
CLINICAL TRIAL DATA SUMMARY:
RADIOFREQUENCY ABLATION WITH
THE HALO ABLATION SYSTEMS FOR TREATING DISORDERS
OF THE GASTROINTESTINAL TRACT

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1. INTRODUCTION

Barrett's Esophagus

Barrett's esophagus (BE) is associated with an increased risk of developing esophageal adenocarcinoma (EAC). BE implies the replacement of a portion of the squamous epithelium of the distal esophagus by specialized intestinal epithelium or intestinal metaplasia (IM) containing goblet cells, under the impetus of refluxed gastric contents of acid and bile. Factors such as genetics, gender and race, may also play a role. Once IM is present, some patients develop further cellular changes, in the form of low-grade (LGD) or high-grade dysplasia (HGD), and/or adenocarcinoma.

In recent years, the prevalence of BE appears to be on the rise. Rex et al. reported a 6.8% prevalence of IM in a general population of patients undergoing colonoscopy, including patients with and without gastroesophageal reflux disease (GERD).¹ Gerson et al. reported a 25% prevalence of IM in a cohort of 110 subjects over 50 years of age, asymptomatic for GERD, undergoing sigmoidoscopy for colorectal cancer screening.² In one series, the frequency of new cases of BE rose from 2.9 to 18.9 cases per 1,000 endoscopies over the last decade.³ According to the National Cancer Institute, 16,470 men and women (12,970 men and 3,500 women) will be diagnosed with and 14,280 men and women will die of cancer of the esophagus in 2008; the majority (>60%) of whom will have EAC.⁴ There has been a 500% rise in U.S. esophageal cancer incidence over the last 30 years, a rise in incidence that surpasses that for all other cancers. The 5-year survival rate for esophageal cancer is 15%, one of the lowest 5-year survival rates for any cancer.

The annual risk for a patient with non-dysplastic IM to develop EAC has been reported as 0.5% (reported as the incidence per patient-year of follow-up), although others have found this rate of progression to be higher.⁵ There are presently no reliable techniques to predict which patients with non-dysplastic IM will progress to HGD or EAC, although it is possible in the future that detection and quantification of molecular markers within the BE tissue may help to stratify patient risk. In a patient population with BE-HGD, a large percentage develop EAC, 16 to 59%, depending on the interval of follow-up.^{6,7,8,9} A recent meta-analysis by Rastogi et al. in patients with BE with HGD who were undergoing surveillance showed that EAC develops in 6% of these patients for every year of subsequent follow-up.¹⁰

Recommendations for the management of BE are based on the histological staging of the disease (non-dysplastic IM, LGD, HGD, or EAC) as well as patient co-morbidities, compliance and preference, physician preference, and institutional factors. For all patients with BE, regardless of histological grade, management of GERD is paramount for maintaining an erosion-free esophagus. Further, based on epidemiological and *ex vivo* evidence, chemoprevention with aspirin or other NSAIDs may be considered, in order to reduce mucosal inflammation and possibly prevent progression to HGD and EAC. In non-dysplastic IM and LGD, management options include surveillance endoscopy with biopsy and, for selected patients, ablative therapy. The endoscopic surveillance interval for IM is every 3 years, while for LGD the interval is every 6-12 months due to the higher-risk for progression. More recently, clinical trial data related to the safety and effectiveness of RFA for IM and LGD has been reported by several authors and may be considered in selected cases. For patients with HGD, recommendations include esophagectomy, endoscopic therapy with endoscopic mucosal resection (EMR) and/or ablation, and surveillance every 3 months to detect progression to cancer. Many centers now offer endoscopic therapy for HGD rather than moving immediately to esophagectomy. Patients with EAC who, after rigorous staging, have disease limited to the mucosa (maximum T1, m1-m3), endoscopic therapy remains a viable option for many patients (EMR and ablation), but when EAC involves the submucosa or deeper, esophagectomy is indicated.

Endoscopic ablative therapy of Barrett's esophagus

Ablation is defined, in this context, as the destruction and ultimate removal of diseased tissue. In the case of BE, ablation refers to the injury and eradication of all IM tissue and its subsequent replacement by a normal neo-squamous epithelium. The intent of eradicating all of the IM clones and stem cells, be it non-dysplastic IM, LGD, or HGD, is to eliminate or reduce the risk for disease progression (specifically cancer), reduce the risk for cancer-related and surgery-related death, and perhaps, pending the results of future clinical trials, reduce or eliminate the need for life-long surveillance.

The pre-ablation work-up must include careful white-light endoscopy of the entire BE segment, categorization of the segment according to its total length, the location of its most proximal extent, and the location of the gastric folds as referenced to the incisors. Biopsies should be obtained from any visible abnormality, as well as from four quadrants from each 1-2 cm level of the BE. Enhanced imaging techniques, such as chromoendoscopy using Lugol's solution or acetic acid, narrow band imaging (NBI), magnification endoscopy, autofluorescence, and high-

definition endoscopy may increase the detection of areas with higher yield for dysplasia and cancer and lead to more precise staging.

Prior to consideration for ablative therapy, any visible abnormality of the mucosa should be resected focally with EMR, to ensure removal of lesions that are too thick for ablative therapy and to detect HGD or occult cancers. In studies of RFA, at least 8 weeks must transpire after EMR prior to ablation to allow complete healing. In cases of HGD, endoscopic ultrasound (EUS) may be performed in order to rule out submucosal or lymph node involvement.

Circumferential radiofrequency ablation system

Circumferential radiofrequency ablation (RFA) is delivered using the HALO³⁶⁰ ablation system, which consists of a high-power energy generator, a sizing balloon catheter [maximum outer diameter (OD) 33.7 mm], and a number of balloon-based ablation catheters having different outer diameters upon full inflation [sizes 22, 25, 28, 31, 34 mm OD].

The RF generator provides automated, pressure-regulated inflation of the sizing balloon and ablation catheters, and delivers a preset amount of RF energy to the ablation catheter electrode. The sizing balloon catheter is inflated within the BE segment (4 psi) and, with the RF generator, measures the esophageal inner diameter (ID) thus allowing the physician to select an ablation catheter of proper size that fits the esophageal luminal diameter. The ablation catheter consists of a 4 cm long, non-compliant balloon, upon which is affixed a 3 cm long flexible bipolar micro-array circuit. The array has 60 independent electrodes that encircle the balloon, each being tightly spaced to its neighbor (250 microns) and each alternating in polarity (plus/minus). Upon inflation to 7 psi, the balloon and electrode transiently flatten the esophageal folds and submit the esophageal wall to a standardized tension or stretch thereby creating a “uniform ablation target”¹¹ Once the ablation catheter is inflated, the RF generator delivers a high-power (~300 W), ultra-short (~ 300 msec) burst of RF energy. The amount of energy is standardized as “energy density” or Joules delivered per unit surface area of the electrode (J/cm²). Others have reported that standardization of power density, energy density, electrode spacing, and inflation pressure result in a uniform ablative injury that does not penetrate the muscularis mucosae.^{12,13,14}

Focal radiofrequency ablation system

Focal RFA utilizes the HALO⁹⁰ ablation system, consisting of an RF generator and endoscope-mounted electrode. The upper surface of the focal device consists of an articulated platform (20 x 13 mm) covered by an electrode array (same electrode pattern as HALO³⁶⁰). The electrode is placed into contact with the BE target by deflecting the tip of the endoscope upwards, causing the platform to articulate and present the electrode to the tissue in a flat manner. This device may be suitable for primary RFA for short segments of BE, for secondary (touch-up) in patients with limited residual disease after circumferential RFA, EMR, or photodynamic therapy (PDT), and for the flared area of the gastroesophageal junction.

Clinical assessment prior to RFA

Prior to RFA, anti-secretory therapy, typically with a proton pump inhibitor (PPI), should be titrated to a dose that will fully control GERD symptoms and eliminate erosive esophageal injury. As described previously, a thorough staging endoscopy is performed with four quadrant biopsies obtained from every 1-2 cm of the BE segment as well as from any visible abnormality. EMR of visible abnormalities should be performed to determine the worst histological grade of BE and to render the mucosa flat prior to ablation (8 weeks should transpire after any EMR prior to undertaking RFA). In cases of HGD or early EAC, a second expert pathologist should review and independently confirm the diagnosis.

Dual channel 24-hour ambulatory pH monitoring while on PPI therapy may also be considered in cases of persistent esophageal injury prior to ablation to confirm absence of pathologic esophageal acid exposure. In the case of HGD or early EAC, EUS and computed tomography (CT) scanning of the chest should be performed to rule out more advanced occult disease.

Post ablation care

Clinical trials have shown that some patients experience discomfort after RFA, but that the majority of symptoms are mild and transient (less than 4 days).^{15,16} All patients are discharged with high-dose PPI (typically 40 mg bid esomeprazole), liquid acetaminophen with codeine, liquid antacid/lidocaine mixture to sip prn, sucralfate slurry for the first 3-4 days, and anti-emetics prn. Diet includes full liquids for 24 hours followed by soft diet for one week. For 7 days before and after RFA, patients are told not to use aspirin or other platelet inhibiting medications.

After primary RFA (usually circumferential), follow-up endoscopy with focal RFA of residual BE may be repeated every 2 months until no endoscopically visible BE remains. Focal RFA is applied to any obvious islands and tongues of BE, as well as an irregular z-line if suspicious for BE. After complete endoscopic resolution is achieved,

four quadrant biopsies are obtained from every 1 cm of the original BE segment location to confirm complete histological eradication (defined as CR-IM). Once CR-IM has been accomplished, GERD symptoms should be controlled (for life) using anti-secretory medication or anti-reflux surgery. For now, surveillance endoscopy schedule indicated by the baseline BE histological grade should be continued.

Clinical Trials Reporting on RFA Outcomes

There is published peer-reviewed clinical trial data regarding the histological effect of RFA on normal esophageal squamous epithelium (dosimetry trials), Barrett's tissue (non-dysplastic IM, LGD, HGD) dosimetry and efficacy trials, and early EAC (intramucosal cancer). These trials have included the porcine model, pre-esophagectomy human subjects, and human subjects with BE. Earlier studies focused on outcomes from circumferential RFA alone, as the focal RFA device was not available. More recently, trials have included a step-wise approach of circumferential and focal RFA (with observed improvement in overall efficacy outcomes) as well as combined EMR-RFA therapy.

Ganz et al., in a multi-phase study, evaluated the endoscopic and histologic effects of circumferential RFA in a porcine model (Phases I through III) as well as in the normal squamous portion of the esophagus of human patients undergoing esophagectomy for EAC (Phase IV).¹² Phase I was an acute treat and resect study, which sought to determine the treatment settings (power and energy density) necessary to completely remove the esophageal epithelium. After gross and histological examination of ablation sites, it was determined that the esophageal epithelium could be ablated completely with energy density settings of 9.7 J/cm² and higher. Phase II was a chronic survival study, which looked at the relationship between energy density dose and stricture formation at 2 and 4 weeks. Low energy density settings (9.7 and 10.6 J/cm²) resulted in no stricture formation whereas higher settings (> 20 J/cm²) universally did. Phase III of this study, also chronic, examined completeness of epithelial ablation and maximum depth of thermal injury for a broad range of energy densities (5-20 J/cm²). Settings of 8 J/cm² and higher resulted in 100% epithelial ablation. Five and 8 J/cm² preserved the muscularis mucosae, whereas 10 J/cm² caused injury to the muscularis mucosae but spared the submucosa. Phase IV, the human phase of this study, looked at the completeness of esophageal ablation and ablation depth in the squamous epithelium of patients who were ablated 24-48 hours prior to esophagectomy. Energy density settings of 10 and 12 J/cm² resulted in complete ablation of the esophageal epithelium and did not penetrate deeper than the muscularis mucosae. Applications of energy in these described trials were 1x, in other words, 1 application of the balloon electrode with no cleaning and no second RF delivery. In summary, this multi-phase study showed that circumferential, complete ablation of porcine and human esophageal epithelium could be performed without obvious injury to the submucosa. In all cases, ablation depth was linearly related to the energy density delivered (1x).

