Published in final edited form as:

Gastrointest Endosc. 2017 October ; 86(4): 626–632. doi:10.1016/j.gie.2017.02.006.

Outcomes after liquid nitrogen spray cryotherapy in Barrett's esophagus-associated high-grade dysplasia and intramucosal adenocarcinoma: 5-year follow-up

Fariha H. Ramay, M.D., M.B.A.¹, Qingping Cui, M.P.H.¹, and Bruce D. Greenwald, M.D.¹

¹Division of Gastroenterology and Hepatology, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD

Abstract

Background—Liquid nitrogen spray cryotherapy (LNSCT) has been shown to be a safe, well-tolerated, and effective therapy for Barrett's esophagus (BE)-associated high grade dysplasia (BE-HGD) and intramucosal adenocarcinoma (IMC). Long-term follow-up is lacking.

Aims—The authors' aim was to assess the efficacy, durability, and rate of neoplastic progression after LNSCT in BE-HGD/IMC at 3 and 5 years.

Methods—In this single-center, retrospective study drawn from a prospective database, patients with BE-HGD/IMC of any length treated with LNSCT were followed with surveillance endoscopy with biopsy for 3 to 5 years. Patients with intramucosal adenocarcinoma completely removed by endoscopic resection were included. Outcome measures included complete eradication of HGD (CE-HGD), dysplasia (CE-D), and intestinal metaplasia (CE-IM), incidence rates (IR), durability of response, location of recurrent IM and dysplasia, and rate of disease progression.

Results—50 and 40 patients were included in 3-year and 5-year analyses. Initial CE-HGD, CE-D, and CE-IM were achieved in 98%, 90%, and 60%, respectively. Overall CE-HGD, CE-D, and CE-IM at 3 years were 96% (48/50), 94% (47/50), and 82% (41/50), and at 5 years were 93% (37/40), 88% (35/40), and 75% (30/40). IRs of recurrent IM, dysplasia, and HGD/esophageal adenocarcinoma per person-year of follow-up after initial CE-IM were 12.2%, 4.0%, and 1.4% per person-year for the 5-year cohort. Most recurrences were found immediately below the neosquamocolumnar junction. Two of 7 HGD recurrences occurred later than 4 years after initial eradication, and 2 patients (4%) progressed to adenocarcinoma despite treatment.

Correspondence to: Fariha H. Ramay, M.D., M.B.A., Division of Gastroenterology and Hepatology, Department of Medicine, University of Maryland School of Medicine, 22 S. Greene Street, Rm N3W62, Baltimore, MD 21201, framay@medicine.umaryland.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Author contributions: F.R. contributed to study design, performed data analysis and interpretation of the data, and drafted the manuscript. Q.C. contributed to data analysis. B.G. conceived the study, contributed to study design, and provided revision of the paper for important intellectual content.

Conflict of Interest Disclosure: F.R. has no conflicts of interest to disclose. Q.C. has no conflicts of interest to disclose. B.G. is a consultant, advisory board member, and receives research funding from CSA Medical, Inc.

Conclusion—In patients with BE-HGD/IMC, LNSCT is effective in eliminating dysplasia and intestinal metaplasia. Progression to adenocarcinoma was uncommon, and recurrence of dysplasia was successfully treated in most cases. Long-term surveillance is necessary to detect late recurrence of dysplasia.

Keywords

Barrett's esophagus; high grade dysplasia; esophageal neoplasms; adenocarcinoma; cryotherapy; treatment efficacy

INTRODUCTION

Barrett's esophagus (BE) is a known precursor to esophageal adenocarcinoma (EAC) (1). Once high grade dysplasia (HGD) has developed, the risk of progression to EAC is considerable, estimated to be at 5.6 to 6.6 per 100 person-years (2). The emergence of endoscopic therapy for treatment of BE-associated dysplasia and EAC has led to a paradigm shift in the management of early esophageal neoplasia and involves the endoscopic removal of visible neoplastic lesions followed by eradication of remaining Barrett's epithelium with ablative techniques such as radiofrequency ablation (RFA) and liquid nitrogen spray cryotherapy (LNSCT)

LNSCT is a noncontact method of cryotherapy in which medical grade -196°C liquid nitrogen is applied through a low-pressure spray catheter directly to targeted tissue. It is a safe, well-tolerated, and effective therapy for BE-associated HGD with rates of complete eradication of HGD (CE-HGD) ranging from 97% to 100%, complete eradication of dysplasia (CE-D) from 81% to 87%, and complete eradication of intestinal metaplasia (CE-IM) from 57% to 84% (3–5). Follow-up beyond 2 years for this modality is not available. The aim of this study was to assess the efficacy, durability, and rate of neoplastic progression after LNSCT in patients with Barrett's esophagus-associated high grade dysplasia and intramucosal adenocarcinoma (IMC) at 3 and 5 years.

