Interventional procedure update overview of Balloon cryoablation for treating Barrett's oesophagus

Contents

Table 1. Abbreviations

Abbreviation	Definition
AE	Adverse event
APC	Argon plasma coagulation (APC)
BE	Barrett's oesophagus
BMI	Body mass index
CBA	Cryoballoon ablation
CED	Complete eradication of dysplasia
CEIM	Complete eradication of intestinal metaplasia
CRD	Complete remission of dysplasia
CRIM	Complete remission of internal metaplasia
EAC	Oesophageal adenocarcinoma
HGD	High grade dysplasia
IM	Internal metaplasia
ImCA	Intramucosal cancer/intramucosal adenocarcinoma
ITT	Intention-to-treat
LGD	Low grade dysplasia
NHS	National Health System
PP	Per protocol
VAS	Visual analogue scale
SAE	Serious adverse event

The condition, current treatments, unmet need and procedure

The condition

The oesophagus is a muscular tube, connecting the mouth and stomach. In Barrett's oesophagus (BE) the cells lining the lower part of the oesophagus change, becoming more like the cells lining the intestines (intestinal metaplasia). The changed cells can become abnormal (dysplasia) over time. There is a small

chance of the abnormal cells becoming cancer. Treatment may be offered to try and remove the affected tissue. This aims to lower the cancer risk.

Current practice

Current management may include lifestyle change, acid-suppressing medicines, endoscopic mucosal resection, endoscopic submucosal dissection, ablative therapies and surgery. Ablative therapies include radiofrequency ablation (RFA), photodynamic therapy, argon plasma coagulation, laser ablation, multipolar electrocoagulation and cryotherapy.

Those with BE whose cells are dysplastic should be offered treatment. However, treatment options depend on the grading of dysplasia. RFA is currently recommended as first-line treatment for BE with low-grade dysplasia (LGD). Endoscopic resection is recommended for high grade dysplasia (HGD) and oesophageal adenocarcinoma.

Unmet need

Current treatment options for BE may not always be feasible or suitable. RFA should be avoided in those with severe co-morbidities (such as cardiopulmonary disease) or those unable to discontinue anticoagulation therapy. It may also be unfeasible because of uneven BE surface, or oesophageal strictures (precluding passage of the RFA catheter). Endoscopic resection may be unsuitable for people with coagulation disorders, portal hypertension, and those unable to discontinue anticoagulation therapy. Endoscopic resection may also be difficult for longer BE segments, or in the absence of an endoscopically visible lesion.

Cryoballoon ablation (CBA) may cause less pain than other ablation techniques in some people. It may also be better tolerated or appropriate for some people with comorbidities.

The procedure

The aim of CBA is to destroy (or 'ablate') the abnormal cells lining the oesophagus. Sedation is usually used. A balloon catheter is inserted through an endoscope, aligned with the affected tissue and inflated. Nitrous oxide gas is sprayed through a radial diffuser head within the balloon aimed at the abnormal tissue. Cryogen is used to ablate (freeze) the unwanted tissue. The extreme cold destroys the tissue. The nitrous oxide gas remains fully contained within the balloon and exits outside the body through the proximal end of the catheter. The ablation sequence is repeated until all abnormal cells are destroyed. Multiple ablations can be done in one session without removing the balloon. Repeat endoscopy will be scheduled 8-12 weeks following the procedure to check if the unwanted tissue has been destroyed. If evidence of unwanted tissue is found, retreatment may be considered.

Outcome measures

Safety and efficacy outcomes are included. Further details are provided below.

Patient safety

Identified outcomes relevant to safety include:

- Pain/discomfort
    - Measured using either a 10-point Likert or visual analogue scale (VAS), with 0 indicating no pain and 10 indicating worst pain
- Adverse events (AE)
    - Bleeding
    - Oesophageal perforation
    - Oesophageal stricture
- Dysphagia
- Device malfunction

Efficacy

Identified outcomes relevant to BE include:

- Complete eradication or remission of dysplasia
- Complete eradication of internal metaplasia
- BE surface regression
    - Proportion of BE converted to squamous epithelium, measured by independent expert assessors comparing pre- and post-CBA images or videos
- Disease progression
    - Progression to more advanced dysplasia or ImCA
- Conversion to neo-squamous epithelium
- Technical success
    - Treatment of all visible BE as intended
- Treatment failure
    - Residual requiring further treatment (CBA or otherwise)

Prague classification

The Prague classification for BE is reported across some studies. This is a standardised system used during endoscopy to measure and describe the extent of BE. The classification includes both the maximal length (M) (including tongues) of BE, and the length of the circumferential Barrett segment (C).

Evidence summary

Population and studies description

This interventional procedures overview includes 4 prospective cohort studies, 4 retrospective analyses, and 1 systematic review and meta-analysis. The overview is based on 743 people from 8 observational studies. This Of the 743 people included, around 444 had the procedure. This figure accounts for a known

overlap of 22 people between studies. However, the figure of 743 does not account for the systematic review, as CBA was only included as a subgroup, with combined population estimates not provided. There is also a notable overlap of studies included in the systematic review and the studies included in this overview as key evidence.

This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1. This overview presents 9 studies as the key evidence in table 2 and table 3, and lists 19 other relevant studies in appendix B, table 5.

The key evidence included 3 single-centre studies (Canto, 2018; Alshelleh 2021; Dbouk, 2022) and 5 multi-centre studies (Schölvinck, 2015; van Munster, 2018; Canto, 2020; Agarwal, 2022; Frederiks, 2022). One did not include location details (Dbouk, 2022). All others included centres in the US (N=5) (Schölvinck, 2015; Canto, 2018; Canto, 2020; Alshelleh, 2021; Agarwal, 2022), or the Netherlands (N=3) (Schölvinck, 2015; van Munster, 2018; Frederiks, 2022). None included UK centres.

Follow-up ranged from 8 weeks (van Munster, 2018) to 4 years (Dbouk, 2022). Most had at least 1 year follow-up (Canto, 2018; Canto, 2020; Alshelleh, 2021; Agarwal, 2022; Dbouk, 2022).

Study populations varied. All required a confirmation of BE. All included LGD and HGD. People with ImCA were included in 5 studies (Schölvinck, 2015; Canto, 2018; Canto, 2020; Agarwal, 2022; Dbouk, 2022). Previous ablation was allowed in 2 studies (van Munster, 2018; Canto; 2018). The remaining 6 studies only included those who were treatment naïve (Schölvinck, 2015; Canto, 2020; Alshelleh, 2021; Agarwal, 2022; Dbouk, 2022; Frederiks, 2022). Mean age ranged from 65 years (Canto, 2020) to 68 years (Frederiks, 2022). Males were more commonly included across all studies. The proportion of males ranged from

82.6% (Alshelleh, 2021) to 93% (Frederiks, 2022). All studies included both LGD and HGD, but HGD was more common. Table 2 presents further study details.

Figure 1 Flow chart of study selection

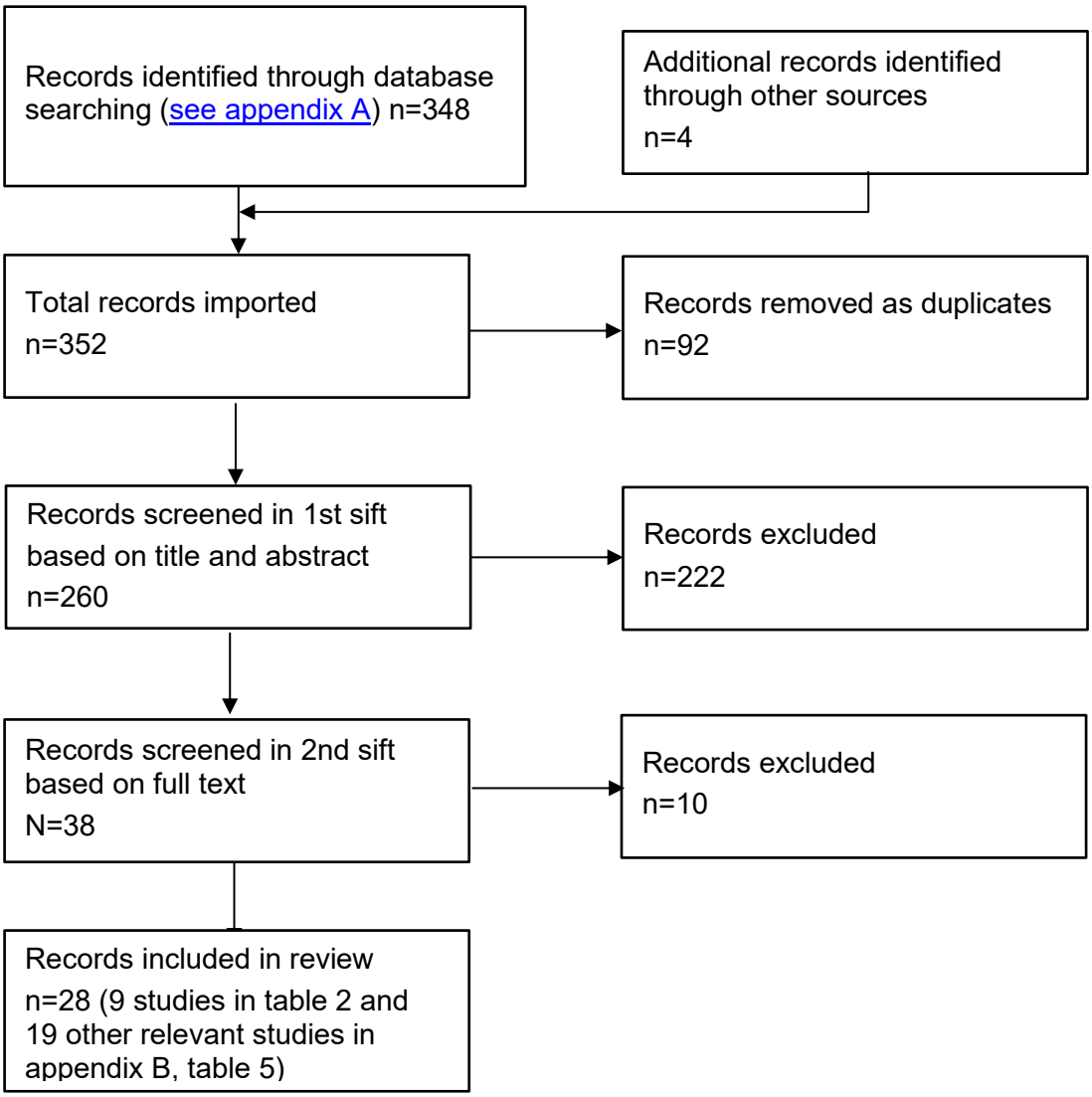

Table 2. Study details overview

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
1	Dbouk (2022) United States	N=59 (all CBA) Mean age: 66.8 (SD 9.6) Male gender: 54 (91.5%) Mean BMI: 29.5 (SD 5.2) LGD: 22 (37.3%) HGD: 33 (55.9%) ImCa: 4 (6.8%) Mean BE length: 5 cm (SD 4.7) <8 cm: 45 (76.3%) >8 cm: 14 (23.7%)	Prospective cohort	Treatment-naïve people with LGD, HGD, or intramucosal cancer (ImCA)	Cryoballoon ablation - cryoballoon focal ablation system, Pentax Medical, Montvale, New Jersey, United States, with touch up argon plasma coagulation (APC) for small residual columnar islands (< 5 mm)	Median 54.3 months (IQR 32.9 – 65)
2	Agarwal (2022) United States	N=311 (85 CBA versus 226 RFA) CBA: Mean age: 67.1 (SD 10.1) Male gender: 71 (83.5%) Mean BMI: 28.9 (SD 4.9) LGD: 32 (37.6%) HGD: 53 (62.4%) Prior resection: 51 (60.0%) RFA: Mean age: 65.6 (SD 10.0) Male gender: 177 (78.3%) Mean BMI: 30.8 (SD 5.9) LGD: 108 (47.8%) HGD: 118 (52.2%) Prior resection: 112 (49.6%)	Retrospective cohort	People with HGD or LGD (segments ≤6 cm), or ImCA using CBA or RFA as their primary ablation modality	Cryoballoon ablation - C2 focal cryoballoon, Pentax Medical Corporation, Montvale, NJ, USA versus radiofrequency ablation - Medtronic, Minneapolis, Minn, USA	Median 2 years (IQR 1.3-2.5) CBA; 1.5 years (IQR 0.8-2.5 RFA)

