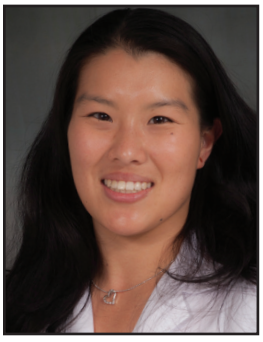
Douglas G. Adler MD, FACG, AGAF, FASGE, Series Editor

Endoscopic Cryotherapy: Indications and Efficacy



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INTRODUCTION

Endoscopic cryotherapy is a technique to achieve destruction of abnormal tissue within the GI tract with extremely cold temperatures. Controlled freezing and thawing of target tissues with a cryogen can result in therapeutic clearance of damaging lesions, thereby potentially allowing the return of normal tissue to these sites. Although widely used in various fields of medicine, cryosurgery is a relatively new addition to the endoscopic armamentarium. Traditional mucosal ablations in gastroenterology have been preformed with non-contact and contact-based thermal sources. By using a non-contact cold source, a two-part obliteration process effectively treats in a way that spares the underlying extracellular matrices, theoretically allowing for improved healing. Endoscopic cryoablation has been used in esophageal dysplasia and cancer, to treat bleeding caused by gastral antral vascular ectasia (GAVE) and radiation proctitis, and in other contexts. This manuscript will review the current applications of endoscopic cryotherapy as well as their efficacy and safety.

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Mechanism of Action

Cooper first described the phenomenon of liquid nitrogen cryosurgery and reported localized tissue necrosis occurring after a minute exposure to -20°C in the 1960s.[1] Further investigations of cryotherapy revealed cellular apoptosis occurred between -70°C and -158°C.[2,3,4] Endoscopic cryoablation is a non-contact method for achieving tissue destruction using a low-pressure spray of liquid nitrogen or carbon dioxide as the cryogen. A cryogenic approach yields tissue injury via two distinct pathways: immediate and delayed destruction.[1,2,3,5] Immediate tissue destruction is accomplished by placing hypothermic stress on target

Figure 1. Cryotherapy for Barrett's Esophagus Endoscope

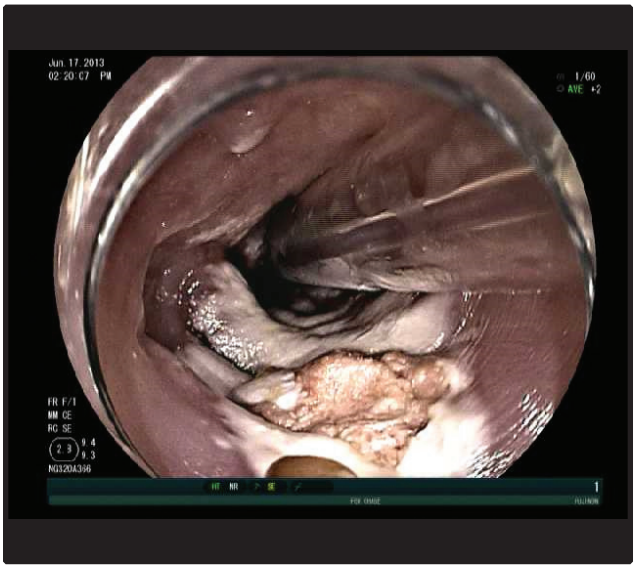

Figure 1a. Endoscopic cryotherapy being applied to an area of high-grade dysplasia in a patient with Barrett's esophagus. Note cap fitted over endoscope tip and suction catheter in view. *Image courtesy of Jeff Tokar, MD*

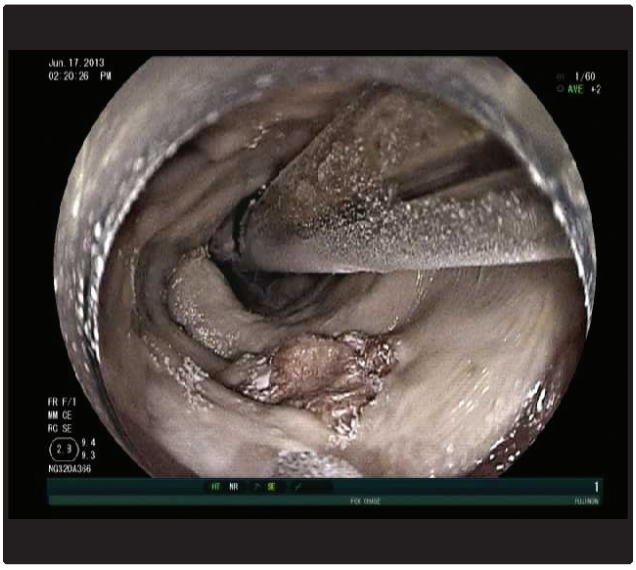

Figure 1b. Same lesion as Figure 1a, after thawing and immediately before initiation of a second cycle of cryotherapy. *Image courtesy of Jeff Tokar, MD*

cells; forcing cells into a low temperature environment causes a decrease in cellular metabolism. Once cells are exposed to freezing temperatures, water crystalizes to create a hyperosmotic extracellular matrix that withdraws water from the cells. As the water crystals grow and propagate, cells continue to shrink and cellular membranes and constituents are damaged. During the freezing stage, cells die in response to dehydration and cellular membrane and organelle disturbances.

