Communication from the ASGE Technology Committee

STATUS EVALUATION REPORT

# Cryotherapy in gastrointestinal endoscopy

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This document was reviewed and approved by the governing board of the American Society for Gastrointestinal Endoscopy (ASGE).

*The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee provides reviews of existing, new, or emerging endoscopic technologies that have an impact on the practice of GI endoscopy. Evidence-based methodology is used, with a MEDLINE literature search to identify pertinent clinical studies on the topic and a MAUDE (U.S. Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported adverse events of a given technology. Both are supplemented by accessing the "related articles" feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but in many cases data from randomized controlled trials are lacking. In such situations, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and Web-based publications, proprietary publications, and informal communications with pertinent vendors.*

*Technology Status Evaluation Reports are drafted by 1 or 2 members of the ASGE Technology Committee, reviewed and edited by the committee as a whole, and approved by the Governing Board of the ASGE. When financial guidance is indicated, the most recent coding data and list prices at the time of publication are provided. For this review, the MEDLINE database was searched through August 2016 for articles related to cryotherapy, using the words cryotherapy, gastrointestinal tract, cryoablation, cryospray, cryosurgery, liquid nitrogen, liquid carbon dioxide, cryoballoon, and Barrett's esophagus. Technology Status Evaluation Reports are scientific reviews provided solely for educational and informational purposes. Technology Status Evaluation Reports are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment or payment for such treatment.*


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## BACKGROUND

Cryotherapy uses extremely cold temperatures for tissue destruction. In the GI tract, cryotherapy can be performed using devices designed for use with endoscopes. During cryotherapy, a cryogen (a substance used to produce very low temperatures) is used to freeze the target tissue, and repeated freeze/thaw cycles result in the destruction of abnormal tissue. In endoscopic cryotherapy, the cryogen is typically a liquefied gas, such as nitrogen or carbon dioxide, that may be either directly applied to tissue or used within a balloon device. Endoscopic cryotherapy was first used for the treatment of Barrett's esophagus (BE), and the indications for its use in other GI disorders are expanding.

## TECHNOLOGY UNDER REVIEW

### Mechanism of action

Cryotherapy induces cell necrosis for therapeutic purposes through cycles of controlled local freezing and thawing of the tissue. Application of a cryogen to tissue is believed to result in necrosis of mucosal and submucosal lesions by several mechanisms. Freezing of tissue results in the formation of ice crystals within the intracellular and extracellular spaces, leading to cell membrane disruption, protein denaturation, and osmotic gradients that lead to cell dehydration.[1-6] Cells in the periphery of ablation zones that are not immediately destroyed by direct cryoablation-induced injury may subsequently die by upregulation of apoptosis, thought to be mediated by cytochrome C release.[1,7,8]

The thawing component of cryotherapy also appears to be an important mechanism for cell death.[9] During thawing, ice crystals fuse and further damage cell membranes. In addition, vascular stasis due to endothelial damage, platelet

aggregation, and formation of microthrombi results in ischemic necrosis.[10-12]

For cell destruction by cryotherapy, the tissue temperature must reach a critical threshold that is unique to the cell type and the environment of the targeted tissue, but typically ranges between −20°C and −50°C.[13] Because collagen and elastin fibers are less sensitive to the effects of cryotherapy than are epithelial cells, the tissue structure remains intact, reducing the risk of perforation.[13-16] The extent of tissue destruction is also dependent on the number of freeze/thaw cycles applied.[12,13,17,18]

## Types of endoscopic cryotherapy and equipment

Three cryotherapy systems developed for use in GI endoscopy have been cleared by the U.S. Food and Drug Administration and are marketed in the United States. Two of the systems use a pressurized liquefied gas spray as the cryogen (truFreeze, CSA Medical, Lexington, Mass, and Polar Wand, GI Supply, Camp Hill, Pa), whereas the third uses a cryogenic balloon that requires direct contact with the target tissue (Coldplay CryoBalloon Focal Ablation System, C2 Therapeutics, Redwood City, Calif). Of note, production and sale of the Polar Wand system was suspended by the manufacturer in March 2016.

