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A novel cryoballoon ablation system for eradication of dysplastic Barrett's esophagus: a first-in-human feasibility study

Authors

Sanne Noortje van Munster[*,1,2], Anouk Overwater[*,1,3], Mihaela G. M. Raicu[4], Kees C. A. Seldenrijk[4], Wouter B. Nagengast[5], Erik J. Schoon[6], Jacques J. G. H. M. Bergman[2], Bas L. A. M. Weusten[1,3]

Institutions

1 Department of Gastroenterology and Hepatology, St. Antonius Hospital, Nieuwegein, the Netherlands
2 Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, the Netherlands
3 Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht University, the Netherlands
4 Pathology DNA, St. Antonius Hospital, Nieuwegein, the Netherlands
5 Department of Gastroenterology and Hepatology, University Medical Center Groningen, the Netherlands
6 Department of Gastroenterology and Hepatology, Catharina Hospital Eindhoven, the Netherlands

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Corresponding author
Bas L. A. M. Weusten, MD, PhD, St. Antonius Hospital and University Medical Center Utrecht, Koekoekslaan 1, 3435 CM Nieuwegein, The Netherlands
b.weusten@antoniusziekenhuis.nl

Fig. 1s
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ABSTRACT

Background Endoscopic cryoablation for Barrett's esophagus (BE) might offer advantages over heat-based ablation. Focal cryoballoon ablation has been promising for short-segment BE, whereas the novel 90°-swipe cryoballoon ablation system (CbSAS[90]) ablates larger areas in a single step (90° over 3 cm). The system allows for dose adjustment. CbSAS[90] has been feasible and safe in animal and pre-esophagectomy studies. This is the first clinical study to assess feasibility, safety, and efficacy of CbSAS[90] for eradication of dysplastic BE.

Methods In this prospective study in dysplastic BE patients, dose finding started with semi-circumferential treatment at 0.8 mm/s (dose 1). The dose was escalated by reducing speed by 0.1 mm/s in six patients until BE surface regression was ≥80 % without complications ("effective dose"). The effective dose was subsequently confirmed with circumferential treatment in 12 new patients. Post-procedural pain (0 – 10) and dysphagia (0 – 4) were evaluated. Outcomes were feasibility, safety, and BE surface regression.

Results 25 patients were included, with technically successful treatment in 92 % (95 %CI 73 % – 99 %). Median (95 % CI) BE surface regression was 78 % (50 % – 85 %) for dose 1 and 85 % (55 % – 95 %) for dose 2 (0.7 mm/s), which was defined as the effective dose. Circumferential treatment resulted in 93 % (88 % – 96 %) regression. Two of 12 patients with circumferential treatment developed strictures that required dilation. Median pain and dysphagia scores were low (0 – 3 and 0, respectively).

Conclusions CbSAS[90] was feasible and effective for ablating larger BE areas. The optimal dose for circumferential treatment that balances safety and efficacy requires further evaluation.

Introduction

Barrett's esophagus (BE) is a premalignant condition with an increased risk of developing into esophageal adenocarcinoma [1]. Therefore, current guidelines recommend endoscopic surveillance of patients with BE, consisting of careful inspection combined with histological assessment to enable early detection of neoplasia. Once BE-related neoplasia is found, this is treated using a two-step approach: visible, nonflat lesions are removed by endoscopic resection, and the remaining flat BE is subsequently eradicated using ablation therapy [2].

Cryotherapy is one of the ablation techniques available for the eradication of BE. Freezing of the esophageal epithelium directly results in ice crystal formation and cellular death, and subsequently causes necrosis, apoptosis, and ischemia. Eventually, the esophagus will regenerate with neosquamous epi-

* These authors contributed equally to this work.

thelium [3]. Cryotherapy holds possible advantages over radiofrequency ablation (RFA), which is the most widely adopted ablation technique and current standard of care [2,4]. Most importantly, cryotherapy might improve patient tolerability and preserve the extracellular matrix, potentially enabling deeper ablation with lower stricture rates [5–7].

Cryoablation can be applied using a spray technique or a balloon [8]. The spray method was introduced in 2005 [9], but various limitations have since been identified. The unstable positioning of the spray catheter resulted in operator dependency and unpredictable ablation depth, with widely varying rates of complete eradication of intestinal metaplasia (CE-IM, 4%–92%) and dysplasia (CE-D, 32%–100%), and subsquamous intestinal metaplasia in the neosquamous epithelium in up to 9% of patients [8,10]. Finally, a decompression tube is needed to prevent gas accumulation in the stomach.

Cryoballoon ablation has been introduced to overcome these limitations. Equal application of the cryogen over the balloon surface is achieved by stabilization of the spray catheter in the center of the cryoballoon [11]. Furthermore, all gas is retained in the balloon and vents back through the controller, which obviates the need for a venting tube.

