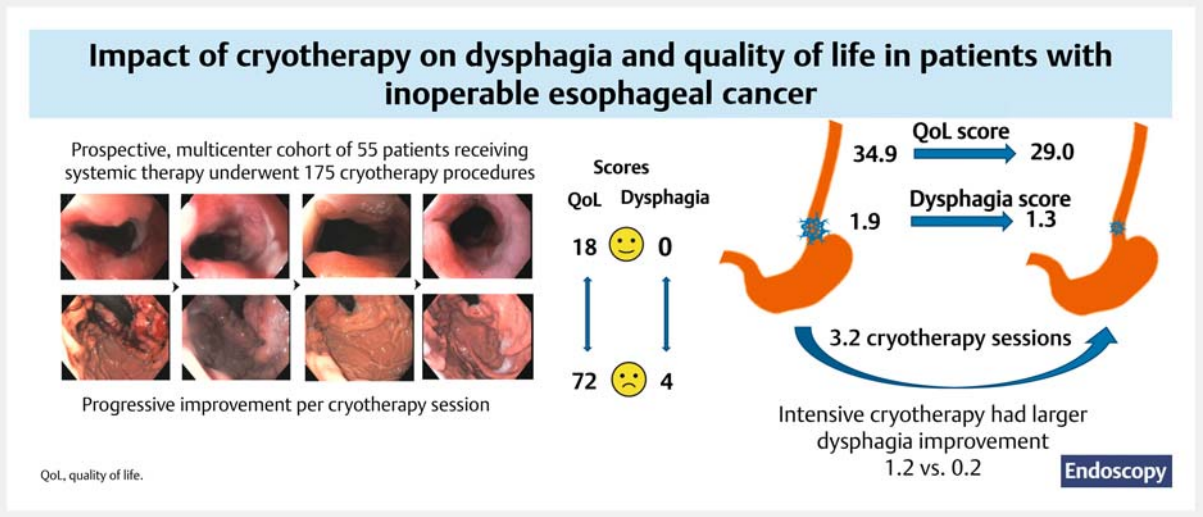
Accepted Manuscript online: 2023-06-02 Article published online: 2023-07-25

A prospective multicenter study to evaluate the impact of cryotherapy on dysphagia and quality of life in patients with inoperable esophageal cancer

OPEN ACCESS

GRAPHICAL ABSTRACT



Authors

Toufic Kachaamy[1], Neil Sharma[2], Tilak Shah[3,4], Sonmoon Mohapatra[5], Kimberly Pollard[6], Christina Zelt[2], Elaine Jewett[1], Rigoberto Garcia[1], Rachel Munsey[4], Saurabh Gupta[2], Mariajose Rojas-DeLeon[2], Digant Gupta[6], Vivek Kaul[7], Rahul Pannala[5], Pankaj Vashi[6]

Institutions

1 Department of Gastroenterology, City of Hope Phoenix, Goodyear, Arizona, United States
2 Division of Interventional Oncology and Surgical Endoscopy, Parkview Cancer Institute, Fort Wayne, Indiana, United States
3 Ellen Leifer Shulman and Steven Shulman Digestive Disease Center, Cleveland Clinic, Weston, Florida, United States
4 Division of Gastroenterology and Hepatology, Mayo Clinic, Phoenix, Arizona, United States
5 Department of Gastroenterology and Nutrition, City of Hope Chicago, Zion, Illinois, United States
6 Division of Gastroenterology and Hepatology, Central Virginia VA Healthcare System, Richmond, Virginia, United States
7 Division of Gastroenterology and Hepatology, University of Rochester Medical Center, Rochester, New York, United States

submitted 18.12.2022
accepted after revision 25.5.2023
accepted manuscript online 2.6.2023
published online 25.7.2023

Bibliography
Endoscopy 2023; 55: 889–897
DOI 10.1055/a-2105-2177
ISSN 0013-726X

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Corresponding author
Toufic Kachaamy, MD, Department of Gastroenterology, City of Hope Phoenix, 14200 West Celebrate Life Way, Goodyear, AZ 85338, United States
tkachaamy@coh.org

Scan this QR-Code for the author commentary.

ABSTRACT

Background Dysphagia palliation in inoperable esophageal cancer continues to be a challenge. Self-expandable metal stents have been the mainstay of endoscopic palliation but have a significant risk of adverse events (AEs). Liquid nitrogen spray cryotherapy is an established modality that can be used with systemic therapy. This study reports the outcomes of cryotherapy, including dysphagia and quality of life (QoL), in patients receiving systemic therapy.

Methods This was a prospective multicenter cohort study of adults with inoperable esophageal cancer who underwent cryotherapy. QoL and dysphagia scores before and after cryotherapy were compared.

Results 55 patients received 175 cryotherapy procedures. After a mean of 3.2 cryotherapy sessions, mean QoL improved from 34.9 at baseline to 29.0 at last follow-up ($P<0.001$) and mean dysphagia improved from 1.9 to 1.3 ($P=0.004$). Patients receiving more intensive cryotherapy (≥ 2 treatments within 3 weeks) showed a significantly greater improvement in dysphagia compared with those not receiving intensive therapy (1.2 vs. 0.2 points; $P=0.003$). Overall, 13 patients (23.6 %) received another intervention (1 botulinum toxin injection, 2 stent, 3 radiation, 7 dilation) for dysphagia palliation. Within the 30-day post-procedure period, there were three non-cryotherapy-related grade ≥ 3 AEs (all deaths). The median overall survival was 16.4 months.

