

ADVANCES IN ENDOSCOPY

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Cryotherapy for the Eradication of Barrett Esophagus or Early Cancer



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G&H What endoscopic ablative therapies are currently available for the treatment of Barrett esophagus with dysplasia or early cancer?

NJS Several endoscopic ablative therapies are currently available. Some of these therapies involve the destruction of the precancerous lesion without resection of any tissue. Other therapies, such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), involve the removal of the lesion for pathologic analysis of the tumor's aggressiveness and extent of local invasion. EMR and ESD differ in terms of their complexity and how they are performed; generally speaking, EMR is a much easier procedure, and it is performed in multiple US centers at high volumes and with great success. On the other hand, although ESD can potentially obtain a much larger specimen, this procedure is much more technically difficult, and it is performed at only a few centers in the United States. However, the basic concept of the 2 procedures is the same overall—to remove the precancerous tissue and to provide a substantial specimen for histologic analysis. If a patient with Barrett esophagus has nodular dysplasia, either EMR or ESD should be performed initially to help stage the disease. Further treatment is determined by the disease stage. If the nodular disease is cancer that is confined to the mucosa and is entirely removed by resection, the likelihood of a good outcome is quite high (>90%), as cancer limited to the mucosa very rarely has lymph node involvement; nearly all studies of these cancers have shown less than 5% lymph node involvement. On the other hand, cancers that are noted on an EMR or ESD specimen to have invaded the submucosa have

markedly higher rates of lymph node involvement and, therefore, worse prognoses. Cancers with submucosal invasion should be considered for surgical resection and, possibly, multimodal neoadjuvant therapy.

If the resected nodular tissue is either noncancerous or a cancer confined to the mucosa, the next step is to perform an endoscopic ablative therapy. Once nodular high-grade dysplasia or superficial cancer has been removed, the remaining Barrett esophagus must be eradicated to prevent the recurrence of lesions; previous data have shown that if a superficial cancer is removed but the underlying Barrett esophagus is not eradicated, the likelihood of recurrence of cancer is unacceptably high. A number of ablative therapies are currently available to eradicate non-nodular Barrett esophagus. Some of these therapies—such as multipolar electrocoagulation and argon plasma coagulation—are not technically complex and have been used for 2 decades or more. More recent therapies include radiofrequency ablation, which is the most common ablative procedure currently performed in the United States, and cryotherapy, which can be performed with either carbon dioxide or liquid nitrogen.

Cryotherapy works under the same premise as other ablative therapies—that after destruction of Barrett esophagus, the regenerating esophageal mucosa will be squamous if regeneration occurs in an anacidic, or only weakly acidic, milieu. Cryotherapy differs from the other modalities in the method used to induce the destruction of the tissue. It is thought that recurrent cycles of freezing and thawing generate superoxide radicals in the tissue that result in cell death. This freezing can be induced with multiple substances, and carbon dioxide— and liquid

nitrogen-mediated systems are commercially available in the United States.

G&H How effective is cryotherapy for the eradication of Barrett esophagus?

NJS Substantial data from cohort studies and retrospective case series have shown that cryotherapy is effective at eradicating non-nodular Barrett esophagus. In over 50% of these patients, cryotherapy not only downgraded the degree of dysplasia in the Barrett esophagus, but it completely eradicated the Barrett esophagus with an acceptable side-effect profile and relatively low rates of strictures and bleeding. These eradication rates compare favorably to those of most other available modalities, but are lower than reported results with radiofrequency ablation. The technology of several of the different cryotherapy systems continues to evolve, and it will be interesting to see if they can meet the high bar set by the radiofrequency ablation data with respect to complete eradication of intestinal metaplasia and dysplasia.

G&H What are the advantages of cryotherapy over other ablative therapies for Barrett esophagus or early cancer?

NJS Unlike many of the therapies, cryotherapy does not require apposition of a device against the Barrett esophagus tissue. In cryotherapy, a catheter is pointed at the tissue, enabling treatment to be administered from a short distance from the tissue; this treatment method can be useful in patients in whom it is difficult to obtain good apposition against the targeted tissue because of the esophageal anatomy.

In addition, cryotherapy can be used to treat both nodular and flat Barrett esophagus, depending on the dosing strategy, whereas most other ablative therapies are generally applied to non-nodular Barrett esophagus. When possible, as mentioned above, it is preferable to remove nodularity prior to treatment of Barrett esophagus, but in certain patients—those with widespread nodularity or a limited life expectancy—it may be more important to administer effective treatment and less important to obtain diagnostic information from EMR tissue. In these settings, cryotherapy may be the tool of choice because it is effective at eradicating both nodular and non-nodular disease.

It is quite possible that these endoscopic therapies will eventually be found to be complementary, as some therapies will distinguish themselves in certain clinical settings, and other therapies will excel in other settings. If this is the case, a unit providing comprehensive care of the Barrett esophagus patient may have a suite of technologies, and the endoscopist will choose which modality

(or modalities) to implement based on patient and lesion characteristics. As there is a lack of head-to-head data comparing the various types of ablative therapies, it is currently difficult to be dogmatic about when to use one therapy over another therapy.