Initially, the Cryoballoon Focal Ablation System (CbFAS) was developed to ablate short-segment BE, as each 10-second application results in ice patches of ±2 cm^2. Previous studies have reported promising CE-IM rates, ranging from 88% for short-segment BE to 100% for BE islands [12–14]. Treatment of large BE segments using CbFAS is however challenging and time-consuming.

Therefore, the Cryoballoon Swipe^{90} Ablation System (CbSAS^{90}) was recently introduced to treat larger BE segments. CbSAS^{90} enables a uniform, 3-cm-long ablation over a quarter of the esophageal circumference in a single application. Early bench, animal, and pre-esophagectomy studies showed that this device is feasible and safe [15]. The current study is the first-in-human study to assess the feasibility, safety, and dose-related efficacy of CbSAS^{90} in patients with dysplastic flat BE.

Methods

In this prospective single-arm study, patients were included from five Dutch tertiary referral centers for endoscopic management of BE. Patients were eligible if they were ≥18 years of age and had a flat BE segment, circumferential extent ≤3 cm, and confirmation of i) low grade dysplasia (LGD), ii) high grade dysplasia (HGD), or iii) residual BE after endoscopic resection (<2 cm in length and <50% of the esophageal circumference) for nonflat lesions containing any degree of dysplasia or low risk mucosal esophageal adenocarcinoma (i.e. not poorly differentiated, negative deep resection margins, and absence of lymphatic and vascular infiltration). Presence of visible nonflat lesions, prior endoscopic ablation therapy, esophageal stenosis preventing passage of a therapeutic endoscope, and active inflammation in the treatment zone were exclusion criteria.

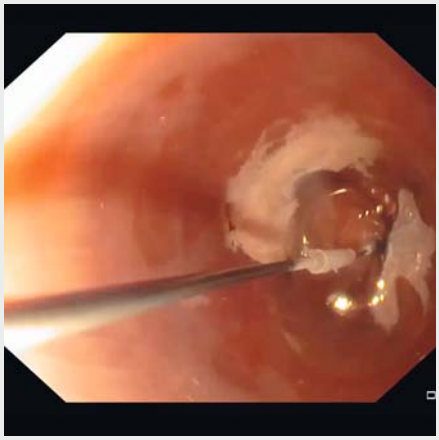
Cryoballoon Swipe^{90} Ablation System (CbSAS^{90})

CbSAS^{90} (Pentax Medical, Redwood City, California, USA) comprises a controller, balloon catheter, foot pedal, and disposable cartridge containing liquid nitrous oxide (▶ **Fig. 1**). It is compatible with therapeutic endoscopes (3.7 mm accessory channel). The balloon is highly compliant and automatically adjusts to the size of the esophagus. The catheter has a rotatable spray diffuser in the middle of the balloon. Using the foot pedal, a continuous flow of nitrous oxide can be delivered to the balloon. The spray diffuser automatically pulls back while emitting cryogen, thereby cooling the esophageal wall to approximately –80 °C, over a quarter of the esophageal circumference and 3 cm in length in a single application (▶ **Video 1**). The controller software allows for dose adjustment, which is the rate at which the diffuser travels along the 3-cm-long axis of the balloon. A decrease in the pullback rate results in an increase in the total ablation time and thus in an increase in dose, and vice versa. During ablation, all gas is vented back through the catheter and exits through the handle.

Treatment

All study procedures were performed by endoscopists with extensive experience in endoscopic treatment of BE (W.N., E.S., J. B., B.W.). Patients underwent upper endoscopy on an outpatient basis, under conscious sedation with intravenous midazolam and fentanyl, or monitored deep sedation using intravenous propofol. The BE segment was carefully inspected, the Prague C&M criteria were documented [16], and still images and videos were obtained, both with white-light endoscopy and narrow-band imaging.

Per-treatment endoscopy, half of the esophageal circumference was treated over a 3 cm length starting at the level of the



Video 1 Endoscopy video of a semi-circumferential ablation treatment using CbSAS90. Semi-circumferential treatment was performed with two CbSAS90 applications between the 9 and 3 o'clock positions.
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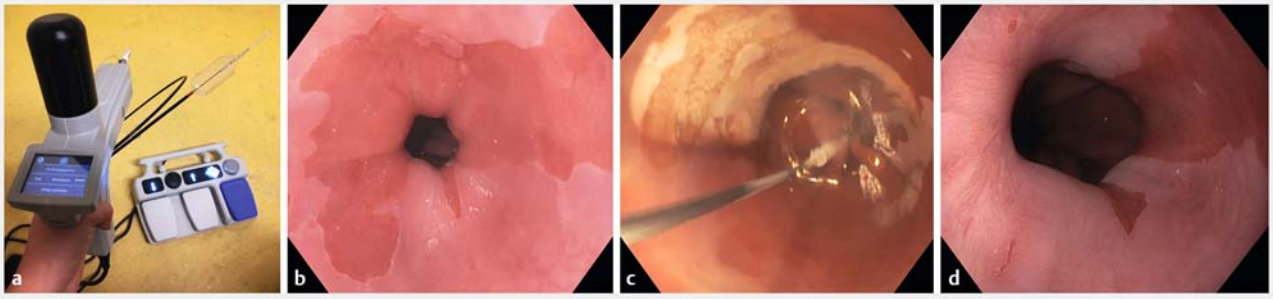


