



4930 Del Ray Avenue  
Bethesda, MD 20814-2513

PH 301-654-2055 MAIN  
FX 301-654-5920

member@gastro.org  
www.gastro.org

## THE AGA INSTITUTE

August 6, 2010

Virginia Calega, MD  
Vice President, Medical Management and Policy  
Medical Policy Department  
Highmark Blue Shield  
1800 Center Street  
Camp Hill, Pennsylvania 17011

### PRESIDENT

Ian L. Taylor, MD, PhD, AGAF  
SUNY Downstate Medical Center  
450 Clarkson Avenue, Box 97  
Brooklyn, NY 11203  
PH 718-270-3173  
FX 718-270-4074  
E [ian.taylor@downstate.edu](mailto:ian.taylor@downstate.edu)

### PRESIDENT-ELECT

C. Richard Boland, MD, AGAF  
PH 214-820-2692  
FX 214-818-9292  
E [rickbo@baylorhealth.edu](mailto:rickbo@baylorhealth.edu)

### VICE PRESIDENT

Loren Laine, MD, AGAF  
PH 323-409-7995  
FX 323-441-8352  
E [llaine@usc.edu](mailto:llaine@usc.edu)

### SECRETARY/TREASURER

J. Sumner Bell III, MD, AGAF  
PH 757-466-0165  
FX 757-363-2563  
E [sumner.bell@verizon.net](mailto:sumner.bell@verizon.net)

### PAST PRESIDENT

Gail A. Hecht, MD, MS, AGAF  
PH 312-996-1565  
FX 312-996-5103  
E [gahecht@uic.edu](mailto:gahecht@uic.edu)

### AGA FOUNDATION CHAIR

Nicholas F. LaRusso, MD, AGAF  
PH 507-284-1006  
FX 507-284-0762  
E [larusso.nicholas@mayo.edu](mailto:larusso.nicholas@mayo.edu)

### COUNCILLORS

John I. Allen, MD, MBA, AGAF  
Eugene B. Chang, MD, AGAF  
Sheila E. Crowe, MD, AGAF  
Francis M. Giardiello, MD  
Helen M. Shields, MD, AGAF  
F. Taylor Wootton III, MD, AGAF

### NATIONAL OFFICE

Interim Executive Vice Presidents  
Lynn P. Robinson  
Thomas J. Serena

### POSTGRADUATE COURSE

May 7-8, 2011  
Chicago, IL

### ANNUAL MEETING

May 7-10, 2011  
Chicago, IL

### SOCIETY PUBLICATIONS

*Gastroenterology*  
Editor: Anil K. Rustgi, MD  
*Clinical Gastroenterology  
and Hepatology*  
Editor: C. Mel Wilcox, MD

Dear Dr. Calega,

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 was recently notified by members who expressed concern about the Highmark Blue Cross Blue Shield's medical policy # Z-24 on Miscellaneous Services that states radiofrequency ablation (RFA) for Barrett's esophagus (BE) is currently considered investigational. We are contacting you in response to our member inquiry to request that the decision be reconsidered based on the rationale below.

Barrett's esophagus (BE) is defined as metaplasia of the esophageal epithelium, with normal squamous epithelium replaced by columnar epithelium containing goblet cells, also known as intestinal metaplasia (IM). This change is mainly associated with gastroesophageal reflux disease (GERD). Approximately 10% of patients with chronic reflux have BE, and the prevalence of the condition in a recent population

study was 1.6%. The condition is associated with an increased risk of esophageal adenocarcinoma. The incidence of this once rare cancer has increased by more than 500% since the 1970s. The cancer remains highly lethal, with a 5-year survival rate of less than 15%.<sup>1</sup>

Diagnosis of BE is based on endoscopic biopsy of the esophagus. Short-segment (less than 2 to 3 cm) and long-segment (greater than 2 to 3 cm) BE are distinguished solely on the length of metaplastic epithelium above the esophago-gastric junction. Schnell and colleagues (1992) reported that patients with short-segment BE exhibited the same incidence of esophageal cancer as their counterparts with long-segment BE. This provided a rationale for surveillance of patients with short-segment BE.<sup>2</sup>

Ablation is defined 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 neosquamous epithelium. The intent of eradicating all IM clones and stem cells, be they non-dysplastic, low grade dysplasia (LGD), or high grade dysplasia (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 lifelong surveillance.