**Cryotherapy using liquid nitrogen.** The first cryotherapy system developed for endoscopic use (truFreeze) uses liquid nitrogen delivered through a spray catheter. Its first endoscopic use was reported in 2005.[19] This system has gone through several iterations, and currently the third-generation device is available.

The truFreeze system allows for freezing of GI mucosal tissue to −196°C with the use of a low-pressure, noncontact spray and comprises a console unit, 2 foot pedal controls, a spray catheter, and a decompression tube. The console houses a liquid nitrogen tank and compressor and a suction canister, and it features a touch screen control (Fig. 1). The single-use spray catheter is 213 cm long, is 7F in diameter, and is constructed of polyimide reinforced with a stainless steel mesh. The catheter connects to a liquid nitrogen compressor within the console and can be inserted through any endoscope with a ≥2.8-mm instrument channel. The foot pedals initiate the flow of liquid nitrogen from the compressor to the catheter and suction through a 20F dual-channel decompression tube that is positioned coaxially with the endoscope for active venting. Liquid nitrogen is dispersed from the catheter in a low-pressure (<5 psi) spraylike fashion, resulting in flash freezing (Fig. 2). The noncontact delivery allows for ablation of topographically variable lesions; flat, nodular, and masslike tissue can be ablated.

Nitrogen rapidly expands from liquid to gas, so a dual-channel decompression tube is placed before treatment to allow active and passive gas venting to prevent GI luminal perforation. The suction tubing connects to the console and allows for continuous suction throughout the entire procedure.[20] The current system also has a pressure-sensing capability that audibly alerts the endoscopist when luminal pressures are elevated above a set threshold.

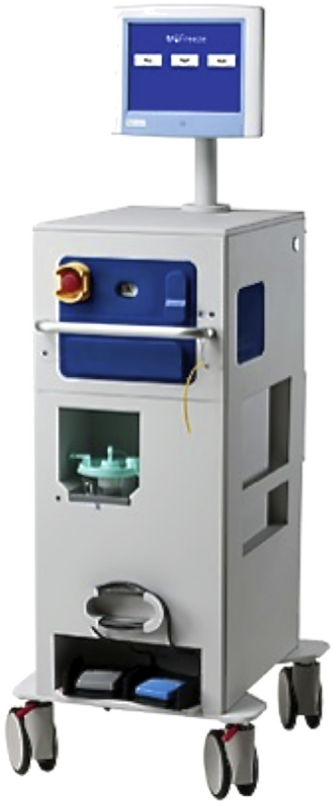

**Figure 1.** Liquid nitrogen spray cryotherapy console. (Image used with permission from CSA Medical, Inc)

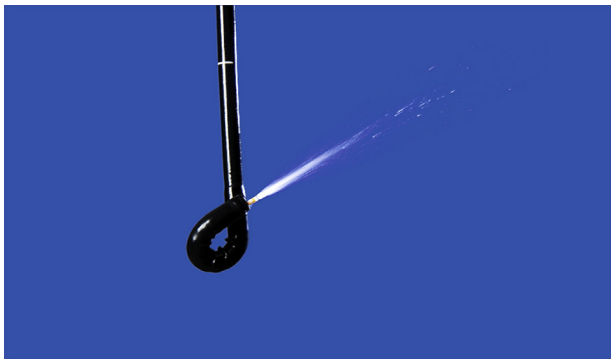

**Figure 2.** Liquid nitrogen spray cryotherapy catheter. (Image used with permission from CSA Medical, Inc)

After endoscopic visualization of the area of interest, the spray catheter is advanced through the instrument channel to the target ablation site. The tip of the catheter is positioned 0.5 cm to 1 cm away from the tissue to be treated. The area of interest is then treated according to the dosimetry protocol for the tissue being ablated.[21-24] The timer is usually started once a white frost is formed. After each application of cryogen, the frozen tissue is allowed to