METHODS

Patients

This is a single-center, retrospective study of prospectively collected data on consecutive cases of endoscopic ablation with LNSCT (CryoSpray Ablation System; CSA Medical, Inc, Lexington, Mass, USA) in patients with BE-associated HGD/IMC of any length treated at the University of Maryland Medical Center (Baltimore, Maryland). Patients who received one or more treatments with spray cryotherapy with successful eradication of HGD and had at least 3 years of follow-up after last ablation were included. Patients with endoscopic mucosal resection (EMR) showing intramucosal adenocarcinoma before cryotherapy were included, provided pathology showed complete resection of a well-differentiated cancer. Patients with prior treatment for esophageal cancer other than EMR were excluded. Before treatment, biopsy specimens from all patients were reviewed by two pathologists, including one with expertise in the assessment of Barrett's esophagus and BE-associated dysplasia.

The IRB approved creation of the research database and its use. Informed consent was obtained from all patients.

Treatment

Patients received twice daily proton pump inhibitor (PPI) therapy during treatment and once daily PPI therapy during follow-up, unless reflux symptoms warranted twice daily dosing. Informed consent was obtained for all endoscopic procedures. Endoscopy was performed on an outpatient basis with moderate sedation using intravenous fentanyl and midazolam or monitored anesthesia care with propofol.

Cryotherapy was performed as previously described (3, 6). The CryoSpray Ablation System (CSA Medical, Inc, Lexington, Mass, USA) is a noncontact method of cryotherapy, applying -196°C liquid nitrogen through a low-pressure spray catheter directly to the tissue targeted for treatment at 25 W. After routine upper endoscopy with identification of the BE segment, a modified orogastric dual-lumen decompression tube was introduced over a guidewire into the gastric antrum. After guidewire removal, the tube was connected to suction, and the endoscope was reintroduced in a side-to-side manner with the decompression tube. The decompression tube allows for evacuation of evaporated nitrogen from the stomach and esophagus during treatment by both passive and active venting. A distal cap was attached to the endoscope in most cases. The cryotherapy catheter was then inserted into the working channel of the endoscope. During application of liquid nitrogen, continuous suction via the dual-lumen decompression tube was applied, and a trained nurse monitored the abdomen for any signs of gastric distension. Spray was applied until a white frost formed, then the timer was activated.

Treatment dosimetry, defined as the duration of the tissue freeze time in seconds and the number of cycles in which the target site was frozen and thawed, was changed over time based on clinical experience and dosimetry studies. Initial dosimetry was 3 cycles of 20 seconds, later changed to 4 cycles of 10 seconds, then 2 cycles of 20 seconds. After the freeze was complete, each site was allowed to thaw until all ice crystals had disappeared and at least 45 seconds had elapsed. Generally, all of the visible BE mucosa was treated. Follow-up procedures were performed every 6 to 12 weeks until there was no endoscopic or histologic evidence of residual BE. Treatment was stopped and surveillance begun after one endoscopy showed no endoscopic evidence of BE and absence of IM on biopsies of both the neo-squamous esophageal epithelium and the biopsied area below the neosquamocolumnar junction. In general, treatment was stopped after 5 cryotherapy sessions if persistent intestinal metaplasia was found.

Surveillance endoscopy was performed every 3 months in surveillance year 1, every 6 months in years 2 and 3, then annually. High-definition endoscopes with narrow-band imaging (GIF-H180; Olympus America, Center Valley, Pa, USA) were used in all cases. Post-treatment surveillance biopsies were obtained of any suspicious lesions and every 1 cm in 4 quadrants in the previously treated esophagus and in 4 quadrants immediately below and 1 cm below the neosquamocolumnar junction (NSCJ) at the top of the gastric folds. Endoscopic resection was performed in any area of nodularity. All biopsies were performed using large-capacity forceps with an outer diameter of 2.4 mm (Radial Jaw 4 Large

Capacity; Boston Scientific Corp., Natick, Mass, USA). Biopsy specimens were reviewed by pathologists with expertise in the assessment of Barrett's esophagus and BE-associated dysplasia. Repeat ablation was performed when dysplastic Barrett's mucosa or IM was identified. Argon plasma coagulation was used for 3 or less islands of intestinal metaplasia less than 5 mm in size.