The annual recurring risk for a patient with non-dysplastic intestinal metaplasia (IM) to develop esophageal adenocarcinoma (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 an analysis by Shaheen (2000) estimates the average risk to be about 0.5%. 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 (2009) reported the risk for progression to cancer from IM, LGD and HGD was 0.6%, 1.7%, and 6.6% per patient-year of follow-up, respectively. In a patient population with BE-HGD, 16-59% develop EAC, depending on the interval of follow-up (Schnell 2001, Overholt 2005). A meta-analysis (Rastogi 2008) 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.<sup>3,4,5,6,7</sup>

Recommendations for the management of BE are based on the histological staging of the disease (non-dysplastic intestinal metaplasia {IM}, low-grade dysplasia {LGD}, high-grade dysplasia {HGD} or esophageal adenocarcinoma {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. In LGD, management options include surveillance endoscopy with biopsy and ablative therapy. For patients with HGD, recommendations include esophagectomy, endoscopic therapy with photodynamic therapy (PDT), endoscopic mucosal resection (EMR) and/or radiofrequency ablation (RFA), and surveillance every 3 months to detect progression to cancer. Standard surgical treatment for Barrett's esophagus with high grade dysplasia or adenocarcinoma includes, but is not necessarily limited to esophageal resection (esophagectomy). Esophagectomy, although almost always curative of

high-grade dysplasia and adenocarcinoma of the esophagus, is associated with significant mortality and morbidity. The mortality rate from this operation ranges from 2% to 7% in centers of excellence with large experience in this procedure, and up to 20% in hospitals where esophagectomy is less frequently performed.<sup>8</sup>

Ablation is defined 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 neosquamous epithelium. With respect to the use of RFA to treat dysplastic Barrett's esophagus, trials demonstrate that RFA can lead to reversion of the metaplastic mucosa to normal-appearing squamous epithelium in a high proportion of subjects.

Dunkin and associates (2006) ascertained the optimal treatment parameters for the ablation of human esophageal epithelium using a balloon-based bipolar radiofrequency (RF) energy electrode. Immediately prior to esophagectomy, participants underwent esophagoscopy and ablation of 2 separate, 3-cm long, circumferential segments of non-tumor-bearing esophageal epithelium using a balloon-based bipolar RF energy electrode. Subjects were randomized to one of three energy density groups: 8, 10, or 12 J/cm<sup>2</sup>. Radiofrequency energy was applied one time (1x) proximally and two times (2x) distally. Outcomes were compared according to energy density group and 1x versus 2x treatment. A total of 13 male subjects (aged 49 to 85 years) with esophageal adenocarcinoma underwent the ablation procedure followed by total esophagectomy. Complete epithelial removal occurred in the following zones: 10 J/cm<sup>2</sup> (2x) and 12 J/cm<sup>2</sup> (1x and 2x). The maximum depth of injury was the muscularis mucosae: 10 and 12 J/cm<sup>2</sup> (both 2x). A second treatment (2x) did not significantly increase the depth of injury. Maximum thickness of residual ablation after tissue slough was only 35 microm. The authors concluded that 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/cm<sup>2</sup> (2x) or 12 J/cm<sup>2</sup> (1x or 2x).<sup>9</sup>

Sharma and colleagues (2007) evaluated the dose-response, safety, and effectiveness of circumferential endoscopic ablation of BE by using an endoscopic balloon-based ablation device. This study was conducted in 2 serial phases: (i) dosimetry phase and (ii) effectiveness phase. In the effectiveness phase, 70 patients (52 men, 18 women; mean age of 55.7 years) were enrolled. At 12 months (n = 69; mean of 1.5 sessions), a complete histological eradication (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). The authors concluded that circumferential ablation of non-dysplastic 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.<sup>10</sup>

Roorda, et al (2007) 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. 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 patients,

