



May 31, 2011

Maria Chaves  
Project Manager  
California Technology Assessment Forum  
50 Beale Street  
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Dear Ms. Chaves,

The American Gastroenterological Association (AGA), American College of Gastroenterology (ACG) and American Society for Gastrointestinal Endoscopy (ASGE), representing virtually all practicing gastroenterologists in the United States, are pleased to submit this comment letter to the California Technology Assessment Forum (CTAF) in regards to the agenda item on **Radiofrequency Ablation (RFA) for the Treatment of Dysplastic Barrett's Esophagus (BE): Low-Grade Dysplasia (LGD)**, to be discussed at the June 29, 2011 CTAF meeting in Los Angeles.

The American Gastroenterological Association (AGA) Medical Position Statement (MPS) on the Management of Barrett's Esophagus states that RFA therapy for patients with BE containing LGD leads to reversion to normal-appearing squamous epithelium in 90% of cases (Quality of Evidence: High) and that RFA can lead to reversion of the metaplastic mucosa to normal appearing squamous epithelium in a high proportion of subjects at any stage of BE. The data to date show that reversion to squamous epithelium can persist for up to 5 years (Quality of Evidence: High). The Medical Position Statement states that RFA should be an option for treatment of BE containing LGD confirmed by two pathologists.<sup>1</sup>

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) 2010 practice guideline states that BE with LGD may be effectively treated with RFA (Level I Evidence).<sup>2</sup> The American College of Gastroenterology (ACG) 2008 practice guidelines

also note that effective technologies such as RFA therapy are among new options physicians should consider and have available when treating patients with BE.<sup>3</sup>

It is our collective recommendation that RFA is a recommended management strategy for patients with BE containing low-grade dysplasia confirmed by at least two pathologists and that RFA for the treatment of BE containing LGD meets CTAF criteria one through five.

**CTAF Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.**

*The Technology Assessment (Radiofrequency Ablation as a Treatment for Dysplastic Barrett's Esophagus) published after the February 2010 CTAF Panel Meeting states that RFA for LGD and HGD meets TA Criterion 1. We concur.*

Three devices for administering RFA for BE have been approved by the Food and Drug Administration (FDA): the HALO<sup>360</sup> System (cleared in 2005), the HALO<sup>90</sup> System (cleared in 2006), and the HALO<sup>FLEx</sup> System (cleared in 2009). The HALO Coagulation Systems have 510k clearance from FDA for the coagulation of bleeding and non-bleeding sites in the gastrointestinal tract including but not limited to BE.

The HALO<sup>360</sup> Coagulation System (BARRX Medical Inc., Sunnyvale, CA) is marketed to be used in the coagulation of bleeding and non-bleeding sites in the gastrointestinal tract including but not limited to the esophagus. The HALO<sup>360</sup> Ablation Catheter can provide radiofrequency energy fully around the esophageal circumference, as well as in smaller areas of the esophagus. The HALO<sup>90</sup> Coagulation System (BARRX Medical Inc., Sunnyvale, CA) is a similar device that enables physicians to provide primary treatment for short and intermediate length segments of BE or provide secondary treatment after ablation with the HALO<sup>360</sup> System (or other therapeutic devices) Each of these systems include endoscopic catheters used by physicians to ablate (eradicate) the diseased BE epithelium either circumferentially (HALO<sup>360</sup> catheters) or focally (HALO<sup>90</sup> catheters).<sup>4,5</sup>

**CTAF Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.**

*The Technology Assessment (Radiofrequency Ablation as a Treatment for Dysplastic Barrett's Esophagus) published after the February 2010 CTAF Panel Meeting states that RFA for LGD and HGD meets TA Criterion 2. We concur.*

There are a number of published peer-reviewed papers evaluating the efficacy of radiofrequency ablation in the treatment of dysplastic BE, including patients with LGD. These studies include two randomized controlled studies, multi-center prospective trials, single-center case series and registries. Due to the quality of these studies, the

number of patients involved in the studies, the number of studies and the diversity of study designs, we submit that the scientific evidence permits conclusions concerning the effectiveness of RFA for the treatment of BE with LGD.

