NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of balloon cryoablation for Barrett's oesophagus or for squamous dysplasia of the oesophagus

In Barrett's oesophagus, the cells lining the lower part of the gullet (oesophagus) are abnormal. In squamous dysplasia, the cells lining the gullet are also abnormal. In both conditions there is a risk that abnormal cells will become cancerous. In this procedure, a balloon is put into the gullet through a flexible tube with a camera on the end (an endoscope). The balloon is inflated and very cold gas is used to freeze the cells and destroy them (cryoablation).

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in May 2019.

Procedure name

- Balloon cryoablation for Barrell's oesophagus or for squamous dysplasia of the oesophagus.

Specialist societies

- British Society of Gastroenterology
- Association of Upper Gastrointestinal Surgeons of GB and Ireland
- Royal College of Surgeons
- Royal College of Surgeons of Edinburgh
- Royal College of Physicians
- Royal College of Physicians of Edinburgh
- Royal College of Physicians and Surgeons of Glasgow

Description of the procedure

Indications and current treatment

In Barrett's oesophagus, the cells lining the lower part of the oesophagus become dysplastic and grow abnormally. Squamous cells in the oesophagus may also become dysplastic (squamous dysplasia). In some people these conditions may become malignant.

Current management includes lifestyle change, acid-suppressing medicines, endoscopic mucosal resection, endoscopic submucosal dissection, ablative therapies and surgery. Ablative therapies include radiofrequency ablation, photodynamic therapy, argon plasma coagulation, laser ablation, multipolar electrocoagulation and cryotherapy (for example, cryospray). NICE's clinical guideline describes endoscopy treatments for Barrett's oesophagus.

What the procedure involves

This procedure is usually done under sedation. A balloon catheter is fed through an endoscope, aligned with the dysplastic tissue in the oesophagus, and inflated. Nitrous oxide is then sprayed through a radial diffuser head within the balloon aimed at the target tissue. The tissue is destroyed by the extreme cold. The nitrous oxide gas remains fully contained within the balloon and exits through the proximal end of the catheter.

The ablation sequence is repeated until all the abnormal cells have been destroyed. Multiple ablations can be done without removing the balloon. The procedure typically takes about 15 to 20 minutes to complete.

Efficacy summary

Barrett's oesophagus

Complete resolution and eradication

Complete eradication of Barrett's oesophagus (BE) was reported in 2 case series[2, 3]. In a case series of 41 patients with neoplastic BE, complete eradication of dysplasia (CE-D) and complete eradication of intestinal metaplasia (CE-IM) rates were 95% and 88%, respectively at a 1-year follow-up. The CE-D rate was statistically significantly lower (67%) in those with ultra-long BE compared with those with less than 8 cm (100%, p=0.02)[2]. In a case series of 30 patients with flat BE islands, at a median endoscopic follow-up of 56 days (interquartile range [IQR] 49 days to 60 days), 95% (42/44) of BE areas achieved complete endoscopic and histologic eradiation of intestinal metaplasia (IM) and dysplasia, 1 BE area achieved complete eradication of dysplasia but not IM, and 1 BE area achieved incomplete eradication of dysplasia and IM[3].

Conversion to neosquamous epithelium

Conversion to neosquamous epithelium was reported in 1 case series[4] and 1 non-randomised comparative study[1]. In the case series of 39 patients with flat BE, full conversion of BE to neosquamous epithelium was statistically significantly more frequent with increasing durations of ablation: in 60% (6/10) of the ablated areas with a 6-second ablation duration; in 82% (23/28) after an 8-

second ablation; and in 100% (18/18) after 10 seconds of ablation (p=0.04)[4]. When comparing cryoballoon treatment with RFA, there were no statistically significant differences for the BE surface regression at 3 months after the treatment between the 2 groups: 88% (IQR 63% to 94%) for cryoballoon and 90% (IQR 77% to 94%) for radiofrequency ablation (RFA) (p=0.62) in the non-randomised comparative study of 46 patients with flat dysplastic BE[1].

Squamous dysplasia of the oesophagus

Complete resolution and eradication

Complete eradication of squamous dysplasia was reported in 2 case series[6, 7]. In a case series of 80 patients with a flat unstained lesion (USL), 90% (70/78) of patients had a complete endoscopic resolution (CR), and biopsy samples confirmed complete remission histologically (normal squamous mucosa, n=64; low-grade intraepithelial neoplasia [LGIN], n=6) at 3 months after the first treatment. The other 8 with persisting USLs were retreated, and all achieved CR after the second treatment[6]. In the same study, at 12-month follow-up, CR was reported in 95% (76/80, 95% confidence interval [CI] 88% to 98%) of patients by intention-to-treat analysis and 97% (76/78, 95% CI 91% to 99%) by per-protocol analysis and recurrent MGIN was shown in 3% (2/78)[6]. In a case series of 10 patients with USLs, 80% (8/10) of patients achieved complete endoscopic and pathological eradication of all oesophageal squamous cell neoplasia (CE-ESCN) after 1 cryoballoon treatment, and all the patients had CE-ESCN within 3 months. At a 1-year follow-up of 7 patients, no neoplastic progression was noted[7].

Safety summary

Barrett's oesophagus

Upper GI bleed

An upper GI bleed happened in 1 patient at day 7 after the procedure in the case series of 41 patients and this adverse event was associated with aspirin use and did not require therapy[2].

Pain and analgesic use

Mild pain with limited use of analgesics was reported in 4 studies[1-4] and severe pain highlighted in 1 case report (abstract)[5]. In the case series of 41 patients with BE, the median pain score was 1 (IQR 1 to 3) immediately after the treatment, decreasing to 0 at day 1[2]. In the case series of 30 patients, 27% (8/30) of patients reported mild pain in the treatment area and the median pain score in all patients was 0 (IQR 0 to 1) directly after cryoablation[3]. In the case series of 39 patients, 27% (10/37) of patients reported pain with a median pain score of

2.5 (IQR 2 to 3) immediately after the procedure. At a median follow-up of 2 days, 14% (5/37) of patients reported pain with a median score of 4 (IQR 3 to 6) and 3 used additional pain medication on the days following the procedure[4]. Severe thoracic pain and heartburn 2 weeks after the procedure was described in the single case report[5].

When comparing cryoballoon treatment with RFA, the median cumulative pain through 14 days was statistically significantly less in the cryoballoon group (4 [IQR 0 to 16]) than the RFA group (22 [IQR 14 to 44], p<0.01), and the mean duration of pain was significantly shorter for the cryoballoon group (5.7 days ± 1.1 days) than the RFA group (11.1 days ± 1.0 day, p<0.01) in the non-randomised comparative study of 46 patients. This led to statistically significantly less use of analgesics in cryoballoon patients (2.6 days ± 0.7 days) compared with RFA patients (6.3 days ± 1.0 days, p<0.01)[1].

Stricture and dysphagia

Stricture or dysphagia was described in 2 case series[2, 4] and 1 non-randomised comparative study[1]. In the case series of 41 patients, the stricture rate was 9.8% (4/41) which needed a median of 1 dilation (range 1 to 3) for resolution of dysphagia[2]. In the case series of 39 patients, 14% (5/37) of patients reported swallowing difficulty with a median score of 4 out of 10 (IQR 2 to 5) at a median follow-up of 2 days[4]. The dysphagia score was statistically significantly lower after cryoballoon compared with RAF (p<0.01) in the non-randomised comparative study of 46 patients[1].