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
3	Frederiks (2022) Netherlands	N=56 (all CBA: 28 10-second duration versus 28 8-second duration) 10-second cohort (N=28): Mean age: 68 (SD 58-73) Male sex: 26 (93%) Mean BMI: 27 (SD 25-30) LGD: 8 (29%) HGD: 8 (29%) Adenocarcinoma: 12 (43%) Prior resection:17 (61%) 8-second cohort (N=28): Mean age: 67 (SD 59-72) Male gender: 23 (82%) Mean BMI: 28 (SD 24-30) LGD: 8 (29%) HGD: 10 (36%) Adenocarcinoma: 10 (36%) Prior resection: 19 (68%)	Retrospective analysis of prospective data	People aged ≥18 years with short BE segments (C≤2 cm and M≤5 cm) and either HGD, LGD or residual BE following prior resection, ablation therapy naïve	Cryoballoon ablation - C2 Cryoballoon Ablation System, Pentax Medical, Redwood City, Calif, USA. Twice daily proton pump inhibitors and once daily (prescribed at physicians discretion) histamine receptor antagonist used alongside.	12 weeks
4	Canto (2020) United States	N=120 (all CBA) Mean age: 65 (45-83) Male gender: 102 (85%) Mean BMI: 32 (18.7-59) Mean Prague C: 1.2 (0–5) Mean Prague M: 3.2 (1–6) White ethnicity: 112 (93.3%) LGD: 29 (24%) HGD: 67 (56%) ImCa: 24 (20%)	Multi-centre prospective cohort	People aged 18 years or older with treatment naïve BE of 6 cm or less, with either HGD, LGD or ImCA	Cryoballoon ablation - C2 Cryoballoon/ Pentax Medical Corporation), with touch up APC for skipped areas if islands <5mm and fewer than 3 in number. Proton pump inhibitor and daily histamine	1 year

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
					receptor antagonists used alongside.	
5	Canto (2018) United States	N=41 (all CBA; 22 treatment naïve versus 19 previously ablated) Mean age: 65.7 (34-79) Male gender: 34 (85%) Mean Prague C: 1.7 (0-9) Mean Prague M: 3.9 (1-14) LGD: 13 (31.7%) HGD: 23 (56.1%) ImCa: 5 (12.2%) Prior resection: 14 (34%) Prior RFA: 19 (46%) Pre-existing stricture due to prior ablation: 9 (22%) Mean maximum BE length: 3.9 cm (1-14)	Prospective cohort	Adult people with >1 cm BE with LGD, HGD, or ImCA. Including treatment naïve or previously ablated people	Cryoballoon ablation - C2 Therapeutics, Inc, Redwood City, Calif. Proton pump inhibitor (dosed once or twice daily) and histamine receptor antagonists (at the discretion of enrolling site) used alongside.	Median 20.9 months (IQR 17.5-24.6)
6	van Munster (2018) Netherlands	N=46 (20 CBA versus 26 RFA) CBA (N=20): Median age: 66 (62-71) Male sex: 17 (85%) LGD: 9 (45%) HGD: 11 (55%) Prior endoscopic resection: 6 (30%) Prior ablation: 2 (paper states 20%) Prior resection and ablation: 4 (20%) RFA (N=26): Median age: 68 (63-74) Male sex: 21 (81%) LGD: 14 (54%)	Retrospective analysis of prospective data	People with flat BE and either LGD, HGD, residual BE post-resection for non-flat lesions with dysplasia or mucosal EAC or residual BE after circumferential or focal ablation	Cryoballoon ablation - C2 Therapeutics, Inc, Redwood City, Calif, versus RFA - Medtronic, Inc, Minneapolis, Minn. Proton pump inhibitor dosed twice daily alongside.	3 months

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		HGD: 12 (46%) Prior endoscopic resection: 5 (19%) Prior ablation: 9 (35%) Prior resection and ablation: 7 (27%)				
7	Alshelleh (2021) United States	N=71 (46 CBA versus 25 cryospray) CBA (N=46): Mean age: 65.5 (45-83) Male gender: 38/46 (82.6%) LGD: 25 HGD/ImCa: 21 Mean BE maximum length: 3.2 cm (1-9) Prior resection: 21 (45.7%) Cryo spray (N=26): Mean age: 65 (49-84) Male gender: 21/26 (84%) LGD: 9 HGD/ImCa: 16 Mean BE maximum length: 3.6 cm (1-12) Prior resection: 15/25 (16%)	Retrospective cohort	People (≥18 years), with histologically confirmed, treatment naïve BE (LGD, HGD or ImCA)	Cryoballoon ablation - C2 Cryoballoon, Pentax Medical, Montvale, NJ versus cryospray - truFreeze, Steris Endoscopy, Mentro, OH	Mean 13 months (range 6-15) CBA; 15 months (range 9-18) cryospray
8	Schölvinck (2015) United States, Netherlands	N=39 (all CBA) Mean age: 66 (57 – 69) Men: 35 (90%) Median Prague C: 2 (2-4) Median Prague M: 5 (3-7) No dysplasia: 9 (23%) Indefinite dysplasia: 1 (3%) LGD: 9 (23%) HGD: 9 (23%) Early adenocarcinoma: 11 (28%)	Multi-centre prospective cohort	People aged 18-80 years who are ablation treatment naïve, with BE (LGD, HGD or ImCA), a flat treatment area, and either a Prague classification score of C≥2	Cryoballoon ablation - C2 Therapeutics, Redwood City, California, USA. various CBA durations explored, including: 6 seconds (n=10), 8 seconds (n=28) and 10 seconds (n=18).Proton pump	8 weeks

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
				and/or M ≥3, or a BE island (≥1 cm)	inhibitors dosed twice daily used alongside.	
9	Papaefthymiou (2024)	SLR, including 9 studies reporting on CBA (included as a subgroup analysis). There is likely significant overlap with other studies included in this overview. The following studies reported in this systematic review have also been included separately in this overview: • Alshelleh (2021) • Agarwall (2022) • Canto (2020) • Van Munster (2018) • Canto (2018) • Schölvinck (2015) • Frederiks (2022) Further details of the combined population are not reported for the subgroup specifically.	Systematic literature review and meta-analysis	Included studies reporting on adult patients (≥18 years old) with BE and dysplasia, cryoablation balloon intervention, reporting on CED and CEIM	Cryoballoon ablation (C2 Cryoballoon Focal Ablation system, Pentax Medical, Redwood City, Calif, USA)	NR

Table 3. Study outcomes

First author, date	Efficacy	Safety
Dbouk (2022)	**CED (per protocol; sensitivity analysis)** • 1 year: 53/56, 95% (CI 85%-99%); 53/59, 90% (SA)	**Stricture** • Strictures requiring dilation: 5/59; 8.5% (CI 2.8%-18.7%)

	• 2 year: 53/53, 100% (CI 93%-100%); 53/53, 100% (SA) • 3 year: 45/45, 100% (CI 92%-100%); 45/47, 96% (SA) • 4 year: 37/37, 100% (CI 91%-100%); 37/38, 97% (SA) **CE-IM** • 1 year: 42/56, 75% (CI 62%-86%); 42/59, 90% (SA) • 2 year: 47/48, 98% (CI 89%-99%); 47/48, 98% (SA) • 3 year: 40/41, 98% (CI 87%-99%); 40/42, 95% (SA) • 4 year: 32/33, 97% (CI 84%-99%); 32/33, 97% (SA) • Median CBA sessions required to achieve CE-IM at 1 year: 3 (IQR 2-4) **Treatment failure:** • Dysplasia recurrence: 1/53 • Dysplasia recurrence rate: 0.59 per 100 person years • Dysplasia recurrence timeframe: 21.7 months • IM recurrence (n): 7/48 • IM recurrence rate: 5 per 100 person years • IM recurrence timeframe: 20.7 months (median) • Touch up APC during treatment: 14/59 • Touch up APC during durability analysis: 11/48 **Disease progression:** • No progression between baseline dysplasia noted • No progression to oesophageal cancer noted	• Ultra-long BE (≥8 cm) is statistically significantly associated with stricture development (P=0.009) • Prior ERM not statistically significantly associated with stricture development (P=0.25) • Baseline dysplasia not statistically significantly associated with stricture development (P=1) • Time from first treatment to stricture: 2 months (median) • No stricture development after CE-IM noted **Post-procedural bleed:** • Post-procedural bleed requiring clipping: 1/59; 1.7% • Person with bleed noted as using clopidogrel for atrial fibrillation
Agarwal (2022)	**CRD** • 1 year: 48.2% (CBA); 46.8% (RFA) • 2 year: 85.7% (CBA); 78.3% (RFA) • Hazard ratio for CRD (CBA versus RFA): 1.12;(95% CI, 0.83-1.50; P=0.46) • Hazard ratio for CRD by BE length (all ablation modalities): 0.94 per cm increase (P=0.01)	**Strictures** • CBA: 9/85, 10.6%; RFA: 10/226, 4.4% (P=0.04) • All strictures were successfully managed endoscopically (all ablation modalities) **Perforation** • CBA: 0/85, 0%; RFA: 0/226, 0%