Dunkin et al. performed a circumferential RFA dosimetry study in the unaffected, normal squamous portion of the esophagus in patients undergoing esophagectomy for cancer. The objective was to determine the optimal energy density and treatment parameters to achieve complete ablation.¹³ Subjects were randomized to one of three energy density groups (8, 10, or 12 J/cm²). RF energy was applied one time (1x) proximally and two times (2x) distally to non-tumor bearing esophageal squamous epithelium. No cleaning between treatments was performed. Complete epithelial ablation was reliably achieved at 10 J/cm² (2x) and 12 J/cm² (1x or 2x). However, 8 J/cm² (1x or 2x) and 10 J/cm² only partly ablated the epithelium. Ablation depth was related to the energy density delivered, with the maximum depth never occurring deeper than the muscularis mucosae. In each specimen, there was a very thin residual amount of ablated tissue, typically corresponding to the lamina propria or muscularis mucosae, mean thickness 35 µm, with all layers deep to this being histologically normal. This implied that the ablation effect was sharply truncated and that the investigators might expect a similar effect once they treated humans with BE who would retain their esophagus.

Smith et al. aimed to determine the optimal circumferential RFA parameters for the ablation of IM containing HGD.¹⁴ Prior to esophagectomy for the indication of HGD, subjects underwent RFA of 1 or 2 segments of BE-HGD (ablation zones). Various combinations of energy density (10, 12, 14 J/cm²) and number of ablation applications (2x, 3x, 4x) were utilized to determine maximum ablation depth and complete ablation of IM and HGD. Ablation depth increased as both energy density and number of applications increased, with the muscularis mucosae being the deepest ablation level achieved at 14 J/cm² and 4x. Complete ablation of all IM and HGD occurred in all but one of the ten ablation zones (12 J/cm² 2x), the latter of which was attributed to incomplete overlap during the second ablation application.

After completion of the pilot dosimetry trials, the Ablation of Intestinal Metaplasia Trial (AIM Trial) was commenced as the first study to enroll patients with BE who would retain their esophagus after ablation.¹² This trial was conducted in two serial phases, a dosimetry phase (AIM-I, n=32) and an effectiveness phase (AIM-II, n=70). All patients had non-dysplastic IM. The dosimetry phase evaluated the dose-response and safety of delivering circumferential ablation using 6 to 12 J/cm² (1x) in patients with up to 3 cm of BE. There were no dose-related

serious adverse events and the outcomes at 1 and 3 months, along with the experience from previous esophagectomy studies, permitted the selection of 10 J/cm² (2x) for the subsequent effectiveness phase of the study. The effectiveness phase involved circumferential ablation using 10 J/cm² (2x) in patients with up to 6 cm of BE. No cleaning step was incorporated between applications of energy, as this concept had not been envisioned. Patients underwent endoscopy with biopsies at 1, 3, 6, and 12 months. The primary endpoint for AIM-II was histology-based and defined as complete response (CR) for IM at 12 months. A CR-IM means all biopsies for a patient show no evidence of IM at that time interval. The percent of patients with CR-IM at 12 months was reported as the primary efficacy outcome variable. At 12 months (n=69; mean 1.5 sessions), a CR-IM was achieved in 70% of patients. The focal RFA device was not incorporated in this first report of AIM-II, as it had not yet been developed.

Fleisher et al. reported on the longer term 2.5 year follow-up of the AIM-II patient cohort.¹⁶ This study looked at secondary focal RFA for patients after initial circumferential RFA, in an attempt to optimize the CR-IM rate. The majority of eligible patients (62 of 70) agreed to participate. After the 12 month biopsy results were available, focal RFA was applied for any residual IM or endoscopic appearance suggesting IM. Then, at 2.5 years, EGD with biopsy was performed. CR-IM was achieved in 98.4% of patients. There were no strictures or buried glandular mucosa.

Roorda et al. assessed the safety and effectiveness of circumferential RFA (without focal RFA) combined with twice-daily PPI therapy confirmed by pH monitoring in a single center, community-based, BE referral center.¹⁷ After symptom evaluation, endoscopy and histopathology assessment, CT/EUS for HGD baseline diagnosis, and EMR for nodularity, they performed serial circumferential RFA (mean sessions 1.4). In 13 total patients, 6 achieved CR-IM. In 7 patients with dysplasia, 5 achieved CR for dysplasia. In all, treatment continued after this interim analysis. A minority of patients (5/13) normalized esophageal acid exposure on bid PPI, with a positive correlation of pH control with response to RFA.

Ganz et al., in a U.S. multicenter registry (16 centers), assessed the safety and effectiveness of circumferential RFA in 142 patients with BE HGD (median length 6 cm).¹⁸ Prior EMR was performed in 24 patients, 5 of whom demonstrated intramucosal adenocarcinoma (IMC). The dose of ablative energy was 12 J/cm² (2x) and median number of treatment sessions was 1. No cleaning step was incorporated and no focal RFA. After the initial ablation session, patients underwent endoscopy at 3 month intervals and repeat circumferential RFA was performed if persistent BE was evident. At a median of 12 months of follow-up, CR-HGD was achieved in 90% of patients, and CR-IM in 54%. There was 1 asymptomatic stricture (which did not require dilation) and no buried glands. The authors note that the most significant limitation of this trial was its “registry” design, allowing for variability in patient work-up, technique, and follow-up. They also noted that the focal RFA device was not available, which limited their CR-IM outcome.

Sharma et al. used step-wise circumferential and focal RFA for patients with BE containing LGD.¹⁹ Circumferential ablation was performed at baseline and repeated at 4 months for any residual IM. Focal ablation was performed after 12 months for any residual IM. Endoscopy with 4 quadrant biopsies every 1 cm was performed at 1, 3, 6, 12 and 24 months. This trial used similar histology based endpoints, including CR-dysplasia (all biopsies negative for IM containing dysplasia) and CR-IM. At 2 years, CR for dysplasia was 100% and CR for IM was 90%. There were no strictures and no evidence of buried glands.

Gondrie et al. have two published studies evaluating RFA +/- EMR for HGD/IMC. In the first report,²⁰ 11 patients were enrolled with HGD and/or IMC. After 6 underwent EMR for visible abnormalities, the pre-RFA remaining histology was LGD (n=2) and HGD (n=9). After RFA, 10/11 patients had CR-IM (and CR-dysplasia). A focal escape EMR in one patient with partial response converted them to CR-IM as well. In the second report,²¹ 12 patients were enrolled having HGD (n=11) and IMC (n=1). After 7 underwent EMR for visible abnormalities, the pre-RFA remaining histology was LGD (n=1) and HGD (n=11). After serial RFA, 11/12 patients had CR-IM (and CR-dysplasia). Again, escape EMR was performed in one patient with partial response, converting them to CR-IM as well. In both studies, the authors note that with RFA plus focal EMR, a 100% CR-IM is possible.

There are two clinical studies preliminarily reported in abstract form assessing the prevalence of abnormal molecular markers in esophageal tissue before and after RFA. Finkelstein, et al.²² evaluated 21 patients with BE-LGD. Microdissection specimens from multiple targets for each patient were assessed (baseline and up to 2.5 years after RFA) for a panel of 16 allelic imbalance mutational markers affecting 1p, 3p, 5q, 9p, 10q, 17p, 17q, 21q, and 22q using quantitative fluorescent PCR with capillary electrophoresis. All patients at baseline had multiple mutational abnormalities. RFA achieved a CR-IM in 15/16 patients, and all of these 15 patients demonstrated absence of the previously detected mutations. Intestinalized mucosal cells bearing highly clonally expanded mutations were more resistant to initial RFA, requiring more ablation sessions, but could be eliminated by repeat treatment. Gondrie et al. assessed a number of genetic abnormalities associated with BE with dysplasia and cancer

in 10 patients before and after RFA.²³ These genetic abnormalities included immunohistochemistry (IHC) for Ki67 and p53, and fluorescent in-situ hybridization (FISH) for numerical and chromosomal changes and loss of p16/p53. All patients demonstrated multiple baseline abnormalities on both IHC and FISH. After RFA, CR-dysplasia and CR-IM was achieved in all patients (100%) and all patients were normal on IHC and FISH.

Shaheen, et al. conducted a randomized, sham-controlled, 19 center U.S. clinical trial comparing RFA/surveillance/PPI versus sham ablation/surveillance/PPI in patients with either LGD or HGD (confirmed by centralized expert pathology review).²⁴ Beginning in 2006, 127 patients were enrolled and randomized according to baseline histology and endoscopic length. At one-year follow-up (interim analysis of 101 patients), higher proportions of RFA subjects had achieved CR for dysplasia and IM compared to sham. In the HGD group, treatment patient CR-dysplasia was 80% ITT (91% PP), while sham was 11% ITT (12% PP)(p<0.001). In the LGD group, treatment patient CR-dysplasia was 90% ITT (95% PP), while sham was 37% ITT (41% PP)(p<0.001). The CR-IM for the RFA cohort overall was 77% ITT (83% PP), compared to 0% ITT (0%PP) of sham (p<0.001). Further, the rate of progression to higher grades of dysplasia or cancer was lower in the RFA group as compared to sham. There were no perforations or deaths with RFA.

Cost-effectiveness Analyses of RFA

Two case-based studies have been preliminary reported in abstract form which assess the cost-effectiveness of various interventions (including RFA) for Barrett's esophagus. Das et al. used a Markov model in a hypothetical 50-year-old with non-dysplastic BE (NDBE) to evaluate three competing strategies: (1) no intervention (natural history), (2) surveillance alone, (3) RFA.²⁵ The assumptions were conservative, using estimates of CR-IM for RFA of 50%, intentionally lower than the published studies have reported. They concluded that patient age, cost of RFA, and CR-IM were critical determinants of the cost-effectiveness of RFA. Within a range of these parameters in this model, RFA was a cost-effective strategy. Inadomi et al. used a mathematical model designed to simulate the natural history of a cohort of patients with BE-LGD from age 50 to 80 years or death.²⁶ It compared the incremental cost-effectiveness between three competing strategies: (1) surveillance, (2) esophagectomy, and (3) RFA. Outcomes included the incremental cost-effectiveness ratio (ICER) comparing total direct costs and quality adjusted life years (QALYs). The ICER of RFA (\$2677 per QALY gained) was lower compared to the ICER for surveillance (\$8193 per QALY gained). They concluded that RFA was a cost-effective option, in this model, in patients with BE-LGD.

Conclusions

While studies are underway to assess whether RFA imparts a reduction in risk for progression of disease in BE patients, the present published literature suggests that RFA is a safe and very effective intervention for eliminating both metaplastic and dysplastic BE. Looking ahead, cost-effectiveness studies may shed further light on what the most optimal combination of interventions (ablation, resection, surveillance, surgery) might be for the spectrum of patients with BE.

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2. THE DEVICES

2.1. Regulatory Clearance

The HALO³⁶⁰ ablation system first received 510(k) clearance from the FDA on December 18, 2001 (K013139). Improvements to the device have been described in more recent 510(k) clearances.

The indication for use statement is:

The HALO³⁶⁰ ablation system is indicated for use in the coagulation of bleeding and non-bleeding sites in the gastrointestinal tract including, but not limited to, the esophagus. Indications include esophageal ulcers, Mallory-Weiss tears, arteriovenous malformations, angiomas, Barrett's esophagus, Dieulafoy lesions, and angiodysplasia.

The HALO⁹⁰ ablation system received 510(k) clearance from the FDA on April 21, 2006 with the indication for use statement:

The HALO⁹⁰ ablation system is indicated for use in the coagulation of bleeding and non-bleeding sites in the gastrointestinal tract including, but not limited to, the esophagus. Indications include esophageal ulcers, Mallory-Weiss tears, arteriovenous malformations, angiomas, Barrett's esophagus, Dieulafoy lesions, and angiodysplasia.

