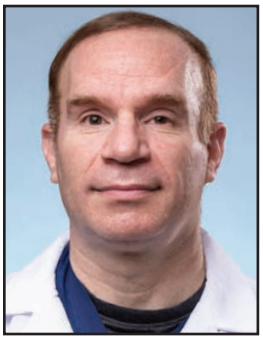
Douglas G. Adler MD, FACG, AGAF, FASGE, Series Editor

Radiofrequency Ablation for Indications Beyond Barrett's Esophagus

Courtney Walker



Douglas G. Adler

INTRODUCTION

Radiofrequency ablation (RFA) was first approved by the United States Food and Drug Administration in 2001 for the treatment of Barrett's esophagus and for gastric hemostatic applications.[1] RFA uses alternating electrical currents in a closed circuit whereby tissues between two electrodes will become coagulated.[2] The acute coagulative necrosis occurs when temperatures within tissue are greater than 60 degrees Celsius and results in denaturing of proteins, melting of the plasma membrane, and near instantaneous cell death.[3]

Within the GI tract, RFA is perhaps best known for treating dysplastic lesions in the esophagus (typically Barrett's esophagus with dysplasia), as well as pancreatic neoplasia, and malignant biliary obstruction.[4]

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This review will focus on the application of RFA in the luminal GI tract for non-Barrett's lesions.

Overview of Endoscopic RFA Technology

Unlike esophageal RFA treatment for Barrett's esophagus, the coagulum that forms after RFA for benign luminal GI conditions is not scraped to minimize the risk of bleeding.[4] In the U.S.A., RFA is performed with the Barrx Flex generator (Medtronic Inc, Sunnyvale, CA). The device is a bipolar radiofrequency (RF) generator which connects to various single-use RFA catheters. The generator measures tissue impedance during RF energy delivery and automatically adjusts energy output to obtain an equal depth of tissue ablation throughout the field.[4] Catheters for use in the GI lumen include over the scope and through - the - scope (TTS) catheters.

RFA for Symptomatic Cervical Inlet Patches

Cervical inlet patches (CIP) are heterotropic gastric mucosa located in the proximal esophagus just below

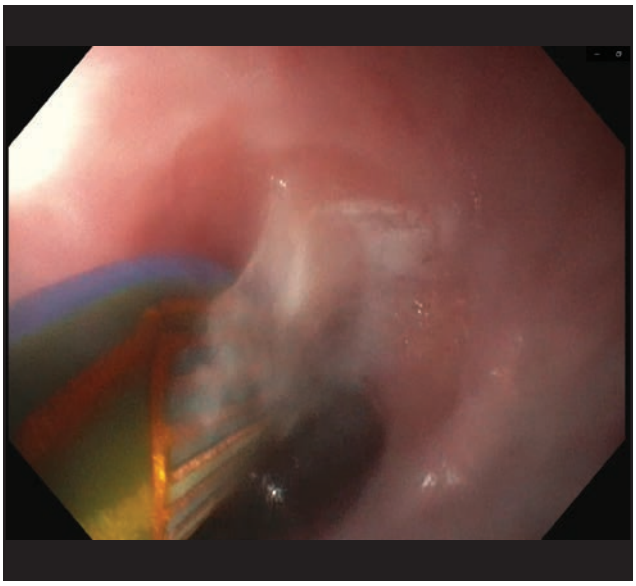

Figure 1a. Positioning a through-the-scope RFA electrode over a large, symptomatic cervical inlet patch.

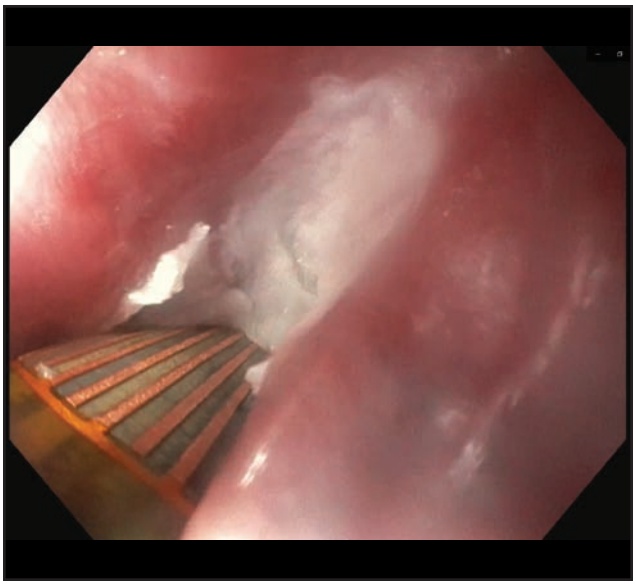

Figure 1b. Same patients as in Figure 1a after RFA treatment. Note that the entire area of the inlet patch has been ablated.