Conclusion In patients with inoperable esophageal cancer receiving concurrent systemic therapy, adding liquid nitrogen spray cryotherapy was safe and associated with improvement in dysphagia and QoL without causing reflux. More intensive treatment showed a greater improvement in dysphagia and should be considered as the preferred approach.

Introduction

Esophageal cancer is the eighth most common cancer worldwide and the sixth leading cause of cancer death [1]. In the USA, the annual new cases and deaths are approximately 20 000 and 16 000, respectively [2]. It continues to have one of the worst 5-year survival rates at 20 % [2]. Approximately only 20 % of patients present with localized disease; the remaining patients have involvement of regional lymph nodes (i. e. locoregional disease [34 %]) or distant metastases (33 %), or are not categorized [3]. Surgical resection is not recommended for metastatic disease. In medically fit patients with locoregional disease, the recommended treatment is neoadjuvant chemoradiation followed by surgical resection. Unfortunately, despite advances in therapy such as pre-operative treatment with 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT regimen) for locoregional disease [4], up to 17 % of potential surgical candidates do not undergo esophagectomy because of comorbidities or disease progression [5].

In patients with esophageal cancer who do not undergo esophagectomy, dysphagia is the most common symptom and significantly decreases quality of life (QoL) and may also contribute to malnourishment and weight loss. As a result, the National Comprehensive Cancer Network (NCCN) recommends an intervention to mitigate dysphagia in patients with severe dysphagia [6], whereas for mild-to-moderate dysphagia the guidelines provide the option for an intervention after weighing up risks and benefits. Systemic therapy (e. g. chemotherapy, immunotherapy) can palliate dysphagia. However, durable dysphagia resolution is observed in only a minority of patients, and systemic therapy is often poorly tolerated. A minority of patients become dysphagia free and typically remain asymptomatic for a few months. The ones who demonstrate improvement continue to have some dysphagia and often experience worsening symptoms within a few weeks [7]. In patients with severe dysphagia, esophageal stents are often utilized. Esophageal stents provide rapid and effective dysphagia relief in the short term but are frequently associated with adverse events (AEs), which include chest pain (sometimes requiring stent removal), reflux symptoms preventing patients from lying flat when stents are placed at the gastroesophageal junction, migration, tumor/tissue overgrowth, bleeding, perforation, and fistula formation, especially in patients with survival beyond 6 months [8, 9]. Overall, studies assessing the impact of stents on QoL have yielded mixed results, with some studies actually documenting worsened QoL with stents [10].

The currently available data suggest that cryoablation or endoscopic spray cryotherapy is safe after chemoradiation [11, 12]. Initial pilot studies also suggest that cryotherapy is safe to combine with chemoradiation [13]. Dysphagia palliation can be expected to improve by around 0.7 points on a 5-point Likert scale per cryotherapy session [12]. While data on dysphagia are available from retrospective studies, data on QoL are only available in abstract form, showing that cryotherapy helped maintain or improve swallowing with an improvement in global QoL and social functioning [14]. Retrospective data also suggest that cryotherapy delays the need for stenting in esophageal cancer patients for about a year, with 23 % eventually requiring stenting [15]. Overall, based on previously published data, cryotherapy seems to be safe and effective, with major AEs being rare and the total AE rate being less than 5 %, making it one of the safest modalities listed in the NCCN guidelines [6]. However, high-quality prospective data on cryotherapy are lacking. We therefore conducted a prospective multi-

center study to assess QoL with liquid nitrogen spray cryotherapy in patients with inoperable esophageal cancer who were also receiving systemic therapy for palliation of dysphagia.

Methods

Study design and patient population

This was a prospective multicenter study including 55 patients with inoperable esophageal cancer who underwent palliative cryotherapy from September 2017 to January 2022 at five hospitals in the USA. The inclusion criteria were: 1) age ≥ 18 years with a tissue diagnosis of esophageal or gastroesophageal junction (GEJ) cancer; 2) unsuitable for surgical resection but expected to receive systemic anticancer therapy; 3) any degree of dysphagia; 4) mild-to-moderate luminal narrowing with the ability to pass the cryotherapy decompression tube and either a standard or ultraslim gastroscope side by side. The exclusion criteria were: 1) Eastern Cooperative Oncology Group performance status > 2; (2) radiation treatment in the previous 8 weeks (to allow sufficient time for radiation effects to stabilize); 3) known brain metastases causing cranial nerve deficits, which can cause dysphagia and interfere with the ability to assess the impact of local esophageal mass on dysphagia; 4) inability to undergo an esophagogastroduodenoscopy; 5) pregnant or nursing females; 6) surgery or anatomy where the capacity of the stomach is reduced making cryotherapy contraindicated; 7) tracheoesophageal fistula; and 8) expected survival < 3 months.

The study was conducted according to the guidelines laid down in the Declaration of Helsinki and was approved by the Western Institutional Review Board. Informed consent was obtained from each patient prior to enrollment into the study.