Oesophagitis

Oesophagitis was reported in 1 case series[2] and 1 case report[5]. In the case series of 41 patients, candida oesophagitis occurred in 4.9% (2/41) of patients after stricture dilation and steroid injection[2]. The single case report highlighted grade D oesophagitis at 2-week follow-up and mild inflammation of the Z-line at a 3-month follow-up[5].

Superficial mucosal lacerations or trauma

Superficial mucosal lacerations or trauma were reported in 2 case series and none of the cases required a specific intervention[2, 4]. In the case series of 39 patients, 15% (6/39) of patients developed a minor longitudinal oesophageal mucosal laceration when deflating the balloon[4]. In the case series of 41 patients, 1 patient developed balloon tip mucosal trauma[2].

Device performance

Device performance issues were reported in 3 case series[2-4]. In the case series of 30 patients, device malfunction was encountered in 17% (5/30) of procedures. Of these, 4 procedures were completed using the same device and 1 used another device to complete the ablation[3]. In the case series of 41 patients, 2% (2/117) of procedures were incomplete and related to balloon migration from a pre-existing stricture[2]. In the case series of 39 patients, device performance issues, including 3 device malfunctions and 3 procedural or anatomic issues, were reported in 9.7% (6/62) of procedures[4].

Squamous dysplasia of the oesophagus

Pain and analgesic use

Mild pain with limited use of analgesics was reported in 2 case series[6, 7]. In the case series of 80 patients, the median pain scores were 1 out of 10 at day 2 (IQR 0 to 2), 0 at day 7 (IQR 0 to 0) and 0 at day 30 (IQR 0 to 0) after the procedure, with 1 patient reporting the use of pain medication at day 2[6]. In the case series of 10 patients, 40% (4/10) of patients developed mild self-limited chest pain needing 1 or 2 doses of intravenous narcotic analgesic medications, which had improved by discharge[7].

Stricture and dysphagia

Stricture or dysphagia were described in 2 case series[6, 7]. In the case series of 10 patients, 20% (2/10) of patients developed mild dysphagia for solids and symptomatic strictures within 6 to 8 weeks of treatment that responded to balloon dilation[7]. In the case series of 80 patients, the median dysphagia score was 0 of 4 (IQR 0 to 0) at days 2, 7 and 30 after the procedure[6].

Pleural effusion

A minimal pleural effusion occurred in 10% (8/80) of patients in the case series of 80 patients[6].

Fever

In the case series of 80 patients, 16% (13/80) of patients developed a short-duration idiopathic fever after the treatment with a mean (± standard deviation [SD]) temperature of 38.5 degrees ± 0.3 degrees (range 38.5 degrees to 39.2 degrees). All were treated symptomatically with indomethacin and the temperature normalised within a maximum of 5 days[6].

Superficial mucosal lacerations or trauma

Superficial mucosal lacerations or trauma were reported in 2 case series and none of the cases required a specific intervention[6, 7]. In the case series of 80 patients, 5% (4/80) of patients developed superficial mucosal lacerations on balloon inflation[6]. In the case series of 10 patients, 1 developed mild mucosal balloon trauma at the gastroesophageal junction[7].

Device performance

Device performance issues were reported in 2 case series[6, 7]. In the case series of 80 patients, diffuser rotation problems occurred in 13% (10/80) of patients; all were successfully completed using another device[6]. False high-pressure were reported in 39% (31/80) and these were completed with the same device[6]. In the case series of 10 patients, 1 rotation problem occurred, and the procedure was completed with another device[7].

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, 1 specialist adviser listed the following anecdotal adverse event: device failure. The specialist adviser considered that the following was the theoretical adverse event: nitrous oxide leakage from ruptured balloon.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to balloon cryoablation for Barrett's oesophagus and for squamous dysplasia of the oesophagus. The following databases were searched, covering the period from their start to the 3 May 2019: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with Barrett's oesophagus or squamous dysplasia of the oesophagus.
Intervention/test	Balloon cryoablation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 157 patients with Barrett's oesophagus from 1 non-randomised comparative study, 3 case series and 1 case report[1-5] and 90 patients with squamous dysplasia of the oesophagus from 2 case series[6, 7].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2a and 2b) are listed in the appendix.

Table 2a Summary of key efficacy and safety findings on balloon cryoablation for Barrett's oesophagus

Study 1 van Munster S N (2018)

Details

Study type	**Non-randomised comparative study**
Country	Netherlands (3 centres)
Recruitment period	2016 to 2017
Study population and number	**N=46 (20 balloon-based focal cryoablation [CRYO] versus 26 RFA) patients** with flat dysplastic Barrett's oesophagus
Age and sex	Median 66 years (85% [17/20] male) in CRYO group versus median 68 years (81% [21/26] male) in RFA group
Patient selection criteria	Inclusion criteria: Patients had flat BE and an indication for focal ablation therapy; completed an electronic diary assessing postprocedural pain and dysphagia after endoscopic therapy for BE; and had at least 1 FU endoscopy. Exclusion criteria: Patients presented a stenosis before treatment.
Technique	Cryoablation was done using CbFAS (C2 Therapeutics, Inc, Redwood City, Calfi) side-by-side applications of 10 seconds. All the patients were under conscious sedation with midazolam and alfentanil or monitored anaesthesia using propofol. All the patients underwent ablation of all visible BE in addition to a circumferential ablation of the oesophagogastric junction. After the procedure, all the 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.
Follow-up	**Mean 3 months**
Conflict of interest/source of funding	Three authors disclosed financial relationships relevant to this publication.

Analysis

Follow-up issues: Patients were followed up from day 1 to day 14 and then at a mean (±SD) of 3 months ±1 month. In the RFA group, 2 patients with poor image quality of the BE surface regression that hampered adequate assessment were excluded from the analysis for post-treatment characteristics.

Study design issues: Retrospective analysis of prospective non-randomised trial. The primary aim of this study was to compare endoscopic BE ablation using CbFAS and focal RFA with respect to eradication rates and postprocedural pain. Both CbFAS and RFA procedures were done by endoscopists highly experienced in endoscopic treatment of BE. A 14-day digital diary was used to assess chest pain (0-10), dysphagia (0-4), and analgesics use: i) retrosternal pain was rated in rest and during eating and drinking on a numeric rating scale ranging from 0 (no pain) to 10 (unbearable pain); ii) dysphagia was assessed using a validated score ranging from 0 to 4; and iii) use of pain medication in the last 24 hours was recorded. The BE surface regression was defined as the percentage of initial BE that had been converted 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. BE surface regression was blindly scored by 2 independent BE expert endoscopists.

Study population issues: All the CRYO treatments were done in the context of a feasibility study registered at clinicaltrials.gov with number NCT02249975. There was no statistically significant difference between the CRYO group and the RFA group in relation to BE length, worst histology diagnosis and previous treatments at baseline.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **46 (20 CRYO versus 26 RFA)**.

Post treatment at 3 months

Characteristics	CRYO group (n=20)	RFA group (n=26)	P value
Median BE surface regression*, % (IQR)	88 (63 to 94)	90* (77 to 94)	0.62
Median number of images per patients, median (IQR)	9 (7 to 11)	9 (8 to 10)	0.91

*BE surface regression was assessed for 24 patients in RFA group. Two patients with poor image quality that hampered adequate assessment of the BE surface regression were excluded for the analysis for post-treatment characteristics.

In the CRYO patients, **neosquamous epithelium was confirmed histologically in all 87 biopsy samples**, and no subsquamous BE glands were found.

In 17 patients with residual BE, 43 additional biopsy samples were taken with pathology assessment showing squamous epithelium in 16% (7/43), nondysplastic BE in 65% (28/43), and BE with LGD in 19% (8/43).

