Diseases of the Esophagus (2020)**33**,1–6
DOI: 10.1093/dote/doz095

DISEASES OF THE ESOPHAGUS

ISDE The International Society for Diseases of the Esophagus

Original Article

Liquid nitrogen spray cryotherapy-based multimodal endoscopic management of dysplastic Barrett's esophagus and early esophageal neoplasia: retrospective review and long-term follow-up at an academic tertiary care referral center

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*SUMMARY.**Background:*** **Endoscopic eradication therapy of dysplastic Barrett's esophagus (BE) and early esophageal neoplasia has emerged as an effective treatment option. Data for the role of spray cryotherapy (SCT) in this setting is relatively limited.** ***Objective:*** **To evaluate the safety and long-term outcomes of SCT-based multimodal therapy in the management of dysplastic BE and early esophageal neoplasia.** ***Design:*** **Single-center, retrospective, cohort study.** ***Setting:*** **Academic, tertiary care center between August 2008 and February 2019.** ***Methods:*** **A retrospective chart review was conducted of the prospectively maintained endoscopic cryotherapy database at our center. Fifty-seven patients were identified who underwent SCT treatment for dysplastic BE and esophageal or Gastro-esophageal (GE) junction adenocarcinoma during the study period. Primary outcome was complete eradication of intestinal metaplasia (CE-IM); secondary outcome was complete eradication of dysplasia (CE-D).** ***Results:*** **A total of 171 SCT procedures were performed in 57 patients. The majority of patients were male (89.5%) with long-segment BE (93%; mean segment length 6.2 cm). Complete follow-up data was available for 56 of these 57 patients. 43.9% (25/57) of patients underwent radiofrequency ablation (RFA) during the course of treatment (e.g. after initiating SCT). 33.3% of patients (19/57) were RFA failures prior to SCT. Additionally, 68.4% (39/57) of patients underwent endoscopic resection (EMR) prior to SCT as part of our multimodal approach to treatment of BE dysplasia/neoplasia. Four patients (7%) are currently undergoing active ablation and/or EMR treatment. CE-IM was achieved in 75% (39/52) of patients, and CE-D in 98.1% (51/52). Mean duration of overall follow-up was 4.8 years, with mean CE-IM durability of 2.6 years.** ***Limitations:*** **Single-center only, retrospective study design.** ***Conclusion:*** **SCT-based multimodal endoscopic therapy can achieve very high CE-IM (75%) and CE-D (>98%) rates in a high-risk population with esophageal dysplasia and/or neoplasia.**

KEY WORDS: **Barrett's esophagus, cryotherapy, dysplasia, endoscopic ablation, esophageal adenocarcinoma.**

INTRODUCTION

Barrett's esophagus (BE) is a metaplastic change in the normal squamous epithelium of the esophagus to an intestinal type columnar mucosa with goblet cells. This change occurs as a consequence of long-standing acid reflux and is considered to be a premalignant change. The risk of development of esophageal adenocarcinoma (EAC) in patients with BE is 40 to 120-fold higher than the general population.[1, 2] The risk of progression of non-dysplastic BE to cancer is estimated to be 0.12 to 0.4% per year;[3, 4] however, the risk increases to 5.6 to 6.6% per year in cases of BE with high-grade dysplasia (HGD).[5]

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Specific author contributions: Planning/conducting of the study, collection of/interpretation of data, and drafting/editing the manuscript. Dr. Kaul has approved the final draft, as submitted. Dr. Kaul serves as a consultant with CSA Medical: Vivek Kaul; Planning/conducting of the study, collection of/interpretation of data, and drafting/editing the manuscript. Ms. Bittner has approved the final draft, as submitted. Krystle Bittner has no relevant conflict of interest to report: Krystle Bittner; Drafting/editing the manuscript. Dr. Ullah has approved the final draft, as submitted collection of/interpretation of data . Dr. Ullah has no relevant conflict of interest to report: Asad Ullah; Planning/conducting of the study, and drafting/editing the manuscript. Dr. Kothari has approved the final draft, as submitted. Dr. Kothari has no relevant conflict of interest to report: Shivangi Kothari.
Guarantor of the article: Vivek Kaul, MD, FACG, FASGE, AGAF.
Financial support: this study was financially supported by CSA Medical. The work was independent of the financial contribution of the sponsor, less for final edits of the manuscript prior to submission.