Data Collection and Analysis

For each patient, baseline demographics (age, gender, and race) as well as initial length of BE segment, prior history of endoscopic resection, number of cryotherapy treatments, need for retreatment, and duration of follow-up were collected. CE-IM was defined as the absence of endoscopic evidence of BE and absence of IM on biopsies of both the neo-squamous esophageal epithelium and the biopsied area below the neosquamocolumnar junction at one endoscopic session. CE-D was defined as the absence of low and high grade dysplasia endoscopically and on biopsy of both areas. Recurrence was defined as histologic evidence of IM, dysplasia or neoplasia on endoscopic biopsy during the surveillance period. Ongoing endoscopic surveillance and retreatment, as needed, was performed in all patients in the initial cohort.

Primary outcomes consisted of rates of complete eradication of HGD (CE-HGD), complete eradication of dysplasia (CE-D), and complete eradication of IM (CE-IM) at the three-year and five-year biopsy session, allowing for interval touch-up ablation. Secondary outcome measures included durability of response, incidence rates (IR) and location of recurrent IM and dysplasia, response to retreatment, and disease progression. Durability of response was calculated as the percentage of patients achieving and maintaining CE-HGD, CE-D and CE-IM without retreatment. For example, durability of response for CE-D was calculated as the percentage of patients with initial CE-D who maintained CE-D during the follow-up period without retreatment. In all analyses, time 0 was considered the last cryotherapy session before the start of the surveillance period. Disease progression was defined as any patient found to have esophageal adenocarcinoma over the course of the study. Incidence rates of recurrent IM, dysplasia, and HGD/EAC per person-year of follow-up after initial CE-IM were determined. In patients achieving initial CE-IM, rates of CE-HGD, CE-D, and CE-IM at 3 and 5-year follow-up were calculated as well. Mean and standard deviation (SD) were calculated for normally distributed continuous variables. Median and interquartile range (IQR) were calculated for continuous variables not normally distributed. Data analysis was performed using SAS software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Three-Year Follow-Up

Between April 2006 and February 2012, 66 patients with BE-associated HGD/IMC presented for endoscopic spray cryotherapy and had a minimum follow-up of 3 years (Figure 1). Sixteen patients were excluded as follows: 7, prior treatment of esophageal cancer other than EMR; 4, lost to follow-up (2, normal mucosa at 12 months; 1, normal mucosa at 24 months; 1, IM at 6 months); 3, withdrawn for less than 3-year follow-up due to advanced age and co-morbidities (2, normal mucosa at 24 and 30 months; 1, LGD at 24

months); 2, death from unrelated causes (lung cancer and cardiac arrest, last follow-up at 9 and 30 months showing normal mucosa).

In the remaining 50 patients, mean age was 61.9 years (SD, standard deviation 8.6, range 36–81) and consisted predominantly of white males (Table 1). Median BE segment length was 3.5 cm (IQR 2–5), and median treatment number was 3 (IQR 2–5). Mean follow-up was 64.6 months (SD 15.5). Initial CE-HGD was achieved in 98% (49/50), CE-D in 90% (45/50), and CE-IM in 30 (60%). Four patients had persistent LGD despite a median of 5 treatments (range 5 – 10), whereas 15 patients had persistent intestinal metaplasia, predominantly at the neosquamocolumnar junction (9/15) after a median of 5 treatments (range 2–10). Endoscopic surveillance was initiated at that time. Durability of response, calculated as the percentage of patients maintaining eradication without retreatment, was 84% (41/49) for CE-HGD, 80% (36/45) for CE-D and 73% (22/30) for CE-IM (Figure 2). For the 30 patients with initial CE-IM, rates of CE-HGD, CE-D, and CE-IM at 3 years were 97% (29/30), 93% (28/30), and 87% (26/30). Incidence rates of recurrent IM, dysplasia, and HGD/EAC per person-year of follow-up after initial CE-IM were 13.3%, 3.6%, and 1.3% per person-year, respectively.