Both systems have CE Mark for Europe, as well as approval for use in Canada and Australia.

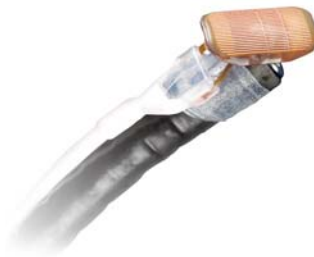
2.2. HALO³⁶⁰ Ablation System

The HALO³⁶⁰ ablation system includes an energy generator, ablation catheters, and sizing balloons. The energy generator is used to inflate the sizing balloons in order to measure the inner diameter of the targeted portion of the esophagus, and is used to deliver RF energy to the ablation catheters to achieve the ablative effect. All catheters are single use, disposable medical devices. The following image depicts a HALO³⁶⁰ ablation catheter.



2.3. HALO⁹⁰ Ablation System

Focal ablation of residual Barrett's tissue may be conducted with the HALO³⁶⁰ device or a focal ablation device, the HALO⁹⁰ device, capable of more selective tissue ablation. The HALO⁹⁰ is substantially equivalent to the HALO³⁶⁰, having the same electrode design and delivering the same energy density and power density to the tissue. The difference is that the surface area is smaller, allowing more focal selective ablation of residual Barrett's tissue, and this device is attached to the endoscope, rather than to a balloon catheter. The following image depicts a HALO⁹⁰ ablation catheter.



3. **ABSTRACTED SUMMARIES OF SELECTED PUBLISHED PAPERS**

3.1. **Circumferential and focal ablation of Barrett's esophagus containing dysplasia**

Virender K Sharma, H Jae Kim, Ananya Das, Christopher D Wells, Cuong C Nguyen, David E Fleischer
Am J Gastroenterol advance online publication 27 January 2009; doi: 10.1038/ajg.2008.142

Objectives: The finding of dysplasia in a Barrett's esophagus (BE) is associated with an increased risk for developing esophageal adenocarcinoma. Ablation using the HALO system has shown promise for the treatment of BE with dysplasia. The objective of this study was to assess the safety and efficacy of a stepwise regimen of circumferential and focal ablation using the HALO system for the treatment of BE with dysplasia.

Methods: Patients with BE containing low-grade dysplasia (LGD) or high-grade dysplasia (HGD) were enrolled. Primary circumferential ablation was followed every 3 months by further circumferential ablation or focal ablation until complete endoscopic eradication of BE was achieved. At 3- or 6-month intervals, depending on baseline grade, targeted and four quadrant random biopsies were obtained to assess the histological response to ablation. A complete response (CR) is defined as all biopsies negative for intestinal metaplasia (IM) (CR-IM) or dysplasia (CR-D) at last available follow-up.

Results: A total of 63 patients were treated (57 men; median age 71 years; median BE length 5 cm), with worst grade of dysplasia being LGD ($n=39$) and HGD ($n=24$). Follow-up is available for 62 patients (median 24 months). Overall, CR-IM is 79% and CR-D is 89%. For the LGD cohort, CR-IM is 87% and CR-D is 95%. For the HGD cohort, CR-IM is 67% and CR-D is 79%.

Conclusions: Stepwise circumferential and focal ablation of BE containing dysplasia appears to be a safe and effective intervention, achieving a CR for dysplasia in 95% and 79% of LGD and HGD patients, respectively.

3.2. Stepwise radiofrequency ablation of Barrett's esophagus preserves esophageal inner diameter, compliance, and motility

H. Beaumont, J.J. Gondrie, B.P. McMahon, R.E. Pouw, H.Gregersen, J.J. Bergman, G.E. Boeckxstaens
Endoscopy 2009;41:2-8

Background and aim: Stepwise endoscopic circumferential and focal radiofrequency ablation is safe and effective for the eradication of Barrett's esophagus. In contrast to other techniques, radiofrequency ablation appears to avoid significant esophageal scarring or stenosis. Our aim was to evaluate whether radiofrequency ablation has an adverse effect on esophageal function in patients treated for Barrett's esophagus containing intramucosal cancer and/or high grade dysplasia.

Methods: Twelve patients with Barrett's esophagus containing intramucosal cancer or high grade dysplasia were included in the study. After endoscopic resection of visible abnormalities, stepwise circumferential and focal ablation were performed every 2 months up to a maximum of five sessions. Measurement of the inner diameter was performed at 1-cm intervals in the distal esophagus. Manometry was performed using a water perfused sleeve catheter. Compliance was evaluated using the functional lumen imaging probe (FLIP), measuring eight cross-sectional areas within a saline filled bag with two pressure side holes, one proximal to and one inside the bag. Esophageal sizing, manometry, and compliance were recorded in patients at baseline and at least 2 months after the final ablation session. In addition, FLIP and manometry measurements were performed in 10 healthy volunteers.

Results: All patients achieved complete eradication of dysplasia and Barrett's esophagus, without severe complications or ablation related stenoses. The esophageal diameter was unchanged by the ablation. Lower esophageal sphincter pressure and length and esophageal contraction amplitude before and after ablation were not significantly different. Baseline compliance was significantly different between healthy volunteers and Barrett's esophagus patients. Compliance was not, however, significantly changed by ablation.

Conclusions: Stepwise circumferential and focal ablation of Barrett's esophagus is an effective and safe treatment modality for early Barrett's neoplasia that appears to preserve the functional characteristics of the esophagus.

3.3. Endoscopic ablation of Barrett's esophagus: a multicenter study with 2.5-year follow-up (AIM-II Long-term follow-up)

David Fleischer, Bergein Overholt, Virender Sharma, Alvaro Reymunde, Michael Kimmey, Ram Chuttani, Kenneth Chang, Charles Lightdale, Nilda Santiago, Doug Pleskow, Patrick Dean, Kenneth Wang

Gastrointest Endosc 2008;68:867-76

Background: For patients with Barrett's esophagus (BE), life-long surveillance endoscopy is recommended because of an elevated risk for developing dysplasia and esophageal adenocarcinoma. Various endoscopic therapies have been used to eradicate BE. Recently circumferential radiofrequency ablation has been used with encouraging short-term results.

Objective: To provide longer follow-up and to assess the long-term safety and efficacy of step-wise circumferential ablation with the addition of focal ablation for BE.

Design: Prospective, multicenter clinical trial (NCT00489268).

Setting: Eight U.S. centers, between May 2004 and February 2007.

Patients: Seventy subjects with 2 to 6 cm of BE and histologic evidence of intestinal metaplasia (IM).

Interventions: Circumferential ablation was performed at baseline and repeated at 4 months if there was residual IM. Follow-up biopsy specimens were obtained at 1, 3, 6, 12, and 30 months. Specimens were reviewed by a central pathology board. Focal ablation was performed after the 12-month follow-up for histological evidence of IM at the 12-month biopsy (absolute indication) or endoscopic appearance suggestive of columnar-lined esophagus (relative indication). Subjects received esomeprazole for control of esophageal reflux.

Main outcome measurements: Complete absence of IM per patient from biopsy specimens obtained at 12 and 30 months, defined as complete remission-IM (CR-IM).

Results: At 12 months, CR-IM was achieved in 48 of 69 available patients (70% per protocol [PP], 69% intention to treat [ITT]). At 30 months after additional focal ablative therapy, CR-IM was achieved in 60 of 61 available patients (98% PP, 97% ITT). There were no strictures or buried glandular mucosa detected by the standardized biopsy protocol at 12 or 30 months, and there were no serious adverse events.

Limitations: This was an uncontrolled clinical trial with 2.5-year follow-up.

Conclusion: Stepwise circumferential and focal ablation resulted in complete eradication of IM in 98% of patients at 2.5-year follow-up.

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

R.E. Pouw, V.K. Sharma, J.J. Bergman, D.E. Fleischer

Endoscopy 2008;40:1033-40

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 applications.

3.5. Eradication of Barrett esophagus with early neoplasia by radiofrequency ablation, with or without endoscopic resection

Ross E. Pouw, Jeop J. Gondrie, Carine M. Sondermeijer, Fiebo J. ten Kate, Thomas M. van Gulik, Kausilia K. Krishnadath, Paul Fockens, Bas L. Weusten, Jacques J. Bergman

J Gastrointest Surg 2008;12:1627-37

Background: Radiofrequency ablation is safe and effective for complete eradication of nondysplastic Barrett esophagus (BE). The aim was to report the combined results of two published and two ongoing studies on radiofrequency ablation of BE with early neoplasia, as presented at SSAT presidential plenary session DDW 2008.

Methods: Enrolled patients had BE ≤ 12 cm with early neoplasia. Visible lesions were endoscopically resected. A balloonbased catheter was used for circumferential ablation and an endoscope-based catheter for focal ablation. Ablation was repeated every 2 months until the entire Barrett epithelium was endoscopically and histologically eradicated.

Results: Forty-four patients were included (35 men, median age 68 years, median BE 7 cm). Thirty-one patients first underwent endoscopic resection [early cancer (n=16), high-grade dysplasia (n=12), low-grade dysplasia (n=3)]. Worst histology remaining after resection was high-grade (n=32), low-grade (n=10), or no (n=2) dysplasia. After ablation, complete histological eradication of all dysplasia and intestinal metaplasia was achieved in 43 patients (98%). Complications following ablation were mucosal laceration at resection site (n=3) and transient dysphagia (n=4). After 21 months of follow-up (interquartile range 10–27), no dysplasia had recurred.

Conclusions: Radiofrequency ablation, with or without prior endoscopic resection for visible abnormalities, is effective and safe in eradicating BE and associated neoplasia.

3.6. Circumferential and focal radiofrequency ablation for the treatment of Barrett's esophagus

AK Roorda, G Triadafilopoulos

Expert Rev Gastroenterol Hepatol 2008;2:627-34

This invited profile summarizes the technical aspects and clinical trial results related to the use of circumferential and focal radiofrequency ablation in the management algorithm for Barrett's esophagus. What makes this relatively new endoscopic intervention unique is its promising safety and efficacy profile reported in published clinical trials. This technology appears to have overcome many of the limitations of prior endoscopic ablative modalities, and is thus garnering a role in the management of this disease state.

3.7. Successful balloon-based radiofrequency ablation of a widespread early squamous cell carcinoma and high-grade dysplasia of the esophagus: A case report

Roos E. Pouw, Joep J. Gondrie, Wouter L. Curvers, Carine M. Sondermeijer, Fiebo J. ten Kate, Jacques J. Bergman

Gastrointest Endosc 2008;68:537-41

Background: For selected patients with high-grade dysplasia (HGD) and/or early esophageal squamous cell cancer (ESCC), endoscopic therapy represents a nonsurgical treatment option. For widespread lesions, however, current endoscopic treatment modalities (eg, endoscopic resection, argon plasma coagulation, photodynamic therapy) are associated with considerable drawbacks, of which esophageal stricturing is the most significant. Balloon-based radiofrequency (RF) ablation (HALO System) is a promising technology for endoscopic treatment of Barrett's esophagus, and may also play a role in treating widespread HGD and early ESCC.

Objective: We describe a case report of balloon-based RF ablation for HGD and early ESCC.

Design: Case report.

Setting: Tertiary care institution, Academic Medical Center, Amsterdam, The Netherlands.

Patient: A 66-year-old male with a 35-mm large, flat-type ESCC with surrounding HGD.

Intervention: Balloon-based RF ablation (HALO System).

Main Outcome Measurements: Endoscopic and histologic eradication of HGD and ESCC, and adverse events.

Results: RF ablation resulted in complete endoscopic and histologic eradication of HGD and ESCC without adverse events such as dysphagia or esophageal narrowing.

Limitations: Single patient report, limited follow-up.

Conclusions: This is the first report of balloon-based RF ablation for esophageal HGD and early ESCC. The treatment resulted in complete eradication of a 35-mm flat ESCC with no adverse events. This suggests that this ablation technique deserves further study for the management of widespread HGD or flat-type ESCC.

