Advances in endoscopic resection and radiofrequency ablation of early esophageal neoplasia
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Endoscopic therapy using radiofrequency ablation for esophageal dysplasia and carcinoma in Barrett’s esophagus

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ABSTRACT

Radiofrequency ablation (RFA) is a novel and promising treatment modality in the treatment of Barrett’s esophagus (BE) with high grade dysplasia or early carcinoma. RFA can be used as a single-modality therapy for flat type mucosa or as a supplementary therapy after endoscopic resection of visible abnormalities. The treatment protocol consists of initial circumferential ablation using a balloon-based electrode, followed by focal ablation of residual Barrett’s epithelium using a focal ablation device mounted on the tip of the endoscope. RFA is not associated with stenosis and buried glandular mucosa as are other ablation techniques such as photodynamic therapy and argon plasma coagulation, and has shown to be safe and effective in the treatment of patients with BE and early neoplasia in recent clinical trials. In this review, the technical background, current clinical experience, and future prospects of RFA are evaluated.
INTRODUCTION

Barrett’s esophagus (BE) is a premalignant condition in which the normal squamous cell lining of the esophagus is replaced by columnar epithelium containing specialized intestinal metaplasia (IM), defined by the presence of goblet cells. The most important risk factor for BE is chronic gastro-esophageal reflux disease (GERD) and BE is found in approximately 10% of patients undergoing endoscopy for chronic GERD symptoms and therefore is hypothesized that the transition from squamous mucosa into mucus-secreting columnar epithelium is an adaptation of esophageal mucosa caused by the erosive effect of the refluxate. Via a gradual process from no dysplasia to low-grade (LGD) and high-grade dysplasia (HGD), BE can develop into adenocarcinoma. The estimated annual incidence of adenocarcinoma in BE is 0.5%. When esophageal cancer enters a symptomatic stage, disease is usually locally advanced and has a poor prognosis with a 5-year survival of approximately 20%. For patients with HGD or early cancer, previously, surgical resection was the gold standard. Surgical esophagectomy is, however, associated with a mortality rate of 3-5% and serious complications occur in 40-50% of patients. In the subset of patients with ‘early neoplasia’, defined as HGD or intramucosal cancer, lymph node involvement is rare: 0% for HGD and 2-3% for intramusculosal cancer. As a result endoscopic treatment of early neoplastic lesion is a viable alternative to surgery for these patients.

Endoscopic treatment modalities

Endoscopic treatment comprises endoscopic resection (ER) and endoscopic ablation techniques. The most important advantage of ER above ablation therapy is that ER results in a resection specimen for histopathological assessment, contributing to optimal staging and patient selection. Although ER is a safe and effective treatment modality, with 5-year disease-specific survival of 95%, metachronous lesions arising in the residual BE segment can be found after ER in 30% of patients. To eliminate the malignant potential after ER, eradication of the residual BE epithelium is advocated. To accomplish this, treatment protocols combining ER and ablation therapy have been developed. Photodynamic therapy (PDT) using amino levulinic acid (ALA) or porfimer sodium (Ps) and Argon Plasma Coagulation (APC) are ablation techniques that have been administered for this purpose, but in both techniques have disappointingly high rates of recurrent early neoplasia and residual IM. In both PDT and APC, ablation depth is not controlled and may vary, resulting in residual BE that still carries preexistent oncogenetic abnormalities. Sometimes residual BE glands become hidden underneath neosquamous epithelium (i.e. ‘buried Barrett’s glands’), and some fear that these may progress to dysplasia or cancer without being detected endoscopically. Another complication from porfimer sodium (Ps-PDT) and APC is a high stenosis rate, which may be a result of submucosal scarring owing to uncontrolled ablation depth. Finally, Ps-PDT is associated with significant photosensitivity for a period of up to 6 weeks after treatment.
An alternative to ablation therapy is the complete removal of the BE by radical endoscopic resection (RER), generally performed in multiple treatment sessions. Small-sized single center studies have reported low recurrence rates of early neoplasia after RER varying from 0% to 9% after up to 28 months follow-up, and newly formed squamous epithelium after RER has been shown free of oncogenetic abnormalities. However, symptomatic stenosis develops in up to 56% of patients, requiring multiple dilations sessions.\textsuperscript{26-29}