Cryotherapy protocol

An upper gastrointestinal (GI) endoscopy was performed using moderate sedation, monitored anesthesia care with propofol, or general anesthesia. A dual-lumen decompression tube was advanced over a guidewire into the stomach and positioned with the markings at the GEJ. The guidewire was then removed, and the decompression tube was attached to suction, which allowed for active and passive venting of the nitrogen gas released during the cryotherapy procedure. The endoscope was then advanced alongside the decompression tube and cryotherapy was performed for ablation of the tumor. Each cryotherapy treatment consisted of a certain number of cryotherapy cycles delivered to several tumor sites for a pre-determined duration of freezing time. Each tumor site was frozen for 20–30 seconds for 2–3 cycles/site, with at least 45 seconds between freezes to allow complete tissue thawing. Cryotherapy targeted the entire esophageal portion of the tumor and the tumor at the GEJ. The cryotherapy procedure was typically repeated every 2–12 weeks. As this was a pragmatic study without dictating clinical care, the number and frequency of cryotherapy procedures was based on local practices and clinical judgment of the treating physician.

Study tools and data collection

The primary outcome measure was change in QoL and dysphagia scores between pre- and post-cryotherapy. QoL was assessed using a modified European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Esophageal Cancer Module (EORTC QLQ-OES18), which has a score range of 18–72, with higher scores indicating worse QoL. This questionnaire was chosen as it is one of the most extensively tested questionnaires recommended for use in assessing QoL in patients with esophageal cancer [16]. Dysphagia scores were measured using a 5-point Likert scale: 0 = no dysphagia, 1 = dysphagia to solids, 2 = dysphagia to semi-solids, 3 = dysphagia to liquids, 4 = dysphagia to own saliva [17, 18]. Patients were assessed at baseline, before every cryotherapy procedure, and 1–2 weeks after every cryotherapy procedure.

The secondary outcome measure was AEs. AEs were recorded with respect to the time of occurrence, duration, and severity according to the common terminology criteria for adverse events (CTCAE) version 4.03 [19]. An AE was defined as any unfavorable and unintended outcome associated with the use of a medical treatment/procedure that may or may not be considered related to it. The severity of AEs was measured using a grade of 1–5 (1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, 5 = death). Patients were also asked if they could lie flat without having reflux symptoms.

Statistical analysis

Continuous variables were expressed as mean (SD) or median, where applicable, whereas nominal data were expressed as number and percentage. Wilcoxon signed-rank test was used to evaluate the change in QoL and dysphagia scores between pre- and post-cryotherapy. For univariable analysis [20], the change in dysphagia and QoL scores was compared across different categories of predictors using Mann–Whitney and Kruskal–Wallis tests. The following factors were evaluated: age at first cryotherapy, sex, tumor stage at cryotherapy, tumor location, prior local treatment for dysphagia, use of concurrent chemotherapy (administration of cryotherapy and chemotherapy within 48 hours of each other), use of intensive cryotherapy (≥ 2 cryotherapy treatments within 3 weeks), and freeze time in seconds per cycle. The effect of individual predictors on change in dysphagia and QoL scores was expressed as "dysphagia or QoL score difference" with 95 %CIs. Overall survival was calculated as the time between the date of diagnosis and the date of death or last follow-up. Median overall survival was calculated using the Kaplan–Meier method.

The estimated sample size for this study was 56 [21]. For sample size calculation, we considered an intervention that could decrease (improve) the EORTC QLQ-OES18 score by 5 points, which is considered clinically significant [1, 6]. A sample size of 56 achieves 80 % power to detect a mean of paired differences in QoL of 5 points with a known SD of differences of 15 points and with a significance level (alpha) of 0.05 using a one-sided paired z-test. All data were analyzed using IBM SPSS version 28.0 (IBM, Armonk, New York, USA). All analyses were

two tailed, and a difference was considered statistically significant if the *P* value was ≤ 0.05.

Results

Patient characteristics

The final study population consisted of 55 consecutive patients (47 men and 8 women) from five hospitals with significant experience in esophageal cancer management and cryotherapy. ▶ **Table 1** describes the patient characteristics. Folinic acid, fluorouracil, and oxaliplatin (FOLFOX) was the most common chemotherapy regimen administered (24/55; 43.6% of patients).

Cryotherapy characteristics

Among 55 patients, a total of 175 cryotherapy treatments were performed (mean of 3.2 treatments per patient). ▶ **Table 1** presents the characteristics of these 175 treatments. ▶ **Fig. 1** shows representative images of a tumor before and after two cryotherapy treatments in a patient who had a near-complete endoscopic response.

Change in QoL and dysphagia scores

Patient-level data

For the primary outcome, the mean QoL score improved significantly from 34.9 at baseline to 29.0 at the last follow-up ($P < 0.001$) (▶ **Table 2**). Using the minimal clinically important difference of 5 points, the improvement of 5.9 points was both clinically and statistically significant. The mean dysphagia score also improved significantly from 1.9 (moderate) at baseline to 1.3 (mild) at the last follow-up (an improvement of 0.6 points; $P = 0.004$) (▶ **Table 2**).

▶ **Table 3** shows univariable analysis for change in QoL scores across the different categories of predictor variables for a total of 55 patients. Only two factors were found to be significantly (both clinically and statistically) associated with an improvement in QoL: tumor stage and tumor location. On univariable analysis for the outcome of dysphagia (▶ **Table 3**), women showed a significantly greater improvement in dysphagia compared with males. Patients receiving intensive cryotherapy showed a significantly greater improvement in dysphagia compared with those not receiving intensive cryotherapy. There was a trend toward greater improvement in dysphagia in patients receiving concurrent chemotherapy compared with those who did not receive chemotherapy, although this finding was not statistically significant ($P = 0.21$).

