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## Cryotherapy in the management of premalignant and malignant conditions of the esophagus

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### Abstract

Endoscopic cryotherapy is a relatively new thermal ablative modality used for the treatment of neoplastic lesions of the esophagus. It relies on cycles of rapid cooling and thawing to induce tissue destruction with a cryogen (liquid nitrogen or carbon dioxide) leading to intra and extra-cellular damage. Surgical treatment was once considered the standard therapeutic intervention for neoplastic diseases of the esophagus and is associated with considerable rates of morbidity and mortality. Several trials that evaluated cryotherapy in Barrett's esophagus (BE) associated neoplasia showed reasonable efficacy rates and safety profile. Cryotherapy has also found applications in the treatment of esophageal cancer, both for curative and palliative intent. Cryotherapy has also shown promising results as salvage therapy in cases refractory to radiofrequency ablation treatment. Cryoballoon focal ablation using liquid nitrogen is a novel mode of cryogen delivery which has been used for the treatment of BE with dysplasia and squamous cell carcinoma. Most common side effects of cryotherapy reported in the literature include mild chest discomfort, esophageal strictures and bleeding. In conclusion, cryotherapy is an effective and safe method for the treatment of esophageal neoplastic processes, ranging from early stages of low grade dysplasia to esophageal cancer.

**Key words:** Esophageal cancer; Barrett's esophagus; Palliative therapy; Cryotherapy

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**Core tip:** Cryotherapy is freezing of tissue to destroy abnormal lesions and has evolving role in management of premalignant and malignant conditions of the esophagus. The currently available cryoablation systems in esophagus are cryospray using liquid nitrogen and cryoballoon focal ablation system using liquid

nitrous oxide. The eradication rates of metaplasia and dysplasia in Barrett's esophagus (BE) with cryotherapy are comparable to those with radiofrequency ablation (RFA). In addition, cryotherapy can be used when RFA is ineffective or not possible in patients with BE and for palliative purposes in advanced esophageal cancer.

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## INTRODUCTION

The application of cold for medicinal purposes have been known since ancient times dating back to Egypt in 3000 BCE where cold compresses were used to reduce inflammation<sup>[1]</sup>. The use of freezing for tumor destruction was first reported by James Arnott in 1851 who used a mixture of salt and crushed ice achieving temperatures of up to -24 °C for treating breast cancer, uterine cancer and some skin cancers<sup>[2]</sup>. Subsequent efforts to lower temperatures led to use of liquefied gases such as air, oxygen, carbon dioxide and subsequently nitrogen. Liquid nitrogen became the most popular cryogen because of its wide availability, lack of explosive potential compared to liquid oxygen, ability to freeze up to -197 °C and predictable effect. Liquid nitrogen has found applications in treatment of nephron-sparing kidney cancers, bone tumors, hepatocellular carcinomas and prostate cancer. The effects of cryotherapy in the esophagus has been studied in 1980's using direct mucosal contact with a cryoprobe which led to unpredictable extent and degree of ablation with some cases of esophageal perforation<sup>[3]</sup>. In 1997, Johnston *et al*<sup>[4]</sup> developed a cryogenic system that permitted delivery of liquid nitrogen *via* an upper endoscope enabling application of cryotherapy under direct visualization and without mucosal contact, thereby allowing precise control of the extent of tissue ablation and potentially reducing complications.

## MECHANISM OF ACTION

Cryotherapy is a thermal ablative modality that utilizes cycles of rapid cooling and thawing to induce tissue destruction with a cryogen, typically a liquefied gas such as nitrogen or nitrous oxide<sup>[4]</sup>. These temperature changes affect several intra- and extracellular mechanisms leading to cell membrane disruption and thrombi formation in the blood vessels inducing apoptosis and ischemia<sup>[5]</sup>. To analyze the effects of cooling process on human cells, Zenzes *et al*<sup>[6]</sup> studied the outcomes of exposure to 0 °C on the morphology of meiotic spindles in human oocytes. He found that after being cooled to 0 °C

for about 2-3 min, the spindles shortened and started to lose their polarity, and in about 10 min, the spindles had totally disappeared.