▶ **Fig. 1** The Cryoballoon Swipe[90] Ablation System (CbSAS[90]; Pentax Medical, Redwood City, California, USA) and treatment. **a** The CbSAS[90] consists of a controller, foot pedal, balloon catheter, and nitrous oxide cartridges (stored under the black cap on the image). **b** Flat-type C0M3 Barrett's esophagus (BE) with low grade dysplasia. **c** CbSAS[90] treatment in the dose-escalation phase with dose 2 (0.7 mm/s); one application has been performed, resulting in a clear ice patch, and the second application has just been started to complete semi-circumferential treatment over a 3-cm length. **d** Follow-up endoscopy at 8 weeks with the treated area shown between the 7 and 1 o'clock positions and a small remaining BE island at the 11 o'clock position, resulting in a median BE surface regression score of 98 %. Of note, the two remaining BE tongues at the 3 and 5 o'clock positions are located in the untreated half of the circumference.

gastric folds. Endoscopy time was recorded as the time between the introduction and removal of the endoscope, and ablation time was recorded as the time between insertion and removal of the CbSAS[90] catheter.

Feasibility

We evaluated ablation time, technical success (defined as treatment of all BE as intended), and device malfunction (defined as failure of one of the CbSAS[90] components, with need for device replacement).

Efficacy assessment

At 8 (± 2) weeks after the last treatment, patients underwent a follow-up endoscopy with careful evaluation (white-light and narrow-band imaging) and photo and video documentation of the entire initial BE segment. Per semi-circumferential CbSAS[90] treatment, four biopsies were taken from the neosquamous epithelium.

Efficacy was defined as the median BE surface regression as evaluated by an Adjudication Committee. The Committee consisted of three independent BE expert endoscopists who were not involved in the study, nor were they involved in clinical decision making for the study patients. Two Committee members initially compared baseline images and videos with those of the follow-up endoscopy in a standardized and systematic manner. If the BE surface regression differed by > 20 % or one of the members reported a regression < 80 % and the other ≥ 80 %, the third Committee member additionally reviewed the images and the median of the three readings was used. The treating physician also estimated the BE surface regression, but the adjudicators were blinded to this estimation.

Safety and tolerability assessment

Patients were telephoned on Days 1, 7, and 30 post-procedure to evaluate adverse events, retrosternal pain (numeric rating scale 0 – 10), dysphagia (validated score 0 – 4 [17]), and the use of painkillers.

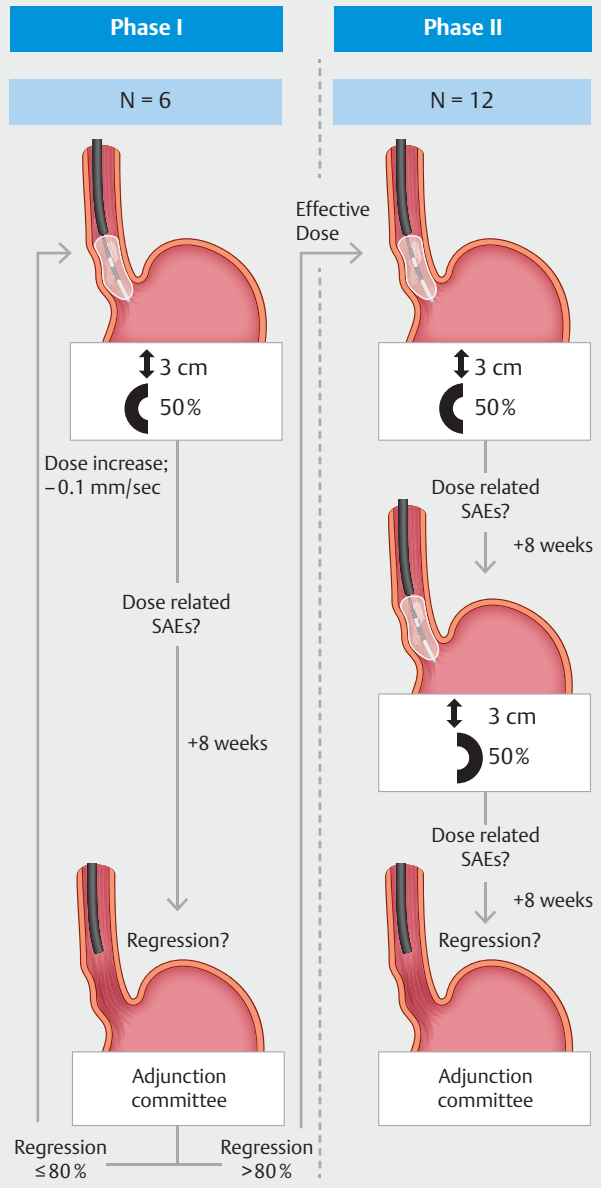
We defined dose-related serious adverse events (DR-SAEs) as severe retrosternal pain (score > 6) at both Days 1 and 7 after treatment, or strictures that required dilation. DR-SAEs and all other SAEs ≤ 30 days after treatment were evaluated by the Data and Safety Monitoring Board for severity and relationship to the dose.