Cryotherapy treatment-level data

▶ **Table 2** also shows the change in dysphagia and QoL scores at the level of the cryotherapy treatment. For a total of 175 cryotherapy treatments, the mean QoL score improved statistically significantly from 30.2 pre-cryotherapy to 26.9 post-cryotherapy, although the difference of 3.3 was not clinically significant using our cutoff of 5 points. Similarly, the mean dysphagia score improved significantly from 1.4 pre-cryotherapy to 1.0 post-cryotherapy (an improvement of 0.4 points; $P = 0.001$).

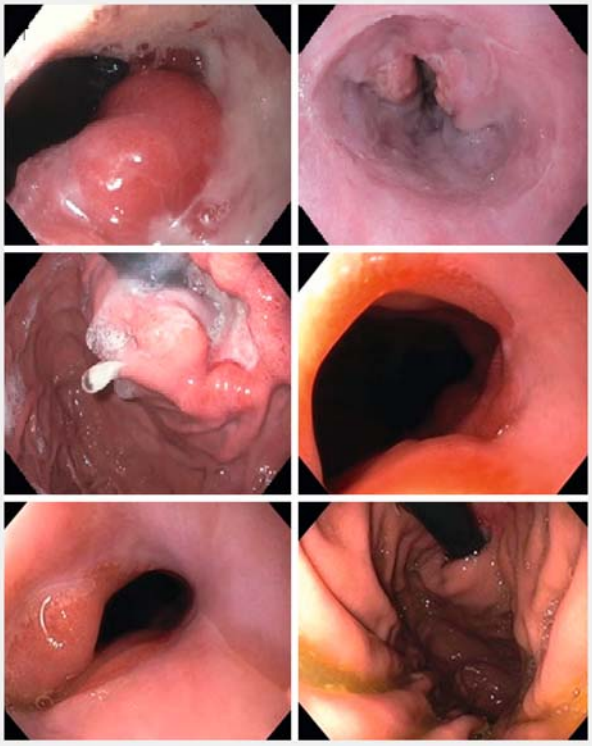
▶ **Table 1** Baseline characteristics.

Patient characteristics (n = 55)	
Sex, n (%)	
▪ Male	47 (85.5)
▪ Female	8 (14.5)
Tumor stage	2
▪ Stage 2	3 (5.5)
▪ Stage 3	10 (18.2)
▪ Stage 4	42 (76.4)
Tumor histology, n (%)	
▪ Adenocarcinoma	51 (92.7)
▪ Squamous cell carcinoma	2 (3.6)
▪ Neuroendocrine	2 (3.6)
Tumor location, n (%)	
▪ Esophagus	36 (65.5)
▪ GEJ	19 (34.5)
Prior local treatment for dysphagia, n (%)	
▪ No	41 (74.5)
▪ Yes	14 (25.5)
Chemotherapy during cryotherapy, n (%)	
▪ No	11 (20.0)
▪ Yes	44 (80.0)
Cryotherapy treatments received, n (%)	
▪ 1	13 (23.6)
▪ 2	10 (18.2)
▪ 3	9 (16.4)
▪ 4	9 (16.4)
▪ ≥ 5	14 (25.5)
Freeze time per cycle, n (%)	
▪ 20 seconds	32 (58.2)
▪ 30 seconds	23 (41.8)
Intensive cryotherapy[1], n (%)	
▪ No	34 (61.8)
▪ Yes	21 (38.2)
Age at first cryotherapy, years	
▪ Mean (SD)	61.2 (10.6)
▪ Median (range)	61.3 (37–86)
Cryotherapy characteristics (n = 175)	
Tumor sites treated, median (range)	2 (1–10)
Cycles per tumor site, median (range)	3 (1–4)
Freeze time, median (range), seconds/cycle	20 (20–30)

▶ **Table 1** (Continuation)

Patient characteristics (n = 55)	
Total freeze time, median (range), seconds/ tumor site[2]	60 (20–120)
Tumor sites treated, n (%)	
▪ 1	73 (41.7)
▪ 2	58 (33.1)
▪ 3	29 (16.6)
▪ 4	5 (2.9)
▪ ≥5	10 (5.7)
Cycles per tumor site, n (%)	
▪ 1	3 (1.7)
▪ 2	19 (10.9)
▪ 3	151 (86.3)
▪ 4	2 (1.1)
Total freeze time per tumor site[2], n (%)	
▪ <60 seconds	101 (57.7)
▪ ≥60 seconds	74 (42.3)

GEJ, gastroesophageal junction.
[1] At least two cryotherapy treatments within 3 weeks.
[2] The total freeze time per tumor site was calculated by multiplying the number of cycles per tumor site with the freeze time in seconds per cycle.



▶ **Fig. 1** Endoscopic images from a patient with esophageal cancer and near-complete endoscopic response to cryotherapy. Top panel Before cryotherapy. Bottom panel After two sessions of cryotherapy.

▶ **Table 3** shows univariable analysis for change in QoL and dysphagia scores across the different categories of predictor variables for a total of 175 cryotherapy treatments. Only tumor stage was significantly (statistically but not clinically) associated with an improvement in QoL. None of the evaluated factors were associated with an improvement in dysphagia.

Other modalities of dysphagia palliation

Of the 55 patients, 13 (23.6%) required other modalities for dysphagia palliation because their dysphagia did not improve significantly with cryotherapy. Of those 13, 7 underwent dilation, 3 received radiation, 2 received esophageal stents, and 1 underwent botulinum toxin injection. A total of 12 patients (21.8%) underwent feeding tube placement during the follow-up period.