The latest treatment modality for complete removal of BE is radiofrequency ablation (RFA). This novel ablation technique has shown excellent results for selected patients with non-dysplastic BE, LGD and HGD with or without prior ER with a follow-up of almost two years. Regarding the safety and efficacy profile RFA compares favorably to other ablation techniques such as PDT and APC.\textsuperscript{30,31}

\section*{Radiofrequency Ablation: The HALO System}

The HALO system (BÂRRX Medical, Sunnyvale, CA, USA) (Figure 1) for RFA is designed to control tissue penetration depth of the RF energy of 0.5 mm, thereby realizing a uniform ablation depth that is operator independent, owing to the use of bipolar electrodes and the automated delivery of a preset amount of RF energy. The HALO system consists of a circumferential and a focal ablation device for stepwise ablation of the BE epithelium. For larger areas of BE, circumferential ablation is performed using the HALO\textsuperscript{360} -device, a balloon-based catheter with spindle shaped electrode covering a length of 3 cm. The HALO\textsuperscript{360} -balloon is available in several diameters: 18, 22, 25, 28, 31, and 34 cm. Ablation using the HALO\textsuperscript{360} -balloon is performed with an energy density of 12J/cm\textsuperscript{2} and 300Watt/
Technical background of RFA

For focal ablation for residual BE epithelium the endoscope-mounted HALO\(^{90}\)-device is developed. The HALO\(^{90}\)-device is equipped with an articulating surface containing an electrode array (13mm wide x 20mm long) to target small areas of BE with an energy density of 15J/cm\(^2\) and a power of 40 Watt/cm\(^2\).

Patient selection for endoscopic management of early neoplasia

To correctly select the subgroup of patients suitable for RFA treatment, a thorough work-up and staging protocol is mandatory. In general, patients with early neoplasia in BE are considered potential candidates for endoscopic treatment, when the lesion is limited in size (< 2 cm), there are no signs of deep submucosal invasion, and no suspicious lymph nodes are found on endoscopic ultrasound (EUS). The tumor characteristics are of importance in staging, as the risk for lymph node involvement increases with increasing infiltration depth, poor differentiation grade and lymphatic/vascular-invasive tumor growth.\(^{11,16,32,33}\)

Imaging endoscopy

Optimal endoscopic treatment of patients with early BE neoplasia starts with at least one high-resolution endoscopy by an experienced endoscopist. During inspection, visible abnormalities are classified according to the Paris classification.\(^{34,35}\) The Prague-CM-classification is used to describe the BE segment, including the length of the circumferential segment (C), and the maximal extent of the BE segment (M).\(^{36}\) Subsequently, targeted biopsies are obtained from visible abnormalities, followed by four-quadrant biopsies of every 1-2 cm of the BE segment (Seattle protocol).\(^{37}\)

Staging procedures: endoscopic ultrasound and Computer-Tomography

Patients with early neoplasia in BE generally undergo endoscopic ultrasound (EUS) for T and N staging, which is superior to computer tomography (CT) scanning. EUS has a high negative predictive value (>95%) for local lymph node involvement and for tumor infiltration in the deeper layers of the esophageal wall (≥T2).\(^{38-40}\) In case of suspicious lymph nodes, fine needle aspiration (FNA) may be performed to exclude malignant disease. The accuracy of EUS in differentiating mucosal from submucosal invasion is, however, relatively poor and EUS does not perform better than simple endoscopic inspection of the lesion by an experienced endoscopist.\(^{41}\) In addition, the high negative predictive value for local lymph node involvement may simply reflect the low prevalence of positive lymph nodes in these lesions. Recent studies have therefore questioned the value of EUS in the work-up of early BE neoplasia.\(^{40,42}\) Many centers still perform a thoracic and abdominal CT scan for patients with early BE cancer to exclude distant metastases. This is however controversial, since the distant metastasis are virtually absent T1 lesions and thus rarely changes the TNM stage.\(^{40}\)
Endoscopic resection

ER is the most important tool for accurate assessment of invasion depth and other histological tumor characteristics (differentiation grade, lymphatic invasion). ER therefore serves both a diagnostic as well as therapeutic purpose. Diagnostic in the sense that it correctly identifies patients with submucosal invasion, poor differentiation grade, and/or lymphatic invasion, therapeutic in the sense that it allows removal of all visible (i.e. non-flat mucosa) lesions thus rendering the remaining BE segment flat and thereby suitable for RFA. The two most widely used techniques are the ER-cap technique and the Multi Band Mucosectomy (MBM) technique, and both are safe and effective for ‘en bloc’ as well as ‘piece meal’ resections.43,44