	• Propensity score–matched analysis showed comparable results for CRD from both ablation modalities (CBA vs RFA: HR, 1.19; 95% CI, .82-1.73; P = 0.36) **CRIM** • 1 year: 25.2 (CBA); 20.1% (RFA) • 2 year: 69.8% (CBA); 57.3% (RFA) • Hazard ratio for CRIM (CBA versus RFA): 1.13 (95% CI, 0.80-1.60; P=0.50) • Hazard ratio for CRIM by BE length (all ablation modalities): 0.87 per cm increase (P=0.01) • Hazard ratio for CRIM with prior endoscopic resection: 1.56 (P=0.01) • Propensity score-matched analysis showed comparable results for CRIM with both ablation modalities (CBA vs RFA: HR, 1.24; 95% CI, .79-1.96; P = 0.35)	**Bleeding** • CBA: 0/85, 0%; RFA: 0/226, 0%
Frederiks (2022)	**BE surface regression** • 12 weeks: 80% (8-second); 80% (10-second) • People with regression below 50%: 5 (8 second); 3 (10-second) • No statistically significant difference in BE regression after a single treatment according to ablation duration (P=0.65) **Technical success** • Technical success: 27/27, 100% (8-second); 26/27, 96% (10-second) (P=1.0)	**Strictures** • Requiring dilation: 4/27, 15% (8-second); 5/27, 19% (10-second) (P=1.0) • Severe stricture requiring over 3 dilations: 0/27, 0% (8-second); 2/27, 7% (10-second) (P=0.44) • Median dilations required: 2, 1-3 (8-second); 1, 1-8 (10-second) • Proportion of strictures developing within 10 ablations: 1/4, 25% (8-second); 5/5, 100% (10-second) **Oesophageal scarring** • None: 12/27,46% (8-second); 11/27, 41% (10-second) (P=0.69) • Mild: 7/27, 27% (8-second); 6/27, 22% (10-second) (P=0.69) • Moderate: 4/27, 15% 4/27 (8-second), 15% (10-second) (P=1.0) • Severe: 3/27, 12% (8-second); 6/27, 22% (10-second) (P=0.47) • Overall rate: 54%, 95% CI, 35-73 (8-second); 59%, 95% CI, 41-78 (10-second) (P=0.69) Bleeding

		• No cases of bleeding occurred during the Euro-Coldplay study (confirmed by correspondence with author) **Pain** • No statistically significant differences in pain over 14-days post-procedure between groups (P=0.92) • No statistically significant differences in major pain (pain scores of 4 or more) over 14-days post-procedure between groups (P=0.95) **Tolerability** • Adjustment to daily activities: 12/27 (8-second); 10/27 (10-second) (P=0.49) • Median duration until activities resumed: 2 days, 95% CI 1-3 (8-second); 2 days, 95% CI 1-4 (10-second) (P=0.57) **Medication use** • No statistically significant difference in medication use over 14-days post-procedure between groups (P=0.36)
Canto (2020)	**CED (per protocol, intention-to-treat)** • 1 year: 91/9, 97% (PP); 91/120, 76% (ITT) • Estimated probability of CED: 96%, SD=2%, 95% CI 90%–100% (ITT) • No statistically significant difference in CED according to baseline dysplasia grade (P=0.42) **CE-IM (PP, ITT)** • 1 year: 86/94 91% (PP); 86/120, 72% (ITT) • Estimated probability of CE-IM: 91%, SD=3%, 95% CI 83%–96% (ITT) • No significant difference in CE-IM according to baseline dysplasia grade (P=0.61) • Median procedures required to achieve CE-IM: 2, IQR 2-3 (ITT) **Technical success (ITT)** • Successful CBA: 290/303, 95.8% • Unsuccessful CBA: 13/303, 4.2%	**Adverse events** • SEA incidence: 3/303 (ablations), 1% • SAE due to/during CBA procedure: 0 • Hospitalisation rate: 3/120, 2.5% **Strictures** • Requiring dilation: 15/120, 12.5% (ITT) • Median dilations required for stricture treatment: 1, IQR 1-2 • Deep laceration related to dilation: 1/120, 0.8% • No significant difference in structures among those with or without previous EMR: 12.3% versus 11.3% (P=1.0) • Baseline BE length was significantly associated with stricture formation: odds ratio 1.45, 95% CI 1.01-2.07 (P=0.04) **Dysphagia (among those with stricture)** • Dysphagia within 30 days of CBA: 9/15 (60%) • Dysphagia 30 days or more after CBA: 6/15 (40%) **Bleeding** • Upper GI bleed (not requiring transfusion): 1 (0.8%)

	• Reasons for CBA failure: device related failure, 9/13; difficulty with balloon positioning, 3/13; mucosal injury secondary to balloon distention 1/13 **Treatment failure (ITT)** • During initial CBA: 3/120, 2.5% • Reasons for treatment failure during initial CBA: balloon positioning, 3/3, 100% • During 1-year follow-up: 2/120, 1.6% **Disease progression (ITT)** • BL HGD maintained at 1 year: 2/67 • BL HGD progression to ImCA: 1/67 with HGD; 1/120, 0.8% of total sample	**Perforation** • Perforation related to stricture dilation: 1 (0.8%) **Post-procedural pain:** • Median post-procedure pain: 2/10, IQR 1-5 • Median 1-day post-procedure chest pain: 1/10, IQR 0-2 • Median 7-day post-procedure chest pain: 0/10, IQR 0-0 **Medication use:** • Immediately post-procedure (post-baseline CBA): 13% • Immediately post-procedure (average across all CBA): 8% • 1-day post-procedure: 1.7% • 7-day post-procedure: 0.3%
Canto (2018)	**CED** • 1 year: 39/41, 95% (ITT); 67% (ultra-long BE 8 cm or over); 100% (BE less than 8 cm); 85.7% (prior EMR); 100% (without prior EMR) • CED is achieved statistically significantly less among those with longer BE lengths (P=0.02) • No statistically significant difference in CED according to prior EMR status (P=0.11) **CE-IM** • 1 year: 35/41, 88% (ITT); 88% (ultra-long BE 8 cm or over); 83% (BE less than 8 cm); 86% (prior EMR); 89% (without prior EMR) • No statistically significant difference in CE-IM according to prior EMR status (P=1.0) • No statistically significant difference in CE-IM according to BE length (P=0.57) **Technical success** • Technical success: 115/117, 98% **Treatment failure** • 1 year: 2/41	**Adverse events** • Treatment-related adverse events: 10/41, 24% • Adverse events including bleeding 1/10; pain requiring analgesics 2/10; stricture 4/10; candida esophagitis post steroid injection 2/10; mucosal trauma 1/10 • Treatment-related SAE: 1/41, 2.4% • Treatment-related SAE: upper GI-bleed 1/1 **Strictures** • Post CBA strictures: 4/41, 9.8% • Median dilations required for stricture treatment: 1, IQR 1-3 **Dysphagia** • Mild dysphagia at 3 months: 4/41, 9.8% **Pain** • Median immediate post-CBA pain: 1/10, IQR, 0-3; 3.5, IQR 2-8 (ultra-long BE 8 cm or over); 0/10, IQR 0-2 (BE less than 8 cm) • Median 1-day post-CBA pain: 0/10, IQR 0-2 • Median 7-day post-ablation pain: 0/10, IQR 0-0 • Median 30-day post-ablation pain: 0/10, IQR 0-0

	Disease progression • Progression to oesophageal cancer at 1 year: 0, 0%	• The presence of pain at day 7 was statistically significantly associated with the development of a post-cryoablation stricture (P=.0001) **Medication use** • Narcotic analgesic immediately post-CBA: 11/41,27%; 4/6, 67% (ultra-long BE 8 cm or over); 7/35, 20% (BE less than 8 cm) • Narcotic analgesic 1-day post-CBA: 2/41, 4.9%; 2/6, 6% (ultra-long BE 8 cm or over); 0/35, 0% (BE less than 8 cm) • Narcotic analgesic over 1 day post-CBA: 0, 0% • Narcotic use was statistically significantly higher immediately post-CBA among those with ultra-long BE (P=0.035)
van Munster (2018)	**BE surface regression** • Median BE surface regression at 3-months: 88%, IQR, 63-94% (CBA); 90%, IQR 77-94% (RFA) • No statistically significant difference in BE surface regression at 3-months between CBA or RFA (P=0.62)	**Pain** • Median cumulative pain: 4, IQR 0-16 (CBA); 22, IQR, 14-44 (RFA) • Median duration of pain: 5.7 days, SD 1.1 (CBA); compared 11.1, SD 1 (RFA) • Median duration of major pain: 3.5 days, SD 0.9 (CBA); 6.5, SD 1.0 (RFA) • Median peak pain score: 2/10, IQR 0-4 (CBA); 4/10, IQR 3-7 (RFA) • Median peak pain duration: 2 days, IQR 0-4 (CBA); 1, IQR 1-4 (RFA) • Cumulative pain, duration of pain, and peak pain were statistically significantly less among CBA compared to RFA (P <0.01) • No statistically significant difference in the duration of major pain was identified (P=0.04) **Dysphagia** • Median dysphagia score 1-day post treatment: 0, IQR 0-1 (CBA); 1, IQR 0-2 (RFA) • Those who had CBA reported statistically significantly less dysphagia than RFA (P=<0.01) **Medication use** • Median duration using pain medication: 2.6 days, SD 0.7 (CBA); 6.3, SD 1.0 (RFA) • Paracetamol use: 2/20, 10% (CBA), 15, 58% (RFA)

		• Nonsteroidal anti-inflammatory drugs: 3/20, 15% (CBA); 3/26, 20% (RFA) • Those who had CBA used statistically significantly less pain medication than those who had RFA (P=<0.01)
Allselleh (2021)	**CRD (CBA, Cryospray - CS)** • 18-month (all): 44/46, 95.6% (CBA); 24/25, 95% (CS) • 18-month (LGD): 24/25 96% (CBA); 9/9, 100% (CS) • 18-month (HGD): 20/21, 95.2% (CBA); 15/16, 94%(CS) • No statistically significant difference in outcomes between ablation modalities **CR-IM (CBA, Cryospray - CS)** • 18-month (all): 39/46, 85% (CBA);20/25, 80% (CS) • 18-month (LGD): 21/25, 84% (CBA); 7/9, 78% (CS) • 18-month (HGD): 18/21, 86%(CBA): 13/16, 81% (CS) • No statistically significant difference in outcomes between ablation modalities (P=0.61-0.72)	**Strictures** • Total strictures: 4/46, 8.7% (CBA); 3/25, 12% (CS) • LGD strictures: 2/25, 8% (CBA); 0/9, 0% (CS) • HGD strictures: 2/21, 9.5% (CBA); 2/16, 19% (CS) • No statistically significant differences in stricture development between CBA or CS (P=0.39-0.65)

Schölvinck (2015)	**Conversion to neo-squamous epithelium** • No conversion (<20%) at 8-weeks: 3, 30% (6-second); 2, 7% (8-second), 0, 0% (10-second) • Partial conversion (20 – 80%) at 8-weeks: 1, 10% (6-second); 3, 11% (8-second); 0, 0% (10-second) • Full conversion (>80%): 6, 60% (6-second); 23, 82% (8-second); 18, 100% (10-second) • conversion to neo-squamous epithelium was observed statistically significantly more frequently with increasing durations of ablation (P=0.04)	**Adverse events** • Minor longitudinal oesophageal mucosal laceration: 6/39, 15% • Minor laceration: 2/10, (6-second), 2/28 (8-second), 2/18 (10-second) **Strictures** • Total strictures at 8-week follow-up: 0, 0% **Treatment failure** • Total treatment failures: 6/62, 9.7% • Reasons for failure: balloon did not contact oesophageal wall (1); device error signal when inflating (2), slippage of balloon into hiatal hernia (1); narrowing of oesophagus (1); ablation accidentally performed in squamous mucosa (1) **Pain** • Median pain score immediately post-procedure (all people): 0/10, IQR 0–2 • Proportion reporting immediate post-procedure pain scores of 1 or more: 10/39 (27%) • Median pain score immediately post-procedure for those with pain scores of 1 or more: 2.5/10, IQR 2–3 • Number reporting pain in treatment area during follow-up:5/39 (14%) • Median pain score in treatment area during follow-up: 4/10, IQR 3–6 • Median swallowing pain score post-procedure: 4/10, IQR 2–5 **Medication use** • Number using additional pain medication post-procedure: 3/37 (8%) • Pain medications used: nonsteroidal anti-inflammatory drugs (2); Acetaminophen (1)

