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Endoscopic Ablation of Barrett's Esophagus Using the Halo® System

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Barrett's, decision-making · Barrett's, endoscopic treatment · Barrett's esophagus · Endoscopic ablation · Halo® system · Radiofrequency ablation

Abstract
There is increasing interest in the endoscopic treatment of Barrett's esophagus. Endoscopic treatment has been utilized for many years, but in the past, no specific method has emerged as an appealing treatment option with appropriate safety, efficacy and ease of treatment for both patients and physicians. Recently there has been a growing literature related to the endoscopic ablation of Barrett's esophagus using radiofrequency ablation (RFA) (Halo® system). In order to discuss when RFA is indicated for Barrett's, one needs to know: (1) What is the 'histology' of the Barrett's? Does the patient have intestinal metaplasia, low-grade dysplasia, high-grade dysplasia or intramucosal carcinoma? (2) What are the endoscopic options to be considered as opposed to RFA? What are the advantages and disadvantages of each? (3) What additional variables need to be examined?

Decision-Making and Barrett's

Endoscopic treatment has been utilized for many years [1]. All of the decisions about endoscopic treatment for Barrett's are based on the presumption that intestinal metaplasia (IM) may advance to low-grade dysplasia (LGD), that LGD may advance to high-grade dysplasia (HGD), and that HGD may progress to intramucosal carcinoma (IMC). The thoughts are that proto-oncogenes are activated and that tumor suppressor genes are inactivated, giving a growth advantage for hyperproliferation. After more genetic changes, neoplasia begins and after more genetic changes, invasive carcinoma occurs. The strategy would be to prevent this progression and to eliminate both the dysplasia or early carcinoma and ideally all of the Barrett's tissue as well.

The majority of patients who are found to have IM with no dysplasia on their initial examination at which Barrett's is diagnosed do not progress to dysplasia. However, in a study with a follow-up of >4 years, Sharma et al. [2] found that 16.1% of patients progressed to LGD, 3.6% of patients progressed to HGD, and 2% of patients progressed to adenocarcinoma. To put this in a more clinical perspective, a physician following a patient with IM might expect that 1.4% per patient per year would progress to HGD or IMC (HGD/IMC), one might expect that 2.7% per patient per year of patients with LGD would advance to HGD (LGD/HGD), and 2–10% per patient per year of patients with HGD would progress to IMC.

Many physicians who manage patients with Barrett's esophagus dictate their follow-up by using guidelines put forth by gastroenterology societies. A recent review from the American College of Gastroenterology authored by Wang and Sampliner [3] outlines the follow-up for pa-

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tients with IM only, LGD and HGD. The recommendation is that for those patients with Barrett's esophagus with IM, after they are negative for dysplasia on two endoscopies, they should undergo surveillance endoscopy in 3 years. The recommendation is that for those patients who have LGD, the procedure should be repeated once and if only LGD is found, an annual surveillance should be carried out until there is no dysplasia on two consecutive endoscopies with biopsies. For patients with HGD, the recommendation is that the endoscopy be repeated with the biopsy evaluated by an expert pathologist. If there is found to be a focal disease, then the most common recommendation is that there be a 3-month surveillance. If there is mucosal irregularity, the most common recommendation is that an endoscopic mucosal resection (EMR) be performed and that further management be based on the findings of the EMR. If there is multifocal disease found and some intervention is necessary, most commonly this has been with esophagectomy. More recently, endoscopic treatment such as radiofrequency ablation (RFA) could be considered. Our own observation is that for patients who have only IM, then surveillance is practiced more commonly than an alternative approach, which is endoscopic therapy. For patients who have LGD, the majority are still followed with surveillance, but increasingly endoscopic therapy is being utilized. For patients who have HGD, unless there is some contraindication to intervention, then esophagectomy or endoscopic treatment is recommended.

There are many challenges in decision-making with Barrett's. The most important is that we simply do not know which patients with non-dysplastic IM, LGD or patients with HGD will progress to more advanced disease. Biomarkers or other predictors would be extremely helpful. In addition, it is appreciated that biopsy sampling error may occur with surveillance. There is also interobserver variability for dysplasia and studies have shown there is a lack of uniformity among expert pathologists about whether dysplasia exists and the grade of dysplasia. Although surveillance is the most common management strategy for IM and LGD, there are no prospective studies that suggest that surveillance prevents cancer. It is also challenging to understand that there are economic implications for each strategy and it is not fully clear which one has the best cost-effectiveness. In addition, the issue of patient anxiety – of being followed with a chronic condition that may lead to cancer – is real, but it has not been quantitated.

