ORIGINAL ARTICLE

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

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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. (Gastrointest Endosc 2008;■:■-■.)

Abbreviations: BE, Barrett's esophagus; CR, complete response; CR-D, biopsy specimens negative for any dysplasia; CR-HGD, biopsy specimen fragments negative for HGD; CR-IM, biopsy specimens negative for IM; GE, gastroesophageal; HGD, high-grade dysplasia; IM, intestinal metaplasia; IMC, intramucosal adenocarcinoma; IQR, interquartile range; LGD, low-grade dysplasia; PDT, photodynamic therapy.

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Barrett's esophagus (BE) is a metaplastic change in the esophageal epithelium that results from acid-and-bile-induced injury and inflammation. Under such conditions, the normal esophageal squamous epithelium is replaced by a specialized intestinal epithelium, also known as intestinal metaplasia (IM).[1-3] Because chronic injury continues over time, the metaplastic tissue may accumulate genetic abnormalities, which results in the phenotypic expression

of histologic features of dysplasia and, in some cases, cancer.[4,5] Once high-grade dysplasia (HGD) is present, the risk for developing adenocarcinoma is 2% to 10% per patient per year.[6-10] Further, the presence of mucosal nodularity and multifocal HGD predicts a higher risk of progression compared with that associated with flat, unifocal disease.[3] This recognized risk for progression to cancer in patients with BE HGD is the basis for offering therapeutic intervention to completely eliminate not only the dysplastic tissue but also the surrounding metaplastic tissue.

Although management for BE HGD has historically included intensive surveillance endoscopy every 3 months for highly selected patients,[11,12] therapeutic management strategies are currently preferred for most patients. These therapies include EMR,[13,14] endoscopic ablation by using photodynamic therapy (PDT)[15,16] or other thermal or nonthermal modalities,[17-19] and esophagectomy.[3] Each therapeutic strategy has specific reported limitations, such as technical complexity and stricture formation (EMR), buried glandular mucosa, photosensitivity, stricture formation (ablation), and operative morbidity and mortality (surgery). The primary benefit shared by the endoscopic techniques is esophageal preservation, whereas esophagectomy has merit because of resection of the entire organ, which allows for complete histologic assessment and removal of all epithelial neoplasia.

Circumferential ablation with a balloon-based radiofrequency device is a more recently available endoscopic ablation technique for BE HGD.[20-24] This patient registry assesses the safety and effectiveness of this ablative modality for the treatment of BE HGD at 16 U.S. academic and community institutions.

Capsule Summary

What is already known on this topic

- Endoscopic therapies for Barrett's esophagus with high-grade dysplasia (BE HGD) include mucosal resection, ablation with photodynamic therapy or other thermal modalities, esophagectomy, and the recently added circumferential ablation with balloon-based radiofrequency device.

What this study adds to our knowledge

- In a multicenter study of 142 patients with BE HGD treated with circumferential ablation, the stricture formation rate was 0.4%; in 92 patients who had at least 1 follow-up biopsy session, 90.2% were free of HGD, 80.4% were free of any dysplasia, and 54.3% were free of metaplasia.

PATIENTS AND METHODS

Study design

This clinical protocol was approved by a central institutional review board, which allowed chart review at 16 participating and approved institutions for patients who had undergone circumferential ablative therapy for BE HGD in the previous 3 years. The institutional review board panel approved a waiver for patient-informed consent for data collection for this study, although each patient had signed a separate institution-specific informed consent form for the endoscopy procedure. Each site reported having a comprehensive esophageal program that typically includes therapeutic endoscopy (EUS, PDT, and EMR), experts in GI pathology, and a foregut surgery program.

Patients

The registry included consecutive adult patients from each institution who met the following criteria: (1) a baseline finding of endoscopically identifiable BE, (2) histologic evidence of HGD in biopsy specimens obtained from the BE region, (3) confirmation of HGD by a second expert pathologist at the same institution, (4) eligibility for EMR if indicated, and (5) eligibility for ablative therapy (no varices or no prior esophageal radiation therapy or surgery other than fundoplication). If nodular disease was present, then the patients underwent an EMR before ablative therapy for staging and to render the epithelium flat for subsequent ablation. All the patients typically had 1 or more of the following to exclude adenocarcinoma: a CT of the chest and the abdomen, an EUS, and/or an EMR. If an EMR was performed before ablation, then histologic persistence of HGD in the remaining BE was confirmed with a biopsy.