Following the freezing cycle comes a thawing period that yields more immediate tissue destruction.[2,4] During the thawing process, the extracellular matrix becomes briefly hypotonic which encourages water to flow into the already damaged cells. This influx results in cell volume increase that may rupture the cell membrane.[1,4] When the tissue reaches -20°C to -25°C, the process of recrystallization is maximized. The hypotonic extracellular matrix created by thawing also contributes to an electrolyte disturbance. The resultant high solute concentration in the extracellular matrix that lowers the freezing temperature while a low solute concentration (due to the influx of water) in the cells favor more ice crystal formation and fusion to further damage the cellular organization.[6] Completion of the thawing process is followed by additional rapid-freeze/slow-thaw cycles as needed, often 1-3 additional cycles in practice. After thawing is complete, affected tissues remain hypothermic for several minutes.[1] By immediately freezing the target tissue again, an enhanced cooling rate is accomplished that favors more intracellular ice crystal formation across a larger and deeper number of cells. The increase of crystallization creates extensive cellular membrane and organelle disturbances that ultimately cause cell death.[2,3,5]

The delayed effects of cryoablation start hours after treatment and can continue for days.[2] Once the frozen lesion thaws, the treated tissue looks normal, but the rapid change from freezing-induced vasoconstriction to vasodilation seen during thawing compromises capillary integrity. Microcirculation in treatment area is subjected to edema, increased vascular permeability, platelet aggregation, and microthrombi formation.[1,4] The consequence of all these events is a decreased blood flow that results in vascular stasis. The combination of anoxia and necrosis in the target area leads to the apoptosis of target cells that survived the immediate tissue damages.[3] This delayed damage is important for the periphery of the treatment area. The cells bordering the cryogenic legion may not have been exposed to enough cryogen to face immediate damage. The delayed effects "clean up" the peripheral tissue and induce apoptosis, thereby expanding the area of tissue death. Thus, cryotherapy yields a complete ablation of the

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target area while sparing the foundational extracellular matrix for normal tissue regeneration.[7]

By inducing apoptosis, cryoablation has the unique ability to stimulate immunological response to the target cells.[1,2,3,4] The inflammatory environment created by the ablative damage recruits cytotoxic T-cells and favors a T_h1 response to antigens released by apoptotic cells. In the case of tumors/malignancies, the immune response could hypothetically create antitumor activity that can extend outside the original treatment area, although this remains unproven at this time.[2,3]

Endoscopic Cryotherapy

Currently there are two cryoablation systems in the market that are used in gastrointestinal endoscopy: the liquid nitrogen-based CryoSpray Ablation System (CSA medical, Baltimore, Maryland, USA) and the carbon dioxide-based Polar Wand cryotherapy device (GI supply, Camp Hill, Pennsylvania, USA).[8,9] Both systems use cryogens that expand as they warm. The expanding nitrogen or carbon dioxide gases place patients at risk for gastrointestinal perforation, and need to be evacuated from the patient during the procedure. A 20-second liquid nitrogen treatment can expand into 6 to 8 liters of gas.[3] In order to avoid perforation, the CryoSpray system uses a nasogastric and/or orogastric decompression tube.[2,6,7,10,11] The decompression tube is composed of two channels that perform passive ventilation and active suctioning to control gas build-up during treatment.[9] Abdominal palpation is often performed during procedures to ensure full decompression.[6] Polar Wand cryotherapy needs to be set at a flow of 6 to 8 liters of CO_2 per minute to accomplish maximum tissue damage.[3,6] In contrast to the nasogastric and orogastric ventilation system, the Polar W.I.N.D. uses a suction catheter that is attached to the tip of the endoscope to remove gas distension throughout the procedure.[6]

Liquid Nitrogen versus Carbon Dioxide as Cryogen

There have been extensive studies involving both cryogens in the role of endoscopic cryoablation. A low-pressure (2-4 psi) spray of liquid nitrogen exposes target tissues to a minimum temperature of -196°C. In comparison, high pressure (>500 psi) carbon dioxide relies on the Joule-Thomson where rapid expansion of the gas at room temperature creates a cooling effect of -78°C.[12,13] Although the two cryogens differ by more than a 100°C, the lowest temperature accomplished by both gases are more than sufficient to induce cellular apoptosis.[1] The drastically lower temperature of liquid nitrogen translates to the potential to ablate larger areas and deliver a greater depth of treatment.[7] The disadvantage to this super-low temperature is frequent stiffening and subsequent immobility of the endoscopic equipment in practice. Having the ability to deliver -196°C often results in freezing of the endoscope and catheter which may sometimes make it difficult to continue treatment and remove the scope.[3] To avoid complications, liquid nitrogen treatments need a heating circuit built into the catheter for easy removal and a warm air pump to maintain mobility of the equipment.[3,6] This additional heating system is not necessary for a CO_2 system because -78°C does not pose a danger to freezing the catheter and endoscope with use.