Safety

Pain and use of pain medication

Characteristics	CRYO group (n=20)	RFA group (n=26)	P value
Median cumulative pain[a] (IQR)	4 (0 to 16)	22 (14 to 44)	<0.01
Mean duration of pain[c]±SD, days	5.7±1.1	11.1±1.0	<0.01
Mean duration of major pain±SD, days	3.5±0.9	6.5±1.0	=0.04
Median peak pain score (IQR)	2 (0 to 4)	4 (3 to 7)	<0.01
Median peak pain duration, days	2 (1 to 2)	1 (1 to 4)	=0.95
Mean duration of using pain medication±SD, days	2.6±0.7	6.3±1.0	<0.01
Paracetamol, % (n)	10% (2)	58% (15)	=0.09
Nonsteroidal anti-inflammatory drugs, % (n)	15% (3)	12% (3)	
Stenosis, % (n)	0 (0)	8 (2)	0.21

[a]Cumulative pain was a composite score based on the 2 pain-related questions in the electronic diary over the 14 days.

[b]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.

[c]The duration of pain was defined as the number of days until daily pain scores were reported to be 0 on all following days.

[d]The duration of major pain as time until daily pain scores were 3 or less.

Dysphagia was statistically significantly lower after CRYO compared with RAF (p<0.01).

Multivariable linear regression analysis adjusting for age, gender, BE length, and prior treatment showed that **CRYO was associated with statistically significantly less cumulative pain compared with RFA** (decrease of 18.1 in AUC; p<0.01).

Abbreviations used: ACU, area under the pain curve; CRYO, balloon-based focal cryoablation; HGD, high-grade dysplasia; LGD, low-grade dysplasia; mEAC, mucosal oesophageal adenocarcinoma; RFA, radiofrequency ablation.

Study 2 Canto M I (2018a)

Details

Study type	**Case series**
Country	US (2 centres)
Recruitment period	2015 to 2016
Study population and number	**n=41 (13 low-grade dysplasia [LGD], 23 high-grade dysplasia [HGD], and 5 intramucosal adenocarcinoma [ImCA]) patients** with BE.
Age and sex	Mean 65.7 years; 85% (34/41) male
Patient selection criteria	Inclusion criteria: Patients had >1 cm BE with LGD, HGD, or ImCA, in biopsy samples within 6 months of study entry. Those with ImCA or nodular dysplastic BE were eligible after endoscopic mucosal resection (EMR) done at least 8 weeks before treatment with at least 1 cm of residual BE. Patients with LGD were included if they had at least 2 endoscopies with a diagnosis of LGD or LGD in 1 endoscopy confirmed by 2 separate pathology readings, with at least 1 from an expert GI pathologist. Previous RFA, cryotherapy, argon plasma coagulation (APC), or photodynamic therapy was allowed. Exclusion criteria: Patients with an oesophageal mass, advanced or metastatic cancer, previous oesophageal resection, active grade B oesophagitis or greater, symptomatic untreated oesophageal stricture or luminal stenosis not allowing passage of a therapeutic endoscope, oesophageal varices, eosinophilic oesophagitis, and uncontrolled coagulopathy were excluded.
Technique	Patients were treated with CbFAS (C2 Therapeutics, INC, Redwood City, Calif) at a dose of 10 seconds of spray per site. EMR was done for nodular lesions. Treatments were repeated every 10 to 12 weeks until complete eradication, with a maximum of 5 treatment sessions. After baseline treatment, a liquid diet was prescribed for 24 hours, soft diet afterward, advancing as tolerated. Patients took twice-a-day proton pump inhibitors (equivalent of omeprazole 40 mg twice daily), histamine receptor antagonist (such as famotidine 40 mg) at bedtime, and sucralfate 91 g 3 times a day) for the duration of their treatment.
Follow-up	**Median 20.9 months**
Conflict of interest/source of funding	Four authors disclosed financial relationships relevant to this publication: i) the first author: Royalty from UpToDate; research grant recipient from C2 Therapeutics and Cosmo Pharmaceuticals; speaker for Cook Medical. ii) Author 2: Consultant for Boston Scientific, Cook Medical, and Shire; research grant recipient from CDx Medical, C2 Therapeutics, and CSA Medical. iii) Author 6: Consultant for C2 Therapeutics, Boston Scientific, and CDx Diagnostics. iv) Author 4: Research grant salary support from C2 Therapeutics. All other authors disclosed no financial relationships relevant to this publication. Research support for this study was provided by an unrestricted research grant from C2 Therapeutics, Inc.

Analysis

Follow-up issues: Patients were followed up at days 1, 7 and 30 after each treatment, at the next scheduled follow-up upper endoscopy visit, and then every 3 months for 1 year. Forty-one patients were enrolled in the study, 2 were lost to follow-up: 1 exited the study because of intervening oesophagectomy and the other from an unrelated death.

Study design issues: Prospective clinical trial. Intention-to-treat analysis was used for CE-D and CE-IM at 1 year. Dysphagia was graded on a 5-point scale ranging from 0 (no dysphagia) to 4 (inability to swallow anything). Pain was assessed using a Likert scale from 0 to 10. There was no information about operator(s), e.g. training and experiences of the procedure.

Study population issues: Of the 41 patients, 32% (13/41) had LGD, 56% (23/41) had HGD, and 12% (5/41) had ImCA. In terms of BE length, 85% had BE <8 cm and 15% had ultra-long BE ≥8 cm. The proportion of patients who had prior EMR was 34% (14/41). Of the 41 patients, 54% (22/41) were in the treatment-naïve group and 46% (19/41) in the previously ablated group. In terms of pre-existing asymptomatic oesophageal stricture because of prior ablation, EMR, and/or GERD, there was a statistically significant difference between the treatment-naïve group (n=1) and the previously ablated group (n=8, p=0.006).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **41**

Cryoablation procedures: n=117

- **Technical success rate: 98%** (115/117)

Cryoablation treatment

Characteristics	BE <3 cm (n=21)	BE 3 cm <6 cm (n=12)	BE ≥6 cm (n=8)	All (n=41)
Median number of ablation procedures (IQR)	2 (2 to 2)	3 (3 to 4)	4 (2 to 5)	3 (2 to 4)
Median number of ablation sites at baseline treatment procedure (IQR)	7 (5 to 9)	10 (7 to 16)	17.5 (16 to 20)	9 (6 to 16)
Median ablation time of baseline treatment procedure (IQR)	18.0 (13 to 21)	16.5 (12 to 21)	23.5 (17.5 to 33.5)	17 (13 to 23)
Mean procedure time of baseline treatment procedure (IQR)	30.0 (27 to 34)	30.0 (20 to 38)	33.5 (22 to 38)	30 (24 to 35)

Complete eradication at 1 year after the treatment – stratified by BE length

Characteristics	BE Length <8 cm (n=35)	BE Length ≥8 cm (n=6)	All (n=41)	P value
CE-CA (n=5), %	100	0	80	0.20
CE-HGD (n=23), %	100	0	95	**0.04**
CE-LGD (n=13), %	100	100	100	1.0
CE-D (n=41), %	95	67	95	**0.02**
CE-IM (n=41), %	89	83	88	0.57

Complete eradication at 1 year after the treatment – comparison by treatment group

Characteristics	Treatment-naïve (n=21)	Previously ablated (n=19)	All (n=41)
CE-CA (n=5), %	75	100	80
CE-HGD (n=23), %	100	92	95
CE-LGD (n=13), %	100	100	100
CE-D (n=41), %	95	95	95
CE-IM (n=41), %	86	89	88

All P values were not significant.

Treatment failure: n=2 patients with ultra-long BE who had persistent neoplasia.

