ADVANCES IN ENDOSCOPY

Current Developments in Diagnostic and Therapeutic Endoscopy

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Endoscopic Cryotherapy for Barrett Esophagus

George B. Smallfield III, MD, MSPH
Assistant Professor of Medicine
Department of Internal Medicine—Gastroenterology
Virginia Commonwealth University Medical Center
Richmond, Virginia

G&H What is cryotherapy, and when did it become available for endoscopic use?

GS Cryotherapy is the use of cold temperature for medical treatment. For gastrointestinal lesions, a cryogen (either a cold liquid or a cold object, such as a balloon) is used to freeze target tissue and induce apoptosis in tissue sections.

The most commonly used cryogens in the United States are liquid nitrogen and carbon dioxide. Although cryotherapy has been used to treat cancers since the 1850s, it only became available for endoscopic use nearly 150 years later, when Dr Mark Johnston developed endoscopic spray nitrogen cryotherapy using leftover hospital equipment and a thermos, compressor, and epoxy. After the spray device was created, Johnston received a grant from the National Institutes of Health to perform animal studies. In 1999, initial data were published reporting that the procedure was safe in swine. The nitrogen device was then released for cryotherapy in humans in 2007.

G&H Which gastrointestinal disorders are amenable to cryotherapy?

GS Cryotherapy is currently used for dysplastic and neoplastic esophageal lesions. This procedure has been successful in both squamous cell esophageal cancer and adenocarcinoma of the esophagus. Cryotherapy is likely underutilized for palliation in esophageal cancer or for salvage therapy in people who are not candidates for further therapy, such as chemoradiation or surgery.

G&H How is cryotherapy performed?

GS When using cryotherapy with nitrogen, endoscopists will develop landmarks to locate the cancer. A ventilation tube is placed across the gastroesophageal junction for ventilation of the stomach as well as the esophagus. Following this step, the endoscopist inserts the spray catheter in the operating channel of the endoscope and performs cycles of freezing and thawing, which result in direct tissue damage.

G&H What are the findings of clinical studies that have examined the efficacy of cryotherapy?

GS I am not aware of any randomized, controlled trials of cryotherapy; however, there have been several retrospective and prospective assessments. A retrospective study by Dr Nicholas Shaheen and colleagues of the treatment of high-grade dysplasia in patients with Barrett esophagus reported complete eradication of high-grade dysplasia in 97% of Barrett esophagus patients, complete eradication of low-grade dysplasia in 87%, and complete eradication of intestinal metaplasia in 57%.

In the safety registry for the nitrogen device, Dr Shireen Ghorbani and colleagues performed a prospective assessment at 4 centers that showed complete eradication of high-grade dysplasia in 90% of Barrett esophagus patients, complete eradication of low-grade dysplasia in 81%, and complete eradication of intestinal metaplasia in 65%.

Both of the studies by Shaheen and colleagues and Ghorbani and colleagues also reported low stricture rates, with only 3% and 1% of patients developing strictures, respectively.

Those statistics compare favorably with Shaheen and colleagues' randomized, controlled trial for radiofrequency ablation (RFA), in which 81% of patients had complete eradication of dysplasia and 74% had complete eradication of intestinal metaplasia.

However, there are limitations to comparing these studies because the randomized, placebo-controlled trial for RFA uses an intention-to-treat methodology, which is more robust, whereas both cryotherapy cohorts are observational and not randomized, controlled trials. The retrospective and prospective studies for cryotherapy also excluded patients who had not completed their therapy, which might have resulted in bias in the findings of those studies.

Overall, when compared with RFA, cryotherapy appears to have a similar efficacy for eradication of dysplasia, but a lower efficacy in complete eradication of intestinal metaplasia. Cryotherapy has also been shown to be effective for treating cancer, whereas there are no data showing that RFA is effective in that situation. However, it is difficult to compare the 2 therapies without a head-to-head trial.

G&H Can cryotherapy be combined with any other therapy?

GS This question requires further investigation, although cryotherapy probably can be combined safely with chemotherapy in a thoughtful manner. Because cryotherapy does not require much lead time for preparation, it could be performed before radiotherapy or chemotherapy is arranged. Cryotherapy also may have a role both before definitive chemoradiation therapy and as an adjunct to chemotherapy in refractory cases. Unfortunately, there are not a lot of data to consider, and further study needs to be performed to determine whether combination therapy works.

G&H What are the advantages of cryotherapy over other therapies?

GS There are 4 main advantages to cryotherapy. One is expense; at my institution, the cost of cryotherapy is lower than the cost of RFA per case.

The second advantage is that patients who receive cryotherapy typically experience less pain. Frequently, patients who undergo RFA for Barrett esophagus require narcotic treatment for pain, whereas the majority of patients who undergo cryotherapy do not need a prophylactic pain treatment.

