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Cryotherapy for persistent Barrett's esophagus after radiofrequency ablation: a systematic review and meta-analysis

Kavel Visrodia, MD[1], **Liam Zakko, MD**[1], **Siddharth Singh, MD, MS**[2], **Cadman L. Leggett, MD**[1], **Prasad G. Iyer, MD, MS**[1], and **Kenneth K. Wang, MD**[1]

[(1)]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA

[(2)]Division of Gastroenterology, University of California San Diego, La Jolla, California.

Abstract

Background and Aims: A small but significant proportion of patients with Barrett's esophagus (BE) have persistent dysplasia or intestinal metaplasia (IM) after treatment with radiofrequency ablation (RFA). Cryotherapy is a cold-based ablative modality that is increasingly being used in this setting. We aimed to better understand the efficacy of second-line cryotherapy in patients with BE who have persistent dysplasia or IM after RFA by conducting a systematic review and meta-analysis.

Methods: We performed a systematic literature search of Pubmed, EMBASE, and Web of Science through September 1, 2017. Articles were included for meta-analysis based on the following inclusion criteria: ≥5 patients with BE treated with RFA had persistent dysplasia or IM; they subsequently underwent ≥1 session of cryotherapy with follow-up endoscopy; the proportions of patients achieving complete eradication of dysplasia (CE-D) and/or IM (CE-IM) were reported. The main outcomes were pooled proportions of CE-D and CE-IM by using a random effects model.

Results: Eleven studies making up 148 patients with BE treated with cryotherapy for persistent dysplasia or IM after RFA were included. The pooled proportion of CE-D was 76.0% (95% confidence interval [CI] 57.7-88.0), with substantial heterogeneity (I^2 = 62%). The pooled proportion of CE-IM was 45.9% (95% CI, 32.0-60.5) with moderate heterogeneity (I^2 = 57%). Multiple preplanned subgroup analyses did not sufficiently explain the heterogeneity. Adverse effects were reported in 6.7% of patients.

Conclusion: Cryotherapy successfully achieved CE-D in three fourths and CE-IM in half of patients with BE who did not respond to initial RFA. Considering its favorable safety profile, cryotherapy may be a viable second-line option for this therapeutically challenging cohort of patients with BE, but higher-quality studies validating this remain warranted. (Gastrointest Endosc 2018;87:1396-404.)

Reprint requests: Kenneth K. Wang, MD, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Ave, SW, Rochester, MN 55905. If you would like to chat with an author of this article, you may contact Dr Wang at wang.kenneth@mayo.edu.

Barrett's esophagus (BE) is thought to be the transfiguration of normal esophageal squamous epithelium to metaplastic columnar epithelium. BE remains the only known histologic precursor to esophageal adenocarcinoma, and the risk of neoplastic progression is closely correlated with the presence of dysplasia. Therefore, after resection of any mucosal nodularity, patients with BE and low-grade dysplasia or high-grade dysplasia are recommended to receive ablative therapy, with the ultimate goal of eradicating the Barrett's epithelium.[1]

Level 1 evidence supports the efficacy of radiofrequency ablation (RFA) in reducing the risk of neoplastic progression in patients with BE and dysplasia.[2,3] Approximately 80% to 90% of patients with BE and dysplasia treated with RFA will achieve complete eradication of dysplasia (CE-D) or intestinal metaplasia (CE-IM), usually within 2 to 3 sessions of therapy.[4] However, patients who fail to respond to RFA within this period and have persistent dysplasia and/or intestinal metaplasia (IM) remain at risk. The optimal strategy for treating these patients has yet to be defined.

Cryotherapy is an alternative thermal ablative modality that induces tissue injury via cycles of rapid cooling and thawing.[5] Studies on cryotherapy in previously untreated patients have demonstrated encouraging efficacy, safety, and durability, but the lack of level 1 evidence currently precludes its widespread use.[6-9] In the small but significant proportion of patients who do not respond initially to RFA, however, cryotherapy is increasingly being used as second-line therapy. Based on recent small series, this approach has been variably successful in achieving CE-D and CE-IM, with rates ranging from 71% to 86% and 29% to 50%, respectively.[10-12] We aimed to better understand the efficacy of cryotherapy in patients with persistent dysplasia or IM after RFA by performing a systematic review and meta-analysis of the literature.

METHODS

Search strategy

We performed a systematic search of the electronic databases Pubmed, EMBASE, and Web of Science from their inception through September 1, 2017, with the assistance of an experienced medical librarian who received input from study investigators. The search strategy included a combination of the following terms: barrett,* esophag,* oesophag,* barrett esophagus, esophageal diseases, dysplas,* metaplas,* columnar,* esophagitis, peptic/or esophageal stenosis, cryosurgery,* cryother,* cryoablat,* cryogen,* freeze,* cryo,* salvag.* We excluded journals in foreign languages because cryotherapy is not available in foreign countries. The search results were independently reviewed by 2 investigators (K.V., L.Z.) for relevant articles based on prespecified inclusion and exclusion criteria. Relevant articles were then reviewed in full text for additional pertinent information and data abstraction. The bibliographies of systematic and narrative reviews were screened for additional relevant articles. Any discrepancies were resolved by discussion with the lead investigator (K.K.W.).