Study design

This study consisted of two phases. The first phase was conducted for dose finding to determine the effective dose, defined as the lowest dose that resulted in BE surface regression of ≥ 80 % in the absence of DR-SAEs. For each dose, six patients underwent a single treatment endoscopy for semi-circumferential treatment (▶ **Fig. 2**). The starting dose was 0.8 mm/s (dose 1) based on results from animal and bench testing [15], and this was escalated by reducing the speed by 0.1 mm/s in six new patients until the effective dose was found. As an extra safety measure, we started with treatment of two patients and only if no DR-SAEs occurred ≤ 7 days after the procedure did we continue treatment in the remaining four patients. When the effective dose was established, the study continued with the confirmation phase. A total of 12 new patients underwent circumferential treatment using the effective dose in two consecutive endoscopies (50 % of the circumference was treated per endoscopy) with 8 (± 2) weeks in between.

Outcomes

The two primary end points of this study were assessed in the confirmation phase after circumferential treatment using the effective dose. The end points were i) safety, defined as the incidence of DR-SAEs, and ii) efficacy, defined as the BE surface regression scored by the Adjudication Committee. Secondary end points included feasibility, adverse events, tolerability, and presence of buried BE in biopsies of the neosquamous epithelium.



▶ **Fig. 2** Dose-escalation schedule. In the dose-finding phase, we aimed to determine the effective dose, defined as the lowest dose that resulted in a Barrett's esophagus (BE) surface regression of ≥80% in the absence of dose-related serious adverse events. For each dose tested, six patients underwent a single treatment endoscopy with semi-circumferential treatment of the BE segment. The starting dose was 0.8 mm/s (dose 1) and this was escalated (by reducing speed) by 0.1 mm/s in six new patients until the effective dose was established. At this point, the study continued with the confirmation phase. A total of 12 new patients underwent circumferential treatment using the effective dose. Circumferential treatment was performed in two consecutive endoscopies with 8 (±2) weeks in between, with half of the esophageal circumference being treated per endoscopy. SAE, serious adverse event.

Histological analysis

All biopsies were fixed in formalin (10%), embedded in paraffin, and stained with hematoxylin and eosin. All baseline and follow-up biopsies in the confirmation cohort were centrally reviewed by two experienced BE pathologists (C.S. and G.R.).

Statistical analysis

As this was a first-in-human feasibility study, no formal sample size calculation was conducted and a sample size of 6 patients per dose in the dose-finding phase and 12 patients in the confirmation phase was considered satisfactory. Statistical analysis was performed using the Statistical Software Package SPSS version 24.0.0.1 for Windows (IBM Corp., Armonk, New York, USA) and R version 3.4.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria). For baseline descriptive statistics, continuous variables were reported as medians with interquartile range (IQR). Outcome variables were reported as medians with adjusted 95% confidence intervals (CIs), which were obtained using simple bootstrapping with 10000 samples. Given the limited number of patients per dose, formal statistical testing for differences between doses was not performed.