Adverse events

AEs reported within 30 days of a cryotherapy procedure are summarized in ▶ **Table 4**. There were no CTCAE grade ≥3 intraprocedural AEs. There were two cryotherapy-related immediate post-procedural grade 3 events of abdominal pain/distension requiring inpatient observation. All other grade ≥3 AEs were non-procedure-related and occurred after a median of 12 days after cryotherapy. Of the 55 patients, 47 (85.5%) reported being able to lie flat without having reflux symptoms.

Overall survival

The median follow-up duration for 55 patients was 15.3 months (range 1.2–65.8 months). During the follow-up period, 47 patients (85.5%) died. The median overall survival was 16.4 months (95%CI 12.2–20.6 months).

Discussion

In patients with inoperable esophageal cancer, stenting is often used for severe dysphagia. While stenting offers prompt relief of dysphagia, the AE rate can be high, and the lifestyle modifications required with stenting at the GEJ are significant and might not be acceptable to some patients. While systemic therapy helps with dysphagia palliation, the effect is often incomplete, necessitating another form of palliation. The most recent Cochrane review on this topic recommended against using systemic therapy alone for dysphagia palliation [22]. The NCCN guidelines have a similar recommendation, stating that long-term management of dysphagia in esophageal cancer can be achieved via cancer ablation or stenting. In patients with mild-to-moderate dysphagia, the guidelines recommend carefully weighing the risks and benefits of interventions, making a therapy with low AE profile such as cryoablation a good option.

The impact of systemic therapy on QoL in patients with stage 4 esophageal cancer is not clear. The most recent Co-

▶ **Table 2** Change in dysphagia and quality of life scores.

Characteristic	Mean (SD)	Median (range)	*P* value[1]
Patient-level data (n = 55)			
Dysphagia score[2]			
▪ Baseline	1.9 (0.93)	2.0 (0–4)	0.004
▪ Last follow-up	1.3 (1.1)	1.0 (0–4)	
QoL score[3]			
▪ Baseline	34.9 (9.5)	34.0 (19–62)	< 0.001
▪ Last follow-up	29.0 (9.3)	27.5 (17–51)	
Cryotherapy treatment-level data (n = 175)			
Dysphagia score			
▪ Pre-cryotherapy	1.4 (1.1)	1.0 (0–4)	0.001
▪ Post-cryotherapy	1.0 (0.98)	1.0 (0–4)	
QoL score			
▪ Pre-cryotherapy	30.2 (9.3)	28.0 (18–62)	< 0.001
▪ Post-cryotherapy	26.9 (8.6)	24.0 (18–55)	

QoL, quality of life; EORTC QLQ-OES18, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Esophageal Cancer Module.

[1] Wilcoxon signed-rank test was used to evaluate the before–after differences in QoL and dysphagia scores for both patient- and cryotherapy-level data.

[2] 0 = no dysphagia; 1 = dysphagia to solids; 2 = dysphagia to semi-solids; 3 = dysphagia to liquids; 4 = dysphagia to own saliva.

[3] QoL was assessed using a modified EORTC QLQ-OES18 questionnaire (score 18–72, higher scores indicating worse QoL).

▶ **Table 3** Univariable analysis of predictors of change in dysphagia and QoL scores.

Predictors	Mean change in dysphagia score[1]	*P* value[2]	Mean change in QoL score[1]	*P* value[2]
Patient-level data (n = 55)				
Age at first cryotherapy				
▪ < 60 years	1.0	0.12	6.3	0.78
▪ ≥ 60 years	0.3		6.1	
Sex				
▪ Male	0.4	0.04	4.9	0.06
▪ Female	1.5		12.8	
Tumor stage at cryotherapy				
▪ Stage 2	0.7	0.92	6.0	0.05
▪ Stage 3	0.5		0.6	
▪ Stage 4	0.6		7.3	
Tumor location				
▪ Esophagus	0.5	0.68	3.9	0.04
▪ GEJ	0.7		10.7	
Prior local treatment for dysphagia				
▪ No	0.6	0.46	7.6	0.13
▪ Yes	0.4		2.5	
Concurrent chemotherapy				
▪ No	0.1	0.21	6.1	0.93
▪ Yes	0.7		6.2	
Intensive cryotherapy[3]				
▪ No	0.2	0.003	6.5	0.92
▪ Yes	1.2		5.7	
Freeze time per cycle				
▪ 20 seconds	0.6	0.77	6.4	0.90
▪ 30 seconds	0.5		5.9	
Cryotherapy treatment-level data (n = 175)				
Age at first cryotherapy				
▪ < 60 years	0.4	0.68	3.6	0.78
▪ ≥ 60 years	0.2		2.8	
Sex				
▪ Males	0.2	0.18	2.8	0.85
▪ Females	0.7		4.6	
Tumor stage at cryotherapy				
▪ Stage 2	0.3	0.47	1.64	0.008
▪ Stage 3	0.1		−0.3	
▪ Stage 4	0.3		4.2	

chrane review on this topic could only conclude that systemic therapy did not worsen QoL [23]. More recent reviews confirmed similar findings, that QoL did not worsen with systemic therapy, and acknowledged that the quality of evidence is poor [24, 25]. In the current prospective multicenter study, we found that adding spray cryotherapy to systemic therapy was associated with an improvement in dysphagia and QoL in patients with inoperative esophageal cancer. The majority of patients in our study were able to lie flat without any significant reflux symptoms. This represents a major advantage of cryotherapy over stenting at the GEJ, after which the majority of patients experience reflux-like symptoms and are unable to lie flat.