Endoscopic Treatment of Barrett's

Assuming endoscopic treatment should be considered, what are the options? A wide variety of endoscopic options have been utilized and are the focus of other articles. They include multipolar coagulation, argon plasma coagulation, photodynamic therapy, laser therapy, cryotherapy, radiofrequency (Halo®) ablation, mucosal/submucosal resection, or a combination of the above. The equipment that is utilized for the radiofrequency (BARRX-Halo®) ablation system includes an energy generator, a sizing balloon for Halo® 360 treatments, a treatment delivery balloon (Halo® 360) for circumferential therapy, and a separate product called a Halo® 90 for non-circumferential treatment. The latter is attached to a standard forward-viewing endoscope. The equipment and the technical details have been described elsewhere [1, 4].

The principle of radiofrequency electrode technology is to deliver high power (approx. 300 W) in a short period of time (<300 ms) and to utilize energy density control. When the Halo® 360 balloon is used, the idea is to have uniform wall tension, which is achievable with a balloon. In addition, tight electrode spacing (<250 μm) leads to more superficial tissue injury. The concept is that this will allow the depth of the penetration to ablate the epithelium and muscularis mucosa without injuring the submucosa. Depths of ablation are generally in the range of 700 μm. The concept is that the Barrett's tissue will not extend into the submucosa. If the submucosa is not injured there will be less risk of bleeding, fibrosis and stricturing.

The technique is performed in the following manner. After the endoscopic esophageal landmarks are defined, the esophageal wall is sprayed with acetylcysteine 1% and then flushed with water to remove excess mucous for the Halo® 360 ablation procedure. The esophageal diameter is sized with a sizing catheter. It is passed over a stiff guidewire, which is passed endoscopically and then removed. An autosizing balloon is used to determine the diameter of the esophagus. This is important to allow good contact between the balloon/electrodes and the esophageal wall on the one hand and not to apply excessive pressure on the other. The electrodes on the Halo® 360 treatment catheter are 3 cm in length and treatment is delivered beginning approximately 1 cm above the proximal margin of Barrett's. The location can be achieved by noting the marks on the shaft of the catheter and is usually confirmed with side-by-side endoscopic observation of the ablation procedure. The treatment is

delivered using between 10 and 12 J. Delivery typically lasts 1–2 s. Moving from proximally to distally, the balloon is progressively repositioned allowing for a very small overlap with the previous treatment zone. Ablation is repeated until the entire Barrett's esophagus has been treated with RF energy. In most cases with the Halo® 360, two treatments are delivered. Generally, the Halo® 360 device is removed after the first series of applications and then cleaned. In addition, the exudative material caused by the burn can be scraped off the esophagus with aggressive washing or using a device similar to the endoscopic cap that is used for mucosal resection. After the initial treatment is delivered, endoscopic observation is made to determine that all the Barrett's has been treated. After that observation is achieved, the procedure for that day is completed. A follow-up endoscopic treatment is usually carried out in 3 months.

At the time of the follow-up, a second treatment may be necessary. This can be repeated with the Halo® 360 balloon if there are large areas of Barrett's in the tubular esophagus that have not been eliminated. However, it is far more common that on subsequent treatments after the initial Halo® 360 treatment that the Halo® 90 device will be utilized. The Halo® 90 electrode is fitted on the tip of the endoscope and then the endoscope is advanced into the esophagus. Care must be taken when advancing from the pharynx to the upper esophageal sphincter into the esophagus. In most patients there is little difficulty, but in some patients, particularly those with unusual anatomy, passage may require patience and at times dilation of the upper esophageal sphincter. Prior to assessing the mucosa for further treatment, 1% acetylcysteine is often sprayed to remove mucus and to highlight mucosal features. Narrow-band imaging may also be applied. After the residual Barrett's is identified, the electrode is brought into close contact with the mucosa, the device is deflected for a close apposition of the device with diseased mucosa and then treatment is carried out. Follow-up is then carried out in 2–3 months to evaluate the esophagus.

