Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	Cryotherapy ablation (truFreeze spray cryotherapy system) for the treatment of oesophageal conditions
Topic exploration report number:	TER245

Introduction and aims

This topic was identified through HealthTechConnect.

The truFreeze spray cryotherapy system uses liquid nitrogen spray for the cryogenic destruction of tissue. The liquid nitrogen is sprayed at the target tissue via a specialised catheter, causing a fast freezing and then thawing of the tissue. This results in cellular destruction whilst preserving the extracellular matrix, promoting rejuvenation and growth of healthy cells. The manufacturer states that truFreeze spray cryotherapy system has a CE mark class IIb.

Health Technology Wales researchers searched for evidence on cryotherapy ablation interventions for the treatment of oesophageal conditions, including gastric antral vascular ectasia (GAVE), oesophageal cancer and Barrett's oesophagus.

Summary of evidence

Guidance

We identified two pieces of interventional procedures guidance on balloon cryoablation, for squamous dysplasia of the oesophagus (IPG683, 2020) and for Barrett's oesophagus (IPG682, 2020). The recommendations state that evidence on the safety and efficacy for both populations "is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. This could be in the form of randomised controlled trials or published registry data…". The recommendations also state that patients should be selected by clinicians experienced in managing the condition, and that further research should report patient selection, longer-term follow-up and complications.

NICE clinical guideline 106 (2010) on ablative therapy for Barrett's oesophagus did not mention cryoablation or cryotherapy.

Barrett's oesophagus

The majority of evidence identified in this exploratory search was on cryotherapy for Barrett's oesophagus.

Secondary evidence

We identified five systematic reviews evaluating cryotherapy: see Table 1 for a summary of these reviews. One review evaluated cryoballoon therapy (Westerveld et al. 2020), one evaluated liquid nitrogen therapy (Mohan et al. 2020), and three evaluated any type of cryotherapy (carbon dioxide, liquid nitrogen or balloon treatment; Tariq et al. 2020, Hamade et al. 2019, Visrodia et al. 2018). Tariq et al. (2019) and Hamade et al (2019) included subgroup meta-analysis of liquid nitrogen cryotherapy. None of the systematic reviews included evidence comparing cryotherapy against other therapeutic options such as standard care, other cryotherapies or other ablative therapies.

All of the evidence within these reviews were observational studies, a mix of prospective or retrospective in design, and many studies were conducted in a single centre. Three of the reviews included studies that were available from abstracts only. Four of the five reviews reported on quality assessment using the Newcastle Ottowa Scale (a tool for assessing the quality of non-randomised studies) which has been included in Table 1.

Across the three reviews evaluating any cryotherapy, pooled complete eradication of dysplasia (CE-D) ranged from 76% to 91%. Pooled proportion of the complete eradication of intestinal metaplasia (CE-IM) ranged from 36% to 46%. For cryoballoon therapy, Westerveld et al. (2020) reported pooled CE-D with cryoballoon therapy as 94% and pooled CE-IM as 86%. These meta-analysis results carried moderate/high levels of heterogeneity (I^2 reported as 56% or higher).

For liquid nitrogen cryotherapy, Mohan et al. (2020) reported pooled CE-D of 84% (low heterogeneity, I^2 = 23%) and pooled CE-IM as 57% (moderate heterogeneity, I^2 = 47%). Overall adverse events ranged between 5% and 13% (reported in 4/5 reviews). Hamade et al. (2019) subgroup analysis for liquid nitrogen reported pooled CE-D of 90%, CE-IM of 69% and CE-N of 98%.

We identified one additional systematic review that searched for randomised controlled trials comparing different ablative therapies for Barrett's oesophagus, including cryotherapy (De Souza et al. 2014); however, no randomised controlled trials evaluating cryotherapy were identified.

Table 1. Summary of systematic reviews for Barrett's oesophagus.

