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Ablation is in the Eye of the Beholder

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Ablation of Barrett's esophagus has taken many forms since Berenson began using laser therapy for ablation in the 1980's¹. This landmark paper described that ablation of intestinalized mucosa could be better achieved if the ablated tissue was contiguous with squamous mucosa and that the squamous regrowth appeared to occur by spreading from the periphery. Berenson felt that this could only occur if gastric acid was suppressed which was accomplished with the advent of proton pump inhibitors. At the initiation of ablation therapy, it was still unclear if re-injury from ablation would eliminate Barrett's esophagus or if it might expand the Barrett's esophagus.

Since this initial publication, randomized controlled multicenter trials have been performed that decisively and consistently found that ablation therapy decreases the amount of dysplasia, eliminate intestinal metaplasia, and significantly decreases cancer development in individuals at highest risk (i.e., those with high-grade dysplasia)^{2, 3}. Long-term follow-up studies of these trials have substantiated the initial findings with up to five-year observations obtained^{4, 5}. Multiple ablation techniques have been developed to achieve these goals, there are several principles that seem to be pervasive through all the mucosal ablation techniques.

The study reported in this month's CGH by Shaheen and colleagues from the University of North Carolina helps us understand these principles applied to an expert referral center. The study data are carefully explained and the results are well analyzed and presented. The data on safety and efficacy are a welcomed addition to the literature that helps illustrates the principles of ablation.

The first principle is that ablation therapy is not completely benign and that there are potential complications to any of the treatments. Common to all is esophageal stricture that occurs with any of the circumferential ablation methods but most often associated with circumferential mucosal resection and photodynamic therapy^{6, 7}. With radiofrequency ablation, there was initial enthusiasm that this precisely delivered therapy could avoid the stricture issue and recent cost-effectiveness models were even constructed with stricture rates assumed to be 2.5% with minimum and maximum ranges of 1-5%⁸. However, in the randomized controlled trial, stricture rate was 6%, and with longer-term follow-up, the stricture formation rate was up to 7.6%, and in this single center study of more "real world" patients, stricture rates are found to be 8.2% of which only 60% of the patients actually received circumferential treatment as opposed to all of the patients in the randomized trial. It

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is important to note that in this study, strictures were primarily asymptomatic and were based upon the need to perform dilatation.

The second principle in ablation therapy is that none of the treatments are completely successful. Despite performance by experts in the procedure, persistence of intestinal metaplasia occurred in 1 of every 5 patients (20%) treated while 1 in ten patients had persistent dysplasia (13%) in this report from the University of North Carolina. This has important implications when discussing ablation therapy with patients. The patient should understand that there is a risk of failure, failure should also be defined in terms of number of treatments that will be attempted. Patients who have no response to therapy in terms of persistence of dysplasia and lack of change in the length of the columnar mucosa may be classified as failures after a minimum of two adequately performed radiofrequency treatments. The study in this issue of CGH found that most patients with dysplasia could be completely ablated with three treatments. If the patient does not respond to radiofrequency ablation, what should be the next step? Once ablation is initiated, gastroenterologists probably should try to continue to treat until the entire metaplastic mucosa is eliminated. Treatments that have been suggested for treatment failures would include aggressive widespread mucosal resection, cryotherapy, and photodynamic therapy^{9, 10}. The rationale for mucosal resection is straightforward, however cryotherapy and photodynamic therapy appear to be successful in this group primarily because of the differences in their mechanism of action. Cryotherapy can cause ischemic necrosis and intracellular formation of ice crystals that can disrupt cells. Photodynamic therapy causes cell death by creation of reactive oxygen species that interact with cell membranes and organelles¹¹. These treatments have been reported to have more adverse events than radiofrequency ablation that emphasizes the need to appropriately select patients for initial ablation therapy.

The third important principle in ablation therapy is that at the current time, ablation is a long-term commitment because of the recurrence of both intestinal metaplasia and dysplasia after ablation in up to 18%¹². Patients must understand that continued surveillance is needed even after complete elimination of intestinal metaplasia because of the potential of recurrence of disease. Although the risk of recurrence is not high, it is likely clinically significant and as cancer and high-grade dysplasia have been reported in 15% of recurrences. It is still unclear the recurrence is due to lack of detection of small cell clusters of Barrett's esophagus that remain after ablation or whether this is de novo development of a new Barrett's esophagus. However, it does raise some questions about the possible origins of Barrett's esophagus and its real world effects on ablation therapy.

Although ablation therapy has been performed for almost two decades, the medical community really does not understand the biological basis for ablation. Unlike polypectomy in the colon where the neoplastic adenoma can be removed and the normal colonic epithelium can completely regrow with elimination of the neoplastic tissue, ablation therapy in Barrett's esophagus involves not only dysplastic tissue therapy, it also involves the reversal of the metaplastic tissue. It is well accepted that acid control is important and inadequate acid control might lead to failure of ablation therapy. However, prospective randomized trials have been performed investigating ablation therapy with varying degrees of acid suppressive medication and no consistent association has been found^{13, 14}. In addition, when deep injury occurs as in endoscopic mucosal resection or dissection, squamous regeneration appears to occur regardless of the degree of acid reflux present. It appears as if there are changes in the stroma of the Barrett's esophagus that need also needs to be treated to obtain reversal. New technologies such as optical coherence tomography that can visualize deeper into the mucosa have found that there are submucosal glands that persist after ablation and may be related to the failure of ablation therapy¹⁵. In addition, recent lineage tracing studies in a genetically engineered mouse model of esophageal

inflammation with IL1B overexpressed in squamous esophageal tissue have found that intestinal stem cells identified by expression of Lgr5 appear to migrate from the gastric cardia into the esophagus¹⁶. This suggests that in some patients, an abnormal stem cell population might not be eliminated if we adhere to a program of only treating the tubular esophagus as was done in the randomized trials. If these animal studies are similar to human Barrett's esophagus, it may be necessary to treat further into the gastric cardia. Finally, there is also evidence that ablative therapies do not appear to work as well when specific genetic abnormalities are present such as loss of p16. The lack of understanding regarding the biology behind ablation has hampered us from getting to a treatment that might well be more permanent than what is being obtained. It also raises opportunities for possible combination therapies for Barrett's esophagus with the use of chemoprevention agents to decrease recurrence of Barrett's esophagus.

It is apparent that we have made great strides in developing newer forms of ablation therapy that have dramatically lowered complication rates and have improved efficacy over previous treatments. It is also clear that we have not achieved all that is needed to really eliminate the disease. Ablation therapy is advancing and with greater understanding of the treatment, future progress will be amazing to behold.

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