Study selection

The titles and abstracts of search results were initially screened for studies reporting outcomes of cryotherapy in the treatment of 5 or more patients with BE. These articles were then reviewed in full text and included for meta-analysis if they met the following specific inclusion criteria: the study included at least 5 patients who had been treated previously with RFA but had persistent dysplasia or IM, and the study reported the rate of CE-D and/or CE-IM in these patients after at least 1 treatment session with cryotherapy (either liquid nitrogen, carbon dioxide gas, or balloon-based liquid nitrous oxide). Studies were excluded if cryotherapy was used (1) as first-line treatment for previously untreated BE, (2) after a treatment modality other than RFA (eg, photodynamic therapy) or (3) after achievement of CE-IM, and (4) if there was insufficient information provided to determine the rate of CE-D or CE-IM in patients undergoing cryotherapy after RFA. The use of EMR was permissible, so long as it was not intended for BE eradication (ie, widespread EMR). If more than 1 publication from a study or institution was identified, the most recent publication with relevant information was included for meta-analysis.

Data extraction and quality assessment

Data related to study and patient characteristics were extracted independently by 2 investigators (K.V., L.Z.) who used a standardized abstraction form. A formal quality assessment was performed by using a modified version of the Newcastle-Ottawa scale for cohort studies,[13] consisting of 6 questions, each valued up to 1 point (Supplemental Table 1, available online at www.giejournal.org): the degree to which the study represented the average adult in the community, large cohort size, performance of EMR before RFA, the number of RFA sessions before cryotherapy, the number of cryotherapy sessions before assessment of outcomes, and adequacy of follow-up. Studies with scores totaling >3 and ≤3 were deemed to be of high and low quality, respectively.

Data synthesis and analysis

The primary outcomes of interest were the proportions of CE-D and CE-IM among patients treated with cryotherapy for persistent dysplasia or IM after RFA. To assess the stability of these findings and identify sources of heterogeneity, preplanned subgroup analyses based on cohort size, cohort histology after RFA (inclusion of patients with persistent dysplasia only vs inclusion of patients with persistent dysplasia and IM), study quality, publication type (full text vs abstract), and publication year (before 2013 vs 2013 or later) were conducted. Progression to cancer and adverse events were recorded when reported.

Statistical analysis

This study was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines by using a predefined protocol.[14] Pooled proportions of CE-D were calculated only among patients treated with cryotherapy for persistent dysplasia after RFA. Pooled proportions of CE-IM were calculated among patients treated with cryotherapy for persistent dysplasia or IM after RFA. We used a random effects model to account for differences in study size. Heterogeneity was assessed by using I^2 statistics, with values of <30%, 30% to 60%, 61% to 75%, and >75% being classified as low,

moderate, substantial, and considerable heterogeneity, respectively. We assessed between-study sources of heterogeneity by using predefined subgroup analyses, with a *P* value for differences between subgroups of < .05 being considered statistically significant. All analyses were performed by using Comprehensive Meta-Analysis software (version 2, Biostat, Englewood, NJ).

RESULTS

Search results

Our search strategy yielded a total of 481 unique articles, of which 11 studies fulfilled inclusion criteria for meta-analysis (Fig. 1).[10-12,15-22] These 11 studies cumulatively reported on 148 patients with persistent dysplasia or IM after RFA who were treated with cryotherapy. Thirty-four studies were excluded because cryotherapy was used as first-line therapy for the treatment of previously untreated BE; 8 studies were excluded because of overlapping cohorts[23-30]; 5 studies were excluded because of insufficient information[31-34]; and 2 studies were excluded because of prior treatment with a modality other than RFA (chemoradiation).[35,36]

Characteristics and quality of included studies

All studies were observational and involved patients treated at U.S. institutions (Table 1). Most studies were single-center in design (n = 9).[10,11,15-20,22] The majority of studies were published in abstract form alone (n = 8),[15-22] whereas 3 were published in full text.[10-12] Cryotherapy was most commonly administered via liquid nitrogen (n = 6),[11,12,15,17,20,22] followed by liquid nitrous oxide balloon treatment (n = 2)[16,21] and carbon dioxide gas (n = 1).[10] One study used both liquid nitrogen and carbon dioxide gas cryotherapy,[18] and the remaining study did not specify the form of cryotherapy used.[19] All but 1 study was composed of fewer than 25 patients.[10]

Most patients were male and older, with mean and/or median lengths of BE consistent with long-segment BE (≥3 cm) or ultra-long segment BE (≥8 cm) (Table 1). All studies included patients who primarily underwent RFA with or without EMR for dysplastic BE before proceeding to cryotherapy; 5 reported a minimum number of RFA sessions (range 2-4) to be administered before a patient was a candidate for cryotherapy.[10-12,19,22] All studies included patients with persistent dysplasia after RFA, whereas 4 also included patients with persistent IM after RFA in varying proportions (range 13%-38%).[12,18,19,22] Most studies reported a mean and/or median of 2 to 3 treatment sessions with cryotherapy before outcomes were assessed. Overall, 5 studies were deemed high quality, and 6 studies were deemed low quality (Supplemental Table 2, available online at www.giejournal.org).

High-quality studies

The 5 high-quality studies included all 3 studies published in full text[10,12,29] and 2 studies published in abstract form alone.[19,22] The size of cohorts completing cryotherapy was relatively moderate to large, ranging from 16 to 44 patients. All studies reported performing EMR before RFA when indicated and specified requiring a minimum number of RFA sessions (range 2-4) before a patient was deemed RFA-refractory and was treated with

cryotherapy. Three of the studies further specified requiring a minimum of 2 cryotherapy sessions, with follow-up endoscopy and biopsy before assessing response to cryotherapy. Notably, 3 of the studies used liquid nitrogen–based cryotherapy.