Two patients (4%) progressed to adenocarcinoma during the study period. One developed adenocarcinoma during treatment and subsequently underwent esophagectomy for stage T2N0M0 disease. He remains disease free with 99-month follow-up. The second patient was found to have adenocarcinoma at 18-month follow-up. She was deemed a poor surgical candidate and was treated with endoscopic resection and repeat cryotherapy with CE-IM at time of last follow-up (74 months).

Recurrence of HGD was identified in 16% (8/49) with median time to recurrence of 8.1 months (IQR 6.4–13.1, range 4.6–15.4). This was successfully treated with cryotherapy with elimination of dysplasia in 7/8 (88%) at time of last follow-up. Recurrence was found just below the NSCJ in 6 patients, in the esophagus in 1 patient, and in both the esophagus and just below the NSCJ in 1 patient. Low-grade dysplasia was identified in an additional 7 patients. Five received repeat cryotherapy. One patient had microscopic recurrent LGD in the body of the esophagus at 6-month follow-up but was not re-treated; subsequent biopsies showed IM and normal tissue with most recent biopsy showing normal tissue at 60 months. The second patient had LGD just below the NSCJ at 6-month follow-up but was not re-treated; subsequent biopsies showed normal tissue and IM with most recent biopsy showing IM at 60 months. For all patients with dysplasia recurrence (both LGD and HGD), 85% (11/15) patients achieved CE-D after repeat treatment. Dysplasia was found at the area just below the NSCJ in 12 patients, in the esophagus in 2 patients, and at both sites in 1 patient. Median time to recurrence was 9.6 months (IQR 6.4–12.7, range 3.5–50.4). In patients with initial CE-D, 24% (11/45) were found to have dysplasia during the follow-up period. In patients with initial CE-IM, 40% (12/30) were found to have intestinal metaplasia during the follow-up period. Overall, for the entire cohort at 3 years, including retreatment, CE-HGD was 96% (48/50), CE-D was 94% (47/50), and CE-IM was 82% (41/50) (Figure 3).

For the 17 patients who underwent repeat cryotherapy, the median number of re-treatments was 1.0 (IQR 1.0–2.0, range 1–9). EMR was performed in 2 for removal of focal areas of

HGD. Argon plasma coagulation was used in 7 for islands of residual BE. Seven underwent RFA for recurrence of HGD (4) and LGD (3) due to small areas of recurrence deemed better treated with RFA than APC or cryotherapy.

Five-Year Follow-Up

Forty-one patients were eligible for 5-year analysis, with one patient lost to follow-up (Figure 1). Baseline characteristics are shown in Table 1. Initial CE-HGD was achieved in 98% (39/40), CE-D in 90% (36/40), and CE-IM in 65% (26/40). Mean follow-up was 69.7 (SD 13.8) months. As described above, persistent LGD was found in 3 and persistent intestinal metaplasia in 10, so durability of response was 82% (32/39) for CE-HGD, 75% (27/36) for CE-D and 65% (17/26) for CE-IM (Figure 2). For the 26 patients in this cohort with initial CE-IM, rates of CE-HGD, CE-D, and CE-IM at 5 years were 96% (25/26), 92% (24/26), and 81% (21/26). Incidence rates of recurrent IM, dysplasia, and HGD/EAC per person-year of follow-up after initial CE-IM were 12.2%, 4.0%, and 1.4% per person-year, respectively.

No additional patients progressed to adenocarcinoma between years 3 and 5. Rates of disease recurrence are similar between the 3-year and 5-year cohorts. Overall, 18% (7/39) of patients developed recurrent HGD, with median time to recurrence of 13.1 months (IQR 6.4–50.2, range 4.6–50.4). This was successfully treated with cryotherapy with elimination of dysplasia in 6 out of 7 (86%) at last follow-up. Two cases of HGD recurrence occurred later than 4 years after initial eradication. Between years 3 and 5, one patient had recurrent HGD on the 48-month biopsy in both the esophagus and immediately below the NSCJ and one patient had LGD on the 48-month biopsy immediately below the NSCJ and was subsequently found to have HGD at 60 months at the same site. Two patients had recurrence of LGD immediately below the NSCJ at 60-month follow-up. Median time to dysplasia recurrence was 11.5 months (IQR 6.4–15.4, range 3.5–57.5). For this cohort, overall CE-HGD was 93% (37/40), CE-D was 88% (35/40) and CE-IM was 75% (30/40) at 5 years, allowing for retreatment (Figure 3). For the 16 patients receiving repeat cryotherapy in this cohort, the median number of retreatments was 1 (IQR 1–2, range 1–9), whereas 15% (6/40) patients received 1 session of APC for islands of residual BE.

