Focal cryoballoon versus radiofrequency ablation of dysplastic Barrett's esophagus: impact on treatment response and postprocedural pain

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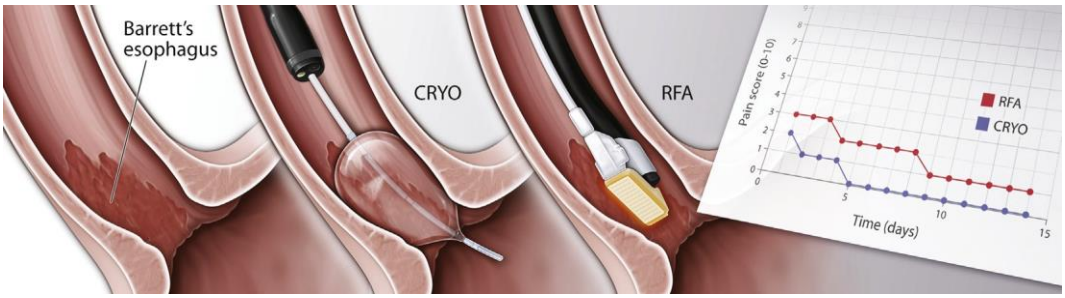
GRAPHICAL ABSTRACT



Background and Aims: Radiofrequency ablation (RFA) is safe and effective for eradicating Barrett's esophagus (BE) but is associated with significant postprocedural pain. Alternatively, balloon-based focal cryoablation (CRYO) has recently been developed, which preserves the extracellular matrix and might therefore be less painful. Although data for CRYO are still limited, uncontrolled studies suggest comparable safety and efficacy to RFA in eradicating limited BE areas. Therefore, secondary endpoints such as pain might become decisive for treatment selection. We aimed to compare efficacy and tolerability between focal CRYO and RFA.

Methods: We identified BE patients undergoing focal ablation (either RFA or CRYO) of all visible BE from our prospective cohort in 2 Dutch referral centers. After ablation, patients completed a 14-day digital diary to assess chest pain (0-10), dysphagia (0-4), and analgesics use. A follow-up endoscopy was scheduled after 3 months to assess the BE surface regression (blindly scored by 2 independent BE expert endoscopists). Outcomes were BE surface regression; 14-day cumulative scores (area under the curves [AUCs]) for pain, dysphagia, analgesics, and peak pain.

Results: We identified 46 patients (20 CRYO, 26 RFA) with similar baseline characteristics. The BE regression was comparable (88% vs 90%, P Z .62). AUCs for pain, dysphagia, and analgesics were significantly smaller after CRYO versus RFA (all P < .01). Peak pain was lower after CRYO (visual analog scale 2 vs 4, P < .01), and the duration of pain was also shorter after CRYO (2 vs 4 days, P < .01). CRYO patients used analgesics for 2 days versus 4 days for RFA (P < .01).

Conclusions: In this multicenter, nonrandomized cohort study, we found no differences in efficacy after a single treatment with CRYO and RFA for short-segment BE. Patients reported less pain after CRYO as compared with RFA. Moreover, CRYO patients used fewer analgesics. Our results suggest a different pain course favoring CRYO over RFA, but a randomized trial is needed for definitive conclusions. (Clinical trial registration number: NCT02249975.) (Gastrointest Endosc 2018;88:795-803.)

The incidence of esophageal adenocarcinoma (EAC) has increased 6-fold in the last 3 decades, making it the most rapidly increasing cancer in the Western world.[1] EAC arises from Barrett's esophagus (BE), which is defined as intestinal metaplasia of the esophageal epithelium.[2,3] As metaplastic cells develop progressive cellular atypia, classified as dysplastic BE, the risk for development of EAC increases significantly.[4] Therefore, dysplastic BE is an indication for endoscopic treatment.[5,6]

Radiofrequency ablation (RFA) is currently the most widely used endoscopic ablation therapy for

eradication of flat-type BE. In a wide range of clinical studies including several randomized trials, this heat-based ablation method has been proven to be effective in eradication of BE with an acceptable safety profile.7-12 Although it is not systemat- ically studied, it is clinically recognized that patients often report substantial postprocedural pain after RFA.13

Endoscopic cryoballoon ablation is a relatively new tech- nique that ablates BE through intracellular ice formation, cell rupture, and hypoxia.14,15 In contrast to heat-based ablation, cryoablation preserves the extracellular matrix and tissue architecture.14 Studies investigating the efficacy and safety of cryoablation using the cryoballoon focal ablation system (CbFAS) have shown the feasibility of BE eradication in up to 100% of small BE islands, with acceptable safety profiles.16-18 When compared with RFA, improved patient tolerance may constitute one of the ad- vantages of cryoablation, but to date no data support this. Potential underlying mechanisms previously described include direct effects of cooling, including an anesthetic effect and blocked nerve conduction; delayed mucosal injury; and/or preservation of the tissue architecture.15,19-21 If efficacy and safety are comparable, postprocedural side effects like patient tolerance may be of importance in select- ing the preferred ablation tool.

To date, no trials have compared CbFAS with RFA. We aimed to systematically compare endoscopic BE ablation using CbFAS and focal RFA with respect to eradication rates and postprocedural pain. We hypothesize that CbFAS is less painful compared with RFA, with comparable efficacy.

