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Salvage cryotherapy in patients undergoing endoscopic eradication therapy for complicated Barrett's esophagus

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ABSTRACT

Background and study aims Some patients with dysplastic Barrett's esophagus (BE) experience suboptimal response to radiofrequency ablation (RFA), endoscopic mucosal resection (EMR), or the combination. Cryotherapy has been used as salvage therapy in these patients, but outcomes data are limited. We aimed to assess clinical outcomes among a large cohort of patients with dysplastic BE whose condition had failed to respond to RFA and/or EMR.

Patients and methods This was a retrospective cohort study of consecutive cases of dysplastic BE or intramucosal carcinoma (IMC) treated with salvage cryotherapy at a tertiary-care academic medical center. The primary goal of cryotherapy treatment was eradication of all neoplasia. The secondary goal was eradication of all intestinal metaplasia. The proportion of patients undergoing salvage cryotherapy who achieved complete eradication of dysplasia (CE-D) and metaplasia (CE-IM), as well as the time to CE-D and CE-IM were calculated.

Results Over a 12-year period, 46 patients received salvage cryotherapy. All patients underwent RFA prior to cryotherapy, either at our center or prior to referral, and 50 % of patients underwent EMR. A majority of patients (54 %) had high-grade dysplasia (HGD) at referral, while 33 % had low-grade dysplasia (LGD), and 13 % had IMC. Overall, 38 patients (83 %) reached CE-D and 21 (46 %) reached CE-IM. Median time to CE-D was 18 months, median number of total interventions (RFA, cryotherapy, and EMR) was five, and median number of cryotherapy sessions was two.

Conclusion Salvage cryotherapy appears safe and effective for treating BE that is refractory to RFA and/or EMR.

Introduction

Barrett's esophagus (BE) is an important risk factor for development of esophageal adenocarcinoma (EAC), incidence of which continues to rise out of proportion to other malignancies [1 – 3]. The condition is characterized by a sequential progression from intestinal metaplasia (IM) to low-grade dysplasia (LGD) to high-grade dysplasia (HGD), and eventually to EAC. Annual risk of EAC is approximately 0.5 % in patients with LGD [4] and 4 % to 8 % in patients with HGD [5, 6]. Because more than 50 % of cases of invasive EAC present with incurable locally advanced or metastatic disease, therapy for BE presents an opportunity to halt neoplastic progression before cancer develops. Consequently, clinical practice guidelines [7 – 11] recommend endoscopic surveillance of patients with known BE and endoscopic eradication therapy (EET) for those who are found to have confirmed HGD or intramucosal carcinoma (IMC). In addition, some data support use of EET for LGD to prevent progression to more advanced lesions [12].

Nodular BE requiring treatment is commonly eradicated with endoscopic mucosal resection (EMR) whereas flat disease is amenable to radiofrequency ablation (RFA). RFA uses thermal energy to destroy tissue to a depth of 1000 microns. Since results of the Ablation of Intestinal Metaplasia (AIM)-dysplasia

trial were published in 2009 [13], RFA has been extensively studied and used for treatment of dysplastic BE. RFA's efficacy and durability have made it the most evidence-based, and often the first-line treatment for dysplastic BE [14, 15]. In contrast, cryotherapy is a more novel treatment option which results in mucosal ablation by delivery of cryogen that causes tissue destruction as a result of extremely cold temperatures. Spray cryotherapy utilizes a spray catheter through which cryogen is applied directly to the esophageal mucosa. Alternatively, balloon cryotherapy uses a self-contained balloon-delivery system which is inflated in the esophagus and cryogen is sprayed into the inside of the balloon in a targeted four-quadrant fashion. Originally applied in the fields of dermatology, urology, and gynecology, cryotherapy has been found to be safe and effective in treatment of BE [16 – 19]. However, data remain limited and rigorous comparative efficacy studies relative to RFA have not been published.

Lacking large placebo-controlled trials and robust comparative data, endoscopists have been reluctant to use cryotherapy as a first-line treatment. However, failure of RFA has often been attributed to the fact that some areas of BE may be too thick. Therefore, cryotherapy, which is thought to produce a deeper treatment effect, has been increasingly used as salvage therapy in patients who have had an incomplete response to RFA or combined EMR and RFA. Hypothesizing that cryotherapy is safe and effective in a salvage capacity, we aimed to assess clinical outcomes among a large cohort of patients who had failed conventional treatments.