3.8. Circumferential ablation of Barrett's esophagus that contains high-grade dysplasia: A U.S. multicenter registry

Robert A. Ganz, Bergein F. Overholt, Virender K. Sharma, David E. Fleischer, Nicholas J. Shaheen, Charles J. Lightdale, Stephen R. Freeman, Ronald E. Pruitt, Shiro M. Urayama, Frank Gress, Darren A. Pavey, M. Stanley Branch, Thomas J. Savides, Kenneth J. Chang, V. Raman Muthusamy, Anthony G. Bohorfoush, Samuel C. Pace, Steven R. DeMeester, Viktor E. Eysselein, Masoud Panjehpour, George Triadafilopoulos

Gastrointest Endosc 2008;68:35-40

Background: The management strategies for Barrett's esophagus (BE) that contains high-grade dysplasia (HGD) include intensive endoscopic surveillance, photodynamic therapy, thermal ablation, EMR, and esophagectomy.

Objective: To assess the safety and effectiveness of endoscopic circumferential balloon-based ablation by using radiofrequency energy for treating BE HGD.

Design: Multicenter U.S. registry.

Setting: Sixteen academic and community centers; treatment period from September 2004 to March 2007.

Patients: Patients with histologic evidence of intestinal metaplasia (IM) that contained HGD confirmed by at least 2 expert pathologists. A prior EMR was permitted, provided that residual HGD remained in the BE region for ablation.

Intervention: Endoscopic circumferential ablation with follow-up esophageal biopsies to assess the histologic response to treatment.

Outcomes: Histologic complete response (CR) end points: (1) all biopsy specimen fragments obtained at the last biopsy session were negative for HGD (CR-HGD), (2) all biopsy specimens were negative for any dysplasia (CR-D), and (3) all biopsy specimens were negative for IM (CR-IM).

Results: A total of 142 patients (median age 66 years, interquartile range [IQR] 59-75 years) who had BE HGD (median length 6 cm, IQR 3-8 cm) underwent circumferential ablation (median 1 session, IQR 1-2). No serious adverse events were reported. There was 1 asymptomatic stricture and no buried glands. Ninety-two patients had at least 1 follow-up biopsy session (median follow-up 12 months, IQR 8-15 months). A CR-HGD was achieved in 90.2% of patients, CR-D in 80.4%, and CR-IM in 54.3%.

Limitations: A nonrandomized study design, without a control arm, a lack of centralized pathology review, ablation and biopsy technique not standardized, and a relatively short-term follow-up.

Conclusions: Endoscopic circumferential ablation is a promising modality for the treatment of BE that contains HGD. In this multicenter registry, the intervention safely achieved a CR for HGD in 90.2% of patients at a median of 12 months of follow-up.

3.9. Stepwise circumferential and focal ablation of Barrett's esophagus with high-grade dysplasia: results of the first prospective series of 11 patients

JJ Gondrie, RE Pouw, CMT Sondermeijer, FP Peters, WL Curvers, WE Rosmolen, KK Krishnadath, F Ten Kate, P Fockens, JJ Bergman

Endoscopy 2008;40:359-69

Background and study aims: Stepwise circumferential and focal ablation of nondysplastic Barrett's esophagus has proven safe and effective. This study assessed the efficacy and safety of ablation for Barrett's esophagus with high-grade dysplasia (HGD), and residual Barrett's esophagus with dysplasia after prior endoscopic resection for visible lesions.

Patients and methods: This was a prospective cohort study. All visible abnormalities were resected prior to ablation. Persistence of dysplasia and absence of invasive cancer was confirmed with biopsies after endoscopic resection. A balloon-based electrode was used for primary circumferential ablation and an endoscope-mounted electrode was used for secondary focal ablation. Eradication of dysplasia and Barrett's esophagus was the main outcome measure.

Results: Eleven patients (eight men; median age 60 years) were treated (median Barrett's length 5 cm). Visible abnormalities were removed with endoscopic resection in six patients. The worst pathological grade of residual Barrett's esophagus after endoscopic resection and prior to ablation was LGD (n = 2) and HGD (n = 9). Patients underwent a median of two circumferential and two focal ablation sessions. Complete remission of dysplasia and complete endoscopic and histological removal of Barrett's esophagus was achieved in 11/11 patients (100 %). There were no adverse events or strictures, and in none of the 473 biopsies of neo-squamous mucosa was subsquamous Barrett's esophagus ("buried Barrett's") observed. During a median follow-up period of 14 months after the last treatment session and a median number of two follow-up endoscopies, none of the patients showed recurrence of dysplasia or endoscopic signs of recurrent Barrett's mucosa.

Conclusions: Stepwise circumferential and focal ablation appears to be a safe and effective treatment for complete removal of Barrett's esophagus containing HGD, and can be safely performed after prior endoscopic resection for endoscopically visible abnormalities.

3.10. Effective treatment of early Barrett's neoplasia with stepwise circumferential and focal ablation using the HALO system

JJ Gondrie, RE Pouw, CMT Sondermeijer, FP Peters, WL Curvers, WE Rosmolen, F Ten Kate, P Fockens, JJ Bergman

Endoscopy 2008;40:370-9

Study aims: The aim of the current study was to evaluate the efficacy and safety of stepwise circumferential and focal ablation using the HALO system for Barrett's esophagus containing flat, high-grade dysplasia (HGD) or residual dysplasia after endoscopic resection for HGD or intramucosal cancer (IMC).

Methods: Visible abnormalities were removed with endoscopic resection prior to ablation. Persistence of dysplasia and absence of IMC were confirmed with biopsy after endoscopic resection. A balloon-based electrode was used for primary circumferential ablation and an endoscope-mounted electrode was used for secondary focal ablation.

Results: Twelve patients (nine men; median age 70 years) were treated (median Barrett's length 7 cm). Visible abnormalities were removed by endoscopic resection in seven patients. The worst pathological grade of residual Barrett's esophagus after resection and prior to ablation was low-grade dysplasia (LGD) (n = 1) and HGD (n = 11). Patients underwent a median of one circumferential and two focal ablation sessions. Complete remission of dysplasia was achieved in 12/12 patients (100 %). Complete endoscopic and histological removal of Barrett's esophagus was achieved in 12/12 patients (100 %). There were no ablation-related stenoses, and no subsquamous Barrett's esophagus was observed in 363 biopsies obtained from post-ablation neo-squamous mucosa. Protocolized cleaning of the ablation zone and electrode in between ablations resulted in superior regression of Barrett's esophagus compared with previous studies. During a median follow-up of 14 months no recurrence of dysplasia or Barrett's esophagus was observed.

Conclusions: Stepwise circumferential and focal ablation for Barrett's esophagus with flat HGD or for Barrett's with residual dysplasia after endoscopic resection for HGD/IMC is a safe and effective treatment modality. Its success rate and safety profile compare favorably with alternatives such as esophagectomy, widespread endoscopic resection or photodynamic therapy.

3.11. A prospective pilot trial of ablation of Barrett's esophagus with low-grade dysplasia using stepwise circumferential and focal ablation (HALO system)

V. K. Sharma, H. Jae Kim, A. Das, P. Dean, G. DePetris, D. E. Fleischer

Endoscopy 2008;40:380-7

Background and study aims: Yearly surveillance endoscopy is carried out for Barrett's esophagus with low-grade dysplasia (LGD) so that progression to high-grade dysplasia and adenocarcinoma can be detected at the earliest stage. The aim of the study was to assess the long-term safety and effectiveness of circumferential ablation followed by focal ablation (HALO system) for eliminating Barrett's esophagus and LGD.

Patients and methods: Patients with 2 - 6 cm of Barrett's esophagus with histology demonstrating LGD on their last two sequential endoscopies over the previous 2 years and confirmed by two pathologists were enrolled in this prospective, single-center trial. Circumferential ablation was carried out at baseline and at 4 months (if residual Barrett's esophagus present). Endoscopy with 4-quadrant biopsies every 1 cm was performed at 1, 3, 6, 12, and 24 months. After 1 year, focal ablation was applied to any visible Barrett's esophagus or irregularity of the squamocolumnar junction. Patients received lansoprazole 30 mg bid. Complete responses for dysplasia (CR-dysplasia) and intestinal metaplasia (CR-IM) at 2-year follow-up, with complete response defined as "all biopsies negative for dysplasia or intestinal metaplasia" were the main outcomes.

Results: Ten patients (nine men, mean age 66.9 years, range 48 - 79) with confirmed LGD (median 4.4 cm, range 3 - 6) underwent circumferential ablation with focal ablation after 1 year as necessary. At 2 years, CR-dysplasia was 100 % and CR-IM was 90 %. There were no strictures or buried intestinal metaplasia at follow-up.

Conclusion: A stepwise regimen of circumferential ablation followed by focal ablation appears to eradicate intestinal metaplasia (90 % CR-IM) and dysplasia (100 % CR-dysplasia) at 2-year follow-up in this trial, without stricture formation or buried intestinal metaplasia.

3.12. Pilot series of radiofrequency ablation of Barrett's esophagus with or without neoplasia

J. C. Hernandez, S. Reicher, D. Chung, B. V. Pham, F. Tsai, G. Disibio, S. French, V. E. Eysselein

Endoscopy 2008;40:388-92

Background and study aims: Radiofrequency ablation is a rapidly evolving therapeutic modality for Barrett's esophagus. The aim of this ongoing 12-month trial is to assess Barrett's esophagus eradication after radiofrequency ablation using a balloon-based (HALO-360) and a plate-based (HALO-90) device. We report here our experience with the first 10 patients (out of 40) who have completed 12 months of follow-up.

Patients and methods: Following radiofrequency ablation using the HALO-360 device all patients were maintained on double-dose proton pump inhibitor therapy. Endoscopic evaluation was performed at 3 and 12 months postablation. Patients with residual Barrett's esophagus at 3 months underwent repeat ablation. Ten patients, seven with nondysplastic Barrett's esophagus, two with low-grade and one with high-grade dysplasia have completed the study to date.

Results: Complete Barrett's esophagus eradication was achieved in seven patients, and partial eradication was achieved in three. There were no major complications. One case of buried Barrett's metaplasia was encountered and successfully re-ablated, with complete Barrett's esophagus eradication achieved at 12 months.

Conclusions: In this study, Barrett's eradication rates were comparable to previously published reports. One case of buried Barrett's metaplasia was identified out of 247 biopsies and was eradicated with repeat ablation.

3.13. Endoscopic ablation of intestinal metaplasia containing high-grade dysplasia in esophagectomy patients using a balloon-based ablation system

C.D. Smith, P.A. Bejarano, W.S. Melvin, M.G. Patti, R. Muthusamy, B.J. Dunkin

Surg Endosc 2007;21:560-9

Background: This study aimed to determine the optimal treatment parameters for the ablation of intestinal metaplasia (IM) containing high-grade dysplasia (HGD) using a balloon-based ablation system for patients undergoing esophagectomy.

Methods: Immediately before esophagectomy, patients underwent ablation of circumferential segments of the esophagus containing IM-HGD using the HALO360 system. The treatment settings were randomized to 10, 12, or 14 J/cm² for two, three, or four applications. After esophagectomy, multiple sections from ablation zones were microscopically evaluated. Histologic end points included maximum ablation depth (histologic layer) and complete ablation of all IM-HGD (yes/no).

Results: Eight men with a mean age of 57 years (range, 45–71 years) were treated, and 10 treatment zones were created. There were no device-related adverse events. At resection, there was no evidence of a transmural thermal effect. Grossly, ablation zones were clearly demarcated sections of ablated epithelium. The maximum ablation depth was the lamina propria or muscularis mucosae. The highest energy (14 J/cm², 4 applications) incurred edema in the superficial submucosa, but no submucosa ablation. Complete ablation of IM and HGD occurred in 9 of 10 ablation zones (90%), defined as complete removal of the epithelium with only small foci of “ghost cells” representing nonviable, ablated IM-HGD and demonstrating loss of nuclei and cytoarchitectural derangement. One focal area of viable IM-HGD remained at the margin of one ablation zone (12 J/cm², 2 applications) because of incomplete overlap.