METHODS

Study setting and patient selection

We performed a retrospective analysis of prospectively collected data. Data were derived from the postprocedural pain after endoscopic therapy for BE (P-PET) cohort. This cohort consisted of patients who completed an electronic diary assessing postprocedural pain and dysphagia after endoscopic therapy for BE in 3 expert centers in the Netherlands (St Antonius Hospital [Nieuwegein], Aca- demic Medical Center [Amsterdam], and University Medi- cal Center [Utrecht]). The diary consisted of daily surveys through 14 days and was initially used for clinical purposes.

All data were prospectively and anonymously gathered in the P-PET cohort. All patients consented to use of their data in the P-PET cohort for the purpose of research. The need for ethics approval was waived by the Medical Research Committees United.

We retrospectively reviewed the P-PET cohort and included all patients with flat BE and an indication for focal ablation therapy, either confirmed low-grade dysplasia (LGD), confirmed high-grade dysplasia, residual BE after endoscopic resection for nonflat lesions containing any degree of dysplasia or low-risk mucosal EAC (ie, not poorly differentiated, negative deep resection margins, and absence of lymphatic and vascular invasion), or residual BE after circumferential or focal ablation performed for one of the indications listed above. Other inclusion criteria were completion of the electronic diary after endoscopic therapy with either CbFAS (CRYO group) or focal RFA (RFA group) and at least 1 follow-up endoscopy. An exclusion criterion was the presence of a stenosis before treatment. If patients completed the electronic diary multi- ple times (ie, if multiple focal ablation sessions were per- formed), we only included the surveys after the first treatment to prevent duplications and/or repeated measurements.

Endoscopic procedures

Both CbFAS and RFA procedures were performed on an outpatient basis, with the patient under conscious sedation with midazolam and alfentanil or monitored anesthesia us- ing propofol. Both procedures were performed by endo- scopists highly experienced in endoscopic treatment of BE (B.L.A.M.W. and J.J.G.H.M.B.).

High-resolution white-light endoscopy and narrow-band imaging were used for all procedures. The BE segment was carefully inspected, the Prague C & M criteria were docu- mented with addition of the location of the most proximal islands,22 and still images of the entire BE segment were acquired. All patients underwent ablation of all visible BE in addition to a circumferential ablation of the esophagogastric junction. After the procedure, all patients were advised in a standardized way to use oral paracetamol (maximum 1000 mg 3 times a day) in case of pain, with additional rectal diclofenac (maximum 100 mg twice a day) if needed. We guaranteed low threshold and easy contact with the clinical team. All patients received high-dose proton pump inhibitors after treatment (equivalent of esomeprazole 40 mg twice daily). In addi- tion, patients were prescribed ranitidine 300 mg before bed and 5 mL sucralfate suspension 3 times daily for a period of 2 weeks after the procedure, as is the standard of care in the Netherlands.

CRYO group

Cryoablation was performed using CbFAS (C2 Thera- peutics, Inc, Redwood City, Calif). A precise description of this therapy has been outlined in earlier studies16,17

The system comprises a handheld, through-the-scope system with a conformable balloon that is simultaneously inflated and cooled using nitrous oxide, resulting in ice patches of approximately 2 cm2 on the targeted mucosa. All patients were treated with side-by-side applications of 10-seconds duration per application.16,23 All CRYO treat- ments were performed in context of a feasibility study registered at clinicaltrials.gov with number NCT02249975.

Focal RFA group

Focal RFA (Medtronic, Inc, Minneapolis, Minn) has been described earlier.9,24,25 The technique uses a bipolar electrode that can be mounted as a cap on the tip of the endoscope. Pa- tients were treated with either a focal RFA regimen consisting of 3 applications with 12 J/cm2 or a regimen that consisted of 2 applications with 12 J/cm2 followed by a cleaning step and another 2 applications with 12 J/cm2.

Electronic diary

All patients completed an electronic diary through 14 days after treatment to report pain and dysphagia scores and use of pain medication (Supplementary Fig. 1, available online at www.giejournal.org). Patients were asked to rate retrosternal pain in rest (question 1) and during eating and drinking (question 2), both on a numeric rating scale ranging from 0 (no pain) to 10 (unbearable pain). We used a validated score to assess dysphagia ranging from 0 to 4 (question 3).26 Last, patients were asked whether they had used pain medication in the last 24 hours (question 4). If patients had

missing data in the electronic diary, we attempted to add information derived from research-related phone calls. We only added data if all the following items were explicitly mentioned: date and time, pain score (range, 0-10), dysphagia score (range, 0-4), and use of pain medication. Verbal pain scores have been shown to correlate well with numeric rating scale pain scores.27

Efficacy assessment

A follow-up endoscopy was performed 3 ± 1 months postprocedure to thoroughly inspect the esophagus for the presence of residual BE, stenosis, and other abnormal- ities. One still image was made on every 1 cm of the original BE segment. The BE surface regression was defined as the percentage of initial BE that had been con- verted to squamous epithelium. This was assessed by review of endoscopic images of the BE segment captured immediately before the initial ablation and during follow- up endoscopy. This was blindly and independently scored in randomized order by 2 endoscopists (R.H. and R.B.), both highly experienced in BE-related endoscopies, both working in centers other than the study hospitals, and both uninvolved in treatments or decision-making for the study patients. In the event the percentage differed by 30% or more, a meeting was held to establish a consensus score. The endoscopists indicated whether the endoscopic images were representative with regard to quality and quantity, scored as excellent, good, fair, or poor.