Papaefthymiou (2024)	**CED** • Rate of successful CED: 94% (94%CI: 89.4–98.6) (CBA); 80.2% (95%CI: 73.3–87.1 (spray catheter) • non-significant (p = 0.076), although moderate (I^2 = 56.5%), heterogeneity compared to the spray catheter (I^2 = 86.8%, p < 0.001) **CEIM** • Rate of CE-IM: 87.2% (95%CI: 80.3–94.2) (CBA); 52.7% (95%CI: 29.5–75.8) (spray catheter) • Heterogeneity remained high in both CBA and spray catheter subgroups (percentages NR) **Recurrence of BO:** • Recurrence: 3.9% (95%CI: 0.0–8.6%) (CBA); spray catheter recurrence NR • CBA heterogeneity (I^2 = 73%, p = 0.024). Only spray catheters achieved non-significant heterogeneity (I^2 = 41.6%, p = 0.081).	**Adverse events** • Overall AE rate: 15.8% (95%CI: 11.6–19.9) (CBA); 12.1% (95%CI: 5.9–18.3) (spray catheter) **Stricture development sub-category** • Rate of stricture development: 6% (95%CI: 2.9–9.2) (CBA); 7.5% (95%CI: 3.0–11.9) (spray catheter)

Procedure technique

Device details were given by all 9 studies. All used the C2 Cryoballoon Focal Ablation System (Pentax Medical, Redwood City, Calif, USA). The pear shaped cryoballoon was noted as an available alternative to the standard balloon in 3 studies (Canto, 2020; Agarwal, 2022; Dbouk, 2022).

Procedure details were given by 7 studies (Schölvinck, 2015; van Munster, 2018; Canto, 2018; Canto, 2020; Agarwal, 2022; Dbouk, 2022; Frederiks, 2022). Procedure details were not included in Alshelleh (2021) or the systematic review by Papaefthymiou (2024).

Setting details were given by 4, which all included the outpatient setting (Canto, 2018; van Munster, 2018; Canto, 2020; Fredericks, 2022). The inpatient setting was also included in 1 multi-centre study (Frederiks, 2022). This was to help meet site specific anaesthesia and sedation policies.

The systematic review by Papaefthymiou (2024) did not specify the CBA duration. A standard 10-second CBA duration was used across the remaining 8 studies. Additional durations were also included in 2 studies. This included 8-seconds (Schölvinck, 2015; Frederiks, 2022), and 6-seconds (Schölvinck, 2015). Frederiks (2022) initially selected a 10-second dose. However, due to comparably high stricture rates compared with comparators for the first 28 procedures, the dose was lowered to 8-seconds to improve safety while preserving efficacy.

Sedation details were given by 6 studies (Schölvinck, 2015; van Munster, 2018; Canto, 2018; Canto, 2020; Agarwal, 2022; Frederiks, 2022). Conscious sedation was specified in 2 (Schölvinck, 2015; van Munster, 2018) and intravenous propofol in 1 (Canto, 2018). Site-specific standard of care was specified in 2

(Canto, 2020; Frederiks, 2022), with either general anaesthesia, propofol or conscious sedation as clinically indicated specified in 1 (Agarwal, 2022).

Details on the maximum number of ablations or treatment sessions was variably reported. The systematic review by Papaefthymiou (2024) did not report this detail for the CBA subgroup. Three studies did not specify a maximum number of ablation sessions (Alshelleh, 2021; Dbouk, 2022; van Munster 2018). Schölvinck (2015) reported a maximum of 2 ablations per person. The remaining studies all specified a maximum of 5 ablative treatment sessions within 12 months (Agarwal, 2022; Canto 2018; Canto 2020; Frederiks 2022). Only Canto (2018) specified the number of ablations allowed per treatment session, with a maximum of 24.

Dbouk (2022) allowed “touch-up” focal ablations using either CBA or APC for small residual columnar islands < 5 mm. Canto (2020) also allowed APC treatment of small flat residual BE islands if fewer than 3 in number and all were < 5 mm in maximum diameter.

Four studies included comparators, including RFA (van Munster, 2018; Agarwal 2022) and cryosrpay (Alshelleh, 2021; Papaefthymiou, 2024). Both van Munster (2018) and Agarwal (2022) provided details of the comparator procedure. Both used focal RFA (Medtronic, Inc, Minneapolis, Minn). van Munster (2018) note that the RFA regimen consisted of either 3 applications with 12 J/cm2, or a regimen consisting of 2 applications with 12 J/cm2 followed by a cleaning step and another 2 applications with 12 J/cm2. Agarwal (2022) note that RFA was applied using standard techniques, using either a balloon-based device or focal device, depending on BE segment length. Alshelleh (2021) and Papaefthymiou (2024) did not include details of the cryospray or spray catheter procedure.

Five studies reported the use of adjunct medical therapies (Schölvinck, 2015; van Munster, 2018; Canto, 2018; Canto 2020; Frederiks 2022). All five reported use of proton-pump inhibitors. Four specified twice-daily dosage (Schölvinck, 2015;

Canto, 2018; van Munster, 2018; Frederiks, 2022), while Canto (2020) specified that dosing could be once or twice daily. Three reported use of histamine receptor antagonists (Canto, 2018; Canto 2020; Frederiks, 2022). Canto (2018) reported once daily use, while Canto (2020) and Frederiks (2022) reported use at physicians' discretion.

Efficacy

Complete eradication or remission of dysplasia

CED or CRD was reported in 6 studies. This included 3 as a primary outcome (Canto, 2020; Dbouk, 2022; Alshelleh 2021), 2 as a secondary (Canto, 2018; Agarwal 2022). The systematic review by Papaefthymiou (2024) included CED from CBA as a subgroup analysis.

Canto (2020) reported CED among 76% (91/120) of people at 1-year using ITT analysis. Adjusting for key baseline differences (age, sex, BE length, and dysplasia grade), the probability of achieving CED increased to 96% (95% CI 90%–100%). No statistically significant difference in CED was observed according to baseline dysplasia (P=0.42).

Dbouk (2022) reported CED among 94.6% (54/56) of people at 1-year using PP analysis. Interim retreatment was allowed. CED reached 100% at 2-year and was maintained across 3-year (45/45) and 4-year (37/37) follow-up. A SA included those lost-to-follow-up as treatment failures. Under this, CED decreased to 96% (45/47) at 3-year, and 97% (37/38) at 4-year. One person had recurrent dysplasia at 21.7 months. This was retreated and CED was achieved by next follow-up. This resulted in a recurrence rate of 0.59 per 100 person-years. No statistically significant relationship was found between BE length and dysplasia recurrence (P=0.6).

Alshelleh (2021) reported CED among 95.6% (44/46) of people who had CBA at 18-months (retrospective analysis). This was compared to 96% (24/25) of people who had cryospray. No statistically significant difference in CED was found between CBA or cryospray (P=0.94). The differences were also not statistically significant when only considering LGD (P=0.55) or HGD (P=0.44).

Canto (2018) reported CED among 95% (39/41) of people at 1-year using ITT analysis. Among people with ultra-long BE (8 cm or more), 67% (4/6) achieved CED. This was compared to 100% (35/35) among people with shorter BE lengths. Those with longer BE were statistically significantly less likely to achieve CED (P=0.02). No statistically significant difference was found based on previous EMR status (P=0.11).

Agarwal (2022) reported that 41 of 85 people (% not reported) who had CBA achieved CRD at 1-year follow-up. This increased to 73 of 85 at 2-year follow-up. This was compared to 106 of 226 and 177 of 226 among those who had RFA. The difference in CRD among those who had CBA and RFA was not statistically significant (P=0.46). Across all people, those with longer BE were statistically significantly less likely to achieve CRD (P=0.01). Propensity score–matched analysis using 1:1 matching (85 CBA and 85 RFA cases) was performed, revealing comparable results for achieving CRD (CBA vs RFA: HR, 1.19; 95% CI, .82-1.73; P=0.36) with both ablation modalities.

Papaefthymiou reported that among 9 studies, CBA was achieved in 94% of people (CI: 89.4–98.6). A non-significant ($p = 0.076$), although moderate ($I^2 = 56.5\%$), heterogeneity was reported among the CBA group compared to the spray catheter group. Among the 11 spray catheter studies, CED was achieved among 80.2% of people (95%CI: 73.3–87.1), with high heterogeneity noted across studies [80.2% (95%CI: 73.3–87.1; I 2 = 86.8%, $p < 0.001$).

Complete eradication/remission of internal metaplasia

CE-IM or CRIM was reported in 6 studies. CE-IM or CRIM was listed as a primary outcome in 4 studies (Canto 2018, Alshelleh 2021, Agarwal 2022, Dbouk 2022), and secondary in 1 (Canto, 2020). The systematic review by Papaefthymiou (2024) reported CE-IM from CBA as a subgroup analysis.

Canto (2018) reported that 88% (35/41) of people achieved CE-IM at 1-year. No statistically significant difference in achieving CE-IM was found for people with (86%) or without (89%) prior endoscopic ablation (P=1.0). No statistically significant difference in CE-IM was found for those with ultra-long (83%) or shorter BE (88%) (P=0.57).

Alshelleh (2021) reported that 84.8% (39/46) of people who had CBA achieved CRIM at 1-year. This was compared to 90% (20/25) of people who had cryospray. No statistically significant difference in CRIM was found between the CBA or cryospray group (P=0.61). The difference was also not statistically significant for either LGD (P=0.67) or HGD (P=0.72).

Agarwal (2022) reported that 25.2% of 85 people achieved CRIM following CBA at 1-year, increasing to 69.8% at 2-year follow-up (number not reported).This was compared to 20.1% from 221 with RFA at 1-year follow-up, and 57.3% at 2-year follow-up. No statistically significant difference in CRIM was found between the CBA or RFA groups (P=0.50). Longer BE length was statistically significantly associated with a decreased chance of CRIM (P=<0.01). Prior endoscopic resection was statistically significantly associated with an increased chance of CRIM (P=0.01). Propensity score–matched analysis using 1:1 matching (85 CBA and 85 RFA cases) was performed, revealing comparable results for achieving CRIM (CBA vs RFA: HR, 1.24; 95% CI, .79-1.96; P =0.35) with both ablation modalities.

Dbouk (2022) reported that 75% (42/56) of people achieved CE-IM at 1-year follow-up. CE-IM increased to 98% (47/48) at 2-year, 98% (40/41) at 3-year, and 97% (32/33) at 4-year follow-up. No statistically significant difference in CE-IM was found after stratifying by baseline dysplasia grade (P value not reported). Recurrent IM was found in 14.6% (7/48) of people after a median of 20.7 months. The IM recurrence rate was 5 in every 100 person-years. CE-IM was maintained in 89% of people at 2-year follow-up, and 86% at 3-year follow-up. No statistically significant association was found between IM recurrence and BE length (P=0.8). No statistically significant associations were found for age, gender, race, BMI, baseline dysplasia, or BE length (P value not reported).