Reference	Intervention	Study type (no. studies, no. participants)	Authors' comment on reliability
Westerveld et al. (2020)	Balloon cryotherapy	Prospective and retrospective observational studies (7 studies, 272 participants). 3 studies were abstract only	5 studies were reported as high quality, 2 studies of low quality (Newcastle Ottowa scale).
Tariq et al. (2020)	Any cryotherapy (carbon dioxide, liquid nitrogen, balloon)	Prospective and retrospective observational studies (14 studies, 405 participants). 5 studies were abstract only.	8 studies were reported as high quality and 6 were low quality (Newcastle Ottowa scale)

Mohan et al. (2019)	Liquid nitrogen cryotherapy	Prospective and retrospective observational studies (9 studies, 386 participants).	All studies were considered high-quality (Newcastle Ottowa scale).
Hamade et al. (2019)	Any cryotherapy (carbon dioxide, liquid nitrogen, balloon)	Retrospective observational studies (6 studies, 282 participants)	Quality assessment not reported.
Visrodia et al. (2018)	Any cryotherapy (carbon dioxide, liquid nitrogen, balloon)	Prospective and retrospective observational studies (11 studies, 148 participants). 7 studies were abstract only.	5 studies were deemed high quality, and 6 studies were deemed low quality (Newcastle Ottowa scale).

Primary evidence

We identified 14 observational studies evaluating different types of cryotherapy for Barrett's oesophagus: four studies evaluating cryoballoon therapy, nine studies evaluating liquid nitrogen therapy, and one evaluating carbon dioxide cryotherapy. Three further primary studies we identified evaluated multiple oesophageal conditions, including Barrett's oesophagus. Further evaluation of the evidence would be required to establish the inclusion of these studies within the secondary evidence, as well as to assess the quality of these studies.

Of the 14 studies, two non-randomised studies compared cryotherapy with radiofrequency ablation. The first (n = 94 participants) compared post-procedural pain between liquid nitrogen spray and radiofrequency ablation (either focal radiofrequency ablation, or circumferential radiofrequency ablation) immediately after treatment and 48 hours after treatment (Solomon et al. 2019). Pain intensity (reported using a numeric pain scale) was significantly lower in the liquid nitrogen group versus both the focal radiofrequency ablation and circumferential radiofrequency groups at both time points. There was no difference in dysphagia after treatment at any time point.

The second study (n = 46) compared focal cryoballoon therapy with focal radiofrequency ablation (van Munster et al. 2018). No difference was reported in Barrett's oesophagus surface regression (88% vs 90%, p = 0.62). Pain, dysphagia, and analgesics were significantly smaller after cryoballoon therapy versus radiofrequency ablation (all $p < 0.01$). Peak pain was lower after cryoballoon therapy (visual analog scale 2 vs 4, $p < 0.01$), and the duration of pain was also shorter after cryoballoon therapy (2 vs 4 days, $p < 0.01$).

Oesophageal neoplasia or oesophageal cancer

Secondary evidence

No secondary evidence was identified.

Primary evidence

We identified six primary studies on cryotherapy for oesophageal cancer or neoplasia, summarised in Table 2. Four studies evaluated liquid nitrogen spray, whereas two evaluated cryoballoon therapy. None of the studies compared cryotherapy against other therapeutic options such as standard care, other cryotherapies or other ablative therapies. On initial exploration of these studies (reviewing the abstract only), the studies vary in design, including

population, procedural methods, and outcomes reported. Complete response (reported in 5 abstracts) ranged from 56% to 100%. Studies reported no serious adverse events.

Three additional studies evaluated cryotherapy in mixed populations, which included oesophageal neoplasia/cancer and Barrett's oesophagus.

Table 2. Summary of primary studies for oesophageal cancer/neoplasia

Reference	Population	Intervention	Study type (no. participants)
Shah et al. (2019)	Advanced oesophageal cancer (pre-chemoradiotherapy)	Liquid nitrogen spray	Prospective observational study (n = 21)
Ke et al. (2019)	Oesophageal squamous cell neoplasia	Cryoballoon therapy	Prospective observational (n = 80)
Kachaamy et al. (2018)	Inoperable oesophageal cancer	Liquid nitrogen spray	Retrospective case series (n = 49)
Canto et al (2018)	Early oesophageal squamous cell neoplasia	Cryoballoon therapy	Prospective observational study (initial results, n = 10)
Tsai et al. (2017)	Oesophageal adenocarcinoma, where conventional therapy had failed or was not appropriate	Liquid nitrogen spray	Prospective and retrospective study (n = 88)
Greenwald et al. (2010)	Oesophageal carcinoma where conventional therapy had failed or was inappropriate	Liquid nitrogen spray	Retrospective observational study (n = 79)

Gastric antral vascular ectasia (GAVE)

Secondary evidence

We did not identify any secondary evidence for this population.