Histopathologic analysis

In all CRYO patients, in context of the previously mentioned feasibility study, 4-quadrant biopsy specimens were taken just below the neosquamocolumnar junction and for every 2 cm of the original BE segment (either from neosquamous epithelium or residual BE). In the RFA patients no biopsy specimens were taken in line with regular clinical care, because robust data have shown that endoscopically visible neosquamous epithelium after RFA treatment will be confirmed histopathologically.7,28

Biopsy samples were fixed in formalin (10%), embedded in paraffin, and stained with hematoxylin and eosin. All specimens, including baseline endoscopic resection speci- mens, baseline biopsy samples, and all biopsy specimens taken thereafter were examined by an expert pathologist in the field of GI pathology (S. Meijer or K. Seldenrijk).

Primary outcomes

We defined 2 primary endpoints for this study. The first primary endpoint was efficacy, defined as the BE surface regression after a single focal ablation treatment. The sec- ond primary endpoint was cumulative pain through 14 days. Cumulative pain is a composite score based on the 2 pain-related questions in the electronic diary (questions 1 and 2) over the entire 14-day period. The daily pain scores, defined as the maximum pain score of questions

1 and 2 per day, were depicted in a daily pain versus time plot through 14 days for each patient. Cumulative pain was defined as the area under the pain curve (AUC) for this pain intensity versus time plot.

Secondary outcome parameters

Several secondary outcomes were reported: (1) the duration of pain, defined as the number of days until daily pain scores were reported to be 0 on all following days, and (2) the duration of major pain as time until daily pain scores were 3 or less. Peak pain score (3) was the maximum pain score reported on any of the 14 days. Cumulative use of pain medication (4) was defined as the AUC of a pain medication (question 4) versus time plot. Cumulative dysphagia (5) was assessed by the AUC of a dysphagia (question 3) versus time plot.

Statistics

Data analysis was performed using IBM SPSS statistical software package (SPSS Inc, Chicago, Ill). Means with stan- dard deviations were computed for normally distributed variables and medians with interquartile ranges (IQRs) for variables with a skewed distribution. Categorical vari- ables were presented as frequencies and percentages of total. Continuous variables with a normal or skewed distri- bution were compared using the Student t test or Mann- Whitney U test, respectively. Categorical variables were compared with the c2 test or the Fisher exact test. The duration of pain

and pain medication was assessed with the Kaplan-Meier analysis, and the 2 groups were compared with a log rank test.

We performed sensitivity analysis to test the consistency and robustness of our findings. An additional analysis with adjustment for potential confounders (ie, age, gender, BE length, and prior treatment) was performed using a multi- variable linear regression model.

RESULTS

Subjects

We identified 46 patients from the P-PET cohort that were treated between April 2016 and February 2017; 20 were treated with CbFAS (CRYO group) and 26 with focal RFA (RFA group) (Figs. 1 and 2). The proportions of patients who previously underwent both endoscopic resection and ablation, endoscopic resection only, or ablation therapy only were 20%, 30%, and 20%, respectively, in the CRYO group and 27%, 19%, and 34%, respectively, in the RFA group ($P = .54$). The mean BE length before the current focal treatment was C0M2 in the CRYO group and C0M1 in the RFA group ($P > .25$). There were no significant differences with regard to any other baseline variable for the 2 groups (Table 1). In total, 558 of 644 expected daily surveys (87%) were completed and 86 (13%) were missing. Thirty-one patients (67%) completed all 14 daily surveys, whereas 15 patients (33%) missed 1 or more surveys.

Efficacy

There were no statistically significant differences for the BE surface regression at 3 months follow-up between the 2 groups: 88% (IQR, 63-94) for CRYO and 90% (IQR, 77-94) for RFA ($P = .62$) (Fig. 3). A median of 9 (IQR, 7-11) endoscopic images were available per patient. The median difference in BE surface regression between the 2 assessors was 10% (IQR, 5-20) and for 2 patients with a difference >30%, the percentage was established in a consensus meeting. The images of 3 patients were scored as poor for either quantity or quality (Table 2). For 2 of these patients, no BE surface regression could be determined, and therefore these patients were excluded from efficacy analysis. In the CRYO patients a total of 87 biopsy samples were taken from endoscopically eradicated areas, neosquamous epithelium was confirmed histologically in all 87 biopsy samples, and no subsquamous BE glands were found. In 17 patients with residual BE, a total of 43 additional biopsy samples were taken from the residual BE epithelium, with pathology assessment showing squamous epithelium in 7 (16%), nondysplastic BE in 28 (65%), and BE with LGD in 8 (19%). The 8 biopsy specimens containing LGD were derived from 3 patients with a baseline diagnosis of LGD (n = 2) or EAC (n = 1).