This is the first prospective study reporting an improvement in dysphagia and QoL in patients receiving systemic therapy and cryotherapy. Our prior study showing an improvement in dysphagia with cryotherapy was retrospective and did not report any QoL data [12]. Even in our study where endoscopists with expertise in spray cryotherapy were performing the procedures, there was considerable variability in practice patterns. The pragmatic nature of the current study allowed us to assess the effect of previously unexplored procedure-related factors on patient outcomes. First, a shorter duration between cryotherapy sessions (defined as two sessions within a 3-week period) was associated with a statistically significant improvement

▶ **Table 3** (Continuation)

Predictors	Mean change in dysphagia score[1]	*P* value[2]	Mean change in QoL score[1]	*P* value[2]
Tumor location				
▪ Esophagus	0.3	0.82	2.3	0.39
▪ GEJ	0.3		4.5	
Prior local treatment for dysphagia				
▪ No	0.3	0.36	4.0	0.07
▪ Yes	0.2		1.6	
Concurrent chemotherapy				
▪ No	0.3	0.49	2.6	0.74
▪ Yes	0.3		3.1	
Intensive cryotherapy[3]				
▪ No	0.2	0.60	4.5	0.23
▪ Yes	0.3		2.0	
Freeze time per cycle				
▪ 20 seconds	0.3	0.56	4.3	0.13
▪ 30 seconds	0.2		2.1	

QoL, quality of life; GEJ, gastroesophageal junction.
[1] Change in dysphagia and QoL scores was calculated by subtracting the dysphagia and QoL scores at last follow-up from the corresponding scores at baseline (a higher change in score indicates improvement for both dysphagia and QoL).
[2] Based on non-parametric Mann–Whitney or Kruskal–Wallis test.
[3] At least two cryotherapy treatments within 3 weeks.

in dysphagia compared with a longer interval, without a concomitant increase in AE rates. In fact, of the four patients who received the most intensive therapy (four cryotherapy sessions within 5 weeks), three became dysphagia free and one had a dysphagia score of 1 after the third treatment. There was a trend toward improved dysphagia with concurrent cryotherapy and systemic chemotherapy (patients receiving both within 48 hours), which suggests that the two modalities may work synergistically; however, the finding was not statistically significant and is therefore worthy of further investigation in future studies with larger sample sizes. Patients with more advanced disease (stage 4) experienced a greater benefit in QoL than patients with stage 3 disease. We postulated that this finding was at least in part related to the higher frequency of patients with stage 3 disease receiving prior radiation therapy, but further study is needed to corroborate. Taken together, these data suggest that QoL outcomes with cryotherapy may be optimized with shorter intervals between sessions (1–2 weeks). The general practice across centers was to perform cryotherapy 1–2 days before systemic therapy to allow for any significant AEs to be identified before giving systemic therapy.

The rate of AEs reported was low. The majority were related to the primary cancer or comorbidities and were not procedure related. Of the total of 175 procedures, there were two procedure-related admissions in the immediate post-procedure period. Within the 30-day post-procedure period, there were three deaths, two of which were related to GI bleeding and one to esophageal cancer. There were no procedure-related perforations, which is likely to reflect the extensive physician experience with cryotherapy in these centers. Although published data on the risk of bleeding in esophageal cancer are scarce, the data available suggest a 5 % risk of major bleeding and 3 % risk of GI bleeding, which is consistent with the risk of bleeding seen in the current study [26]. It is our practice and recommendation that all patients with esophageal cancer undergoing cryotherapy be placed on twice-daily proton pump inhibitors.

Dysphagia palliation in many centers is dependent on the local expertise. Patients with stage 3 disease who are not surgical candidates are often treated with radiation given the potential for complete clinical response. These patients were not included in this study as they would have received radiation instead of cryotherapy. The data on radiation for stage 4 esophageal cancer are mostly retrospective. The data show that if chemotherapy is combined with radiation, the rate of AEs can be high, including a treatment-related 30-day mortality of up to 5 % [27]. Most centers have limited the radiation to lower palliative doses and typically withhold chemotherapy, as combining palliative radiation with chemotherapy has been shown to increase AEs without added benefits [27]. The most recent and largest study on radiation for stage 4 disease showed no survival benefit, with a median survival of 9.9 months [28]. It can takes weeks after radiation therapy before improvement in dysphagia is seen and sometimes dysphagia worsens before it improves. Furthermore, radiation treatment often requires chemotherapy to be delayed to avoid synergistic AEs [27, 29]. Some advantages of cryotherapy over radiation include faster improvement, lower AE rate, lack of maximal dose, and no need to withhold chemotherapy. Although the median survival in our study was 16.4 months compared with 9.9 months in the study mentioned above [28], future head-to-head comparative studies are needed to draw conclusions about the merit of one modality over another.

There are no guidelines on what constitutes a clinically significant change in EORTC QLQ-OES18. Guidelines for change in the EORTC QLQ-30 recommended considering 10 points as a significant change [16, 30]. The authors noted that studies have considered 5, 8, and 10 points as clinically significant for EORTC QLQ-30 [30]. They did, however, caution that seeing changes in the QoL score is difficult and studies comparing the score with baseline should carefully consider this fact. The authors attributed this to many factors, including psychological adaptation with time [30]. Given this consideration, we opted to choose a 5-point change as a clinically meaningful difference on the scale, which has 18 questions as opposed to 30.