Tissue destruction involves formation of ice crystals when the cell is exposed to sub-zero temperatures. The osmotic gradient created by these crystals facilitates cell destruction by drawing water out of the cells<sup>[7]</sup>. In addition, the cell membrane composed of lipid bilayer is also sensitive to hypothermia. During the cooling process, the membrane becomes highly permeable and allows mass transfers of ion, resulting in destructive changes in the ionic composition of the cell. The thawing process is the final step when the crystals dissolve due to increased temperatures, creating a reverse osmotic gradient. Water re-enters the cells, causing swelling and rupture<sup>[8]</sup>. Furthermore, it has also been hypothesized that freezing results in vascular injury by causing stasis in blood flow<sup>[9]</sup>. The resulting ischemia causes cell death by necrosis. Delayed mechanism of cell injury involves immune mediated toxicity leading to cell death. The factors that are important in modulating the degree of cell injury include frequency of cooling-thawing cycles, duration of each cycle and end temperature<sup>[10]</sup>.

Cryotherapy employs a non-contact method, where a cryogen is sprayed on the targeted mucosa leading to necrosis of superficial esophageal mucosal layers. Since cryotherapy is targeted, the focused area gets deeper ablation compared to other techniques<sup>[11,12]</sup>. As a result of this targeted approach, the architecture of the surrounding mucosa after cryotherapy stays relatively intact, explaining the low risk of stricture formation compared to radiofrequency ablation (RFA)<sup>[13]</sup>. There are various types of cryogens available, including nitrogen gas, carbon dioxide gas, and other compressed gases, but the most common cryogen by far is liquid nitrogen.

## TYPES OF CRYOTHERAPY SYSTEMS

There are 3 systems for endoscopic cryotherapy that are approved by the United States Food and Drug Administration and commercially available for clinical use in the gastrointestinal (GI) tract. Two of those three systems use a pressurized liquefied gas spray as the cryogen (truFreeze, CSA Medical, Lexington, Mass, and Polar Wand, GI Supply, Camp Hill, Pa), while the third one uses a cryogenic balloon that requires direct contact with the target tissue (C2 CryoBalloon Focal Cryoablation System, Pentax Medical, Montvale, NJ, United States)<sup>[14]</sup>.

The truFreeze system delivers liquid nitrogen through a low-pressure, non-contact, 213 cm long, 7F spray catheter and results in flash freezing the mucosa to -196 °C. The catheter is inserted through the working channel of the endoscope, the cap attached to the tip of endoscope allows correct positioning and manipulation of the cryospray. The delivery of liquid nitrogen is initiated by the foot pedal, which causes dispersion of

the cryogen from compressor to the catheter in a low-pressure fashion while the endoscopist monitors for frost formation. Another consideration during this process is provision of a dual channel decompression tube, since nitrogen expands rapidly from liquid to gas, a method for active and passive venting of the gas is required to prevent mucosal perforation secondary to increased pressure. Freeze is applied for 10-20 s followed by thawing which is repeated 2-4 times for each treatment site.

Another system that used a non-contact method of delivering a cryogen was Polar Wand, which is a liquid carbon-dioxide cryotherapy system. This system works similarly to truFreeze, employing a catheter through the working channel of the endoscope through which carbon-dioxide is delivered which cools down rapidly to  $-78^{\circ}\text{C}$  upon exiting the catheter. The freeze is applied for 15 s followed by thaw and this cycle is repeated 6-8 times. A decompression tube is passed along the endoscope to vent the gas to prevent high intraluminal pressure. The catheters for this device were discontinued by the manufacturing company in 2016.