Clinical Trials of Radiofrequency Ablation for Barrett's

Since the device was released in 2003, there have been an increasing number of abstracts and full publications describing the technology and its clinical use. The first work occurred in patients who were undergoing esophagectomy and treatment was carried out just prior to surgery so that clinical and histologic information could be obtained about the utility of treatment in patients who were already scheduled to have surgery. In 2003, the Ablation of Intestinal Metaplasia (AIM) I Trial began to clarify benefit in patients who had metaplasia without dysplasia [5]. Subsequently, studies in patients with LGD and HGD were undertaken. In addition, information has been gathered through patient registries and through cooperative studies.

It can be confusing to 'analyze' the results of RFA treatment for Barrett's without substratifying the analysis. Radiofrequency has been used to treat IM only, to treat LGD only, to treat HGD only, and to treat LGD + HGD ± IMC. In addition, RFA has been combined with additional endoscopic modalities and radiofrequency has been studied in patients with squamous dysplasia. Therefore, when one looks at the results, one needs to understand which group of patients is being treated. The results of some of the most important studies are reviewed below.

Some individuals believe that it is appropriate to use RFA for IM, while others do not. Those who support its use state that initial studies on its efficacy and safety have been encouraging. They also point out that without predictive markers some patients with a family history or anxiety may desire treatment even if it is not clear that their disease will progress. It is also known that 50% of patients who progress to HGD or esophageal adenocarcinoma, have no dysplasia on as many as two previous endoscopies. These are the arguments that are posed in opposition to those who say that only 10% of patients with IM will progress. Therefore, why treat 90% of patients who will not have more advanced disease? The longest follow-up study for patients who underwent endoscopic ablation of Barrett's esophagus with IM only is the AIM II Study [6]. In this study, 70 patients were enrolled in the initial effectiveness phase of the trial and underwent circumferential ablation. They had a subsequent endoscopy at 1, 3, 4, 6 and 12 months. After 12 months, 62 patients were enrolled into a study extension, which followed these patients for another 1.5 years. At the end of 2.5 years (30 months) 61 had endoscopy with biopsy. Of those, there was complete remission (CR) of IM (CR-IM) in 98.4% of patients. There were >1,000 biopsies collected in these patients at 12 months. No strictures or buried glands were seen.

Some have argued that it is unwise to treat patients with IM only, since most will not go on to more advanced disease. Das et al. [7] performed a study assessing the cost-effectiveness of a combined modality using Halo®

360 followed by Halo® 90 ablation in the management of patients with non-dysplastic Barrett's. The mathematical model compared different strategies in a 50-year-old patient. The assumptions were that the treatment would get rid of Barrett's in 50% of patients and that the costs were 'high'. With this mathematical model, the patient age, cost of ablation and CR rate associated with an ablation are critical determinants of its cost-effectiveness. The authors concluded that ablative therapy is cost-effective over 'surveillance' if the patients are treated at an age <55 years, the cost for the procedure is less than USD 7,450 and the CR rate is >66%.

A study from Sharma et al. [8] presented a 2-year follow-up on patients who had been treated for LGD with RFA. Ten patients were treated initially with the Halo® 360 and then the Halo® 90; biopsies were taken at 1, 3, 6, 12 and 24 months. There was CR of dysplasia (CR-D) in 100% of the patients and in all but 1 of the 10 patients there was CR-IM.

A cost-effectiveness study comparing endoscopic surveillance or esophagectomy with RFA for patients with Barrett's and LGD was written by Inadomi et al. [9]. In this study, ablation is the most cost-effective option for patients with LGD if you can achieve CR-IM in 60% of patients and CR of LGD in 70% of patients. For this group of patients ablation 'dominates' surveillance, which means it is less expensive and more effective.

There are some studies that look at RFA for HGD. The largest series of patients is included in the HGD Registry [10], 142 patients from 16 centers were included. Eight had previous EMRs. In this collection of patients, all but two patients were treated with circumferential ablation with 12 J/cm^2 because Halo® 90 treatments were unavailable at this time. 92 of the patients were available for follow-up beyond 6 months; the median follow-up was 12 months. The CR for HGD was 90% and the CR-IM was 53%.