Persistent oesophageal IM: n=3

Safety

Incomplete procedures: 2% (2 incomplete treatments [2 patients] related to balloon migration from a pre-existing stricture).

Adverse event rate: 24% (10/41)

Adverse events	Patients, % (n)
Upper gastrointestinal bleed at day 7[a]	2.4 (1)
Pain requiring a narcotic analgesic after discharge	4.9 (2)
Stricture[b]	9.8 (4)
Candida oesophagitis after stricture dilation and steroid injection	4.9 (2)
Balloon tip mucosal trauma	2.4 (1)

[a]From a post ablation gastroesophageal junction ulcer associated with aspirin use that did not require endoscopic therapy.

[b]Needing a median of 1 dilation (range 1 to 3) for resolution of dysphagia. The presence of pain at day 7 was statistically significantly associated with the development of a post-cryoablation stricture (3/4, p<0.0001).

Pain scores and narcotic analgesic use

Characteristics	BE Length <8 cm (n=35)	BE Length ≥8 cm (n=6)	All (n=41)
Median pain scores (IQR)			
Immediately post procedure	0 (0 to 2)	3.5 (2 to 8)[c]	1 (0 to 3)
Day 1	0 (0 to 1)	1 (0 to 4)	0 (0 to 2)
Day 7	0 (0 to 0)	0 (0 to 1)	0 (0 to 0)
Day 30	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Pain requiring narcotic analgesia, % (n)			
Post procedure	20 (7)	67 (4)[d]	27 (11)
Day 1	0	33 (2)	4.9 (2)
Day 7	0	0	0
Day 30	0	0	0

[c]p=0.04, Wilcoxon rank sum test, all other comparisons not statistically significant.

[d]p=0.035, Fisher exact test, all other comparisons not statistically significant.

Abbreviations used: BE, Barrett's oesophagus; CA, intramucosal cancer; CE, complete eradication; D, dysplasia; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; IM, intestinal metaplasia; IQR, interquartile range; LGD, low-grade dysplasia.

Study 3 Künzil H T (2017)

Details

Study type	**Case series**
Country	Netherlands (2 centres)
Recruitment period	2015 to 2016
Study population and number	**n=30 (14 LGD, 7 HGD, and 9 early adenocarcinoma) patients** with 47 BE islands.
Age and sex	Median 66 years; 87% (26/30) male Median BMI 28 kg/m^2 (range 21 to 25)
Patient selection criteria	Inclusion criteria: All the patients with dysplastic BE or residual BE after removal of early adenocarcinoma who were scheduled for focal RFA treatment were reviewed. Previous treatment with circumferential RFA was allowed. Patients aged 18 to 80 years with the presence of one or more flat BE islands of approximately 1 cm^2. Patients gave written informed consent. Exclusion criteria: Patients presented a visible lesion requiring endoscopic resection, severe oesophageal stenosis, and active oesophageal inflammation.
Technique	Cryoablation was done using CbFAS (C2 Therapeutics, Inc, Redwood City, Calfi) with 10-second applications and the second-generation controller was used, including a radial positioning feature that enables the location of the diffuser to be adjusted by tilting the controller in a clockwise or counter-clockwise direction. All the patients had upper endoscopy under sedation with midazolam and alfentanil, or propofol. For each patient, up to 2 BE islands of approximately 1 cm^2 were ablated with no additional treatment for the remaining BE segment after cryoablation. All the patients received high-dose proton pump inhibitors after treatment (40 mg twice day).
Follow-up	**Median 56 days**
Conflict of interest/source of funding	This study was supported by C2 Therapeutics (Redwood City, California, USA). One author has received research support for IRB approved studies from Olympus Endoscopy, Fujifilm, Boston Scientific, GI Solutions Medtronic, Erbe, Ninepoint Medical, C2 Therapeutics, Cernostics, Interpace and Lumen-R. He also received financial support for training programs from Boston Scientific and GI Solutions Medtronic, Olympus Endoscopy, Fujifilm and WATTS-3D. Another author has received research support for IRB approved studies from Covidien GI Solutions, Erbe Medical, C2 Therapeutics. He is also a consultant for Boston Scientific and C2 Therapeutics.

Analysis

Follow-up issues: Patients were followed up immediately after the procedure, at 2 days and after a median of 56 days. Of the 30 patients with 47 BE areas, 1 patient with 2 BE areas treated was lost to follow-up.

Study design issues: Prospective trial. Pain was assessed using a visual analogue scale, where 0 indicated 'no pain at all' and 10 represented 'unbearable pain'. There was no information about operator(s), such as training and experience of the procedure.

Study population issues: Patients had a median BE duration of 4 years (IQR 3 years to 7 years). Using the Prague classification, the median BE length was 0 (IQR 0 to 0). Of the 30 patients, 47% (14/30) had low grade dysplasia, 23% (7/30) had high grade dysplasia and 30% (9/30) had early adenocarcinoma. Of these patients, 50% (15/30) had endoscopic mucosal resection prior to cryoablation. Of the 47 BE areas eligible for cryoablation treatment, 1 island could not be ablated because of difficulty positioning the balloon.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **30**

Cryoablation treatment (n=46)

Characteristic	By ablated BE island**
Ablated completely, % (n)	96 (44)
Ablated incompletely, % (n)	4 (2)
Median endoscopy duration, minutes (IQR)	13 (11 to 16)
Median procedure duration, minutes (IQR)	4 (3 to 6)

**Of the 47 eligible BE areas cryoablation, 1 could not be ablated because of difficulty positioning the balloon.

Complete eradication of dysplasia and IM (n=44)

Complete eradication	By BE island**
Complete eradication of dysplasia and IM, % (n)	95 (42)
complete eradication of dysplasia but not IM, % (n)	2 (1)
Incomplete eradication of dysplasia and IM, % (n)	2 (1)

Safety

Device malfunction: 5/30 (17%) procedures, including a motor rotation problem (n=1), start button dysfunction (n=1), trigger dysfunction (n=1), erroneous deflation of the balloon (n=1), erroneous disconnection of the catheter from the handle (n=1), and premature ending of 10-second ablation at 9 seconds (n=1). Four procedures were completed using the same device and 1 used another device to complete the ablation.

Pain immediately after the procedure and at day 2

Pain	Directly after cryoablation	2 days after cryoablation
Median pain score in all patients (IQR)	0 (0-1)	0 (0-0)
Patients reporting pain, % (n)	27 (8)[a]	10 (3)

[a]No analgesics were needed.

Adverse events related to cryoablation

Adverse events	Occurrence	Intervention
Bradycardia	During cryoablation	Intravenous atropine
Chest discomfort	Directly after cryoablation	Echocardiogram (no abnormalities)

Abbreviations used: BE, Barrett's oesophagus; IM, intestinal metaplasia; IQR, interquartile range.

Study 4 Schölvinck D W (2015)

Details

Study type	**Case series**
Country	USA (5 centres) and Netherlands (3 centres)
Recruitment period	2012 to 2014
Study population and number	**n=39 patients** with flat Barrett's epithelium; 62 cryoablations.
Age and sex	Median 66 years; 90% (35/39) male
Patient selection criteria	Inclusion criteria: Patients were included if they had known Barrett's epithelium; had been scheduled for surveillance, endoscopic resection or ablative therapy; had a Prague classification score of at least C ≥2 and/or M ≥3, and/or a Barrett's epithelium island ≥1 cm^2; had a flat treatment area (according to the Paris classification); and aged 18 to 80 years. All patients gave written informed consent. Exclusion criteria: Patients were excluded in case of: the presence of active inflammation; visible nodules within 4 cm of the treatment area at endoscopy; a stenosis within 4 cm of the treatment area that would prevent advancement of the endoscope; and prior treatment with any energy-based ablation system.
Technique	Cryoablation was done using CbFAS (C2 Therapeutics, INC, Redwood City, Calif). A single application of a 6, 8 or 10 seconds of focal cryoablation was given and in each patient 1 or 2 focal areas were treated. To prevent any active inflammation, acid suppression using double-dose proton pump inhibitors was administered to each patient at enrolment. All patients received conscious sedation by the administration of midazolam or monitored anaesthesia care using propofol. At discharge additional medication was administered at the discretion of the endoscopist.
Follow-up	**Median 54 days**
Conflict of interest/source of funding	This study was supported by C2Therapeutics, Inc. (Redwood City, California, USA).