Conclusion: Complete ablation of IM-HGD without ablation of submucosa is possible using the HALO360 system. Ablation depth is dose related and limited to the muscularis mucosae. In one patient, small residual foci of IM-HGD at the edge of the ablation zone were attributable to incomplete overlap, which can be avoided. This study, together with non-esophagectomy IM-HGD trials currently underway, will identify the optimal treatment parameters for IM-HGD patients who would otherwise undergo esophagectomy or photodynamic therapy.

3.14. Endoscopic endoluminal radiofrequency ablation of Barrett's esophagus in patients with funduplications

N. Hubbard, V. Velanovich

Surg Endosc 2007;21:625–8

Background: Endoscopic endoluminal radiofrequency ablation using the Barrx device is a new technique to treat Barrett's esophagus. This procedure has been used in patients who have not had antireflux surgery. This report presents an early experience of the effects of endoluminal ablation on the reflux symptoms and completeness of ablation in post-fundoplication patients.

Methods: Seven patients who have had either a laparoscopic or open Nissen fundoplication and Barrett's esophagus underwent endoscopic endoluminal ablation of the Barrett's metaplasia using the Barrx device (Barrx Medical, Sunnyvale, CA). Preprocedure, none of the patients had significant symptoms related to gastroesophageal reflux disease. One to two weeks after the ablation, patients were questioned as to the presence of symptoms. Preprocedure and postprocedure, they completed the GERD-HRQL symptom severity questionnaire (best possible score, 0; worst possible score, 50). Patients had follow-up endoscopy to assess completeness of ablation 3 months after the original treatment.

Results: All patients completed the ablation without complications. No patients reported recurrence of their GERD symptoms. The median preprocedure total GERD-HRQL score was 2, compared to a median postprocedure score of 1. One patient had residual Barrett's metaplasia at 3 months follow-up, requiring reablation.

Conclusions: This preliminary report of a small number of patients demonstrates that endoscopic endoluminal ablation of Barrett's metaplasia using the Barrx device is safe and effective in patients who have already undergone antireflux surgery. There appears to be no disruption in the fundoplication or recurrence of GERD-related symptoms. Nevertheless, longer-term follow-up with more patients is needed.

3.15. Balloon-based, circumferential, endoscopic radiofrequency ablation of Barrett's esophagus: 1-year follow-up of 100 patients

Virender K. Sharma, Kenneth K. Wang, Bergein F. Overholt, Charles J. Lightdale, M. Brian Fennerty, Patrick J. Dean, Douglas K. Pleskow, Ram Chuttani, Alvaro Reymunde, Nilda Santiago, Kenneth J. Chang, Michael B. Kimmey, David E. Fleischer

Gastrointest Endosc 2007;65:185-95

Objective: To assess the dose-response, safety, and efficacy of circumferential endoscopic ablation of Barrett's esophagus (BE) by using an endoscopic balloon-based ablation device (HALO360 System).

Design: This study was conducted in 2 serial phases (dosimetry phase and effectiveness phase) to evaluate a balloon-based ablation device that delivers a pre-set amount of energy density (J/cm^2) to BE tissue. The dosimetry phase evaluated the dose-response and the safety of delivering 6 to 12 J/cm^2 . The effectiveness phase used 10 J/cm^2 (delivered twice for all patients, followed by EGD with biopsies at 1, 3, 6, and 12 months. A second ablation procedure was performed if BE was present at 1 or 3 months. Patients received esomeprazole 40 mg twice a day for 1 month after ablation, and 40 mg every day thereafter. Postablation symptoms were quantified by using a 14-day symptom diary (scale, 0-100). A complete response (CR) was defined as all biopsy specimens negative for BE at 12 months.

Setting: Eight U.S. centers, between September 2003 and September 2005.

Patients: Patients were 18 to 75 years of age, with a diagnosis of BE (without dysplasia), with histopathology reconfirmation of the diagnosis within 6 months of enrollment.

Results: In the dosimetry phase, 32 patients (29 men; mean age, 56.8 years) were enrolled. Median symptom scores returned to a score of 0 of 100 by day 3. There were no dose-related serious adverse events, and the outcomes at 1 and 3 months permitted the selection of 10 J/cm^2 (2) for the subsequent effectiveness phase of the study. In the effectiveness phase, 70 patients (52 men, 18 women; mean age, 55.7 years) were enrolled. Median symptom scores returned to a score of 0 of 100 by day 4. At 12 months (n = 69; mean, 1.5 sessions), a CR for BE was achieved in 70% of patients. There were no strictures and no buried glandular mucosa in either study phase (4306 biopsy fragments evaluated).

Conclusions: Circumferential ablation of nondysplastic BE by using this balloon-based ablation device can be performed with no subsequent strictures or buried glands and with complete elimination of BE in 70% of patients at 1-year follow-up.

3.16. Early experience with radiofrequency energy ablation therapy for Barrett's esophagus with and without dysplasia

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Dis Esophagus 2007;20:516-22

Background: Radiofrequency (RF) ablation using the HALO360 system combined with proton pump inhibitor (PPI) therapy is a new treatment for Barrett's esophagus (BE).

Methods: We assessed the safety and effectiveness of this combination therapy at a community-based, BE referral center. After symptom evaluation, endoscopy and histologic assessment, esophageal motility, pH monitoring on PPI, computed tomography, endoscopic ultrasonography and mucosal resection for nodules, we performed HALO360 ablation followed by twice daily PPI and 3-monthly surveillance for up to 12 months. If metaplasia or dysplasia were present at follow-up, the patients received a second ablation.

Results: Thirteen patients (12 male) were treated, three with high-grade dysplasia, four with low-grade and six with non-dysplastic intestinal metaplasia. The mean baseline BE length was 6 cm (range 2–12); nine patients had an hiatal hernia and two had a prior fundoplication. Esophageal pH < 4.0 for < 4% of time was achieved only in 5/13 patients. A mean of 1.4 ablation sessions were performed, without serious adverse events or strictures. Complete eradication of BE was achieved in 6/13 (46%) patients. The mean endoscopic surface regression was 84% (from a mean length of 6 ± 1 cm to 1.2 ± 0.5 cm, $P < 0.001$). Complete elimination of dysplasia was achieved in 5/7 (71%) patients.

Conclusions: Ablation efficacy was better in those patients who had maximal pH control ($P < 0.05$). HALO360 ablation of BE with or without dysplasia is safe, well-tolerated and effective in the community setting. Follow-up ablation further reverses residual BE or dysplasia.

3.17. Barrett's esophagus and new therapeutic modalities

Virender K. Sharma, David E. Fleischer

Therapy 2007;4:825-40

Abstract: Barrett's esophagus is a metaplastic change of the epithelium of the esophagus, caused by injury and inflammation related to gastroesophageal reflux disease. Metaplasia is defined as the transformation from one cell type to another cell type. In the case of Barrett's esophagus, the normal squamous epithelium is replaced by a columnar epithelium-containing goblet cells, deemed intestinal metaplasia (IM). Owing to a significantly elevated risk for the development of esophageal adenocarcinoma associated with the presence of IM, patients with this diagnosis undergo surveillance endoscopy with multiple biopsies of the diseased tissue every 2–3 years, in order to detect adenocarcinoma at the earliest possible tumor stage. Development of dysplastic cellular changes within the Barrett's epithelium often precedes the development of cancer. In cases of IM containing dysplasia, surveillance endoscopy is performed more frequently (every 3–12 months). For many patients with high-grade dysplasia, the esophagus may be removed surgically in order to preempt the development of cancer.

3.18. Changing attitudes toward endoluminal therapy

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Surg Endosc 2007;21:445-8

Background: As with new laparoscopic techniques, the ability to convince surgeons and gastroenterologists to embrace endolumenal techniques and the additional training required to perform the new procedures will correlate with how rapidly endolumenal therapies are adopted. The authors measured their ability to change attitudes among surgeons, who may or may not perform endoscopy as a part of their practice, toward endolumenal therapies.

Methods: As part of the endolumenal therapy postgraduate course presented at the annual Society of American Gastrointestinal Endoscopic Surgeons (SAGES) meeting in Ft. Lauderdale, Florida 2005, experts presented current literature and data on new endolumenal techniques. The participants, primarily of surgeons, were polled electronically about a number of case scenarios before and after their presentation. Each scenario was relevant to the topic presented and chosen to reflect potentially controversial disease processes with traditional or endolumenal treatment options. The responses were collected in real time and displayed to course participants.

Results: A panel of 10 experts presented data on a range of endolumenal therapies including endolumenal treatment for gastroesophageal reflux disease (GERD), endoscopic stenting, endoscopic treatments in bariatric surgery, intraoperative endoscopy, endoscopic mucosal resection (EMR), transanal endoscopic microsurgery (TEM), mucosal ablation for Barrett's esophagus, intraluminal resection, transluminal endoscopic surgery, and how to educate surgeons in new endolumenal techniques. Demographic data showed that 83.6% of the participants performed endoscopy as part of their practice. A comparison with traditional surgical options showed a statistically significant positive attitude change ($p < 0.05$) toward adoption of most endolumenal techniques after expert presentation. Only EMR and TEM did not show a statistically significant change in the participants willingness to adopt these techniques. There was no significant change in the attitudes of how best to train surgeons. After presentation of the training options, 76% of the respondents believed that these techniques should be taught in residency.

Conclusions: The education of surgeons in new endolumenal therapeutic techniques can have a significant impact in terms of changing practice attitudes and may accelerate adoption of new endoscopic techniques.

3.19. Thin-layer ablation of human esophageal epithelium using a bipolar radiofrequency balloon device

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Surg Endosc 2006;20:125-30

Background: The goal of this study was to determine the optimal treatment parameters for the ablation of human esophageal epithelium using a balloon-based bipolar radiofrequency (RF) energy electrode.

Methods: Immediately prior to esophagectomy, subjects underwent esophagoscopy and ablation of two separate, 3-cm long, circumferential segments of non-tumor bearing esophageal epithelium using a balloon-based bipolar RF energy electrode (BARRX Medical, Inc., Sunnyvale, CA, USA). Subjects were randomized to one of three energy density groups: 8, 10, or 12 J/cm². RF energy was applied one time proximally and two times distally. Following resection, sections from each ablation zone were evaluated using H&E and diaphorase. Histological endpoints were complete epithelial ablation (yes/no), maximum ablation depth, and residual ablation thickness after tissue slough. Outcomes were compared according to energy density group and 1 vs 2· treatment.

Results: Thirteen male subjects (age, 49–85 years) with esophageal adenocarcinoma underwent the ablation procedure followed by total esophagectomy. Complete epithelial removal occurred in the following zones: 10 J/cm² and 12 J/cm². The maximum depth of injury was the muscularis mucosae: 10 and 12 J/cm². A second treatment did not significantly increase the depth of injury. Maximum thickness of residual ablation after tissue slough was only 35 microns.

Conclusions: Complete removal of the esophageal epithelium without injury to the submucosa or muscularis propria is possible using this balloon-based RF electrode at 10 J/cm² or 12 J/cm². A second application does not significantly increase ablation depth. These data have been used to select the appropriate settings for treating intestinal metaplasia in trials currently underway.

3.20. Complete ablation of esophageal epithelium with a balloon-based bipolar electrode: a phased evaluation in the porcine and in the human esophagus

Robert A. Ganz, David S. Utley, Roger A. Stern, Jerome Jackson, Kenneth P. Batts, Paul Termin

Gastrointest Endosc 2004;60:1002-10

Background: The aim of this study was to evaluate the endoscopic and the histologic effects of a balloon-based bipolar radiofrequency electrode for ablation of porcine and human esophageal epithelium.