The third benefit is that cryotherapy does not depend on tissue contact the way that RFA does. Not every esophagus is of a size and contour amenable to fitting a cylindrical balloon; if a patient has an irregular-shaped esophagus, a sigmoid-shaped esophagus, or an esophagus with a very large or small diameter, cryotherapy provides an alternative therapy for patients who have failed RFA. I have had patients whose esophagus is too small for an 18-mm balloon, which is the smallest RFA balloon size, and patients in whom a 31-mm balloon—the largest size for RFA—does not appose all of the tissue in the esophagus. Cryotherapy allows the endoscopist to treat the whole esophagus freehand.

The final advantage is that cryotherapy offers the ability to ablate and sample tissue in the same day, whereas a technique that uses thermal ablation, such as RFA, does not provide an opportunity to sample tissue posttreatment.

G&H How common is the risk of perforation associated with the rapid expansion of liquid nitrogen, and what can be done to prevent this risk?

GS Perforation appears to be a rare event in the literature—there were no described perforations in the 3 large cohorts of cryotherapy using liquid nitrogen involving 333, 332, and 331 treatments—but my colleagues and I have seen this complication at our institution. Thus, perforations occur, but the rate is relatively low.

Using caution is the best way to prevent this complication. The endoscopist should ensure that there is appropriate ventilation tube placement throughout the procedure, not just at the beginning. A technician should be assigned to observe the tube to make sure that there is no kinking or movement of the tube during treatment; when the cryogen starts freezing the materials in the esophagus, there is a chance that the ventilation tube may move along with the endoscope. A nurse should palpate the abdomen during the procedure at all times to evaluate for firmness, which could be a sign of inadequate ventilation and a risk of perforation. Lastly, the endoscopist should try to avoid or limit therapies in patients who have had disrupted mucosal surfaces through biopsy, dilation, or recent surgery.

G&H Are there any other disadvantages associated with cryotherapy?

GS Yes. The cryotherapy device is limited in how much cooling it can provide; the machine can become so cold that it is unable to extrude the liquid nitrogen. Additionally, the endoscope loses function as it becomes cold. For patients with very large tumors or long-segment Barrett esophagus—who can require multiple ablation areas—or individuals with a vascular tumor requiring long spray times to achieve a hard freeze, the device can become too cold to properly function.

Another issue is that the cryogen will freeze any liquid material in the esophagus (eg, secretions), and visualization can be impeded if those secretions splash back onto the endoscope. It is common for endoscopists who are learning the technique to lose visualization of the esophagus or the structures being treated. Likewise, the catheter and supply line are very fragile. Most fellows in training will typically break at least 1 catheter in their first

few cases by torquing the endoscope or not paying attention to the location of the driveline.

Additionally, dosing is not as well established for cryotherapy as it is for RFA. With RFA, there is a fixed dose of treatment set by the machine, which indicates the start and stop of treatment for the endoscopist. The dose of cryotherapy depends largely on the endoscopist, who is painting the nitrogen freeze onto the mucosa and monitoring for a hard freeze to start timing. The endoscopist is also responsible for timing the freeze.

Lastly, storing the nitrogen can be a problem. The device will lose its entire supply of nitrogen in a little less than a week, even if the nitrogen is unused. Therefore, the device needs to be refilled regularly, or the endoscopy laboratory needs to house a large storage container to refill the device.

G&H What training is required to perform cryotherapy safely and effectively?

GS I am not aware of any guideline that states how to train someone to perform cryotherapy safely. Cryoablation is more technically challenging than competing treatments such as RFA; it involves more equipment and more subjective starting and stopping points for treatment, as well as more challenges in maintaining visualization. Performing a multitude of cases with an experienced practitioner seems logical. I spent 6 months with a mentor to learn the technique before I began performing it on my own.

G&H Are there any patients in whom this procedure should be avoided?

GS Endoscopists should exercise caution in patients who have had procedures that may decrease mucosal integrity, including recent surgery, endoscopic mucosal resection, biopsy, and dilation.

G&H How should the patient be followed up? What are the recommended surveillance intervals?

GS For Barrett esophagus, a 3-month follow-up treatment is typical, similar to what is recommended in RFA guidelines. After complete eradication of intestinal metaplasia, patients are usually followed every 3 months for a year, then every 6 months for a year, and then once a year. For cancer, patients are placed on a 4- to 6-week treatment interval (or shorter for patients who are not responding or not responding well). A typical treatment cycle is 3 freeze-and-thaw cycles of 30 seconds. To increase the effect for patients who do not respond, 4 to 5 cycles should be completed, or freeze times should be increased.

G&H How do you view the future of this procedure?

GS Cryotherapy has distinct advantages over RFA. Patient access to practitioners who provide cryotherapy likely limits the number of cases that are performed; however, as the device becomes easier to use, and the uptake by gastroenterologists in both academic and community settings increases, cryotherapy will likely be performed more often for the treatment of Barrett esophagus. Having better data, similar to the randomized, controlled trials that have been conducted in RFA, or perhaps even comparative studies, such as pain after RFA compared with pain after cryotherapy, may help practitioners in deciding the treatment that is best for their patients.

Dr Smallfield has no relevant conflicts of interest to disclose.

Suggested Reading

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