Although carbon dioxide does not carry the risk of freezing the endoscope or delivery catheter, the combined ventilating-endoscope probe is bulky and can be difficult to navigate through the esophagus.[6] Another problem with using the CO_2-based Polar Wand Cryotherapy device is lens fogging that compromises visualization during procedures.[3] The Liquid nitrogen system, CryoSpray Ablation System, places a clear plastic cap at the end of the endoscope to decrease fogging during procedure.

Liquid nitrogen has been successfully used for more than 5 decades in various fields of medicine such as dermatology, oncology and ophthalmology. Added to its familiarity, liquid nitrogen is an attractive cryogen because it is a readily available, inert agent.[3,6,7] However the cost of using liquid nitrogen is higher than the cost of using carbon dioxide for several reasons. Foremost is the price of the CryoSpray Ablation system being higher than the Polar Wand Cryotherapy System.[6,14] To enter a liquid state, carbon dioxide gas needs to be compressed under intense pressures (60.4 psi). The reliance of pressure allows this cryogen to be stored at room temperature.[2,6] In contrast, liquid nitrogen's cryogenic properties are reliant on being stored between -195.8°C to -210°C; therefore it needs to be stored in an expensive refrigerant system that can maintain the necessary temperature.[2,15] As stated before, liquid nitrogen uses a low-pressure spray to achieve therapy, so a 25 W external energy source is necessary for it's delivery to target tissues.[5,8]

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Although there is no study directly comparing the efficacy of ablation by the two cryogens, carbon dioxide and liquid nitrogen are commonly used in treating Barrett's esophagus and esophageal malignancies. The various studies will be discussed later in this paper but the results reflect high success rates when either cryogen is used. Along with favorable outcomes, both carbon dioxide and liquid nitrogen have similar minimal adverse effects.

Technique and Dosimetry

For endoscopic cryotherapy performed in the context of upper and lower endoscopy, standard preparations are required.[3,16] For esophageal cryotherapy, some recommend the addition of a high dose proton pump inhibitor (PPI) if the patient is not already on an regimen, at least one week before the first session and maintained throughout the length of treatment, although this is not universally performed.[3,8,17]

Endoscopic cryotherapy treatment is typically delivered over multiple sessions. The number, duration, and time between the sessions are all variable based on the condition being treated and the severity of disease. At each session, a variable duration and number of freeze-thaw cycles will be administered to the several sites of the target tissue. During the freeze-thaw cycle, time of freezing starts after the frozen lesion is formed and thawing time is that amount of time necessary for the frosted lesion to return to normal mucosal appearance.[1,8]

The amount of variability with treatment is due to the lack of studies concerning cryoablation dosimetry and clinical outcomes in humans.[3,8,9] In general, depth and degree of tissue destruction is proportional to the number of freeze-thaw cycles, the distance from the cryogen release point, and the duration of freezing.[9] Initial dosimetry experiments based on short-term results have been conducted in animal models for both carbon dioxide and liquid nitrogen.[8] Johnston et al.tested liquid nitrogen dosimetry effecting swine esophagus by varying freeze times from 10 to 60 seconds. The resultant tissue destruction ranged from superficial mucosal inflammation to submucosal necrosis without correlation to the freeze time.[8] Raju et al. completed a similar study using varying freeze times (15 second to 120 seconds) with carbon dioxide as the cryogen on swine esophagus. Resultant range of tissue destruction was dose-dependent: 15 seconds of CO_2 cryospray yielded minimal mucosal necrosis, 30 seconds of cryospray involved submucosal damage and 120 seconds of spray extended damage to the muscularis propria.[15]

There are several major contraindications to endoscopic spray cryotherapy.[2,3,8] In general, cryospray should be avoided in pregnant patients or if food is present in stomach and proximal duodenum.[8] The lack of extensive studies involving cryotherapy and pregnancy means that effects of treatment are unknown.[3] The presence of food is in the gastrointestinal tract may compromise decompression and ventilation efforts that may increase the risk perforation.[2,3] Cryogens should, in general, not be applied to compromised tissues.[8] The presence of mucosal breaks or ulcerations promotes transmural necrosis by the cryogen that allows improper communication with the mediastinum or peritoneum that manifests into larger problems.[3] Patients undergoing cryotherapy may be at increased risk if they have anatomic variations or alterations that could complicate equipment passage during treatment and gas decompression efforts.[2,8] Examples of such alterations include strictures, eosinophilic esophagitis, loss of tissue elasticity, or bariatric procedures that all increase the risk of perforation.[3,8,12]