Study device

Endoscopic circumferential ablation was performed with a balloon-based radiofrequency energy electrode array catheter introduced in a side-by-side manner with an endoscope (HALO^{360} system, BÂRRX Medical, Inc, Sunnyvale, Calif). The electrode array is 3 cm in length and contains multiple tightly spaced bipolar pairs (Fig. 1). An energy generator is used to inflate the balloon and to deliver ablative energy to the targeted tissue. Dosimetry to the tissue is fixed at 12 J/cm^2 (energy density) and controlled by the energy generator, as is the pressure used to inflate the balloon.

Pathology

Baseline and follow-up esophageal biopsy specimens were processed and interpreted at each institution. Specimens were fixed in formalin, embedded in paraffin wax, and stained with hematoxylin and eosin. BE was confirmed by the presence of goblet cells within a columnar-lined epithelium in the esophageal body. All biopsy specimens were reviewed by at least two expert pathologists to confirm the initial presence of metaplasia, low-grade dysplasia (LGD), HGD, or cancer (HGD required

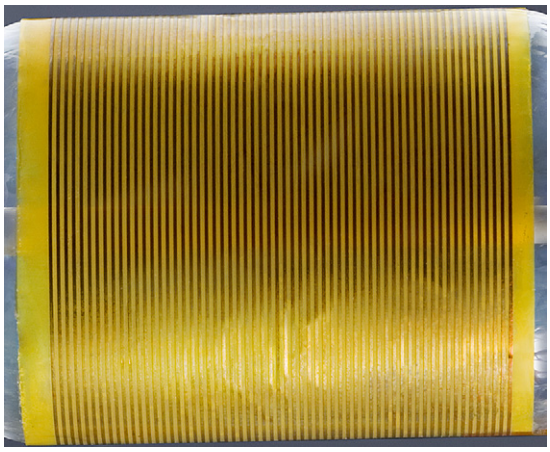

Figure 1. Magnified view of electrode array, showing multiple bipolar electrodes with approximately 250-micron spacing.

for enrollment), as well as the histologic response to therapy. Accepted histologic findings for HGD include nuclei that are markedly enlarged, hyperchromatic, and crowded, with loss of polarity. The glandular crypts are significantly distorted and may display branching.

Ablation procedure

Circumferential ablation procedures were performed on an outpatient basis. Most patients received conscious sedation, although selected patients received propofol or general anesthesia based on previous issues with upper endoscopies, physician preference, or comorbidity. During an upper endoscopy, the esophagus was irrigated with dilute acetic acid to highlight the areas of BE. The total length of the BE segment was then measured from the most proximal columnar tissue margin to the top of the gastric folds. The inner diameter of the targeted esophagus was measured by using a noncompliant sizing balloon coupled with a pressure/volume algorithm within the energy generator. Based on the inner diameter measurement, an ablation catheter of appropriate size was selected (22, 25, 28, 31, or 34 mm).

By using a guidewire, the ablation catheter was introduced into the esophagus, followed by the endoscope in a side-by-side manner. By using endoscopic visualization, the proximal edge of the electrode was positioned 1 cm above the proximal margin of the BE segment, automatically inflated to approximately 0.5 atm, and a preset dose of ablative energy delivered (12 J/cm^2, 40 W/cm^2). Successive ablations were performed by moving proximal to distal in 3-cm increments, avoiding overlap between segments, until reaching the gastric folds. The entire ablation zone was then treated a second time, thereby providing all targeted areas of BE with 2 applications of energy. Some centers reported cleaning the ablation catheter surface in the stomach (with irrigation) before the second pass, but this was not uniformly performed. After ablative treatment, all patients received high-dose proton pump inhibitor therapy with twice daily dosing.

Follow-up ablation and biopsy

After the primary ablation session, the patients underwent an endoscopy at approximately 3-month intervals. If persistent BE was evident, then another circumferential ablation was performed. If the esophagus appeared reconstituted with squamous epithelium, then 4-quadrant biopsy specimens were obtained every 1 to 2 cm of the original BE-segment length. Endoscopic images from a representative registry patient are shown in Figure 2.

