
CLINICAL TRIAL OUTCOMES:
RADIOFREQUENCY ABLATION (RFA) FOR
BARRETT'S ESOPHAGUS

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Identification of published peer-reviewed papers or abstracts for inclusion in this “Clinical Trial Outcomes” document was performed via a search of www.pubmed.gov. All published papers and abstracts that had not been converted to manuscripts were included.

1. INTRODUCTION

Barrett's esophagus

Barrett's esophagus (BE) is associated with an increased risk of developing esophageal adenocarcinoma (EAC). BE is defined as the replacement of a portion of the squamous epithelium of the distal esophagus by a specialized intestinal epithelium, also known as intestinal metaplasia (IM). This metaplastic change occurs as a result of chronic injury due to reflux of 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 that can be detected and graded on microscopy of biopsy specimen as 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 It does not appear that this rising incidence or prevalence of BE is due to an increase in detection, as one series recently showed that 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 of whom will have a Barrett's derived adenocarcinoma.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 recurring risk for a patient with non-dysplastic IM to develop EAC is estimated as 0.5% per patient-year of follow-up. Studies vary in this estimate from about 0-3% per patient-year, but a funnel analysis by Shaheen, et al. estimates the average risk to be about 0.5%.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. Wani, et al. recently reported the risk for progression to cancer from IM, LGD and HGD was 0.6%, 1.7%, and 1.6% per patient-year of follow-up, respectively. 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 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. 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 radiofrequency ablation (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

Circumferential 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 18, 22, 25, 28, 31 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 4 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

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. Patients should avoid liquids and foods that are hot (temperature), acidic, or crunchy for at least a week after treatment. 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 (EMR used as staging prior to RFA).

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 sequential 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 the 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 step had not yet been established. 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 was not available.

Fleisher et al. reported on the long-term 2.5 year follow-up of the AIM-II patient cohort.¹⁶ Patients with persistent IM at 1 year had focal RFA followed by biopsy at 25 years. 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 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 22 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.

In early 2009, several single-center studies, each with subjects exhibiting a variety of Barrett's grades, were published. Velanovich reviewed his experience performing RFA on 66 subjects (18% of which had HGD).²⁴ He achieved a CR-dysplasia and CR-IM of 93% in the 27 subjects who had been followed for > 1 year. Of interest, he noted that 4 subjects developed strictures, but each had at baseline a Barrett's segment > 6 cm in length. This led him to recommend that no more than 6 cm of Barrett's be ablated in a single session. Eldaif, et al. published their outcomes employing RFA for 27 subjects (25 with IM and 2 with LGD).²⁵ A CR-dysplasia and CR-IM of 100% was achieved after no more than 2 RFA sessions. None of their subjects developed strictures or buried glands. Sharma VK, et al. reported RFA results for 63 subjects with LGD (n=39) and HGD (n=24).²⁶ They realized a CR-dysplasia of 89% and CR-IM of 79% despite the fact that some of their subjects were still undergoing treatment. One subject had a mild stricture that responded to a single dilation and another, who was on aspirin, had a minor bleed that did not require therapy. No buried glands were noted.

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).²⁷ Beginning in 2006, 127 patients were enrolled and randomized according to baseline histology and endoscopic length. At one-year follow-up, higher proportions of RFA subjects had achieved CR for dysplasia and IM compared to sham. In the HGD group, treatment patient CR-dysplasia was 81.0% ITT (89.5% PP), while sham was 19.0% ITT (20.0% PP)(p<0.001). In the LGD group, treatment patient CR-dysplasia was 90.5% ITT (95.0% PP), while sham was 22.7% ITT (26.3% PP)(p<0.001). The CR-IM for the RFA cohort overall was 77.4% ITT (83.3% PP), compared to 2.3% ITT (2.6%PP) of sham (p<0.001). Overall, the rate of progression to higher grades of dysplasia or cancer was significantly lower (p<0.05) in the RFA group (3.6%) as compared to sham (16.3%). In the highest risk cohort (high-grade dysplasia), ablative therapy significantly reduced the risk of progression to cancer by nearly 90% compared to control (2.4% in treated patients versus 19.0% in untreated controls). As for adverse events, 6% of the RFA cohort experienced a stricture, but all resolved with a mean of 2 dilations. At baseline, 25.2% of the subjects had buried glands. At one-year follow up, only 5.1% of those treated with RFA were found to have buried glands as compared to 40.0% of subjects in the sham group (p<0.001). There were no perforations or deaths.

Cost-effectiveness analyses of RFA

Two case-based studies have been conducted 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.²⁸ 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.²⁹ It compared the incremental cost-effectiveness between three competing strategies: (1) surveillance, (2) esophagectomy, and (3) RFA. Endoscopic ablation for patients with HGD could increase life expectancy by 3 quality-adjusted years at an incremental cost of <\$6,000 compared with no intervention. Patients with LGD or no dysplasia can also be optimally managed with ablation, but continued surveillance after eradication of metaplasia would be expensive. If ablation permanently eradicates >28% of LGD or 40% of nondysplastic metaplasias, ablation would be preferred to surveillance. *Conclusions:* Endoscopic ablation could be the preferred strategy for managing patients with BE with HGD. Ablation might also be preferred in subjects with LGD or no dysplasia, but the cost effectiveness depends on the long-term effectiveness of ablation and whether surveillance endoscopy can be discontinued after successful ablation.

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3. DEVICES

3.1. 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.