Shaheen, et al. (2009) reported on 127 patients with LGD or HGD randomized to receive sham vs. RFA. At one year follow-up, patients with LGD or HGD treated with RFA had a higher rate of complete eradication of intestinal metaplasia (IM) and dysplasia and less disease progression as compared to sham. In the intention-to-treat analyses, among patients with LGD, 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 ( $P < 0.001$ ). Overall, 77.4% of patients in the ablation group had complete eradication of IM, as compared with 2.3% of those in the control group (ITT,  $P < 0.001$ ). 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%,  $P = 0.045$ ).<sup>6</sup>

A second randomized controlled trial, by van Vilsteren, et al. (2011) compared the safety and efficacy of RFA vs. endoscopic mucosal resection (EMR) for BE with HGD and early cancer. This study, while including more severe grades of dysplasia than LGD, is pertinent to TA 1 as it is a level one study design and its results comport with those of Shaheen in terms of effectiveness outcomes of RFA in dysplastic BE. RFA and EMR groups had similar complete response for IM and dysplasia at 2 years, however, RFA had a significantly better safety profile than EMR.<sup>7</sup>

Additional papers evaluating the effectiveness of RFA in the treatment of dysplastic BE, including patients with LGD, include:

- Wani, et al. (2009) reported that the annual rate of progression to esophageal adenocarcinoma in patients with LGD who were undergoing management with surveillance-only (natural history) was 1.7% per patient per year, compared to patients who underwent ablative therapy (0.16% per patient per year). This yielded a number of LGD patients needed to treat to avoid 1 cancer in the five year follow-up of only 13.<sup>8</sup>
- Shaheen, et al. (2011) reported on the long-term outcomes of the randomized trial described in the previous section at 2 and 3 years. The long-term outcomes yielded no new safety concerns. RFA induced high rates of eradication of both IM and dysplasia (>90%). Disease progression was rare compared to controls. Kaplan-Meier survival curves for histological response showed that >90% of patients retain their complete response for dysplasia eradication after initial cure for a mean of 3 years. Specific to the LGD cohort, complete response for dysplasia eradication was achieved in 98% of patients at 2 years and 100% of patients at 3 years.<sup>9</sup>

- Sharma, et al. (Am J Gastroenterol, 2009) reported on the Mayo Clinic experience using RFA to treat dysplastic BE. Of 63 patients, 39 had confirmed LGD at baseline. For the LGD cohort, a complete response for dysplasia eradication was achieved in 95% of patients with an acceptable safety profile.<sup>10</sup>
- Lyday, et al. (2010) reported on the use of RFA in 429 patients with BE treated with RFA. In this trial, 24% of patients had dysplastic BE at baseline (about half LGD) and 100% of these patients achieved a complete response for dysplasia eradication at the primary endpoint.<sup>11</sup>

A number of additional papers report on use of combined modality treatment of patients with BE containing HGD and early cancer, where nodules are first removed with EMR followed by RFA 8 weeks later. In some of these HGD/cancer patients, the entry grade of patients after EMR and prior to RFA included patients with LGD as the worst grade of dysplasia prior to RFA. In these studies, at the primary endpoint, the complete response rate of dysplasia eradication was 90% or greater.<sup>12,13, 14,15,16,17,18,19</sup>

**CTAF Criterion 3: The technology must improve the net health outcomes.**

*The Technology Assessment (Radiofrequency Ablation as a Treatment for Dysplastic Barrett's Esophagus) published after the February 2010 CTAF Panel Meeting states that RFA for LGD and HGD meets TA Criterion 3. We concur.*