The full-text publication by Canto et al[10] represents the largest experience in this meta-analysis. This was a nonrandomized, single-center study that included 44 patients with BE refractory to prior therapy (minimum 3 RFA, 1 photodynamic therapy session, and/or EMR). Patients were treated with liquid carbon dioxide–based cryotherapy until at least 2 EGDs with biopsies from the last cryotherapy session had negative results. At baseline, the majority of patients were aged >65 years (70%) and male (74%), with typical BE segments <8 cm (83%) and high-grade dysplasia (76%). At 1 year, the rates of CE-D and CE-IM were 86% and 48%, respectively.

Low-quality studies

All 6 of the low-quality studies were published in abstract form alone, with relatively small cohort sizes (range 5-9 patients).[15-18,20,21] Only 2 of these studies specified performing EMR before RFA. None of the studies reported a minimum number of RFA sessions before they determined whether to proceed with cryotherapy. Moreover, none of the studies reported a minimum number of cryotherapy sessions before outcomes were assessed. As with the high-quality studies, long-term follow-up was absent in the majority of studies.

CE-D and CE-IM

Among 10 studies reporting on 129 patients with persistent dysplasia after RFA, 100 patients achieved CE-D with cryotherapy (Fig. 2).[10-12,15-18,20-22] The pooled proportion of CE-D was 76% (95% confidence interval [CI], 57.7-88.0) with I^2 = 62% in the random effects model (Table 2). Among 9 studies reporting on 148 patients with persistent dysplasia or IM after RFA, 67 patients achieved CE-IM (Fig. 2).[10-12,17-22] The pooled proportion of CE-IM was 45.9% (95% CI, 32.0-60.5) with I^2 = 57% in the random effects model (Table 2).

Subgroup analyses and publication bias

Multiple preplanned subgroup analyses were performed to assess for stability of these findings and identify potential sources of heterogeneity (Table 3). However, cohort size, period of publication, inclusion of patients with persistent IM (in addition to patients with persistent dysplasia), publication type, or study quality did not sufficiently explain heterogeneity for the calculated proportions of CE-D and CE-IM. The rates of CE-D and CE-IM among high-quality studies were lower compared with those of low-quality studies (70.1% vs 84.6% and 40.9% vs 57.3%, respectively), but these differences were not statistically significant (P = 0.38 and P = 0.34, respectively). Notably, heterogeneity among studies published in full text was nearly absent, yielding pooled proportions of CE-D (80.1%, 95% CI, 68.3-88.3, I^2 = 4) and CE-IM (45.1%, 95% CI, 34.2-56.5, I^2 = 0) comparable to those of the overall meta-analysis.

Progression to esophageal adenocarcinoma and adverse events

Only 1 study reported progression to esophageal adenocarcinoma during treatment with cryotherapy, which occurred in 2 of 23 patients (both cases of intramucosal carcinoma).[22] Among 8 studies in which 134 patients were treated with cryotherapy, a total of 9 adverse events (6.7% of patients) were reported, including 4 strictures, 2 distal esophageal ulcers, 1 mucosal tear, 1 small contained perforation, and 1 hospitalization.

DISCUSSION

Cryotherapy is emerging as an option for the small but significant proportion of patients with BE who do not attain CE-D or CE-IM with RFA, but its efficacy in this setting is not well-understood. In this meta-analysis of 11 studies made up of 148 patients with BE, we found that second-line cryotherapy was successful in achieving CE-D in 76% and CE-IM in 46% of patients. These findings suggest a modest benefit with cryotherapy in patients who do not respond initially to RFA.

The benefit of cryotherapy after RFA may be linked to certain intrinsic and technical differences between the 2 modalities. Although both induce thermal injury, cold-based cryotherapy is different from heat-based therapies like RFA. The rapid freeze and thaw cycles delivered by cryotherapy appear to achieve a greater depth of tissue penetration with relative preservation of tissue architecture.[37] Cooling from cryotherapy also may serve as an anesthetic.[37] These properties are believed to contribute to a lower rate of esophageal stricturing and less postprocedural discomfort than is seen with RFA. Another potential advantage of cryotherapy lies in its noncontact application. A spray catheter is used to apply cryogen (liquid nitrogen and carbon dioxide gas) to the Barrett's epithelium, facilitating treatment of mucosal irregularity, hiatal hernia, or esophageal tortuosity that render contact therapy with RFA electrodes more challenging.

The ultimate goal for patients with BE and dysplasia is to eliminate the risk of neoplastic progression by completely eradicating the precursor Barrett's epithelium. In patients falling short of this goal, there is no consensus regarding how many RFA treatments are necessary before being deemed refractory or nonresponsive to RFA. Granted that the majority of patients achieve CE-D, if not CE-IM, within 2 to 3 sessions of RFA, patients with longer segments of BE may benefit from additional sessions of RFA.[38] However, patients with longer BE segments or a poor initial response (defined as <50% regression in BE length within 3 months of 1 circumferential RFA session) are less likely to achieve CE-D/CE-IM with RFA. If a patient is suboptimally responding to ablative therapy, it would be prudent to ensure adequate treatment of the underlying GERD. This may entail verifying compliance with and escalating the proton pump inhibitor regimen, pH-impedance testing, or fundoplication in the setting of a hiatal hernia.[39,40]

In patients who do not respond initially to RFA despite an optimized anti-reflux regimen, the optimal management strategy remains undefined. Although level 1 evidence exists for photodynamic therapy in patients with BE and high-grade dysplasia, photodynamic therapy remains limited by its high procedural cost and potential adverse effects, including the up to 1-in-3 chance of developing a post-ablation esophageal stricture.[41] Widespread EMR of the

entire Barrett's epithelium also may be effective, but similarly carries a significant risk of stricturing.[42] Argon plasma coagulation may be most suitable for treating residual disease limited to the gastroesophageal junction or scattered islands. At extreme ends of the spectrum, esophagectomy poses substantial risks of morbidity and mortality, whereas a surveillance-only strategy leaves patients at risk for neoplastic progression. Hence, patients with persistent disease after RFA represent a challenging cohort in which cryotherapy may offer a distinctly favorable efficacy and safety profile.