3.2. 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.

3.3. 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.

4. ABSTRACTS FROM PEER-REVIEWED PAPERS OF RFA FOR BE

4.1. Radiofrequency ablation in Barrett's esophagus with dysplasia

Nicholas J. Shaheen, Prateek Sharma, Bergein F. Overholt, Herbert C. Wolfsen, Richard E. Sampliner, Kenneth K. Wang, Joseph A. Galanko, Mary P. Bronner, John R. Goldblum, Anna E. Bennett, Blair A. Jobe, Glenn M. Eisen, M. Brian Fennerty, John G. Hunter, David E. Fleischer, Virender K. Sharma, Robert H. Hawes, Brenda J. Hoffman, Richard I. Rothstein, Stuart R. Gordon, Hiroshi Mashimo, Kenneth J. Chang, V. Raman Muthusamy, Steven A. Edmundowicz, Stuart J. Spechler, Ali A. Siddiqui, Rhonda F. Souza, Anthony Infantolino, Gary W. Falk, Michael B. Kimmey, Ryan D. Madanick, Amitabh Chak, Charles J. Lightdale

N Engl J Med 2009;360:xxx-xx

Background: Barrett's esophagus, a condition of intestinal metaplasia of the esophagus, is associated with an increased risk of esophageal adenocarcinoma. The condition may progress through stages of dysplasia before cancer. We assessed whether an endoscopic intervention, radiofrequency ablation, could eradicate dysplastic Barrett's esophagus and decrease the rate of neoplastic progression.

Methods: In a multicenter, sham-controlled trial, we randomly assigned 127 patients with dysplastic Barrett's esophagus in a 2:1 ratio to receive either radiofrequency ablation (ablation group) or a sham procedure (control group). Randomization was stratified according to the grade of dysplasia (low-grade or high-grade) and the length of Barrett's esophagus (<4 cm or 4 to 8 cm). Primary outcomes at 12 months included the complete eradication of dysplasia and intestinal metaplasia. Secondary outcomes included progression to more severe dysplasia or cancer and adverse events.

Results: In the intention-to-treat analyses, among patients with low-grade dysplasia, complete eradication of dysplasia occurred in 90.5% of those in the ablation group, as compared with 22.7% of those in the control group ($P<0.001$). Among patients with high grade dysplasia, complete eradication occurred in 81.0% of those in the ablation group, as compared with 19.0% of those in the control group ($P<0.001$). Overall, 77.4% of patients in the ablation group had complete eradication of intestinal metaplasia, as compared with 2.3% of those in the control group ($P<0.001$). Patients in the ablation group had less disease progression (3.6% vs. 16.3%, $P = 0.03$) and fewer cancers (1.2% vs. 9.3%, $P = 0.045$). Patients reported having more chest pain after the ablation procedure than after the sham procedure. In the ablation group, one patient had upper gastrointestinal hemorrhage, and five (6.0%) patients had esophageal stricture.

Conclusions: In patients with dysplastic Barrett's esophagus, radiofrequency ablation was associated with a high rate of complete eradication of both dysplasia and intestinal metaplasia and a reduced risk of disease progression. (ClinicalTrials.gov number, NCT00282672.)

4.2. Properties of the neosquamous epithelium after radiofrequency ablation of Barrett's esophagus containing neoplasia

RE Pouw, JJ Gondrie, AM Rygiel, CM.Sondermeijer, FJ ten Kate, RO Odze, M Vieth, KK Krishnadath, JJ Bergman

Am J Gastroenterol Epub on 21 April 2009 ahead of print, DOI 10.1038/ajg.2009.88

Objectives: Endoscopic radiofrequency ablation (RFA) eradicates intestinal metaplasia and intraepithelial neoplasia associated with Barrett's esophagus (BE), restoring an endoscopically normal neosquamous epithelium (NSE). We evaluated the post-RFA NSE for genetic abnormalities and buried glandular mucosa.

Methods: Eligible patients underwent RFA for BE containing early cancer and/or high-grade intraepithelial neoplasia with subsequent complete histological reversion to normal NSE. At baseline, the BE was sampled by brush cytology and biopsies. At least 2 months after RFA, the NSE was sampled by brush cytology, keyhole biopsies, and endoscopic resection. The untreated squamous epithelium was biopsied as a control. The baseline BE and post-RFA NSE were evaluated for immunohistochemical expression of Ki-67 and p53, and genetic abnormalities (DNA-fluorescent *in situ* hybridization: chromosome 1 and 9, p16 and p53). In addition, biopsy depth was compared for biopsies from the NSE and untreated squamous epithelium. The presence of buried glandular mucosa in NSE was assessed with primary and keyhole biopsy, and endoscopic resection.

Results: All pretreatment specimens from all 22 patients showed abnormalities on immunohistochemical staining and fluorescent *in situ* hybridization, whereas all post-RFA NSE specimens were normal. All the post-RFA biopsies from the NSE contained full epithelia, whereas 37% contained lamina propria, a finding no different from biopsies from untreated squamous epithelium (36% lamina propria). Deeper keyhole biopsies contained lamina propria in 51%. All endoscopic resection specimens contained submucosa, whereas no biopsy or endoscopic resection specimen contained buried glandular mucosa.

Conclusions: Rigorous evaluation of the post-RFA NSE in patients who, at baseline, had BE containing early cancer high-grade intraepithelial neoplasia, showed neither persistent genetic abnormalities nor buried glandular mucosa.