Primary evidence

We identified one study assessing endoscopic cryotherapy for the management of GAVE (Cho et al. 2008). The study was single centre and prospectively followed up patients who had received cryotherapy endoscopy (n = 12). Six patients (50%) had a complete response, and 6 patients had a partial response. The mean number of units of blood transfused in the period of 3 months before cryotherapy and during the period of follow-up of 3 months was 4.6 and 1.7 units, respectively. In 32 of 36 cryotherapy treatment sessions performed (89%), it was technically possible to treat more than 90% of GAVE lesions.

Areas of uncertainty

- The evidence for cryotherapy to treat oesophageal conditions is limited to observational studies, and most studies were intervention-only (i.e. no studies compared cryotherapy against other treatment options). In the systematic reviews for Barrett's oesophagus, authors reported moderate to high heterogeneity across the studies. Fuller appraisal would be required to ascertain the level and quality of the evidence, and whether they provide enough certainty on the outcomes reported.
- There is a potential overlap between oesophageal neoplasia/cancer and Barrett's oesophagus, as Barrett's oesophagus is a precursor to cancer. Three of the primary studies identified evaluated cryotherapy for both populations. If cryotherapy was to be appraised, then consideration is needed on how this overlap should be addressed.
- The studies evaluating cancer/neoplasia varied in the specific population that was included in the study (e.g. all stages, early neoplasia, inoperable or where conventional therapy had failed). It is unclear at this stage whether it would be appropriate to apply the evidence to appraise cryotherapy for cancer/neoplasia as a whole, or whether each indication would need to be considered individually.

Conclusions

The use of truFreeze and other cryotherapy technologies can be used in different oesophageal populations. This exploratory report aimed to identify the available evidence across these populations to inform where there might be gaps and where there might be enough evidence for fuller appraisal.

The clinical evidence we identified, for all oesophageal indications, was limited to observational studies, some retrospective in nature. Most of the studies did not include a comparator group, but we did identify two non-randomised comparative studies for Barrett's oesophagus. We did not identify any economic evidence.

The majority of evidence we identified, and the only secondary evidence, was in the use of cryotherapy for Barrett's oesophagus (six systematic reviews, 14 primary studies). Two of the systematic reviews included pooled outcomes for liquid nitrogen spray, specifically. One of the comparative studies showed that pain intensity was significantly lower with liquid nitrogen versus radiofrequency ablation; this study did not report complete eradication outcomes. The other comparative study demonstrated similar surface regression between cryoballoon therapy and radiofrequency ablation, and that cryoballoon resulted in less pain for a shorter time. Neither of these studies reported complete eradication outcomes.

Six primary studies evaluated cryotherapy in oesophageal neoplasia or cancer, although these varied in regards to the target population in each study. Three additional studies included a mixed population including people with Barrett's oesophagus and oesophageal neoplasia or cancer.

The evidence we identified for gastric antral vascular ectasia was limited to one study and so a fuller evidence review is not likely to be warranted in this group.

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland	We did not identify any relevant guidance or evidence review from this source.
Health Technology Assessment Group	Department of Health (2019). Diagnosis, staging and treatment of patients with oesophageal or oesophagogastric junction cancer (NCEC National Clinical Guideline No. 19). Available at: https://health.gov.ie/national-patient-safety-office/ncec/national-clinical-guidelines/
Health Information and Quality Authority	We did not identify any relevant guidance or evidence review from this source.
EUnetHTA	We did not identify any relevant guidance or evidence review from this source.
International HTA Database	We did not identify any relevant guidance or evidence review from this source.
UK guidelines and guidance	
SIGN	We did not identify any relevant guidance or evidence review from this source.
NICE	Barrett's oesophagus: ablative therapy. Clinical guideline [CG106]. 2010. https://www.nice.org.uk/guidance/cg106 Does not mention cryoablation. Balloon cryoablation for squamous dysplasia of the oesophagus. Interventional procedures guidance [IPG683]. 2020. https://www.nice.org.uk/guidance/ipg683 Evidence on the safety and efficacy of balloon cryoablation for squamous dysplasia of the oesophagus is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. This could be in the form of randomised controlled trials or published registry data. Find out what only in research means on the NICE interventional procedures guidance page. Patient selection should be done by clinicians experienced in managing squamous dysplasia of the oesophagus. Further research should report patient selection, longer-term follow up and complications, including oesophageal stricture. Balloon cryoablation for Barrett's oesophagus. Interventional procedures guidance [IPG682]. 2020. https://www.nice.org.uk/guidance/IPG682 Evidence on the safety and efficacy of balloon cryoablation for Barrett's oesophagus is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. This could be in the form of randomised controlled trials or published registry data. Find out what only in research means on the NICE interventional procedures guidance page. Patient selection should be done by clinicians experienced in managing Barrett's oesophagus.