Because of the limited literature pertaining to second-line cryotherapy, we consolidated data from all 3 clinically studied systems of cryotherapy. However, this decision may have introduced heterogeneity because there are differences in delivery, freezing temperatures, and dosimetry among the systems worth highlighting.

The majority of experience in this review stems from a noncontact, liquid nitrogen–based cryotherapy system (truFreeze; CSA Medical, Lexington, Mass). This is delivered with a 7F flexible catheter, which is inserted through the working channel of the endoscope with the tip of the catheter held 1 to 2 cm away from the BE mucosa. A cap that is usually attached to the tip of the endoscope allows the correct positioning of the cryospray. Spray delivery of low-pressure liquid nitrogen is then initiated by using a foot pedal as the endoscopist monitors for visible frost formation (freezing occurs to −196 C). Varying dosimetries have been studied, with applications ranging from 10 to 20 seconds and repeated for 2 to 5 cycles, allowing for 45 to 60 seconds of thawing in between. Because of the rapid expansion of nitrogen gas, a 5-mm decompressive oral-gastric tube is necessary to insure against downstream perforation.

The largest study in this review used a noncontact, liquid carbon dioxide–based cryotherapy system (Polar Wand; GI Supply, Camp Hill, Pa). However, the catheters this device uses are no longer commercially available.[43] This system also uses a through-the-scope catheter for directing cryogen toward the mucosa (freeze occurs to −80 C) in multiple freeze-thaw cycles and requires continuous decompression. A suction catheter is attached to the tip of the endoscope via a cap to perform decompression.

The third system of cryotherapy is a contact, balloon-based, hand-held device that uses liquid nitrous oxide as its cryogen (Cryoballoon Focal Ablation System; C2 Therapeutics, Redwood, Calif). Because of its recent release, experience with this system is currently limited. This system requires passage of a through-the-scope balloon catheter that can fit through a therapeutic channel (3.2 mm) or through an accessory sheath that can be attached to the tip of a diagnostic endoscope. After inflating the balloon, the endoscopist peers through the proximal end of the balloon and can rotate the catheter (360 degrees) within the 3 cm balloon to direct cryogen delivery from its nozzle toward the portion of balloon overlying the target area. Cryogen delivery is activated by the hand-held device, and a preset dose is delivered for 6 to 12 seconds (freeze occurs to −85 C). Repeated applications are not performed with this system. Liquid nitrous oxide is available in small portable cartridges for insertion into the hand-held device, and more than one is likely necessary per treatment session. Because the cryogen is contained within the balloon and diffuses back out through the catheter, a decompressive oral-gastric tube is not necessary.

This meta-analysis has several potential limitations in addition to those already discussed. All included studies were relatively small and observational, and most studies were single-center series published in abstract form alone, amounting to a limited set of data from which we derived the earlier conclusions. This is not surprising given that the vast majority of patients will respond to RFA. Because there is no uniformly accepted definition for RFA-refractory BE, criteria for proceeding to cryotherapy varied among institutions. However, 5 studies had a reported minimum number of RFA sessions, and most studies reported a mean-median 2 to 3 RFA sessions before cryotherapy was initiated. We recognize that it is not uncommon for patients to require >2 to 3 RFA sessions to achieve CE-D or CE-IM, and so switching to a second-line therapy at this juncture may be considered premature. However, we suspect this was done in select patients who had a very poor initial response to RFA, and additional RFA was deemed low yield, but we cannot be sure. Long-term follow-up was not reported in the majority of studies, limiting conclusions regarding the risk of recurrence or progression in this seemingly higher risk cohort. We encountered moderate to substantial heterogeneity that could not be explained by several preplanned subgroup analyses. However, such heterogeneity is not uncommon in studies of prevalence and/or proportion, and conceptually the studies were similar based on our strict inclusion and exclusion criteria.

In conclusion, cryotherapy appears effective when used second-line in patients after RFA, successfully achieving CE-D in three fourths and CE-IM in approximately half of patients. Considering its encouraging safety profile, cryotherapy may be a viable option in an otherwise therapeutically challenging cohort of patients with BE who do not initially respond to RFA. However, higher quality studies with more rigorous inclusion criteria, treatment protocols, and follow-up should be performed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BE	Barrett’s esophagus
CE-D	complete eradication of dysplasia
CE-IM	complete eradication of intestinal metaplasia
IM	intestinal metaplasia

RFA radiofrequency ablation.