4.3. An economic analysis of endoscopic ablative therapy for management of nondysplastic Barrett's esophagus

A. Das, C. Wells, H.J. Kim, D.E. Fleischer, M.D. Crowell, V.K. Sharma

Endoscopy 2009;41:400-8

Background and aims: Advances have occurred in the development of safe and effective ablative therapies for Barrett's esophagus. The aim of the current study was to perform an economic analysis evaluating the cost-effectiveness of endoscopic ablation of nondysplastic Barrett's esophagus.

Methods: A Markov model evaluated three competing strategies in a hypothetical 50-year-old cohort with nondysplastic Barrett's esophagus from a societal perspective. Strategy I – natural history of Barrett's disease (without surveillance); Strategy II – surveillance performed according to the American College of Gastroenterology practice guidelines; Strategy III – endoscopic ablative therapy. The model was biased against ablative therapy with a conservative estimate of complete response and continued standard surveillance even after complete ablation. All potential complications were accounted for, and an incomplete histological response after ablation was presumed to have the same risk of progression as untreated Barrett's. Transitional probabilities, discounted cost, and utility values to estimate quality-adjusted life-years (QALY) were obtained from published information. Direct costs were used in our analysis.

Results: In baseline analysis, the ablative strategy yielded the highest QALY and was more cost-effective than endoscopic surveillance. In a Monte Carlo analysis, the relative risk of developing cancer in the strategy based on endoscopic ablation was decreased compared with the other strategies. In threshold analysis, the critical determinants of cost-effectiveness of the ablative strategy were rate of complete response to ablation, total cost of ablation, and risk of progression to dysplasia.

Conclusions: Within the limits of the model, ablation for nondysplastic Barrett's esophagus is more cost-effective than endoscopic surveillance. Clinical trials of ablative therapy in nondysplastic Barrett's esophagus are needed to establish its effectiveness in reducing cancer risk.

4.4. A cost-utility analysis of ablative therapy for Barrett's esophagus

John M Inadomi, Ma Somsouk, Ryan D Madanick, Jennifer P Thomas, Nicholas J Shaheen

Gastroenterology Epub on 6 March 2009 ahead of print, DOI 10.1053/j.gastro.2009.02.062

Background & Aims: Recommendations for patients with Barrett's esophagus (BE) include endoscopic surveillance with esophagectomy for early-stage cancer, although new technologies to ablate dysplasia and metaplasia are available. This study compares the cost-utility of ablation with that of endoscopic surveillance strategies.

Methods: A decision analysis model was created to examine a population of patients with BE (mean age 50), with separate analyses for patients with no dysplasia, low-grade dysplasia (LGD), or high-grade dysplasia (HGD). Strategies compared were: no endoscopic surveillance; endoscopic surveillance with ablation for incident dysplasia; immediate ablation followed by endoscopic surveillance in all patients or limited to patients in whom metaplasia persisted, and esophagectomy. Ablation modalities modeled included radiofrequency, argon plasma coagulation, multipolar electrocoagulation and photodynamic therapy.

Results: Endoscopic ablation for patients with HGD could increase life expectancy by 3 quality adjusted years at an incremental cost of < \$6,000, compared with no intervention. Patients with LGD or no dysplasia can also be optimally managed with ablation, but continued surveillance after eradication of metaplasia is expensive. If ablation permanently eradicates at least 28% of LGD or 40% of non-dysplastic metaplasias, ablation would be preferred to surveillance.

Conclusions: Endoscopic ablation could be the preferred strategy for managing patients with BE with HGD. Ablation might also be preferred in subjects with LGD or no dysplasia, but the cost-effectiveness depends on the long-term effectiveness of ablation and whether surveillance endoscopy can be discontinued following successful ablation. As further post-ablation data become available, the optimal management strategy will be clarified.

4.5. Endoscopic ablation of Barrett's esophagus using the Halo System

David.E. Fleischer, Virender K. Sharma

Dig Dis 2008;26:280-4 (appears in February 2009 issue)

There is increasing interest in the endoscopic treatment of Barrett's esophagus. Endoscopic treatment has been utilized for many years, but in the past, no specific method has emerged as an appealing treatment option with appropriate safety, efficacy and ease of treatment for both patients and physicians. Recently there has been a growing literature related to the endoscopic ablation of Barrett's esophagus using radiofrequency ablation (RFA) (Halo® system). In order to discuss when RFA is indicated for Barrett's, one needs to know: (1) What is the 'histology' of the Barrett's? Does the patient have intestinal metaplasia, low-grade dysplasia, high-grade dysplasia or intramucosal carcinoma? (2) What are the endoscopic options to be considered as opposed to RFA? What are the advantages and disadvantages of each? (3) What additional variables need to be examined?

4.6. Endoscopic endoluminal radiofrequency ablation of Barrett's esophagus: Initial results and lessons learned

Vic Velanovich

Surg Endosc Epub on 5 March 2009 ahead of print, DOI 10.1007/s00464-009-0364-z

Background: Ablating Barrett's epithelium may reduce the risk of developing esophageal adenocarcinoma. This study reports the experience of a single surgeon using an endoscopic endoluminal device that delivers radiofrequency energy (the BARRX device) to ablate Barrett's esophagus.