Cumulative pain

Cumulative pain through 14 days was significantly less in the CRYO group compared with the RFA group (Fig. 4). Median AUCs for pain intensity versus time plots were 4 (IQR, 0-16) for the CRYO group and 22 (IQR, 14-44) for the RFA group ($P < .01$). Median pain scores at each single day were consistently lower in the CRYO group (Fig. 4). Sensitivity analysis adjusting for age, gender, BE length, and prior treatment showed that CRYO was associated with a significantly smaller AUC ($P < .01$; Supplementary Table 1, available online at www.giejournal.org).

Secondary outcomes

The duration of pain was significantly shorter for the CRYO group compared with the RFA group (Fig. 4). Patients in the CRYO group were free of pain after 5.7 1.1 days, compared with 11.1 1.0 days for the RFA group ($P < .01$). The duration of major pain was similarly shorter for the CRYO group when compared with the RFA group (3.5 .9 and 6.5 1.0 days, respectively; $P = .04$). Peak pain score was significantly lower after CRYO compared with RFA (median visual analog scale 2 [IQR, 0-4] vs 4 [IQR, 3-7], $P < .01$). CRYO patients reported peak pain a median of 2 days (IQR, 1-2) after treatment, compared with 1 day (IQR, 1-4) for the RFA group ($P = .95$).

CRYO patients used significantly less analgesics compared with RFA patients (Fig. 4). Patients in the CRYO group used pain medication for 2.6 .7 days compared with 6.3 1.0 days in the RFA group ($P <$ .01). In the CRYO group, 2 (10%) patients used paracetamol and 3 (15%) used nonsteroidal anti- inflammatory drugs, whereas this was 15 (58%) and 3 (12%) patients, respectively, in the RFA group ($P = .09$). CRYO patients reported significantly less dysphagia compared with RFA patients. No patients in the CRYO group and 2 patients (8%) in the RFA group developed an esophageal stenosis after treatment. No other adverse events were reported in either of the 2 groups.

DISCUSSION

This multicenter study of prospectively collected data shows that although the efficacy after a single treatment with CRYO and RFA for eradication of short-segment BE is comparable, CRYO is associated with less postprocedural pain and dysphagia than focal RFA. Moreover, CRYO patients used less analgesics, and this use was of shorter duration. Although a randomized trial is needed for definitive conclusions, our data suggest differences in postprocedural tolerability favoring CRYO over RFA.

RFA is a heat-based ablation technique and can be applied using circumferential or focal devices. Multiple large-scale studies of RFA have shown robust and reproducible data on efficacy and safety outcomes, and RFA is therefore recommended as the standard ablation technique in current clinical guidelines.[5,29]

CRYO is a relatively new ablation method, which causes cell death through freezing. Application of liquid nitrous oxide cools the mucosa to approximately –85oC and results in mucosal ablation. CbFAS is currently the most commonly used device for CRYO, but data on efficacy, safety, and durability are limited and preliminary.

The first important criterion in selecting the preferred treatment is efficacy. Our study demonstrated no statistically significant differences in BE surface regression rates after CbFAS and focal RFA for eradication of short-segment BE. The efficacy rates we found for CRYO and RFA are in line with previous studies, showing regression rates of 82% to 100% and 78% to 90% after a single treatment with CbFAS (for small BE areas only) and RFA, respectively.[16,17,30,31] When assessing the proportion of patients achieving a complete eradication of BE on consecutive treatment sessions, rates vary between 77% and 93% after RFA,[10,12,32] and the only study on CbFAS reported a 1-year success proportion of 88% for complete eradication of intestinal metaplasia.[33] The efficacy results of the current study can be considered an early and rough estimation, and we therefore encourage additional prospective studies on CbFAS alone as well as in comparison with RFA to further assess the role of CbFAS in treatment of BE.

Robust data have already shown that endoscopically eradicated areas after RFA will contain neosquamous epithelium without subsquamous BE glands in histology.[7,28] Because these data are lacking for CRYO, we performed additional biopsy sampling from endoscopically eradicated areas after CbFAS. All these biopsy specimens from endoscopically eradicated areas were confirmed histologically to contain neosquamous epithelium with no evidence for subsquamous BE glands.

This is the first study that systematically compared patient tolerability after CRYO and RFA, and this is relevant because improved patient tolerability might constitute one of the most important advantages of CRYO over RFA. We found significantly lower pain and dysphagia scores after CRYO, and, moreover, CRYO patients used significantly less analgesics.

The exact mechanism for the differences in pain remains unknown, but several factors may play a role. Cryoablation might reduce pain through a direct anesthetic effect of cooling the mucosa and its surrounding,[15] and pain transmission might be minimized because cold temperature decreases or blocks nerve conduction.[19] In addition to electrophysiologic effects, vasoconstriction of blood vessels

may minimize edema and reduce the release of pain-producing substances from damaged tissue.34 Others speculate that the delay in mucosal injury after cryoablation might play a role.20 Cryoablation leaves the tissue architecture intact, whereas RFA results in denaturation of proteins and permanent changes in tissue structure.21 It is interesting to note that the choice between CRYO and RFA also applies to other fields of medicine, such as cardiac ablation for atrial flutters or ablation of solid tumors in liver, kidney, or bone. A large number of comparative studies including several randomized trials in this regard consistently demonstrate that CRYO is less painful compared with RFA.[19,35-37]

Although no concrete definition exists for clinically rele- vant differences in pain, a difference of 20% is frequently reported in this regard.38,39 Both the cumulative pain score (median 22 vs 4) and the peak pain score (median 4 vs 2) after RFA were >20% higher compared with CRYO. The absolute pain scores were, however, relatively low.