The third and the latest system uses a contact method comprising a handheld controller and a balloon catheter, the cryoballoon focal ablation system (CbFAS)<sup>[15]</sup>. It is a through-the-scope catheter with battery-powered handle that delivers cryogenic fluid, liquid nitrous oxide into an inflated balloon. This system was designed to overcome the shortcomings of spray system, including the need of a decompression channel, unequal distribution of the cryogen and operative challenges. The balloon-catheter is introduced through the scope and is inflated in the esophagus to establish direct contact with the mucosa. The endoscopist navigates the system by rotating the catheter within the inflated balloon to ensure targeted delivery of the cryogen from its nozzle to the affected area. Cryogen delivery is controlled by the handheld device, and liquid nitrous oxide ( $-85^{\circ}\text{C}$ ) is released through the catheter. In contrast to the other cryotherapy systems, cryogen is applied for 10 s at each ablation site. Also, the cryogen is contained in the balloon and diffuses back through the catheter, allowing more consistent application of cryogen and also eliminating the need to use the decompression channel. A second-generation device became available in June 2018.

## DOSIMETRY

There are multiple studies in the literature evaluating the efficacy and safety profile of cryotherapy as a treatment modality in esophageal neoplastic processes. As outlined above, cryotherapy works by the freeze and thaw process which causes ice crystal formation intracellularly resulting in tissue destruction. Studies have shown that rapid rates of cooling and longer duration of freezing result in increased crystal formation. There are, however, very few dosimetry studies in the literature and it is still unclear whether the freeze or thaw period is more important or the number of freeze-thaw cycles in

determining the overall treatment effect.

In an attempt to answer that question, Raju *et al.*<sup>[16]</sup> evaluated the extent of transmural damage at 48 h after cryotherapy for varying durations. They found a linear correlation between the duration of therapy and depth of damage; necrosis was limited to lamina propria after 15 s of therapy, extended to submucosa after 30 s, muscularis propria after 45 s and extensive transmural necrosis after 120 s of cryotherapy. Ribeiro *et al.*<sup>[11]</sup> studied the dose of 2 cycles for 20 s and 4 cycles for 10 s. Their findings demonstrated that 20 s cycle achieved greater depth of submucosal ablation, however they did not draw a direct comparison between 10 s and 20 s. Schölvinck *et al.*<sup>[15]</sup> performed cryotherapy with CbFAS on porcine and human models to assess the duration of ablation that can be used safely without causing serious adverse events. In the porcine model, they observed deep mucosal edema and inflammation after 6 s of cryoablation, which penetrated deeper into the mucosa after 4 d. These delayed effects did not cause any long-term damage. Even the models treated for supra-therapeutic durations of up to 24 s did not show persistent damage. The 6 s ablation procedure in human models only caused necrosis in the mucosal and submucosal layers, the sites targeted for BE ablation without causing any deeper layer damage.

## CRYOTHERAPY IN BARRETT'S ESOPHAGUS

Surgical esophagectomy used to be the standard therapeutic intervention for Barrett's esophagus (BE) with high grade dysplasia (HGD) but was associated with considerable rates of morbidity and mortality<sup>[17]</sup>. This approach was based on studies showing up to 40 % prevalence of cancer in esophagectomy specimens of patients with HGD<sup>[18,19]</sup>. In a meta-analysis<sup>[20]</sup> of patients who had esophagectomy for HGD in BE, the true prevalence of invasive esophageal adenocarcinoma (EAC) was found to be around 12.7%. It is clinically relevant to make the distinction between invasive EAC (t1b or higher) and intra- mucosal cancer (IMC), since the latter carries minimal nodal metastasis risk and can potentially be treated with endoscopic treatment modalities including endoscopic mucosal resection (EMR), RFA and cryotherapy.