DISCUSSION

Liquid nitrogen spray cryotherapy has been previously shown to be a safe, well-tolerated, and effective therapy for patients with BE-associated HGD/IMC. In a retrospective study of 60 patients, 97% of patients achieved CE-HGD, 87% achieved CE-D, and 57% achieved CE-IM with mean follow-up of 10.5 months (3). A multicenter study from the National Cryospray Registry showed CE-D of 81% (46/57) and CE-IM of 65% (37/57) with mean follow-up of 21 months (5). We previously reported two year follow-up of a cohort of 32 patients with CE-HGD and CE-IM of 100% and 84%, respectively. HGD recurrence requiring additional treatment with cryotherapy was seen in 18% (6). The current study extends follow-up beyond 2 years.

The present study demonstrates that the majority of patients treated with liquid nitrogen spray cryotherapy maintain CE-HGD, CE-D and CE-IM at 5 years. Allowing for interval

touch-up therapy (performed in 40% of patients), CE-HGD was achieved in 93%, CE-D in 88%, and CE-IM in 75% of patients. Two patients (4%) progressed to adenocarcinoma – one during cryotherapy treatment (likely a prevalent cancer not detected on pre-treatment surveillance) and one during post-cryotherapy surveillance. Dysplasia was identified in 24% and 28% at 3 and 5 years and responded to repeat treatment. Most dysplasia recurrences were identified below the neosquamocolumnar junction (87% at 3 years, 93% at 5 years) rather than in the body of the esophagus. This is consistent with a previous report with shorter follow-up (7).

Eradication rates with liquid nitrogen spray cryotherapy are comparable with those reported for RFA. A recent systematic review and meta-analysis of 18 studies treating Barrett's dysplasia with RFA showed CE-D of 91% and CE-IM of 78%, with recurrence of IM identified in 13% (8). Similarly in the UK National Halo RFA Registry, CE-HGD was achieved in 86%, CE-D in 81%, and CE-IM in 62% at 12 month follow-up (9). A recent prospective multicenter trial of RFA and endoscopic resection for treatment of HGD and early esophageal cancer in 132 patients showed CE-HGD of 92% and CE-IM of 87% per intention to treat analysis and 98% and 83% respectively per intention to treat analysis (10).

Similar to RFA, recurrence of intestinal metaplasia and dysplasia after successful eradication is not uncommon. In this study, incidence rates of recurrent IM, dysplasia, and HGD/EAC per person-year of follow-up after initial CE-IM were 12.2%, 4.0% and 1.4%, respectively. This is somewhat higher than reported in a recent systematic review of Barrett's eradication therapy, which showed rates of 9.5%, 2.0%, and 1.2%, respectively, for RFA and 7.1%, 1.3%, and 0.8% for all endoscopic modalities (11). The higher rates in this study may be due to extensive sampling below the neosquamocolumnar junction identifying intestinal metaplasia in this area. High grade dysplasia was discovered in 2 cases later than 4 years after initial eradication. Whether this represents recurrence or the development of metachronous disease cannot be distinguished. In a prospective study of patients with HGD and early stage cancer undergoing endoscopic resection followed by RFA, Kaplan-Meier analysis showed sustained complete remission of neoplasia and intestinal metaplasia in 90% of patients at 5-year follow-up (12). Cancer recurrences were noted in 3 patients after 5 years of follow-up. These results support the continued use of endoscopic surveillance, including in those patients who have achieved complete eradication of intestinal metaplasia and dysplasia.

This is the first study to examine the long-term success of endoscopic liquid nitrogen spray cryotherapy in patients with BE-HGD/IMC. Limitations of this study include a small sample size, retrospective design and lack of central pathology. Despite our best efforts, 5 patients were lost to follow-up, which could further bias results. Additionally, all patients were treated at a tertiary academic referral center with expertise in the management of BE-associated dysplasia and cancer and the results may not be generalizable.

In summary, this study demonstrates that treatment of Barrett's esophagus with high grade dysplasia and intramucosal adenocarcinoma using liquid nitrogen spray cryotherapy can successfully eradicate dysplasia and intestinal metaplasia with low risk of progression to adenocarcinoma. Like other ablation modalities, recurrence is not uncommon, but allowing

for interval touch-up therapy, the majority of patients treated maintain CE-HGD, CE-D and CE-IM at 5 years. Continued endoscopic surveillance is still necessary due to the risk of dysplasia recurrence up to 4 years after initial eradication.