Analysis

Follow-up issues: Forty-two patients were enrolled in the study, 3 did not have cryoablation because of withdrawal of informed consent (n=1), food remnants in the stomach during endoscopy (n=1), and the presence of a visible lesion in the intended treatment area (n=1). Patients were followed up immediately after the procedure, at 2 days and after a median of 54 days (range 6 to 8 weeks).

Study design issues: Multicentre, prospective non-randomised trial. The primary aim of this study was to assess the safety, feasibility, and dose response of the CbFAS in patients with flat BE. A step-up approach for cryoablation dosing was followed. The first 8 patients were treated with a 6-second focal cryoablation. After approval by the DMC, the duration of cryoablation was increased to 8 seconds in the next 21 patients and the last 10 patients were treated with a 10-second cryoablation. Pain and swallowing difficulty were scored on a 10-point scale from none (0) to severe (10). Stenoses were graded as none; mild (visible stenosis upon endoscopy, but asymptomatic); moderate (clinical symptoms of dysphagia combined with visible stenosis upon endoscopy); severe (any stenosis impairing passage of the endoscope). Neo-squamous epithelium conversion: 'no conversion' if <20% of the total ablated area appeared to have been converted; 'partly converted' if >20% and <80%; and 'full conversion' if >80%. The procedure was done by multiple endoscopists from different tertiary care centres, but information about their training and experiences of the procedure were absent. A gastrointestinal pathologist, blinded for the duration of ablation and location within the oesophagus, recorded a detailed description of the presence of any squamous epithelium and/or any residual Barrett's epithelium in every specimen.

Study population issues: Of the 39 patients, 23% (9/39) had LGD, 23% (9/39) had HGD, 28% (11/39) had early adenocarcinoma, 3% (1/39) had indefinite for dysplasia, and 23% (9/39) did not have dysplasia. Of these patients, 90% (35/39) reported the use of proton pump inhibitors prior to enrolment and 31% (12/39) had pre-cryoablation EMR. The median circumferential extent was 2 cm (IQR 2 to 4 cm) and the median maximum extent was 5 cm (IQR 3 to 7 cm).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **39** patients with 62 ablations.

Successful ablations: 95% (37/39) of patients with 90% (56/62) of successful ablations.

Cryoablation treatment (n=37)

Characteristics	1 ablation area	2 ablation areas
Patients, % (n)	49 (18)	51 (19)
Median treatment duration from introduction to retraction of CbFAS, minutes (IQR)	4 (2 to 7)	8 (4 to 13)
Median treatment duration, minutes (IQR)	7 (4 to 10)	

Duration of ablation for the 56 cryoablations successfully performed:

- 6 seconds: 18% (10)
- 8 seconds: 50% (28)
- 10 seconds: 32% (18)

Effect of cryoablation at follow-up endoscopy after 6 to 8 weeks, n=56

Areas with evidence of conversion*	Length of ablation			P value**
	6 seconds (n=10)	8 seconds (n=28)	10 seconds (n=18)	
No conversion <20%, % (n)	30 (3)	7 (2)	0	
Partly converted >20% to 80%, % (n)	10 (1)	11 (3)	0	0.04
Full conversion >80%, % (n)	60 (6)	82 (23)	100 (18)	

*Assessment based on the impression of the endoscopist at the time of endoscopy and a secondary check of the endoscopic images.

**Chi-squared test for trend analysis.

Safety

Device and procedural done caused ablation failure (n=6)

Characteristics	n
The balloon did not properly make contact with the oesophageal wall	1
The device gave an 'error' signal when trying to inflate the balloon	2
Slippage of balloon into hiatal hernia	1
Narrowing of the oesophagus	1
Ablation accidentally performed in squamous mucosa	1

A minor longitudinal oesophageal mucosal laceration occurred in 15% of patients (n=6) when deflating the balloon. All the durations of these procedures were affected (6 seconds [n=2], 8 seconds [n=2], and 10 seconds [n=2]), but no additional treatment was needed.

Pain and swallowing difficulty (n=37)

Characteristics	Immediately after the procedure	A median 2-day follow-up
Pain, % (n)	27 (10)[a]	14 (5)[b]
Median pain score, (IQR)	2.5 (2 to 3)	4 (3 to 6)
Swallowing difficulty, % (n)		14 (5)
Median swallowing difficulty, (IQR)		4 (2 to 5)

[a]None of these patients required any additional pain medication.

[b]Three patients used additional pain medication on the days following the cryoablation procedure.

Abbreviations used: EMR, endoscopic mucosal resection; IQR, interquartile range.

Study 5 Joana C (2018)

Details

Study type	**Single case report (abstract)**
Country	Not reported
Recruitment period	Not reported
Study population and number	n=1 patient with BE and developed multifocal low-grade dysplasia without visible lesions
Age and sex	53; male
Patient selection criteria	The patient had multifocal low-grade dysplasia without visible lesions
Technique	The BE was treated with CbFAS (C2 Therapeutics, Redwood City, California, USA). The device was recently adapted to include a foot pedal control, allowing the endoscopist to self-control the axial and radial position of the diffuser head and the application of nitrous oxide. The addition of axial control avoids the needs to reposition the balloon. the treatment lasted for 15 minutes until complete cryoablation of BE had been achieved.
Follow-up	**3 months**
Conflict of interest/source of funding	One author has received consultancy fees from C2 Therapeutics.

Key efficacy and safety findings

Safety
Number of patients analysed: **1** At 2-week follow-up: • **Severe thoracic pain and heartburn** • **Grade D esophagitis** Symptoms resolved after optimisation of anti-acid therapy At 3-month follow-up, **mild inflammation of the Z-line** happened.

Table 2b Summary of key efficacy and safety findings on balloon cryoablation for squamous dysplasia of the oesophagus

Study 6 Ke Y (2019)

Details

Study type	**Case series**
Country	China (single centre)
Recruitment period	2016 to 2018
Study population and number	**n=80 (59 moderate-grade intraepithelial neoplasia [MGIN] versus 21 high-grade intraepithelial neoplasia [HGIN]) patients** with a flat USL.
Age and sex	Mean 59 years; 48% (38/80) male
Patient selection criteria	Inclusion criteria: Patients were eligible for the study if they were aged 18 to 85 years; had a baseline qualifying high-resolution Lugol's chromoendoscopy within 3 months before primary ablation, were showing a single flat (Paris type 0-IIb) USL ≤6 cm in length and ≤50% (≤180 degrees) of the oesophageal circumference; had a histologic diagnosis of MGIN or HGIN on biopsy specimens. Exclusion criteria: Patients were excluded from the study if they had a pink-colour sign after Lugol's staining; non-flat visible abnormalities, synchronous USLs containing MGIN or worse, oesophageal stenosis preventing passage of the endoscope, previous endoscopic resection or ablation, or a history of oesophageal cancer.
Technique	Cryoablation was done using cryoballoon focal ablation system (CbFAS, C2 Therapeutics, INC, Redwood City, Calif) side-by-side applications of 10 seconds. Treatment was repeated at 3-month interval until a complete response was established, with 12 months being the primary trial endpoint and a maximum of 3 treatments per patient. All patients had a median of 5 side-by-side applications (IQR 4 to 7) over a median of 8 minutes (IQR 5 minutes to 10 minutes). Double-dose proton pump inhibitors (equivalent to esomeprazole 40mg twice daily) were prescribed for 1 month after treatment to optimise mucosal healing.
Follow-up	**12 months**
Conflict of interest/source of funding	All authors disclosed no financial relationships relevant to this publication. Research support for this study was provided by C2 Therapeutics, INC, and the National Key R&D Programme of China and CAMS Innovation Fund for Medical Sciences.