Majority of the experience in cryotherapy in BE associated dysplasia involves cryoablation with cryospray using liquid nitrogen (Table 1). The initial use was reported in 2005 in 11 patients with BE with varying degrees of dysplasia from none to multifocal HGD<sup>[21]</sup>. There was reversal of BE in all patients. In 9 of 11 (78%) patients who completed the protocol, there was complete eradication of intestinal metaplasia (CE-IM). There were no reported complications and no recurrence of metaplasia at the 6-mo follow up. In a multi-center retrospective cohort of 60 patients with BE and HGD, 52 (87%) patients had complete eradication of dysplasia



**Table 1 Cryotherapy in Barrett's esophagus**

Author (yr)	No. of patients	Cryotherapy system used	Results of the study	Adverse events
Johnston <i>et al</i> <sup>[23]</sup> (2005)	11	Liquid nitrogen at -196 °C	100% CE-D and CE-IM	-
Canto <i>et al</i> <sup>[26]</sup> (2015)	44	Modified low-pressure CO <sub>2</sub> cryotherapy system (Polar Wand, GI supply)	95.6% CE-D in LGD, 91.3% CE-D in HGD	4.5% (2) developed transient mild discomfort post-procedure.
Dumot <i>et al</i> <sup>[42]</sup> (2009)	30	LNSCT (CSA Medical Inc, Baltimore, Md)	68% CE-D in HGD, 80% CE-D in IMC	3.3% (1) developed perforation in a patient with known Marfan's syndrome
Ghorbani <i>et al</i> <sup>[24]</sup> (2016)	96	LNSCT (2 <sup>nd</sup> generation, CSA Medical, Baltimore, MD, United States)	91% CE-D in LGD, 81% CE-D in HGD, 61% CE-IM in LGD and 65% CE-IM in HGD respectively.	1% (1) developed stricture, which did not require dilation. 1% (1) hospitalized for bleeding in the setting of NSAID use
Ramay <i>et al</i> <sup>[44]</sup> (2017)	90 (50 for 3-yr analysis, 40 for 5-yr analysis)	LNSCT	3-yr analysis: 96% CE-D in HGD, 94% CE-D in LGD, 82% CE-IM; 5-yr analysis: 93% CE-D in HGD, 88% CE-D in LGD, 75% CE-IM	-

BE: Barrett's esophagus; CE-D: Complete eradication of dysplasia; CE-IM: Complete eradication of intestinal metaplasia; HGD: High grade dysplasia; LGD: Low grade dysplasia; LNSCT: Liquid nitrogen spray cryotherapy; IMC: Intra-mucosal cancer.

(CE-D) and 34 (57%) had CE-IM<sup>[22]</sup>. In another multicenter study of 77 patients with BE associated neoplasia (52 had HGD), CE-D was observed in 88% of patients and CE-IM in 53% during a mean follow up of 9.9 mo<sup>[23]</sup>. Finally, in a recent report from cryospray registry<sup>[24]</sup> of 80 patients with BE and HGD or low-grade dysplasia (LGD) treated with either two to three cycles of 20-s freezes or four cycles of 10-s freezes with cryospray, CE-D was reported in 91% with LGD and 81% in HGD, while the CE-IM was found to be 61% in LGD and 65% in HGD respectively during a mean follow up of 21 mo.

### Cryotherapy with carbon dioxide

In a single center case series of 10 patients (7 with IMC and 3 with HGD), 9 patients underwent EMR and pre-cryoablation diagnoses were nondysplastic BE in 4, LGD in 5, and HGD in 1 patient. CE-IM was observed in 11% (1/9; one patient died) and CE-D in 44% (4/9) of the patients at 6 mo of follow-up<sup>[25]</sup>. In a larger single center trial of 64 patients (44 had prior failed treatments, 20 were treatment naïve; 50 had HGD), all patients underwent EMR for nodular lesions prior to carbon-dioxide cryoablation<sup>[26]</sup>. At 6-mo follow up, CE-D was seen in 89% of patients and CE-IM in 55%. Of note, production and sale of the Polar Wand system was suspended by the manufacturer in March 2016.