Histopathological assessment

For the histopathological evaluation of biopsies or resection specimens, the revised Vienna classification is used.45,46 After ER, patients are suitable candidates for further endoscopic management, if the resection specimen shows: negative vertical resection margins; no submucosal tumor infiltration; well- or moderately tumor differentiation (G1-G2); and no lymphatic/vascular invasion. Since early BE neoplasia is not frequently encountered by community pathologists it is imperative that the histopathological evaluation is performed by a pathologist with experience in this field.

Work-up for Radiofrequency ablation

Prior to RFA, all carcinoma has to be completely removed and the epithelium should be endoscopically flat. This is required because the HALO electrodes for RFA are designed to perform controlled superficial ablation of 0.5 mm and is unlikely to be effective for neoplasia in thickened mucosa. Most RFA studies have excluded patients with invasive cancer at baseline and biopsies should therefore be taken from the residual BE segment after ER. Also, in most studies an additional endoscopy was performed 4-6 weeks after the ER session to exclude visible abnormalities and to obtain 4 quadrant biopsies the BE segment to rule out invasive cancer. At that time, however, the edges of the ER scar may be slightly elevated due to reactive changes which may be misinterpreted as visible abnormalities. The most optimal time to exclude the presence of residual visible abnormalities and to obtain biopsies from the residual BE is thus immediately after the ER in the same session.

When the mucosa is flat and biopsies contain no invasive cancer, the patient is scheduled for a RFA session 6 to 8 weeks after ER.

Performing circumferential ablation: use of the HALO360-device

RFA procedures can be performed on an outpatient basis using conscious sedation. At the initial ablation session, the extent of the BE segment determines if the patient will be treated with the HALO360-balloon or with the focal HALO90-device. When the circumferential BE segment is smaller than 2 cm in length, or only consists of tongues and/or islands smaller than 2 cm in size, the patient can be primarily treated with focal
ablation. Most frequently, patients initially require circumferential ablation, which involves the following steps:

1. Inspection and recording of esophageal landmarks:
   Prior to ablation, the esophagus is inspected to confirm the flat aspect of the mucosa, to exclude the presence of esophagitis and to record the esophageal landmarks according to the Prague CM-classification. After inspection the esophagus wall is sprayed with 20 mL of acetylcysteine (1%, watery solution) to remove excessive mucus, followed by flushing with plain water.

2. Sizing procedure (Figure 2):
   Subsequently, the esophageal inner diameter (EID) is measured, in order to select an appropriate ablation balloon, allowing for optimal contact between electrode and esophageal without applying too much pressure. A 4-cm long non-compliant sizing balloon-catheter is connected to the generator with an interposed air filter. After calibration, the sizing balloon is inserted over a 0.035-inch guide-wire (Amplatz extra stiff, Cook Endoscopy, Limerick, Ireland), omitting lubricant jelly for introduction, exclusively using water. Sizing is performed for every cm of the BE segment, starting 5 cm above the most proximal extent of the BE, using the centimeter scale on the catheter shaft for reference (discordant to the centimeter scale of the endoscope). For sizing, the balloon is automatically inflated to 4 psi (0.28 atm) after pressing a foot switch, and automatically deflated after measurement. The mean EID over 4 cm is then calculated with a pressure-volume algorithm and displayed on the generator. When a strong increase in the measured EID indicates that the sizing balloon has reached the hiatal hernia or stomach, the sizing balloon is removed, leaving the guide-wire in place.

3. Selection of the appropriate ablation balloon:
   The smallest measured EID defines the appropriate balloon-diameter. For patients without prior ER, the recommended balloon-diameter is the one closest to the smallest measurement (e.g. if the smallest EID is 24-mm, a 25-mm ablation balloon is chosen;
if the EID is 23-mm, the 22-mm ablation balloon is appropriate). For patients with a prior ER or stenosis, a balloon that is two sizes smaller than the smallest measurement has to be selected, to reduce the risk for laceration. (e.g. if the smallest EID is 26-mm, a 22-mm ablation balloon should be used).