Patients and methods

Study design

This was a retrospective cohort study of consecutive cases of dysplastic BE or IMC treated with EET at a single tertiary care academic medical center (Medical University of South Carolina in Charleston, South Carolina, United States) over a 12-year period from 2007 to 2018. Cryotherapy was first used at our center in 2012, but prior endoscopic interventions from as early as 2007 were included. Our local institutional review board approved the study. Patients who declined consent for their medical records to be used for research were excluded.

Patients

Potentially eligible patients were identified using a clinical database and electronic medical record query. Records were manually reviewed to identify patients who met the following inclusion criteria: 1) pathology reviewed at our center showing BE with dysplasia or IMC arising from BE; and 2) underwent EET using cryotherapy as salvage therapy at our center. Two investigators (BJE, PE) independently reviewed procedure reports for each potentially eligible subject to adjudicate whether cryoablation was implemented primarily as salvage therapy due to refractoriness to EMR and/or RFA. A subject was deemed to have undergone salvage cryoablation if one or more of the following criteria were satisfied: (1) the procedure report explicitly stated that cryoablation was for salvage purposes; (2) the procedure report explicitly stated that cryoablation was selected because the BE was refractory to EMR and/or RFA; (3) nodularity or IMC was present, but EMR was not feasible due to nonlifting or inability to adequately capture target tissue; or (4) cryoablation was used after both EMR and RFA were performed, but prior to achieving remission. Cases in which cryoablation was used even though EMR or RFA were suitable and feasible were not considered salvage. For example, patients who underwent cryoablation as the first modality or those who underwent cryoablation of flat BE after EMR of nodularity were not considered eligible. Cases in which cryoablation was used as salvage therapy, including those in which other treatment modalities (RFA, EMR) were subsequently used after the initial cryotherapy session, were included.