Advances in endoscopic treatment modalities have revolutionized the management of BE and early esophageal neoplasia. In recent years, the paradigm for management of dysplastic BE and early esophageal neoplasia has shifted from esophagostomy (with high risk of morbidity and mortality) to endoscopic ablation [radiofrequency ablation (RFA), cryotherapy] and resection techniques [endoscopic mucosal resection (EMR), endoscopic submucosal dissection] aimed at complete endoscopic eradication of the BE segment. Endoscopic management is less invasive and may be more cost-effective than surgery while yielding greater quality-adjusted life years.

Liquid nitrogen spray cryotherapy (SCT) is a safe and effective therapeutic modality for patients with dysplastic BE and/or neoplasia. SCT has demonstrated complete eradication of intestinal metaplasia (CE-IM) in 53 to 77% of patients and complete eradication of dysplasia (CE-D) in 81 to 100% of patients with dysplastic BE.[6–10] The aim of our study was to evaluate the efficacy and safety of SCT using the multimodality therapy approach in the management of BE dysplasia and early esophageal neoplasia, in a high-risk cohort.

METHODS

Patients

This study is a retrospective review of a prospectively maintained cryotherapy database of patients who underwent SCT with the indication of dysplastic BE or early adenocarcinoma of the esophagus at our academic tertiary care referral center from August 2008 to February 2019. Baseline demographics, length of BE segment, indication for SCT treatment, and prior/concurrent treatment modalities (EMR and RFA) were recorded. Biopsies at our institution were reviewed by expert Gastrointestinal (GI) pathologists trained (and experienced) in Barrett's pathology assessment prior to beginning any ablation or resection treatment. Patient outcomes were recorded. This study was approved by the University of Rochester Medical Center Institutional Review Board.

Treatment approach

In our neoplasia-rich cohort, a multimodality treatment approach was followed to achieve CE-D and CE-IM. EMR was performed on any visible raised and/or focal nodular areas in the BE segment, and then at the subsequent Esophagogastroduodenoscopy (EGD), the remaining flat BE was treated with SCT as described below. For any patient with biopsy-proven residual or recurrent IM detected and/or visually confirmed residual focal IM, these sites were treated with "touch-up" RFA at the endoscopists' discretion. In three patients, a novel EMR device (Endorotor; Interscope Inc., USA) was utilized for salvage EMR of persistent non-dysplastic BE segment that was not amenable to standard EMR techniques.

Cryotherapy protocol

Cryotherapy was performed by three highly experienced interventional endoscopists (VK, SK, and AU), with extensive and specific experience in BE ablation and endotherapy, including SCT. All endoscopists had received formal training utilizing the SCT device (CSA Medical, Inc.; Baltimore, MD). This cryotherapy system utilizes liquid nitrogen at −196°C that is sprayed through a 7 F catheter at the target tissue at a cooling rate of 25 watts. For patients enrolled between 2008 and 2013, the G2 CryoSpray Ablation System (SCS System, Model CC2-NAM, CSA Medical Inc., Baltimore, MD) was utilized for SCT treatment. In 2014, the TruFreeze system (CSA Medical Inc., USA) was introduced at our institution and has been in use since.

After adequate sedation was achieved (using moderate sedation or general anesthesia), a standard upper endoscopy was performed to examine the esophageal anatomy and BE segment and identify any focal lesions. A cap-fitted endoscope was used. The examination was performed using high-definition white light and narrow band imaging, after cleaning the esophagus with n-acetylcysteine solution. Detailed photo documentation of the BE segment and any focal target areas was performed at each session. A dual-lumen decompression tube was introduced over a Savary guidewire to allow for proper placement in the gastric antrum to facilitate decompression of the nitrogen gas, in anticipation of SCT treatment. Active venting was performed for decompression. The spray catheter was introduced through the working channel of an adult gastroscope and advanced 3 to 4 mm beyond the tip of the cap-fitted endoscope. Active venting through the decompression tube was initiated by pressing on the suction pedal, followed by liquid nitrogen spray using the blue foot pedal. Gentle abdominal pressure and monitoring of distension was performed by a nurse assistant during the treatment phase. Another staff person, typically a GI technologist, assisted with the equipment and console management.