Canto (2020) reported that 72% (86/120) achieved CE-IM at 1-year using ITT analysis. CE-IM was 91% (86/94) under PP analysis. No statistically significant difference in CE-IM was found according to baseline dysplasia grade (P=0.61).

Papaefthymiou reported that among 9 studies, CE-IM was achieved in 87.2% of people (CI: 80.3–94.2). CE-IM was achieved among 52.7% of people among the 11 studies on spray catheters. It was noted that heterogeneity remained high across both CBA and spray catheter subgroups (percentages not reported).

Disease progression

Disease progression was reported as a secondary outcome in 3 studies (Canto, 2018; Canto 2020; Dbouk, 2022).

Canto (2018) reported 0% (0/41) progression from baseline dysplasia to oesophageal cancer at 1 year.

Canto (2020) reported that 1 patient (1/120, 0.8%) with Prague C5M6 progressed from HGD to ImCA during treatment. The patient received 3 CBA treatments. No ImCA was presented at 1-year, but 1 of 3 modules resected at 15 months

showed ImCA. No residual or buried BE was found at 2-year follow-up. No other people had progression over the study period.

Dbouk (2022) reported 0% (0/59) progression of baseline disease among any patient during treatment. No new ImCA or dysplasia were noted over the 4-year follow-up.

BE surface regression

BE surface regression was reported as a primary outcome in 2 studies (van Munster, 2018; Frederiks, 2022). Both measured median regression percentage after a single CBA treatment using images/videos of the treatment area. Van Munster (2018) used 2 experts to independently rank regression, and Frederiks (2022) used 3.

Van Munster (2018) reported a median regression of 88% (IQR 63-94%) at 3 months among 20 people who had CBA. This was compared with a median regression of 90% (IQR 77-94%) among 26 people who had RFA. No statistically significant difference in median regression was found between CBA and RFA (P=0.62). Regression scoring was similar between experts with a median difference of 10% (IQR 5-20%). Regression scores for 2 people were excluded from analysis due to low image quality.

Frederiks (2022) reported a median regression of 80% (95% CI 75-90%) at 12 weeks for the 10-second CBA group. This was compared with a median regression of 80% (95% CI, 66-90%) among the 8-second CBA group. In total, 8 people had regression below 50%. This included 5 (5/27) from the 8-second group, and 3 (3/27) from the 10-second group. No statistically significant difference in median surface regression was found between the 8-second and 10-second groups (P=0.65). Regression scoring was similar between experts, with less than 30% difference in 66% (35/53) of images.

Conversion to neo-squamous epithelium

Conversion to neo-squamous was reported as a secondary outcome in 1 study (Schölvinck, 2015).

Schölvinck (2015) reported that 100% (18/18) of people in the 10-second cohort had full conversion to neo-squamous epithelium at 8-weeks. This was compared to 82% (23/28) for the 8-second group, and 60% (6/10) for the 6-second group. Increasing ablation duration was statistically significantly associated with conversion to neo-squamous epithelium (P=0.04).

Technical success

Technical success was reported in 3 studies (Frederiks 2022, Canto 2018, Canto 2020). This refers to the treatment of all visible BE as intended. Schölvinck (2015) reported number of ablations successfully performed.

Frederiks (2022) reported a technical success rate of 96% (26/27) for the 10-second CBA group. This is compared to 100% (27/27) for the 8-second CBA group. No statistically significant difference in technical success was found between the 8-second and 10-second CBA groups (P=1.0).

Canto (2018) reported a technical success rate of 98% (115/117 procedures). Details were provided. Balloon migration from pre-existing strictures caused 100% (2/2) of failures.

Canto (2020) reported a technical success rate of 96% (290/303 procedures). Details were provided. Device failure caused 69.2% (9/13), mucosal injury caused 7.7% (1/13), and balloon positioning caused 23.1% (3/13) of failures.

Schölvinck (2015) reported number of ablations successfully performed, 56/62 procedures (90.3%). Of the 6 ablations that were not successfully performed, these were attributed to device malfunction (3/6, 50%), stenosis in treatment area

(1/6, 16.7%), proximity to oesophageal junction (1/6, 16.7%), and accidental CBA in squamous mucosa (1/6, 16.7%).

Treatment failure

Treatment failure was reported in 4 studies (Schölvinck 2015, Canto 2018, Canto 2020, Dbouk 2022).

Canto (2018) defined treatment failure as any patient requiring intervening alternative ablative or surgical treatment for residual BE. At 1-year follow up, 5% (2/41) of people had treatment failure. Both people had ultra-long BE, measuring 8 cm or more.

Canto (2020) did not explicitly define treatment failure. During the first or subsequent procedure, 2.5% (3/120) of people had RFA and were considered treatment failures. This was due to technical difficulties (details provided in the safety section). At 1-year follow-up, 1.6% (2/120) of peoples BE did not respond to treatment. Both had HGD. One had persistent dysplasia, despite 3 CBA and 2 EMR treatments. One achieved CE-IM at 9-months but had buried HGD at 12-months.

Schölvinck (2015) did not explicitly define treatment failure. At 8-weeks, 0% (0/18) of people in the 10-second group had ‘no conversion’ (less than 20%). This compared to 30% (3/10) in the 6-second and 7% (2/28) in the 8-second groups.

Of the 5 treatment areas considered failures, 40% (2/5) were not biopsied (the study noted that the CBA treatment failed at first attempt for 2 people, so this could be why biopsies were not taken for 2 people), 20% (1/5) contained no squamous epithelium, and 40% (2/5) contained mixed squamous and BE.

Dbouk (2022) defined treatment failure as any recurrence needing retreatment across the 4-year follow-up. Of the 53 people who achieved CED, 1 had

recurrent LGD after 21.7 months. The dysplasia recurrence rate was 0.59 per 100 person-years. Of the 48 people who achieved CE-IM, 7 had recurrent IM after a median of 20.7 months. The IM recurrence rate was 5 per 100 person years.

Safety

Pain

Post-procedural pain was reported in 4 studies. Pain was listed as a primary outcome in 1 (van Munster, 2018), and a secondary outcome in 3 (Schölvinck 2015, Canto 2018, Canto 2020). All used a 0-10 rating scale, ranging from no pain (0) to most severe (10).

Van Munster (2018) reported a median cumulative pain score of 4 (IQR 0-16) for 20 people in the CBA group, across 14-days post-procedure. This was compared to a median score of 16 (IQR 14-44) among 26 people in the RFA group. Several secondary pain outcomes were available. Cumulative pain was statistically significantly less among the CBA group compared with the RFA group (P=0.01). The median duration of pain was 5.7 days (SD 1.1 day) for the CBA group, compared to 11.1 days (SD 1 day) for the RFA group. The duration of pain was statistically significantly shorter for the CBA group compared with the RFA group (P=<0.01). The peak pain score was 2 (IQR 2-4) for the CBA group, compared with 4 (IQR 3-7) for the RFA group. Peak pain was statistically significant lower after CBA compared with RFA (P=<0.01).

Schölvinck (2015) reported that 27% (10/37) of people had pain immediately post-procedure. The median immediate post-procedure pain score was 0 (IQR 0-2). This increased to 2.5 (IQR 2-3) if only including those who reported some pain. Pain was reported by 14% (5/37) of people 2-days post-procedure. This included a median pain score of 4 (IQR 3-6) in the treatment area, and 4 (IQR 2-5) when swallowing.

Canto (2018) reported that 27% (11/41) of people had pain requiring analgesics immediately post-procedure, with a median pain score of 1 (IQR 0-3). Among people with ultra-long BE (8 cm or more), 67% (4/6) reported pain, with a median score of 3.5 (IQR 2-8). Among those with shorter BE lengths, 20% (7/35) reported pain with a median score of 1 (IQR 0-3). Immediate post-procedural pain was statistically significantly higher for those with ultra-long BE (P=0.04). Pain was reported by 4.9% (2/41) of all people 1-day post-procedure, with a median score of 0 (IQR 0-2). No statistically significant difference was found according to BE length 1 day post-procedure. No people reported any pain on days 7 or 30 post-procedure.

Canto (2020) reported a median immediate post-procedure pain score of 2 (IQR 0-5) among 120 people. This decreased to 1 (IQR 0-2) at 1 day post-procedure. No people reported any pain on day 7 post-procedure.

Adverse events

AE were measured and included across all studies. Schölvinck (2015) included AE as a primary outcome. All other studies included AE as a secondary outcome (Canto, 2018; van Munster, 2018; Canto 2020; Alshelleh, 2021; Agarwal 2022; Dbouk, 2022; Frederiks, 2022).

Procedural AE rates were reported in 2 studies. Schölvinck (2015) reported that 15% (6/39) of people had an AE during the procedure. Canto (2020) reported that 1 person had a device related AE during the procedure.

AE rates (excluding SAE) among people during follow-up were reported for 8 studies. Schölvinck (2015) reported 0% (0/42) during 8-weeks. Canto (2018) reported 24% (10/41) during 1-year. Van Munster (2018) reported 0% (0/26) during 3-months. Canto (2020) reported 12.5% (15/120) during 1-year. Aslhelleh (2021) reported 8.7% (4/46) during 18-months. Agarwall (2022) reported 10.6% (9/85) over 2-year follow-up. Dbouk (2022) reported 10.2% (6/59) over 4-year

follow-up. Further details are provided in relevant sub-sections. Papaefthymiou (2024) reported AE rates for subgroups of 9 CBA studies and 11 spray catheter studies. AE rates were similar at 15.8% (95%CI: 11.6–19.9) for the CBA subgroup and 12.1% (95%CI: 5.9–18.3) for the spray catheter. However, only the CBA subgroup achieved low heterogeneity (I^2 = 24.97%, p = 0.22).

SAE rates during follow-up were reported in 4 studies. Some reported the data as SAEs for individuals undergoing the procedure, or SAEs associated with the procedures overall. Canto (2018) reported 2.4% (1/41) SAEs for people, and 0.9% (1/117) for procedures during 1-year. Canto (2020) reported 1% (3/303) for procedures during 1-year. Dbouk (2022) reported 1.7% (1/59) for people over 4-year follow-up. Frederiks (2022) reported 2 SEA over 12-weeks (proportion not provided).

Oesophageal strictures or narrowing

Stricture formation was reported in 8 studies (Schölvinck, 2015; Canto 2018; Canto 2020; Alshelleh 2021; Agarwall 2022; Dbouk 2022; Frederiks 2022; Papaefthymiou, 2024). Oesophageal stenosis was reported in 1 (van Munster, 2018).

Schölvinck (2015) reported strictures among 0% (0/39) of people over 8-weeks follow up.

Canto (2018) reported strictures among 9.8% (4/41) of people over 1-year follow up. Half (50%, 2/4) happened in people who were treatment naïve prior to CBA. These reported relevant symptoms (dysphagia) 5 and 10 weeks after CBA. Half (50%, 2/4) happened in people with previous strictures. These reported symptoms 2 and 4 days after CBA. All strictures were successfully treated using a median of 1 dilation (range 1-3).