Because this may reflect the limited size of BE, and thus the limited extent of ablation, in our study population, comparisons in larger BE areas will be of interest. The dif- ferences in use of pain medication can also be considered an indication of clinical relevance. In summary, we believe that our results indicate clinically relevant differences in pain between CRYO and RFA, and we encourage compar- isons for larger BE areas.

Our study has several strengths. All data were prospec- tively collected. All patients were treated in a homoge- neous fashion, consisting of circumferential treatment of the gastroesophageal junction and ablation of all endo- scopically visible BE. We quantified the complete course of postprocedural pain and dysphagia through 14 days after treatment, and we specifically asked the patients to score retrosternal pain to filter out other causes of pain. The response rate in our study was high: All patients completed the day-1 survey and all but 9 completed the day-14 survey; however, all 9 patients reported no pain or dysphagia at their last assessment. The influence of missing surveys in between was further minimized by the assessment of AUCs. The BE surface regression percentage was independently and blindly assessed in random order by 2 BE expert endoscopists.

Our study has several limitations as well, including 3 major limitations. First is the nonrandomized design of our study with 2 important implications. Although baseline characteristics were not significantly different between the 2 groups and additional analysis that was corrected for potential confounders found similar results, other unknown confounding factors might have influenced our findings. We have no data on the baseline pain score, and the median pain score in the RFA group is still >0 after 14 days. This can be caused either by the severity of pain after RFA or by other pre-existing differences (ie, in patient characteristics and/or baseline pain scores). Second, patients were not blinded for treatment. All CRYO treat- ments were performed in the context of a clinical trial, whereas RFA treatments were not, and psychological effects in this regard might have influenced the pain scores. We tried to minimize this by informing patients in an identical way on pain and analgesics.

The second major limitation is the limited length of the BE segment in our study population. Longer BE length is known to be associated with increased postprocedural pain and decreased efficacy. Therefore, our conclusions are applicable to focal ablation treatment for patients with short-segment BE (<3 cm), and the generalizability to treat- ment of longer BE segments should be cautioned against.

The third major limitation applies to the efficacy endpoint, which was assessed as a derivate endpoint after a single treatment session. Because current clinical guide- lines advocate consecutive treatment sessions until all BE is eradicated, this is an important field for further research. Moreover, we included patients with relatively short-segment BE in absence of a stenosis, and prior

endoscopic therapy was allowed. Thereby we might have selected those patients with a high chance for a suc- cessful outcome.

Other limitations include a lack of a pain survey directly after the procedure and a clinically relevant question, such as return to normal daily activities. We, however, decided to start the diary not directly post-treatment given the vari- ation in intravenous analgesic administration during endo- scopic ablation and to minimize the number of questions. The type of sedation was not standardized; however, given the relatively short-term effects of both propofol and mida- zolam, the effects on the postprocedural pain course from day 1 to day 14 would be negligible. The multivariable anal- ysis included too many variables in relation to the number of patients included in this study, with a risk for over*fi*tting. Some of the secondary outcomes might relate to each other, like the peak pain score and the duration of pain.

In conclusion, this study shows that a single treatment with CRYO might be comparably effective with focal RFA for treatment of short-segment BE. We also show that CRYO is better tolerated in terms of pain and dysphagia as compared with RFA in patients with short-segment BE. We encourage validation of our *fi*ndings in a randomized trial.

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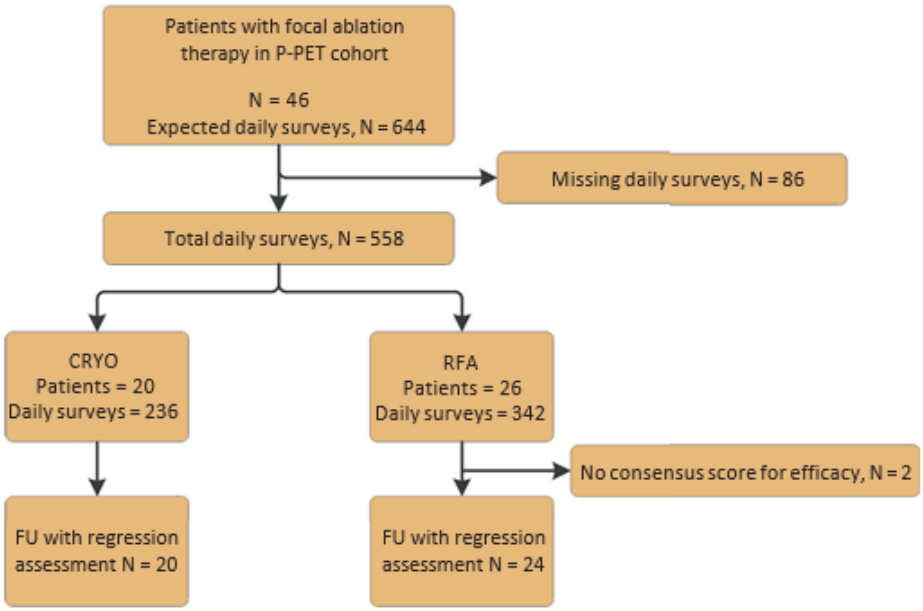


