Radiofrequency ablation for nondysplastic Barrett's esophagus: certainly not for all

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Combined with EMR of visible lesions, radiofrequency ablation (RFA) has revolutionized the treatment of high-grade dysplasia (HGD) and intramucosal adenocarcinoma in Barrett's esophagus (BE). EMR and RFA are preferred over esophagectomy in patients with HGD and intramucosal adenocarcinoma because studies show similar survival with significantly less morbidity.[1,2] In a randomized controlled trial, RFA resulted in a significant decrease in the progression of HGD and low-grade dysplasia (LGD) to cancer compared with endoscopic surveillance.[3] LGD is a difficult target because of inconsistent pathology interpretation, but LGD confirmed by expert pathologists is increasingly seen as an important marker of high risk of progression to HGD and cancer. In a recently published randomized controlled trial of patients with confirmed LGD, RFA significantly reduced progression to HGD and cancer compared with surveillance.[4]

The proven benefits of RFA in patients with dysplasia elicited enthusiastic proposals to broaden the indication for RFA to nondysplastic BE (NDBE).[5] After all, it is only a short leap from the success of endoscopic therapy for BE with dysplasia to infer that RFA would also decrease the progression to cancer in NDBE. Why not wield RFA like the sword of Alexander to cut through the Gordian knot of sampling error and variable pathology that confounds and limits the impact of our current practice of endoscopic surveillance for NDBE?

Abbreviations: BE, Barrett's esophagus; HGD, high-grade dysplasia; IM, intestinal metaplasia; LGD, low-grade dysplasia; NDBE, nondysplastic Barrett's esophagus; RFA, radiofrequency ablation.

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It is easy to be sympathetic to this notion, but there are major problems with it. Although there is published, high-quality, level-one evidence for a protective effect of RFA in BE with HGD and LGD, no such data are available for RFA of NDBE. There are no randomized controlled trials of RFA versus surveillance in NDBE because the necessarily large numbers of patients required makes proposed budgets for such studies too expensive to fund. Meanwhile, recent and cumulative experiences with RFA have added to our understanding of long-term outcomes and limitations. Many questions of risk-to-benefit and cost-to-benefit must be considered when recommending RFA for most patients with NDBE.

The central issue is the low incidence of cancer developing in patients with NDBE. For NDBE, the most recent estimates of progression to cancer are less than the long-accepted .5% per year. A meta-analysis in 2012 estimated the rate at .33% per year.[6] In a multicenter outcomes study, most cases of BE with HGD and cancer were diagnosed at the index endoscopy or within the first year after diagnosis (prevalent cases). Of 1204 cases followed after 1 year, the incidence rate of cancer was .27% per year.[7] Progression of NDBE to cancer seems to be cumulative but certainly not linear, with a lifetime risk of cancer estimated to be as low as 1%. The implication of treating all NDBE patients with RFA is that millions of people would receive RFA unnecessarily.

RFA has a very acceptable safety and morbidity profile when treating BE in the setting of HGD, which untreated has a progression to cancer risk of 6% per year.[2] In a study from the Netherlands, progression of expert-confirmed LGD to HGD or cancer was 13.4% per year.[8] In a recent meta-analysis of RFA in which 59% of patients had BE with neoplasia and 41% had NDBE, the most serious adverse event associated with RFA was esophageal stricture, which occurred in 5%, similar to the 6% results in the randomized controlled trial of RFA in BE with HGD and LGD.[9] In the recently reported randomized controlled trial of RFA for LGD, the stricture rate was 11.8%.[4] Other adverse events less common than stricture include hemorrhage from mucosal lacerations and chest pain severe enough to require hospitalization.[3] Most patients experience lesser degrees of pain after RFA, but about half require narcotic analgesics. To expose millions of people

with NDBE (most will receive no benefit) to these risks from RFA seems unacceptable.

In terms of efficacy, RFA eradication of dysplasia has been consistently reported to be higher than for intestinal metaplasia (IM) associated with BE. In a recent meta-analysis, dysplasia was completely eliminated in 91% and IM in 78%.[9] Most studies required a mean of 2 to 3 RFA sessions to achieve these results. Therefore, multiple sessions are usually needed, and still nearly a quarter of patients continue to show IM on biopsy specimens. The reasons some patients are less than totally responsive to RFA are still not clear. Difficulties in obtaining adequate RFA catheter contact in irregular anatomy, longer segments, large hiatal hernias, and continued reflux of gastric contents have all been implicated, but some Barrett's mucosa may also be intrinsically more resistant.