When a suitable ablation balloon-size has been selected, the ablation balloon is inserted over the guide-wire followed by introduction of the endoscope for visualization of the ablation procedure.

4. First ablation pass (Figure 3):
For ablation with the HALO\textsuperscript{360} device, the surface is treated with two energy deliveries of 12 J/cm\textsuperscript{2} with cleaning of the ablation zone in between ablation passes, referred to as the ‘double’ regimen. Ablation is performed from proximal to distal starting 1 cm above the most proximal extent of the BE segment, allowing for a maximal overlap of 0.5 to 1 cm. Prior to ablation, the endoscope and ablation catheter are fixated to the bite block to avoid dislocation of the balloon by inflation. After inflation of the ablation balloon, as initiated by the endoscopist using the foot switch, suctioning is applied for optimal contact between electrode and epithelium. Next, the endoscopist starts the ablation, resulting in RF energy delivery and automatic deflation of the balloon. Ablation renders the BE epithelium white, which helps identifying the subsequent BE zone when advancing the deflated ablation balloon distally. After ablation of the complete BE segment, ablation balloon, guide wire and endoscope are removed simultaneously.

\textbf{Figure 3.} The ablation procedure using the HALO system. Ablation is performed from proximal to distal starting 1 cm above the most proximal extent of the Barrett’s segment. Upper: The ablation balloon is inflated and ablation is performed upon activation using the foot switch. Middle: After ablation, the Barrett’s epithelium shows a white debris, which helps identifying the subsequent BE zone when advancing the deflated ablation balloon distally. Lower: Subsequent ablations are performed allowing for a maximal overlap of 0.5 to 1 cm, until the complete Barrett’s segment has been ablated.
5. Cleaning procedure:
   After the first ablation pass, the coagulum is cleaned off the ablation surface and the balloon electrode prior to the second ablation pass. Cleaning in between the ablation passes has been shown to increase the efficacy of the initial ablation session from 90% to 95%.

   Debris is gently pushed off the ablated area using the rim of the small flexible cap (e.g., HALO cap; BÂRRX Medical, Sunnyvale, CA, USA or Olympus zoom cap, MB0-046; Olympus, Tokyo, Japan), mounted on the tip of the endoscope, followed by forcefully spraying with plain water using a spraying catheter (e.g., Olympus PV-5-1; Olympus, Tokyo, Japan) and a high-pressure pistol (e.g., Alliance; Boston Scientific, Limerick, Ireland). Cleaning of the balloon electrode is performed outside the patient using plain water and a gauze.

6. Second ablation pass:
   After the cleaning procedure, guide-wire and ablation balloon are re-inserted followed by the endoscope and a second ablation pass is performed from proximal to distal, resulting in a brownish discoloration of the previously ablated BE epithelium.

Performing focal ablation: use of the HALO\(^{90}\)-device

Two to three months after initial ablation, upper endoscopy with NBI is performed to assess BE regression. Patients with a residual circumferential BE segment with a length of more than 2 cm and/or multiple isles or tongues are subjected to a second circumferential ablation session. In case the circumferential extent of residual BE is less than 2 cm in length, and/or an irregular gastro-esophageal junction, and/or tongues and islands smaller than 2 cm in size, this can be treated with the HALO\(^{90}\)-device for focal ablation. The focal ablation procedure is carried out as follows:

1. Inspection and recording of esophageal landmarks:
   Again the esophagus is inspected to confirm the flat aspect of the mucosa and to exclude the presence of esophagitis. Additionally, the presence of a Zenker’s diverticulum has to be excluded because this may complicate the introduction of the HALO\(^{90}\)-device. After recording of the esophageal landmarks, the esophagus wall is sprayed with acetylcysteine (1%) and flushed with plain water.