Data collection and analysis

Data were collected from each institution for consecutive patients with BE HGD treated with circumferential ablation between September 2004 and March 2007. The following parameters were entered into the registry database by each site: age at first ablation, sex, baseline endoscopic length of BE, history of prior EMR with histologic findings, the number of ablation procedures, the worst histologic grade at the last postablation biopsy session (normal squamous mucosa, nondysplastic IM, LGD, HGD, or cancer), the number of months from the primary ablation to the last biopsy, the presence of buried glandular mucosa in any follow-up biopsy, and complications related to the ablation procedure. All treated patients were considered for purposes of the safety analysis, whereas only those with at least one postablation endoscopy with biopsies were included in the effectiveness analysis.

The effectiveness outcomes were histology based and derived from the last available endoscopy with a biopsy session. A complete response (CR) was considered for 3 separate outcomes: (1) all biopsy specimen fragments 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). The percentage of patients in the efficacy analysis cohort with a CR for each outcome is reported.

If biopsy specimens within 3 months of the primary ablation revealed adenocarcinoma, then the case was deemed a prevalent cancer, and the patient was included in the safety analysis but not the effectiveness analysis.

RESULTS

A total of 142 patients (125 men; median age 67 years, interquartile range [IQR] 59-75 years) with confirmed BE HGD underwent endoscopic circumferential ablation. The baseline median endoscopic BE length was 6 cm (IQR 3-8 cm). A prior EMR was performed in 24 patients (17%), 5 of whom demonstrated intramucosal adenocarcinoma (IMC) with negative deep and lateral margins. The patients underwent a median of 1 ablation session (IQR 1-2).

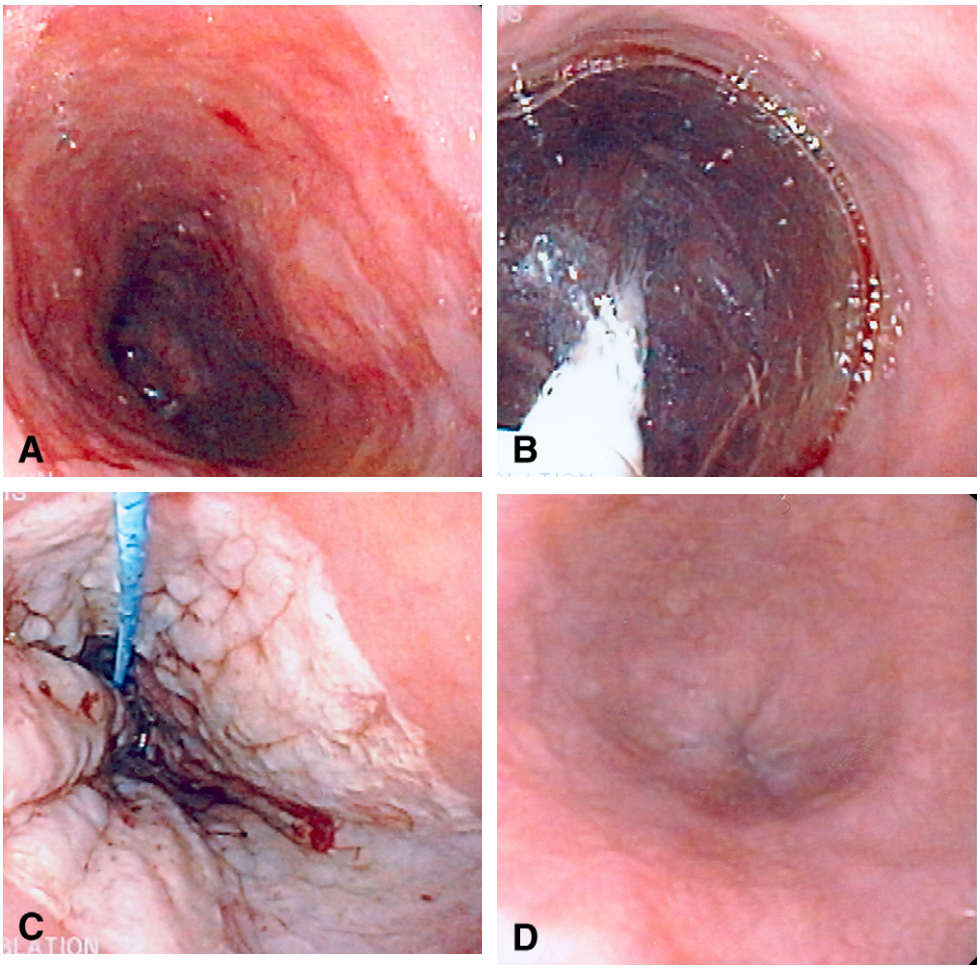

Figure 2. Endoscopic images of study patient. **A,** Circumferential segment of BE HGD at baseline. **B,** Balloon-based ablation catheter inflated within the BE segment. **C,** Immediate appearance of ablation zone. **D,** Healed ablation zone with normal squamous mucosa appearance on endoscopy 3 months after ablation with all biopsy specimens negative for IM.