REFERENCES

1. Shaheen NJ, Falk GW, Iyer PG, et al. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol 2016;111:30–50; quiz 51. [PubMed: 26526079]
2. Phoa KN, van Vilsteren FG, Weusten BL, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. JAMA 2014;311:1209–17. [PubMed: 24668102]
3. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 2009;360:2277–88. [PubMed: 19474425]
4. Orman ES, Li N, Shaheen NJ. Efficacy and durability of radiofrequency ablation for Barrett's esophagus: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2013;11:1245–55. [PubMed: 23644385]
5. Johnston CM, Schoenfeld LP, Mysore JV, et al. Endoscopic spray cryotherapy: a new technique for mucosal ablation in the esophagus. Gastrointest Endosc 1999;50:86–92. [PubMed: 10385730]
6. Dumot JA, Vargo JJ 2nd, Falk GW, et al. An open-label, prospective trial of cryospray ablation for Barrett's esophagus high-grade dysplasia and early esophageal cancer in high-risk patients. Gastrointest Endosc 2009;70:635–44. [PubMed: 19559428]
7. Shaheen NJ, Greenwald BD, Peery AF, et al. Safety and efficacy of endoscopic spray cryotherapy for Barrett's esophagus with high-grade dysplasia. Gastrointest Endosc 2010;71:680–5. [PubMed: 20363409]
8. Ramay FH, Cui Q, Greenwald BD. Outcomes after liquid nitrogen spray cryotherapy in Barrett's esophagus-associated high-grade dysplasia and intramucosal adenocarcinoma: 5-year follow-up. Gastrointest Endosc 2017;86:626–32. [PubMed: 28235596]
9. Ghorbani S, Tsai FC, Greenwald BD, et al. Safety and efficacy of endoscopic spray cryotherapy for Barrett's dysplasia: results of the National Cryospray Registry. Dis Esophagus 2016;29:241–7. [PubMed: 25708903]
10. Canto MI, Shin EJ, Khashab MA, et al. Safety and efficacy of carbon dioxide cryotherapy for treatment of neoplastic Barrett's esophagus [Erratum for Endoscopy. 2015 Jul;47:582–91 Note: Khashab, Mouen [corrected to Khashab, Mouen A]; PMID: 25826275. Endoscopy 2015;47:591. [PubMed: 25920007]
11. Sengupta N, Ketwaroo GA, Bak DM, et al. Salvage cryotherapy after failed radiofrequency ablation for Barrett's esophagus-related dysplasia is safe and effective. Gastrointest Endosc 2015;82:443–8. [PubMed: 25887715]
12. Trindade AJ, Inamdar S, Kothari S, et al. Feasibility of liquid nitrogen cryotherapy after failed radiofrequency ablation for Barrett's esophagus. Dig Endosc 2017;29:680–5. [PubMed: 28303613]
13. Stang A Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5. [PubMed: 20652370]
14. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9; W64. [PubMed: 19622511]
15. Brauer BC, Wani S, Freeman SR, et al. Endoscopic eradication of Barrett's esophagus using radiofrequency ablation alone or in conjunction with endoscopic resection and cryotherapy: a single center's experience [abstract]. Gastrointest Endosc 2012;1:AB474–5.
16. Canto MI, Shin EJ, Khashab MA, et al. Multifocal nitrous oxide cryoballoon ablation with or without endoscopic mucosal resection (EMR) for treatment of neoplastic Barrett's esophagus (BE): preliminary results of a prospective clinical trial in treatment-naive and previously ablated patients [abstract]. Gastrointest Endosc 2016;1:AB159.
17. Gross S, Zfass A, Habr F, et al. Salvage cryotherapy for Barrett's esophagus with high grade dysplasia after RFA failure. Am J Gastroenterol 2010;105:S23–4.
18. Patel M, Hemminger L, Wolfsen H. Cryotherapy after radiofrequency ablation (RFA) failure in patients with Barrett's dysplasia. Am J Gastroenterol 2012;107:S1–2. [PubMed: 23074713]