2. Introduction of the HALO\(^{90}\)-catheter (Figure 4):
   The HALO\(^{90}\)-catheter is attached to the distal end of the endoscope, and the electrode-cap placed at the 12 o’clock position in the endoscopic field of view. The HALO\(^{90}\)-device is inserted without using lubricant jelly but only water to facilitate introduction. After advancing the HALO\(^{90}\)-electrode surface over the tongue, the top of the electrode is deflected downwards when the laryngeal cavity is visualized, to allow the electrode to pass behind the arytenoids. Subsequently, the patient is asked to swallow and the catheter is gently advanced.
   When introduction of the HALO\(^{90}\)-device is difficult a biopsy forceps or the spraying catheter can be used to guide the instrument into the esophagus. With the endoscope in the hypopharynx, the forceps is advanced under direct view dorsal to the arytenoids deep into the esophagus. The endoscope is angled down so that the leading edge of the HALO\(^{90}\)-device can slide over the forceps while the endoscope is gently advanced.
3. First ablation pass (Figure 5):

In the esophagus, the HALO\textsuperscript{90}-electrode surface is positioned against the wall at the target area. Optimal contact between electrode and esophageal wall is obtained by upward deflection of the tip of the endoscope. For ablation with the HALO\textsuperscript{90}-device, the ‘double-double’ regimen is administered. Ablation is initiated by the endoscopist using the foot switch, and after an area has been treated with an energy delivery of 15 J/cm\textsuperscript{2}, a second energy delivery of 15 J/cm\textsuperscript{2} is realized immediately after the first, while keeping the electrode in place. After treatment of the residual BE areas, the Z-line is ablated by circumferentially applying the HALO\textsuperscript{90}-device, to eliminate the potential of a small rim of residual BE epithelium at the Z-line, which is endoscopically indistinguishable from gastric epithelium.

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**Figure 4.** A: The leading edge of the HALO cap is visible 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 HALO cap 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.

**Figure 5.** Endoscopic appearance of a focal ablation procedure using the HALO\textsuperscript{90} system. A: Antegrade view of an initial C6M7 Barrett esophagus 6 weeks after primary circumferential ablation; B: Residual isles of Barrett mucosa; C: Corresponding image with NBI; D: Ablation effect immediately after ablation with the HALO\textsuperscript{90} 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 (2x 15 J/cm\textsuperscript{2}) and cleaning of the ablation zones; F: After the second ablation pass (2x2 15 J/cm\textsuperscript{2}) the ablation zones have a tan-colored appearance.
4. Cleaning procedure:
   After the first ablation pass, debris is cleaned off the ablated area by carefully pushing with the HALO$^{90}$-electrode in the proximal-to-distal direction, combined with suctioning away the debris through the working channel of the endoscope. This is followed by spraying off debris using the high-pressure pistol with plain water. Next, the endoscope with the HALO$^{90}$-device is removed and coagulum is cleaned from the electrode using a wet gauze.

5. Second ablation pass:
   After cleaning, endoscope and HALO$^{90}$-device are re-introduced and two more energy deliveries of 15 J/cm$^2$ are performed.

Post-procedural care
Adequate acid-suppressant medication is key in the post-RFA treatment period to promote healing and re-epithelialization with normal squamous epithelium.$^{52-54}$ It is recommended to keep patients on a maintainage dosage of esomeprazole 40 mg BID during the entire treatment period. In our institution, patients are additionally prescribed ranitidine 300 mg at bedtime and sucralfate 1gram QID for a period of 14 days after each RFA treatment. Patients are advised to use a liquid diet during 24 hours after RFA, and to slowly return to normal diet normal thereafter. After RFA treatment, patients may experience chest pain and difficulty swallowing for 3 to 4 days. For pain management viscous lidocaine, liquid acetaminophen, or acetaminophen suppositories and anti-emetics are used.

Treatment protocol and follow up
RFA treatment is repeated every two to three months until all visible BE has been eradicated. Most studies have limited the number of RFA sessions to two HALO$^{360}$- and three HALO$^{90}$-procedures. Generally, patients will require one HALO$^{360}$- and one or two HALO$^{90}$-procedures. To assess whether all visible BE epithelium is removed, the use of high resolution endoscopy with NBI (or comparable techniques such as iScan or FICE) is important since this facilitates detection of small islands of residual BE epithelium that are easily overlooked with standard white light endoscopy.

Two months after the final treatment session, four quadrant biopsies are taken every 1 to 2 cm of the original BE segment to exclude the presence of buried Barrett’s. Complete removal of BE can be difficult to assess endoscopically and when in doubt biopsies should be taken immediately distal to the neosquamocolumnar junction to rule out residual intestinal metaplasia and/or dysplasia. After histology has confirmed the complete eradication of IM and dysplasia, patients are scheduled for follow-up endoscopy at 6 months, at 12 months and annually thereafter.