The strengths of our study include a prospective multicenter design making the results more generalizable, a consecutive series of eligible patients at each center minimizing the possibility of selection bias, and a large post-cryotherapy follow-up period for AE monitoring. To the best of our knowledge, this is the first and the largest study investigating the safety and effi-

▶ **Table 4** Adverse events reported within 30 days of a cryotherapy procedure.

Adverse event	Time from the procedure, days	Severity grade[1]	Etiology reported	Comments
Procedure-related				
Hospitalization for abdominal distension	Immediate post-procedure[2]	3	Post-procedure pain	Resolved with observation
Hospitalization for abdominal pain	Immediate post-procedure[2]	3	Post-procedure pain	Resolved with observation
Non-procedure-related				
Death in hospice at home	10	5	Esophageal cancer	
Admission and death	12	5	GI bleeding and aspiration from radiation-related AVMs	Declined EGD
Admission and death	20	5	GI bleeding and elected hospice with no investigation	Declined EGD
Hospital admission	12	4	Stroke	
Hospital admission	14	3	GI bleeding from reflux esophagitis and gastric outlet obstruction	
Hospital admission	11	3	Jaundice	
Hospital admission × 2	> 10	3	COPD exacerbation	
Hospital admission	3	3	Abdominal pain and abnormal LFTs	
Bradycardia	Intra-procedural	2	Likely procedure related; the procedure was aborted	Resolved with no specific intervention
Atrial fibrillation	17	2	–	Controlled medically

AE, adverse event; GI, gastrointestinal, AVM, arteriovenous malformation; EGD, esophagogastroduodenoscopy; COPD, chronic obstructive pulmonary disease; LFT, liver function test.
[1] According to the common terminology criteria for AEs.
[2] AE occurring in the post-procedure recovery area before the patient was discharged.

cacy of cryotherapy in relieving dysphagia and improving QoL in patients with inoperable esophageal cancer, including those on systemic anticancer therapy. Finally, this is the first study that starts to define best practices for cryotherapy, given the lack of previous data on dosing and treatment algorithms.

The important limitations of this study are a small sample size and the lack of a comparison group, for example esophageal stents or argon plasma coagulation [31]. Patients most likely to benefit from stents (such as those with poor performance status or severe dysphagia) might not be optimal candidates for cryotherapy. Conversely, patients included in our study had a high likelihood of stent failure due to migration as their symptoms were mild to moderate. Being an observational study, the cryotherapy duration and interval between sessions varied among investigators. However, this variability in practice patterns allowed us to assess the factors associated with improved outcomes with cryotherapy. Larger studies are needed to elucidate the impact of factors such as the use of intensive cryotherapy and concurrent chemotherapy on improvement in dysphagia and QoL. Other areas that need to be researched on this subject include evaluating whether there is any difference in response among patients receiving immunotherapy, the impact of cryotherapy on the response to immunotherapy, and whether there is any abscopal effect of local cryotherapy treatment especially in patients receiving immunotherapy. The abscopal effect refers to a phenomenon of tumor regression at a site distant from the primary site of treatment, traditionally associated with radiation treatment and now being used more generally with any local ablation modality; this phenomenon is thought to be immune mediated [32]. Finally, all associations reported in this study should be considered observational and hypothesis generating rather than causal, and the possibility of selection bias cannot be ruled out.

In summary, this study suggests that in patients with inoperable esophageal cancer receiving concurrent systemic therapy, adding liquid nitrogen spray cryotherapy is safe and associated with improvement in dysphagia and QoL without causing reflux.

Competing interests

T. Kachaamy is a consultant for Steris, Pentax, Microtech, Medtronics, and Boston Scientific; he also serves on an advisory board for Steris, has a product licensing agreement with Microtech, and has intellectual property partnership with an international private bank. N. Shar-

ma is a consultant for Steris, Boston Scientific, Medtronic, and Olympus. T. Shah is a consultant for Steris. M. Rojas-DeLeon is a consultant for Boston Scientific. V. Kaul is a consultant for Steris, CDX Diagnostics, Ambu, Cook Medical, and Motus GI. R. Pannala is a consultant for HCL Technologies, advisory board member for Nestle and Bluestar Genomics, and has received research support from ERBE USA and Fractyl Labs. S. Mohapatra, K. Pollard, C. Zelt, E. Jewett, R. Garcia, R. Munsey, S. Gupta, D. Gupta, and P. Vashi declare that they have no conflict of interest.

Clinical trial

Trial Registration: ClinicalTrials.gov | Registration number (trial ID): NCT03285035 | Type of study: Prospective

References

[1] Uhlenhopp DJ, Then EO, Sunkara T et al. Epidemiology of esophageal cancer: update in global trends, etiology and risk factors. Clin J Gastroenterol 2020; 13: 1010–1021

[2] National Cancer Institute Surveillance Epidemiology, and End Results Program. Cancer stat facts: esophageal cancer. Available at (Accessed 06/06/2023): https://seer.cancer.gov/statfacts/html/esoph.html

[3] Siegel RL, Miller KD, Fuchs HE et al. Cancer statistics, 2022. CA Cancer J Clin 2022; 72: 7–33

[4] Karadag I, Karakaya S, Ates O et al. CROSS or FLOT in distal esophageal and gastroesophageal cancer. J Coll Physicians Surg Pak 2021; 31: 326–329