Canto (2020) reported strictures among 12.5% (15/120) of people over 1-year follow-up. These developed after a median of 39 days (IQR 31–45). All strictures were treated using a median of 1 dilation (IQR 1-2). Previous EMR was reported in 47% (7/15) of people with strictures. No statistically significant difference in stricture rate was found among those with or without previous EMR (P=1.0). BE length was the only statistically significant predictor of strictures (P=0.04).

Alshelleh (2021) reported strictures among 8.7% (4/46) of people who had CBA over 18 months. This was compared to 12% (3/25) in the cryospray group. No statistically significant difference in stricture rate was found between CBA or cryospray (P=0.65). Differences in stricture rates were also not statistically significant when comparing those with LGD (P=0.39) or HGD (P=0.42).

Agarwall (2021) reported strictures among 10.6% (9/85) of people who had CBA over the median 2-year follow-up (IQR 1.3-2.5). This was compared to 4.4% (10/226) in the RFA group over the median 1.5-year follow-up (IQR 0.8-2.5). Statistically significantly more people who had CBA developed strictures compared to those who had RFA (P=.04). All strictures were successfully treated in both groups.

Dbouk (2022) reported strictures among 8.5% (5/59, 95% CI 2.8%-18.7%) of people within 4 months post treatment. These developed after a median of 2 months. All developed within 4 months of CBA. People with BE of 8 cm or more developed statistically significant more strictures than those with shorter lengths (28.6% versus 2.2%, P=0.01). Prior EMR (P=0.15) and baseline dysplasia (P=1) were not statistically significantly associated with stricture development.

Frederiks (2022) reported strictures among 19% (5/27) of people who had 10-second CBA over 12 weeks. This was compared to 15% (4/26) of people who had 8-second CBA. No people with 8-second CBA had severe strictures, compared with 7% (2/27) in among the 10-second group. No statistically

significant difference in strictures (P=1) or severe strictures (P=0.44) was found between groups. Strictures were treated with a median of 1 dilation (range 1-8) in the 10-second group. This compared to 2 dilations (range 1-3) in the 8-second group. No statistically significant difference in the number of dilations was found between groups (P=0.78).

The systematic review and meta-analysis by Papaefthymiou (2024) reported similar rates of stricture development among the CBA and spray catheter subgroups. Of people in the CBA group, 6% (95%CI: 2.9–9.2) developed strictures, compared with 7.5% (95%CI: 3.0–11.9) for the spray catheter subgroup. Only the CBA group yielded non-significant heterogeneity (I^2 = 53.7%) across studies.

Van Munster (2018) reported stenosis among 0% (0/20) of people during 3 months follow up post procedure. This was compared to 8% (2/26) in the RFA group. No statistically significant difference in stenosis was found between CBA and RFA (P=0.21).

Oesophageal perforation

Oesophageal perforation was reported in 4 studies (Schölvinck, 2015; Canto, 2018; Canto, 2020; Agarwal, 2022).

Schölvinck (2015) reported within their discussion that there was an ‘absence of major bleeding or perforations’ within their study population.

Canto (2018) reported no perforations (0%, 0/42) over 1-year follow-up.

Canto (2020) reported no perforations related to balloon inflation over 1-year follow-up. Perforation related to stricture dilation was reported among 1 (0.8%, 1/120) person. This was treated with oesophageal stent and the person made a full recovery.

Agarwal (2022) reported perforation among 0% (0/85) of people who had CBA and 0% (0/226) who had RFA over 2 years.

Bleeding

Bleeding was reported in 5 studies (Canto, 2018; Canto, 2020; Agarwall, 2022; Dbouk 2022; Frederiks 2022).

Canto (2018) reported an upper GI bleed among 1 person (2.4%, 1/41) over 1 year. This happened 7 days post CBA and related to a gastroesophageal junction ulcer associated with aspirin use that did not require therapy. Dbouk (2022) also reported moderate-grade bleeding in 1 person (1.7%, 1/59) over 1 year follow-up. Both reported bleeds refer to the same AE due to an overlap of 22 people between studies.

Canto (2020) reported upper GI bleed among 1 person (1/120, 0.8%) over 1 year. This happened 1 week post CBA and related to ongoing clopidogrel use. Treatment was not required.

Agarwall (2022) reported no clinically significant bleeding among people who had CBA (0%, 0/85) or RFA (0%, 0/226) over 2 years. Frederiks (2022) also note that no cases of bleeding occurred during the Euro-Coldplay study, confirmed by correspondence with the key authors.

Dysphagia

Dysphagia was reported in 4 studies (Canto, 2018; van Munster, 2018; Canto 2020; Frederiks, 2022).

Canto (2018) reported mild dysphagia from stenosis requiring dilation among 9.7% (4/41) of people over 1-year follow-up. This included 2 treatment naïve people who reported dysphagia 5- and 10-weeks post CBA. Dilation occurred at 3months for treatment.

Van Munster (2018) reported that dysphagia scores post treatment were statistically significantly lower among people who had CBA compared with RFA (P=<0.01).

Canto (2020) reported dysphagia among 12.5% (15/120) of people over 1-year. All had symptomatic oesophageal strictures requiring dilation. Dysphagia developed within 30 days for 60% (9/15), and after 30 days in 40% (6/15).

Device malfunction

Device malfunction/failure was reported in 3 studies (Schölvinck 2015, Canto 2020, Frederiks 2022).

Schölvinck (2015) reported 3 records of device malfunction. An error signal appeared on balloon inflation in 2 instances. The balloon did not make proper contact with the oesophageal wall in 1 instance. The reported device malfunctions caused 50% (3/6) of procedure failures.

Canto (2020) reported 9 instances of device-related failure. Furthers details were not provided. The device-related failure caused 69.2% (9/13) of procedure failures.

Frederiks (2022) reported 2 instances of device malfunction which required a switch from CBA to RFA. Further details were not provided, and these were excluded from the per-protocol analysis. An additional 8 device malfunctions were reported. This included 26% (7/27) of people in the 8-second group, compared with 4% (1/27) in the 10-second group. The difference between groups was statistically significant (P=0.05). Malfunctions happened either during the procedure (5/8) or set-up (3/7). Further details were not provided. All procedures were completed successfully following replacement of a CBA component.

Medication use

Analgesic medication use was reported in 5 studies (Schölvinck, 2015; Canto, 2018; van Munster, 2018; Canto, 2020; Frederiks, 2022).

Schölvinck (2015) reported no pain medication use (0%, 0/37) immediately post-procedure. After a median of 2-days, 8% (3/37) of people used additional pain medication. This included non-steroidal anti-inflammatory drugs (2/3) and acetaminophen (1/3).

Canto (2018) reported that 27% (11/41) of people required pain medication immediately post-procedure. This decreased to 4.9% (2/41) 1 day post-procedure, with none (0%, 0/41) required on either day 7 or 30. Immediately post-procedure, 67% (4.6) of people with long BE (8 cm or more) required medication compared to 20% (7/35) of those with shorter lengths. The difference in immediate post-procedure medication use was statistically significant (P=0.04).

Van Munster (2018) reported that people who had CBA used statistically significantly less pain medication than those who had RFA (P value not reported). Average use lasted 2.6 days (SD 0.7) for those who had CBA. This was compared to 6.3 days (SD 1.0) for those who had RFA. The difference in length of use was statistically significant (P=0.01). Medications used included paracetamol (10%, 2/20) and non-steroidal anti-inflammatory drugs (15%, 3/20). Types of medication used were not statistically significant between groups (P=0.09).

Canto (2020) reported that 8% of 120 people required pain medication immediately post-procedure. This reduced to 1.7% at day 1 post post-procedure, and 0.3% by day 7. More people required pain medication after their initial treatment, where 13% used analgesics.

Frederiks (2022) compared medication use for 14 days post-procedure among people receiving 10-second and 8-second CBA. The exact figures for analgesics use are not provided. Differences are presented graphically. Differences in medication use between people receiving 8-second and 10-second CBA were not found to be statistically significant (P=0.36).

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).

When this procedure was assessed previously, 1 specialist adviser noted device failure as an anecdotal adverse event, and considered nitrous oxide leakage from ruptured balloon was a theoretical adverse event.

Four professional expert questionnaires were submitted for this assessment. Three noted perforations as a theoretical adverse event, and pain and strictures as anecdotal events. Find full details of what the professional experts said about the procedure in the https://www.nice.org.uk/guidance/indevelopment/gid-ipg10413/documents.

Validity and generalisability

- Total sample size ranged from 39 (Schölvinck, 2015) to 311 (Agarwal, 2022). The number of people who had CBA ranged from 20 (van Munster, 2018) to 120 (Canto, 2020).
- Follow-up ranged from 8 weeks (Schölvinck, 2015) to 4 years (Dbouk, 2022) across studies. Most follow-up covered at least 12-months (Canto, 2018; Canto, 2020; Alshelleh, 2021; Agarwal, 2022; Dbouk, 2022).

- One study did not disclose the location (Dbouk, 2022). Of those providing location details, none included the UK. Included study centres were either in the US (Schölvinck, 2015; Canto, 2018; Canto, 2020; Alshelleh, 2021; Agarwal, 2022), or the Netherlands (N=3) (Schölvinck, 2015; van Munster, 2018; Frederiks, 2022).
- All studies were observational and did not include random assignment. Adjustments for potential confounders (i.e., age, gender, BE length, etc.) at least in part of the analyses were noted in 4 studies (van Munster, 2018; Canto, 2020; Agarwal, 2022; Frederiks 2022). Agarwal (2022) used propensity and score matching to minimise bias which may result from non-randomisation.
- All studies used the cryoballoon focal ablation system (Pentax Medical, Montvale, New Jersey, United States). The pear shaped cryoballoon was explicitly noted as an available alternative to the standard focal balloon in 3 studies (Canto, 2020; Agarwal, 2022; Dbouk, 2022). Canto (2020) noted no technical difficulties after the pear-shaped balloon was made available.
- All studies used a 10-second CBA duration as standard. This enables some comparability across studies. Two studies also measured effects using an 8-second duration (Schölvinck, 2015; Frederiks, 2022), with 1 study including an additional 6-second duration (Schölvinck, 2015). Frederiks (2022) had initially planned to only include 10-second duration, but due to an unexpected high stricture rate compared with the literature, the initial 10-second dose was lowered to 8 seconds to improve safety while preserving efficacy.
- Alshelleh (2021) and Papaefthymiou (2024) did not include procedure details. All other studies provided at least some detail on procedure technique. Where reported, techniques were similar. Only slight variation was noted for sedation, due to site-specific policies.
- Papaefthymiou (2024) only included CBA as a subgroup within the systematic review and meta-analysis. Therefore, details on the combined sample are very

limited, which may limit the ability to generalise the findings to wider populations.