Figure 1. Flow chart for study patients. All patients with focal ablation therapy (CRYO or RFA) in the P-PET cohort were included in the study. All bu patients were eligible for the efficacy assessment. *CRYO*, Cryoablation; *FU*, follow-up; *P-PET cohort*, postprocedural pain after endoscopic therapy : Barrett's esophagus cohort; *RFA*, radiofrequency ablation.

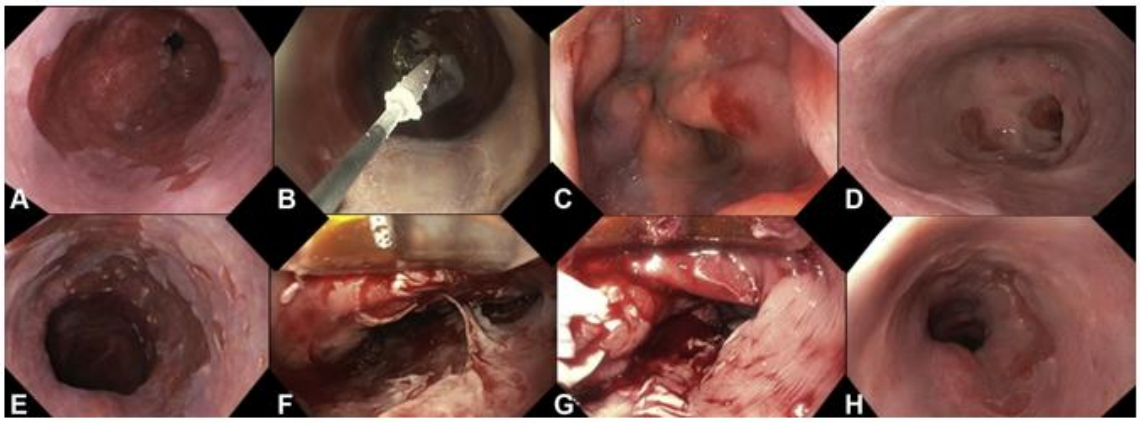


Figure 2. Baseline, treatment, and follow-up images for CRYO and RFA. The images show a typical case for CRYO (A-D) and RFA (E-H). A, Initial BE before treatment. B, CbFAS treatment, ice patch visible at 6 o'clock. C, CbFAS effect directly post-treatment. D, Follow-up endoscopy 3 months after CbFAS, with partial eradication of BE. E, Initial BE before treatment. F and G, Focal RFA treatment. Treatment effect is visible as sloughing mucosa with slight bleeding. H, Follow-up endoscopy 3 months after focal RFA with partial eradication of BE. *CRYO*, Cryoablation; *RFA*, radiofrequency ablation; *BE*, Barrett's esophagus; *CbFAS*, cryoballoon focal ablation system.

TABLE 1. Baseline characteristics

	CRYO group (n = 20)	RFA group (n = 26)	*P* value
Sex, male	17 (85)	21 (81)	.71
Median age, y (IQR)	66 (62-71)	68 (63-74)	.38
BE length before focal ablation, cm			
Circumferential extent, median (IQR)	0 (0-0)	0 (0-0)	.45
Maximum extent, median (IQR)	2 (1-3)	1 (0-3)	.25
Most proximal BE island, median (IQR)	3 (2-5)	2 (1-5)	.61
Worst histology diagnosis before first treatment			
LGD	9 (45)	14 (54)	.59
HGD or mEAC	11 (55)	12 (46)	
Prior treatment			
ER and ablation	4 (20)	7 (27)	.54
ER	6 (30)	5 (19)	
Ablation	2 (20)	9 (35)	
Type of sedation			
Propofol	19 (95)	22 (85)	.26
Midazolam	1 (5)	4 (15)	

Values are n (%) unless otherwise defined. Baseline characteristics were not significantly different for the CRYO and the RFA group.
BE, Barrett's esophagus; *CRYO*, cryoablation; *ER*, endoscopic resection; *HGD*, high-grade dysplasia; *IQR*, interquartile range; *LGD*, low-grade dysplasia; *mEAC*, mucosal esophageal adenocarcinoma; *RFA*, radiofrequency ablation.