19. Ramanathan V, Mallam D, Singh I, et al. Combined radiofrequency and cryoablation in Barrett's esophagus eradication. Am J Gastroenterol 2012;107:S14.
20. Tannous M, Kappus M, Farooq I, et al. Cryoablation of Barrett's esophagus with high grade dysplasia and carcinoma: safety and efficacy 2011 ACG presidential poster. Am J Gastroenterol 2011;106:S528.
21. Wang KK, Chen AM, Friedland S, et al. Multi-center experience with the cryoballoon focal ablation system (CAS) for esophageal dysplasia [abstract]. Gastrointest Endosc 2015;1:AB522.
22. Visrodia K, Zakko L, Leggett C, et al. Cryotherapy in Barrett's esophagus refractory to radiofrequency ablation. Am J Gastroenterol 2017;112:S356–7.
23. Berkowitz J, Kaul V, Kothari S, et al. Efficacy of salvage liquid nitrogen cryospray ablation after failed radiofrequency ablation for dysplastic Barrett's esophagus. Am J Gastroenterol 2016;111:S220.
24. Canto MI, Gorospe EC, Shin EJ, et al. Carbon dioxide (CO2) cryotherapy is a safe and effective treatment of Barrett's esophagus (BE) with HGD/intramucosal carcinoma [abstract]. Gastrointest Endosc 2009;69:AB341.
25. Chan DK, Leggett CL, Zakko L, et al. Salvage cryoablation is effective for treating persistent dysplasia after radiofrequency ablation of Barrett's esophagus [abstract]. Gastrointest Endosc 2016;1:AB556.
26. Flores AG, Reicher S, Chung DS, et al. Barrett's esophagus eradication by radiofrequency and cryoablation [abstract]. Gastrointest Endosc 2009;69:AB256.
27. Flores AG, Reicher S, Chung DS, et al. Combination of cryoablation and radiofrequency ablation improves eradication rates of Barrett's esophagus [abstract]. Gastrointest Endosc 2010;71:AB125.
28. Gorospe E, Ragunathan K, Timmer M, et al. Cryotherapy for persistent Barrett's dysplasia after radiofrequency ablation: If you can't burn it, freeze it! Am J Gastroenterol 2012;107:S26–7.
29. Ketwaroo GA, Sengupta N, Sethi S, et al. Salvage cryotherapy is a safe and effective therapy for patients who have persistent or recurrent dysplasia after radiofrequency ablation for dysplastic Barrett's esophagus [abstract]. Gastrointest Endosc 2014;1:AB394–5.
30. Sprung B, Granato CM, Kothari S, et al. Role of spray cryotherapy and wats in dysplastic Barrett's esophagus refractory to radiofrequency ablation [abstract]. Gastrointest Endosc 2015;1:AB507–8.
31. Hogan C, Iorio N, Walzer E, et al. Liquid nitrogen spray cryotherapy does not increase blood loss when used in patients who remain on anti-platelet or anti-coagulant medication during treatment. Am J Gastroenterol 2015;110:S728.
32. Potosky D, Greenwald BD. NBI characterization of the gastroesophageal junction after endoscopic spray cryotherapy [abstract]. Gastrointest Endosc 2009;69:AB355.
33. Walp KK, Hallquist SP, Bults A, et al. Liquid nitrogen spray cryotherapy can be used safely in retroflexion for treatment of lesions at the esophagogastric junction and gastric cardia. Gastroenterology 2014;1:S–662.
34. Suchniak-Mussari K, Dye CE, Moyer MT, et al. Efficacy and safety of liquid nitrogen cryotherapy for treatment of Barrett's esophagus. World J Gastrointest Endosc 2017;9:480–5. [PubMed: 28979713]
35. Barthel JS, Kucera S, Harris C, et al. Cryoablation of persistent Barrett's epithelium after definitive chemoradiation therapy for esophageal adenocarcinoma. Gastrointest Endosc 2011;74:51–7. [PubMed: 21549371]
36. Kucera S, Harris C, Canchi D, et al. Cryotherapy treatment of residual dysplastic Barrett epithelium in patients with esophageal adenocarcinoma treated with definitive chemoradiation. 2010 ACG/astrazeneca fellow award. Am J Gastroenterol 2010;105:S15.
37. Overwater A, Weusten B. Cryoablation in the management of Barrett's esophagus. Curr Opin Gastroenterol 2017;33:261–9. [PubMed: 28441152]
38. Dulai PS, Pohl H, Levenick JM, et al. Radiofrequency ablation for long- and ultralong-segment Barrett's esophagus: a comparative long-term follow-up study. Gastrointest Endosc 2013;77:534–41. [PubMed: 23290719]
39. O'Connell K, Velanovich V. Effects of Nissen fundoplication on endoscopic endoluminal radiofrequency ablation of Barrett's esophagus. Surg Endosc 2011;25:830–4. [PubMed: 20676687]

40. Komanduri S, Kahrilas PJ, Krishnan K, et al. Recurrence of Barrett's esophagus is rare following endoscopic eradication therapy coupled with effective reflux control. Am J Gastroenterol 2017;112:556–66. [PubMed: 28195178]

41. Overholt BF, Lightdale CJ, Wang KK, et al. Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: international, partially blinded, randomized phase III trial. Gastrointest Endosc 2005;62:488–98. [PubMed: 16185958]

42. Konda VJ, Gonzalez Haba Ruiz M, Koons A, et al. Complete endoscopic mucosal resection is effective and durable treatment for Barrett's-associated neoplasia. Clin Gastroenterol Hepatol 2014;12:2002–10; e1-2. [PubMed: 24732285]

43. Canto MI. Cryotherapy for Barrett's esophagus. Gastrointest Endosc Clin N Am 2017;27:503–13. [PubMed: 28577771]

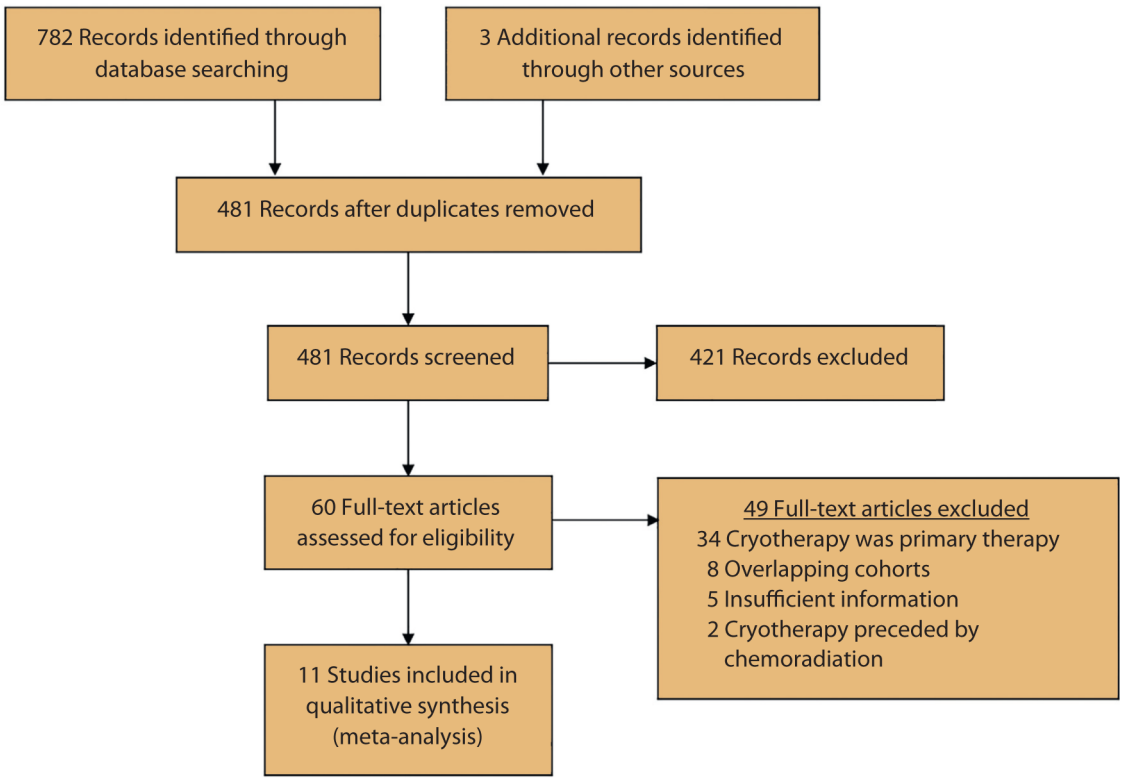

Figure 1.
Flow diagram summarizing study identification and selection.