For treatment of flat BE, SCT was applied until a visible, 2 to 3-mm thick white frost was attained over a 2 to 3-cm hemi-circumferential area of the target BE segment. The timer was then started and the spray continued for 10 to 30 seconds (dosimetry varies per device, per indication for SCT, and per the discretion of the endoscopist). Same dosimetry was used for treatment of flat BE, whether it was flat dysplastic or post EMR residual IM. For flat BE, the dosimetry protocols have varied during the study period, per device specifications (10 seconds × 4

applications, 20 seconds × 2 applications, and most recently 30 seconds × 2 applications). The treated segment was allowed to thaw (minimum 45 seconds) in between the cryospray cycles. Cryospray treatment was repeated (10–30-second applications × 2–4 applications) after the thawing was visibly complete. The thaw period allowed for reperfusion of the treated area, and then the freeze cycle was repeated. On an average, 3 to 5 sites were ablated at each session.

All patients were discharged with prescriptions for liquid acetaminophen with codeine and Benadryl, Maalox, and Xylocaine, as needed for pain. Follow-up treatment was performed approximately every 6 weeks until there was no evidence of residual BE visualized on endoscopy with confirmed histology.

Surveillance

All patients (excluding those in current treatment or lost to follow-up) underwent post-SCT surveillance EGD's with cold forceps biopsy utilizing the Seattle protocol (defined as 4-quadrant jumbo biopsies (every 1 cm) in the original Barrett's segment). Surveillance endoscopies in the post-endotherapy setting were performed as follows: every 3-6 months in the first year, every 6 months in the 2nd and 3rd years after achieving CE-IM, and annually thereafter. CE-IM was defined as at least two consecutive negative forceps biopsies in the surveillance period. Expert GI pathologists at our institution reviewed the histology on the forceps biopsies. Many patients (53.8%) also underwent concurrent wide area trans-epithelial sampling (WATS-3D) brush biopsy, after this device became commercially available in 2012. In this subset of patients, CE-IM was defined as two consecutive negative forceps and brush biopsies. This is a much more rigorous standard for achieving CE-IM than has previously been defined in the literature.

Data collection and analysis

At initiation of SCT treatment, the patient's age, sex, BE segment length, and indication for SCT ablation were recorded. Information regarding EMR and RFA treatment was collected throughout the study period, including the number of sessions needed to achieve complete eradication of BE (if applicable) as well as any repeat sessions performed in the event of recurrence. All surveillance pathology reports in the study period were documented. Occurrence of any adverse event with probable or likely association with SCT was entered into the cryotherapy database. A procedure-related adverse event was defined as esophageal perforation, GI bleed, ED visit, hospital admission, significant chest pain requiring ED or hospital admission, or clinically significant dysphagia occurring within 4 weeks of the procedure.

The primary outcome measure was complete eradication of CE-IM, with a secondary outcome measure of CE-D. Calculation of frequency (%) and mean was performed for categorical and continuous variables, respectively.

RESULTS

A total of 57 patients (Table 1) underwent SCT for indications of dysplastic BE or early esophageal neoplasia between August 2008 and February 2019. One hundred seventy-one SCT procedures were performed. Mean patient age was 68.5 years (all Caucasian; majority (89.5%) male). Mean BE segment length was 6.2 cm. Complete follow-up data was available for 56 of these patients. 43.9% (25/57) of patients underwent RFA during the course of treatment (e.g. after initiating SCT). 33.3% of patients (19/57) were RFA failures (defined as persistent IM or dysplastic BE despite treatment with 3 or more sessions of RFA). Additionally, 68.4% of all patients underwent endoscopic mucosal resection (EMR) prior to SCT.

CE-IM was achieved in 75% (39/52) of patients, and CE-D in 98.1% (51/52). Four patients are currently in treatment and were not included in the CE-IM/CE-D calculations. A novel resection device (Endorotor; Interscope, Inc., USA) has been utilized for salvage EMR in three cases with persistent non-dysplastic BE, which was not amenable to standard EMR.

