ADVANCES IN GERD

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Radiofrequency Ablation for the Treatment of Barrett Esophagus With Low-Grade Dysplasia

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G&H What are the primary advantages and disadvantages of radiofrequency ablation for the treatment of Barrett esophagus with low-grade dysplasia?

HW Radiofrequency ablation (RFA) is a safe and effective technique for the treatment of patients with Barrett esophagus (BE) with either low- or high-grade dysplasia (LGD/HGD). The safety and efficacy of RFA have been demonstrated in several rigorous trials using stringent study criteria that are supported by centralized histopathology centers. There are not yet similar high-quality treatment results to support the use of other endoscopic treatments for patients with LGD, such as photodynamic therapy or spray or balloon cryotherapy using liquid nitrogen or carbon dioxide. Endoscopic resection, which has demonstrated to be an effective and durable treatment technique in patients with HGD or superficial adenocarcinoma, has been associated with a significantly higher stenosis rate compared with RFA.

For RFA, the primary disadvantages are cost and the destructive effect of an ablative technique on tissue. Because the tissue is destroyed following treatment, it cannot be used for analysis. Thus, other modalities, such as previous biopsy or advanced imaging techniques, are needed to target the abnormal tissue for ablation treatment. Another disadvantage of RFA is that it does not remove the entire segment in a single session; rather, patients typically undergo 2 to 4 treatment sessions over a period of 3 to 6 months in order to completely eradicate the dysplasia or cancer. Therefore, patients need to be medically compliant and reliable. For the best results, symptoms associated with gastroesophageal reflux disease should be completely controlled, and erosive (peptic) esophagitis should be fully healed, which usually requires a twice-daily proton pump inhibitor acid blocker to be taken 20 to 30 minutes prior to morning and evening meals.

G&H How does RFA compare to other ablative techniques and endoscopic surveillance in reducing rates of progression to HGD?

HW In a pivotal multicenter, randomized, controlled trial, Dr Nicholas J. Shaheen and colleagues found that in patients with LGD or HGD, RFA significantly reduced the progression to adenocarcinoma compared with sham treatment (rate of progression, 2% vs 19%, respectively). A subgroup analysis of patients with LGD found that the risk of progression to HGD was reduced from 13.6% to 4.8% following RFA treatment. This was not a statistically significant difference because the number of LGD patients included in the trial was too small; however, subsequent studies have since confirmed this finding.

Dr K. Nadine Phoa and colleagues conducted a study across 9 European centers from July 2007 to June 2011 comparing RFA to endoscopic surveillance. A total

of 136 patients were randomized to either RFA (n=68) or surveillance endoscopy (n=68), with the primary endpoint being a subsequent diagnosis of HGD or adenocarcinoma. The investigators estimated that there would be a 90% relative risk reduction in patients treated with RFA for the progression to HGD or adenocarcinoma. However, the study was terminated early, as there was a dramatic and statistically significant difference between the 2 groups. Patients in the RFA group were less likely than patients in the endoscopic surveillance group to progress to HGD or adenocarcinoma (1 patient [1.5%] vs 18 patients [26.5%], respectively). RFA significantly reduced the risk of progression to HGD by 25% and to adenocarcinoma by 7.5%.

> ... RFA for patients with confirmed LGD was more effective, but also more expensive, than surveillance endoscopy in reducing the risk of progression to HGD and adenocarcinoma.

G&H What do data show regarding the efficacy of RFA in eradicating LGD?

HW In the European study mentioned previously, 68 patients with LGD were treated with RFA. During a 3-year follow-up, with a maximum of 5 RFA treatment sessions permitted, 63 patients (92.6%) were found to have complete eradication of dysplasia at the end of their treatment sessions. Sixty patients (88.2%) had complete eradication of all BE intestinal metaplasia at the end of their treatment sessions. The efficacy and durability of RFA for the treatment of patients with LGD have been confirmed in several other studies.

G&H What adverse events are associated with RFA?

HW In both the study by Dr Shaheen and colleagues and the study by Dr Phoa and colleagues, the most frequently noted adverse event following RFA treatment was esophageal stricture, which occurred in 6% and 11.8% of patients, respectively. These strictures were considered mild and required an average of 2.6 dilations and 1 dilation, respectively, to restore normal swallowing function. In the European study, 1 patient was hospitalized for abdominal discomfort and treated with pain medicine. Severe adverse events, such as bleeding and perforation, are very rarely associated with RFA for the treatment of patients with LGD.

In a 2017 systematic review by Dr Madhav Desai and colleagues, focal endoscopic resection followed by RFA for patients with HGD was associated with strictures, bleeding, and perforations in 10.2%, 1.1%, and 0.2% of patients (N=774), respectively. The rate of recurrence of adenocarcinoma, dysplasia, and intestinal metaplasia was 1.4%, 2.6%, and 16.1%, respectively. In patients with LGD who underwent RFA without endoscopic resection, the most common adverse event was stricture, with a pooled estimate of 5.6%. Bleeding, perforation, and postprocedural chest pain requiring hospital admission were rare but did occur.