Methods: All patients who underwent ablation of Barrett's epithelium with the BARRX system were reviewed for length of Barrett's metaplasia, presence of high-grade dysplasia, postprocedure complications, completeness of ablation at first follow-up endoscopy, need for additional ablation, completeness of ablation at second follow-up endoscopy, and concomitant performance of a Nissen fundoplication.

Results: Sixty-six patients underwent Barrett's ablation. The median length of the Barrett's esophagus was 3 (range, 1-14) cm. Twelve patients (18%) had high-grade dysplasia. There were no immediate procedure-related complications. Four strictures occurred: three in patients with ≥ 12 -cm segments of Barrett's and one in a 6-cm segment. Twenty-nine of 49 patients (59%) who had planned 3-month follow-up endoscopy had complete ablation. Five patients had planned two-stage ablation. Twenty patients with incomplete ablation had additional ablation. Twenty-seven patients had planned follow-up endoscopy at ≥ 1 year: 25 of 27 (93%) had biopsy-proven normal esophageal mucosa. The median length of Barrett's esophagus in patients with initially incomplete ablation was 6 cm, compared with 2 cm in the initially complete ablation patients. Seven Nissen funduplications were present at the time of ablation, whereas six were performed concomitantly with the ablation without increased difficulty.

Conclusions: Complete ablation of Barrett's esophagus with radiofrequency endoluminal ablation is achievable in $>90\%$ of patients. Patients with longer segments are likely to require additional ablation. Patients with very long segments are at risk for stricture and should be approached cautiously. Performance of a fundoplication is not hindered by concomitant ablation.

4.7. Radiofrequency ablation of Barrett's esophagus: Short-term results

Shady M. Eldaif, MD, Edward Lin, DO, Kimberly A. Singh, MD, Seth D. Force, MD, Daniel L. Miller, MD
Ann Thorac Surg 2009;87:405–11

Background: The presence of Barrett's esophagus (BE) increases the risk of esophageal cancer. Total regression of BE is uncommon with medication or laparoscopic fundoplication, and endoscopic techniques to obliterate BE have varied results. This study evaluated the early results of a balloon-based catheter radiofrequency ablation (RFA) system in patients with medically refractory reflux symptoms and biopsy-proven BE.

Methods: The medical records of 27 consecutive patients who underwent RFA for BE from March 2005 through January 2007 were reviewed. Esophagogastroduodenoscopy was performed before ablation to document presence of BE and no cancer and at 8 weeks after the RFA to assess the presence of residual BE.

Results: Mean patient age was 53.6 ± 12.5 years; 16 (59%) were men. The average length of the Barrett segment treated was 4.6 - 4.7 cm. Two patients (7.4%) had low-grade dysplasia. No patient had high-grade dysplasia and cancer. There was no periprocedural morbidity or at follow-up, no postprocedure dysphagia or stricture. In all patients, the BE was completely replaced with normal squamous epithelium. Symptoms regressed in 16 patients (60%) with RFA and proton pump inhibitor therapy. Eleven required an antireflux procedure for persistent symptoms.

Conclusions: Short-term results show that RFA for BE is safe and achieves 100% replacement of intestinal metaplasia. RFA of BE combined with fundoplication may be offered to patients with BE and medically refractory reflux symptoms. Long-term endoscopic surveillance is needed to determine if the risk of cancer is reduced with this bimodality therapy.

4.8. 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 2009;104:310-7

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.

4.9. 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. Boeckstaens

Endoscopy 2009;41:2-8

Background & Aims: 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.

4.10. 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.

4.11. 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.

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

Ross E. Pouw, Joep 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 \leq 12 cm with early neoplasia. Visible lesions were endoscopically resected. A balloon based 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.

4.13. 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.

4.14. 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.

4.15. 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 & 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 & 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.

4.16. 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.

4.17. 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 & 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 & 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.

4.18. 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 & 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 & 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.

4.19. 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.

4.20. 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.

4.21. 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.

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

A.K. Roorda, S.N. Marcus, G. Triadafilopoulos

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.

4.23. Barrett's esophagus and new therapeutic modalities

Virender K. Sharma, David E. Fleischer

Therapy 2007;4:825-40

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.

4.24. Changing attitudes toward endoluminal therapy

JW Hazey, BJ Dunkin, WS Melvin

Surg Endosc 2007;21:445-8

Background: As with new laparoscopic techniques, the ability to convince surgeons and gastroenterologists to embrace endoluminal techniques and the additional training required to perform the new procedures will correlate with how rapidly endoluminal 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 endoluminal therapies.

Methods: As part of the endoluminal 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 endoluminal 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 endoluminal 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 endoluminal therapies including endoluminal 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 endoluminal 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 endoluminal 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 endoluminal therapeutic techniques can have a significant impact in terms of changing practice attitudes and may accelerate adoption of new endoscopic techniques.

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

B.J. Dunkin, J. Martinez, P.A. Bejarano, C.D. Smith, K. Chang, A.S. Livingstone, W.S. Melvin

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.

4.26. 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.