the upper esophageal sphincter, usually 15-20 cm from the incisors and are considered a congenital condition.[5] CIP is often an incidental finding, but in some patients, it can cause symptoms, and rarely may have evidence of Barrett's esophagus and/or dysplasia necessitating treatment. Symptomatic patients most commonly present with dysphagia and cough, but ulcers, bleeding, and even peptic strictures can develop.[6] Medical management of CIP begins with proton pump inhibitors and while this may improve some symptoms, it is at times ineffective and endoscopic therapy is warranted.[7]

Endoscopic therapy includes argon plasma coagulation (APC) and RFA. (Figure 1) Unlike APC, the uniform depth of ablation with RFA is felt to reduce the risk of adverse events such as stricture formation, perforation, and buried glands that may be seen following treatment with APC. One of the first studies to show safety and efficacy of RFA ablation for CIP was a ten-patient pilot study using a TTS RFA device. In this study by Dunn et al, all visible CIP was treated with three energy applications at 12 J/cm^2 with a median of two RFA sessions and a total of 179 ablations. Follow up esophagogastroduodenoscopy (EGD) was performed at three and 12 months. Complete endoscopic and histologic resolution of CIP was seen in 80% of patients.[8] RFA of the CIP also had clinical success with improvement in globus sensation, sore throat, and cough. Treatment with RFA was durable as there was no recurrence of buried glands on biopsies or symptoms at 14 months follow up and no adverse events including strictures were reported.[8]

An additional study evaluated patients with large, symptomatic CIP (greater than 20 mm) and found that 80% of patients achieved macroscopic and histologic resolution of CIP after two RFA ablations. These patients had significant improvement in globus sensation, mental health scores, and laryngopharyngeal reflux. Similarly, no strictures or chronic adverse events were seen after mean follow up of 1.9 years.[9] Overall, RFA for the treatment of CIP is effective for histologic removal of CIP and symptom improvement and with potentially less risk of deeper mucosal damage compared to APC.

RFA for Gastric Antral Vascular Ectasia

Gastric antral vascular ectasia (GAVE), often referred to as "Watermelon stomach," is the endoscopic appearance of erythematous stripes, which are visibly convoluted columns of vessels, extending from the pylorus into the distal gastric body.[10] The dilated, fragile, and ectatic blood vessels are located within the superficial

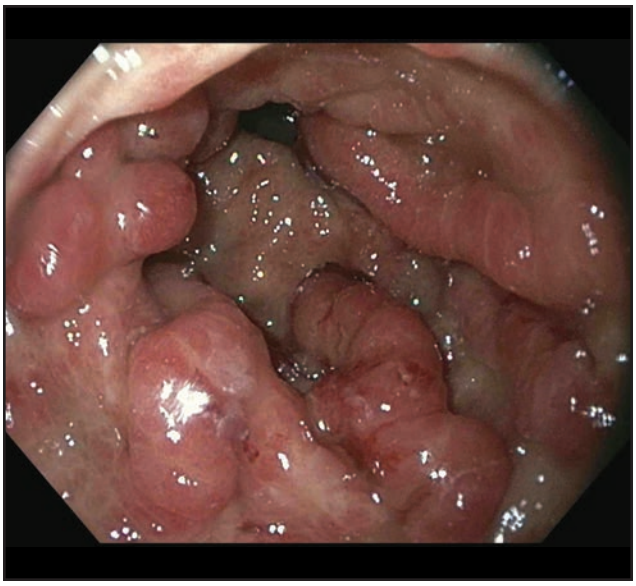

Figure 2a. Severe GAVE in a patient with cirrhosis.