A total of 79.2% of dysplastic patients ($n = 6/7$ LGD; $n = 13/17$ HGD) and 67.9% of those with early esophageal neoplasia ($n = 13/17$ adenocarcinoma T1a; $n = 6/11$ invasive adenocarcinoma) achieved CE-IM. Dual-modality tissue sampling (biopsies and WATS-3D brush sampling) was performed in 53.8% of patients ($n = 28/52$). A total of 57 WATS biopsies were performed in these 28 patients. WATS was able to detect additional IM in 14.0% ($n = 8/57$), IM/indefinite for dysplasia in 5.3% ($n = 3/57$), LGD in 1.8% ($n = 1/57$), and HGD in 1.8% ($n = 1/57$) cases, where forceps biopsy was negative in these cases. Of the five invasive EAC patients wherein CE-IM was not achieved, three (60%) patients ultimately required esophagectomy (despite SCT treatment) (Table 2).

"Touch-up" RFA (in cases with residual focal IM following SCT treatment) was performed in 51.3% (20/39) of patients to achieve CE-IM. The majority of patients that achieved CE-IM (79.4%; 27/34) have remained consistently negative (e.g. never had recurrence of IM, dysplasia, or neoplasia). The mean durability of CE-IM in these patients is 3.4 years. Five patients have achieved CE-IM within the last 3 months and have not yet returned for their 6-month surveillance. Of the remaining current CE-IM patients, a recurrence of IM (3), LGD (2), or HGD (2) has occurred since their initial achievement of CE-IM. Of HGD recurrences, one patient progressed

Table 1 Total cohort demographics

	Total cohort ($n = 57$)
Age at time of 1st SCT, mean, *y*	68.5
Male, % (*n*/*N*)	89.5 (51/57)
Mean BE length, cm	6.2
Indication for SCT, % (*n*/*N*)	
Low-grade dysplasia	14.0 (8/57)
HGD	35.1 (20/57)
Adenocarcinoma, T1a	31.6 (18/57)
Invasive adenocarcinoma[a]	19.3 (11/57)
Mean number of SCT sessions	3.0
RFA treatment, % (*n*/*N*)[b]	77.2 (44/57)
Mean number of RFA sessions (overall)	3.9
EMR treatment, % (*n*/*N*)[c]	73.7 (42/57)
Mean number of EMR sessions (overall)	2.1
Follow-up, years[d]	4.8

[a]adenocarcinoma patients include esophageal and GE junction adenocarcinoma stage T1b or higher. 4/11 (36.7%) required chemotherapy ($n = 1$), radiation ($n = 1$), and/or chemotherapy + radiation treatment (2/11) prior to SCT. 3/11 (27.3%) ultimately required esophagectomy.
[b]19/57 (33.3%) of patients that underwent RFA did so prior to initiating SCT treatment (mean number of RFA sessions prior to SCT = 5.2);
[c]25/57 (43.9%) underwent RFA at some point in their course of treatment following initiation of SCT.
39/42 (92.9%) of patients that underwent EMR did so prior to initiating SCT treatment (mean number of EMR sessions prior to SCT = 1.9).
[d]Follow-up calculated from time initial treatment for BE at our center.

Table 2 CE-IM & CE-D rates

	CE-IM after SCT % (*n*/*N*)	CE-D after SCT % (*n*/*N*)
Total cohort ($n = 52$)[a]	75 (39/52)	98.1 (51/52)
Pathology before SCT		
Low-grade dysplasia	85.7 (6/7)	100 (7/7)
HGD	76.5 (13/17)	100 (17/17)
Adenocarcinoma, T1a	76.5 (13/17)	100 (17/17)
Invasive adenocarcinoma	63.6 (7/11)	90.9 (10/11)

CE-IM, complete eradication of intestinal metaplasia; *CE-D*, complete eradication of dysplasia.
[a]Four patients in active treatment were not included in the CE-IM or CE-D calculations; one patient was lost to follow-up.

from LGD at baseline, while the second had an initial presentation of T1a EAC. Both LGD recurrences occurred in patients with a baseline of HGD. IM recurrences were in patients with a baseline of T1a EAC ($n = 2$) or LGD ($n = 1$). Surveillance (1/3) or touch-up RFA (2/3) was performed in those with recurrent IM. Repeat RFA (1 session) was performed in each patient with recurrence of LGD. Patients with recurrence of HGD underwent SCT (1 session) or salvage EMR (1 session). The mean follow-up for all patients (from the time of the first endoscopic therapy for BE/BE-related neoplasia at our institution) was 4.8 years.