Methods: All procedures were performed with a balloon based, bipolar radiofrequency system that creates a circumferential, thin-layer epithelial ablation zone within the esophagus. In Phase I, multiple ablations were created in 10 farm swine, followed by acute euthanasia and histologic assessment for completeness of epithelial removal and ablation depth. In Phase II, multiple ablations were created in 19 farm swine, with varying power and energy density, followed by endoscopy at 2 and 4 weeks to assess stricture formation. In Phase III, 3 ablations were created in 12 farm swine, with varying energy density (5, 8, 10, 12, 15, or 20 J/cm²) at 350 W. Animals were euthanized at 48 hours. Histologic examination determined the percentage of epithelium removed and the ablation depth. In Phase IV, 3 patients underwent esophageal epithelial ablation before esophagectomy, creating separate lesions proximal to the tumor. Completeness of epithelial ablation and ablation depth was quantified histologically.

Results: In Phase I, complete removal of esophageal epithelium was achieved at energy density settings of 9.7 to 29.5 J/cm². In Phase II, 9.7 and 10.6 J/cm² produced no stricture, whereas more than 20 J/cm² produced a stricture in every case. In Phase III, 8-20 J/cm² resulted in 100% epithelial ablation. Five and 8 J/cm² spared the muscularis mucosae, whereas 10 J/cm² caused injury to the muscularis mucosae but preserved the submucosa. In Phase IV, histologic examination demonstrated full thickness epithelial removal in areas of electrode contact. Ablation extended only to the muscularis mucosae, without injury to submucosa.

Conclusions: In the porcine and the human esophagus, circumferential, full-thickness ablation of epithelium without direct injury to the submucosa is possible and was well tolerated. In all cases, depth of ablation was linearly related to energy density of treatment.

3.21. Endoscopic mucosal ablation for the treatment of gastric antral vascular ectasia with HALO⁹⁰ system: a pilot study

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Gastrointest Endosc 2008;67:324-7

Background: Gastric antral vascular ectasia (GAVE) often results in GI bleeding and chronic anemia. Treatment options are limited and include medical, endoscopic, and surgical therapies.

Objective: To assess the utility of endoscopic mucosal ablative therapy by using the HALO90 system for patients with GAVE and recurrent bleeding.

Design: Prospective open-label case series.

Setting: Tertiary referral center.

Patients: Six consecutive patients with GAVE, bleeding, and blood transfusion dependence.

Main Outcome Measurements: Comparison of preablation and postablation Hb levels and transfusion requirements. To assess the number of ablation sessions needed to stabilize the Hb level and eliminate the need for blood transfusion.

Results: Six patients, (4 men, mean age 58 years, range 47-65 years) underwent endoscopic mucosal ablation of antral lesions (mean procedure time 29 minutes; mean treatments 1.7, range 1-3). The mean Hb level improved from 8.6 to 10.2 g/dl (mean 2 months after the last ablation). Five of 6 patients are no longer dependent on blood transfusions to maintain a stable Hb level.

Limitations: This is a pilot study, with a small number of patients at a single center, with limited patient follow-up.

Conclusions: This study suggests that endoscopic mucosal ablation by using the HALO90 system is a promising treatment option for chronic bleeding related to GAVE.

4. SELECTED PUBLISHED ABSTRACTS AND SUMMARIES

4.1. **A randomized, multicenter, sham-controlled trial of radiofrequency ablation (RFA) for subjects with Barrett's esophagus (BE) containing dysplasia: interim results of the AIM Dysplasia Trial**

Nicholas J. Shaheen, Prateek Sharma, Bergein F. Overholt, Charles J. Lightdale, Herbert C. Wolfsen, Richard E. Sampliner, Kenneth K. Wang, Mary P. Bronner, John R. Goldblum, Blair A. Jobe, Glenn M. Eisen, David E. Fleischer, Virender K. Sharma, Brenda Hoffman, Richard I. Rothstein, Hiroshi Mashimo, Kenneth Chang, Raman Muthusamy, Steven A. Edmundowicz, Stuart J. Spechler, Ali Siddiqui, Anthony Infantolino, Gary W. Falk, Michael B. Kimme, Amitabh Chak

Gastroenterology 2008;134:A37

Background: The optimal management strategy for BE with dysplasia is not known. In cohort studies, RFA is effective in inducing reversion of dysplastic BE to squamous.

Aim: To assess the efficacy of RFA for the treatment of BE containing dysplasia.

Methods: We performed a randomized sham-controlled trial of RFA for subjects with BE containing dysplasia at 19 U.S. centers. The baseline diagnosis was confirmed by Cleveland Clinic (CC) pathology laboratory. Subjects were then randomized to RFA or sham (2:1), stratified by dysplasia grade (HGD,LGD) and BE length (<4 vs. 4-8 cm). Step-wise circumferential and focal ablation was performed using the HALO System (max 4 sessions). Every 3 mos (HGD) or 6 mos (LGD) after randomization, biopsies were obtained throughout the original BE length (four quadrant, q1cm), and processed by CC. Primary outcomes included: 1) complete histological clearance of dysplasia in HGD and LGD cohorts at 12 mos, and, 2) complete histological clearance of intestinal metaplasia (IM) at 12 mos, comparing RFA vs. sham. Secondary outcomes included: 1) progression/regression of dysplasia, and 2) adverse events. Intent-to-treat (ITT) and per protocol (PP) analyses are reported.

Results: Randomization is complete. Of 127 subjects (63 HGD/64 LGD), 58 have reached the primary endpoint with results reported below (male 84%, mean age 65, mean BE length (cm): LGD 4.6, HGD 5.2.) Randomization resulted in similar demographics and BE length in RFA vs. sham. Mean # of treatment sessions was 3.5. Higher proportions of RFA subjects had clearance of dysplasia and IM. By ITT, 74% of RFA subjects achieved complete clearance of IM (83% PP), compared to 0% of sham ($p<0.0001$, NNT for ITT=1.35). There were no perforations or deaths related to RFA. In 39 RFA subjects (ITT) at 12 mos, there was 1 stricture (2.6%) which resolved with 1 dilation. No RFA subject had progression of dysplasia, while 3 sham subjects had progression (2 LGD→HGD; 1 HGD→CA).

Conclusions: Interim results of the AIM Dysplasia Trial suggest that RFA is superior to sham for clearance of dysplasia and IM in BE containing dysplasia. In subjects randomized to RFA, 74% (ITT) have no evidence of IM at 12 mo follow-up (83% PP), and 85% are free of dysplasia (94% PP). The procedure is associated with a favorable side-effect profile. This trial will be completed June 2008.

4.2. Stepwise circumferential and focal radiofrequency energy ablation of Barrett's esophagus with early neoplasia: first European multi-centre trial

Roos E. Pouw, Carine Sondermeijer, Fiebo J. Ten Kate, Paul Fockens, Pierre Eisendrath, Jacques Deviere, Katja Wirths, Horst Neuhaus, Jacques J. Bergman

Gastrointest Endosc 2008;67:AB137

Background: Stepwise circumferential and focal radiofrequency ablation of Barrett's esophagus (BE) with high-grade dysplasia (HGD) or intramucosal cancer (IMC) has been proven safe and effective in single-centre studies. Aim of this study was to assess safety and efficacy of this modality in a European multi-centre setting.

Methods: Eligible patients had BE \leq 10cm with HGD and/or IMC. Visible lesions were removed with the cap or multiband mucosectomy (MBM) technique. Exclusion criteria: any cancer stage $>$ T1m3, residual IMC after ER but prior to ablation. Primary balloon-based circumferential ablation (CA) was performed 6 weeks after the last ER, followed every 2 months by focal ablation (FA). Two CA and 3 FA sessions were allowed. Thereafter, any persisting BE was focally resected with "escape" MBM. Two months after the last treatment, EGD (NBI) with 4Q/1cm biopsies was performed to assess histological eradication of dysplasia and intestinal metaplasia (IM).

Results: 24 patients (19 men, median age 65 years, median Prague C5M7) were included. In 22 patients, 24 ER sessions were performed prior to ablation (11 cap, 12 MBM, 1 ESD; 9 en-bloc, 15 piecemeal). Worst ER-histology by patient: 16 IMC, 6 HGD. Worst residual histology prior to ablation, after any ER: 11 HGD, 9 LGD, 4 IM. Complete eradication of dysplasia was achieved in 22 patients after 1 CA, a median of 1.5 FA sessions (IQR 1-2), and one focal MBM in a patient having a persistent 8-mm island of IM. In 4 patients a non-transmural laceration occurred during CA within a prior ER site; none required treatment or caused complaints. One patient presented with melena 2 weeks after FA, on EGD no active bleeding was seen, 2 vessels in the ablated area were prophylactically clipped. One patient with widespread prior ER and a mucosal laceration after CA developed dysphagia that resolved with dilation. After a mean additional FU of 8 (\pm 4) months beyond the first biopsy session, no dysplasia has recurred in any of the patients. In one patient (at 16 months) we identified a 1-mm island of IM at the proximal margin of the original C9M10 BE. This was likely missed at the preceding EGDs and not treated adequately. Two patients had focal IM detected distal to the top of the gastric folds. None of the 456 biopsies from neosquamous epithelium showed subsquamous IM.

Conclusion: Preliminary data of this first European multi-centre study of stepwise CA and FA of BE with HGD and/or IMC, with or without prior ER, suggest that dysplasia can be eradicated completely in 100% of treated patients, without serious adverse events. These outcomes compare favorably to esophagectomy, radical ER or photodynamic therapy.

4.3. Properties of the neosquamous epithelium after radiofrequency ablation of Barrett esophagus with early neoplasia

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Gut 2008;57:A82

Introduction: Radiofrequency ablation (RFA) is safe and effective for eradication of Barrett esophagus (BE) and associated dysplasia but, it has been suggested that the neosquamous epithelium (NSE) that regenerates after RFA may retain genetic abnormalities of the baseline BE and may harbor buried Barrett glands (BB) that can not be adequately sampled with standard biopsies.

Aims & Methods: At baseline and 2 mo after final ablation the pre-RFA BE and post-RFA NSE were sampled by brush cytology. Multi-color fluorescent in-situ hybridization (FISH) was performed on cytology brushes using probes for centromeric regions of chromosome 1 & 9, and location-specific probes for 9p (p16) and 17p (p53). At least 12 mo after the last RFA, 4Q biopsies were obtained for every 2 cm of the NSE, and from untreated squamous mucosa. Keyhole biopsies were taken from all NSE biopsy sites. An endoscopic resection (ER) specimen was obtained from the NSE. Two expert pathologists, blinded to the origin of the specimens, scored histological depth for each biopsy and ER fragment and determined if BB were present.

Results: 23 consecutive BE patients with HGD (n=20)/LGD (n=3) were included. Complete removal of dysplasia and intestinal metaplasia was achieved on all patients. All pre-RFA BE cyto-brushes showed FISH abnormalities: numerical chromosomal changes (60%), loss of p16/p53 (90%), both (50%). All post-RFA NSE cyto-brushes, however, showed a normal diploid signal count for all FISH probes. Of the 23 patients included, 15 participated in the histology depth evaluation (exclusions: unrelated death (1), co-morbidity (3), initial BE <2 cm (4)). There was no difference in biopsy depth between NSE and untreated squamous mucosa. Keyhole biopsies sampled sub-epithelial structures more often than standard biopsies (59% vs 39%). All ER specimens included submucosa. No BB was found in any NSE biopsies or ER specimens.

Conclusion: RFA of BE-dysplasia results in eradication of all oncogenetic abnormalities and results in endoscopically and histologically normal appearing NSE. Biopsies from NSE after RFA contain full epithelium in all cases and ~ 40% of biopsies contain lamina propria, comparing favorably to biopsies from normal untreated squamous mucosa. No biopsies or ER specimens had BB. The hypothesis that absence of BB after RFA reflects insufficient biopsies sampling depth is, therefore, invalid.