Then there is the problem of disease recurrence with time after what appears to be complete eradication by RFA of dysplasia and IM in patients with BE. Recurrence has been variously defined as happening after a single surveillance endoscopy shows no evidence of disease or after 2 consecutive negative surveillance procedures. The cohort of patients treated in the randomized controlled trial for HGD and LGD was followed prospectively, and the results at 3 years showed that dysplasia remained eradicated in >85% and IM in >75%. More procedures for additional touch-up treatments were needed to achieve 3-year eradication rates of 98% for dysplasia and 91% for IM.[10] In a prospective study of 50 patients available at 5 years after RFA treatment for NDBE, 92% were in continued remission and 4 recurrences were all successfully retreated.[11]

However, a much higher rate of recurrence was reported by a research consortium in a retrospective review where only 56% of patients (mostly with HGD) had complete remission of IM after 24 months. In these patients, the recurrence rate was 33% after an additional 2 years, mostly NDBE and easily treated, but neoplasia was present in 22% of recurrences.[12] Fewer recurrences were seen in a recent 5-year analysis of a prospective study cohort from the Netherlands, where complete remission was achieved in 90% of patients after 5 years.[13] Only 3 of 54 patients developed recurrent neoplasia (all successfully treated with endoscopy), but all of these were late recurrences after 4 to 5 years. In the context of these data, continued surveillance after RFA-induced remission is essential. Modeling studies of cost for RFA in NDBE have shown variable results, but the need for continued surveillance usually makes RFA for NDBE prohibitively expensive and not cost-effective.[14]

The reasons for recurrence are unclear. One possibility is that the fundamental conditions leading to Barrett's metaplasia and dysplasia are still present after RFA and the process basically repeats itself. Another possibility is residual disease missed by sampling error. A third possibility that has plagued all ablative treatments is the potential of buried Barrett's glands underneath the neosquamous epithelium. Most studies looking for buried glands after RFA using large-capacity biopsy forceps or even EMR have shown no buried glands or only a small percentage. In the randomized controlled trial in patients with LGD and HGD, both the RFA treatment arm and the control arm showed a high percentage of buried glands (25%) on index biopsy samples that were reduced to 5% after RFA at 1 year.[3] However, controversy exists as to whether biopsy forceps consistently provide sufficient lamina propria for analysis. Furthermore, there is now a new endoscopic advanced optical coherence tomography method (optical frequency domain imaging, also called volumetric laser endomicroscopy) reported to show a higher incidence of buried glands after RFA.[15] These results need to be confirmed, and the entire issue of the incidence and clinical significance of buried glands remains an open question.

Another unanswered question is the clinical significance of IM in the gastric cardia. Because cardia IM is common in Western populations, in initial prospective studies testing RFA for ablation of NDBE and for the randomized controlled trial of RFA for LGD and HGD, eradication of IM and dysplasia in the esophagus was the goal, and biopsy samples of the cardia were avoided. The study protocols rigorously required that the most distal biopsy samples be taken 5 mm above the top of the gastric folds in the decompressed esophagus (perhaps the best endoscopic marker of the esophagogastric junction).

After RFA, the neosquamocolumnar junction is frequently at or below the top of the gastric folds. In post-RFA surveillance, most endoscopists take a biopsy specimen from the squamocolumnar junction routinely In the prospective cohort from the Netherlands, where the esophagogastric junction was treated with RFA multiple times per protocol, at 5 years 35% of patients had been found at least once to have focal IM in the cardia on biopsy specimens.[13] The clinical significance of this is unknown and seems slight. Yet continued monitoring and research is needed to better understand the nature of cardia IM in patients with BE. Adenocarcinoma of the gastric cardia in the United States today accounts for as many lethal cancers as esophageal adenocarcinoma.[16]

It has been suggested that RFA of NDBE is intellectually the same as colonoscopic polypectomy—the removal of premalignant tissue for cancer prevention.[17] In practice, however, there are important differences. RFA is an excellent method for wide-field ablation of flat BE mucosa but is not as effective a tool as the wire snare for polyp resection. On surveillance colonoscopy, polyps that are encountered can be resected during the procedure. Follow-up after RFA is more complicated. After RFA, recurrent IM or dysplasia may not be apparent until surveillance biopsy specimens are evaluated, requiring an additional endoscopy for treatment. In the future, it is possible that "optical biopsy" methods might allow "on the spot" treatment decisions