Ethics

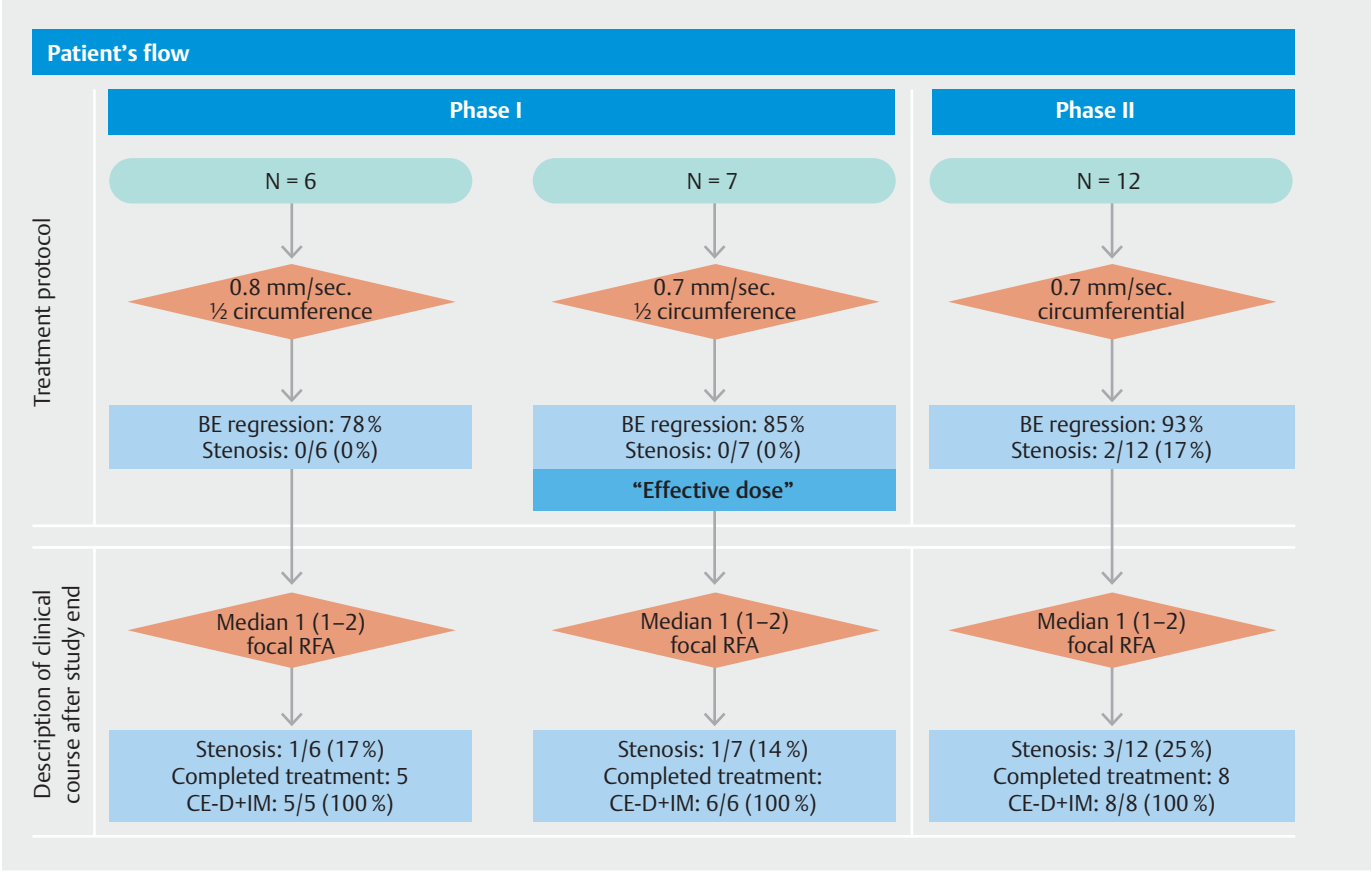
This study was registered at ClinicalTrials.gov (NCT03097666) and at www.trialregister.nl (NTR6191). The AMC Medical Ethical Review Committee approved the study and the informed consent form. Written informed consent was obtained from all patients participating in the study.

Description of clinical course following completion of the study protocol

Patients with persisting BE after completion of the study underwent additional treatment with focal RFA (Barrx 90, Covidien/Medtronic, Minneapolis, USA; dose 3×12 J/cm^2 without cleaning in between applications) until CE-IM. These treatments were standardized, with ablation of all visible BE and the gastroesophageal junction in 3–4-month intervals. Argon plasma coagulation was used as rescue treatment for persisting small (<5 mm) BE islands after RFA. Although these procedures were not part of the formal study protocol and were performed in the context of regular clinical care, the treatment strategy was in line with national BE guidelines [18] and was thus standardized. We retrospectively collected final outcomes for all patients (number of additional treatments, CE-IM rates, and adverse events). These outcomes are reported at the end of the results section to provide complete data on efficacy and safety after additional ablation.

Results

We included a total of 25 patients between March 2017 and January 2018; 13 patients were treated in the dose-escalation phase and 12 in the confirmation phase (▶ **Fig. 3**). Baseline pathology after central pathology revision was indefinite for dysplasia (n=1, 4%), LGD (n=19, 76%), HGD (n=2, 8%), and cancer (n=3, 12%). Five patients (20%) had undergone endoscopic



▶ **Fig. 3** Study outcomes including description of clinical course outside the study protocol. During dose finding, the first dose (0.8 mm/s) resulted in a median Barrett's esophagus (BE) surface regression of < 80 %; thus, we escalated to 0.7 mm/s. This second dose resulted in a median BE surface regression > 80 % without dose-related serious adverse events, and was therefore defined as the effective dose. During the confirmation phase, the effective dose resulted in a median BE surface regression of 93 %, but two strictures occurred. The lower part of the figure reports the clinical course (overall stricture rates, completion of treatment, and complete eradication of intestinal metaplasia [CE-IM] and dysplasia [CE-D]) after the study protocol was completed and patients were further treated according to current clinical guidelines. RFA, radiofrequency ablation.

mucosal resection (EMR) for a visible lesion prior to study inclusion. Baseline characteristics are reported in ▶ **Table 1**.