Indications for Endoscopic Cryotherapy

Gastral Antral Vascular Ectasia

Gastral antral vascular ectasia (GAVE) is the term used for the presence of friable gastric mucosal microscopic vessels. GAVE is a cause of iron deficiency anemia and can sometimes cause acute upper gastrointestinal (GI) bleeding. Accounting for 4% of non-variceal upper GI hemorrhage, GAVE is likely under-diagnosed; the true prevalence of the condition is likely unknown.[16,18] First described in 1953 by Rider et al., there is still mystery surrounding its pathogenesis and treatment.[16,18,19] GAVE in its classical presentation is called "watermelon stomach" due to the longitudinal stripes of erythematous vessels running from pylorus to the antrum along the antral rugae. The second form of GAVE presents as diffuse angiomas studding the antrum and is usually related to liver cirrhosis and/or portal hypertension.[16,18] In both forms, GAVE is primarily limited to the antrum but there have been cases arising in other GI mucosal sites including other parts of the stomach, duodenum, and rectum.[18]

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Figure 2. Palliative use of cryotherapy to treat recurrent esophageal adenocarcinoma following chemoradiation therapy in a patient who is not a surgical candidate.

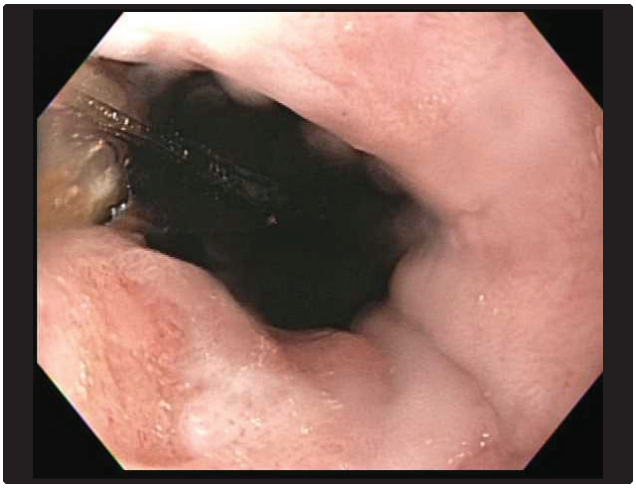

Figure 2a. Malignant lesion seen in the distal esophagus.

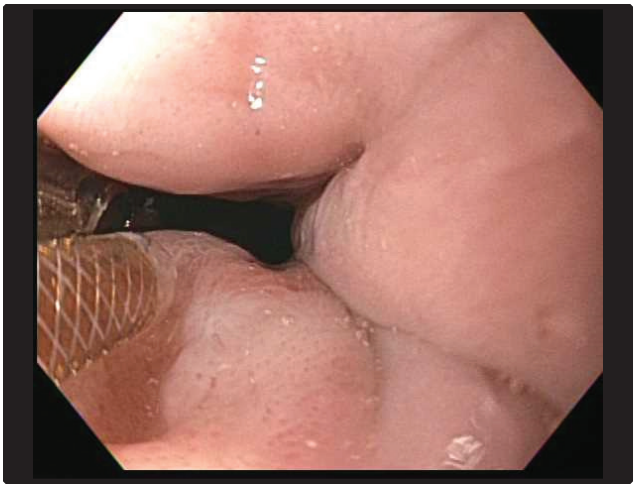

Figure 2b. Cryotherapy catheter positioned over lesion.

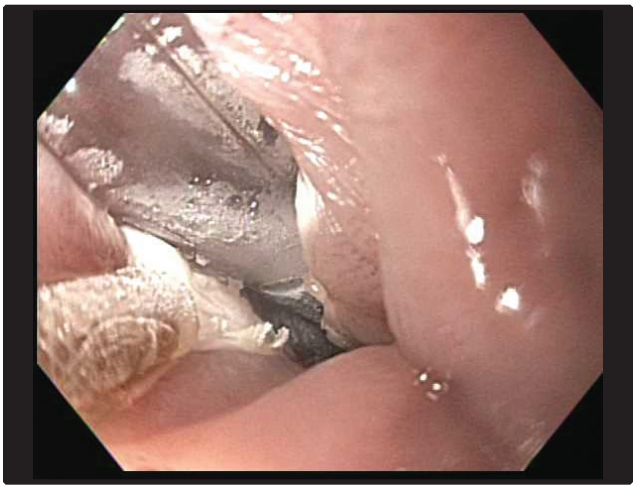

Figure 2c. Initiation of cryotherapy with the beginning of lesion freezing. Note suction catheter in view.

Endoscopic ablation by argon plasma coagulation (APC) is the current gold standard endoscopic treatment for GAVE.[16,18,19] APC is a non-contact technique that generally avoids deeper mucosal damage and therefore decreases the risk of perforation. APC results in superficial mucosal ablation and destruction of the offending blood vessels in patients with GAVE. As the gastric wall reconstitutes itself, the tissue regrows without the offending vessels. APC results are generally favorable, with some rare reports of post-treatment complications such as antral stenosis from scarring.[1] APC can rarely result in inflammatory or hyperplastic polyps that can evolve to become future bleeding sources.[18,19] GAVE often presents as large, diffuse involved areas in the antrum and APC is the most commonly used treatment for this illness.[19]