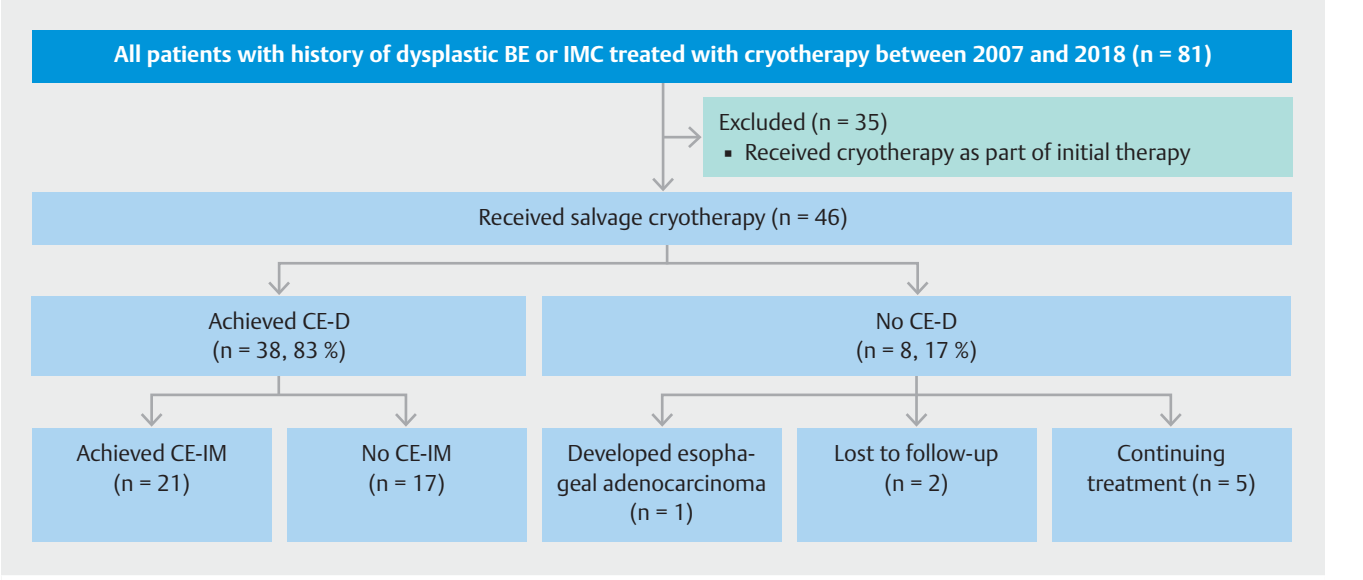
Treatment and follow-up

EET was performed by one of four endoscopists who had at least 5 years of experience with advanced BE treatment. In some cases, advanced endoscopy fellows assisted under the direct supervision of the attending endoscopists. Consistent with standard practice, EMR was typically attempted for nodular lesions, those with known IMC, and those that were deemed by the endoscopist to have a morphologically concerning appearance. RFA was generally reserved for flat BE with HGD using the treatment protocol described by Shaheen et al [13]. Cryotherapy was performed using both the spray and balloon liquid nitrogen delivery systems. Liquid nitrogen spray cryotherapy (truFreeze Spray Cryotherapy, Lexington, Massachusetts, United States) was the mainstay of cryotherapy treatment at our center until early 2017. Patients who received treatment with cryotherapy after this date received either spray cryotherapy or balloon cryotherapy (C2 CryoBalloon, Pentax Medical, Redwood City, California, United States). If patients were responding to spray cryotherapy, the delivery modality was not altered. Ablation sessions generally occurred every 1 to 3 months. In some cases, argon plasma coagulation (APC) was used in limited capacity as an adjunct therapy at the discretion of the endoscopist. The primary goal of cryotherapy treatment was eradication of all neoplasia. The secondary goal was eradication of all intestinal metaplasia.

Follow-up endoscopy typically occurred 2 to 3 months after the last treatment session. Once remission was achieved, targeted biopsies were obtained from any visible lesions concerning for recurrence. In addition, random four-quadrant biopsies were obtained every 1 to 2 cm from the gastroesophageal junction and the prior treatment area (neosquamous-lined esophagus) according to the Seattle protocol [20]. Patients received twice-daily proton pump inhibitors as maintenance therapy. Biopsy and EMR specimens were evaluated by two expert gastrointestinal pathologists for presence of BE, dysplasia, and cancer according to standard definitions. Pathologists were not blinded to endoscopic treatments.

Outcomes

We aimed to determine the proportion of patients undergoing salvage cryotherapy who achieved CE-D and CE-IM, defined according to accepted pathologic standards. Recurrence was de-



▶ **Fig. 1** Patient flow diagram.

fined as intestinal metaplasia or dysplasia identified on post-remission surveillance biopsies prompting reinitiation of EET. Adverse events (AEs) related to EET were defined according to published data [21].

Data collection and analysis

Data collected included age, gender, race and ethnicity, body mass index (BMI), tobacco use history, alcohol use history, personal and family cancer history, gastrointestinal surgical history, prior gastroesophageal reflux disease (GERD), presence and characteristics of hiatal hernia, BE segment length, Prague classification, presence of nodules, intervention type (RFA, cryotherapy, EMR), location and extent of treatment, and pathology results. The index endoscopy, defined as the first treatment session at our institution, was used to calculate time to CE-D and CE-IM. Results for the primary analysis are presented using descriptive statistics. In an exploratory analysis, stepwise logistic regression was used to identify factors associated with CE-D in patients undergoing salvage cryotherapy.

Results

Over a 12-year period, 352 patients underwent EET at our center. Eighty-one of them underwent cryotherapy as part of their treatment regimen. Of that group, 46 patients received salvage cryotherapy (▶ **Fig. 1**). The majority of these patients (40/46) received spray cryotherapy as salvage therapy, while six received balloon cryotherapy. Six patients in the cohort had previously failed to respond to RFA at another institution. The majority of patients were white (98 %), male (91 %), and the median age at the time of index endoscopy at our center was 66 years (▶ **Table 1**). Most had a significant smoking history (52 % had at least a 20-pack-year history) and the median BMI was 27. A majority (87 %) had a history of symptomatic GERD. Six patients had undergone previous fundoplication. Most (98 %) had a hiatal hernia, with median size of 3 cm. A majority of patients (54 %) had HGD at referral, while 33 % had LGD, and 13 % had IMC. All patients had long-segment BE (≥ 3 cm) with 59 % of patients having nodularity noted. All patients underwent RFA treatment prior to cryotherapy, either at our center or prior to referral, and 50 % of patients underwent previous EMR at our institution. Pathology immediately prior to treatment with cryotherapy is reported in ▶ **Fig. 2**.