Feasibility

The median procedure time was 24 minutes (95 %CI 19 – 27), and median ablation time was 10 minutes (95 %CI 8 – 11). The procedure was technically successful in 23 of the 25 patients (92 %, 95 %CI 73 % – 99 %). One procedure failed due to repetitive slippage of the balloon into the hiatal hernia. This patient was treated in the dose-escalation phase with dose 2. Given, the importance of the efficacy and safety assessment in the dose-escalation phase to guide future decision making in the study, an extra (seventh) patient was included to guarantee accurate assessments. The second procedure was impeded by condensation of the balloon. Device malfunction occurred in 2/25 patients (8 %, 95 %CI 1 % – 28 %) or 2/37 procedures (5 %, 95 %CI 1 % – 20). In all cases, the procedure was completed successfully after device replacement.

Efficacy

In the dose-escalation phase using dose 1 (0.8 mm/s), the median BE surface regression after a single semi-circumferential treatment was 78 % (95 %CI 50 % – 85 %) (▶ **Table 2**). Upon dose escalation (reduction in speed) to dose 2 (0.7 mm/s), the median regression score after semi-circumferential treatment increased to 85 % (95 %CI 55 % – 95 %). Dose 2 (0.7 mm/s) was thus defined as the effective dose (▶ **Fig. 3**). In the confirmation phase, the median BE surface regression with the effective dose after circumferential treatment was 93 % (95 %CI 88 % – 96 %) (▶ **Fig. 3**).

The BE surface regression scores reported by the treating physicians during the follow-up endoscopy were higher than those reported by the Adjudication Committee (▶ **Table 2**).

All follow-up biopsies from endoscopically eradicated areas (n = 48, 100 %, 95 %CI 91 % – 100 %) in the 12 patients treated circumferentially were confirmed to contain squamous epithelium, without buried BE.

▶ **Table 1** Baseline characteristics.

	Overall n = 25	Dose-escalation phase, Dose 1 n = 6	Dose-escalation phase, Dose 2 n = 7	Confirmation phase n = 12
Male sex, n (%)	19 (76)	5 (83)	4 (57)	10 (83)
Age, median (IQR), years	67 (63 – 70)	67 (58 – 73)	67 (64 – 67)	67 (62 – 71)
Worst pre-treatment histology, n (%)				
▪ Indefinite for dysplasia	1 (4)	–	1 (14)	–
▪ LGD	19 (76)	6 (100)	3 (43)	10 (83)
▪ HGD	2 (8)	–	1 (14)	1 (8)
▪ EAC	3 (12)	–	2 (29)	1 (8)
Prior endoscopic resection, n (%)	5 (20)	1 (17)	3 (43)	1 (8)
Worst pre-ablation histology, n (%)				
▪ Indefinite for dysplasia	1 (4)	–	1 (14)	–
▪ LGD	20 (80)	6 (100)	4 (57)	10 (83)
▪ HGD	2 (8)	–	–	2 (17)
▪ Unknown[1]	2 (8)	–	2 (29)	–
Pre-ablation BE extent, median (IQR) cm				
▪ Circumferential	0 (0 – 1)	1 (0 – 1)	0 (0 – 2)	0 (0 – 1)
▪ Maximum	3 (3 – 4)	3 (2 – 3)	4 (2 – 5)	4 (3 – 5)

IQR, interquartile range; LGD, low grade dysplasia; HGD, high grade dysplasia; EAC, esophageal adenocarcinoma; BE, Barrett's esophagus; EMR, endoscopic mucosal resection.
* In two patients, no additional biopsies were performed from the flat BE segment after EMR.

▶ **Table 2** Efficacy results: percentage of Barrett's epithelium that converted to normal squamous epithelium after CbSAS[90] treatment.

	Dose-escalation phase		Confirmation phase
	Dose 1 (n = 6)	Dose 2 (n = 7)	Dose 2 (n = 12)
Adjudication committee			
▪ BE surface regression, median (95 %CI), %	78 (50 – 85)	85 (55 – 95)	93 (88 – 96)
▪ Third assessor needed, n	3	4	0
Direct assessment by endoscopist			
▪ BE surface regression median, % (95 %CI)	93 (80 – 100)	99 (88 – 100)	96 (90 – 98)

BE, Barrett's esophagus; CI, confidence interval.

Safety

None of the patients in the dose-escalation phase developed a stenosis. In the confirmation phase, 2/12 patients (17 %; 95 %CI 3 % – 50 %) developed a stenosis that required dilation after the second treatment (▶ **Fig. 3**). Both stenoses were successfully treated with 1 and 3 dilations, respectively.

No severe bleeding, perforation, or other SAEs occurred. Mild adverse events occurred in three patients (12 %, 95 %CI 3 % – 32 %), which all resolved spontaneously.