Cryotherapy is a novel treatment for recurrent and non-APC responsive GAVE. Cryoablation is potentially advantageous in treating GAVE because it is able to treat large lesions with the non-contact spray and promote normal epithelial regrowth after mucosal or submucosal damage.[16,18] Using cryoablation as a secondary line of GAVE treatment is somewhat less appealing as it requires the purchase and training of specialized cryoablative equipment. Without proper dosimetry studies, variability in spray duration, number of cycles, and sessions are problems when using cryoablation. Although there is favorable improvement after treatment completion, several sessions are needed to accomplish a sustained response and long-term efficacy of cryoablation is not well studied.[20]

In a small pilot study of cryotherapy and GI mucosal bleeding by Kantsevoy et al., 7 out of 26 participants were undergoing treatment for GAVE.[21] All of the participants for the study had previously underwent endoscopic treatment but continued to have active bleeding. Using nitrous oxide as the cryogen, GAVE patients were considered responders to cryotherapy treatment as there was no evidence of subsequent melena and hematemesis as well a stable hematocrit level on follow up. Nitrous oxide is no longer widely used as a cryogen. After an average of 3.6 cryotherapy session, 5 out of the 7 (71.4%) of the GAVE patients displayed control of their upper GI bleeding. In all 26 patients, only one patient developed transient abdominal pain that was unremarkable in CT scan.

In a pilot study using CO_2 to treat GAVE, Cho et al. recruited 12 recruits that fit their inclusion criteria.[16]

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Of the 12 total participants, 8 had GAVE recurrence or failed prior APC treatment. Participants underwent three cryotherapy treatments that averaged 5 minutes, however CO_2 spray duration decreased with following appointments. In 4 out of the 36 preformed sessions, less than 90% of the GAVE lesion was treated due to technical problems concerning overtube placement (1/4), cryogen unit (1/4), and learning curve of the endoscopists (2/4). In the other 32 treatments, more than 90% of the lesion was treated. Success of the procedure was determined by 3 month post-treatment hemoglobin levels and amount of blood transfused to counter participant blood loss from the ailment. The study had 6/12 patients achieve a complete response. In this group, there was an average of 2.6 g/dL hemoglobin increase and decrease of 5.7 units of blood transfused after three sessions of treatment. The remaining 6 participants experienced partial response with a 0.1 g/dL increase in hemoglobin levels and a decrease of 0.2 units of blood transfusion. There were four cases with minor adverse effects to the cryotherapy. Three patients developed asymptomatic antral scarring and ulcerations. During placement of the overtube, one patient experienced bleeding from a tear in n Schatzki's ring that was managed with an adrenaline injection.

Radiation Proctitis

Radiation proctitis is common complication from pelvic radiation therapy especially in the treatment of anal, prostatic and gynecologic malignancies.[22] Radiation damages the colorectal mucosa to produce endothelial dysfunction, fibrosis, microvascular injury, and neovascular lesions.[23,24] The neovascularization of the rectum is often the most prominent feature and the one typically requiring treatment. Radiation proctitis can have an endoscopic appearance very similar to that seen in the stomach in GAVE, with innumerable small mucosal vessels that are friable and lead to blood loss, both acute and chronic. Radiation proctitis manifests in two forms—acute and chronic; both forms presents as rectal pain and bleeding, diarrhea, tenesmus and passage of mucus with stools.[22] The acute form is a more mild presentation of radiation proctitis. It commonly shows within 3 months after radiation treatment and is self-limiting with the discontinuation of radiation.[22,23,24] On endoscopy, lower colonic mucosa appears edematous and erythematous with possible ulcerations. Microscopically, there is microvillus disruption or loss due to processes of hyperemia, edema

Figures 2d, 2e, and 2f. These images show the progressively deeper freezing of the lesion during the treatment cycle. Not that the cryotherapy is focally targeted onto the lesion of concern but there is some local effect in the surrounding tissues.

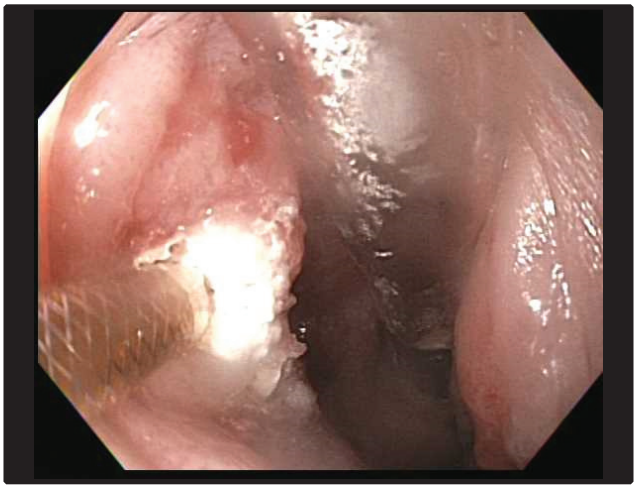

Figure 2d.