Analysis

Follow-up issues: Patients were followed up at 2 days, 7 days and 30 days and then 3 months, 6 months and 12 months. 80 patients were enrolled and 79 received a first treatment. One developed mucosal laceration after inflation of the CbFAS balloon, was not treated and withdrew consent, and another withdrew consent after baseline CbFAS because of moving to another city. Therefore, 78 patients completed the 12-month study.

Study design issues: Prospective trial. There was no information about operator(s) but the procedures were done in an expert centre for ESCN. Postprocedural retrosternal pain was assessed using an 11-point visual analogue scale for pain. Dysphagia was assessed using a validated 5-item scale, ranging from 0 (no problem swallowing for solids or liquids) to 4 (total inability to swallow). Both intention-to-treat analysis and per-protocol analysis were used when analysing the complete remission of neoplasia rate at 12 months, and the remaining outcomes used per-protocol analysis. It was planned to assess the association using logistic regression, but the small number of treatment failures hampered this analysis.

Study population issues: Of the 80 patients with a flat-type USL, 74% (59/80) had MGIN and 26% (21/80) HGIN. The median USL length was 3 cm (IQR 2 cm to 3 cm), with a median circumferential extent of 60 degrees (IQR 30 degrees to 90 degrees). The median length of treatment areas was 4 cm (IQR 3 cm to 5 cm) with a median total circumferential extent of 120 degrees (IQR 60 degrees to 150 degrees).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **80 (59 MGIN versus 21 HGIN)**

CbFAS treatment

Characteristics	Value
Initial cryoablation	
Technically successful ablation, % (n/N)	100 (79/79)
Median total applications** per patient, n (IQR)	5 (4 to 8)
Median endoscopy time, min (IQR)	24 (19 to 32)
Median ablation time, min (IQR)	8 (5 to 10)
Follow-up cryoablation	
Patients receiving follow-up cryoablation, % (n/N)	10% (8/10)
Total follow-up procedures, n	8
Total cryoablation procedures, n	87
Median cryoablation procedures per patient, n (IQR)	1 (1 to 1)

*Complete applications were defined as applications with a duration>6 seconds.

Complete remission of neoplasia rates

Complete histologic response	% (n/N)	95% CI
3 months	90 (70/78)	
Normal squamous mucosa	82 (64/78)	
LGIN	8 (6/78)	
6 months	89 (7/8)	
Normal squamous mucosa	75 (6/8)	
LGIN	13 (1/8)	
12 months		
Intention to treat analysis	95 (76/80)	88 to 98
Per-protocol analysis	97 (76/78)	91 to 99
Normal squamous mucosa	82 (64/78)	72 to 89
LGIN	15 (12/78)	9 to 25
MGIN	3 (2/78)	1 to 9
HGIN	0 (0/78)	0 to 4

Recurrent USL at 12 months: MGIN in the biopsy sample **n=2**

The first treatment failure had a baseline USL (3 cm in length and 30 degrees of the circumference) containing MGIN and was treated with 4 side-by-side ablations of 10 seconds duration. And second treatment failure had a USL (2 cm, 180 degrees) containing MGIN at baseline and was treated with 8 side-by-side ablations.

Safety

Device performance prematurely ended ablation

Device issues	% (number of patients) n=79	% (number of procedures) n=87
Diffuser rotation problems[a]	13% (10)	11% (10)
False high-pressure notifications[b]	39% (31)	36% (31)

[a]All procedures were successfully completed with another device component.

[b]All these procedures were completed with the same device.

Pain and dysphagia

Tolerability	Day 2	Day 7	Day 30
Median pain score (IQR)[c]	1 (0 to 2)	0 (0 to 0)	0 (0 to 0)
Median dysphagia scores (IQR)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)

[c]One patient reported the use of pain medication at 2 days after treatment, with no need for further pain medication at days 7 and 30.

Adverse events

Adverse events	% (number of events) n=80
Superficial mucosal lacerations on balloon inflation[d]	5% (4)
Short-duration idiopathic fever[e]	16% (13)
Minimal pleural effusion	10% (8)

[d]No intervention was required.

[e]A mean (±SD) temperature of 38.5 degrees ± 0.3 degrees (range 38.5 degrees to 39.2 degrees). All were treated symptomatically with indomethacin, and the temperature normalised within a maximum of 5 days.

Abbreviations used: CbFAS, cryoballoon focal ablation system; CI, confidence interval; CR, complete remission of neoplasia; HGIN, high-grade intraepithelial neoplasia; LGIN: low-grade intraepithelial neoplasia; MGIN, moderate-grade intraepithelial neoplasia; TA, treatment area; USL, unstained lesion.

Study 7 Canto M I (2018b)

Details

Study type	**Case series**
Country	US (3 centres) and Netherlands (2 centres)
Recruitment period	2014 to 2016
Study population and number	**n=10 (2 LGIN, 7 HGIN, and 1 ESCC after EMR) patients** with 24 USLs.
Age and sex	Median 69.5 years; 40% (4/10) male
Patient selection criteria	Inclusion criteria: Patients had early ESCN; had at least 1 USL in the oesophagus after Lugol's chromoendoscopy with pathologically confirmed ESCN (LGIN, HGIN, or early T1 ESCC); and with or without previous endoscopic eradication therapy. Exclusion criteria: Patients had previous oesophageal resection, oesophageal varices, oesophageal stricture, and/or nodular mucosa; and had a visible oesophageal mass, evidence of advanced/metastatic disease, or contraindication to endoscopic eradication therapy.
Technique	Cryoablation was done using CbFAS (C2 Therapeutics, INC, Redwood City, Calif) and cyogen was automatically delivered according to a pre-set dose (8, 10 or 12 seconds). Patients were treated every 6 to 12 weeks until Lugol's chromoendoscopy and biopsy specimens demonstrated eradication of all USLs and biopsy specimens demonstrated absence of ESCN. All the patients had sedated upper endoscopy using intravenous propofol, with or without midazolam or alfentanil. After cryoablation, routine medications were continued, and diet was advanced as tolerated. Proton pump inhibitors or sucralfate (1 g 3 times a day, tablets or slurry) was prescribed according to each site's standard post ablation clinical protocol.
Follow-up	**Median 10.7 months**
Conflict of interest/source of funding	Two authors have received research grants from C2 Therapeutics; 1 author has consulted for C2 Therapeutics; and 1 has received research grants from C2 Therapeutics and consulted for C2 Therapeutics. All other authors disclosed no financial relationships relevant to this publication.

Analysis

Follow-up issues: Patients were followed up at day 1, day 7 (day 30) or at the next scheduled visit within 6 to 12 weeks, and then 3 months and a median time of 10.7 months (IQR 4 to 14 months). At a follow-up of 1 year, 7 patients had endoscopic and pathologic results, and the other 3 were followed up by their primary gastroenterologist, with a plan to return to the tertiary referral centre if needed.