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.<sup>11</sup>

Ganz et al (2008) reported that endoscopic circumferential RF ablation is a promising modality for the treatment of BE. In this study, researchers used registry data to identify 142 patients with BE (mean length, 6 cm) and HGD who underwent circumferential ablation at any of 16 academic and community medical centers in the United States. HGD was confirmed by at least two pathologists. After the initial ablative therapy, patients had follow-up endoscopy at 3-month intervals with repeat circumferential ablation. Prior endoscopic mucosal resection for focal lesions had been performed in 17% of participants. At 1-year follow-up, biopsy data were available for 92 of the 142 patients; the data showed complete HGD responses in 90.2% and complete remission of specialized columnar metaplasia in 62.5%.<sup>12</sup>

Data also suggest that reversion of the metaplastic mucosa to normal-appearing squamous epithelium persists for at least 2-3 years (the current length of follow-up of such trials). Fleisher, et al (2008) reported on the long-term 2.5 year follow-up of the AIM-II patient cohort. Patients with persistent IM at 1 year had focal RFA followed by biopsy at 2.5 years. CR-IM was achieved in 98.4% of patients. There were no strictures or buried glandular mucosa.<sup>13</sup>

Pouw, et al (2009) examined a prospective cohort of 23 HGD/IMC patients undergoing RFA +/- EMR at 3 European institutions. The reported CR-early cancer/dysplasia was 95% and the CR-IM was 88% with a favorable side effect profile (melena, not requiring further investigation, in 1 patient and transient dysphagia in another).<sup>14</sup>

Cost-effectiveness analyses suggest that treatment with RFA in the setting of high-grade dysplasia can be more cost-effective than competing strategies (esophagectomy or intensive endoscopic surveillance), and associated with a longer life expectancy. Das (2009) used a Markov model in a hypothetical 50-year-old cohort with nondysplastic IM to evaluate three competing strategies: (1) no intervention (natural history), (2) surveillance alone, and (3) RFA. 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.<sup>15</sup>

Inadomi (2009) 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. 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 are also optimally managed with ablation if >28% of patients have permanent eradication of dysplasia. The cost-effectiveness of ablation for patients with BE and no dysplasia would be acceptable if >40% of patients experienced

permanent eradication of metaplasia, but continued surveillance after ablation would be expensive. The authors concluded that endoscopic ablation could be the preferred strategy for managing patients with BE with HGD or LGD. Ablation might also be preferred in subjects with no dysplasia, but the cost effectiveness depends on the long-term effectiveness of ablation and whether surveillance endoscopy can be discontinued after successful ablation.<sup>16</sup>

Data from a recent randomized, sham-controlled trial (Shaheen, 2009) demonstrate less progression from low- to high-grade dysplasia and from high-grade dysplasia to cancer in subjects with dysplastic Barrett's esophagus treated with RFA, compared to controls. In this multicenter trial, 127 patients with dysplastic Barrett's esophagus were randomly assigned in a 2:1 ratio to receive either radiofrequency ablation or a sham procedure (control group). Patients were randomized according to the length of Barrett's esophagus and the grade of dysplasia. In the intention-to-treat analyses, among patients with high-grade dysplasia, complete eradication occurred in 81.0% of those in the ablation group, compared to 19.0% of those in the control group ( $P<0.001$ ). Among patients with low grade dysplasia, complete eradication of dysplasia occurred in 90.5% of those in the ablation group, compared to 22.7% of those in the control group ( $P<0.001$ ). Patients in the ablation group experienced complete eradication of intestinal metaplasia at a rate of 77.4% versus 2.3% of those in the control group ( $P<0.001$ ). Patients in the ablation group had a lesser amount of disease progression (3.6% vs. 16.3%,  $P=0.03$ ) and a smaller incidence of cancers (1.2% vs. 9.3%,  $P=0.045$ ). In the ablation group, five patients (6.0%) had esophageal stricture and there was one incident of upper gastrointestinal hemorrhage. In >90% of subjects with low-grade dysplasia, reversion to normal-appearing squamous epithelium was demonstrated following RFA therapy. The authors concluded that in patients with dysplastic Barrett's esophagus, radiofrequency ablation was associated with a reduced risk of disease progression and a high rate of complete eradication of both dysplasia and intestinal metaplasia.<sup>1</sup>