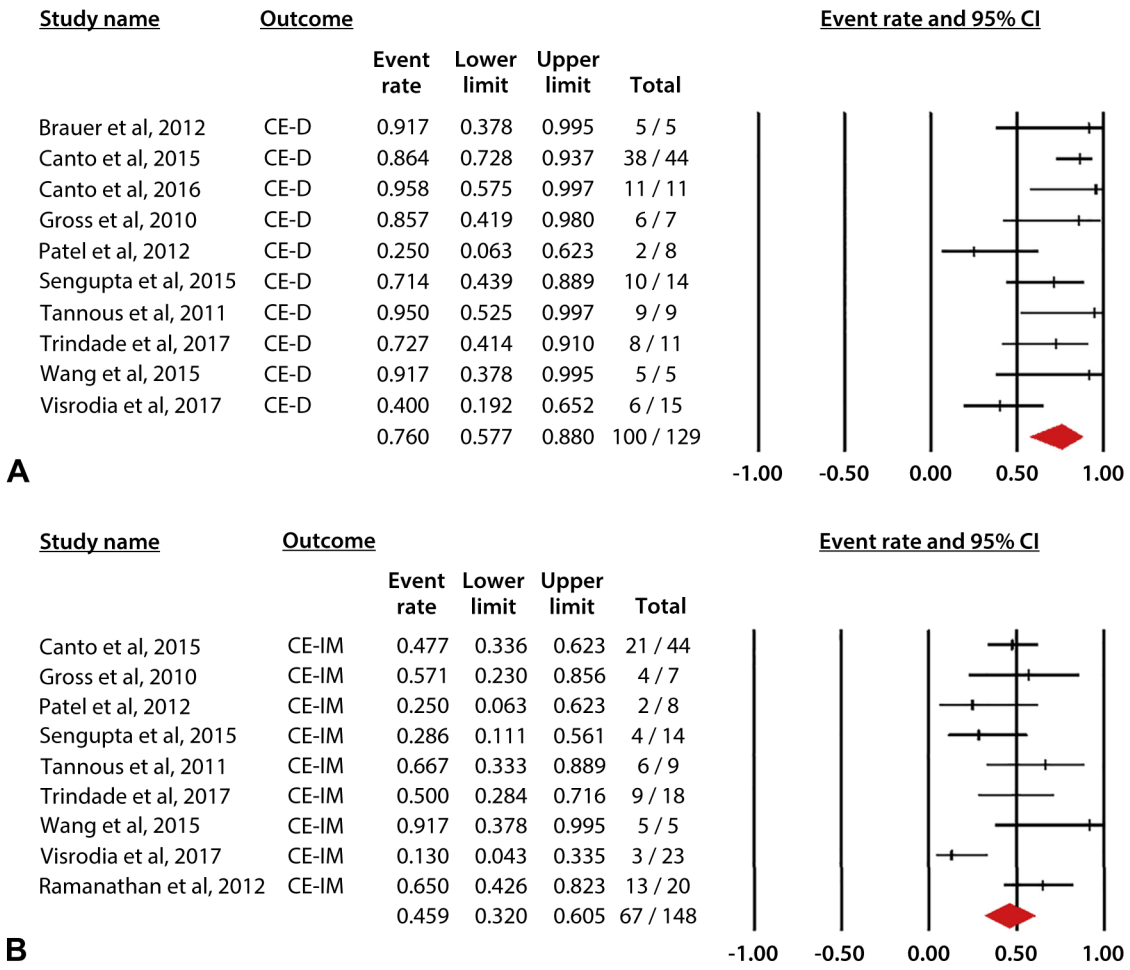

Figure 2.

Forest plots of (**A**) CE-D and (**B**) CE-IM among included studies. *CI,* confidence interval; *CE-D,* complete eradication of dysplasia.

TABLE 1.