We submit that the net health outcome in the management of patients with a high risk neoplastic lesion such as BE LGD is achievement of complete eradication of the lesion. In the case of BE with confirmed LGD, the risk of progression to esophageal adenocarcinoma (EAC) is unacceptably high (approximating that of HGD in recent trials when the baseline LGD diagnosis is confirmed by two pathologists) and the morbidity and mortality associated with EAC and esophagectomy is particularly grim. The evidence associated with RFA for BE shows that both dysplasia and IM can be completely eradicated in at least 90% of treated patients and that such reversion to normal squamous epithelium persists for at least 5 years. For this reason, the AGA Medical Position Statement (2011) states that RFA should be an option for treatment of BE with LGD confirmed by two pathologists. We therefore submit that RFA for BE with LGD meets TA Criterion 3.<sup>1</sup>

Elimination of dysplasia is a health outcome that has been accepted for many ablative technologies. The ASGE evidence-based technology assessment concluded that mucosal ablation techniques including RFA are effective in treating dysplastic BE.<sup>20</sup> The literature reporting on the safety and efficacy of RFA for BE permits conclusions concerning the effectiveness of the technology and that RFA improves health outcomes for patients with LGD.

Risk of LGD progression to esophageal adenocarcinoma:

- Wani, et al. (2009) determined that the incidence of EAC in LGD patients was 16.98 per 1000 patient-years or approximately 1.7% per patient-year.<sup>8</sup>
- Published studies have reported higher rates of progression of LGD when initial readings have been confirmed by expert pathologists, thereby eliminating or minimizing the rate of false positive diagnoses of LGD:
  - Skacel, et al. (2000) found that LGD progressed to HGD or EAC at a rate of 12.9% per patient year, and to EAC at 3.7% per patient year.<sup>21</sup>
  - Gatenby, et al. (2009) reported that LGD progressed to HGD or EAC at 4.6% per patient year and to EAC at 2.7% per patient year.<sup>22</sup>
  - Lim et al. reported that LGD progressed to HGD or EAC at a rate of 3.4% per patient year.<sup>23</sup>
  - Veith, et al. reported that LGD progressed to HGD or EAC at a rate of 17.2% per patient year, and to cancer at a rate of 14.6% per patient year.<sup>24</sup>
  - Curvers, et al. studied patients diagnosed with LGD between 2000 and 2006 in six non-university hospitals and confirmed the diagnosis with two expert pathologists. Patients with confirmed LGD progressed to HGD or cancer at a rate of 85% over 109.1 months (9.3% per patient per year).<sup>25</sup>
  - von Rahden, et al. followed 1,438 BE patients (1,381 non-dysplastic IM, 57 confirmed LGD) over a median follow-up period of 24 months. During the follow-up period, the rate of progression to HGD or cancer was 0.6% in the non-dysplastic group and 9.7% in the LGD group (per patient per year), indicating that LGD behaves much more aggressively than IM and much more akin to the progression rate of HGD to cancer.<sup>26</sup>

These data on the rate of LGD progression to EAC are highly relevant when evaluating the risk-benefit of a therapeutic management strategy, such as RFA, for a LGD BE patient population. This high rate of progression from confirmed LGD to EAC supports the premise that the net health outcome for LGD is complete eradication of the lesion.

#### Evidence for magnitude of complete eradication of the neoplastic lesion

As stated in the section for TA Criterion 2, there are outcomes data from two randomized trials and a number of prospective open label trials demonstrating the safety and effectiveness of RFA for BE, including cohorts with LGD. Data from these trials demonstrate high rates of complete response of IM and dysplasia eradication in patients with dysplastic BE including LGD, and an acceptable low rate of adverse events.