The safety profile of the treatment, generally, is good, which has been borne out in other studies. Lyday, et al (2009) published their experience performing RFA at four community hospitals. Four hundred and twenty-nine patients were examined as part of safety cohort with 1.1% of them experiencing a stricture and .5% having a self-limited bleed. Of those subjects that completed therapy and underwent a one year follow-up biopsy, CR-dysplasia was 100% and CR-IM was 77%, which when combined with the adverse event data supported the authors' initial hypothesis.<sup>17</sup> Most subjects have some chest pain following RFA, which is manageable in >95% with oral analgesics. Esophageal stricture has been reported to occur in 0-6% of subjects, and has been responsive to esophageal dilatation. Clinically significant bleeding occurs in 0-3% of subjects. Perforation has been reported, however the risk appears to be less than 1%.<sup>1, 11, 18</sup>

A meta-analysis (Wani 2009) for HGD patients showed a cancer incidence of 65.8 per 1000 patient years, whereas the incidence of cancer was 16.8 per 1000 patient years in the ablation group. The cancer incidence was 16.98 per 1000 patient years in LGD patients and 1.58 per 1000 patient years in the ablation group. In view of the high risk of cancer incidence in dysplasia, ablation of dysplasia appears to reduce cancer risk (Triadafilopoulos 2010).

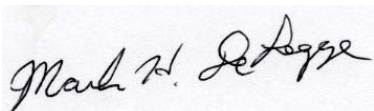
Given these data, when consideration is given to the safety and effectiveness of RFA in patients with BE and the high rates of disease progression, RFA therapy for subjects with high-grade dysplasia appears to be an effective therapeutic alternative to the competing strategy of long-term surveillance alone leads to reversion to normal-appearing squamous epithelium in >90% of cases.<sup>19, 20</sup>

In patients with Barrett's esophagus containing low-grade dysplasia as the worst histological grade, the risk of progression to esophageal adenocarcinoma is 560 times that of the general population. When consideration is given to the safety and effectiveness of RFA in patients with LGD in BE and the high rates of progression to EAC, RFA therapy for subjects with dysplasia appears to be an effective therapeutic alternative to the competing strategy of long-term surveillance alone and leads to reversion to normal-appearing squamous epithelium in >90% of cases, with an acceptable safety profile. As stated above, Wani, et al. have shown that eradication of the dysplastic epithelium LGD patients results in a significant reduction in risk for developing esophageal adenocarcinoma (compared to surveillance alone) with a favorable number-needed-to-treat.<sup>18</sup>

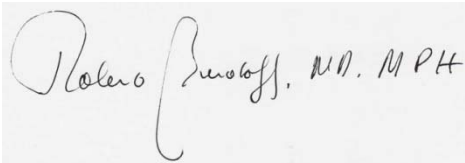
In summary, radiofrequency ablation has received clearance by the FDA. The scientific evidence is of adequate quality to allow conclusions to be drawn regarding the net health outcome, and the net health outcome of complete eradication of the high-risk epithelial lesion (dysplasia) has been shown to be improved/achieved. The technology has been compared head-to-head with surveillance alone for LGD patients in a randomized sham-controlled trial (Shaheen, et al.) 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 Highmark review the current status of this procedure and consider radiofrequency ablation medically necessary for the treatment of dysplastic Barrett's esophagus.<sup>1,17</sup>

Thank you for the opportunity to review and comment on this draft assessment. Please do not hesitate to contact Adam R. Borden, MHA, Manager of New Technologies and Reimbursement at the AGA Institute, at [aborden@gastro.org](mailto:aborden@gastro.org) should you have any questions. We look forward to your review.