No serious adverse events occurred in the safety analysis cohort (n = 142). Of a total of 229 ablations, there was 1 stricture noted at a follow-up endoscopy (0.4% incidence) in an asymptomatic patient who required no dilation. Two patients (1.4%) underwent an esophagectomy after the 3-month observation period. Both patients had a normal EUS at baseline and no evidence of nodularity on baseline endoscopy. In one of the patients, the 3-month biopsy specimens of flat, residual, columnar mucosa (after ablation) showed residual HGD, and both the patient and the physician opted for an esophagectomy; surgical pathology showed IMC. In the second patient, a nodule noted on an endoscopy at 3 months was removed with EMR and revealed IMC. Again, both the patient and the physician opted for an esophagectomy; surgical pathology showed IMC.

Ninety-two of the 142 patients had at least 1 follow-up biopsy session that qualified them for the efficacy cohort. The efficacy cohort did not differ significantly in baseline demographics and BE length from the safety cohort as a whole, with median age 68 years, IQR 59 to 75 years, and median BE length 6 cm, IQR 5 to 8 cm for the group. The median duration of follow-up from the primary ablation to the last available endoscopic biopsy was 12 months [IQR 8-15 months]). A CR-HGD was achieved in 90.2% of patients, CR-D in 80.4% (9 patients without HGD had persistent LGD at last follow-up), and CR-IM in 54.3%. Buried glandular mucosa was not evident in any esophageal biopsy specimen obtained from the reepithelialized esophagus after ablation.

A subgroup analysis of the histologic response rates between those patients with a baseline EMR (n = 24) versus those with no baseline EMR (n = 68) revealed similar results. The CR-HGD was 87.5% (EMR) versus 90.8% (no EMR). The CR-dysplasia was 81.3% (EMR) versus 80.3% (no EMR). The CR-IM was 62.5% (EMR) versus 52.6% (no EMR). Of the 5 patients with baseline mucosal adenocarcinoma resected with an EMR before ablation, all achieved CR-IM on the last biopsy. To date, no patient from the effectiveness cohort has been referred for an esophagectomy. All registry patients with any persistent

IM, regardless of dysplasia status, remain in the ablative treatment and biopsy process until achieving CR-IM.

DISCUSSION

This registry, which involved 16 academic and community centers and 142 patients, is the first to report on the use of circumferential ablation for BE HGD and shows promising initial results, with 90.2% of patients from the efficacy cohort achieving a CR-HGD, with a median 12 months of follow-up. There were no serious adverse events. One patient developed an asymptomatic stricture after ablation. No cancers were detected beyond the 3-month follow-up prevalence window described in the Patients and Methods section. A prior EMR did not influence the likelihood of achieving a CR for any end point.

The 2 main strengths of this registry study include the large number of patients with the relatively uncommon condition of BE HGD and the multicenter contribution from both tertiary referral sites and community-based programs. In contrast, the main limitation of this registry is the lack of centralized pathology review. A mitigating factor to this limitation is that baseline and follow-up pathology were reviewed by 2 pathologists. Other limitations include the nonrandomized design without a control arm, a lack of standardization between centers for the ablation and biopsy technique, and a relatively short-term follow-up (12 months). Several prospective randomized, controlled trials, as well as cohort trials, are currently underway in the United States and Europe, with a more rigorous design, standardization of the ablation and biopsy technique, and centralized expert GI pathologist adjudication committees. Outcomes from these studies may or may not corroborate our findings. Nevertheless, given its nature, our trial represents a real-life experience on the use of this ablative modality in the management of BE HGD.