In case of residual Barrett’s islands after the maximum number of RFA sessions, further management can be subsequent HALO ablation, APC or escape ER, left to the discretion of the endoscopist. When lesions suspicious for dysplasia or cancer are encountered during the RFA treatment period or at control endoscopy after RFA, directed biopsies should be obtained of the lesion with a low threshold to remove visible abnormalities by ER.
Chapter 4

CHALLENGES IN RFA

Although RFA with the HALO System is a simple and fast technique in majority of patients, occasionally more challenging RFA cases are encountered, e.g. patients with a severely stenosed esophagus, a very long BE segment, or patients that show poor healing or poor regression of the BE epithelium. In patients with an esophageal stenosis (e.g. a reflux stenosis at the upper end of the BE, or narrowing after widespread ER or prior ulceration in the BE) dilations should be performed to render patients eligible for RFA treatment. In case the EID varies over the length of the BE segment, treatment with two different HALO\textsuperscript{360}-balloon sizes is an option. For a focally narrowed esophagus, use of the HALO\textsuperscript{360}-balloon can be combined with the HALO\textsuperscript{90}-device in a single session in selected patients. Secondly, in patients with a very long BE segment it may be beneficial to treat the BE in two sessions to reduce patient discomfort and complication risk. A small subgroup of patients (<10% in our hands) may show delayed healing of the ablated area, requiring postponing the RFA session. Generally, these patients will also show a high rate of regeneration of BE instead of squamous mucosa. In these patients we confirm adherence to the prescribed medication, again exclude the use of any caustic co-medication, and increase the dosage of anti-acid medication (e.g., esomeprazole 80mg BID). Finally, there is a very small subset of patients in which RFA treatment fails because of poor regression of BE for unknown reasons.

RESULTS OF RFA

Since the HALO system was introduced in 2003, several groups have evaluated the safety and efficacy of RFA for BE patients with and without dysplasia. The most important results will be discussed below.

Dose-escalation of RF energy

After dose-escalation studies in the porcine model and in patients prior esophagectomy,\textsuperscript{55,56} the first large study to report the results of RFA for Barrett’s esophagus was performed from 2003-2005 in patients with non-dysplastic BE (AIM-study). In this study, dose response and safety of the HALO\textsuperscript{360}-device was further tested. Because there were no dose-related adverse events, the dose-escalation phase (n=32) was followed by an effectiveness phase (n=70) using two applications of radiofrequency energy with an energy level of 10 J/cm\textsuperscript{2}. After 12 months of follow up, complete eradication of IM was reached in 70% of 70 patients.\textsuperscript{57}

Focal ablation comes into play

Once the HALO\textsuperscript{90}-device for focal ablation became available, much higher eradication rates for IM were reached. The HALO\textsuperscript{90}-device not only enables the precise targeting of small residual BE areas but also allows for effective treatment at the level of the gastro-
esophageal junction where the HALO$^{360}$-device may not always come in optimal contact with the epithelium.

The aforementioned AIM-study incorporated HALO$^{90}$ for focal ablation of residual BE in the study protocol and entered 62 patients in a study extension phase. Thirty months after the initial focal ablation, complete remission of IM was achieved in 98% of 61 available patients with a mean of 2 focal ablation procedures without serious adverse events or strictures. No buried Barrett’s glands were detected in 4,306 biopsies during the first 12 months and 923 biopsies collected at 30 months after primary circumferentially ablation.$^{47}$

**Introduction in Europe**

After initial trials in the US using a bottom-up approach, the promising RFA technique was also introduced in Europe. Our group was the first to use a combined treatment approach of ER followed by RFA for BE with early neoplasia (Figure 6). In the first series of 11 patients that underwent RFA for a median BE length of 5 cm, a prior ‘en bloc’ ER was performed for visible lesions in 6 of 11 patients. The HALO$^{90}$-device was implemented in the second half of the study period and used at 12 and 15 J/cm$^2$. After a median follow-up of 14 months after initial ablation, 100% of the patients had been histologically cleared of all IM and dysplasia.$^{50}$ The second series of 12 patients also enrolled patients after a prior piecemeal resection of visible lesions. In this study the ablation area and the electrode were cleaned between ablation passes.$^{49,51}$ Again, in 100% of patients eradication of IM and dysplasia was reached, and despite the fact that patients with a significantly longer BE were enrolled, fewer treatment sessions were required.