In addition to the efficacy outcomes data indicating that RFA is associated with a high rate of complete eradication of IM and dysplasia (inclusive of patient cohorts having BE with LGD), Inadomi, et al. in a cost-utility study found that ablation for LGD was the preferred strategy versus the established alternative of surveillance (more effective, most cost-effective) if only 28% of patients could achieve a complete eradication of dysplasia and if 40% of patients achieved a complete eradication of IM. These clinical thresholds

for RFA to be cost-effective for treating BE with LGD are quite low, and have been significantly surpassed in published prospective clinical trials. In the LGD cost-utility sensitivity analysis of Inadomi's paper, the preferred strategy for LGD was RFA, even when assuming that all RFA patients would continue surveillance.<sup>27</sup>

- Shaheen, et al. evaluated patient quality of life parameters in patients with dysplastic BE at baseline in their RCT, and again at one year after randomization to either RFA or sham. Compared with the sham group, patients treated with RFA had significantly less worry about esophageal cancer ( $P = 0.003$ ) and esophagectomy ( $P = 0.009$ ). They also had significantly reduced depression ( $P = 0.02$ ), general worry about the condition of their esophagus ( $P \leq 0.001$ ), impact on daily QoL ( $P = 0.009$ ), stress ( $P = 0.03$ ), dissatisfaction with the condition of their esophagus ( $P \leq 0.001$ ), and impact on work and family life ( $P = 0.02$ ). The authors suggest that these QoL improvements may be related to the significant difference between RFA and sham for achieving complete eradication of IM and dysplasia.<sup>28</sup>

**CTAF Criterion 4: The technology must be as beneficial as any established alternatives.**

*The Technology Assessment (Radiofrequency Ablation as a Treatment for Dysplastic Barrett's Esophagus) published in advance of the February 2010 CTAF Panel Meeting stated that RFA for LGD does not meet TA Criterion 4. We respectfully disagree.*

Prior to the availability of outcomes data related to RFA for BE containing LGD, there was only one recommended management strategy for patients with BE containing LGD. That strategy was intensive endoscopic surveillance every 6 to 12 months in order to detect neoplastic progression to HGD and EAC. There have been no randomized trials demonstrating that surveillance in this patient population (LGD) reduces cancer incidence or patient morbidity, and no cost-utility study has shown that surveillance in this LGD population is cost-effective.

The randomized sham-controlled trial by Shaheen, et al. (2009) directly compared RFA vs. intensive surveillance in patients with confirmed LGD in BE. RFA resulted in a high rate of complete eradication of both IM and dysplasia, and less disease progression, as compared to sham control. This comparative trial shows that RFA for patients with LGD in BE is as beneficial as any established alternative (intensive surveillance).<sup>6</sup>

There were several statements in the 2010 TA cited by the reviewer as the basis for the conclusion that RFA for LGD does not meet TA Criterion 4. These are addressed as follows:

- *The 2010 TA asserts that RFA for LGD may not be warranted because not all patients with LGD will progress to cancer. We have provided the evidence showing that*

LGD can progress to HGD and EAC, a devastating condition for patients. We also know that most of the oncogenetic changes that are present in HGD and EAC are also commonly present in the LGD (neoplastic) cells, although morphologically (histologically) the LGD cells have just begun to express the more advanced phenotype in response to these genetic alterations.

- *The 2010 TA asserts that RFA for LGD may not be warranted because some reports indicate that LGD may regress without intervention.* Expert pathologists and endoscopists indicate that regression is a false explanation for not finding LGD on a subsequent biopsy. Rather, this finding may be due to: 1) biopsy sampling error (missed dysplasia) on subsequent endoscopy due to random sampling methods, and 2) interobserver variability in grading the histology (false positive baseline LGD).

Other alternatives which are not recommended for LGD are esophagectomy and photodynamic therapy. Esophagectomy is associated with substantially greater mortality, particularly with surgeons with low volumes of procedures.<sup>29</sup> If volumes of esophagectomy were judged as medium (5-7 per year) to very low (<2 per year), surgical mortality rates were respectively 16.9-23.1%, clearly indicating that esophagectomy is not a benign procedure. Even with high volume surgeons (>19), surgical mortality rates were 8.1%.<sup>30, 31</sup>