5. PEER-REVIEWED ABSTRACTS OF RFA FOR BE

5.1. **A multi-center randomized trial comparing stepwise radical endoscopic resection versus radiofrequency ablation for Barrett esophagus containing high-grade dysplasia and/or early cancer**

Frederike G. Van Vilsteren, Roos E. Pouw, Stefan Seewald, Lorenza Alvarez Herrero, Carine Sondermeijer, Fiebo J. Ten Kate, Paul Fockens, Karl C. Yu Kim Teng, Thomas Rosch, Nib Soehendra, Bas L. Weusten, Jacques Bergman

Gastrointest Endosc 2009;69:AB133-4

Background: After endoscopic resection (ER) of high-grade dysplasia (HGD) and early cancer (EC) in Barrett esophagus (BE), the residual BE remains at risk for neoplasia. Complete eradication of all BE is therefore a preferred approach. One method is stepwise radical ER (SRER), which is highly effective and provides a pathology specimen, yet is technically challenging and has a moderate complication risk. By comparison, radiofrequency ablation (RFA) is highly effective with a low complication risk, yet yields no pathology specimen.

Aim: Compare the safety and efficacy of SRER vs. RFA for treatment of BE-HGD/EC.

Methods: Under an IRB approved protocol, 3 centers enrolled patients BE \leq 5 cm containing HGD and/or EC (max T1sm1). Patients were stratified for visible lesions at baseline (yes/no) then randomized 1:1 to SRER or RFA. SRER patients underwent piecemeal ER of 50% of BE (including visible lesions if present) followed by ER sessions every 2 mos. RFA patients (after focal ER of visible lesions if present) underwent RFA every 2 mos. Treatment was continued until a complete response for intestinal metaplasia (CR-IM, no IM on biopsy) was achieved. After CR-IM, biopsy (4Q/2cm) was performed at 2, 6, and 12 mo.

Results: 47 patients were randomized (25 SRER, 22 RFA). By Dec '08, data is available for 43 (22 SRER, 21 RFA). Age, gender, BE length (median C2M4 in both), entry histology (SRER: 10 HGD/12 EC vs. RFA: 7 HGD/14 EC), and the proportion of patients with visible lesions at entry were similar between SRER and RFA. A CR-HGD/EC was achieved in 22 (100%) SRER and 20 (95%) RFA, and CR-IM in 21 (96%) SRER and 20 (95%) RFA. The total number of therapeutic sessions to achieve CR was similar (median SRER 2, RFA 3). SRER, however, required more sessions when dilations were included (6 vs. 3; $p < 0.001$). Acute SRER-related complications: 1 perforation (5%), 5 bleeds (23%). There was one RFA-related delayed bleeding (5%). Prior RFA, 3 of 18 bled (17%) after entry ER. The incidence of stenosis was higher in SRER (86%) vs. RFA (14%) ($p < 0.001$). All RFA stenoses had an entry ER. All stenoses resolved with dilation. Median follow-up is 13 mo in both groups. Once CR-IM was achieved, no patient in either group had recurrence of dysplasia or visible BE.

Conclusion: In patients with BE \leq 5 cm containing HGD/EC, SRER and RFA achieved comparably high rates of CR for both IM and neoplasia. However, SRER carried a higher risk of complications and had more procedures per patient. Based on these results, we recommend a combined approach of focal ER for visible lesions followed by RFA for complete eradication of remaining BE.

5.2. What are the outcomes of endoscopic radiofrequency ablation for very long segments of Barrett esophagus containing neoplasia?

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Background: Radiofrequency ablation (RFA) is safe and effective for eradicating Barrett esophagus (BE) and neoplasia. Most studies have limited the baseline length of BE (<10cm) and little is therefore known about RFA for very long BE segments.

Aim: Assess the safety and efficacy of RFA for BE \geq 10cm containing neoplasia.

Methods: Eligible patients (pts) had BE \geq 10cm with LGD, HGD or early cancer (EC). Pts underwent focal endoscopic resection (ER) for visible lesions, followed by circumferential (C-RFA) and focal RFA (F-RFA) every 2-3 mo until complete remission achieved (CR, defined as endoscopic resolution of BE and no evidence of intestinal metaplasia (IM) or neoplasia on biopsy). Follow-up (FU) endoscopy with 4Q/2cm biopsies was performed at 2, 6, and 12 mo.

Results: 26 consecutive pts were included (21 M, age 66 yrs, median BE length 11cm, range 10-20). Baseline ER was performed in 18/26 pts: EC (11), HGD (6), LGD (1). Worst grade of residual BE prior to RFA (and after ER as applicable): HGD (16), LGD (10). At entry, 13 pts (50%) had a proximal reflux stenosis (3 required dilation). After circumferential RFA, 7/26 (27%) had a non-transmural laceration (4 at the reflux stenosis, 3 at the prior ER). All were able to complete RFA. One pt with a relative stenosis after ER, developed dysphagia after RFA and required dilatation. By Nov'08, 9 pts are still under treatment (median regression: 95%), in 3 pts (12%) treatment was discontinued due to poor neosquamous regeneration. 14 pts have completed treatment with CR-IM and CR-neoplasia achieved after a median of 1(IQR 1-1) C-RFA and 2(IQR 1-3) F-RFA sessions. Two pts had a focal ER for small persisting islands after RFA. After a median FU of 9 mo, no recurrence of neoplasia was found. In 1 pt a 0.5 mm island was found during FU, distal to a reflux stenosis at the upper end of the initial BE. One pt had focal IM detected at the neo-z-line at a single FU endoscopy. No buried BE was found in 752 neosquamous biopsies.

Conclusion: Pts having very long segments of BE (10-20cm in this evaluation) present challenges that we have not observed in our more typical BE pts: 12% of our pts with BE \geq 10cm showed poor healing after RFA, probably reflecting the severity of the underlying reflux disease. Reflux stenoses and scarring after ER resulted in superficial laceration after circumferential RFA in 27% of pts, but these events were manageable. Overall we were able to achieve a CR in 14/17 who have completed therapy in a similar number of RFA sessions as required in shorter segment BE cohorts. Aside from the challenges noted, very long segments of BE can be treated safely and effectively with RFA.