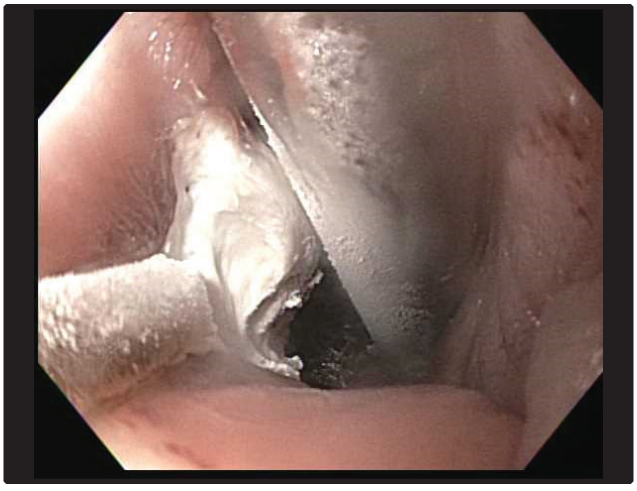

Figure 2e.

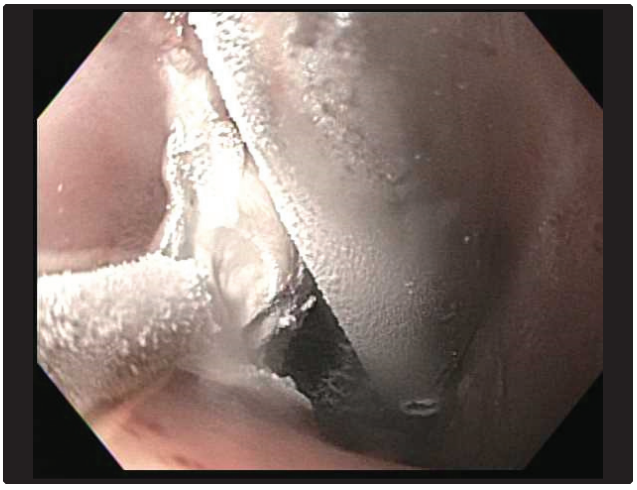

Figure 2f.

and ulcerations.[22,24]

Chronic radiation proctitis (CRP) is a more severe disease that affects 2-20% pelvic radiation cases.[25] Symptoms of CRP present 8 to 12 months after completion of radiation therapy. As the disease progresses from an acute presentation, compromised blood supplies to the lower colon progresses to ischemia and fibrosis that increases the risk of obstruction and perforation.[22,24,26] On top of normal radiation proctitis symptoms, CRP also presents with severe bleeding and fistula. Endoscopically, CRP effected colons appear pale with telangiectasias and may also have strictures, ulcerations and fistulas.[27] Biopsy analysis exposes focal destruction and fibrotic change in small arteries.[22] The persistent bleeding cumulates into iron deficient anemia requiring patients to undergo transfusions.[23] With its symptoms, CRP negatively impacts patients' daily activities and quality of life.

In the small pilot study of endoscopic cryotherapy by Kantsevoy et al., 7 of the 26 patients recruited were undergoing secondary cryoablation treatment for radiation proctitis.[21] During the study, participants were monitored for reduction in melena and hematemesis as well as improvement to hematocrit levels. The 26 participants underwent an average of 3.4 sessions and follow up endoscopy at 3 and 6 months. Cryotherapy had the best response in the radiation proctitis patients, where 7 out of 7 showed reduction of bleeding.

Hou et al. conducted a prospective study on the tolerability and efficacy of cryoablation in treating CRP.[25] Ten participants (all male) were recruited and underwent CO_2 cryoablation. The participants received a single treatment composed of three sessions of 5 second freeze followed up by 45 second thaw. Follow-up endoscopy was performed an average of 3.3 months after treatment. Seven out of the 10 participants showed improvement in symptoms and on endoscopy. The rest of the patients (3/10) showed no change before and after treatment. In general, the patients tolerated cryotherapy well with prevalent adverse effect of discomfort during and immediately after. Two cases experienced complicated adverse effects. One of the patients experienced cecal perforation from distension caused by decompression tube failure and another patient developed a rectal ulcer post-treatment that healed on two subsequent endoscopies.

In another study, liquid nitrogen cryotherapy was used on ten patients (9 males and 1 female) with CRP.[28] None of the participants used prior pharmaceutical agents and 3 of the 10 previously underwent APC without improvement. Four cycles of 10 second freezing time and 90 second thawing time was performed per treatment. Participants received up to four treatments with four-week intervals or until symptoms resolution were achieved (6/10 received one treatment, 2/10 received two, 1/10 received three, and 1/10 received four). Of the ten participants, 7 reported their primary complaint as rectal bleeding; 6 of those 7 participants saw improvement in their bleeding. Overall 9 out of 10 participants reported relief from rectal bleeding and pain as well as overall wellbeing. Overall, the participants tolerated the cryotherapy well with one patient suffering from cecal perforation due to distension during treatment.

