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EDITORIAL

Radiofrequency Ablation of Barrett's Esophagus: Let's Not Get Ahead of Ourselves

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Radiofrequency ablation (RFA) represents an exciting advance for the treatment of Barrett's esophagus. The research work on RFA performed to date has involved a stepwise progression from initial animal studies to human studies prior to esophagectomy, human dosimetry studies, single-center studies, multicenter nonrandomized studies, and ultimately multicenter, randomized, controlled trials [1–5]. This process also led to modifications in the RFA technique and to the development of the focal ablation device. Regardless of the eventual role of RFA, this series of studies illustrates the appropriate steps in the development and application of future ablative technologies. However, this approach may be limited to certain subsets of patients by the high costs required for the development and widespread application of new endoscopic therapeutic technologies. Nevertheless, the impact of this development paradigm in the evolution of RFA is obvious, and both the investigators and the manufacturer of the RFA device are to be congratulated on their achievements. However, in a special article in this issue of *Digestive Diseases and Sciences*, Fleischer and colleagues [6] make an impassioned plea for the widespread application of RFA to all patients with Barrett's esophagus regardless of the grade of dysplasia that is premature based on the available data. Let's take a careful look at the facts, with an emphasis on the application of RFA in patients with nondysplastic Barrett's esophagus.

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There is universal agreement that high-grade dysplasia poses a major risk for the development of cancer, and current practice guidelines recommend intervention in these patients [7]. Studies to date, including the landmark randomized controlled trial of Shaheen et al. (ablation of intestinal metaplasia [AIM] dysplasia trial), demonstrate a clear benefit for RFA in the treatment of high-grade dysplasia, ideally with endoscopic mucosal resection of any mucosal abnormalities prior to application [5, 8]. In addition, preliminary results of a randomized controlled clinical trial of circumferential endoscopic mucosal resection versus focal endoscopic mucosal resection plus RFA for high-grade dysplasia and early adenocarcinoma suggest that the two techniques are comparable for the important endpoints of elimination of neoplasia and intestinal neoplasia, but the complication rate for endoscopic mucosal resection plus RFA is substantially lower [9]. Thus, RFA represents a clear advance for the management of patients with high-grade dysplasia. It is important to recognize, however, that a small subset of these patients may still progress onto cancer (2% in the AIM dysplasia trial), and histologic confirmation of complete ablation is never possible with RFA.

Low-grade dysplasia has many more nuances, including a natural history that is poorly understood. In addition, the diagnosis is often elusive and not confirmed with repeat endoscopy and biopsies [10, 11]. In part, this may be due to the high degree of interobserver variability in establishing the diagnosis of low-grade dysplasia, and the variable biopsy sampling protocols by which these patients are followed. While the majority of patients with low-grade dysplasia do not progress to high-grade dysplasia or adenocarcinoma, a subset of these patients do progress to a higher-grade lesions. Recent studies suggest an intermediate risk of progression to cancer, with a weighted average

incidence rate of 1.69% per year for patients with low-grade dysplasia [12]. Factors associated with progression to cancer include a consensus agreement among two or more pathologists and the extent of low-grade dysplasia [13, 14]. In the AIM dysplasia study, the 64 patients with low-grade dysplasia had their diagnosis confirmed by a central pathology reading at the Cleveland Clinic prior to entry into the study [5]. By intention-to-treat analysis, complete eradication of low-grade dysplasia was accomplished in 90%, complete elimination of intestinal metaplasia was accomplished in 81%, and progression to high-grade dysplasia occurred in 5% at 12 months. Thus, in low-grade dysplasia, especially if multifocal and documented by a consensus review by a panel of expert gastrointestinal pathologists, it is reasonable to consider RFA. However, it is premature to use RFA in patients with indefinite dysplasia or low-grade dysplasia when biopsies are not reviewed by an expert pathologist. Patients need to understand that progression may occur and cancer risk is not eliminated by RFA. Furthermore, it is important to emphasize that the majority of patients with low-grade dysplasia never progress onto a higher-level lesion.