### Cryoablation with nitrous oxide

In the only reported trial on CbFAS, 41 patients with LGD ( $n = 13$ ), HGD ( $n = 23$ ), or IMC ( $n = 5$ ) were treated<sup>[27]</sup>. CE-D and CE-IM rates at one year were 95% and 88%, respectively. CE-D rate was significantly lower (67%) in those with ultra-long BE compared with those with < 8 cm (100%,  $P = 0.02$ ). The eradication rates appear to be higher than those observed with liquid nitrogen (CE-D, 91%; CE-IM, 53%-65%) and CO<sub>2</sub> cryotherapy (CE-D, 89%; CE-IM, 55%).

## CRYOTHERAPY FOR EAC (CURATIVE INTENT)

Endoscopic therapy for EAC is emerging as a treatment of choice, especially in patients with T1 stage cancer and a low risk of nodal metastasis<sup>[28]</sup>. The standard treatment is resection of any visible lesions with EMR followed by ablation of residual BE segment. Since cryotherapy leads to deeper injury than RFA, it may be an option in patients with early esophageal cancer (Table 2). Greenwald *et al*<sup>[29]</sup> reported on 49 patients with esophageal cancer in a multi-center, retrospective cohort who underwent cryospray with liquid nitrogen. Of those 49 patients, 30 demonstrated complete luminal disease resolution after a mean treatment period of 10.6 mo and 3 treatment sessions. Biopsy results after treatment completion showed 16 patients with CE-IM, 25 patients with CE-D, 4 patients with LGD and 1 patient with persistent HGD. Similarly, Tsai *et al*<sup>[30]</sup> studied the safety profile and efficacy of cryotherapy in treating esophageal cancer in 88 patients using cryospray system. Eighty-eight patients with EAC underwent therapy up to the point of complete local eradication of the intraluminal tumor or progression of the disease. Eighty-six patients completed the treatment achieving complete response, including 76.3% for T1a, 45.8% for T1b, 66.2% for all T1, and 6.7% for T2. Another study analyzed treatment naïve patients who underwent EMR for IMC with residual dysplasia who were then treated with liquid nitrogen cryospray as the salvage therapy. The results showed that cryospray was effective in achieving CE-D in 82% and CE-IM in 70% with 4% (one patient) rate of progression to invasive cancer<sup>[31]</sup>.

## CRYOTHERAPY FOR EAC (PALLIATIVE INTENT)

Dysphagia is a debilitating symptom in esophageal can-



**Table 2 Cryotherapy in esophageal cancer**

Author (yr)	No. of patients	Cryotherapy system used	Results	Adverse events
Cryotherapy in EAC				
Greenwald <i>et al</i> <sup>[29]</sup> (2010)	79 (49 completed the treatment)	Low-pressure liquid nitrogen (< 5 psi) cryotherapy system	CE-D in 32%.	Benign strictures (12.6%), pain post treatment (25.3%)
Tsai <i>et al</i> <sup>[30]</sup> (2017)	88	Low-pressure liquid nitrogen (< 5 psi) cryotherapy system	CE of intraluminal disease in 76.3% T1a, 45.8% T1b, 66.2% T1, and 6.7% T2	Abdominal pain (19.3%), dysphagia (10.2%), sore throat (9%), and chest pain (8%)
Kachaamy <i>et al</i> <sup>[32]</sup> (2018)	49	Low-pressure liquid nitrogen system (CryoSpray Ablation System; CSA Medical, Inc, Lexington, Mass)	Improvement in mean dysphagia score	2% (1) developed a severe intra-procedural perforation, 2% (1) developed a benign stricture requiring dilation.
Cryotherapy in SCC				
Cash <i>et al</i> <sup>[33]</sup> (2007)	1	Liquid nitrogen cryospray ablation	100% CE-D	Stricture development
Canto <i>et al</i> <sup>[34]</sup> (2018)	10	Nitrous oxide (CbFAS)	100% CE-D in LGIN, HGIN, SCC	Post-procedure pain (40%), esophageal stricture (20%)