	Further research should report patient selection, longer-term follow up and complications, including oesophageal stricture.
Secondary literature and economic evaluations	
https://www.epistemonikos.org/en/	**Early oesophageal neoplasia and Barrett's oesophagus:** Tariq R, Enslin S, Hayat M, et al. (2020). 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: Journal of the Moffitt Cancer Center. 27(1): 1-9. doi: 10.1177/1073274820976668 **Barrett's oesophagus:** 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 international open. 8(2): E172-E8. doi: 10.1055/a-1067-4520 Hamade N, Desai M, Thoguluva Chandrasekar V, et al. (2019). Efficacy of cryotherapy as first line therapy in patients with Barrett's neoplasia: a systematic review and pooled analysis. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus. 32(11). doi: 10.1093/dote/doz040 Mohan BP, Krishnamoorthi R, Ponnada S, et al. (2019). Liquid Nitrogen Spray Cryotherapy in Treatment of Barrett's Esophagus, where do we stand? A Systematic Review and Meta-Analysis. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus. 32(6). doi: 10.1093/dote/doy130 Visrodia K, Zakko L, Singh S, et al. (2018). Cryotherapy for persistent Barrett's esophagus after radiofrequency ablation: a systematic review and meta-analysis. Gastrointestinal endoscopy. 87(6): 1396-404.e1. doi: 10.1016/j.gie.2018.02.021 De Souza TF, Artifon EL, Mestieri LH, et al. (2014). Systematic review and meta-analysis of endoscopic ablative treatment of Barrett's esophagus. Revista de gastroenterología del Perú : órgano oficial de la Sociedad de Gastroenterología del Perú. 34(3): 217-24. Souza TFd. (2011). Systematic literature review on endoscopic ablative therapies of Barrett´s esophagus. 86-.
Cochrane library	We did not identify any relevant secondary evidence from this source.
Medline	We did not identify any relevant secondary evidence from this source.
Primary studies	
https://www.epistemonikos.org/en/	**GAVE:** Cho S, Zanati S, Yong E, et al. (2008). Endoscopic cryotherapy for the management of gastric antral vascular ectasia. Gastrointestinal endoscopy. 68(5): 895-902. doi: 10.1016/j.gie.2008.03.1109
Cochrane library	**Barrett's oesophagus:**

	van Munster SN, Overwater A, Haidry R, 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. doi: 10.1016/j.gie.2018.06.015
Medline	**Barrett's oesophagus and oesophageal neoplasia:** Greenwald BD, Dumot JA, Horwhat JD, et al. (2010). Safety, tolerability, and efficacy of endoscopic low-pressure liquid nitrogen spray cryotherapy in the esophagus. Diseases of the Esophagus. 23(1): 13-9. doi: https://dx.doi.org/10.1111/j.1442-2050.2009.00991.x Kaul V, Bittner K, Ullah A, et al. (2020). Liquid nitrogen spray cryotherapy-based multimodal endoscopic management of dysplastic Barrett's esophagus and early esophageal neoplasia: retrospective review and long-term follow-up at an academic tertiary care referral center. Diseases of the Esophagus. 33(4): 15. doi: https://dx.doi.org/10.1093/dote/doz095 Thota PN, Arora Z, Dumot JA, et al. (2018). Cryotherapy and Radiofrequency Ablation for Eradication of Barrett's Esophagus with Dysplasia or Intramucosal Cancer. Digestive Diseases & Sciences. 63(5): 1311-9. doi: https://dx.doi.org/10.1007/s10620-018-5009-4 **Barrett's oesophagus:** Canto MI, Shaheen NJ, Almario JA, et al. (2018). Multifocal nitrous oxide cryoballoon ablation with or without EMR for treatment of neoplastic Barrett's esophagus (with video). Gastrointestinal endoscopy. 88(3): 438-46.e2. doi: https://dx.doi.org/10.1016/j.gie.2018.03.024 Canto MI, Shin EJ, Khashab MA, et al. (2015). Safety and efficacy of carbon dioxide cryotherapy for treatment of neoplastic Barrett's esophagus. Endoscopy. 47(7): 582-91. doi: https://dx.doi.org/10.1055/s-0034-1391734 Canto MI, Trindade AJ, Abrams J, et al. (2020). Multifocal Cryoballoon Ablation for Eradication of Barrett's Esophagus-Related Neoplasia: A Prospective Multicenter Clinical Trial. American Journal of Gastroenterology. 115(11): 1879-90. doi: https://dx.doi.org/10.14309/ajg.0000000000000822 Dumot JA, Vargo JJ, 2nd, Falk GW, et al. (2009). An open-label, prospective trial of cryospray ablation for Barrett's esophagus high-grade dysplasia and early esophageal cancer in high-risk patients. Gastrointestinal endoscopy. 70(4): 635-44. doi: https://dx.doi.org/10.1016/j.gie.2009.02.006 Ghorbani S, Tsai FC, Greenwald BD, et al. (2016). Safety and efficacy of endoscopic spray cryotherapy for Barrett's dysplasia: results of the National Cryospray Registry. Diseases of the Esophagus. 29(3): 241-7. doi: https://dx.doi.org/10.1111/dote.12330 Gosain S, Mercer K, Twaddell WS, et al. (2013). Liquid nitrogen spray cryotherapy in Barrett's esophagus with high-grade dysplasia: long-term results. Gastrointestinal endoscopy. 78(2): 260-5. doi: https://dx.doi.org/10.1016/j.gie.2013.03.002