Of the 46 patients who underwent salvage cryotherapy, 38 (83 %) reached CE-D and 21 (46 %) reached CE-IM (▶ **Fig. 3**). In 15 of the 17 patient who reached CE-D, but not CE-IM, additional treatment was intentionally discontinued because competing illness rendered the risk-benefit ratio of ongoing treatment unfavorable. The remaining two patients are undergoing ongoing treatment with a goal of CE-IM. Of the eight patients who had not achieved CE-D or CE-IM, five are still undergoing treatment, two were lost to follow-up, and one developed endoscopically untreatable esophageal cancer.

Among the 38 patients who achieved CE-D, median time to CE-D was 18 months, median number of total interventions (RFA, cryotherapy, and EMR) at our center was five and median number of cryoablation sessions was two (▶ **Table 2**). Among the 21 patients who achieved CE-IM, median time to CE-IM was 22 months, median number of total interventions at our center was six, and median number of cryoablation sessions was two. In four cases, patients reached CE-D with RFA and/or EMR, and cryotherapy was first used in an attempt to reach CE-IM. In each of these cases, CE-IM was obtained with a median number of two cryotherapy sessions. All patients with IMC in our study sample had T1a lesions. Of the six patients, five had lesions that were resected endoscopically, in accordance with clinical practice guidelines. Cryotherapy in these patients was used to eradicate residual BE after EMR. A single patient with IMC (T1a lesion) had disease not amenable to EMR and under-

▶ **Table 1** Cohort characteristics.

	Treatment cohort (n = 46)	Achieved CE-D (n = 38)	No CE-D (n = 8)
Age, median	66	66	63
Male %, (n/N)	91 (42/46)	89 (34/38)	100 (8/8)
Tobacco history %, (n/N)			
▪ None	37 (17/46)	42 (16/38)	13 (1/8)
▪ 1 – 20 PY	11 (5/46)	8 (3/38)	25 (2/8)
▪ > 20 PY	52 (24/46)	50 (19/38)	63 (5/8)
Alcohol %, (n/N)			
▪ None	57 (26/46)	58 (22/38)	50 (4/8)
▪ Past	11 (5/46)	5 (2/38)	38 (3/8)
▪ At time of treatment	33 (15/46)	37 (14/38)	13 (1/8)
BMI, median	27	27	26
History of symptomatic GERD, %, (n/N)	87 (40/46)	95 (36/38)	50 (4/8)
Hiatal hernia > 3 cm %, (n/N)	26 (12/46)	29 (11/38)	13 (1/8)
Nodularity %, (n/N)			
▪ None	41 (19/46)	39 (15/38)	50 (4/8)
▪ Focal	35 (16/46)	37 (14/38)	25 (2/8)
▪ Multifocal	20 (9/46)	21 (8/38)	13 (1/8)
▪ Diffuse	4 (2/46)	3 (1/38)	13 (1/8)
Initial pathology %, (n/N)			
▪ LGD	33 (15/46)	34 (13/38)	25 (2/8)
▪ HGD	54 (25/46)	50 (19/38)	75 (6/8)
▪ IMC	13 (6/46)	16 (6/38)	0 (0/8)
Prior RFA %, (n/N)	100 (46/46)	100 (38/38)	100 (8/8)
Prior EMR %, (n/N)	50 (23/46)	47 (18/38)	63 (5/8)

CE-D, complete eradication of dysplasia; PY, pack years; BMI, body mass index; LGD, low-grade dysplasia; HGD, high-grade dysplasia; IMC, intramucosal carcinoma; RFA, radiofrequency ablation; EMR, endoscopic mucosal resection

