
Endoscopic Ablation of Barrett's Esophagus Using the HALO® System

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Abstract

There is increasing interest in endoscopic treatment for Barrett's esophagus because it is the primary risk factor for adenocarcinoma of the esophagus, and the incidence is increasing. Of the various endoscopic treatments available, radiofrequency ablation is the one that has been studied the most. The principle of radiofrequency technology is to deliver a high power (approx. 300 W) over a short period of time (<300 ms) and to utilize energy density control. Recent studies suggest its utility for patients with low-grade dysplasia and high-grade dysplasia. In most instances, patients with intestinal metaplasia only with no dysplasia are followed with endoscopic surveillance rather than endoscopic treatment. Radiofrequency ablation treatment may be delivered by either a balloon device (HALO³⁶⁰; HALO® system, BÂRRX, Sunnyvale, Calif., USA) or a paddle device attached to the tip of the endoscopy (HALO⁹⁰). After initial endoscopic treatment a repeat endoscopy is performed in 2–3 months to determine the completeness of the ablation. At the current time, even if there is no residual Barrett's seen at the follow-up examination, surveillance is still advised. This is because the device was first used in 2003 and long-term durability had not been established. It is hoped that when durability has been demonstrated for the removal of both metaplasia and dysplasia, long-term surveillance will not be needed.

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There is increasing interest in the endoscopic treatment of Barrett's esophagus (BE). Endoscopic treatment has been utilized for many years [1], but in the past no specific treatment has emerged as an appealing treatment option with appropriate safety, efficacy and ease of treatment for both patients and physicians. Recently there has been a growing amount of literature related to the endoscopic ablation of BE using radiofrequency ablation (RFA) (HALO® system). The indications for RFA are not clearly established. However, there is consensus that this technique is useful for patients with BE and high-grade dysplasia (HGD), BE and intra-mucosal carcinoma as an adjunct to endoscopic mucosal resection (EMR). The use of RFA for BE with LGD or intestinal metaplasia is not clearly established, and currently considered a relative indication.

Table 1. Endoscopic options for treatment of BE

Multipolar coagulation
Argon plasma coagulation
Photodynamic therapy
Laser therapy
Cryotherapy
RFA (HALO)
Mucosal/submucosal resection
Combination therapy

Table 2. Use of radiofrequency for esophageal diseases

Intestinal metaplasia only
LGD only
HGD only
LGD + HGD
Intramucosal carcinoma
Squamous dysplasia

Procedural Aspects (tables 1, 2)

Patient Preparation

The patient is prepared as for any standard interventional upper endoscopy. Patients with blood dyscrasias or those taking anticoagulant therapy should undergo laboratory tests including a complete blood count and PT-INR.

Technical Aspects

The principle of radiofrequency electrode technology is to deliver high power (approx. 300 W) in a short period of time (<300 ms) and to utilize energy density control. When the HALO³⁶⁰ balloon is used, the idea is to have uniform wall tension, which is achievable with a balloon. In addition, tight electrode spacing (<250 μm) leads to more superficial tissue injury. The concept is that this will control the depth of energy penetration to ablate the Barrett epithelium up to the superficial muscularis mucosa without injuring the submucosa. Depths of ablation are generally in the range of 700 μm . The concept is that the Barrett's tissue will not extend into the submucosa. If the submucosa is not injured and there will be less risk of bleeding, fibrosis and stricturing.

The equipment that is utilized for the RFA (HALO[®] system, BÂRRX, Sunnyvale, Calif., USA) system includes an energy generator, a sizing balloon for HALO³⁶⁰ treatments, a treatment delivery balloon (HALO³⁶⁰) for circumferential therapy, and a separate product called the HALO⁹⁰ for focal treatment. The latter is attached to a standard forward-viewing endoscope.