Barrett's Esophagus and Esophageal Malignancies

Barrett's esophagus (BE) is pre-cancerous condition of the distal esophagus where the normal squamous epithelium is replaced with goblet cell-containing columnar cells. BE is often a consequence of long-standing, uncontrolled gastroesophageal reflux disease (GERD), although some patients can develop BE in the absence of GERD symptoms. Generally, BE is treated as early possible because it's progression from a low-grade dysplasia (LGD) to a high-grade dysplasia (HGD) is associated with an increased 30 fold risk of developing esophageal adenocarcinoma, a cancer with a 5 year survival of only 5-15%.[3,4,10] Globally, esophageal malignancies (encompassing esophageal adenocarcinoma and squamous cell carcinoma) are the eighth most common cancer and the sixth most common cause of cancer mortality.[29]

BE is not a self-limiting condition and does not typically resolve when patients are treated with GERD medication therapies therefore specific treatment can be performed to prevent progression to malignancy. BE treatment includes esophagectomy, the standard care for early stage cancer, of the affected part and endoscopic ablation of the dysplastic lesion, although this is essentially only performed in patients with high-grade dysplasia in whom the risk of cancer is felt to be very high.[4,5,7] Ablative therapies destroy the pre-cancerous portion of the esophagus in a controlled fashion to allow normal re-epithelization. Radiofrequency Ablation (RFA) is the most studied ablative technique and is most commonly applied to patients with BE and

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dysplasia, either low-grade or high-grade. RFA can be used in a circumferential and focal ablative fashion to treat BE with LGD and HGD. It is associated with an excellent safety profile. When used in cases with previous mucosal resections or longer segments of disease, strictures have been seen on follow up in 1-8% of patients.[10] RFA remains the most widely studied and used therapy to ablate BE.

Cryotherapy has often been used to treat refractory or recurrent BE after other forms of ablation, most commonly RFA. (Figure 1) In a pilot study using cryotherapy to treat BE, 11 patients were enrolled from a BE registery into a prospective study.[13] The 11 participants had an average BE length of 4.6 cm. (range 1-8 cm) and had dysplasia ranging from no dysplasia to multifocal HGD. Liquid nitrogen treatment was applied in a hemi-circumferential fashion in monthly intervals until BE reversal was confirmed with biopsy. Each session was composed of varied cycles (maximum of three depending on the length of the BE) of 20 second freezing followed by complete thawing. An average of 3.6 treatments (range 1-6 treatments) were performed in this study. Nine out of the 11 participants completed the study with evidence of BE recovery. At the 6-month follow up, 2 out of the 9 patients showed presence of columnar cells distal to the squamo-colmnar junction while the other 7 patients still had complete histological BE eradication. Patients generally tolerated cryotherapy well. There were 2 cases of mild post-treatment complications: one patient reported solid-food dysphagia and another experienced chest pain. Both episodes resolved within a day of onset.

Dumont and colleagues further explored the potential of liquid nitrogen cryoablation by evaluating it's efficacy in treating BE with HGD and intramucosal carcinoma (IMCA).[30] In this study, 30 participants were enrolled who were diagnosed with either HGD or IMCA and were deemed inoperable based on co-existing conditions or personal choice. The patient pool for this study was quite complex in makeup; 8 patients had previously received ablation therapy and the average BE length for the group was 6.1 cm (range 1-15 cm). A mean of 5 cryoablative treatments (range 3-6) were delivered at 6-week intervals until disease resolution or progression was observed. During each appointment, 3 to 6 sites would be treated. Dosimetry was initially performed at 3 cycles of 20-second spray time but was changed half way through the study to 4 cycles of 10-second spray time to decrease the amount of gas generation in response to a serious adverse effect that will be discussed later.

The study had four follow up appointments, with a median follow up at 12 month after treatment completion. At median follow-up, 92% of the HGD patients and 80% of the IMCA patients showed histological improvement; this accounts for 27 out of 30 participatants. Complete eradication of dysplasia was seen in 32% HGD patients and 40% IMCA patients. At final follow-up, 22 out of 30 patients were alive and cancer free. Minor complications of cryotherapy were self-resolving after 1-3 days post-treatment. The most common side effect was heartburn-like pain that was reported in 7 patients. Three of the 7 patients required narcotic analgesics due to severe pain that lasted up to a week. Three patients developed strictures that needed endoscopic dilation. While using the initial dosimetry protocol, a serious adverse event occurred in a patient with Marfan's syndrome. Gastric overdistention from nitrogen gas production resulted in a gastric perforation. Surgical repair was performed and the patient was no longer treated with cryotherapy.