EAC: Esophageal adenocarcinoma; CE-D: Complete eradication of dysplasia; CE: Complete eradication; CSA: Cryospray ablation; SCC: Squamous cell carcinoma; LGIN: Low-grade intraepithelial neoplasia; HGIN: High-grade intraepithelial neoplasia; CbFAS: Cryoballoon focal ablation system.

cer, especially if the cancer is not resectable. Already existing palliative treatment modalities include esophageal stent placement and radiation therapy with associated side effects. Kachaamy *et al*<sup>[32]</sup> studied use of cryospray for relief of dysphagia in 49 patients with inoperable esophageal cancer. Dysphagia was measured using a 5-point Likert scale: 0, no dysphagia; 1, dysphagia to solids; 2, dysphagia to semisolids; 3, dysphagia to liquids; 4, dysphagia to saliva. The mean dysphagia score improved significantly from 2.4 pre-cryotherapy to 1.7 post-cryotherapy (improvement of 0.7 points;  $P < 0.001$ ). Before the start of cryotherapy, only 8.2% of patients ( $n = 4$ ) had a dysphagia score  $\leq 1$ , whereas after the last cryotherapy treatment 40.8% of patients ( $n = 20$ ) has a dysphagia score  $\leq 1$ . So, cryotherapy may be safe and effective for dysphagia palliation in inoperable esophageal cancer.

## CRYOTHERAPY FOR ESOPHAGEAL SQUAMOUS CELL CANCER AND SQUAMOUS DYSPLASIA

There is very limited data on the use of cryotherapy for the treatment of esophageal squamous cell cancer (ESCC) or squamous dysplasia (Table 2). Several reports on liquid nitrogen cryospray included small subgroup of patients with ESCC however, the efficacy of treatment in this subgroup was not reported<sup>[23,29]</sup>. In one case report, Cash *et al*<sup>[33]</sup> used liquid nitrogen cryospray ablation in the palliative treatment of ESSC 3 years after the initial treatment with chemoradiation. At 1-mo follow up, the tumor had completely resolved endoscopically but persisted on biopsy. Repeat cryotherapy was then performed which resulted in CE-D and the surveillance biopsies taken at 24-mo period remained negative for cancer. Canto *et al*<sup>[34]</sup> described the first clinical application of nitrous oxide *via* the CbFAS for treatment of esophageal squamous cell neoplasia. Ten patients

were included in the study, with LGIN ( $n = 2$ ), HGIN ( $n = 7$ ), and ESSC ( $n = 1$ ). All 10 patients demonstrated complete eradication of the tumor within three months of treatment. This study warrants further trials using cryotherapy for the treatment of esophageal squamous cell neoplasia for a detailed documentation of efficacy and safety analysis.

## CRYOTHERAPY IN CASES REFRACTORY TO RFA

RFA is an effective treatment modality for BE resulting in CE-D, however, there is limited data on efficacy of other options in cases refractory to RFA. To evaluate the safety and efficacy of Cryotherapy in RFA refractory cases, Sengupta *et al*<sup>[35]</sup> treated 121 patients with RFA, 75% (91) of which achieved CE-D with resolution of clinical symptoms. Among the cases who failed the initial treatment, 16 were treated with salvage cryotherapy with liquid nitrogen (Cryospray Ablation System; CSA Medical, Lexington, MA, United States). Post cryotherapy treatment, 12 (75%) achieved CE-D in HGD, 5 (31%) achieved CE-IM whereas patients with IMC had 100% CE-D. Trindade *et al*<sup>[36]</sup> studied 18 patients who had persistent intestinal metaplasia after RFA and underwent salvage cryotherapy. Eleven of them had BE with dysplasia while seven had metaplasia in the absence of dysplasia. Similar to Sengupta *et al*<sup>[35]</sup>, liquid nitrogen was used as a cryogen applied for at least 20 s for two cycles on a 2-cm, one-half circumference area. Post treatment, CE-D was achieved in 75% of the cases with LGD and 71% with HGD, while 100% subjects showed certain degree of improvement in histopathology. None of the cases who had CE-D showed any recurrence, endoscopically or microscopically. Suchniak-Mussari *et al*<sup>[37]</sup>, in a retrospective, single-center study carried out in a tertiary care center included 45 patients with BE who underwent cryotherapy after