The technique is performed in the following manner [1–4]. After the endoscopic esophageal landmarks are defined, the esophageal wall is sprayed with acetylcysteine 1% and then flushed with water to remove excess mucous for the HALO³⁶⁰ ablation procedure. The esophageal diameter is measured with a sizing catheter. It is passed over a stiff guidewire, which is passed endoscopically. After the guidewire passage, the endoscope is removed. An auto-sizing balloon is used

to determine the diameter of the esophagus. This is important to allow good contact between the balloon/electrodes and the esophageal wall on the one hand and not to apply excessive pressure on the other. The electrodes on the HALO³⁶⁰ treatment catheter are 3 cm in length and treatment is delivered beginning approximately 1 cm above the proximal margin of Barrett's. The location can be achieved by noting the marks on the shaft of the catheter and is usually confirmed with side-by-side endoscopic observation of the ablation procedure. The treatment is delivered using between 10 and 12 J energy settings. Delivery typically lasts 1–3 s. Moving from proximally to distally, the balloon is progressively repositioned allowing for a very small overlap with the previous treatment zone. Ablation is repeated until the entire BE has been treated with radiofrequency energy. In most cases with the HALO³⁶⁰, two treatments are delivered. Generally, the HALO³⁶⁰ device is removed after the first series of applications and then cleaned. In addition, the exudative material caused by the burn can be scraped off the esophagus with aggressive washing or using a device similar to the endoscopic cap that is used for mucosal resection. After the initial treatment is delivered, endoscopic observation is made to determine that all the Barrett's has been treated. After that observation is achieved, the procedure for that day is completed. A follow-up endoscopic treatment is usually carried out in 2–3 months.

At the time of the follow-up, a second treatment may be necessary. This can be repeated with the HALO³⁶⁰ balloon if there are large areas of Barrett's in the tubular esophagus that have not been eliminated. However, it is far more common that on subsequent treatments after the initial HALO³⁶⁰ treatment that the HALO⁹⁰ device will be utilized. The HALO⁹⁰ electrode is fitted on the tip of the endoscope and then the endoscope is advanced into the esophagus. Care must be taken when advancing from the pharynx to the upper esophageal sphincter into the esophagus. In most patients there is little difficulty, but in some patients, particularly those with unusual anatomy, passage may require patience and at times dilation of the upper esophageal sphincter. Prior to assessing the mucosa for further treatment, 1% acetylcysteine is often sprayed to remove mucus and to highlight mucosal features. Narrow band imaging may also be applied. After the residual Barrett's is identified, the HALO⁹⁰ electrode is brought into close contact with the mucosa, the device is deflected for a close apposition of the device with diseased mucosa and then treatment is carried out.

Post-Procedure Care

The procedure is generally well tolerated. However, chest pain occurs in the majority of patients who are treated and generally lasts for a few days. Management with a local solution of viscous Xylocaine® and antacids with non-narcotic analgesics has been effective in most patients. In 1–2% of the patients, the pain has been more severe and longer lasting, and rarely, hospitalization for pain management is required. Follow-up is then carried out in 2–3 months to evaluate the esophagus (see above).

Complications

The RFA using BARRX has proven to be a safe procedure, but as with any procedure there are some complications. The most common delayed complication has been the development of esophageal strictures. This is more likely to occur in patients who have had EMRs and in some areas where treatment has been overlapped. The exact incidence is not known, but in published series it has been in the range of 1%. To date, approximately 20,000 patients have been treated and no deaths have been reported. Perforations have occurred, but they are extremely rare and usually happened during insertion or removal of the ablation catheter.

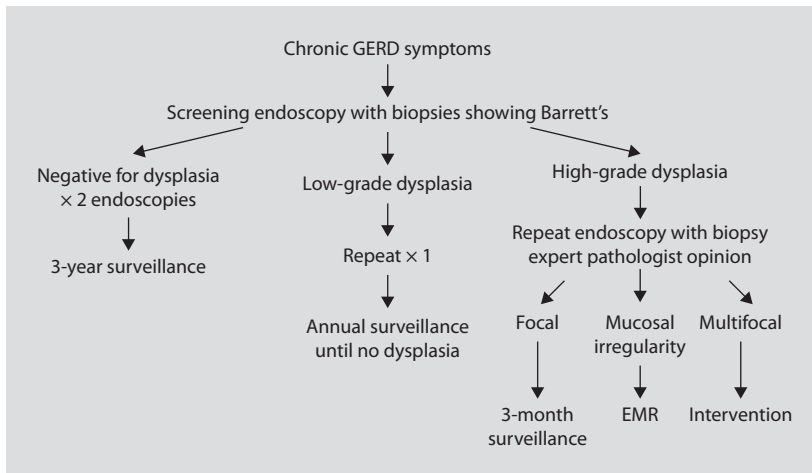


Fig. 1. Surveillance guidelines by the American College of Gastroenterology for BE (2008) [from 3].

