

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Update on the Use of Radiofrequency Ablation for Treatment of Barrett Esophagus



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G&H What is the current understanding of the relationship between Barrett esophagus/cancer and gastroesophageal reflux disease?

GF Barrett esophagus is a well-known complication of gastroesophageal reflux disease (GERD). What remains unclear is why Barrett esophagus develops in some patients with GERD and not in others. In terms of risk factors, overweight white males, especially those with central pattern obesity, are more predisposed to development of Barrett esophagus than other individuals.

Observational studies have shown that frequent GERD symptoms present an increased risk for the development of esophageal adenocarcinoma. However, approximately 40% of individuals with esophageal adenocarcinoma do not remember having any antecedent symptoms of heartburn or acid regurgitation with any regularity.

G&H Can early treatment of GERD prevent the development of Barrett esophagus/cancer?

GF We do not yet have data to definitively answer this question. Recent data from observational studies suggest that proton pump inhibitor therapy may attenuate the risk of neoplastic progression in patients with Barrett esophagus. There are no data as of yet that antireflux surgery can prevent the development of esophageal adenocarcinoma nor are there any data that either therapy prevents the development of Barrett esophagus.

G&H What ablative therapies are currently being used to treat Barrett esophagus?

GF Currently, the 2 most important ablative therapies in this setting are radiofrequency ablation and endoscopic mucosal resection. Radiofrequency ablation involves the use of thermal energy to ablate the superficial layer of the esophagus (where the metaplastic columnar tissue characteristic of Barrett esophagus is located). What makes this technology exciting, compared with older technologies such as photodynamic therapy, is that it is performed in a controlled manner to a specified depth. The disadvantage of radiofrequency ablation is that tissue confirmation of the epithelial lining being ablated is not achieved.

Endoscopic mucosal resection is essential prior to radiofrequency ablation in the setting of mucosal abnormalities; as such, any mucosal abnormality should be removed by endoscopic mucosal resection prior to commencing radiofrequency ablation. Endoscopic mucosal resection provides larger samples than conventional forceps biopsies, thereby allowing for the determination of the depth of cancer (if it is present) as well as lymphovascular invasion. This procedure may be performed as a stand-alone ablation technique, but this is associated with a higher stricture rate than radiofrequency ablation for flat mucosa.

Other ablative techniques used for the treatment of Barrett esophagus include cryotherapy, which involves freezing, and endoscopic submucosal dissection, which is more commonly used in Asia and Europe than North

America. The eventual role for these 2 techniques remains to be determined.

G&H According to studies, how effective is radiofrequency ablation for management of dysplastic Barrett esophagus?

GF Radiofrequency ablation has been shown to have excellent efficacy for treatment of dysplastic Barrett esophagus. The best-quality evidence comes from the AIM Dysplasia Trial, the results of which were published in *The New England Journal of Medicine*, which found that radiofrequency ablation eradicated low-grade dysplasia in 90% of patients and high-grade dysplasia in 81% of patients. Both of these rates were superior to those found in patients in the sham treatment arm.

Similarly, in a presentation at this year's Digestive Disease Week (DDW), researchers from the Academic Medical Center in Amsterdam, The Netherlands reported results of a randomized controlled trial in which radiofrequency ablation led to a marked decrease in progression rates of confirmed low-grade dysplasia to high-grade dysplasia or adenocarcinoma at 3 years, compared with patients who received no ablation. These positive results led to early termination of the study.

G&H What long-term research has been reported in this area?

GF In a long-term follow-up of the AIM Dysplasia Trial, 98% of patients who experienced complete eradication of dysplasia with radiofrequency ablation maintained their status at Year 3, and 91% of patients who experienced complete eradication of intestinal metaplasia maintained their status at Year 3 when retreatment was allowed.

A series of studies published in 2013 have given additional information in this area. In the *American Journal of Gastroenterology*, Orman and associates reported a recurrence rate of high-grade dysplasia/cancer of 4.2% per year, with a median time to recurrence of 173 days. In a study published in *Gastroenterology*, Phoa and colleagues found that, among 54 patients who underwent radiofrequency ablation with or without endoscopic mucosal resection of high-grade dysplasia and intramucosal cancer, 90% remained free of both dysplasia and intestinal metaplasia at 5 years.

On the other hand, in a study published in *Gastroenterology*, researchers from Columbia University, the Mayo Clinic, and the University of Pennsylvania BETERNET consortium found very different results, namely that radiofrequency ablation was not as durable as in previous studies. In this study, patients with Barrett esophagus who underwent radiofrequency ablation had

an intestinal metaplasia recurrence rate of 20% at Year 1 and 33% at Year 2, with 22% of these recurrences being dysplastic. Unfortunately, it was not possible to identify any factors that predicted recurrence.