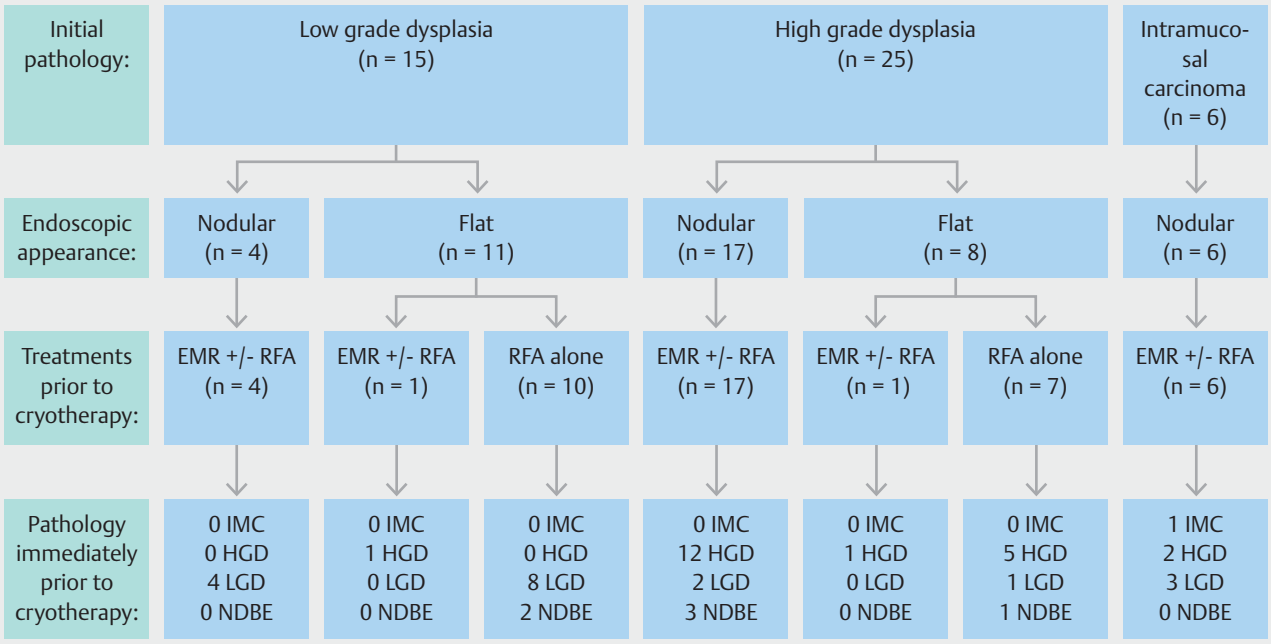
went cryotherapy as salvage therapy and eventually reached CE-IM.

Two patients who achieved remission had recurrence during follow-up. In one patient who reached CE-D at our center after two RFA sessions, recurrence with LGD was seen after 48 months. The patient was treated with six additional RFA treatments, again reached CE-D, then received one cryotherapy to reach CE-IM. Another patient was found to have a recurrence of HGD 25 months after CE-IM, which was successfully eradicated by EMR. That patient has since undergone one additional surveillance exam with no evidence of recurrence.

Three patients developed treatment-related strictures requiring dilation. One patient developed a stricture 1 month after the third cryotherapy treatment and required seven dilations, although cryotherapy was able to be resumed and CE-IM was obtained in 19 months following six cryotherapy sessions. Another developed a stricture 1 month after initial cryotherapy treatment and required four dilations. Again, cryotherapy was able to be resumed and CE-IM was obtained in 29 months following two cryotherapy sessions. A third patient developed a stricture following a second session of cryotherapy which had CE-D. One dilation was performed and further treatment was not pursued.