5.3. Endoscopic radiofrequency ablation of Barrett's esophagus: Safety and efficacy outcomes in 429 patients treated in a multi-center community practice registry

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Gastrointest Endosc 2009;69:AB114

Background: Radiofrequency ablation (RFA) for dysplastic and non-dysplastic Barrett's esophagus (BE) has shown favorable outcomes in several cohort studies, a randomized sham-controlled trial, and a multi-center registry; all predominantly conducted at tertiary centers under controlled circumstances. Less is known about the outcomes of RFA when performed in expert community practices.

Aim: Determine the safety and efficacy of RFA for dysplastic and non-dysplastic BE in a community practice setting.

Methods: Subjects had BE with biopsy confirming non-dysplastic intestinal metaplasia (IM), low-grade (LGD) or high-grade dysplasia (HGD). RFA was performed every 2-4 months with follow-up biopsy at each endoscopy after RFA and/or upon achieving complete endoscopic eradication of BE. The primary endpoint is histology-based: complete response for dysplasia (CR-D) and IM (CR-IM), defined as no biopsy showing each respective finding. Three cohorts were considered: Safety (all subjects); Efficacy-A (subjects with any post-RFA biopsy despite some not having completed therapy); 3) Efficacy B (subjects with post-RFA biopsy >1 year post-RFA).

Results: In the Safety cohort (429 patients, 788 RFA procedures), there were no serious adverse events. By procedure, there were 9 strictures (1.1%), 4 mild bleeding during RFA (0.5%), 1 mucosal injury during RFA (0.1%), 1 fever (0.1%), 1 hematemesis, no intervention (0.1%). Efficacy-A achieved a CR-D and CR-IM in 89% and 72% of subjects, respectively; median BE 3 cm (IQR 2-4), median follow-up 9 mos (IQR 4-18). Efficacy-B achieved a CR-D and CR-IM in 100% and 77% of subjects, respectively; median BE 3 cm (IQR 2-4), median follow-up 20 mos (IQR 17-26).

Conclusion: Published clinical trial data reporting on RFA for BE comes from expert tertiary centers conducting the trials under tightly controlled circumstances. We sought to add to this body of evidence by evaluating the outcomes of RFA in the hands of expert community practitioners. In this large series of patients (n=429), we demonstrated a very favorable safety profile, as well as histology-based efficacy outcomes that are comparable to those from published studies.

5.4. **How durable is the reversion to neosquamous epithelium in subjects undergoing radiofrequency ablation for dysplastic Barrett's esophagus? Two year follow-up of the AIM-Dysplasia Randomized Sham-Controlled Trial**

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Gastroenterology 2009;136:A-158

Background: Radiofrequency ablation (RFA) of dysplastic Barrett's esophagus (BE) results in high rates of eradication of both dysplasia and intestinal metaplasia (IM). The durability of this reversion of dysplastic BE is not known.

Aim: Assess the 2-year biopsy results from subjects who were treated for baseline dysplastic BE with RFA, and achieved a histological complete response at 1-year follow-up (complete remission of IM, CR-IM).

Methods: The AIM-Dysplasia trial is a randomized, sham-controlled multi-center trial of RFA plus surveillance vs. surveillance alone for dysplastic BE. Subjects were stratified by degree of dysplasia (high-grade (HGD) vs. low-grade dysplasia (LGD)) and BE length (4-8 vs. <4 cm), and then randomized 2:1 to receive RFA or sham, respectively. In the RFA group, step-wise circumferential and focal RFA were performed using the HALO system. Both groups then underwent surveillance with biopsy every 3 (HGD) or 6 (LGD) mos, 4-quadrant every 1 cm based on baseline BE length. The primary endpoints at 12 mos were histology based: CR-IM and CR-dysplasia (all biopsies negative for IM and dysplasia, respectively). Cleveland Clinic was the central lab and read all slides in a blinded manner. After 12 months, RFA subjects continued surveillance while sham subjects were offered cross-over. All patients have a final biopsy session at 2 yrs. To assess the durability of the reversion to neosquamous epithelium, we analyzed the 2-year biopsy results in those subjects with CR-IM at 1 yr.

Results: Histology data from 2-year follow-up are available for 30 subjects who were CR-IM at 1 yr (19 LGD/11 HGD, mean age 63.1 yrs, 83% male, mean BE length 4.2 cm). Of these, 28 (93.3%) continued to be free of IM at 2 yrs. For the 2 subjects not sustaining CR-IM at 2 yrs, both had 6 cm of BE with HGD at baseline. At 2 yrs, both showed no visible BE in the esophageal body, with biopsy confirmation. However, both were graded as 99% eradication due to a small (<5 mm) irregularity of the squamocolumnar junction near the gastric folds. Biopsy of these irregular z-lines revealed LGD. One of 30 subjects developed a stricture (3%) requiring one dilation for resolution, and there was one overnight hospitalization for chest pain to rule out MI.

Conclusion: Reversion to a histologically normal neosquamous epithelium after RFA treatment for dysplastic BE is durable at 2-year follow-up. Further systematic assessment of this cohort will allow determination of longer-term durability and assessment of the safety and efficacy of additional RFA intervention should IM recur.