Greenwald et al. completed a liquid nitrogen based cryotherapy study in the treatment of esophageal cancers in patients who were ineligible or refused conventional esophagectomy.[7] This multicenter, retrospective study recruited 79 participants (64 men and15 women) comprising 74 cases of adenocarcinoma and 5 cases of SCC. The average length of both cancers was 4.0 cm. (adenocarcinoma range 1-15 cm, SCC range 1-12 cm.) and 53 patients had undergone previous treatment for their malignancy. Participants underwent a median of three treatments (range 1-25) consisting of three sessions over 1-5 sites composed of 20 second freezing followed by 40 second thawing. Of the 79 participants that were recruited, 49 subjects were available for analysis while the other 30 were still receiving treatment. Patients who were available for analysis had various tumor stages: 36 cases were T_1, 10 cases were T_2, and 2 cases were T_3. Complete response to cryotherapy was achieved in 30 out of the 49 patients: 26 T_1 cases, 3 T_2 cases and 1 T_3 case. Of the patients who completed treatment, three of them received concurrent alternative treatments including endoscopic resection, chemotherapy, PDT, RFA, and APC. No serious adverse effects were reported. Ten of out 79 participants developed benign esophageal strictures but all ten of these patients had

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received previous treatment and nine of the ten had narrowing before initiating cryoablation. Twenty patients were administered narcotic analgesics due to post-cryotherapy pain.

Success in treating BE with carbon dioxide based cryotherapy appears to be comparable to those achieved with liquid nitrogen. A pilot study focused on BE was performed by Xue et al. and included 22 participants (14 males and 8 females).[31] The patient pool had an average BE length of 2.6 cm. (range 1-6 cm.) and two participants had previously undergone APC therapy. Participants underwent a median of 2 treatments (range 1-3 treatments) at dosimetry of 5-7 cycles of 20-30 second freezing followed by complete thawing. Out of 22 patients, two declined to continue cryotherapy treatments. The remaining 20 patients had complete eradication of BE immediately after treatment. At 6 month follow-up, three patients developed recurrence of BE and two were lost during the follow-up interval. Cryoablation was well tolerated by the patients in the study. Two patients complained of mild chest discomfort that resolved without intervention. After two sessions, three patients developed esophagitis and one was found to have a small ulceration. All three cases were successfully treated with an omeprazole regimen.

The role of carbon dioxide cryoablation in the treatment of neoplastic BE was reported in two separate studies. Canto et al. evaluated the effects and safety of cryotherapy in 68 participants.[17] The average length of BE for the group was 5.3 cm. and 47 patients had failed previous treatment. Early in the study, dosimetry was set at 4-8 cycles of 10-second freeze and 30-second thaw. Later in the study, cryogen dosage was increased to 15 seconds for 6-8 cycles. At study completion, 64 patients were deemed evaluable and of those, 56 showed complete response to the cryoablation. Of the patients with complete response, cryotherapy was the primary intervention for 29 patients and secondary for the remaining 27 patients. During the course of the study, two patients had to be hospitalized for post-treatment complications of bradycardia and presence of mild sub-diaphragmatic gas. Six other patients experienced mild complications that were resolved or addressed without hospitalization.

Verbeek et al. evaluated 10 participants, three of which had BE with HGD and seven had intramucosal carcinoma (ICM).[32] None of the participants had received previous treatments for their diagnoses and EMR procedures were performed in the presence of abnormal nodules before initiation of cryotherapy. Cryoablation was performed at four week intervals until elimination of BE mucosa or for a maximum of 7 treatments. A median of 2.5 treatments was performed and 9 of the participants had nodular lesions resected. At 6-month follow-up, one patient had passed away for reasons unrelated to their disease so the participant pool was reduced to nine patients. A total of 5 of the 9 participants (one with ICM and four with HGD) had complete eradication of their condition. The study experienced early problems with dosimetry that resulted with adverse effects in 3 patients including gastric perforation and lacerations of the stomach and esophagus. After adjusting spray time to 20 seconds and refining catheter positioning, mild complications were usually self-resolving within 4 days and included odynophagia, dysphagia and retrosternal pain.

Palliative Use of Cryotherapy

Liquid nitrogen based cryotherapy has been studied as a palliative modality for esophageal squamous cell carcinoma and has been reported in a limited manner.[33] (Figure 2) One case focused on a 73-year-old African American male who presented with recurrent esophageal SCC. He was deemed unfit for both surgical and radiation therapy due to the combination of past maximum radiation treatments and the severity of the recurrent SCC. After two sessions of cryoablation, the patient remained disease free for over two years. The cryotherapy caused development of a stricture that was treated with dilation and stent placement. Future studies should be conducted to assess the efficacy of palliative care between cyrotherapy and other endoscopic and oncologic therapies.

CONCLUSION

Cryoablation is novel form of endoscopic ablation. Cryotherapy applications include treating primary and secondary GAVE, radiation proctitis, Barrett's esophagus, and esophageal malignancies. Cryotherapy has shown clinical efficacy and favorable safety profiles in limited studies to date. In cases where patients are unable to receive traditional therapies, cryoablation is a viable alternative therapeutic option. Long-term cryotherapy effects have not been well studied in any of the currently used GI indications. To prevent serious

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complications in clinical application, dosimetry studies are needed for standardization of practice. Large, well-controlled studies involving direct comparison of both cryogens (liquid nitrogen and carbon dioxide) are still needed at this time.

The performance of cryotherapy in comparison to other ablative therapies has also not been extensively studied. Although there have been studies of cryoablation as second line treatment to diseases that have failed ablative treatments like APC and RFA, high-quality studies comparing cryotherapy to other treatment modalities are still very much needed. ■

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