**Figure 6.** A: Antegrade view on a C6M10 Barrett esophagus; B: A lesion suspicious for early cancer at the 2-4 o’clock position; C: View on the resection wound after endoscopic resection of the lesion in two pieces; D: Histopathological evaluation of the specimens showed a radically resected adenocarcinoma infiltrating in the muscularis mucosae (T1m3); E: Same area 6 weeks after the endoscopic resection. The wound has healed completely with scarring; F: Ablation effect after primary circumferential ablation using the HALO360 system (2x 12 J/cm$^2$); G: Residual isle of Barrett mucosa remaining 6 weeks after prior circumferential ablation; H: After additional focal ablation of residual isles of Barrett mucosa, complete removal of the whole Barrett segment was reached.
To study the functional characteristics of the normal appearing esophagus after RFA, esophageal manometry and a functional lumen imaging probe (FLIP) were used, showing unchanged esophageal motility and compliance after RFA.\textsuperscript{58}

**Results of RFA after two-year follow up**

Recently, our group reported the combined results of the first 44 patients with BE containing early neoplasia, treated with RFA with or without prior ER after a median follow up of 21 months. In addition to the abovementioned studies, patients from two other study protocols were included in this combined group; a series of 9 patients who participated in an ongoing European multicenter trial studying RFA for patients with BE < 12 cm, and a series of 12 patients that were randomized to RFA in a study comparing stepwise radical endoscopic resection (SRER) and RFA in patients with BE < 5 cm. In these 44 patients of whom 31 underwent ER prior or RFA, the clearance rate of IM and dysplasia was 98% after a median follow up of 21 month. No strictures were found.\textsuperscript{30,50,51}

Sharma et al. reported the single center results of RFA for LGD (n=39) and HGD (n=24) with a median follow up of 24 months.\textsuperscript{31} An overall clearance rate for dysplasia of 89%, and clearance rate for IM of 79% was achieved. In the HGD group, the clearance rate of HGD was 100%, while the clearance rate of all dysplasia was 79%, and the clearance rate for IM was 67%. In the LGD group the clearance rate of all dysplasia was 95% and the clearance rate for IM was 87%. In this cohort only 2 HGD patients underwent ER prior to RFA. There were no buried glands in 2,500 biopsies.

**Multicenter registration**

After the promising first results of treating HGD, a prospective multicenter registry was initiated in which 16 US centers participated. After 12 months of follow up complete eradication of HGD was achieved in 90% of 92 patients. The eradication rate of IM was only 54%, possibly because the HALO\textsuperscript{90} was not yet used in this cohort. In this large series only 8 patients previously underwent ER. There were no serious adverse events, but there was one asymptomatic stenosis. Buried glands were not reported. The large number of patients and the multicenter set-up of this study show that RFA using the HALO\textsuperscript{360}-device can be safely implemented in clinical practice.\textsuperscript{59}

**A randomized clinical trial**

Essential evidence that RFA is highly effective in the treatment of dysplastic Barrett’s esophagus, comes from the multicenter AIM-Dysplasia trial.\textsuperscript{60} In this trial 127 patients with BE containing either LGD (n=64) or HGD (n=63) were randomized 2:1 to RFA or a sham-procedure. Eleven patients underwent ER prior to RFA. Twelve months after the initial RFA treatment, patients underwent a biopsy session to assess if dysplasia and intestinal metaplasia were completely eradicated. In an intention to treat (ITT) analysis, 86% (92% per protocol (PP)) of RFA-patients was cleared of dysplasia versus 21% (23% PP) of sham-patients (p<0.001). In the RFA-arm, 77% (83% PP) of patients was completely cleared of IM versus 2% (3% PP) of sham-patients (p<0.001). In the HGD cohort separately,
RFA patients showed a clearance rate of dysplasia of 81% (90% PP) versus 19% (20% PP) of sham patients (p<0.001). The clearance rate of dysplasia in LGD-patients was comparably high, with 90% (95% PP) of patients in the RFA-arm cleared from dysplasia versus 23% (26% PP) in the sham-arm (p<0.001). For the HGD cohort, the progression rate was lower in the RFA-arm, as in the RFA-arm 1 of 42 patients developed carcinoma versus 4 of 21 patients in the sham-arm (p=0.03). This suggests that RFA changes the natural course of the disease.