Tolerability

The procedures were well tolerated and none of the patients reported severe pain. Overall median pain scores (out of 10) after treatment were 3 (95 %CI 2 – 4), 1 (95 %CI 0 – 1), 0 (95 %CI 0 – 0), and 0 (95 %CI 0 – 0) at Days 0, 1, 7, and 30, respectively (see **Fig. 1 s** in the online only supplementary material). In total, eight patients (32 %) took oral pain medication (all paracetamol) after discharge and no patients continued to use pain medication at Day 6. Overall median dysphagia scores were 0 (95 %CI 0 – 0) at all time points.

Description of clinical course outside the study protocol

After finishing the study, three patients developed a stenosis upon additional focal RFA treatment. Thus overall, of the 25 patients included in this study, 5 (20 %, 95 %CI 9 % – 39 %) developed a stenosis that required dilation (▶ **Table 3**, ▶ **Fig. 3**). All stenoses were classified as mild and required a median of 2 (range 1 – 3) dilations (▶ **Table 3**, ▶ **Fig. 3**).

Discussion

This prospective multicenter study is the first-in-human application of this first large-area cryoballoon ablation device (CbSAS^{90}). Cryoballoon ablation is a relatively new method of applying endoscopic cryotherapy and is gaining increasing attention for eradication of dysplastic BE. Studies performed thus far have used focal cryoballoon ablation and have shown promising results regarding efficacy, safety, and tolerability [6, 12 – 14]. However, the focal system is only feasible for treatment of short-segment BE and this limits the use of the technique on a larger scale. A recent case report demonstrated that CbSAS^{90} enables successful treatment of longer BE segments [20], but clinical studies are lacking. Therefore, we performed the first study to assess the feasibility, safety, and dose-related efficacy of CbSAS^{90}.

In the current study, the new CbSAS^{90} system was feasible and this finding is an important prerequisite to further clinical testing. The system is easy to use, ablation time is short (24 minutes procedure time with 10 minutes ablation time), and the treatment has a high technical success rate (92 %). As a reference, procedure times are comparable to RFA, which vary between 18 – 26 and 17 – 36 minutes for short- and long-segment BE, respectively [21 – 24]. Device malfunctions occurred in a small proportion of patients and were all easily resolved during the same procedure with device replacement. Moreover, CbSAS^{90} eradicated dysplastic BE effectively, with a median BE surface regression percentage of 93 % (95 %CI 88 % – 96 %) at a dose of 0.7 mm/s. As a reference, BE surface regression rates after single RFA treatment vary between 78 % – 90 % [25 – 27]. No SAEs occurred and the procedures were well tolerated. This is in accordance with two recent studies on tolerability of ablation therapy, which were in favor of cryoablation when compared with RFA [6, 7].

As this study is the first-in-human study with CbSAS^{90}, several precautions were incorporated into the study design. First, we selected a two-phase study design. We anticipated that ablation of a larger area at once could theoretically result in deeper ablation of the esophageal wall compared with focal ablation only, and therefore, we started with initial evaluation of efficacy and safety after semi-circumferential treatment. Only when this cautious first phase showed that treatment was feasible and safe, and resulted in a considerable efficacy (> 80 % BE surface regression), did we continue to the confirmation phase for stepwise circumferential treatment. Second, for every new dose, we embedded a 1-week safety period after treatment of the first two patients before treating the remaining four patients. Moreover, the maximum circumferential BE length was restricted to 3 cm to prevent multiple longitudinal ablations. Finally, upon completion of the dose-finding phase, we presented a progress report and interim evaluation to the Data and

▶ **Table 3** Summary of treatment and outcomes in patients with stenosis.

	Patient 1 (#3)	Patient 2 (#11)	Patient 3 (#16)	Patient 4 (#20)	Patient 5 (#21)
Baseline BE extent, cm					
▪ Circumferential	0	0	3	1	0
▪ Maximum	4	3	4	3	5
Treatment					
▪ Prior endoscopic resection, size in mm	–	–	–	–	–
▪ Study phase	I	I	II	II	II
▪ Study dose	0.8 mm/s	0.7 mm/s	0.7 mm/s	0.7 mm/s	0.7 mm/s
▪ Ablation sessions prior to stenosis	1 CbSAS^{90} 2 focal RFA	1 CbSAS^{90} 2 focal RFA	1 CbSAS^{90} 1 focal RFA	2 CbSAS^{90}	2 CbSAS^{90}
Stenosis					
▪ Severity[1]	Mild	Mild	Mild	Mild	Mild
▪ Dysphagia score[2]	2	3	1	2	1
▪ Dilation, n	2	3	1	1	3

CbSAS^{90}, Cryoballoon Swipe Ablation System; RFA, radiofrequency ablation.
[1] Mild (unplanned hospital admission, hospitalization ≤ 3 days); moderate (4 – 10 days' hospitalization); severe (> 5 endoscopic dilations, stent placement, or incision therapy [19].
[2] Validated dysphagia score ranging from 0 (no dysphagia) to 4 (no passage) [17].