Halsey KD, Chang JW, Waldt A, et al. (2011). Recurrent disease following endoscopic ablation of Barrett's high-grade dysplasia with spray cryotherapy. Endoscopy. 43(10): 844-8. doi: https://dx.doi.org/10.1055/s-0030-1256649

Kunzli HT, Scholvinck DW, Meijer SL, et al. (2017). Efficacy of the CryoBalloon Focal Ablation System for the eradication of dysplastic Barrett's esophagus islands. Endoscopy. 49(2): 169-75. doi: https://dx.doi.org/10.1055/s-0042-120117

Ramay FH, Cui Q, Greenwald BD. (2017). Outcomes after liquid nitrogen spray cryotherapy in Barrett's esophagus-associated high-grade dysplasia and intramucosal adenocarcinoma: 5-year follow-up. Gastrointestinal endoscopy. 86(4): 626-32. doi: https://dx.doi.org/10.1016/j.gie.2017.02.006

Shaheen NJ, Greenwald BD, Peery AF, et al. (2010). Safety and efficacy of endoscopic spray cryotherapy for Barrett's esophagus with high-grade dysplasia. Gastrointestinal endoscopy. 71(4): 680-5. doi: https://dx.doi.org/10.1016/j.gie.2010.01.018

Solomon SS, Kothari S, Smallfield GB, et al. (2019). Liquid Nitrogen Spray Cryotherapy is Associated With Less Postprocedural Pain Than Radiofrequency Ablation in Barrett's Esophagus: A Multicenter Prospective Study. Journal of Clinical Gastroenterology. 53(2): e84-e90. doi: https://dx.doi.org/10.1097/MCG.0000000000000999

Trindade AJ, Inamdar S, Kothari S, et al. (2017). Feasibility of liquid nitrogen cryotherapy after failed radiofrequency ablation for Barrett's esophagus. Digestive Endoscopy. 29(6): 680-5. doi: https://dx.doi.org/10.1111/den.12869

Trindade AJ, Pleskow DK, Sengupta N, et al. (2018). Efficacy of liquid nitrogen cryotherapy for Barrett's esophagus after endoscopic resection of intramucosal cancer: A multicenter study. Journal of Gastroenterology & Hepatology. 33(2): 461-5. doi: https://dx.doi.org/10.1111/jgh.13909

Oesophageal cancer:

Canto MI, Abrams JA, Kunzli HT, et al. (2018). Nitrous oxide cryotherapy for treatment of esophageal squamous cell neoplasia: initial multicenter international experience with a novel portable cryoballoon ablation system (with video). Gastrointestinal endoscopy. 87(2): 574-81. doi: https://dx.doi.org/10.1016/j.gie.2017.07.013