Therefore, recurrence rates appear to be highly variable. Most likely, the best that can be predicted is that recurrence rates will be somewhere between those described in the above studies. The take-home message is that, while radiofrequency ablation is durable in some patients, it is not durable in all patients. It is important to remember that no procedure is perfect and that radiofrequency ablation is a process that requires long-term commitment by both the patient and the physician for follow-up care, particularly because of the rapidly evolving information on durability.

G&H Is surveillance required in all patients who undergo radiofrequency ablation?

GF Surveillance is still needed following radiofrequency ablation, particularly since there have been several reports of subsquamous cancer developing after successful ablation. Furthermore, there is a small but definite risk of recurrence of both intestinal metaplasia and dysplasia after successful eradication therapy. The rates of recurrence are variable in different studies, in part due to varying definitions of both complete response and recurrence. Given that the underlying pathophysiologic factors and reflux milieu that led to both Barrett esophagus and adenocarcinoma may still be in play, this should come as no surprise. However, currently, there is no agreement on the technique and frequency of surveillance.

Unfortunately, it appears that, in the real world, patients are not routinely undergoing surveillance following radiofrequency ablation. According to data presented at this year's DDW, only approximately 60–70% of patients who underwent the technique also underwent surveillance.

G&H Is radiofrequency ablation now considered to be the first-line treatment option for patients with dysplastic Barrett esophagus?

GF Currently, radiofrequency ablation is a first-line treatment option for patients with high-grade dysplasia after mucosal abnormalities have been removed by endoscopic mucosal resection and for patients with early cancer, namely intramucosal cancer, after the cancer has been completely resected. In patients with high-grade dysplasia, it is clear that radiofrequency ablation is preferred over esophagectomy, given the encouraging results of this technology to date, the morbidity of esophagectomy, and the marked decrease in finding unsuspected cancer in

these patients with the advent of high-definition white-light endoscopy and endoscopic mucosal resection.

Low-grade dysplasia is still an evolving area because of the difficulty associated with its pathologic diagnosis. However, research from the Academic Medical Center and other institutions has shown that low-grade dysplasia that has been confirmed by expert gastrointestinal pathologists has an increased risk of progression to high-grade dysplasia or adenocarcinoma than does unconfirmed low-grade dysplasia. Thus, radiofrequency ablation is also now a reasonable approach for patients with confirmed low-grade dysplasia.

G&H Thus far, what have studies reported on the use of radiofrequency ablation in patients with nondysplastic Barrett esophagus?

GF This is a controversial issue that leads to spirited debates. Research by Fleischer and colleagues found that, of 50 nondysplastic patients treated with radiofrequency ablation, 92% remained free of intestinal metaplasia at 5 years. It is unclear whether the cost of this technology (which includes the cost of disposable equipment and extra procedures and sedation) is worthwhile in patients at low risk (0.1–0.5% per year) for development of cancer (ie, patients with Barrett esophagus who have no dysplasia). Although the risks of this procedure are small, it is clear from emerging data that there is a failure rate, albeit of varying magnitude, of the procedure over time, making continued surveillance a requirement and a further cost. In addition, there are no data showing that the application of radiofrequency ablation actually decreases this already low cancer risk. Thus, while these patients can be ablated, I find it difficult to justify the use of radiofrequency ablation in this setting, particularly in the current economic environment. This approach will only make sense if we can determine true biomarkers of increased risk of progression, eliminate the need for surveillance, or demonstrate a decrease in cancer risk in these patients.

G&H Has any cost-effectiveness analysis compared radiofrequency ablation with other treatment modalities for Barrett esophagus?

GF The most recent cost-effectiveness study, conducted by Hur and colleagues and published in *Gastroenterology* in 2012, suggests that radiofrequency ablation is more effective and less costly than continued surveillance for patients with

high-grade dysplasia. The researchers also concluded that radiofrequency ablation may be cost-effective for patients with confirmed and stable low-grade dysplasia. However, this study also noted that radiofrequency ablation is not cost-effective for patients without dysplasia, given new estimates of cancer risk in these patients. Furthermore, from a health policy perspective, such a strategy would be cost-prohibitive.

G&H What are the next steps in research in this area?

GF A number of questions are still unanswered, such as whether there are predictors of response to ablative techniques; whether subsquamous intestinal metaplasia is a curiosity or a real cause for concern; whether there is an effective technology (such as 3-dimensional optical coherence tomography) to help detect subsquamous intestinal metaplasia; and whether the optimal technique and interval for following patients after the application of ablation therapy can be determined (because current surveillance techniques and intervals are arbitrary and not based on objective data).

An additional area of research involves the biologic characteristics of neosquamous epithelium. Research from Jovov and colleagues at the University of North Carolina suggests that neosquamous epithelium has an increased paracellular permeability, which results in a defective barrier function. This finding may have implications for disease recurrence.

Dr. Falk is a consultant for Olympus and CDx.

Suggested Reading

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