Study design issues: Patients were either prospectively enrolled in ongoing clinical trials (n=7) or treated as part of standard care for refractory and/or recurrent disease (n=3). There was no information about operator(s), such as training and experience of the procedure.

Study population issues: Of the 10 patients, 22% (2/10) had LGIN, 70% (7/10) had HGIN, and 1 had ESCC. Of these patients, 40% (4/10) had no previous endoscopic therapy and 60% (6/10) had refractory ESCN not completely responding to previous EMR, RFA, argon plasma coagulation, and/or spray cryotherapy using liquid nitrogen or carbon dioxide gas. Of the 10 patients, 40% (4/10) had single, small USL, 20% (2/10) had multiple small USLs and 20% (2/10) had large or extensive multifocal USLs. The median maximum diameter of the largest USL was 1.5 cm (IQR 1 cm to 2 cm), and the median total length of all neoplastic USLs was 2 cm (range 1 cm to 10 cm).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **10** patients with 24 USLs which were treated by 15 procedures**.**

Cryoablation treatment

Characteristics	Value
Median number of USLs treated, (range)	2 (1 to 6)
Median ablations per procedure, (IQR)	4 (1 to 4)
Median procedure time, minutes (range)	34 (18 to 57)
Size and number of USL and number of procedures	
Small (≤2cm), single USL treated in 1 procedure*, n	4
Small (≤2cm), multiple USLs but <3 cm in the oesophagus treated in 1 procedure**, n	2
Large (≥3 cm) USLs or extensive multifocal USLs involving 4 to 10 cm of the oesophagus length treated in 1 to 5 procedures***, n	4

*With 2 to 4 cryoablations

**With 3 to 5 cryoablations

***With 1 to 11 cryoablations

Complete eradication after the treatment

Characteristics	Value
CE-ESCN after the first procedure, % (n)	80 (8)
CE-ESCN within 3 months, % (n)	100 (10)

No neoplastic progression at 1 year: n=7

Endoscopic and pathologic follow-up results at 1 year were available for 7 patients. The other 3 patients were followed up by their primary gastroenterologist, with a plan to return to the tertiary referral centre if needed.

Safety

Device malfunction: 1 rotation problem occurred, and the procedure was completed with another device.

Adverse events occurred

Adverse events	Value
Mild dysphagia for solids and symptomatic stricture[a], % (n)	20 (2)
Mild mucosal balloon trauma[b], % (n)	10 (1)
Mild self-limited postprocedure pain[c], % (n)	4 (4)

[a]Treated with 1 or 2 dilations.

[b]Not requiring treatment.

[c]Improved by discharge, after 1 or 2 doses of intravenous narcotic medications Of these 4 patients, 3 were asymptomatic by 48 hours, but 1 took a narcotic analgesic for chest pain and odynophagia for 2 day with pain quickly diminishing over 4 days.

Abbreviations used: CE-ESCN, complete endoscopic and pathological eradication of oesophageal squamous cell neoplasia; ESCC, oesophageal squamous cell carcinoma; HGIN, high-grade intraepithelial neoplasia; LGIN, low grade intraepithelial neoplasia; USL, Lugol's unstained lesion.

Validity and generalisability of the studies

Barrett's oesophagus

- Evidence came from 1 non-randomised comparative study, 3 case series and 1 case report[1-5]. Of these, studies 1 to 4 came from the Netherlands, the US or both countries and were done in multiple centres, whereas study 5 did not report the country.
- All the studies sought to assess the efficacy and safety of balloon-based cryoablation, but study 1 compared this procedure with focal radiofrequency ablation.
- There was probably an overlap of patients in studies 1, 2, and 4.
- The device from C2 Therapeutics, Inc, Redwood City, Calif was used in all the studies. Two generations of the device were reported with the second-generation being mentioned in study 3.
- Studies 1 to 3 applied side-by-side applications of 10 seconds and study 4 followed a step-up approach for cryoablation dosing from 6 seconds, 8 seconds to 10 seconds. Study 4 also reported full conversion of BE to neo-squamous epithelium was seen significantly more frequently with increasing durations of ablation.
- The procedure was done in specialist centres, but only study 1 reported that the procedure was done by endoscopists highly experienced in endoscopic treatment of BE.
- The longest follow-up was a median of 20.9 months (IQR 17.5 months to 24.6 months) in study 2.

Squamous dysplasia of the oesophagus

- Evidence came from 2 case series[6, 7]; one was done in China (single centre)[6] and the other in the Netherlands and US (multiple centres)[7].
- The device from C2 Therapeutics, Inc, Redwood City, Calif was used in both studies.

- Study 6 applied side-by-side applications of 10 seconds and study 7 used a pre-set dose (8, 10 or 12 seconds).
- The procedure was done in specialist centres, but the operator's training and experiences of the procedure, which affected the number of successful ablations and procedure times, were absent in both studies.
- The longest follow-up was 12 months in study 2.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Endoscopic radiofrequency ablation for squamous dysplasia of the oesophagus. NICE Interventional procedures guidance 497 (2014). Available from https://www.nice.org.uk/guidance/ipg497
- Endoscopic radiofrequency ablation for Barrett's oesophagus with low-grade dysplasia or no dysplasia. NICE Interventional procedures guidance 496 (2014). Available from https://www.nice.org.uk/guidance/ipg496
- Endoscopic submucosal dissection of oesophageal dysplasia and neoplasia. NICE interventional procedures guidance 355 (2010). Available from https://www.nice.org.uk/guidance/ipg355
- Photodynamic therapy for Barrett's oesophagus. NICE interventional procedures guidance 350 (2010). Available from https://www.nice.org.uk/guidance/ipg350
- Epithelial radiofrequency ablation for Barrett's oesophagus. NICE interventional procedures guidance 344 (2010). Available from https://www.nice.org.uk/guidance/ipg344

NICE guidelines

- Barrett's oesophagus: ablative therapy. NICE clinical guideline 106 (2010). Available from https://www.nice.org.uk/guidance/cg106

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. One Specialist Advisor Questionnaire for balloon cryoablation for Barrett's oesophagus and for squamous dysplasia of the oesophagus was submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing trials

- Multi-center Clinical Study to Evaluate the C2 CryoBalloon Focal Ablation System (ColdPlayIII). NCT02514525. Active. Case series. Estimated study completion date: May 2021. Estimated enrolment: 150 patients. US.
- Evaluation of Effect of CryoBalloon Focal Ablation System on Human Esophageal Epithelium (ColdPlay2). (NCT02534233). Active. Case series. Estimated study completion date: December 2019. Estimated enrolment: 60 patients. US.

- Multicenter European prospective study on the efficacy and safety of the Focal C2 CryoBalloon Ablation System in patients with Barrett's Esophagus-related neoplasia - EURO-COLDPLAY. Case series. Estimated enrolment: 107 patients. Estimated study completion date: December 2020. The Netherlands.