G&H Which patients are good candidates for the use of cryotherapy?

NJS Thus far, several patient populations have been shown to be good candidates for cryotherapy. One group consists of patients whose anatomy does not allow application of other devices, either because good apposition cannot be obtained onto the tissue to effect therapy or because previous attempts at other types of ablation have been unsuccessful. Additionally, patients who have mixed nodular and non-nodular Barrett esophagus who are not good candidates for EMR for any reason may be good candidates for cryotherapy. Patients with routine segments of non-nodular dysplastic Barrett esophagus may also be candidates for this procedure; however, as previously mentioned, head-to-head evaluation of cryotherapy with other types of ablation has not yet occurred, making it difficult to know which modality will prove most efficacious. Because cryotherapy is newer than some of the modalities listed above, it has less data than older modalities.

In addition, cryotherapy can be used for palliation of cancer, so it is often used in patients who have extensive cancer that may not be curable and who are experiencing dysphagia. These patients may respond well to cryotherapy.

G&H Could you discuss any safety concerns or difficulties associated with cryotherapy?

NJS One significant concern associated with liquid nitrogen cryotherapy involves the need for ventilation and elimination of excess gas. Although this problem has been reduced by design improvements in the newer generations of cryotherapy devices, it can still be a concern during the procedure.

However, overall, I think some of the safety concerns associated with cryotherapy and ablative therapy in general have been overstated. Because most gastroenterologists have not performed cryotherapy, and they may not be familiar with how the procedure works, they may place too much stock in the adverse outcomes cited in related single case reports or small case series. Although this field is still evolving, cryotherapy devices (as well as ablative devices in general) have been shown to be safe overall, and several of these therapies have been shown to be quite effective. Nevertheless, the risks and benefits of these therapies—as with all therapies—should be weighed before they are performed.

G&H How common is the development of a perforation during cryotherapy?

NJS Perforation rates are less than 1%. Although one type of cryotherapy involves placing cryogen into a balloon that is held next to the tissue, cryotherapy is usually administered by a spray inside the body. Spray cryotherapies have the potential to cause barotrauma (trauma due to the expansion of gas). This complication may occur during liquid nitrogen cryotherapy because liquid nitrogen experiences a remarkable expansion in volume when it evaporates into gaseous nitrogen. Early experience with liquid nitrogen cryotherapy showed that patients may experience distension of the abdomen; therefore, recent generations of liquid nitrogen cryotherapy devices have included a decompression tube that is inserted into the patient prior to spraying liquid nitrogen. This tube both actively and passively ventilates the gastrointestinal tract in order to expel gas more easily. With the development of this tube, along with close monitoring of the abdomen while administering the spray, the risk of perforation in the gastrointestinal tract is very low during these procedures.

G&H Do you foresee cryotherapy becoming more widely available in the future, or will it remain a specialized endoscopic procedure?

NJS First of all, I think that all ablative therapies and EMRs should be performed in centers with experienced endoscopists who have adequate case volumes for maintaining their skills. I do not think that these procedures necessarily need to be performed in academic settings—they can certainly be performed in private practices—as long as the endoscopists make the procedures a focus of their practice.

Having said this, I think that the future of cryotherapy will be determined by the safety and efficacy data being generated at multiple sites throughout the world.

As cryotherapy devices continue to improve, the clinical setting in which they are most effective will be better defined. Although cryotherapy and ablative therapies in general have a great deal of potential, we need more data to completely understand the position of these procedures in our current armamentarium for Barrett esophagus or early cancer.

G&H What are the next steps in research in this area?

NJS One of the most significant research needs involves refining the dosimetry of the cryotherapy devices to determine the optimal exposure of the tissue to the cryogen. Data to date give us some idea as to the amount of cryogen needed to induce tissue death without inducing stricturing or other side effects, but refinement of these protocols is essential.

Also, as previously mentioned, it is important to understand where cryotherapy will be most efficacious. A good deal of research is already underway, and there will be more research in the future to understand which lesions will be most amenable to cryotherapy. In addition, researchers are trying to locate any other areas in the gastrointestinal tract or elsewhere in the body where cryotherapy could be efficacious.

Suggested Reading

- Greenwald BD, Dumot JA, Abrams JA, et al. Endoscopic spray cryotherapy for esophageal cancer: safety and efficacy. *Gastrointest Endosc*. 2010;71:686-693.
- Shaheen NJ, Greenwald BD, Peery AF, et al. Safety and efficacy of endoscopic spray cryotherapy for Barrett's esophagus with high-grade dysplasia. *Gastrointest Endosc*. 2010;71:680-685.
- Garman KS, Shaheen NJ. Ablative therapies for Barrett's esophagus. *Curr Gastroenterol Rep*. 2011;13:226-239.
- Greenwald BD, Lightdale CJ, Abrams JA, et al. Barrett's esophagus: endoscopic treatments II. *Ann N Y Acad Sci*. 2011;1232:156-174.
- Xue NB, Tan HH, Lui WZ, et al. A pilot study of endoscopic spray cryotherapy by pressurized carbon dioxide gas for Barrett's esophagus. *Endoscopy*. 2011;43:379-385.