- Three studies with shorter follow-up did not offer retreatment (Schölvinck, 2015; van Munster, 2018; Frederiks, 2022), and Alshelleh (2021) did not specify whether retreatment was offered. Retreatment was offered every 10-12 weeks, if required, in 4 studies (Canto, 2018; Canto, 2020; Agarwal, 2021; Dbouk, 2022). Of these, 2 allowed retreatment (Canto, 2018, Canto, 2020), and 2 classed people who had retreatment as treatment failures (Agarwal, 2021; Dbouk, 2022).
- All studies reported at least some industry funding or involvement from the device manufacturer (Pentax Medical). All included authors who had financial ties with the manufacturer. Canto (2020) received a research grant from the manufacturer.
- Inclusion criteria varied. All studies included people with LGD or HGD, with 5 also including people with ImCA (Schölvinck, 2015; Canto, 2018; Canto, 2020; Agarwal, 2022; Dbouk, 2022). Two studies included both previously ablated and treatment naïve people (van Munster, 2018; Canto; 2018). Six studies included only treatment naïve people (Schölvinck, 2015; Canto, 2020; Alshelleh, 2021; Agarwal, 2022; Dbouk, 2022; Frederiks, 2022).Schölvinck (2015) only included BE islands.
- A range of BE lengths were represented within the inclusion criteria. No BE length was specified in 3 studies (van Munster, 2018; Aslhelleh, 2021; Dbouk, 2022). BE lengths of 6 cm or less were specified in 2 studies (Canto, 2020; Agarwal, 2022). BE lengths of 1 cm or more were specified in 2 studies (Schölvinck, 2015; Canto, 2018).
- Participant overlap was explicitly reported among 22 people, included in both Canto (2018) and Dbouk (2022). There is potential for overlap among other studies, particularly the retrospective studies.

- Pain outcomes were measured across variable time frames. For instance, Canto (2020) and van Munster (2018) measured pain up to 7-days post procedure, Frederiks (2022) measured pain up to 14 days post-procedure, Canto (2018) measured pain up to 30-days, and Schölvinck (2015) measured pain over the entire 3-month follow-up period. Variability in time frames presents a difficulty when trying to draw comparison between studies.
- Definitions of treatment failure varied across studies. Canto (2018) and Schölvinck (2015) did not explicitly define treatment failure. Canto (2018) defined treatment failure as any requirement for alternative ablative therapies. Whereas Dbouk (2022) defined treatment failure as any requirement for re-treatment. This variability presents difficulty with trying to compare outcomes between studies.
- BE length was most commonly found to be statistically significant across the various safety and efficacy outcomes. BE length has 5 reports of significance across 4 outcomes. However, conflict was identified across studies, with 3 instances of non-significance across 2 outcomes for BE length.
- All included studies reported that CBA was safe and effective. The 3 studies which compared CBA with alternative ablation modalities all reported equal effect (van Muster, 2018; Alshelleh 2021; Agarwal, 2022). The 5 studies which evaluated CBA exclusively all reported that the procedure is safe and effective, with no contention across studies (Schölvinck, 2015; Canto, 2018; Canto 2020; Alshelleh, 2021; Dbouk, 2022; Frederiks, 2022).

Ongoing trials

- C2 CryoBalloon™ 180 Ablation System Dose De-escalation Study. NCT03311451. N=30. Netherlands. Expected completion: December 2025.
- Nitrous Oxide For Endoscopic Ablation of Refractory Barrett's Esophagus (NO FEAR-BE) (NO FEAR-BE). NCT03554356. N=70. United States. Expected completion: December 2026.

Existing assessments of the procedure

Diagnosis and management of Barrett esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Guideline | ESGE

- ESGE recommend endoscopic eradication therapy using ablation for LGD and endoscopic ablation treatment for HGD. ESGE recommend offering complete eradication of all remaining BE by ablation after endoscopic resection of visible abnormalities containing any degree of dysplasia or oesophageal adenocarcinoma (EAC). Regarding the preferred method of ablation, RFA is most extensively studied and has been proved to be safe and effective. Alternative treatment methods include argon plasma coagulation, hybrid argon plasma coagulation, and cryoablation (cryoballoon and cryospray).

ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus

- Endoscopic ablative therapy is recommended for patients with BE and high-grade dysplasia. Endoscopic ablative therapy is also recommended for patients with BE and low-grade dysplasia, although endoscopic surveillance continues to be an acceptable alternative. RFA is currently the preferred endoscopic ablative therapy.

Related NICE guidance

Interventional procedures

Endoscopic radiofrequency ablation for squamous dysplasia of the oesophagus (2014) Interventional procedures guidance 497. (Recommendation: special arrangements).

Endoscopic radiofrequency ablation for Barrett's oesophagus with low-grade dysplasia or no dysplasia (2014) Interventional procedures guidance 496.

(Recommendation: standard arrangements with low-grade dysplasia, research only for no dysplasia).

Photodynamic therapy for Barrett's oesophagus (2010). Interventional procedures guidance 350. (Recommendation: standard arrangements for high grade dysplasia, special arrangements for low-grade or no dysplasia).

Epithelial radiofrequency ablation for Barrett's oesophagus (2010). Interventional procedures guidance 344, partially replaced by IPG496. (Recommendation: for high grade dysplasia, standard arrangements recommendation is still in place).

Endoscopic submucosal dissection of oesophageal dysplasia and neoplasia (2010) Interventional procedures guidance 355. (Recommendation: research for oesophageal adenocarcinoma or high-grade dysplasia in Barrett's oesophagus).

Medical technologies

Narrow band imaging for Barrett's oesophagus (2019) NICE MedTech innovation briefing [179].

NICE guidelines

Barrett's oesophagus and stage 1 oesophageal adenocarcinoma: monitoring and management (2023) NICE guideline NG231.
Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management (2019) NICE guideline CG184.

Professional societies

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

Patient organisations:

- OPA Cancer Charity
- Guts UK
- Macmillan Cancer Support
- Heartburn Cancer UK

Societies / organisations for consultation:

- NHS England
- NHS Scotland

Evidence from people who have had the procedure

NICE received 5 questionnaires from people who have had the procedure (or their carers). The views of people who have had the procedure were consistent with the published evidence and the opinions of the professional experts.

Company engagement

NICE asked companies who manufacture a device potentially relevant to this procedure for information on it. NICE received 1 completed submission. This was considered by the interventional procedures technical team, and any relevant points have been taken into consideration when preparing this overview.

References

1. Dbouk, M, et al., (2022). Durability of Cryoballoon Ablation in Neoplastic Barrett's Esophagus. Techniques and Innovations in Gastrointestinal Endoscopy; 136-144.
2. Agarwal, S, et al., (2022). Comparative outcomes of radiofrequency ablation and cryoballoon ablation in dysplastic Barrett's esophagus: a propensity score-matched cohort study. Gastrointestinal Endoscopy; 95 (03): 422-431.
3. Frederiks, C et al., (2022). Comparison of focal cryoballoon ablation with 10- and 8-second doses for treatment of Barrett's esophagus–related neoplasia: results from a prospective European multicenter study (with video). Gastrointestinal Endoscopy 96: 743-751.

4. Canto, M, et al., (2020). Multifocal Cryoballoon Ablation for Eradication of Barrett's Esophagus-Related Neoplasia: A Prospective Multicenter Clinical Trial. The American Journal of Gastroenterology 115(11): 1879-1890.
5. Canto, M, et al., (2018). Multifocal nitrous oxide cryoballoon ablation with or without EMR for treatment of neoplastic Barrett's esophagus (with video). Gastrointestinal Endoscopy;88 (03): 438-446.
6. Van Munster, S, et al., (2018). Focal cryoballoon versus radiofrequency ablation of dysplastic Barrett's esophagus: impact on treatment response and postprocedural pain. Gastrointestinal Endoscopy; 88(5):795-803.
7. Alshelleh, M., et al (2021). Cryoballoon and Cryospray Ablation Therapies are Equivalent for Eradication of Barrett's Esophagus. Techniques and Innovations in Gastrointestinal Endoscopy; 110-112.
8. Schölvinck, D, et al., (2015). Treatment of Barrett's esophagus with a novel focal cryoablation device: a safety and feasibility study. Endoscopy; 47: 1106-1112.
9. Papaefthymiou et al., (2024). Cryoablation in Barrett's Esophagus and Comparison with Radiofrequency Ablation: A Meta-Analysis. Cancers (Basel): 23;16(17):2937.

Appendix A: Methods and literature search strategy

Methods and literature search strategy

NICE has identified studies and reviews relevant to balloon cryoablation for Barrett's oesophagus from the medical literature.

Search strategy design and peer review

This search report is informed by the Preferred Reporting Items for Systematic reviews and Meta-Analyses literature search extension (PRISMA-S).

A NICE information specialist ran the literature searches on 19/02/2025. See the search strategy history for the full search strategy for each database. Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The principal search strategy was developed in MEDLINE ALL (Ovid interface). It was adapted for use in each of the databases listed in table 4a, taking into account the database's size, search functionality and subject coverage. The MEDLINE ALL strategy was quality assured by a NICE senior information specialist. All translated search strategies were peer reviewed to ensure their accuracy. The quality assurance and peer review procedures were adapted from the Peer Review of Electronic Search Strategies (PRESS) 2015 evidence-based checklist.

Review management

The search results were managed in EPPI-Reviewer version 5 (EPPI-R5). Duplicates were removed in EPPI-R5 using a 2-step process. First, automated deduplication was done using a high-value algorithm. Second, manual deduplication was used to assess low-probability matches. All decisions about inclusion, exclusion and deduplication were recorded and stored.

Limits and restrictions

The CENTRAL database search removed trial registry records and conference material. The Embase search excluded conference material.

English language limits were applied to the search when possible in the database.

The search was limited from 26/03/2024 to 19/02/2025. The date limit was included to update searches undertaken for an earlier version of this guidance.

The limit to remove animal studies in the searches is standard NICE practice, which has been adapted from Dickersin K, Scherer R, Lefebvre C (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. BMJ 309(6964): 1286.

Main search

Table 4. Main search results

Database	Date searched	Database platform	Database segment or version	Number of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	19/02/2025	Wiley	Issue 2 of 12, February 2025	2
Cochrane Database of Systematic Reviews (CDSR)	19/02/2025	Wiley	Issue 2 of 12, February 2025	0
Embase	19/02/2025	Ovid	1974 to February 18 2025	45
INAHTA International HTA Database	19/02/2025	INHTA	-	2
MEDLINE ALL	19/02/2025	Ovid	1946 to February 18 2025	21

Search strategy history

MEDLINE ALL search strategy

1 Barrett Esophagus/ 8980

2 (barrett* adj4 (esophag* or oesophag* or epithelium* or syndrome* or metaplas*)).tw. 10646

3 ((columnar* or specialised* or specialized* or intestinalized* or intestinalised* or metaplas*) adj4 (epithelium* or oesophag* or esophag* or muscosa*)).tw. 6549

4 (CELLO or CLO).tw. 6168

5 exp Esophageal Neoplasms/ 62779

6 ((oesophag* or esophag*) adj4 (dysplas*or lesion* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumor* or tumour* or malignan* or angiosarcoma* or leiomyosarcoma* or lump*)).tw. 71289

7 (ESCN or ESCC).tw. 10363

8 or/1-7 100427

9 Cryosurgery/ 14633

10 Ablation Techniques/ 3805

11 Freezing/ 26818

12 ((balloon* or focal* or endoscop*) adj4 (cryoablat* or cryosurg* or cryotherap* or freez* or ablat*)).tw. 3748

13 (cryoballoon* or cryo-balloon* or cryo balloon*).tw. 2021

14 coldplay*.tw. 3

15 or/9-14 48477

16 8 and 15 738

17 animals/ not humans/ 5273696

18 16 not 17 724

19 limit 18 to ed=20240326-20250219 16

20 limit 18 to dt=20240326-20250219 19

21 19 or 20 22

22 limit 21 to english language 21

Embase search strategy

Embase <1974 to 2025 February 18>

1 Barrett Esophagus/ 20572

2 (barrett* adj4 (esophag* or oesophag* or epithelium or syndrome* or metaplas*)).tw. 18256