4.4. Predictors and quantitative assessment of incomplete response after radiofrequency ablation for dysplastic Barrett's esophagus: analysis of randomized sham-controlled clinical trial (The AIM Dysplasia Trial)

Charles J. Lightdale, Bergein F. Overholt, Kenneth K. Wang, Hiroshi Mashimo, Virender K. Sharma, David E. Fleischer, Joseph Galanko, Nicholas J. Shaheen, Prateek Sharma

Gastrointest Endosc 2008;67:AB182

Background: Radiofrequency ablation (RFA) has been shown to completely eradicate dysplastic intestinal metaplasia (IM) in most patients, yet residual IM may persist in some.

Aims: The primary endpoint for RFA therapy is complete response-IM (CR-IM, no histological evidence of IM). We sought to describe pt characteristics related to incomplete response-IM (IR-IM, any residual IM). We also assessed dysplasia grade, and extent/location of any residual IM. Methods: We enrolled 127 pts with dysplastic BE (63 HGD, 64 LGD) in a multi-center trial of RFA. Pts were randomized 2:1 (RFA vs. sham) then biopsied q 3 or 6 mo, with centralized path review. RFA was performed until CR-IM or max 4 sessions.

Results: 52 pts (35 RFA, 17 sham) have evaluable 12 mo histology. This sub-analysis of the RF group compares CR-IM to IR-IM at 12 mo. The groups had similar hiatal hernia size. IR-IM had a longer pre-treatment period with dysplasia ($p < 0.05$). They were also older and had higher BMI, more years with BE, longer BE cm, and more multi-focal dysplasia, but given the small sample size of IR-IM, none of these was significant (table). All IR-IM pts had downgrading of dysplasia. For the 3 IR-IM pts with baseline HGD, the worst grade of residual IM was non-dysplastic (1), indefinite (1), or LGD (1). For the 3 IR-IM pts with baseline LGD, all were downgraded to non-dysplastic IM. Of the 6 IR-IM pts at 12 mo, 4 had a single-level IM focus, while 2 had multi-level disease. Five of 6 IR-IM pts had IM only within 1 cm of the top of gastric folds (TGF), while 1 pt had more proximal IM (4-5 cm from the TGF). One IR-IM pt had persistent GERD esophagitis, 1 had ibuprofen-induced ulceration, and 1 had a baseline stricture preventing focal balloon contact.

Conclusions: All IR-IM had downgrading of dysplasia and substantial reduction of IM burden. IR-IM pts had a longer pre-treatment period with dysplasia than CR-IM. IR-IM also had insig increases in age, baseline BE length, BMI and % multi-focal. Follow-up RFA is planned for these pts, with the goal to eliminate residual disease.

4.5. Subsquamous intestinal metaplasia is a common finding in ablation-naïve patients with dysplastic Barrett's esophagus, and significantly decreases in prevalence after radiofrequency ablation

Nicholas J. Shaheen, Mary P. Bronner, David E. Fleischer, Richard I. Rothstein, Virender K. Sharma, Charles J. Lightdale, Bergein F. Overholt, Glenn M. Eisen, Richard E. Sampliner, Prateek Sharma, Ana E. Bennett

Gastrointest Endosc 2008;67:AB176

Background: Subsquamous intestinal metaplasia (SSIM) has been reported as an adverse outcome of endoscopic ablative therapy for dysplastic Barrett's esophagus (BE). However, the prevalence of SSIM in ablation-naïve patients with dysplastic BE is unknown, as is the response of SSIM to ablative therapy.

Aim: To assess the prevalence of SSIM in ablation-naïve patients with BE containing HGD or LGD, and then to assess the prevalence of SSIM after ablative therapy. **Methods:** The AIM Dysplasia Trial is a U.S. multi-center, randomized, sham-controlled trial evaluating the safety and effectiveness of radiofrequency ablation (RFA) for treatment of dysplastic BE. All baseline endoscopic biopsies were reviewed by Cleveland Clinic pathology to confirm the diagnosis of BE and the grade of dysplasia. Each biopsy fragment for each esophageal level for each patient was prospectively assessed in a blinded manner for worst pathological grade of dysplasia and for findings of SSIM (defined as IM covered by squamous epithelium with no communication to the surface).

Results: For the 127 subjects randomized, baseline pathology included a total of 2,151 fragments from 438 blocks. SSIM was present in 32 patients (25.2%). The percentage of fragments displaying SSIM was 3.1% (67 of 2,151). An analysis according to baseline worst pathological grade (HGD vs. LGD) is shown in the table. There are 35 RFA pts and 16 sham pts with evaluable histology at 12 mos. In 1,223 fragments from the RFA group, there was a marked decrement in SSIM prevalence with only one fragment positive for SSIM (0.1%, $p < 0.001$ vs. pre-RFA). In 490 fragments from the sham group, there was no change in prevalence of SSIM (20 SSIM fragments (4.1%) in 8 subjects, $p = \text{NS}$ vs. baseline). Amongst the 1 RFA and 8 sham pts with SSIM at 12 mos, 1 fragment from 1 sham pt harbored a worse dysplasia grade than any surface biopsy for that patient (indefinite vs. non-dysplastic).

Conclusions: Although often considered a result of incomplete ablation, SSIM is a common finding in ablation-naïve dysplastic BE pts, occurring in 25% of our pts at baseline. A finding of SSIM was more common in LGD than HGD. The RFA group had a significant decrease in SSIM prevalence at 12 mos, while the sham group did not. The pre-treatment status of a pt undergoing ablative therapy should be thoroughly assessed, as post-therapy SSIM may represent the patient's natural state, rather than ineffective ablative therapy.

4.6. The molecular pathology of radiofrequency mucosal ablation of Barrett's esophagus

Sydney D Finkelstein, William D Lyday

Gastroenterology 2008;134:A436

Background: The objective of mucosa ablation techniques in Barrett's esophagus is to eradicate mutation bearing intestinalized mucosa cells and induce their replacement by normal squamocolumnar lining cells. We integrated mutational analysis into microscopic evaluation to better understand the biology of the mucosal ablative approach and to personalize the diagnosis and predict treatment efficacy.

Materials and Methods: Recut microscopic sections (4 um thick) from tissue blocks of 21 patients undergoing radiofrequency mucosal ablation (RMA) for Barrett's metaplasia and low grade dysplasia were microdissected at multiple target sites. 16 patients underwent a single RMA and 5 were treated twice with histopathology available pre and post treatment for up to a 2.5 year follow-up. A total of 51 microdissection targets were analyzed for a broad panel of 16 allelic imbalance (loss of heterozygosity [LOH]) mutational markers affecting 1p, 3p, 5q, 9p, 10q, 17p, 17q, 21q, 22q using quantitative fluorescent PCR/capillary electrophoresis. The presence, cumulative number and extent of clonal expansion (% of microdissected target cells bearing individual mutations; less than 75% = lowly expanded mutations, greater than 75% = high) was correlated with the histopathologic features.

Results: RMA induced replacement of Barrett's metaplasia by normal mucosa in 15 or 16 patients (94%). In each case, mutations that were present in the metaplastic cells were no longer detectable in postablative specimens indicating that the mutated clone and its precursors had been eradicated. In the one patient with persistent disease, all mutations that were shown to be lowly clonally expanded were eradicated but the highly expanded mutations remained. Similarly, in patients requiring two RMA procedures, highly clonally expanded mutations remained present in intestinalized cells after initial treatment. Such highly expanded mutations were seen to affect a wide range of markers and were not confined to a single genomic locus. Of note, mutational regression did not necessary take place immediate after treatment but could occur at 6-12 months.

Conclusions: RMA is shown to induce regression of mutation bearing and cause reversion of intestinalized to normal squamocolumnar cells. Regression is time dependent and can occur at 6-12 months following treatment. Intestinalized mucosal cells bearing highly clonally expanded mutations are more resistant to regression but can be eliminated by repeat treatment. Integrated microscopic/molecular analysis provides sensitive parameters with which to classify, plan RMA and monitor patient with Barrett's metaplasia on a more personalized basis.

4.7. Focal ablation for treatment of dysplastic and non-dysplastic Barrett's esophagus: safety profile and initial experience with the HALO⁹⁰ device in 508 cases

Richard Rothstein, Kenneth Chang, Bergein F. Overholt, Jacques Bergman, Nicholas Shaheen

Gastrointest Endosc 2007;65:AB155

Introduction: Several modalities have been evaluated for focal treatment of Barrett esophagus (APC, MPEC, laser, EMR) and for wide-field ablation of BE (PDT, balloon-based circumferential RF ablation or HALO³⁶⁰).

Aims: Assess the initial safety experience associated with the HALO⁹⁰ focal ablation device for secondary ablation of residual BE after primary wide-field ablation, as well as primary ablation of short segment BE.

Methods: The HALO⁹⁰ focal ablation device (BARRX Medical, Sunnyvale, CA) fits on the distal tip of a standard gastroscope, preserving visualization. The upper surface is a 20x15 mm articulated platform covered by a bipolar electrode array. The device uses high power RF (40 W/cm²) and a pre-set energy density (12 J/cm²) to control ablation depth. Using the endoscope, the electrode is positioned at the target, deflected upward, and energy delivered.

In 2006, 508 focal ablation procedures were performed in the U.S. and the Netherlands with this device for BE, with 182 of these cases performed under one of several IRB-approved clinical trials for non-dysplastic BE, LGD-BE and HGD-BE. For trial cases in this series, treatment data (procedure time and medication use) were collected and post-ablation symptoms were assessed (chest, throat, abdominal pain; odynophagia; dysphagia) using a standardized 14-day diary (visual analog scale, 0-100). For all cases, a monitoring system was used to detect adverse events.

Results: Of 182 trial cases, median procedure time was 20 min (IQR 14-32). Sedation included midazolam 7 mg (IQR 5-8), and either meperidine 75 mg (IQR 50-100) or fentanyl 100 mcg (75-175). One site used propofol as a single agent (median 410 mg, IQR 337-521.)

Post-ablation Symptom Queried	Day 1 Median VAS* (IQR) (n=156)	Day Median VAS Returned to Zero
Chest Pain	9 (0-20)	Day 4
Dysphagia	2 (0-40)	Day 2
Odynophagia	10 (0-45)	Day 4
Throat Pain	10 (0-36)	Day 3
Abdominal Pain	0 (0-0)	Day 1

* VAS (visual analog scale) is out of 100 possible points

There were no perforations, mucosal lacerations, bleeds, stricture formation, or other adverse events. One patient (0.5% of trial cases) reported symptoms of esophageal spasm on day 1 and was admitted for pain control.

Conclusions: This represents the first report of the safety profile of this focal ablation device. Its use appears to be very well-tolerated by the patient with post-ablative symptoms that were minor and short-lived, and an adverse event incidence in this review of 0.5%. This technique may significantly complement wide-field ablative therapy for achieving the goal of complete BE ablation. Future studies are evaluating this device as primary therapy of short segment BE.

4.8. Balloon-based circumferential ablation followed by focal ablation of Barrett esophagus containing high-grade dysplasia effectively removes all genetic alterations

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Gastroenterology 2007;132:A64

Background: Balloon-based circumferential ablation (CA) and endoscope-mounted focal ablation (FA) are promising new ablative modalities for treating Barrett esophagus (BE) with dysplasia. Ablation with these devices has been shown to eliminate BE and restore a normal appearing neo-squamous epithelium.

Aim: The aim of this study was to evaluate whether genetic abnormalities, as found in dysplastic BE, are effectively eradicated by this ablative modality and absent in the resulting neo-squamous epithelium.

Methods: 10 consecutive BE patients with high-grade dysplasia (HGD) underwent CA using a balloon-based electrode (HALO³⁶⁰ System, BARRX Medical, Sunnyvale, CA, USA) as primary therapy, followed by FA using an endoscope-mounted electrode (HALO⁹⁰ System) as secondary therapy.