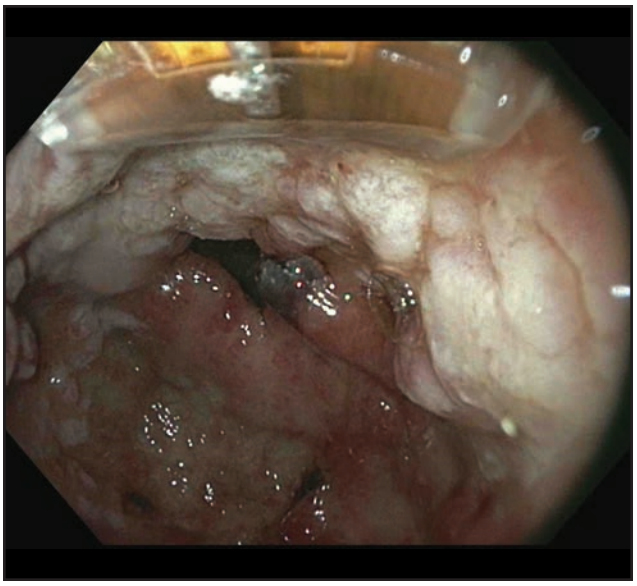

Figure 2b. RFA applied to treat GAVE.

submucosa and mucosa and, when disrupted, cause gastrointestinal bleeding, iron deficiency anemia, and need for red blood cell transfusion.[10] GAVE is seen in 30% of patients with cirrhosis and is also associated with autoimmune conditions such as scleroderma, CREST syndrome, Raynaud's, and chronic kidney disease.[11,12] The severity of GAVE has yet to establish a correlation with degree of chronic disease severity.[13] Distinguishing GAVE from portal hypertension gastropathy (PHG) is critical as GAVE will not respond to therapy aimed at reducing portal pressures, unlike PHG.[14]

Prior to RFA, endoscopic treatment for GAVE was generally performed via thermal therapy with APC or the now obsolete laser therapy.[15] The objective of thermal therapy is the eradication of the ectatic vessels that result in blood loss. APC has been widely used due to ease of use, low cost, and overall safety.[13] However, unlike RFA, APC can be difficult to apply over large areas, and the depth of injury is highly variable. (Figure 2)

One of the first studies to evaluate RFA for treatment of GAVE was a pilot study of six patients with hemorrhagic GAVE and blood transfusion dependence.[16] In this study, four of the six patients had failed prior APC. The HALO90 ablation system with over the scope RFA catheter fixed at the 12 0'clock position was used, four pulses per GAVE site were applied with a uniform depth of ablation created over 3 cm.[2] The maximum depth of ablation was limited to the superficial mucosa (14 J/cm^2 of energy applied). Overall, there was an improvement in hemoglobin of 1.2 g/dL with only one patient still being transfusion dependent at the end of the study.[16] No adverse events were reported.

Other studies also evaluated GAVE refractory to APC, treated with RFA, including use of the HALO90 ULTRA ablation catheter (with a surface area of 5.2 cm^2).[17,18] Technical success was defined as complete eradication of endoscopic GAVE. In these prospective studies patients required a median number of 2 - 2.5 RFA sessions to achieve a goal of 90% technical success in one study and 100% in the other. In the study by Jana et al., 71% of patients achieved clinical success and were transfusion independent at 6 months follow-up.[18]

In addition to the classic flat, striped, watermelon appearance of GAVE there is a nodular phenotype. Nodular GAVE is seen in 30% of cases and described as endoscopically smooth, benign-appearing nodules in the antrum, often associated with cirrhosis.[19] Previously, nodular GAVE was considered a distinct histopathologic entity, but now

Figure 2c. RFA applied to treat GAVE.