3 ((columnar or specialised or specialized or intestinalized or intestinalised or metaplas*) adj3 (epithelium or oesophag* or esophag* or mucosa)).tw. 8639

4 (CELLO or CLO).tw. 4973

5 exp Esophageal tumor/ 114545

6 ((oesophag* or esophag*) adj4 (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. 107567

7 (ESCN or ESCC).tw. 13633

8 or/1-7 156478

9 Cryosurgery/ 9012

10 Ablation Therapy/ 28425

11 Freezing/ 36074

12 ((balloon* or focal* or endoscop*) adj4 (cryoablat* or cryosurg* or cryotherap* or freez* or ablat*)).tw. 7021

13 (cryoballoon* or cyro-balloon* or cryo balloon*).tw. 4125

14 coldplay*.tw. 7

15 or/9-14 81456

16 8 and 15 1969

17 nonhuman/ not human/ 5582310

18 16 not 17 1942

19 limit 18 to english language 1853

20 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 6162273

21 19 not 20 945

22 limit 21 to dc=20240326-20250219 45

23 limit 21 to dd=20240326-20250219 40

24 22 or 23 45

Cochrane Library (CDSR and CENTRAL) search strategy

ID Search Hits

#1 MeSH descriptor: [Barrett Esophagus] explode all trees 344

#2 (barrett* near/4 (esophag* or oesophag* or epithelium* or syndrome* or metaplas*)) 827

#3 ((columnar* or specialised* or specialized* or intestinalized* or intestinalised* or metaplas*) near/4 (epithelium* or oesophag* or esophag* or muscosa*)) 146

#4 (CELLO or CLO) 469

#5 MeSH descriptor: [Esophageal Neoplasms] explode all trees 2640

#6 ((oesophag* or esophag*) near/4 (dysplas*or lesion* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumor* or tumour* or malignan* or angiosarcoma* or leiomyosarcoma* or lump*)) 7920

#7 (ESCN or ESCC) 582

#8 #1 or #2 or #3 or #4 or #5 or #6 or #7 8830

#9 MeSH descriptor: [Cryosurgery] this term only 526

#10 MeSH descriptor: [Ablation Techniques] this term only 171

#11 MeSH descriptor: [Freezing] this term only 152

#12 ((balloon* or focal* or endoscop*) near/4 (cryoablat* or cryosurg* or cryotherap* or freez* or ablat*)) 668

#13 (cryoballoon* or cryo-balloon* or cryo balloon*) 471

#14 coldplay* 1

#15 #9 or #10 or #11 or #12 or #13 or #14 1740

#16 #8 AND #15 111

#17 "conference":pt or (clinicaltrials or trialsearch):so 804706

#18 #16 NOT #17 with Cochrane Library publication date Between Mar 2024 and Feb 2025, in Cochrane Reviews, Cochrane Protocols 0

#19 #16 NOT #17 with Publication Year from 2024 to 2025, in Trials 2

INAHTA HTA Database search strategy

1 "Barrett Esophagus"[mh] 30

2 (barrett* AND (esophag* or oesophag* or epithelium* or syndrome* or metaplas*)) 38

3 ((columnar* or specialised* or specialized* or intestinalized* or intestinalised* or metaplas*) AND (epithelium* or oesophag* or esophag* or muscosa*)) 5

4 (CELLO or CLO) 0

5 "Esophageal Neoplasms"[mh] 68

6 (oesophag* or esophag*) AND (dysplas*or lesion* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumor* or tumour* or malignan* or angiosarcoma* or leiomyosarcoma* or lump*)) 106

7 (ESCN or ESCC) 0

8 #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 125

9 "Cryosurgery"[mh] 30

10 "Ablation Techniques"[mh] 35

11 "Freezing"[mh] 1

12 ((balloon* or focal* or endoscop*) AND (cryoablat* or cryosurg* or cryotherap* or freez* or ablat*)) 46

13 (cryoballoon* or cryo-balloon* or cryo balloon*) 159

14 coldplay* 0

15 #14 OR #13 OR #12 OR #11 OR #10 OR #9 251

16 #15 AND #8 90 Search was limited from 2024-2025 and English Language but limits do not display on the search strategy. This search yielded 2 results.

Inclusion criteria

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events not available in the published literature.
- People with Barrett's oesophagus.
- Intervention or test: Balloon cryoablation.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in Appendix B: Other relevant studies.

Find out more about how NICE selects the evidence for the committee.

Appendix B: Other relevant studies

Other potentially relevant studies that were not included in the main evidence summary (tables 2 and 3) are listed in table 5 below.

Table 5. Additional studies identified

Article	Number of people/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Hamade N, Desai M, Thoguluva Chandrasekar V et al. (2019) Efficacy of cryotherapy as first line therapy in people with Barrett's neoplasia; a systematic review and pooled analysis. Diseases of the Esophagus, 32: 1-10	Systematic review and meta-analysis N=6 studies (232 people)	There are scarce data on the use of cryotherapy as the primary modality for the treatment of BE dysplasia. The published data demonstrate efficacy rates of 69% and 98% for complete eradication of metaplasia and neoplasia, respectively.	Only 1 cited paper for cryoballoon is included 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 people with BE treated with cryotherapy for persistent dysplasia or IM after RFA 2 studies on balloon cryotherapy; N=16 people.	Cryotherapy successfully achieved CE-D in 3 quarters and CE-IM in half of people with BE who did not response to initial RFA and adverse effects were reported in 6.7% of people.	There are only 2 studies on balloon cryotherapy included and they are both abstracts.
Westerveld DR, Nguyen K, Banerjee D et al. (2020) Safety and effectiveness of balloon cryoablation for treatment of Barrett's associated neoplasia: systematic review and meta-analysis. Endoscopy	Systematic review and meta-analysis N=7 studies (272 people)	This meta-analysis suggests that balloon cryoablation is a safe and effective ablative technique for	Of the 7 studies, 5 full-text articles are included in table 2 and 2 are abstracts.

International Open, 18:E172-E178		treatment of Barrett's oesophagus neoplasia; future prospective comparative trials are needed to corroborate these initial findings.	
Alzoubaidi D, Hussein M, Sehgal V et al. (2020) Cryoballoon ablation for treatment of people with refractory oesophageal neoplasia after first line endoscopic eradication therapy. Endoscopy International Open, 08:E891-E899	Case series N=18 (median 71.5 years; 83% [15/18] male)	CR-D was achieved in 78% and CR-IM in 39% of people. There were no device malfunction or adverse events. Stenosis was noted in 11% of cases. At a median follow up of 19-months, CR-D was maintained in 72% of people and CR-IM in 33%.	This study includes a small sample.
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 people 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	This is an abstract but contains complications associated with learning curve.

		time per site reduced.	
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 people (17% (1/6) female; and mean 68 years) treated with the cryoballoon swipe ablation system (CbSAS)	Six people 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 of the Esophagus 30, 1-8, DOI: 10.1093/dote/dox019	Case series N=4 people 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	This study includes a small sample.

		resulting in severe early ablation.	
Spiceland CM, Joseph Elmunzer B, Paros S et al. (2019) Salvage cryotherapy in people undergoing endoscopic eradication therapy for complicated Barrett's oesophagus. Endoscopy International Open, 07: E904–E911	Case series N=46 (6 balloon cryotherapy and 40 spray cryotherapy; mean 66 years; 91% [42/46] male) Follow-up: 12 years	This study showed that cryotherapy appears effective for salvage treatment of people with refractory dysplastic BE and IMC, successfully achieving CE-D and CE-IM in of 82.6% and 45.6% of people respectively. Higher-quality studies, ideally including randomized trials, are needed.	The clinical outcomes of the 6 people who received balloon cryotherapy are not separated from the overall results.
Trindade AJ and Canto MI (2019) Circumferential treatment of long-segment Barrett's oesophagus using the next-generation cryoballoon. Endoscopy, 51: E69-E70	Case report N=1	This case demonstrates that the next generation cryoballoon ablation system enables successful treatment of wider and longer segments of Barrett's oesophagus. Studies are ongoing to determine optimal dosing strategies and technique.	This is a single case report.
Barrett M and Prat F (2018) Diagnosis and treatment of superficial oesophageal	Review	Balloon-based cryoablation of early squamous	The main cited papers for

cancer. Annals of Gastroenterology, 31(3), 256-265, DOI: 10.20524/aog.2018.0252		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.	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, people 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	Review	Cryotherapy using nitrous oxide-inflated	The main cited paper for

endoscopy. American Society for Gastrointestinal Endoscopy, 2(5), 89-95, DOI: 10.1016/j.vgie.2017.01.021		balloon has shown effective in conversing BE to neosquamous epithelium at a follow-up o f6 to 8 weeks, with minor pain being reported.	cryoballoon is included in table 2.
Visrodia K, Zakko L and Wang KK (2018) Mucosal ablation in people 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 people with (residual) BE islands.	The main cited papers for cryoballoon are all included in table 2.
Wang KK (2020) How I treat people with Barrett oesophagus when endoscopic ablation fails. Gastroenterology & Hepatology, 16(2): 82-87	Review	If initial ablation was started with radiofrequency ablation, switching to cryotherapy as an alternative appears to be successful in most cases.	The mainly cited papers relating to balloon cryotherapy are included in table 2 or the appendix.
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	Case series N=30 (14 LGD, 7 HGD, and 9 early adenocarcinoma) patients with 47 BE islands Follow up: 56 days (Median)	Cryoablation of BE islands using the CryoBalloon is effective. BE islands were effectively targeted.	Deprioritized due to small sample size and short follow-up.
van Munster SN, Overwater A, Raicu MGM et al. (2019) A novel cryoballoon ablation system for eradication of dysplastic Barrett's oesophagus: a first-in-human feasibility study. Endoscopy, 52: 193-201	Case series N=25 (13 in the dose-escalation phase and 12 in the confirmation phase) Follow up: 8 weeks	CBA was feasible and effective for ablating larger BE areas.	Deprioritized due to small sample size and short follow-up.
Joana G, Demedts I and Bisschops R (2018) Treatment	Case report N=1	At the 3-month follow-up,	Deprioritized due to lack of

of low-grade dysplasia in Barrett's oesophagus with a new-generation cryoballoon device [abstract]. Endoscopy, 50, E318-E319	Follow-up: 3-month	complete regeneration of BE to neosquamous epithelium was observed. The treatment was effective and was facilitated by the axial movement of the diffuser.	reported outcomes, small sample and newer available evidence.
Tariq R, Enslin S, Hayat M, Kaul V. Efficacy of Cryotherapy as a Primary Endoscopic Ablation Modality for Dysplastic Barrett's Esophagus and Early Esophageal Neoplasia: A Systematic Review and Meta-Analysis. Cancer Control. 2020 Jan-Dec;27(1):1073274820976668.	SLR (subgroup analysis reporting on CBA) N=1	CED and CE-IM rates are very comparable to the CE-D and CE-IM rates of RFA	Deprioritized as only 1 relevant study reported on CBA, included as a subgroup analysis. The included study (Canto 2018) was already included within this overview as a key study.