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September 9, 2011

Allan J. Chernov, MD
Medical Director
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Dear Dr. Chernov,

The American Gastroenterological Association is the trusted voice of the GI community. Founded in 1897, the AGA has grown to include 17,000 members from around the globe who are involved in all aspects of the science, practice and advancement of gastroenterology. The AGA Institute administers the practice, research and educational programs of the organization.

The AGA Institute is pleased to offer comments on the clinical utility of radiofrequency ablation (RFA) for Barrett's esophagus (BE) with low-grade dysplasia (LGD) as a medically necessary treatment option. We believe the clinical literature and current recommendations demonstrate that RFA also shows a benefit in health outcomes for patients with BE with LGD confirmed by two pathologists and should be a treatment option for these patients. We would appreciate your review and consideration of this issue based on the information provided below.

The American Gastroenterological Association (AGA) released a Medical Position Statement (MPS) on BE in March 2011 recommending that RFA should be a treatment option for patients with HGD and patients with LGD confirmed by two pathologists. The MPS 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).¹

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%, $P = 0.045$).²

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.³

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 13.⁴
- 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.⁵
- 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.⁶

- 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.⁷

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.^{8,9, 10,11,12,13,14,15}

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.¹⁶ 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.

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.¹⁷
- 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.¹⁸
- Lim et al. reported that LGD progressed to HGD or EAC at a rate of 3.4% per patient year.¹⁹
- 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.²⁰
- 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).²¹
- 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.²²

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.

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.

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. 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).²

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.²³

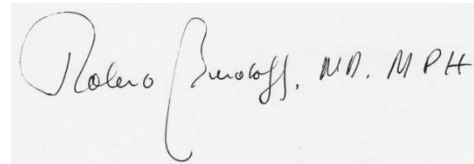
In summary, the scientific evidence is of adequate quality to allow conclusions to be drawn regarding the net health outcome, and the net health outcome of complete eradication of the high-risk epithelial lesion (dysplasia) has been shown to be improved/achieved. The technology has been compared head-to-head with surveillance alone for LGD patients in a randomized sham-controlled trial and demonstrated superior outcomes for eradication of the lesion. Further, when compared to surveillance alone, RFA for patients with LGD is the most cost-effective intervention. Lastly, as evidenced by Lyday, et al. and other single center reports, the net health outcomes of complete eradication of the lesion can be achieved outside of formal investigational settings. In view of such, the AGA Institute recommends that RFA is medically necessary as treatment option for patients with BE with HGD and patients with LGD confirmed by two pathologists.^{1,2,7}

Thank you for the opportunity to review and comment on this issue. Please do not hesitate to contact Adam R. Borden, MHA, Senior Manager of Technology and Reimbursement at the AGA Institute, at aborden@gastro.org should you have any questions. We look forward to your review.

Sincerely,



Lawrence R. Kosinski, MD, MBA, AGAF
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Robert Burakoff, MD, MPH, AGAF
Chair, AGA Public Affairs and Advocacy Committee



John M. Inadomi, MD, AGAF
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