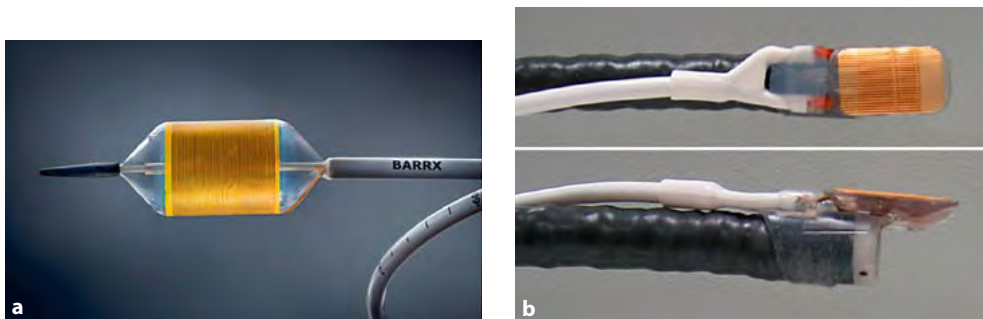


Fig. 2. **a** HALO³⁶⁰ balloon with circumferential coils. **b** HALO⁹⁰ with attachment for distal endoscope.

Outcomes

Since the device was released in 2003, there have been an increasing number of abstracts and full publications describing the technology and its clinical use. In 2003 the AIM (ablation of intestinal metaplasia) I Trial began to clarify benefit in patients that had metaplasia without dysplasia [5]. Subsequently, studies in patients with low-grade dysplasia (LGD) and HGD were undertaken. In addition, information has been gathered through patient registries and through cooperative studies.

It can be confusing to ‘analyze’ the results of RFA treatment for BE without substratifying the analysis. RFA has been used to treat intestinal metaplasia only; to treat LGD only; to treat HGD only; and to treat LGD + HGD +/- intramucosal carcinoma. In addition, RFA has been combined with additional endoscopic modalities and RFA has been studied in patients with squamous dysplasia. Therefore, when one looks at the results, one needs to understand which group of patients is being treated.

Some individuals believe that it is appropriate to use RFA for intestinal metaplasia, while others do not. Those who support its use state that initial studies on its efficacy and safety have

been encouraging. They also point out that without predictive markers some patients with a family history or anxiety may desire treatment even if it is not clear that their disease will progress. It is also known that 50% of patients who progress to HGD or esophageal adenocarcinoma have no dysplasia on as many as two previous endoscopies. These are the arguments that are posed in opposition to treating intestinal metaplasia only. They argue that only 10% of patients with intestinal metaplasia will progress. Therefore, why treat 90% of patients who will not have more advanced disease? The longest follow-up study for patients who underwent endoscopic ablation of BE with intestinal metaplasia only is the AIM II Study [6]. In this study, 70 patients were enrolled in the initial effectiveness phase of the trial and underwent circumferential ablation. They had a subsequent endoscopy at 1, 3, 4, 6 and 12 months. After 12 months, 62 patients were enrolled into a study extension, which followed these patients for another 1.5 years. At the end of 2.5 years (30 months), 61 had endoscopy with biopsy. Of those, there was complete remission (CR) of intestinal metaplasia (CR-IM) in 98.4% of patients. There were >1,000 biopsies collected in these patients at 12 months. No strictures or buried glands were seen.

Some have argued that it is unwise to treat patients with intestinal metaplasia only, since most will not go on to more advanced disease. Das et al. [7] performed a study assessing the cost-effectiveness of a combined modality using HALO³⁶⁰ followed by HALO⁹⁰ ablation in the management of patients with non-dysplastic BE. The mathematical model compared different strategies in a 50-year-old patient. The assumptions were that the treatment would get rid of Barrett's in 50% of patients and that the costs were 'high'. With this mathematical model, the patient age, cost of ablation and CR rate associated with an ablation are critical determinants of its cost-effectiveness. The authors concluded that ablative therapy is cost-effective over 'surveillance' if the patients are treated at the age less than 55 years, the cost for the procedure is less than USD 7,450 and the CR rate is greater than 66%.