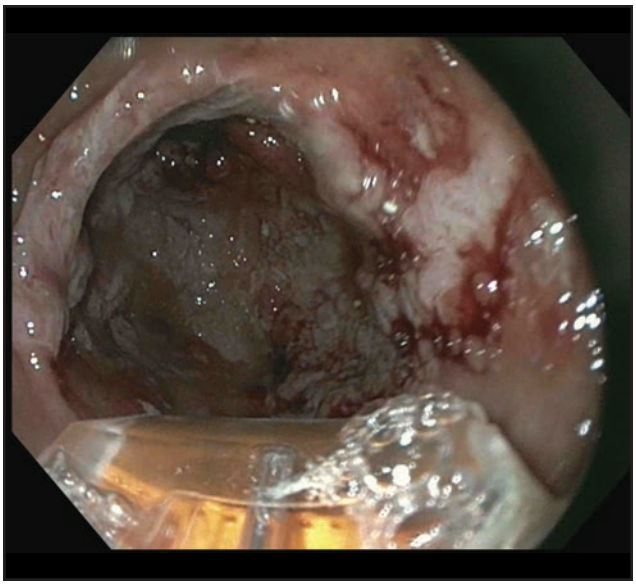

Figure 2d. Final appearance of stomach after RFA application. Note large surface area of stomach treated.

is thought to be gastric hyperplastic polyps arising in a background of GAVE.[20,21] Similar to flat GAVE, nodular GAVE can also present with chronic iron deficiency anemia and gastrointestinal bleeding. Treatment involves APC, RFA, and the possible addition of endoscopic band ligation (EBL) for refractory nodular GAVE. Case series have shown that nodular GAVE may be more difficult to treat and multimodal therapy, either APC or RFA with banding have improved hemoglobin concentrations with less blood transfusions.[22,23,24]

RFA versus APC for GAVE

A large, systemic review and meta-analysis of APC (24 studies, 508 patients) vs. RFA (9 studies, 104 patients) found those treated with RFA required fewer treatment sessions (2.10 vs. 3.39 for APC, $p < 0.001$) and had improved endoscopic ablation success (97% for RFA and 66% for APC, $p < 0.001$). Post-treatment pooled hemoglobin increase, and number of blood transfusions was statistically better in the APC group. However, 47% of the RFA patients had GAVE refractory to APC therapy, suggesting some heterogeneity in the samples between modalities. Overall, RFA was associated with fewer adverse events compared to the APC group.[25]

Regarding adverse events of RFA, ulcerations and traumatic laceration to the gastric cardia, nausea, vomiting, and abdominal pain have been reported upon removal of the HALO90 ULTRA device.[26] Less common are reports of sepsis and bacteremia. A case report of a patient with cirrhosis and GAVE without evidence of infective endocarditis or spontaneous bacterial peritonitis developed streptococcus intermedius bacteremia almost two weeks after the fourth and final session of RFA with a total of 50 pulses, at least raising the possibility that these two events were related.[27] Mucosal injury from RFA was the suspected cause of bacterial translocation. While there are overall limited reports of RFA adverse events, perhaps the largest deterrent to RFA use is the overall cost, which is approximately five times greater per use than APC.[28] Furthermore, almost all endoscopy facilities have APC technology on hand, while RFA is in much more limited use.

RFA for Radiation Proctitis

RFA also has a role in the treatment of radiation proctitis. Approximately 5-20% of patients receiving radiotherapy for pelvic malignancies such as: prostate, cervical, vaginal, ovarian, and bladder cancer, etc., will develop radiation proctitis.[29,30] Cell death and apoptosis from radiation damage to DNA, lipids, and proteins occurs.[31] This microvascular injury to the rectal mucosa gives rise to ischemia, fibrosis, and the development of fragile and friable

Figure 3. Severe radiation proctitis.

neovascular lesions susceptible to hemorrhage.[32] (Figure 3) Chronic rectal bleeding from radiation proctitis may result in iron deficiency anemia and blood transfusion dependence.

APC has been the primary therapy for radiation proctitis for many years, but with limitations. Following APC, post-treatment ulcerations can develop from the deeper depth of thermal injury associated with this technology.[33,34] Adverse events from APC for radiation proctitis include perforation and tissue necrosis in up to 14% of patients.[34]

With regards to RFA, the tightly spaced bipolar RFA catheter limits the RF energy penetration to the superficial mucosa, where the vessels of interest exist, reducing the risk of deep tissue injury as can occur with APC.[35]

While less common, radiation-induced sigmoiditis is also seen following radiotherapy for pelvic malignancy. Radiation sigmoiditis may be more resistant to treatment with ablation therapy due to difficulty in targeting affected tissue with APC in the sigmoid colon.[36]