The results of this important study confirm that RFA treatment of patients with HGD is safe and highly effective. Due to the randomized design, the study demonstrates that treatment with RFA for patients with HGD is more effective than 3-monthly surveillance endoscopies, making surveillance for patients with HGD no longer acceptable. The results also show that the use of other ablation techniques or surgery for patients with HGD in BE is questionable, since RFA is an excellent minimal-invasive alternative with a low complication rate.

Adverse events

RFA using the HALO system is associated with a low complication rate. After RFA treatment, patients have reported chest pain and difficulty swallowing for 3 to 4 days, that resolves spontaneously and can be adequately managed by pain medication. However, sporadically, patients with severe chest pain are admitted for observation and conservatively managed by optimizing pain medication and acid-suppressants. Small non-transmural lacerations are sometimes observed during RFA procedures. We have recently analyzed all patients treated with RFA in our center, including patients that were treated with RFA out of study protocols. A non-transmural laceration was reported in 6% of the patients, and exclusively in patients with a prior ER and/or a balloon of a too large diameter according to the rule of thumb ‘two sizes smaller than the smallest diameter in case of a prior ER’. Also, some patients (8%) developed dysphagia resolving upon dilation, and this was only encountered in patients with an extended ER of more than 2 cm in size or comprising more than 50% of the circumference of the esophagus.\(^6^1\) These findings underline the importance of limiting the extent of the ER, and it is likely that ongoing trials will provide more information on how to optimize the combination of ER and RFA. No perforations and no RFA associated deaths were reported.\(^3^0,3^1,4^7,5^0,5^1,5^7,6^1\) In summary, the complication profile of RFA compares favorably to that of other ablation techniques such as PDT and APC.\(^1^9,2^0,2^2\)

Characteristics of the neosquamous epithelium after RFA

One of the striking findings in all these clinical studies, was the virtual absence of buried Barrett’s glands (BBG) after RFA, while these are typically reported after all previously used ablation techniques in BE. Only in one RFA trial the presence of BBG after RFA was reported.\(^6^0\) In the AIM-Dysplasia trial, comparing RFA versus a sham-procedure in patients with dysplastic BE, 25.2% of patients had BBG at baseline, which was reduced to 5.1% at 12 months after RFA, while in the sham-arm there was an increase of BBG in 40.0% of patients. The use of an aggressive biopsy protocol only during follow up (four
quadrant jumbo biopsies each 1 cm) could address this rise in BBG in patients in the sham-arm. It has been suggested that in other studies BBG were not detected, because of less deep biopsy sampling in the theoretically altered mucosa after RFA. Our group conducted a study to assess biopsy depth and presence of BBG after RFA. Biopsies and ER specimens were obtained from neosquamous and untreated squamous epithelium from patients treated with RFA for BE containing early neoplasia. Blind assessment by three expert pathologists showed no difference in biopsy depth between the neosquamous and untreated squamous epithelium and in none of biopsies or ER specimens BBG were found. This study also evaluated the presence of oncogenetic abnormalities in the BE epithelium before and after RFA. Fluorescent in situ hybridization (FISH) of brush cytology specimens and immunohistological evaluation of biopsies obtained from the BE epithelium at baseline and from the neosquamous epithelium after RFA showed, absence of pre-existing oncogenetic alternations, which was confirmed by others. The absence of BBG and oncogenetic alternations in the newly formed squamous epithelial lining suggest that the risk for malignant progression in these patients is reduced to the normal level of individuals without BE.

**SUMMARY**

RFA is a novel and promising treatment modality in the treatment of BE with HGD or mucosal cancer, and is not associated with stenosis or buried glandular mucosa, which are known side-effects from other ablation techniques as PDT and APC. The combination of ER followed by RFA for removal of the residual flat BE is a power management strategy. Several clinical trials have shown that RFA is safe and highly effective for the removal of dysplasia and complete conversion of the BE into normal appearing squamous esophagus. Although no long-term results are available yet, RFA should be regarded the treatment of choice in patients with early neoplasia in BE with or without a prior ER. Future research will focus on the natural course of dysplastic and non-dysplastic BE, biomarkers predicting disease progression, and cost-effectiveness plus quality of life to assess if RFA treatment is justified for patients with non-dysplastic BE.
REFERENCES


Chapter 4