Study and patient characteristics

Study	Publication type	Study design, center, period	No. patients enrolled in cryotherapy	Mean age, y; male, %; BE length, cm	Baseline histology before any endoscopic therapy	Type and no. of prior endoscopic therapy sessions	No. of completed cryotherapy (histology before cryotherapy)	Cryogen; no. of cryotherapy sessions	Cryotherapy dosimetry
Brauer[15]	Abstract	Retrospective, SC, 2005-2011	5	NR; NR; NR	NR	RFA; NR	5 (all dysplastic)	N_2; NR	NR
Canto[10]	Full text	Retrospective, SC, 2006-2013	47	67; 74; 5.1 (mean)	NR	RFA ± PDT or EMR *; NR (min. 3 RFA ± min. 1 PDT)	47 (36 HGD, 7 T1a, 4 T1b)	CO_2; NR	10-15 sec/site, 4-8 cycles; 4-6 weeks
Canto[16]	Abstract	Prospective, SC, NR	12	66.2; 83; NR	NR	RFA ± EMR/APC/ cryotherapy; NR	11 (all dysplastic)	NO (cryoballoon); median 2	10 sec/site; 10-12 weeks
Gross[17]	Abstract	Retrospective, SC, NR	12	69; 100; 5.6 (mean, range 1-13)	7 (all HGD)	RFA ± EMR; mean 2.1 RFA (range 1-4)	7 (all HGD)	N_2; mean 2.3 (range 1-5)	10-30 sec/site, 2-4 cycles
Patel[18]	Abstract	Prospective, SC, 2000-2011	11	72; 100; 4.8 (mean, range 1-12)	11 (4 LGD, 7 HGD)	RFA; mean 3.2 RFA (range 1-9)	8 (1 NDBE, 3 LGD, 4 HGD)	N_2 or CO_2; mean 1.8 (range 1-4)	10-20 sec/site, 4-10 cycles
Ramanathan[19]	Abstract	NR, SC, 2005 onward	24	NR; NR; NR	24 (19 NDBE, 5 dysplastic)	RFA ± EMR; NR (min. 2-3 RFA)	20 (NDBE, dysplastic)	NR; NR	NR
Sengupta[11]	Full text	Retrospective, SC, 2006-2013	21	68; 80; 7 (median)	NR	RFA ± EMR; median 3 RFA (min. 3)	16 (1 IND, 6 LGD, 7 HGD, 2 T1a) *	N_2; median 3 (min. 2)	20 sec/site, 2 cycles; 4-8 weeks
Tannous[20]	Abstract	Retrospective, SC, 2007-2011	15	NR; NR; NR	9 (all HGD)	Ablation modalities; NR	9 (all HGD)	N_2; NR	NR
Trindade[12]	Full text	Prospective, MC, 2008-2014	18	64.5; 83; 8 (median)	18 (7 LGD, 11 HGD)	RFA ± EMR; median 5 RFA (min. 4)	18 (7 NDBE, 4 LGD, 7 HGD)	N_2; mean 3 (min. 2)	20 sec/site, 2 cycles; 8-12 weeks
Wang[21]	Abstract	Retrospective, MC, NR	5	65; 86; NR	NR	RFA; NR	5 (4 HGD, 1 T1a)	NO (cryoballoon); NR	10 sec/site
Visrodia[22]	Abstract	Retrospective, SC, 2008-2017	23	65; 74; 9 (median)	23 (8 LGD, 14 HGD, 1 T1a)	RFA ± EMR; median 4 RFA (min. 3)	23 (8 NDBE, 2 IND, 7 LGD, 5 HGD, 1 T1a)	N_2; median 3 (min. 2)	NR

BE, Barrett's esophagus; *SC,* single center; *NR,* not reported; *RFA,* radiofrequency ablation; *N_2,* nitrogen; *PDT,* photodynamic therapy; *HGD,* high-grade dysplasia; *CO_2,* carbon dioxide; *APC,* argon plasma coagulation; *NO,* nitrous oxide; *LGD,* low-grade dysplasia; *NDBE,* nondysplastic Barrett's esophagus; *IND,* indefinite; *MC,* multicenter.

*Includes 2 patients with recurrent dysplasia after achieving complete eradication of dysplasia with RFA.

TABLE 2.

Pooled proportions of CE-D and CE-IM among included studies

Outcome	No. of studies	Eradication	Pooled proportion	95% CI	I^2
CE-D	10	100/129	76.0	57.7-88.0	62
CE-IM	9	67/148	45.9	32.0-60.5	57

CE-D, complete eradication of dysplasia; *CE-IM*, complete eradication of intestinal metaplasia; *CI*, confidence interval.

TABLE 3.

Subgroup analyses assessing sources of heterogeneity

Subgroup	No. of studies	Eradication	Pooled proportion	95% CI	I^2	$P_{interaction}$
Cohort size						
CE-D						
≥15 patients	7	48/59	81.0	56.4-93.3	53	.51
<15 patients	3	52/70	69.5	35.5-90.4	81	
CE-IM						
≥15 patients	5	21/43	49.3	26.8-72.1	48	.72
<15 patients	4	46/105	43.6	25.1-64.0	72	
Publication type						
CE-D						
Full text	3	56/69	80.1	68.3-88.3	4	.85
Abstract	7	44/60	77.7	47.1-93.2	66	
CE-IM						
Full text	3	34/76	45.1	34.2-56.5	0	.77
Abstract	6	33/72	49.4	25.2-73.9	70	
Year published						
CE-D						
After 2013	6	78/100	76.1	55.2-89.1	64	.90
Before 2013	4	22/29	78.5	32.0-96.6	69	
CE-IM						
After 2013	5	42/104	39.5	21.8-60.4	66	.22
Before 2013	4	25/44	56.8	39.1-72.9	19	
Study quality						
CE-D						
High	4	62/84	70.1	45.7-86.7	72	.38
Low	6	38/45	84.6	52.7-96.4	61	
CE-IM						
High	5	50/119	40.9	25.1-58.9	68	.34

Subgroup	No. of studies	Eradication	Pooled proportion	95% CI	I^2	$P_{interaction}$
Low	4	17/29	57.3	30.2-80.6	42	
Cohort histology after RFA						
CE-D	N/A					
CE-IM						
Persistent dysplasia only	5	40/79	51.2	34.6-67.6	36	.40
Persistent dysplasia and IM	4	27/69	37.5	16.4-64.7	75	

CI, Confidence interval; *CE-D,* complete eradication of dysplasia; *CE-IM,* complete eradication of intestinal metaplasia; *RFA,* radiofrequency ablation; *N/A,* not applicable; *IM,* intestinal metaplasia.