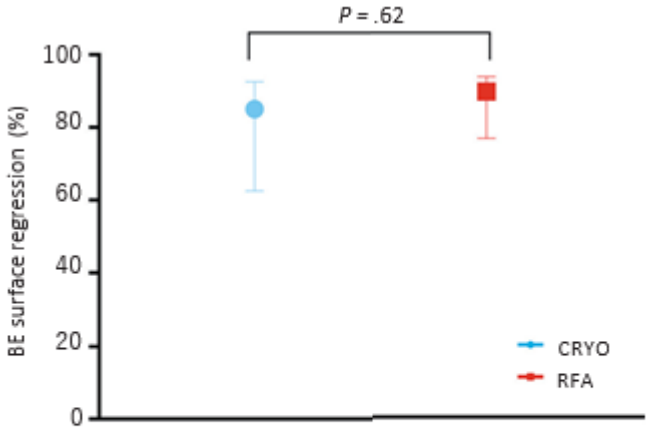


Figure 3. Efficacy. BE surface regression for both groups, scored by 2 independent BE expert endoscopists at 3 months follow-up after a single treatment session. The *blue circle* (CRYO) and *red square* (RFA) indicate median scores and error bars denote interquartile ranges. *BE*, Barrett's esophagus; *CRYO*, cryoablation; *RFA*, radiofrequency ablation.

TABLE 2. Post-treatment characteristics

	CRYO group (n = 20)	RFA group (n = 26)	*P* value
BE surface regression, median (IQR)	88 (63-94)	90* (77-94)	.62
Images per patient, median (IQR)	9 (7-11)	9 (8-10)	.91
Stenosis	0 (0)	2 (8)	.21
Other adverse events	0 (0)	0 (0)	NA

Values are n (%) unless otherwise defined. Efficacy after a single treatment session was defined as the BE surface regression percentage and was independently assessed by 2 expert endoscopists. This score was comparable for CRYO and RFA.

BE, Barrett's esophagus; *CRYO*, cryoablation; *IQR*, interquartile range; *RFA*, radiofrequency ablation; *NA*, not applicable.
*BE surface regression was assessed for 24 patients. Two patients with poor image quality that hampered adequate assessment of the BE surface regression were excluded for this analysis.