**Table 3 Radiofrequency ablation vs cryotherapy**

	Radiofrequency ablation	Cryotherapy
Mechanism of action	Bipolar electrode delivering radiofrequency energy to mucosa which generates heat and causes a uniform thermal injury on contact	Rapid freeze and thaw cycles cause immediate effects of slowing cellular metabolism and freezing intracellular water. Subsequently, ice formation results in disruption of cellular membranes and organelle dysfunction and eventually cellular apoptosis.
Maximal depth of injury	Mucosa (500-1000 microns)	Depends on the dose delivered; upto submucosa
Eradication of metaplasia	66.7%-100 %	41.3%-60% with cryospray; 84%-100% with cryoballoon
Eradication of dysplasia	87.5%-100%	78.8%-90% with cryospray; 92%-100% with cryoballoon
Post procedure pain requiring analgesics	4 d	2 d
Side effects	Esophageal strictures in 10.2%, bleeding 1.1%, perforation 0.2%	Esophageal strictures in 0%-12.5%, bleeding in 2 cases, perforation in 3 cases
Durability	CE-D 98% and CE-IM 91% at 3 yr	CE-D 92%, and CE-IM 81% at 5 yr (with cryospray only, cryoballoon data not available)
Recurrent metaplasia	16.10%	13.30%
Recurrent dysplasia	2.60%	3.60%
Recurrent high grade dysplasia or cancer	1.40%	1.30%

CE-D: Complete eradication of dysplasia; CE-IM: Complete eradication of intestinal metaplasia.

failing the initial therapy. Of those 45, 33 completed the surveillance protocol and were included in the final data analysis. Among those 33 patients, 29 (88%) responded to cryotherapy, with 84% having complete regression of all dysplasia and cancer. CE-D was seen in 75% of subjects with IMC. A meta-analysis performed by Visrodia *et al.*<sup>[38]</sup> reported successful achievement of CE-D in three-fourths and CE-IM in one-half of the patients who did not respond to the initial RFA therapy. Cryotherapy is deemed safe and efficient in the setting of RFA treatment unresponsiveness.

## CRYOTHERAPY COMPARED TO RFA

Cryotherapy has several theoretical advantages over RFA. Since it is a noncontact method of ablation, it can be used for treating uneven, nodular surfaces and can be passed through strictured areas. The depth of ablation extends to submucosa which makes it useful for treating superficial cancers. In cryotherapy, the tissue architecture of the superficial squamous layers is left relatively intact, and there is less tissue damage, which may underlie the reduced stricture formation rate with this modality. There are very few trials comparing the results and adverse events of cryotherapy and RFA (Table 3).

In a retrospective study<sup>[39]</sup> comparing RFA ( $n = 73$ ) and cryotherapy ( $n = 81$ ), CE-IM rates in RFA and cryotherapy were 66.7% vs 41.3% respectively ( $P = 0.002$ ) and CE-D were 87.5% and 78.8% respectively ( $P = 0.15$ ). Progression was noted in 12.5% in both groups and recurrent disease was noted in 11.1% and 14.3% in RFA and cryotherapy groups. Patients who underwent RFA had a threefold higher odd of having CE-IM than those who underwent cryotherapy [odds ratio (OR) = 2.9, 95% confidence interval (CI): 1.4-6.0,  $P = 0.004$ ], but CE-D were similar between the two groups (OR = 1.7, 95%CI: 0.66-4.30,  $P = 0.28$ ).