On the other hand, application of RFA to patients with nondysplastic Barrett's esophagus is premature at this time. In fact, I would make the case that RFA of nondysplastic Barrett's esophagus is akin to performing plastic surgery on the esophagus; we can make it look pretty, but does RFA really change anything for the patient? Since Fleischer et al. [6] tout RFA as a cancer-prevention method, I would like to use the endpoint of development of cancer to make the case that RFA in nondysplastic Barrett's esophagus is not ready for "prime time" for a number of reasons.

Cancer Risk for a Given Patient with Barrett's Esophagus Is Already Low

The cancer risk for a patient with nondysplastic Barrett's esophagus is extraordinarily low, with the most recent meta-analysis showing a pooled estimate of 0.6% per year [15]. The rate of progression to the combined endpoint of high-grade dysplasia or adenocarcinoma was 1% per year, and the pooled incidence of fatal esophageal adenocarcinoma was 3% per year. Most importantly, this study again confirmed that adenocarcinoma was an uncommon cause of death in Barrett's patients; only 7% of deaths were due to adenocarcinoma whereas 93% of deaths were due to other causes, the most common being cardiovascular disease that accounted for 35% of the deaths. These data, which confirm multiple other studies demonstrating both the low cancer risk in these patients and the tendency of Barrett's esophagus patients to die of cardiopulmonary disease and not from esophageal adenocarcinoma, should put to rest any rationale for considering widespread application of RFA for nondysplastic Barrett's esophagus [16]. Furthermore, it is important to remember that patients routinely are unable to accurately assess their own cancer risk and hence justification for such an intervention [17].

The Need for Surveillance Is Not Changed

RFA does not eliminate the need and costs of continued endoscopic surveillance. Currently, nobody would consider eliminating the need for surveillance in these patients after RFA, although enthusiasts for RFA believe that these patients may be able to be removed from surveillance programs in the future. A 5-year follow-up of 50 patients with nondysplastic Barrett's esophagus treated with RFA was just presented at DDW 2010 [18]. Compete remission of intestinal metaplasia was maintained in 92% of these patients. Similarly, durability for complete remission of intestinal metaplasia in the AIM dysplasia trial was 91% by intention-to-treat analysis at 2 years [19]. These results are certainly encouraging, but the number of patients treated remains small. However, it is also important to keep in mind provocative work presented by the University of Kansas group at DDW 2010 that suggests that the lamina propria is seen after ablation by a variety of different techniques in only 13% of biopsy specimens [20]. In contrast, the AIM dysplasia trial reported subsquamous intestinal metaplasia in 5.1% of patients in biopsies obtained with a jumbo forceps, a device not used commonly in clinical practice today. As such, there may be more buried intestinal metaplasia than we are currently aware of. Why is this important?

Several reports suggest that the cardia behaves in unexpected and potentially undesirable ways after ablation therapy by techniques other than RFA. Nodules with high-grade dysplasia or cancer may develop months to years after ablation therapy [21, 22]. The reason for this is unknown. While squamous epithelium may develop below the gastroesophageal junction after ablation, it is unclear what the natural history of that metaplastic mucosa is [23]. Not only can problems develop at the cardia, but techniques such as RFA may be difficult to apply to the cardia, even with the focal probe, due to positioning and the anatomic alterations in the setting of a large hiatal hernia.

Cost

RFA of nondysplastic Barrett's esophagus involves considerable financial cost that cannot be ignored. First, the decision to use RFA in nondysplastic Barrett's esophagus by definition adds in multiple extra endoscopic procedures

that do not eliminate the costs encumbered from continued endoscopic surveillance as described above. The long-term study of ablation of nondysplastic Barrett's by Fleischer et al. [4] required a mean of 1.5 procedures with circumferential ablation followed by 1.9 procedures with focal ablation. This results in an average increase in 3.4 endoscopies in this patient group! In the best of times, this added cost could be finessed, but given the current economic realities in the world we live in, this simply cannot be ignored. Costs include the upfront capital equipment cost of the radiofrequency ablation generator needed for all procedures as well as disposables for each procedure which include a sizing balloon, the HALO^{360} balloons, HALO^{90} probes, disposable guidewires, and cleaning caps to remove the coagulated mucosa. Furthermore, many will use anesthesia administered propofol for RFA, given the duration of the procedure, thereby further escalating costs. These costs are not likely to be borne by insurance carriers now or in the foreseeable future.