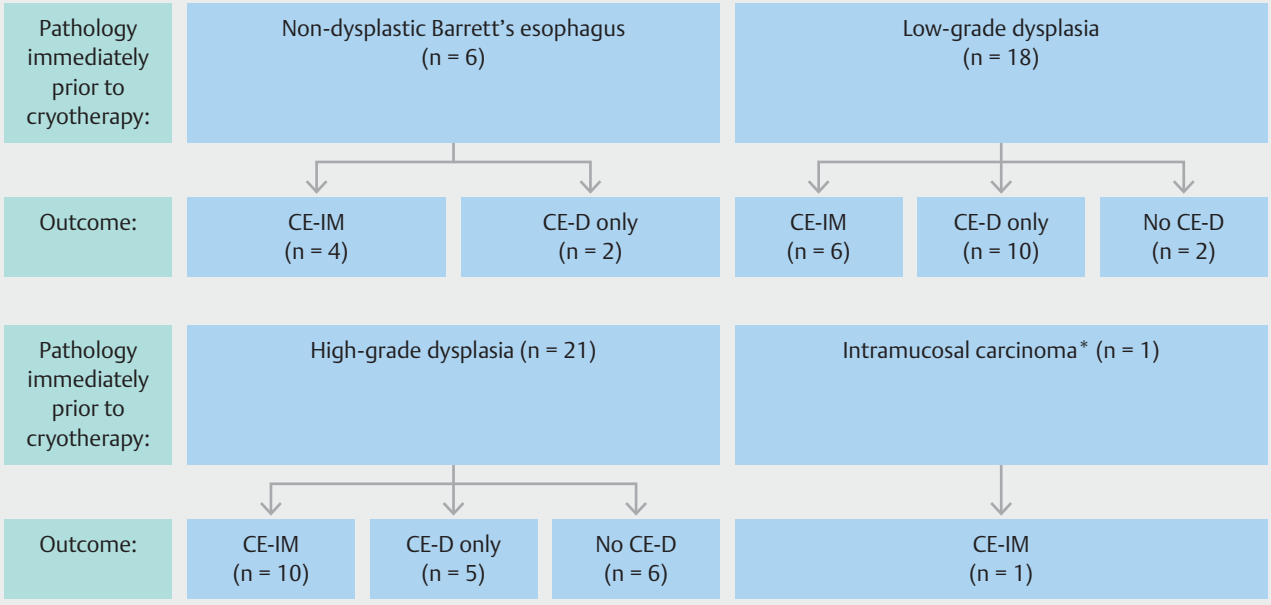
Discussion

We present a 12-year retrospective cohort study of consecutive cases of refractory dysplastic BE or IMC treated with salvage cryotherapy at a single tertiary care academic medical center. Our study demonstrated CE-D and CE-IM rates of 82.6 % and 45.6 %, respectively, in this cohort of patients who failed conventional treatment. Among patients who achieved CE-D, me-



EMR – endoscopic mucosal resection; RFA – radiofrequency ablation; IMC – intramucosal carcinoma; HGD – high grade dysplasia; LGD – low grade dysplasia; NDBE – non-dysplastic Barrett's esophagus

▶ **Fig. 2** Initial pathology, nodularity, and pre-cryotherapy treatments.



CE-IM – Complete eradication of intestinal metaplasia; CE-D – Complete eradication of dysplasia
*The single patient with pre-cryotherapy pathology of IMC was not amenable to EMR

▶ **Fig. 3** Pre-cryotherapy pathology and outcomes.

▶ **Table 2** Results.

	Achieved CE-D (n = 38)	Achieved CE-IM (n = 21)	No CE-IM (n = 17)
Time to CE-D, median months (range)	18 (4 – 59)	15 (5 – 59)	26 (4 – 59)
Median number of RFA treatments at our center to achieve CE-D (range)	2 (0 – 5)	2 (0 – 5)	2 (0 – 5)
Median number of EMR treatments at our center to achieve CE-D (range)	0 (0 – 4)	0 (0 – 3)	1 (0 – 4)
Median number of cryotherapy treatments at our center to achieve CE-D (range)	2 (0 – 10)	2 (0 – 8)	2 (1 – 10)
Median number of total interventions at our center to achieve CE-D (range)	5 (1 – 14)	4 (1 – 10)	5 (2 – 14)
Time to CE-IM, median months (range)	n/a	22 (7 – 65)	n/a
Median number of RFA treatments at our center to achieve CE-IM (range)	n/a	2 (0 – 8)	n/a
Median number of EMR treatments at our center to achieve CE-IM (range)	n/a	0 (0 – 3)	n/a
Median number of cryotherapy treatments at our center to achieve CE-IM (range)	n/a	2 (1 – 8)	n/a
Median number of total interventions at our center to achieve CE-IM (range)	n/a	6 (1 – 12)	n/a

CE-D, complete eradication of dysplasia; RFA, radiofrequency ablation; EMR, endoscopic mucosal resection; CE-IM, complete eradication of intestinal metaplasia.

dian time to CE-D was 18 months and median number of cryoablation sessions was two. In addition, there was a very low progression to invasive EAC (one case; 2.1 %) in this high-risk cohort, despite six patients having IMC at referral. The stricture rate was 6.5 %; there were no other serious complications.