Greenwald BD, Dumot JA, Abrams JA, et al. (2010). Endoscopic spray cryotherapy for esophageal cancer: safety and efficacy. Gastrointestinal endoscopy. 71(4): 686-93. doi: https://dx.doi.org/10.1016/j.gie.2010.01.042

	Halsey KD, Greenwald BD. (2010). Cryotherapy in the management of esophageal dysplasia and malignancy. Gastrointestinal Endoscopy Clinics of North America. 20(1): 75-87, vi-vii. doi: https://dx.doi.org/10.1016/j.giec.2009.07.009 Kachaamy T, Prakash R, Kundranda M, et al. (2018). Liquid nitrogen spray cryotherapy for dysphagia palliation in patients with inoperable esophageal cancer. Gastrointestinal endoscopy. 88(3): 447-55. doi: https://dx.doi.org/10.1016/j.gie.2018.04.2362 Ke Y, van Munster SN, Xue L, et al. (2019). Prospective study of endoscopic focal cryoballoon ablation for esophageal squamous cell neoplasia in China. Gastrointestinal endoscopy. 90(2): 204-12. doi: https://dx.doi.org/10.1016/j.gie.2019.03.017 Tsai FC, Ghorbani S, Greenwald BD, et al. (2017). Safety and efficacy of endoscopic spray cryotherapy for esophageal cancer. Diseases of the Esophagus. 30(11): 1-7. doi: https://dx.doi.org/10.1093/dote/dox087
Ongoing primary or secondary research	
PROSPERO database	We did not identify any relevant ongoing secondary evidence from this source.
Clinicaltrials.gov	Phase 1 Dose-Frequency Escalation Study of Neoadjuvant Cryotherapy in Locally Advanced Esophageal Cancer. Recruiting. Estimated primary completion date July 2021. https://clinicaltrials.gov/ct2/show/NCT04248582 A Prospective Single Arm Multicenter Study Evaluating the Effects of Spray Cryotherapy in Patients With Persistent Local Esophageal Cancer. Active, not recruiting. Estimated primary completion date November 2021. https://clinicaltrials.gov/ct2/show/NCT03243734 Quality of Life Assessment in Patients Receiving Cryotherapy in Addition to Chemotherapy for Palliation of Unresectable Esophageal or Gastroesophageal Cancer. Recruiting. Estimated primary completion date July 2020, study completion date January 2021. https://clinicaltrials.gov/ct2/show/NCT03285035 Evaluation of Effect of CryoBalloon Focal Ablation System on Human Esophageal Epithelium (ColdPlay2). Enrolling by invitation. Estimated primary completion date August 2023. https://clinicaltrials.gov/ct2/show/NCT02534233 Post Procedural Pain Assessment in Patients Undergoing Balloon Cryotherapy Compared to Radiofrequency Ablation (RFA) for Dysplastic Barrett's: A Prospective Study. Estimated primary completion date October 2022. https://clinicaltrials.gov/ct2/show/NCT03387982 CryoSpray Ablation for Barrett's Esophagus After Treatment Failure With Serial RadioFrequency Ablation. Estimated primary completion date June 2021. https://clinicaltrials.gov/ct2/show/NCT01882478

	trūFreeze® Spray Cryotherapy Patient Registry. Estimated primary completion date August 2021. https://clinicaltrials.gov/ct2/show/NCT01802203 Gastric Antral Vascular Ectasia Treatment With Balloon Cryotherapy: A Multicenter Prospective Trial. Estimated primary completion date February 2023. https://clinicaltrials.gov/ct2/show/NCT04760873
Other	
Provided by the company	Shah T, Kushnir V, Mutha P, Majhail M, Patel B, Schutzer M, Mogahanaki D, Smallfield G, Patel M, Zfass A. Neoadjuvant cryotherapy improves dysphagia and may impact remission rates in advanced esophageal cancer. Endosc Int Open. 2019 Nov;7(11):E1522-E1527. doi: 10.1055/a-0957-2798. Barthel JS, Kucera S, Harris C, et al. (2011). Cryoablation of persistent Barrett's epithelium after definitive chemoradiation therapy for esophageal adenocarcinoma. Gastrointestinal endoscopy. 74(1): 51-7. doi: https://doi.org/10.1016/j.gie.2011.03.1121

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Concepts used:	Cryotherapy (cryotherapy*), cryoablation (cryoablat*), oesophageal/oesophagus (*esophag*), truFreeze