Post procedural pain was compared between cryo-

therapy and RFA in two studies. In a study comparing outcomes after a single session of ablation with either RFA ( $n = 26$ ) and cryotherapy with CbFAS ( $n = 20$ )<sup>[40]</sup>, BE regression was similar in both groups (88% vs 90%,  $P = 0.62$ ). Peak pain was lower after cryotherapy (visual analog scale 2 vs 4,  $P < 0.01$ ), and the duration of pain was also shorter after cryotherapy (2 d vs 4 d,  $P < 0.01$ ). Also, cryotherapy patients used analgesics for 2 d vs 4 d for RFA ( $P < 0.01$ ). Similar findings were noted in a study comparing RFA to cryospray ablation. Pain intensity scores and the presence of dysphagia were assessed immediately before and after treatment, 48 h post-treatment and at 3 wk post-treatment using validated instruments<sup>[41]</sup>. The odds of pain after RFA were at least 5 times greater than that after cryospray immediately post-treatment and at 48 h post-treatment. There was no difference in dysphagia after treatment in either group.

## ADVERSE EVENTS

Cryotherapy treatment has produced durable results with good safety profile and very few adverse events. Abdominal pain (19.3%), dysphagia (10.2%), sore throat (9%), and chest pain (8%) are the most common post-procedural side effects<sup>[29]</sup>. Esophageal strictures are reported in 0%-12.5% of the patients<sup>[32]</sup>. With cryospray ablation, pain requiring narcotics is reported in 3%-10% of patients<sup>[22,42]</sup>. Most of the side effects caused by cryotherapy are effectively managed with minimum interventions and the benefits of the therapy outweigh the risks in most cases. Gastric perforation has been reported in a patient with known Marfan's syndrome<sup>[42]</sup>. Subsequently, there has been modifications in the decompression tube. Another case of esophageal perforation has been reported with post cryotherapy stricture dilation in a patient with inoperable esophageal cancer<sup>[33]</sup>. Samarasena *et al.*<sup>[43]</sup> reported a case of a jejunal perforation after cryotherapy which was

thought to be secondary to barotrauma. It was closed successfully with an over-the- scope clip. With carbon dioxide cryotherapy, esophageal strictures were noted in 1.5% of patients<sup>[26]</sup>. One case of microperforation led to hospitalization but did not require surgical intervention. Limited data are available with CbFAS. Four patients (9.7%) developed mild dysphagia from stenoses requiring dilation<sup>[27]</sup>. One patient (2.4%) on aspirin developed upper GI bleeding that did not require therapy.

## DURABILITY AND RECURRENCES

In a single center cohort of 50 patients followed up for 3 years and 40 patients followed up for 5 years, initial rates were CE-D of 90% (45/50) and CE-IM of 60% (30/50)<sup>[44]</sup>. The authors examined durability (lack of a need for retreatment) at 5 years in their cohort of 40 patients, and they found that the durability of CE-D was 92%, and of CE-IM was 81%. For patients who achieved CE-IM, rates of CE-D and CE-IM at 3 years were 93% (28/30), and 87% (26/30). Recurrent dysplasia, which usually occurred below the neosquamocolumnar junction, was able to be managed with retreatment in most cases. Incidence rates of recurrent intestinal metaplasia, dysplasia, and HGD/EAC per person- year of follow-up after initial CE-IM were 13.3%, 3.6%, and 1.3% per person-year, respectively. There were 2 cases of incident EAC in this cohort, one of which developed during treatment and one that occurred 18 mo after treatment with no reported mortality.

## CONCLUSION

In conclusion, cryotherapy is an effective and a safe method for the ablation of wide range of esophageal lesions from LGD to advanced cancers. Even though the efficacy is slightly inferior to RFA, it can be used in situations when RFA is ineffective or not feasible. Large randomized controlled trials are needed before cryotherapy has an established role in the management of neoplastic processes in the esophagus.

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