Safety Monitoring Board and Ethics Committee, and only after approval did we continue to the confirmation phase.

During the dose-finding phase with semi-circumferential treatment, no strictures occurred. However, in the confirmation phase with circumferential treatment, the stricture rate was 17 % (95 %CI 3 % – 50 %) and the overall stricture rate, including additional out-of-study focal RFA treatment, was 20 % (95 %CI 9 % – 39 %). Although the numbers are low and therefore these percentages should be interpreted with caution, these stricture rates are remarkable and higher than expected. In fact, based on the literature on the mechanism of cryoablation in general [3, 5] and the reported stricture rates in previous clinical cryoablation studies [8], we hypothesized that we would find low stricture rates. RFA studies report stricture rates varying from 0 % to 8 % and a maximum up to 14 %, although this was reported in a single study that included patients after previous extensive EMR [28 – 30]. We therefore express our concerns in using the dose we defined as the effective dose (0.7 mm/s) and we recommend further studies to determine the optimal dose. We will elaborate on several factors that might have contributed to our findings.

First, although assessment of the BE surface regression after a single circumferential ablation procedure has been used in several previous studies on RFA [25 – 27], accurate assessment of this surrogate end point is challenging. As we anticipated assessment after semi-circumferential ablation to be even more challenging, several precautions were taken to optimize the evaluations. High quality images and videos were provided and highly experienced endoscopists were selected for the Adjudication Committee. In cases of discrepancies between the first two adjudicators, a third adjudicator was consulted to establish a consensus score. Despite these precautions, we observed considerable variability between the Adjudication Committee regression scores, especially after semi-circumferential treatment in the dose-finding phase. This interobserver variability in the first phase of our study might have exceeded true differences between the different dosages. Based on the scores of the treating endoscopists, our starting dose might already have led to a BE surface regression that exceeded the 80 % boundary.

Second, the 80 % boundary in the definition for the effective dose is arbitrary. We considered this boundary to be comparable to regression percentages after single circumferential RFA treatment, which vary from 78 % to 90 % [25 – 27]. However, these studies included patients with long BE segments and this might limit direct comparisons. Small, remaining BE islands are not uncommon after a single ablation treatment. In patients with long BE segments, persisting small islands still result in regression scores of around 95 %. However, in patients with short-segment BE, as in the current study, small persisting BE islands are likely to result in lower regression scores.

In addition, evaluation of the risk of stenosis after semi-circumferential treatment might also have been suboptimal. If semi-circumferential ablation would have resulted in fibrosis and retraction of the treated area, patients might experience no complaints of dysphagia because of compensation by the untreated contralateral half of the esophagus.

This study has several strengths. This is the first clinical study with this new large-area cryoballoon ablation device and is therefore relevant for the future introduction of this technique to clinical daily practice. Other strengths of this study are the multicenter setting in BE expert centers, and that all CbSAS^{90} treatments were performed by experienced endoscopists. BE surface regression percentages were evaluated by independent expert endoscopists based on both images and videos, and central pathology revision was performed by experienced BE pathologists.

The limitations of this study have already been discussed and mostly relate to semi-circumferential treatment and the definition of the effective dose. One additional limitation is the small sample sizes for each dose and for the entire study, which hamper firm conclusions. We considered six patients per dose to be sufficient for this first-in-human feasibility study, but larger series are needed for an in-depth assessment of safety and efficacy. The most important lessons we learned are that evaluation of efficacy after semi-circumferential treatment is challenging, leads to high interobserver variability, and limits adequate safety assessments. Therefore, we advocate the use of circumferential treatment for evaluation of dose-related efficacy and safety in future studies.

Future research on optimal dosing with CbSAS^{90} is recommended. Based on our results, further dose-finding studies could start with direct circumferential treatment at the lowest possible dose to optimally balance efficacy and risk of stenosis. Next, the effect of multiple longitudinal ablations should be evaluated in patients with longer BE segments. Ultimately, after establishment of the optimal dose, consecutive treatment sessions (e. g. first with the swipe system and then followed by focal treatment(s)), should be performed, with CE-IM and CE-D as the outcome parameters and with subsequent assessment of durability. The development of new balloon catheters with wider spray openings (i. e. 180 degrees for treatment of larger areas in a single step) and new balloon shapes (i. e. hourglass or pear shape to ensure a stable position at the level of the gastroesophageal junction) might optimize cryoballoon ablation treatment.

In conclusion, use of the CbSAS^{90} system is feasible and the device is a promising tool for ablation of larger areas of dysplastic Barrett's epithelium. The optimal dose that balances efficacy and safety needs further evaluation in larger clinical studies with direct circumferential treatment.

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Competing interests

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