Although other ablative therapy interventions, such as PDT, argon plasma coagulation, and multipolar electrocoagulation, have been associated with reports of buried glandular mucosa,[15,17,19] we did not discover any buried glands related to circumferential radiofrequency ablation. One could argue that this absence of buried glands is because of a lack of a central pathology methodology and a lack of an agreed-upon definition of buried glands for this registry. However, other investigators who studied the circumferential ablation technique also reported an absence of buried glands in follow-up biopsy specimens. For example, Sharma et al[21] followed 102 patients for 1 year after circumferential ablation and found no buried glands in 4306 biopsy specimen fragments. Sharma et al[21] and other investigators proposed that uniformity of ablation achieved with the electrode array design of the study device, balloon effacement of the target tissue, and standardization of energy and power density dosimetry contribute to the absence of buried glandular mucosa.[20-24]

Although there were no serious adverse events and only one stricture reported in this registry, it should be noted that there is the potential for complications with any therapeutic intervention for BE HGD. One limitation of the registry is that we did not use standardized adverse event–tracking forms to assist in the collection and classification of adverse events; therefore, some events may have been underreported. However, as with the absence of buried glands noted after ablation, the rather low incidence of adverse events may be attributed, in part, to the ablation depth control associated with the study device. Several animal and human dosimetry trials have demonstrated that the doses used to treat BE HGD in this trial penetrate only to the muscularis mucosae.[20,23,24]

The CR-IM reported for this technique from other trials is higher than that observed in this registry. Sharma et al[21] reported a 70% CR-IM at 1 year for patients with long-segment nondysplastic BE, whereas Fleischer et al[22] reported a 98.2% CR-IM for the same group at 2.5 years after the addition of a focal ablation adjunctive technique. In this study, the CR-IM was lower (54.3%), although CR-HGD and CR-D were much higher. For those patients with residual IM in this registry, it was our observation that this was typically limited disease in the form of small islands or tongues of BE. One hypothesis for the persistence of IM could be that adherent coagulum on the ablation electrode accumulated during the first and second ablation passes and thereby prevented adequate contact of the electrodes with the targeted esophageal epithelium. Based, in part, on these findings, many physicians now remove the catheter between ablation passes to clean both the electrode and the ablated zone (by using an EMR cap or water irrigation), which may augment the effectiveness of the second ablation. Another hypothesis for the lower than expected CR-IM is that this registry was limited to the use of circumferential ablation only, which we consider excessive for re-treatment of small residual islands and suboptimal for treating flared areas of the gastroesophageal (GE) junction in some patients with a large hiatal hernia. To solve these challenges, an endoscope mounted focal ablation device recently became available to more directly ''touch-up'' residual areas of IM and treat the flared GE junction. Also, the outcomes of this registry represent a ''point-in-time'' interim report, rather than a completed trial. Many patients considered in the efficacy cohort have not yet completed therapy and would be expected to improve their individual outcomes with further ablative therapy and observation.

By using lessons learned thus far in this registry, we continue to treat new and existing patients and to collect outcomes data under the auspices of this trial protocol by using serial circumferential and additional focal ablation, with the objective to achieve a CR for each histologic end point for each patient. Based on our results from this registry, we conclude that circumferential ablation has a role in the comprehensive treatment of patients with BE HGD. In

our experience, the technique compares favorably with PDT, wide-field EMR, and esophagectomy, with respect to safety, patient tolerability, and the histologic CR outcomes that we tracked. Further, there may also be an adjunctive role for circumferential ablation and EMR, with EMR used to remove visible abnormalities for staging followed by circumferential ablation to eliminate all remaining dysplastic and metaplastic disease. Additional studies are underway to confirm our registry results.

In conclusion, the results of our study suggest that endoscopic circumferential ablation is a promising modality for the treatment of BE HGD, because the intervention achieved a CR-HGD of 90.2% at an average of 1-year follow-up while avoiding many of the adverse events associated with other modalities currently used in this disease.

DISCLOSURE

The following authors report that they have no disclosures relevant to this publication: S. R. Freeman, R. E. Pruitt, S. M. Urayama, F. Gress, D. A. Pavey, M. S. Branch, T. J. Savides, A. G. Bohorfoush, S. C. Pace, S. R. DeMeester, V. E. Eysselein. The following authors have disclosed actual or potential conflicts: R. A. Ganz has licensed intellectual property related to the study device, serves on the board of directors and has an equity position in BÂRRX Medical, Inc. B. F. Overholt, V. K. Sharma, D. E. Fleischer, N. J. Shaheen, C. J. Lightdale, K. J. Chang, V. R. Muthusamy, and M. Panjehpour receive research support from BÂRRX Medical, Inc. G. Triadafilopoulos receives lecture honoraria from BÂRRX Medical, Inc.

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