Since the development and initial clinical use of esophageal cryotherapy in 1999 [22], studies in treatment-naive patients have demonstrated encouraging efficacy, safety, and durability [18, 23 – 25]. In addition, because it can be applied to non-lifting and nodular tissue, cryotherapy has become increasingly popular as a salvage modality when patients are not candidates for, or have experienced suboptimal response to EMR, RFA, or the combination. Given its molecular effects, cryoablation allows for deeper tissue ablation, which makes it an attractive treatment option for RFA-refractory BE, which may be the result of increased mucosal thickness [26]. However, absence of level I data has limited its widespread use. A recent review and meta-analysis of 11 studies comprising 148 BE patients treated with cryotherapy for persistent IM or dysplasia after RFA [19] demonstrated CE-D and CE-IM in 76.0 % and 45.9 % of patients, respectively. Our study, which to our knowledge is the largest single-center report on this topic, demonstrated similar CE-D and CE-IM rates, affirming the efficacy of cryoablation in the salvage capacity. Despite the high-risk nature of our cohort—54 % with HGD and 13 % with IMC—there was a very low progression to invasive EAC (2.1 %). This is similar to the 2.9 % progression reported by Canto et al [16].

The median number of cryotherapy sessions required per patient to achieve CE-D was two, which is fewer than has been reported previously. Canto et al [16] reported a median of four CO_2 cryotherapy sessions to achieve a complete response for HGD. Previously studies have cited comparable data for liquid nitrogen cryotherapy (mean 3.9) [18], APC (mean 4) [27], and for RFA (mean 3.5) [13]. The most likely explanation is that we allowed for continued treatment with RFA, EMR, and APC concurrently with cryotherapy treatment at the discretion of the endoscopist. In patients who reached CE-D, the median number of total interventions (RFA, cryotherapy, and EMR) at our center was five, which is comparable to published data. Based on our data, although cryotherapy played an important role in salvage therapy, outcomes may not have been solely due to this intervention. The additive impact of continued RFA, EMR, and APC may have contributed to the CE-D and CE-IM rates observed in this study.

On this basis, the precise role of cryotherapy in the dysplastic BE treatment algorithm remains debatable. Some experts favor a more limited role for cryotherapy, arguing that the population of patients whose disease is truly RFA-refractory should be much smaller than commonly reported due to the lack of stringent adherence to a strict RFA treatment algorithm [26]. According to this philosophy, only those whose disease meets the strict definition of RFA-refractory should be considered for cryotherapy. In contrast, although impossible to fully infer intent in a retrospective cohort, the approach to cryotherapy in our study was more liberal. Future studies will clarify the precise place for cryotherapy in the treatment algorithm and whether strict adherence to the definition of RFA refractoriness is clinically important.

Our study adds to the excellent safety profile reported for cryotherapy. Aside from stricture formation, no other AEs were noted, which is comparable to the low (2.9 %) overall serious AE rate reported in CO_2 cryotherapy by Canto et al [16] and published AE data for RFA (3.4 %) [28]. Treatment was complicated by stricture formation requiring dilation in three patients (6.5 %), which is comparable to RFA (6.0 % to 7.6 %) [13, 28]. Of these three patients in our study, two were able to resume treatment and reach CE-IM. Furthermore, our study is an appraisal of real-world treatment of unselected patients by four endoscopists, adding to generalizability compared to prior studies that involved only one or two expert endoscopists.

The results of this study should be considered in the context of several important limitations. First, retrospective collection

of data could not ensure definitive and systematic determination of whether cryotherapy was used in a salvage capacity. This eligibility criterion was adjudicated post hoc by manual review of procedure reports using aforementioned criteria that are based on clinical assumptions aiming to determine endoscopist intent. While we believe these assumptions are reasonable, cases may have been misclassified if the intent was misinterpreted, potentially biasing study results. Second, the small sample size, retrospective nature, non-randomized design, and lack of a comparison arm limit any definitive conclusions. In addition, pathologic interpretation of BE samples was not performed in a blinded manner. Lastly, because treatments were not limited to cryotherapy and included alternative endoscopic therapies, the study allowed for a more real-world experience, but that makes the multimodal treatment data more difficult to interpret.

Conclusion

In summary, this study showed that cryotherapy appears effective for salvage treatment of patients with refractory dysplastic BE and IMC, successfully achieving CE-D and CE-IM in of 82.6 % and 45.6 % of patients, respectively. Higher-quality studies, ideally including randomized trials, are needed to confirm these findings and establish the exact role of cryotherapy in the treatment armamentarium for BE.

Competing interests

Dr. Elias has ongoing study support from C2/Pentax. Dr. Hoffman consults with Cook Medical and Boston Scientific and has served on advisory boards for TruFreeze and C2 therapeutics, receiving research support from each.

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