G&H What are the surveillance recommendations for patients who have undergone RFA for BE with LGD?

HW The optimal endoscopic surveillance intervals after complete resolution of BE dysplasia and intestinal metaplasia are unknown. The guidelines from the American College of Gastroenterology recommend endoscopy with biopsies obtained in areas of prior BE mucosa at intervals appropriate for the previous dysplasia grade until there is reasonable certainty of complete ablation in 3 or more endoscopic procedures (grade D recommendation). The American Society for Gastrointestinal Endoscopy also states that ideal surveillance intervals after complete BE ablation are unknown. Based on expert opinion, surveillance endoscopy can be performed every 3 to 6 months for 1 year, then every 6 months for another year, followed by annual surveillance thereafter.

G&H How common is recurrence of disease following treatment with RFA?

HW Results from the AIM Dysplasia (Ablation in Intestinal Metaplasia Containing Dysplasia) trial suggest that most patients stay in remission following complete BE ablation. Although BE recurrence was found in approximately 1 in 3 patients, it was usually successfully treated with additional RFA, with subsequent high rates of complete ablation (95%-97%) after 5 years. Nearly all of the risks of recurrent disease were found in the first 2 years of follow-up after complete BE ablation. However, more information is required to determine if

and when surveillance endoscopy can be stopped after complete BE ablation.

G&H Have any cost-effectiveness studies been conducted on the use of RFA for the treatment of LGD?

HW A cost-effectiveness analysis (Surveillance Versus Radiofrequency Ablation [SURF] trial) was performed on the results of the European trial assessing the use of RFA for BE LGD patients. All 136 patients were followed for 3 years to quantify their use of health care services, including endoscopic procedures, treatment of adverse events, and medication. The analysis found that RFA for patients with confirmed LGD was more effective, but also more expensive, than surveillance endoscopy in reducing the risk of progression to HGD and adenocarcinoma. However, the higher costs are worthwhile and justified to prevent progression to cancer. These findings are consistent with previous studies of patients with HGD who are treated with RFA, namely the studies conducted by Dr John Inadomi and colleagues and Dr Chin Hur and colleagues.

G&H What are the priorities of research in this field?

HW The use of RFA for the treatment of patients with BE dysplasia is a safe and effective technique. However, we continue to study refinements, such as the need for mucolytic agents prior to treatment, and the effect of mucosal biopsy obtained immediately prior to RFA. Several researchers are using advanced imaging techniques, such as volumetric laser endomicroscopy, to better characterize the mucosal depth and microstructure of the Barrett mucosa in order to determine the ideal dose and method of endoscopic therapy to optimize treatment outcomes (eg, improve eradication efficacy while limiting adverse events such as bleeding and stricture). Intensive research continues to study the role of advanced imaging modalities, biomarker analysis with immunohistochemistry, and 3-dimensional analysis using artificial intelligence and neural networks for more rapid and reliable diagnoses and prognostic information in BE patients, especially those with dysplasia. As discussed previously, we need additional long-term data to determine the risk of BE dysplasia recurrence after complete ablation, as well as the role of long-term control of gastroesophageal reflux disease with acid-blocker medications or surgery. Further research is needed to determine if aspirin, anti-inflammatory agents, or other chemoprevention agents may decrease the risk of BE dysplasia recurrence. This information is critically important so that we can reliably and confidently recommend surveillance intervals after complete ablation and for surveillance to be safely discontinued.

Dr Wolfsen has no relevant conflicts of interest to disclose.

Suggested Reading

Cotton CC, Wolf WA, Overholt BF, et al; AIM Dysplasia Trial Group. Late recurrence of Barrett's esophagus after complete eradication of intestinal metaplasia is rare: final report from Ablation in Intestinal Metaplasia Containing Dysplasia Trial. *Gastroenterology*. 2017;153(3):681-688.e2.

Desai M, Saligram S, Gupta N, et al. Efficacy and safety outcomes of multimodal endoscopic eradication therapy in Barrett's esophagus-related neoplasia: a systematic review and pooled analysis. *Gastrointest Endosc*. 2017;85(3):482-495.e4.

Phoa KN, Rosmolen WD, Weusten BLAM, et al; SURF investigators. The cost-effectiveness of radiofrequency ablation for Barrett's esophagus with low-grade dysplasia: results from a randomized controlled trial (SURF trial). *Gastrointest Endosc*. 2017;86(1):120-129.e2.

Phoa KN, van Vilsteren FG, Weusten BL, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. *JAMA*. 2014;311(12):1209-1217.

Qumseya BJ, Wani S, Desai M, et al. Adverse events after radiofrequency ablation in patients with Barrett's esophagus: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2016;14(8):1086-1095.e6.

Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med*. 2009;360(22):2277-2288.