5.5. Buried Barrett after radiofrequency ablation for neoplastic Barrett esophagus: Undetectable due to mucosal scarring or truly a rare occurrence?

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Gastroenterology 2009;136:A-592

Background: Radiofrequency ablation (RFA) is safe and effective for eradicating neoplastic Barrett esophagus (BE). Although buried Barrett (BB) glands underneath the neosquamous epithelium (NSE) are an extremely rare finding during follow-up, some have hypothesized that BB cannot be adequately sampled due to presumptive mucosal fibrosis after RFA.

Aim: Prospectively evaluate sampling depth of primary and keyhole biopsies obtained from NSE vs. untreated squamous epithelium (USE) as control. Compare sampling depth of standard vs. jumbo biopsy forceps in NSE and USE. Assess for BB beneath the NSE using primary biopsy, keyhole biopsy and endoscopic resection (ER).

Methods: We considered 23 patients for enrollment, all of whom had undergone RFA for neoplastic BE under protocol. After signing informed consent, patients were randomized to undergo standard vs. jumbo biopsies from the NSE and USE (4Q/2cm). After each primary biopsy a “keyhole” biopsy was obtained from the same site in order to obtain deeper tissue. In addition an ER specimen was obtained from an area of NSE. Three expert pathologists independently scored (blinded to biopsy source) histological depth for each biopsy and ER specimen and determined if BB was present.

Results: 16 of 23 patients participated (exclusions: unrelated death (1), co-morbidity (2), initial BE <2 cm (4)). Complete eradication of neoplastic BE had been achieved and sustained in all patients prior to enrollment; median follow-up 26 months (IQR 21-28). There was no difference in primary biopsy depth between NSE vs. USE: lamina propria was sampled in 37% and 36% of cases, respectively. Keyhole biopsies sampled significantly deeper than primary non-keyhole biopsies. There was no significant difference in sampling depth between standard and jumbo biopsy forceps. All ER-specimens included submucosa. BB was not found in any of the (keyhole) biopsies and ER specimens.

Conclusion: Primary biopsies from NSE after RFA sample as deeply as biopsies from control USE. It is thus unlikely that the reported absence of BB after RFA reflects insufficient biopsy depth due to mucosal scarring. We found no benefit in terms of additional biopsy depth for using jumbo biopsy forceps in surveying post-RFA patients. The absence of BB in (keyhole) biopsies and ER specimens suggests that RFA obliterates all Barrett mucosa, both superficial and deep.

5.6. Importance of verifying complete eradication of endoscopically evident Barrett mucosa in the neosquamous epithelium prior to surveillance endoscopy and biopsy, in order to avoid false positive interpretation of buried Barrett

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Gastrointest Endosc 2009;69:AB344

Background: Radiofrequency ablation (RFA) for Barrett esophagus (BE) achieves complete reversion to a normal neosquamous epithelium (NSE) in the majority of cases. After RFA, buried Barrett (BB) glands beneath the NSE are a rare finding. If, however, a residual island of BE is not recognized endoscopically (small size, inadequate imaging) after RFA, and is then inadvertently biopsied and reported to the pathologist as normal NSE, we questioned whether or not this could lead to a false positive histological finding of BB.

Aim: Using high-resolution endoscopy and NBI to detect small residual islands of BE (<5 mm) after RFA, we sought to determine how often targeted biopsies of these islands would lead to a false positive histological diagnosis of BB as compared to the rate of BB found when sampling endoscopically normal NSE.

Method: Patients from several IRB-approved protocols at our center were included. All had BE (LGD, HGD, IMC) treated with endoscopic resection for visible lesions, followed by RFA every 2 months until all BE mucosa was eradicated. Interim biopsies of the NSE and visible BE were obtained prior to achieving complete eradication. Final biopsies of the entire NSE (4Q/2cm) were taken after achieving endoscopic eradication. For this evaluation, any “qualifying” BE island (<5 mm) detected at an interim biopsy session was biopsied and placed in a separate container. A single expert GI pathologist reviewed all biopsies and diagnosed BB if glandular mucosa was present beneath an intact layer of squamous epithelium without surface communication.

Results: 2,515 biopsies were obtained from NSE in 69 patients, while 52 biopsies of 52 qualifying islands (median 1mm (IQR 1-2)) were obtained from 18 patients. NBI facilitated the detection of qualifying islands. Of the NSE biopsies, 2/2,515 (0.08%) were interpreted as having BB. Of the qualifying island biopsies, 11/52 (21%) were interpreted as having BB.

Conclusion: In our evaluation, the prevalence of BB in post-RFA NSE was extremely rare (0.08%), which comports with results of published studies. A finding of BB in biopsies from qualifying islands (<5 mm), however, was common (21%), despite that these islands were endoscopically visible. This false positive finding may be explained by undermining of BE island mucosa beneath surrounding NSE, the steep angle of attack of the biopsy forceps in the esophagus, and possible artifact of embedding or sectioning. In order to avoid a false positive diagnosis of BB post-RFA, the NSE should be sampled only after careful examination with high-resolution endoscopy, NBI, or other comparable techniques have completely ruled out small islands of residual BE.

5.7. Radiofrequency ablation for eradication of Barrett esophagus containing high-grade dysplasia or early cancer: A prospective series of 73 patients

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Objective: Radiofrequency ablation (RFA) is a novel endoscopic ablation technique for eradication of Barrett esophagus (BE) with and without dysplasia.

