is in discordance with the rate of subsquamous IM (0-53%) found after other ablative techniques, 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 presence of buried glands in biopsies and ER specimens from neosquamous epithelium after RFA should enlighten this issue. In this respect, 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’s. The same holds when a biopsy is taken from presumably neosquamous epithelium, while there is in fact a small isle of IM 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’s. A diagnosis of buried Barrett’s glands should, therefore, only be made if the endoscopist is positive that there were no BE 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.”

Fifth, it is questionable if every endoscopist should be trained in RFA. Although this novel ablation technique is relatively easy to apply, RFA is just one aspect in the whole spectrum of endoscopic management of BO patients. Selection of patients with a proper indication for RFA involves thorough endoscopic work-up, the possibility to safely perform ER, 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 centres with multidisciplinary expertise in this field. To realize this, adequate training courses (e.g. www.endosurgery.eu), aimed at the whole spectrum of endoscopic 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. An important question that remains is from where the neosquamous epithelium originates. Different hypotheses have arisen over the last years, involving outgrowth from existing pools of squamous cell progenitors, repopulation from adjacent areas with squamous epithelium, or multipotent progenitor cells. 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 enlighten if replacing BO with neosquamous epithelium by RFA, indeed reduces the risk of developing cancer.

Furthermore, identification of factors that are associated with a good or poor response after RFA may enable prediction of what patients will respond well and will only need 1-2 ablation sessions, and what patients will respond with poor healing and will need multiple treatment sessions. In those rare patients that respond poorly to RFA, measurements 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 gastro-oesophageal junction, to assess if these contain IM and thus require immediate treatment during the same endoscopy session.

Summary

Current data suggest that RFA is an encouraging modality for eradication of BO with many appealing aspects. RFA has been proven to be highly effective in eradicating IM and its associated dysplasia, it has a low complication rate, preserves the oesophageal functional integrity, is relatively easy to apply, and the regenerating neosquamous epithelium is free of the pre-existing oncogenic alterations. There are, however, still some unanswered ques-
tions concerning the optimal use of the HALO® catheter, the optimal combination of ER with RFA, the presence of buried Barrett’s glands following RFA, and if the effect is maintained on the long run. For patients with IM and HGD, RFA appears to be a less invasive and valid alternative to PDT, APC or oesophagectomy, be it after thorough endoscopic work-up and ER of IM and visible lesions. For patients with LGD or non-dysplastic BO, RFA treatment is more debatable but in our opinion justified in selected cases. Further clinical studies, long-term follow-up data after RFA, and development of biological markers to predict malignant progression of IM, however, will enlighten which patients should be treated with RFA for BO eradication.

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