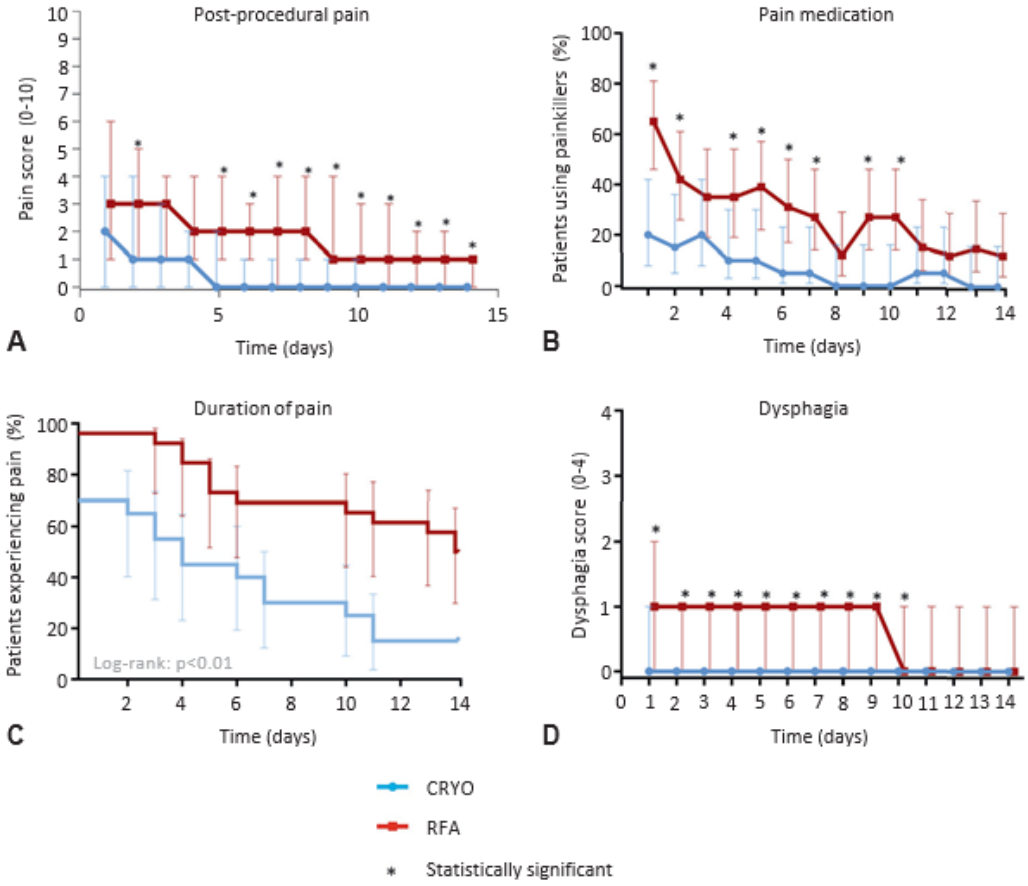


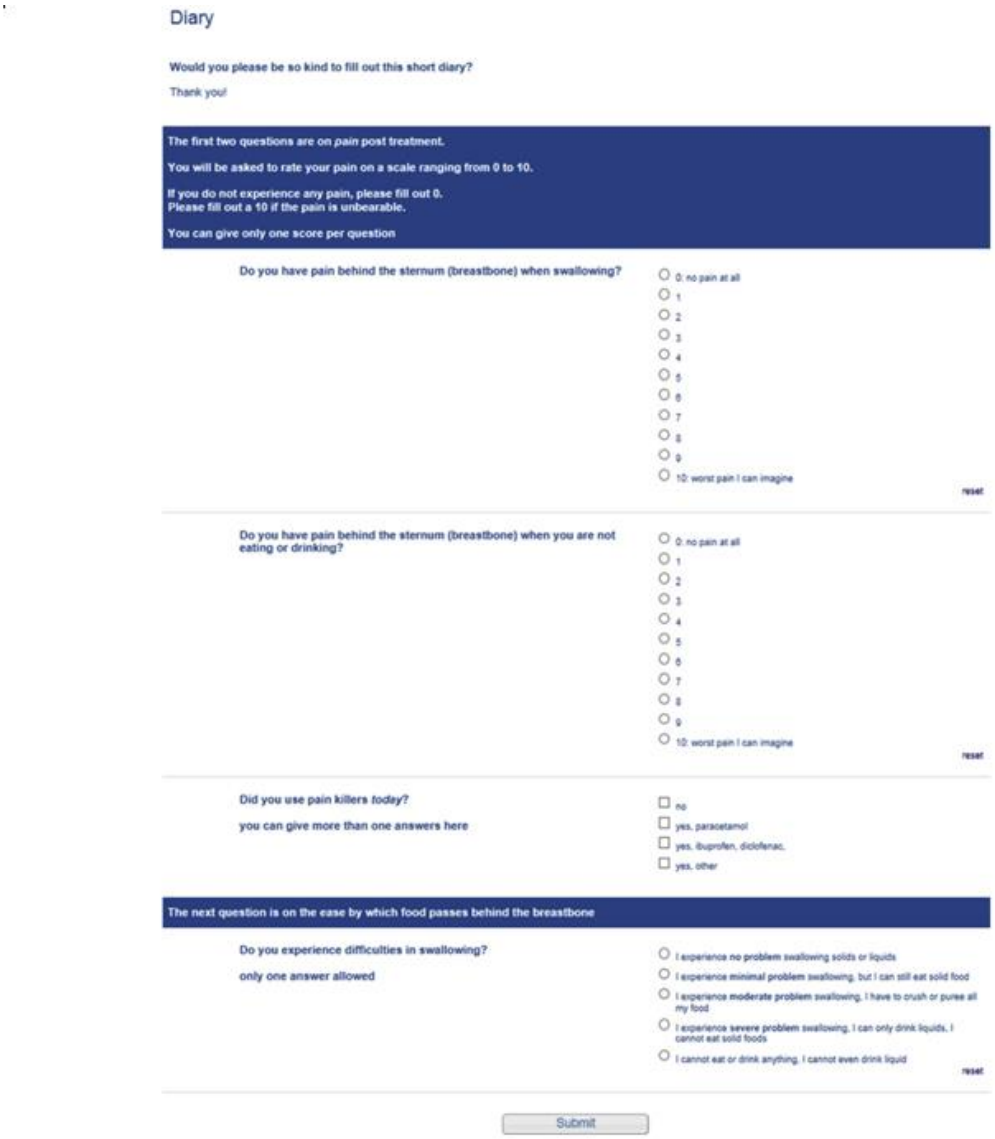
Figure 4. Postprocedural pain. A, Median daily pain scores through 14 days after treatment as recorded in the electronic diary. B, Percentage of patients using pain medication. C, Duration of pain, defined as number of days until a pain score of 0. D, Median dysphagia scores through 14 days after treatment. *Blue circles* (CRYO) and *red squares* (RFA) indicate median scores and error bars denote interquartile ranges. *CRYO*, Cryoablation; *RFA*, radiofrequency ablation.

SUPPLEMENTARY TABLE 1. Sensitivity analysis correcting for potential confounders

	B coefficient [95% CI]	*P* value
	Univariable analysis	
Treatment	−14.9 [−26.7 to −3.1]	.02
	Multivariable analysis	
Treatment	−17.3 [−29.8 to −4.7]	<.01
Age	−.6 [−1.4 to .2]	.15
Sex	−2.2 [−19.3 to 14.8]	.80
BE length	1.6 [−2.0 to 5.1]	.37
Prior ablation	−8.2 [−20.8 to 4.4]	.19
Prior endoscopic resection	2.8 [−9.6 to 15.2]	.65
Sedation type	2.7 [−18.4 to 23.8]	.80

On multivariable linear regression analysis correcting for potential confounders in the association between treatment type and cumulative pain, CRYO was associated with significantly less cumulative pain compared with RFA (decrease of 18.1 in AUC; $P < .01$). Treatment is presented as 0 for RFA and 1 for CRYO; age in years, sex as 0 for female, BE length is in cm, prior ablation and endoscopic resection as 0 for no, sedation type as 0 for propofol, and 1 for conscious sedation with midazolam. Example: prior ablation therapy is associated with a decrease of 13.8 in the area under the curve for cumulative pain ($P \geq .02$).

BE, Barrett's esophagus; *CI*, confidence interval; *CRYO*, cryoballoon ablation; *RFA*, radiofrequency ablation.



Supplementary Figure 1. Daily survey in the electronic diary. This survey questioning pain, dysphagia, and pain medication was sent out daily to all patients through 14 days after treatment.