Magnitude of Treatment Effect

Currently, there are no data that allow us to determine the magnitude of the treatment effect of RFA for development of cancer or high-grade dysplasia. Yes, RFA can eliminate the columnar epithelium in most patients. At the end of the day, short of a long-term randomized clinical trial, we will not know how RFA compares to continued surveillance for the clinically important endpoints of high-grade dysplasia or cancer. The use of hypothetical numbers in the work by Fleischer et al. simply does not provide any information on the magnitude of the benefit, if any, for RFA in the setting of nondysplastic Barrett's epithelium. If we hypothesize that RFA decreases cancer risk by 50% from 0.6 to 0.3% per year for an absolute risk reduction of 0.3% annually, then the number needed to treat to prevent one cancer is 1/absolute risk reduction (1/0.003), which calculates to 333 patients per year.

Generalizability

Data to date on RFA have primarily come from large centers of excellence with high volume RFA practices and expertise in the application of endoscopic mucosal resection and RFA, along with adherence to strict biopsy protocols and biopsy evaluation by expert pathologists. However, we still do not know the learning curve for RFA. While the technique is relatively simple, there are multiple steps involved which include the following: high-quality white light endoscopy to map out the Barrett's segment and exclude any mucosal abnormality, cleaning the segment with the mucolytic agent acetylcysteine, deployment of a sizing balloon to determine optimal size of the balloon-based ablation device, application of the balloon or probe device, removal of the coagulative debris, repeat ablation, and then continued surveillance after healing. This requires time and attention to detail.

Safety

Risks of RFA appear to be low, but adverse events still occur. These include perforation, mucosal tears, bleeding, stricturing, chest pain in the short term, and progression of disease in the long term. In the AIM dysplasia trial, serious adverse events were reported in 4% of patients and strictures developed in 6% [5]. In the multicenter long-term study of nondysplastic Barrett's epithelium, minor adverse events were encountered in 15.1% after the circumferential ablation phase of the study and 2.6% after the focal ablation phase of the study [4]. Any post-ablation symptoms resolved within 4 days of the procedure and no strictures developed. It is not clear what the exact complication rate for RFA of non-dysplastic Barrett's esophagus will be, but it is likely to eventually settle in between these two studies.

Summary

In fact, the real problems in the management of Barrett's esophagus continue to be twofold: (1) identification of patients at risk for development of adenocarcinoma in the absence of mucosal abnormalities or histologic dysplasia; and (2) only the minority of patients with esophageal adenocarcinoma have undergone prior endoscopy [24]. Is the fact that many gastroenterologists do not perform rigorous surveillance as recommended by practice guidelines a reason to default to the position of ablation of Barrett's esophagus? How will this practice help the vast majority (95%) of adenocarcinoma patients who do not know about their pre-existing diagnosis of Barrett's esophagus?

The technique of RFA represents a major advance in the treatment of Barrett's esophagus with high-grade dysplasia. With further clinical outcomes, data RFA will likely have an important role in selected individuals with well-documented low-grade dysplasia in the following settings: (1) meticulous biopsies performed on high-dose therapy with a proton pump inhibitor; (2) confirmation by one or more expert gastrointestinal pathologists; and (3) multifocal low-grade dysplasia. It is entirely possible that widespread application of RFA to patients with nondysplastic Barrett's esophagus will become the preferred approach in the future. I will be the first to participate in a randomized clinical trial to evaluate that possibility, as even a negative

study will likely prove that we can extend our surveillance intervals. However, until that day arrives, I urge the gastroenterology community to avoid the temptation of performing RFA of nondysplastic Barrett's epithelium—a management strategy not supported by rigorous clinical studies.

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