Aim: To report the combined results of published and ongoing studies on RFA of BE containing high-grade dysplasia (HGD) and/or early cancer (EC), with baseline endoscopic resection (ER) in case of visible lesions.

Methods: We included all patients treated with RFA at our centre starting July 2005, under IRB approved protocols. Enrolled patients had BE \leq 12cm with HGD/EC. Non-flat lesions were removed with ER prior to RFA. Exclusion criteria: cancer $>$ T1sm1 or N+ disease on EUS. Primary circumferential RFA was performed using a balloon-based catheter, secondary focal RFA was performed with an endoscope-based catheter (BARRX Medical). Primary RFA was performed 6 weeks after ER, followed by secondary RFA every 2 months until clearance of BE was confirmed endoscopically by inspection with narrow-band imaging, and histologically by biopsies. Thereafter, follow-up endoscopy and biopsy was performed at 2, 6, and 12 months and then annually.

Results: 73 patients were included (59M, mean age 65yrs, median BE 5cm). 57/73 patients (78%) underwent ER (20 en-bloc, 37 piecemeal) prior to RFA revealing EC (n=32), HGD (n=20), LGD (n=4) or non-dysplastic BE (n=1). The worst histological grade of residual BE prior to RFA was HGD (n=42), LGD (n=24), or non-dysplastic (n=7). By November 2008, 11 patients are still under treatment, while 62 patients have completed treatment (results of 44 patients have been published). Complete histological eradication of dysplasia and intestinal metaplasia (IM) was achieved in 59/62 patients (95%) after a median of 1 (IQR 1-1) circumferential RFA and 2 (IQR 1-2) focal RFA sessions, and additional ER in 5 patients. There were 3 protocol failures: 2 patients had persisting dysplasia (5%), in 1 patient (2%) treatment was ceased due to poor mucosal healing after RFA. Complications following RFA: asymptomatic non-transmural laceration at an ER-scar after circumferential RFA (n=7), dysphagia (n=5), melena (n=1). No lacerations or dysphagia occurred in patients without prior ER. Seventeen months (IQR 14-33) after the last treatment, no dysplasia had recurred. In one patient a 1mm BE island was identified at 12 months follow-up. Eight patients had focal IM detected immediately distal to the neo-Z-line at a single FU. Of 2515 biopsies obtained from neosquamous epithelium during any follow-up, 2 showed buried IM (0.08%).

Conclusion: RFA of BE-HGD/EC with or without prior ER of visible lesions is effective in achieving complete eradication of dysplasia and IM (95%) without serious adverse events.

5.8. Are biopsies from the neosquamous epithelium (NSE) after photodynamic therapy (PDT) and radiofrequency ablation (RFA) for Barrett's esophagus (BE) comparable in depth to those obtained from untreated squamous epithelium (USE), and, are these biopsies sufficiently deep to detect buried glandular mucosa (BGM)?

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Gastrointest Endosc 2009;69:AB343-4

Background: PDT and RFA are effective for BE, achieving complete response for IM (CR-IM) in most cases. While BGM after ablation is infrequent, its occurrence is of concern. A further concern is that post-ablation mucosal changes may limit the ability to biopsy deeply enough to detect BGM and that “true” rates of BGM may be higher than reported.

Aim: Determine the histological depth of biopsies from squamous epithelium in 3 cohorts: ablation-naïve (USE), post-PDT (NSE) and post-RFA (NSE), and compare presence of “lamina propria (LP) or deeper” per biopsy for each.

Methods: Ablation-naïve patients had biopsy of USE (BE, GERD, dyspepsia). Post-PDT patients had PDT, achieved CR-IM, biopsy NSE at 12+ mos. Post-RFA patients (AIM trial) had RFA for BE, achieved CR-IM, biopsy NSE at 30 mos. Jumbo or max cap forceps used. Depth graded by a single expert GI pathologist (blinded to cohort) as full epithelium (full EPI), LP, muscularis mucosae (MM), submucosa (SM). “LP or deeper” considered adequate depth to detect BGM, if present.

Results: There were no differences between cohorts for proportion of biopsies containing “LP or deeper”: ablation-naïve USE (90%), post-PDT (88%), post-RFA NSE (91%)(p=NS) or proportion of biopsies containing “MM or deeper”: ablation-naïve USE (7%), post-PDT NSE (16%), post-RFA NSE (14%)(p=NS). No BGM was noted in any biopsy.

Conclusion: While BGM after ablation for BE is an infrequent finding, its occurrence raises concern. A further concern is the possibility that post-ablation NSE is altered (i.e. fibrosis) and limits the depth of biopsy. This hypothesis, if true, could suggest that BGM occurs more frequently than reported. We evaluated squamous biopsies from control (USE) and post-ablation (NSE) patients. We compared the proportion of biopsies containing “LP or deeper” in each group (adequate depth to detect BGM.) The majority of NSE biopsies after PDT and RFA were “LP or deeper” (88% and 91%, respectively) and there were no biopsy depth differences between NSE and controls (USE). Therefore, the hypothesis that biopsies from post-ablation NSE are different from controls and of inadequate depth to detect for BGM is refuted. The reported rates of BGM after ablative therapy are likely reflective of the true rates of BGM.

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

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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.

5.10. 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)

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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 insignificant 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.

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

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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.

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

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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.

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

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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 Query	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.

5.14. 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.