Only two adverse events were reported out of the 171 SCT procedures (1.2%): one self-limited post-SCT upper gastrointestinal bleeding and one esophageal microperforation. Both were managed conservatively with excellent outcomes. In the post-SCT bleeding case, the patient developed a superficial ulcer at the site of treatment. The patient was admitted and evaluated endoscopically the following day, which revealed a non-bleeding clean-based esophageal ulcer; however, the patient did require four units of blood to stabilize hematocrit prior to discharge (LOS: 3 days). This patient received no further endoscopic treatment (deceased 2 months following admission, unrelated to procedure).

In the microperforation case, the event was related to difficult esophageal intubation using the linear echoendoscope, not related to the SCT procedure itself. The patient was admitted for 4 days for close monitoring and, however, experienced no further adverse events and was able to undergo further ablative treatment (two additional SCT's). Information regarding tolerability and post-procedure pain was not collected reliably throughout the study period; however, no significant post-SCT adverse events (beyond the abovementioned) were observed.

DISCUSSION

Endoscopic management of dysplastic BE and EAC has now been established as a highly effective, safe and feasible treatment option. The paradigm in the recent years has shifted from surgery (esophagectomy) to an organ sparing comprehensive endoscopic eradication therapy (ablation, EMR). Multiple studies have shown the efficacy and safety of liquid nitrogen SCT

and outcomes comparable to other BE eradication therapies.[6]

Our study highlights the efficacy, safety and durable long-term outcomes of SCT-based multimodal therapy in the management of dysplastic BE and EAC. Previous studies have reported efficacy and safety of SCT in treating patients with BE-HGD and esophageal cancer.[6, 11] In a large multicenter study of 60 patients with BE-HGD, liquid nitrogen-based cryotherapy has been reported to achieve CE-D and CE-IM in 87 and 57% of cases, respectively.[6] Ninety-seven percent of patients (58/60) had complete eradication of HGD. Mean length of BE segment was 5.3 cm and SCT dosimetry included 2×20 and 4×10 seconds cycles of treatment.

Another recent study of SCT in 32 patients with HGD reported CE-D in 100% of cases and CE-IM in 84% of cases at 2-year follow-up.[7] Recurrence was seen in 18% of cases with CE-D achieved in >80% of those cases after repeat treatment. These CE-D and CE-IM rates are comparable to the published RFA data, wherein CE-D has been reported in 90.5% patients with LGD, 81% CE-D in patients with HGD, and overall CE-IM of 77.4%.[8] Post-RFA recurrence rate has been reported to be as high as 31%.[12]

The largest prospective data on SCT was recently reported in a multicenter, open-label registry of 96 patients with LGD and HGD.[9] Ninety-six subjects with Barrett's dysplasia (67% HGD; 65% long-segment BE; mean length 4.5 cm) underwent 321 SCT treatments. Eighty-three percent of patients (80/96) completed treatment with follow-up endoscopy evaluation (mean duration of follow-up was 21 months). In patients with LGD, the rate of CE-D was 91% (21/23), and the rate of CE-IM was 61% (14/23). In patients with HGD, CE-D was achieved in 81% (46/57) and CE-IM in 65% (37/57). In patients with short-segment BE (SSBE) with any dysplasia, CE-D and CE-IM were seen in 97% (30/31) and 77% (24/31), respectively. There were no esophageal perforations or procedure-related deaths reported in the study group.[9] Also, recently a long-term follow-up data of patients receiving SCT for HGD and intramucosal adenocarcinoma at 3 years and 5 years reported the efficacy and durability of SCT in treatment of IM and dysplasia. Fifty and 40 patients were included in the 3-year and 5-year analyses, respectively. Initial CE-HGD, CD-D, and CE-IM were reported in 98, 90, and 60%, respectively. At 3 years, overall CE-HGD, CE-D, and CE-IM rates were 96% (48/50), 94% (47/50), and 82% (41/50), respectively. At 5 years CE-HGD was seen in 93% (37/40), CE-D in 88% (35/40), and CE-IM in 75% (30/40). In the 5-year cohort, recurrent IM, dysplasia, and HGD/EAC per person-year of follow-up after achieving initial CE-IM were 12.2, 4.0, and 1.4% per person-year, respectively.[10]