In comparing RFA with other endoscopic ablative therapies, a large scale multicenter randomized controlled trial found that the morbidity, in particular in regards to esophageal stricture formation, was 30% in the photodynamic therapy treatment arm and only 6% in the RFA treatment arm. In addition, photodynamic therapy was associated with cutaneous photosensitivity in two thirds of treated patients.<sup>29</sup>

**CTAF Criterion 5: The improvement must be attainable outside the investigational settings.**

*The Technology Assessment (Radiofrequency Ablation as a Treatment for Dysplastic Barrett's Esophagus) published in advance of the February 2010 CTAF Panel Meeting stated that RFA for LGD does not meet TA Criterion 5. We respectfully disagree.*

A number of single center case series and registries have been published related to RFA for BE Lyday, et al. reported on their community practice experience of 429 patients with BE of all grades treated with RFA. Of the total patients enrolled, 24% had dysplasia as their entry diagnosis, about half of which were LGD. The investigators report that 100% of these patients achieved a complete response for dysplasia eradication (CR-D) and 78% a complete response for IM (CR-IM).<sup>11</sup>

Endoscopic RFA for BE including LGD is presently available as standard of care at approximately 600 U.S. hospitals and 100 non-U.S. hospitals. Based on information provided by the manufacturer, we estimate that 80,000 RFA procedures for BE have

been performed in the U.S. and Europe in the last 8 years in both the academic and community practice settings. This adoption and utilization by a wide variety of gastroenterologists and endoscopic surgeons are indirect measures of the safety, efficacy, and utility of this intervention.

In Shaheen, et al. (2009), investigators included community practitioners. There were no differences in safety or efficacy outcomes between an academic institution and a community practice.<sup>6</sup>

A national U.S. registry of RFA for BE currently has 156 centers and has enrolled over 5,000 patients since 2007. Of these patients, 2,500 have dysplastic BE at study entry and approximately 1,250 of these had LGD. In this national registry, community practices represent 80% of the investigative sites. There is no difference in the complete histological response rate or safety outcomes (interim analysis) according to site of service or practice type. (Digestive Disease Week, May 7, 2011, Chicago IL).

### **Summary**

Radiofrequency ablation for BE is an FDA approved technology.

The available scientific evidence permits conclusions concerning the effectiveness of RFA regarding health outcomes in patients with BE containing LGD and confirm the initial findings on RFA in ACG's 2008 practice guidelines. The AGA medical position statement recommends that RFA should be a therapeutic option for treatment of patients with confirmed LGD in BE.

RFA improves the net health outcome in patients with BE containing LGD, as demonstrated by the by the high rate of complete eradication of IM and dysplasia achieved in these patients combined with the potential of LGD to progress to HGD and EAC when left untreated.

RFA for BE containing LGD is as beneficial as the established alternative of intensive endoscopic surveillance, as compared directly in a RCT by Shaheen, et al. (2009).<sup>6</sup>

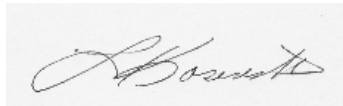
The results of RFA for BE are attainable outside of the investigational setting.

**In view of such, the AGA, ACG and ASGE recommend that the use of RFA for Barrett's Esophagus with low-grade dysplasia meets CTAF technology assessment criteria 1 through 5 for safety, effectiveness and improvement in health outcomes.**

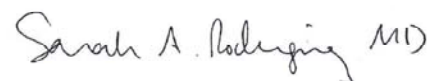
Thank you for your consideration of this important issue. If we may answer any questions, please contact Adam R. Borden, MHA, Manager of New Technologies and Reimbursement, AGA, at 301-941-2629 or [aborden@gastro.org](mailto:aborden@gastro.org); Brad Conway, Vice

President of Public Policy, ACG, at 301-263-9000 or [bconway@acg.gi.org](mailto:bconway@acg.gi.org); or Martha Espronceda, Quality and Coding Manager, ASGE, at 630-570-5613 or [mespronceda@asge.org](mailto:mespronceda@asge.org).

Sincerely,



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