RFA can potentially be used to treat radiation sigmoiditis as well. A retrospective study used 12 J/cm2 instead of 15 J/cm2 when radiation proctitis lesions were greater than 8 cm proximal to the dentate line.[37] No significant adverse events were seen. Mild to moderate anal pain was found in 34.2% of patients and controlled with acetaminophen or combined with non-steroidal anti-inflammatory drugs, or topical analgesics.[37] An initial proof of concept *ex vivo* study to evaluate RFA for the treatment of radiation proctitis was performed in 2011 by Trunzo et al. In this study, RFA was performed with two to four applications of energy applied to surgically resected left colon and rectum segments with a range of 12 to 20 J/cm.[2] Sites receiving two applications of RFA showed no serosal alteration compared to 15% ($p = 0.11$) of sites receiving four applications. Histologic depth of ablation within the muscularis propria was seen in 25% of two-application sites and 63% of four-application sites ($p < 0.05$). Regardless of increasing energy density, there was no correlation with deeper ablation injury. This study suggested RFA for treatment of radiation proctitis was feasible and without significant risk of deep submucosal injury with only two RFA applications.[38]

Other case studies evaluated patients with chronic radiation proctitis with hemorrhage using RFA HALO90 or HALO90 ULTRA catheters and found that broad areas of active bleeding could be treated in two to four RFA sessions to control rectal bleeding.[39,39] In one study, endoscopic optical coherence tomography (EOCT) was used to identify ectatic blood vessels in the rectum greater than 50 um in diameter. After RFA, EOCT showed re-epithelialization over the treated areas.[40] Follow up after 2 sessions of RFA, 12-17 months later, showed new epithelium without development of ulcerations, strictures, or rebleeding.[39]

One of the larger studies to investigate RFA therapy for radiation proctitis evaluated 39 Veteran's Affairs patients. Enrolled patients had a history of endoscopically confirmed chronic radiation proctitis with recurrent hematochezia for at least three months and were treated with a mean number of 1.49 RFA sessions with the RFA catheter mounted in the 6 o'clock position on the endoscope. Rectal bleeding stopped in all patients at follow-up, and mean hemoglobin increased from 11.8 g/dL to 13.5 g/dL ($p < 0.001$).[41] Discontinuation of red blood cell transfusion and iron therapy was seen in 92% and 82% of patients respectively.[40] Endoscopic improvement was assessed via the rectal telangiectasia density score (range 0: normal mucosa to 3: two or more coalescing patches of rectal telangiectasias) with initial scores of 3 at the start of therapy, decreased to 0 ($p < 0.0001$)

during follow-up.

Findings of improvement in radiation proctitis were reported in a retrospective single arm cohort study of 35 patients. In this study, the mean follow up was 18.6 months and rectal telangiectasia density score decreased from mean of 2.96 to 0.85 ($p < 0.0001$) at the end of follow up.[37] All patients in this study had resolution of hematochezia and statistically improved levels in hemoglobin at the end of the study. Rectal ulcers, fistulas, and strictures did not occur.[41] A systematic review and metanalysis of six studies (71 patients) in which 38% of patients with chronic radiation proctitis had failed prior APC treatment, required a mean of 1.71 RFA sessions to achieve a pooled clinical and endoscopic success of 99% and 100% ($p < .0001$). Patients were followed for a mean of 19.73 months. There were no serious adverse events and there was a mean weighted difference of hemoglobin improvement post-RFA of 2.49 g/dL.[42]

CONCLUSION

The use of RFA has expanded well beyond the treatment of Barrett's esophagus. RFA has shown great efficacy in the treatment of symptomatic cervical inlet patches, GAVE, and radiation proctitis in patients with and without other prior endoscopic treatments.

Among patients with symptomatic inlet patches, RFA was shown to effectively ablate endoscopic and histologic evidence of heterotropic gastric mucosa in most patients. Many patients had clinical resolution of globus, sore throat, and cough and without stricture formation or serious adverse events. Patients with GAVE also have high rates of endoscopic eradication following RFA and may be an alternative to patients with refractory GAVE previously treated with APC. RFA in radiation proctitis results in the development of new epithelium with decreased risk of bleeding or need for blood transfusions. Application of RFA for these indications is effective, with an acceptable level of adverse events. ■

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