Sincerely,



Mark H. DeLegge, MD, AGAF  
Chair, AGA Institute Practice Management and Economics Committee



Robert Burakoff, MD, MPH, AGAF  
Chair, AGA Public Affairs and Advocacy Committee



John M. Inadomi, MD, AGAF  
Chair, AGA Institute Clinical Practice and Quality Management Committee

#### References

- <sup>1</sup> Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med* 2009;360: 2277-88.
- <sup>2</sup> Schnell TG, Sontag SJ, Chejfec G. Adenocarcinomas arising in tongues or short segments of Barrett's esophagus. *Dig Dis Sci* 1992;37:137-143.
- <sup>3</sup> Shaheen NJ, Crosby MA, Bozymski EM, et al. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? *Gastroenterology* 2000;119:333-8.
- <sup>4</sup> Wani S, Mathur S, Sharma P. How to Manage a Barrett's Esophagus Patient With Low-Grade Dysplasia. *Clin Gastroenterol Hepatol* 2009;7:27-32.
- <sup>5</sup> Schnell TG, Sontag SJ, Chejfec G, et al. Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. *Gastroenterology* 2001;120:1607-19.
- <sup>6</sup> Overholt BF, Lightdale CJ, Wang KK, et al. Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: International, partially blinded, randomized phase III trial. *Gastrointest Endosc* 2005;62:488-498.
- <sup>7</sup> Rastogi A, Puli S, El-Serag HB, et al. Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. *Gastrointest Endosc* 2008;67:394-8.
- <sup>8</sup> Birkmeyer JD, Siewers AE, Finlayson EVA, Stukel TA, Lucas FL, Batista I, Welch G, Wennberg DE. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002; 346:1128-37.
- <sup>9</sup> Dunkin BJ, Martinez J, Bejarano PA, Smith CD, Chang K, Livingstone AS, Melvin WS. Thin-layer ablation of human esophageal epithelium using a bipolar radiofrequency balloon device. *Surg Endosc* 2006;20:125-30.

- 
- <sup>10</sup> Sharma VK, Wang KK, Overholt BF, et al. Balloon-based, circumferential, endoscopic radiofrequency ablation of Barrett's esophagus: 1-year follow-up of 100 patients. *Gastrointest Endosc* 2007;65:185-95.
- <sup>11</sup> Roorda AK, Marcus SN, Triadafilopoulos G. Early experience with radiofrequency energy ablation therapy for Barrett's esophagus with and without dysplasia. *Dis Esophagus* 2007;20:516-22.
- <sup>12</sup> Ganz RA, Overholt BF, Sharma VK, et al. Circumferential ablation of Barrett's esophagus that contains high-grade dysplasia a U.S. multicenter registry. *Gastrointest Endosc* 2008;68:35-40.
- <sup>13</sup> Fleischer DE, Overholt BF, Sharma VK, et al. Endoscopic ablation of Barrett's esophagus: a multicenter study with 2.5-year follow-up. *Gastrointest Endosc* 2008;68:867-76.
- <sup>14</sup> Pouw RE, Wirhth K, Eisendrath P, et al. Efficacy of Radiofrequency Ablation Combined With Endoscopic Resection for Barrett's Esophagus With Early Neoplasia. *Clin Gastroenterol Hepatol* 2010;8:23-9.
- <sup>15</sup> Das A, Wells C, Kim HJ, Fleischer DE, Crowell MD, Sharma VK. An economic analysis of endoscopic ablative therapy for management of nondysplastic Barrett's esophagus. *Endoscopy* 2009;41:400-8.
- <sup>16</sup> Inadomi JM, Somsouk M, Madanick RD, et al. A cost-utility analysis of ablative therapy for Barrett's esophagus. *Gastroenterology* 2009;136:2101-14.
- <sup>17</sup> Lyday W, Corbett, FS, Kuperman DA, et al. Endoscopic Radiofrequency Ablation of Barrett's Esophagus: Safety and Efficacy Outcomes in 429 Patients Treated in a Multi-Center Community Practice Registry. *Gastrointest Endosc* 2009;69:AB114.
- <sup>18</sup> Wani S, Sayana H, Sharma P. Endoscopic eradication of Barrett's esophagus. *Gastrointest Endosc* 2010;71:147-66.
- <sup>19</sup> Wani S, Puli SR, Shaheen NJ, et al. Esophageal adenocarcinoma in Barrett's esophagus after endoscopic ablative therapy: a meta-analysis and systematic review. *Am J Gastroenterol*. 2009;104:502-13.
- <sup>20</sup> Triadafilopoulos G. Blitzkrieg for Barrett's Esophagus Containing Early Neoplasia. *Clin Gastroenterol Hepatol* 2010;8:7-9.