References

1. Van Munster SN, Overwater A, Haidry R et al. (2018) Focal cryoballoon versus radiofrequency ablation of dysplastic Barrett's oesophague: impact on treatment response and postprocedural pain. Gastrointestinal Endoscopy, 88(5), 795-803
2. Canto MI, Shaheen NJ, Almario JA et al. (2018a) Multifocal nitrous oxide cryoballoon ablation with or without EMR for treatment of neoplastic Barrett's oesophagus. Gastrointestinal Endoscopy, 88(3), 438-446.e2, DOI: 10.1016/j.gie.2018.03.024
3. Künzli HT, Schölvinck DW, Meijer SL et al. (2017) Efficacy of the cryoballoon focal ablation system for the eradication of dysplastic Barrett's oesophague islands. Endoscopy, 49, 169-175, DOI: 10.1055/s-0042-120117
4. Schölvinck DW, Künzli HT, Kestens C et al. (2015) Treatment of Barrett's oesophagus with a novel focal cryoablation device: a safety and feasibility study. Endoscopy, 47, 1106-1112, DOI: 10.1055/s-0034-1392417
5. Joana G, Demedts I and Bisschops R (2018) Treatment of low grade dysplasia in Barrett's oesophagus with a new-generation cryoballoon device [abstract]. Endoscopy, 50, E318-E319
6. Ke Y, van Munster SN, Xue L et al. (2019) Prospective study of endoscopic focal cryoballoon ablation for oesophageal squamous cell neoplasia in China. Gastrointestinal Endoscopy, 1-9, DOI: 10.1016/j.gie.2019.03.017
7. Canto MI, Abrams JA, Künzli HT et al. (2018b) Nitrous oxide cryotherapy for treatment of oesophageal squamous cell neoplasia: initial multicentre international experience with a novel portable cryoballoon ablation system (with video). Gastrointestinal Endoscopy, 87(2), 574-581

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	03/05/2019	Issue 5 of 12, May 2019
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane)	03/05/2019	Issue 5 of 12, May 2019
HTA database (CRD website)	03/05/2019	n/a
MEDLINE (Ovid)	03/05/2019	1946 to May 01, 2019
MEDLINE In-Process (Ovid)	03/05/2019	1946 to May 01, 2019
MEDLINE Epubs ahead of print (Ovid)	03/05/2019	May 02, 2019
EMBASE (Ovid)	03/05/2019	1974 to 2019 Week 17
BLIC (British Library)	03/05/2019	n/a

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Barrett Esophagus/
2	(barrett* adj3 (esophag* or oesophag* or epithelium or syndrome* or metaplas*)).tw.
3	((columnar or specialised or specialized or intestinalized or intestinalised or metaplas*) adj3 (epithelium or oesophag* or esophag* or mucosa)).tw.
4	(CELLO or CLO).tw.
5	exp Esophageal Neoplasms/
6	((oesophag* or esophag*) adj3 (dysplas* or lesion* or neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or angiosarcoma* or sarcoma* or teratoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump*)).tw.
7	(ESCN or ESCC).tw.
8	or/1-7

9	Cryosurgery/
10	Ablation Techniques/
11	Freezing/
12	((balloon* or focal or endoscop*) adj3 (cryoablat* or cryosurg* or cryotherap* or freez* or ablat*)).tw.
13	(cryoballoon* or cyro-balloon*).tw.
14	coldplay*.tw.
15	or/9-14
16	8 and 15
17	animals/ not humans/
18	16 not 17
19	limit 18 to english language

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2a and 2b). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Visrodia K, Zakko L, Singh S et al. (2018) Cryotherapy for persistent Barrett's oesophague after radiofrequency ablation: a systematic review and meta-analysis. Journal of Gastrointestinal Endoscopy 87(6), 1396-1404	Systematic review and meta-analysis n=11 studies; 148 patients with BE treated with cryotherapy for persistent dysplasia or IM after RFA 2 studies on balloon cryotherapy; n=16 patients.	Cryotherapy successfully achieved CE-D in 3 quarters and CE-IM in half of patients with BE who did not response to initial RFA and adverse effects were reported in 6.7% of patients.	There are only 2 studies on balloon cryotherapy included and they are both abstracts.
John GK, Almario JAN, Skshintala VS et al (2017) Cryoballoon ablation for Barrett's oesophagus: A prospective single operator learning curve and time-efficiency study. Journal of Gastrointestinal Endoscopy 85(5S), AB566	Case series n=74 BE patients with 174 consecutive cryoablation procedures.	Device malfunction and balloon migration were associated with prolonged ablation time per site. The threshold number of procedures to overcome the **learning curve was 18**. After this threshold number was reached, the median ablation time per site reduced.	This is an abstract but contains complications associated with learning curve.
Louie BE, Hofstetter W, Triadafilopoulos G et al (2018) Evaluation of a novel cryoballoon swipe ablation system in bench, porcine, and human oesophagus models. Journal of Diseases of the Esophagus 31, 1-7	Case series n=6 patients (17% (1/6) female; and mean 68 years) treated with the cryoballoon swipe ablation system (CbSAS)	Six patients tolerated the procedure without adverse events. CbSAS was simple to operate, and balloon contact with tissue was easily and uniformly maintained. The maximal effect on the mucosa is achieved with a 0.8 mm/second dose. The CbSAS device enables uniform 3 cm long, quarter-circumferential mucosal ablation in a one-step process by using a novel, through-the-scope balloon.	This is a pilot study with a small sample.
Schölvinck DW, Friedland S, Triadafilopoulos G et al (2017) Balloon-based oesophageal cryoablation with a novel focal ablation device: dose-finding and safety in porcine and human models. Diseases	Case series n=4 patients with an area ≥2 cm of squamous epithelium or BE treated with CbFAS.	Direct postablation mucosal necrosis was observed; after 4 days necrosis and inflammation were limited to the submucosa. CbFAS cryoablation penetrates deeply into the oesophageal wall layers resulting in severe early ablation.	This study includes a small sample.

of the Esophagus 30, 1-8, DOI: 10.1093/dote/dox019			
Barrett M and Prat F (2018) Diagnosis and treatment of superficial oesophageal cancer. Annals of Gastroenterology, 31(3), 256-265, DOI: 10.20524/aog.2018.0252	Review	Balloon-based cryoablation of early squamous neoplasia has a high efficacy at 1 year and a good safety profile. This procedure has also been reported as an effective modality for ablating residual Barrett's islands after endoscopic resection.	The main cited papers for cryoballoon are all included in table 2.
Lal P and Thota PN (2018) Cryotherapy in the management of premalignant and malignant conditions of the oesophagus. World Journal of Gastroenyterology, 24(43), 4862-4869, DOI: 10.3748/wjg.v24.i43.4862	Review	Cryoballoon focal ablation using liquid nitrogen has been shown as an effective and a safe method for the treatment of BE with dysplasia and squamous cell carcinoma. Most common side effects include pain and oesophageal strictures.	The main cited papers for cryoballoon are all included in table 2.
Overwater A and Weusten BLAM (2017) Cryoablation in the management of Barrett's oesophagus. Current opinion in gastroenterology, 33(4), 261-269	Review	Cryotherapy using CbFAS is safe and well tolerated. The most common complaint is chest pain or discomfort. When compared with RFA, patients treated with CbFAS reported less pain.	The main cited papers for cryoballoon are all included in table 2.
Parsi MA, Trindade AJ, Bhutani MS et al. (2017) Cryotherapy in gastrointestinal endoscopy. American Society for Gastrointestinal Endoscopy, 2(5), 89-95, DOI: 10.1016/j.vgie.2017.01.021	Review	Cryotherapy using nitrous oxide-inflated balloon has shown effective in conversing BE to neosquamous epithelium at a follow-up o f6 to 8 weeks, with minor pain being reported.	The main cited paper for cryoballoon is included in table 2.
Visrodia K, Zakko L and Wang KK (2018) Mucosal ablation in patients with Barrett's oesophagus: fry or freeze? Digestive Diseases and Sciences, 63, 2129-2135, DOI: 10.1007/s10620-018-5064-x	Review	Cryoballoon therapy has shown effective in inducing CE-IM for patients with (residual) BE islands.	The main cited papers for cryoballoon are all included in table 2.