In our study, we report that SCT-based multimodal endoscopic management (including EMR and RFA) can achieve very high CE-IM (75%) and CE-D (>98%) rates in a high-risk population over a mean duration of follow-up of approximately 5 years. Our study confirms SCT is a safe and effective modality for eradication of dysplastic BE and/or early esophageal neoplasia. It is important to note that 33.3% (19/57) of our patients who were treated with SCT were initially referred to us as "RFA failures," which is inherently a much more difficult subgroup to achieve CE-IM regardless of modality. Our CE-IM in this population was 64.7% (11/17), with two of these patients in current treatment (new referrals, not eligible for inclusion in calculation of CE-IM), five with persistent IM, and one with progression to invasive EAC requiring esophagostomy. SCT was well-tolerated, and there were no significant post-procedure symptoms reported by the patients. We have previously reported in a multicenter study that SCT is associated with less post-procedural pain when compared with RFA.[13]

Our results for CE-IM and CE-D are also more robust than previously reported outcomes since we used a dual-modality tissue sampling technique for post-ablation monitoring and surveillance in most of our patients (forceps biopsies and WATS-3D brush biopsies were done in 53.8% patients). No previous study has reported outcomes with this degree of rigor in post-ablation surveillance tissue sampling, especially using the WATS-3D device. WATS-3D sampling adds increased durability to our CE-IM and CE-D rates,[14] in our opinion. Coupled with a long period of follow-up, dual-modality tissue sampling for surveillance represents very robust and reliable efficacy data for SCT-based therapy. Our cohort, in addition to having RFA failures, had long-segment disease (mean length 6.2 cm), and >50% of patients had cancer making this an inherently difficult and high-risk group to treat. Despite these factors and our stringent criteria for defining CE-IM, our CE-IM rate of 75% further solidifies the efficacy of the SCT in the treatment of the dysplastic BE and early esophageal neoplasia, especially in this very high-risk population. Complete eradication of early mucosal tumor (T1a) was seen in 76.5% of cases. In patients with submucosal invasion (T1b or greater pathology), complete eradication was seen in 63.6%. The mechanism by which SCT works, causing endothelial damage and vascular thrombi, helps in treatment of early and advanced neoplasia.

Our study does have its limitations. It is a single-center, retrospective study with variable SCT dosimetry over a decade long study period.

Future prospective multicenter studies with the new SCT platforms and standardized technique and dosimetry for all patients could help further solidify our study findings.

CONCLUSION

Liquid nitrogen-based SCT along with multimodal endoscopic eradication therapy of liberal EMR and "touch-up" RFA can achieve very high CE-IM (75%) and CE-D (>98%) rates in patients with dysplastic BE and early esophageal cancer. SCT has been shown to be effective and safe in multiple studies evaluating its role in patients with BE-HGD and early esophageal cancer and also patients who have failed other ablative therapies; however, studies evaluating the role of SCT in this population are limited to small cohorts and short duration of follow-up. Our study demonstrates very high rates of efficacy in this difficult-to-treat and high-risk population with a long duration of follow-up. In addition, post-ablation surveillance using dual-modality forceps and WATS-3D sampling is being reported for the first time, which gives new enhanced meaning to our CE-IM and CE-D rates.

Although direct comparison between SCT and RFA is lacking, our study coupled with existing literature confirms liquid nitrogen-based SCT to have similar efficacy and recurrence rates when compared to published RFA data, for dysplastic BE. In summary, SCT is a safe and effective tool for ablation of dysplastic BE and early esophageal neoplasia with outcomes comparable to other well-established BE ablation modalities.

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