A study by Sharma et al. [8] presented a 2-year follow-up on patients who had been treated for LGD with RFA. Ten patients were initially treated with the HALO³⁶⁰ and then HALO⁹⁰; biopsies were taken at 1, 3, 6, 12 and 24 months. There was CR of dysplasia (CR-D) in 100% of the patients and in all but 1 of the 10 patients there was CR-IM.

A cost-effectiveness study comparing endoscopic surveillance or esophagectomy with RFA for patients with BE and LGD was written by Inadomi et al. [9]. In this study, ablation is the most cost-effective option for patients with LGD if you can achieve CR-IM in 60% of patients and CR of LGD in 70% of patients. For this group of patients, ablation 'dominates' surveillance, which means it is less expensive and more effective.

There are some studies that look at RFA for HGD. The largest series of patients is included in the HGD Registry [10], where 142 patients from 16 centers were included. Eight had previous EMRs. In this collection of patients, results for only 2 patients were treated with circumferential ablation with 12 J/cm² because HALO⁹⁰ treatments were unavailable at this time. 92 of the patients were available for follow-up beyond 6 months; the median follow-up was 12 months. The CR for HGD was 90% and the CR for intestinal metaplasia was 53%.

The most important study assessing RFA for dysplasia is the randomized multicenter sham-controlled trial by Shaheen et al. [11], published recently. There were 120 patients with dysplasia, 60 of which had LGD and 60 of which had HGD. In each arm, 2 of 3 patients were randomized to RFA and one third to sham control. The initial treatment was with HALO³⁶⁰ and at the follow-up points focal ablation could be instituted if there was residual Barrett's. Follow-up endoscopies with biopsies were carried out at 6, 12, 18 and 24 months in the patients with LGD and at

3, 6, 9, 12, 15, 18, 21, and 24 months in the patients with HGD. The primary endpoints were CR-IM in all patients and CR-D in those with HGD and LGD. The evaluations were done both 'per protocol' and 'intention-to-treat'. Per protocol, 83% of the treated patients had CR-D in the HGD group and none in the sham group. For those patients with LGD, 100% of the treated patients had CR-D and 36% of the patients had CR-D. Regarding CR-IM, it was found in 75% of the patients who were treated with HGD and 87% of the patients with LGD. None of the sham patients had CR-IM. The reason that these results are so impressive is the complete response for a patient is defined as all biopsies negative for either dysplasia or intestinal metaplasia. That is, 1 positive biopsy out of 40 is considered a failure.

For patients with dysplasia and intramucosal carcinoma, many patients are treated with EMR followed by RFA. This is a particularly common strategy if there is an irregularity or nodule seen in the Barrett's segment. The thinking is that the EMR will both remove the pathologic tissue, but also clarify whether or not this management is sufficient for removing the HGD or IMC. After a localized EMR is performed, RFA could then be performed on the flatter and more extensive Barrett's tissue. The leading group in the world for this approach is the group from the Amsterdam Medical Center in the Netherlands led by Bergmann and his colleagues. An example of the efficacy of this strategy is a publication by Gondrie et al. [12, 13], in which 44 patients with dysplasia and intramucosal carcinoma were treated. At 12 months the CR for dysplasia was 98% and the CR for intestinal metaplasia was 98%. Other studies from this group and the European Multicenter Study Group are underway.

Conclusion

RFA with the HALO treatment system is a logical and well-conceived therapy. The device and the technique are still evolving. RFA is effective for eliminating intestinal metaplasia and dysplasia in most patients with BE. Although complications occur, the rate is acceptable. It is the view of the authors that this represents the best endoscopic treatment for flat Barrett's at this time. Combining EMR and RFA has an appeal in certain patients, particularly those who have nodular or elevated foci within the Barrett's. Answers to the questions expressed above will lead to further refinement of this treatment and better definition of the patients for whom this treatment is most appropriate.

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