At baseline and 2 mos after the final ablation, patients underwent EGD with 4Q/q 1cm large cup biopsies from the BE (baseline) or neosquamous mucosa (follow-up). Additionally, brush cytology specimens were obtained from the BE (baseline), neosquamous mucosa (follow-up and proximal squamous mucosa (baseline and follow-up) using 5-cm and 1-cm cytology brushes (Wilson-Cook Medical, Limerick, Ireland). Biopsy specimens were investigated by an expert pathologist for dysplasia and intestinal metaplasia (IM). Proliferative activity (Ki67) and p53 accumulation were evaluated using immunohistochemical (IHC) staining.

Multi-color fluorescent in-situ hybridization (FISH) was performed on all brush cytology specimens using DNA probes for the centromeric regions of chromosome 1 and 9, and locus-specific probes for 9p(p16) and 17p(p53). Results were analyzed with manual scoring and an automated fluorescence microscope with Spot counting software (Applied Imaging, Newcastle, UK). Normal proximal squamous epithelium was used as control.

Results: All 10 patients were effectively treated, resulting in complete endoscopic eradication of visible BE. Baseline BE biopsies showed abnormal Ki67 and p53 staining for all patients (100%). Of 149 follow-up biopsies, none showed IM or dysplasia (100% histological response to ablation). Further, there were no abnormalities of Ki67 or p53 in any follow-up biopsy.

All baseline BE cytology brush samples demonstrated FISH abnormalities, either numerical chromosomal changes (n=7; 70%), loss of p16/p53 (n=9; 90%) or both (n=5; 50%). All follow-up brush cytology specimens, however, showed a normal diploid signal count for all FISH probes.

Conclusions: Ablation of BE-HGD using these devices successfully eliminates all IM and dysplasia, eradicates all pre-existing genetic abnormalities, and results in restoration of a neosquamous epithelium without these genetic abnormalities.

4.9. Circumferential ablation of Barrett's esophagus containing high-grade dysplasia can be performed without impairment of the functional integrity of the distal esophagus or gastroesophageal junction

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Background: Balloon-based circumferential ablation (CA) and endoscope-mounted focal ablation (FA) are promising new ablative modalities for Barrett esophagus (BE) with high-grade dysplasia (HGD). Previous studies suggest that CA and FA, contrary to other ablative techniques, do not result in significant scarring or stricture formation.

Aims: Measure esophageal inner diameter (E-ID) and perform manometry and impedance planimetry (IP) to assess esophageal functional motility and compliance before and after CA plus FA for BE-HGD.

Methods: Ten patients (8 male, median age 72 yrs) with BE-HGD (median length 7 cm (IQR 6-10)) were included. A balloon-based electrode (HALO³⁶⁰ System, BARRX Medical, Sunnyvale, CA, USA) was used for primary CA and an endoscope-mounted electrode (HALO⁹⁰ System) for secondary FA of residual BE. Measurement of E-ID, manometry and IP were performed at baseline and 2 months after final ablation session. E-ID measurement was obtained every 1 cm of the distal 10 cm of esophagus with a non-compliant balloon (HALO³⁶⁰ System) and an automated pressure/volume system. Manometry was performed using a 10-channel water-perfused sleeve catheter. IP was performed using a functional lumen imaging probe (FLIP) that measures 8 cross sectional areas (CSA) at 4-mm intervals inside a saline-filled bag with 2 pressure side holes; one proximal to and one inside the bag. The FLIP was positioned with the bag straddling the gastroesophageal junction (GEJ). The bag was filled with saline (25 ml/min, max 60 ml). Bag pressure and CSA were recorded at a rate of 10Hz.

Results: All patients had complete eradication of dysplasia and 9 had complete eradication of IM. There were no strictures or narrowing noted on final endoscopy. E-ID did not change; pre 31.5mm (IQR 25-33 mm), post 31.3mm (IQR 29-33 mm)(p=NS, paired Student t-test). LES pressure did not change (pre 4.0 ± 0.4 mm Hg; post 5.5 ± 1.2 mm Hg, p=NS), nor did the amplitude of peristaltic contractions per measured segment (pre 41.2 ± 11.1 mmHg; post 46.2 ± 9.9 mmHg, p=NS). IP showed no significant change in compliance; narrowest CSA pre 147 ± 12.4 mm² with a mean bag pressure of 16.0 ± 0.7mmHg; narrowest CSA post 118 ± 5.6 mm² (p=0.056) with a mean bag pressure of 15.7 ± 0.9mmHg (p=0.93).

Conclusion: This is the first report on the effects of CA and FA indicated for BE-HGD on the functional integrity of the treated esophagus. No difference was seen in the esophageal inner diameter, motility function or compliance between baseline and post-ablation measurements, suggesting that this method of ablation not only effectively removes dysplasia and BE but also preserves the functional integrity of the esophagus.

4.10. Optimizing the technique for circumferential ablation of Barrett esophagus containing high-grade dysplasia using the HALO³⁶⁰ system

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Background: The optimal technique for applying circumferential ablation (CA) to Barrett esophagus (BE) containing high-grade dysplasia (HGD) using the HALO³⁶⁰ System (BARRX Medical, Sunnyvale, CA, USA) has evolved at our center over the past 2 years with increased case experience and availability of clinical trial results.

Methods: We compared the efficacy of 2 CA techniques in 2 clinical trials (AMC-I and AMC-II) for BE-HGD. All CA sessions were performed with the HALO³⁶⁰ ablation catheter (40 W/cm², 12 J/cm²). Patients received esomeprazole 40 mg BID.

AMC-I: 1% acetic acid, ablate proximal to distal, reposition using shaft cm markings. After first pass, reposition electrode, repeat ablation.

AMC-II: 1% acetylcysteine, ablate proximal to distal, reposition using visual landmarks. After first pass, remove and clean electrode, thoroughly suction coagulum from ablation zone, reintroduce catheter, repeat ablation.

Endpoints: procedure time, sedation, post-ablation symptom scores, and regression of BE 10 wks post-ablation (% surface area regression, reduction “C” and “M”, Prague Criteria).

Results:

	AMC-I	AMC-II	p-value
N	11	12	
Time (min)	27 (25-34)	37 (33-51)	0.009
Midazolam (mg)	10 (5-10)	9 (5-10)	NS
Fentanyl (mcg)	100 (25-150)	100 (100-100)	NS
“C” Baseline (cm)	4 (0-5)	6 (3-7)	
“C” 10 wks (cm)	0 (0-0)	0 (0-0)	NS
“M” Baseline (cm)	5 (4-7)	7 (5-8)	
“M” 10 wks (cm)	5 (3-6)	0 (0-0)	<0.001
% C regression	75% (0-100)	100 (89-100)	NS
% M regression	14% (0-44)	100 (91-100)	<0.001
% surface area regression	90 (60-99)	99% (60-100)	0.035

Values are median (IQR)

Conclusions: There is a significant difference between the efficacy outcomes between the techniques. While AMC-II technique requires more procedure time, it results in superior BE regression results for M category (Prague) and surface area regression. It appears that cleaning the electrode and ablation zone after the first pass provides more assured eradication. A more assured regression after primary CA allows more optimal focal ablation of any residual BE and achievement of complete eradication for this patient population.

4.11. Radiofrequency ablation is more cost-effective than endoscopic surveillance or esophagectomy among patients with Barrett's esophagus and low-grade dysplasia

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Background/Aim: Management of patients with Barrett's esophagus (BE) with low-grade dysplasia (LGD) is controversial. Strategies include endoscopic surveillance, esophagectomy, or radiofrequency ablation (RFA). The aim of this study was to compare the incremental cost-effectiveness between these competing strategies.

Methods: A mathematical model was created to simulate the natural history of a cohort of patients with BE and LGD from age 50 to 80 years or death using a third-party payer perspective. Interventions included annual endoscopic surveillance with esophagectomy for cancer (SURV), immediate esophagectomy (ESOPH), or ablation using RFA with surveillance depending on whether there was residual LGD (1-year intervals) or no dysplasia (3-year intervals). Outcomes included the incremental cost-effectiveness ratio (ICER) comparing total direct costs and quality adjusted life years (QALYs) between competing strategies, and a sensitivity analysis identifying the thresholds at which the preference for strategies changed. Diagnostic error was incorporated. Utilities were based on existing literature, as was the efficacy of ablation therapy (BARRX device: residual LGD=30%; BE without dysplasia=10%, no BE=60%). RFA was modeled using a combination of the Halo 360 device, a circumferential ablation balloon catheter, with follow-up treatment using the Halo 90 device, a treatment device for focal disease, as necessary. Complications of endoscopy and surgery were included, as were increased rates of stricture and perforation in the ablation arm.

Results: Compared to the natural history of LGD (total direct costs \$615, 14.34 QALYs), the ICER of SURV (\$8081, 15.25 QALYs) was \$8193 per QALY gained. However, the ICER for RFA (\$10457, 16.14 QALYs) was lower: \$2677 per QALY gained over SURV, thus RFA was preferred to SURV based on extended dominance. ESOPH (\$39720, 14.84 QALYs) was more expensive and less effective (dominated) than SURV and RFA. Using more conservative estimates, assuming that no complete ablation of metaplasia was achieved, RFA remained the preferred strategy if the proportion of patients with residual LGD after ablation was 0% (willingness to pay [WTP] \$50000 per QALY) or <40% (WTP \$100000 per QALY); otherwise SURV was optimal. These results were robust to variation in other variables.

Conclusions: Our base case suggests that RFA therapy may be the most cost-effective option in patients with BE and LGD. If the effectiveness of RFA is substantially lower than current estimates, however, surveillance may be preferred.

4.12. Endoscopic ablative therapy is a cost-effective management for non-dysplastic Barrett esophagus

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Background: Advances have been made in the development of safe and effective ablative therapies for non-dysplastic Barrett esophagus (NDBE), although the cost-effectiveness (CE) of such a management strategy remains controversial. We performed a CE analysis to identify the determinants of CE of EAT in NDBE.

Methods: Using a Markov model, we evaluated 3 competing strategies in a hypothetical 50-year old cohort with NDBE over the lifetime of the cohort with a third party payer's perspective. **Strategy I:** natural history of NDBE without surveillance or intervention. **Strategy II:** surveillance per ACG guidelines. **Strategy III:** ablative therapy, up to 3 sessions, HALO ablation system (BARRX Medical, Sunnyvale, CA), conservative underestimate of histological complete response (CR) of NDBE 50%.

The model considered complications of all treatments and allowed for continued surveillance even after CR. An incomplete histological response after ablation was presumed to have same risk of progression as NDBE. Transitional probabilities, cost estimates, utility values (appropriately discounted) were obtained from published information.

Results: In a Monte Carlo analysis using ablation; incremental average net health benefit ratio was achieved only with a threshold willingness to pay of \$40,000 or higher. Compared to the Strategy I, the relative risk of developing cancer in the strategy III were 0.59 (95% CI, 0.55-0.64), respectively & NNT for preventing cancer were 16 (95% CI, 14-19). The threshold values of the determinants of the CE of ablation were age at entry into the model <55 years, total cost of ablation < \$11,300 and with > 45% achieving CR of NDBE. The incremental cost-effectiveness ratio (ICER) of strategy III over strategy II is ≤ \$50,000 if cost of ablation falls below \$ 7,450 (baseline estimate \$10,000) or if the probability of CR increases to 0.66 (baseline estimate 0.5). The ICER of strategy III over strategy I reached \$50,000 at total cost of ablation = \$ 11,340 (baseline estimate \$10,000) or if the probability of CR with ablation ≤ 0.41 (baseline estimate 0.5).

Strategy	Cost(\$)	QALY gained	ICER (\$/QALY)
I	2611	18.057	-
II	13348	18.349	36,776 (vs. strategy I)
III	22442	18.480	46882 (vs. strategy I) 69,270 (vs. strategy II)

Conclusions: Patient age, cost of ablation, and CR associated with ablation are critical determinants of its CE. Within a range of these parameters, ablation for NDBE is a CE strategy, in this model, by currently accepted standards. Considering that published histological CR rates are 70% or higher, and that total costs per procedure of <\$2,000, the real-world values fall within the parameter range for CE.