[5] Depypere L, Thomas M, Moons J et al. Analysis of patients scheduled for neoadjuvant therapy followed by surgery for esophageal cancer, who never made it to esophagectomy. World J Surg Oncol 2019; 17: 89

[6] NCCN Guidelines. Available at (Accessed 06/13/2023): https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1433

[7] Ilson DH, Forastiere A, Arquette M et al. A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. Cancer J 2000; 6: 316–323

[8] Bakheet N, Park JH, Hu HT et al. Fully covered self-expandable esophageal metallic stents in patients with inoperable malignant disease who survived for more than 6 months after stent placement. Br J Radiol 2019; 92: 20190321

[9] Medeiros VS, Martins BC, Lenz L et al. Adverse events of self-expandable esophageal metallic stents in patients with long-term survival from advanced malignant disease. Gastrointest Endosc 2017; 86: 299–306

[10] Diamantis G, Scarpa M, Bocus P et al. Quality of life in patients with esophageal stenting for the palliation of malignant dysphagia. World J Gastroenterol 2011; 17: 144–150

[11] Barthel JS, Kucera S, Harris C et al. Cryoablation of persistent Barrett's epithelium after definitive chemoradiation therapy for esophageal adenocarcinoma. Gastrointest Endosc 2011; 74: 51–57

[12] Kachaamy T, Prakash R, Kundranda M et al. Liquid nitrogen spray cryotherapy for dysphagia palliation in patients with inoperable esophageal cancer. Gastrointest Endosc 2018; 88: 447–455

[13] Shah T, Kushnir V, Mutha P et al. Neoadjuvant cryotherapy improves dysphagia and may impact remission rates in advanced esophageal cancer. Endosc Int Open 2019; 7: E1522–e1527

[14] Eluri S, Kaul V, Sharma NR et al. Palliative endoscopic spray cryotherapy to prevent worsening of dysphagia and improve quality of life in esophageal cancer. J Clin Oncol 2021; 39: 219

[15] Hanada Y, Leggett CL, Iyer PG et al. Spray cryotherapy prevents need for palliative stenting in patients with esophageal cancer-associated dysphagia. Dis Esophagus 2022; 35: doab051

[16] Blazeby JM, Conroy T, Hammerlid E et al. Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES18, to assess quality of life in patients with oesophageal cancer. Eur J Cancer 2003; 39: 1384–1394

[17] Mellow MH, Pinkas H. Endoscopic therapy for esophageal carcinoma with Nd:YAG laser: prospective evaluation of efficacy, complications, and survival. Gastrointest Endosc 1984; 30: 334–339

[18] Ogilvie AL, Dronfield MW, Ferguson R et al. Palliative intubation of oesophagogastric neoplasms at fibreoptic endoscopy. Gut 1982; 23: 1060–1067

[19] U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common terminology criteria for adverse events (CTCAE) version 4.03, June 14 2010. Available at (Accessed 19/06/2023): https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[20] Peters TJ. Multifarious terminology: multivariable or multivariate? Univariable or univariate? Paediatr Perinat Epidemiol 2008; 22: 506

[21] Hintze J. PASS 11. Kaysville, Utah, USA: NCSS, LLC; 2011: www.ncss.com

[22] Dai Y, Li C, Xie Y et al. Interventions for dysphagia in oesophageal cancer. Cochrane Database Syst Rev 2014; 10: CD005048

[23] Janmaat VT, Steyerberg EW, van der Gaast A et al. Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer. Cochrane Database Syst Rev 2017; 11: CD004063

[24] Santero M, Pérez-Bracchiglione J, Acosta-Dighero R et al. Efficacy of systemic oncological treatments in patients with advanced esophageal or gastric cancers at high risk of dying in the middle and short term: an overview of systematic reviews. BMC Cancer 2021; 21: 712

[25] van Kleef JJ, Ter Veer E, van den Boorn HG et al. Quality of life during palliative systemic therapy for esophagogastric cancer: systematic review and meta-analysis. J Natl Cancer Inst 2020; 112: 12–29

[26] Mulder FI, Hovenkamp A, van Laarhoven HWM et al. Thromboembolic and bleeding complications in patients with oesophageal cancer. Br J Surg 2020; 107: 1324–1333

[27] Ikeda E, Kojima T, Kaneko K et al. Efficacy of concurrent chemoradiotherapy as a palliative treatment in stage IVB esophageal cancer patients with dysphagia. Jpn J Clin Oncol 2011; 41: 964–972

[28] Zhan PL, Canavan ME, Ermer T et al. Utilization and outcomes of radiation in stage IV esophageal cancer. JTO Clin Res Rep 2022; 3: 100429

[29] Penniment MG, De Ieso PB, Harvey JA et al. Palliative chemoradiotherapy versus radiotherapy alone for dysphagia in advanced oesophageal cancer: a multicentre randomised controlled trial (TROG 03.01). Lancet Gastroenterol Hepatol 2018; 3: 114–124

[30] Cocks K, King MT, Velikova G et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Eur J Cancer 2012; 48: 1713–1721

[31] Sigounas DE, Krystallis C, Couper G et al. Argon plasma coagulation compared with stent placement in the palliative treatment of inoperable oesophageal cancer. United European Gastroenterol J 2017; 5: 21–31

[32] Chen J, Qian W, Mu F et al. The future of cryoablation: an abscopal effect. Cryobiology 2020; 97: 1–4