The most important study assessing RFA for dysplasia is the Randomized Multicenter Sham Controlled Trial by Shaheen et al. [11], which has been presented in an oral form and published in an abstract form. There were 120 patients with dysplasia, 60 of which had LGD and 60 of which had HGD. In each arm, 2 of 3 patients were randomized to RFA and 1 of 3 to sham control. The initial treatment was with Halo® 360 and at the follow-up points focal ablation could be instituted if there was residual Barrett's. Follow-up endoscopies with biopsies were carried out at 6, 12, 18 and 24 months in the patients with LGD and at 3, 6, 9, 12, 15, 18, 21, and 24 months in the patients with HGD. The primary endpoints were CR-IM in all patients, and CR-D in those patients with HGD and LGD. The evaluations were done both per protocol and intention to treat. Per protocol, 83% of the treated patients had CR-D in the high-grade group and none in the sham group. For those patients with LGD, 100% of the treated patients had CR-D and 36% of the patients had CR-D. Regarding CR-IM, that was found in 75% of the patients who were treated with HGD and 87% of the patients with LGD. None of the sham patients had CR-IM. The reason that these results are so impressive is the complete response for a patient is defined as all biopsies negative for either dysplasia or IM. That is, 1 positive biopsy out of 40 is considered a failure.

For patients with dysplasia and IMC, many patients are treated with EMR followed by RFA. This is a particular common strategy if there is an irregularity or nodule seen in the Barrett's segment. The thinking is that the EMR will both remove the pathologic tissue, but also clarify whether or not this management is sufficient for removing the HGD or IMC. After a localized EMR is performed, a RFA can be performed on the flatter and more extensive Barrett's tissue. The leading group in the world for this approach is the group from the Amsterdam Medical Center in the Netherlands led by Bergmann and his colleagues. An example of the efficacy of this strategy is a publication by Gondrie et al. [12, 13] in which 44 patients with dysplasia and IMC were treated. At 12 months the CR-D was 98% and the CR-IM was 98%. Other studies from this group and the European Multicenter Study Group are underway.

Complications

The RFA has proven to be a safe procedure, but as with any procedure there are some complications. Chest pain occurs in the majority of patients who are treated and generally lasts for a few days. Management with a local solution of viscous Xylocaine® and antacids with non-narcotic analgesics has been effective in most patients. In 1–2% of the patients, the pain has been more severe and longer lasting, and rarely, hospitalization for pain management is required. The most common delayed complication has been the development of esophageal strictures. This is more likely to occur in patients who have had EMRs and in some areas where treatment has been overlapped. The exact incidence is not known, but in published series it has been in the range of 1%. To date, approximately 20,000 patients have been treated and no deaths have been reported. Perforations have oc-

curred, but they are extremely rare and usually happened during insertion or removal of the ablation catheter.

Unanswered Questions and Future Directions

In addition to studies looking at clinical efficacy, there has been great interest in the following topics. Enthusiasts and skeptics both wonder if there will be a problem with 'buried' glands, foci of Barrett's that are either left behind or developed below the epithelialized squamous layer. There have been questions about whether or not the depth of endoscopic biopsies would enough to discover submucosal Barrett's if it existed. In order to answer some of these questions about depth an endoscopic ultrasonography has been utilized, but has not been consistently beneficial. Since either short or long segments of mucosa are being treated, the question has been asked about how that affects the subsequent esophageal diameter, esophageal compliance and esophageal motility. Investigators continue to look for improvement in the current existing devices with hopes that they can become more effective, safer and easier to use. And paramount to all of the work on endoscopic treatment of Barrett's is the need to identify 'biomarkers' that predict disease progression and efficacy of therapy.

Conclusions

RFA with the Halo® treatment system is a logical and well-conceived therapy. The device and the technique are still in evolution. RFA is effective for eliminating IM and dysplasia in most patients with Barrett's esophagus. Complications occur, but the rate of complications is acceptable. It is the view of the authors that this represents the best endoscopic treatment for flat Barrett's at this time. Combining EMR and RFA has an appeal in certain patients, particularly those that have nodular or elevated foci within the Barrett's. Answers to the questions expressed above will lead to further refinement of this treatment and better definition of the patients for whom this treatment is most appropriate.

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