Acknowledgments

Financial support: Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award Number T32DK067872. The content is solely the responsibility of the authors and does not necessarily reflect views of the National Institutes of Health. Support was also provided by the Frenkil Family Foundation.

List of Abbreviations

APC	Argon plasma coagulation
BE	Barrett's esophagus
BE-HGD	Barrett's esophagus (BE)-associated high grade dysplasia
CE-D	Complete eradication of dysplasia
CE-HGD	Complete eradication of high grade dysplasia
CE-IM	Complete eradication of intestinal metaplasia
EMR	Endoscopic mucosal resection
EAC	Esophageal adenocarcinoma
HGD	High grade dysplasia
IQR	Interquartile range
IM	Intestinal metaplasia
IMC	Intramucosal adenocarcinoma
IR	Incidence ratio
LNSCT	Liquid nitrogen spray cryotherapy
NSCJ	Neosquamocolumnar junction
PPI	Proton pump inhibitor
RFA	Radiofrequency ablation
SD	Standard deviation

References

1. 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]
2. Rastogi A, Puli S, El-Serag HB, et al. Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. *Gastrointest Endosc*. 2008; 67:394–8. [PubMed: 18045592]

3. 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]
4. Greenwald BD, Dumot JA, Horwhat JD, et al. Safety, tolerability, and efficacy of endoscopic low-pressure liquid nitrogen spray cryotherapy in the esophagus. *Dis Esophagus.* 2010; 23:13–9. [PubMed: 19515183]
5. 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]
6. Gosain S, Mercer K, Twaddell WS, et al. Liquid nitrogen spray cryotherapy in Barrett's esophagus with high-grade dysplasia: long-term results. *Gastrointest Endosc.* 2013; 78:260–5. [PubMed: 23622979]
7. Halsey KD, Chang JW, Waldt A, et al. Recurrent disease following endoscopic ablation of Barrett's high-grade dysplasia with spray cryotherapy. *Endoscopy.* 2011; 43:844–8. [PubMed: 21826629]
8. 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]
9. Haidry RJ, Dunn JM, Butt MA, et al. Radiofrequency ablation and endoscopic mucosal resection for dysplastic barrett's esophagus and early esophageal adenocarcinoma: outcomes of the UK National Halo RFA Registry. *Gastroenterology.* 2013; 145:87–95. [PubMed: 23542069]
10. Phoa KN, Pouw RE, Bisschops R, et al. Multimodality endoscopic eradication for neoplastic Barrett oesophagus: results of an European multicentre study (EURO-II). *Gut.* 2016; 65:555–62. [PubMed: 25731874]
11. Krishnamoorthi R, Singh S, Ragunathan K, et al. Risk of recurrence of Barrett's esophagus after successful endoscopic therapy. *Gastrointest Endosc.* 2016; 83:1090–1106 e3. [PubMed: 26902843]
12. Phoa KN, Pouw RE, van Vilsteren FG, et al. Remission of Barrett's esophagus with early neoplasia 5 years after radiofrequency ablation with endoscopic resection: a Netherlands cohort study. *Gastroenterology.* 2013; 145:96–104. [PubMed: 23542068]

Figure 1. Flowchart of patients undergoing cryotherapy for Barrett's esophagus with high-grade dysplasia/intramucosal adenocarcinoma. *BE-HGD/IMC*, Barrett's esophagus with high-grade dysplasia or intramucosal cancer.

Figure 2. Durability of Response for Barrett's high-grade dysplasia, dysplasia and intestinal metaplasia at 3-year and 5-year follow-up without retreatment. *CE-HGD*, complete eradication of high-grade dysplasia; *CE-D*, complete eradication of dysplasia; *CE-IM*, complete eradication of intestinal metaplasia.

Figure 3. Complete eradication rates for Barrett's high-grade dysplasia, dysplasia and intestinal metaplasia at 3-year and 5-year follow-up allowing for interval touch-up therapy. *CE-HGD*, complete eradication of high-grade dysplasia; *CE-D*, complete eradication of dysplasia; *CE-IM*, complete eradication of intestinal metaplasia.

Table 1

Baseline Characteristics.

	3-Year analysis	5-Year analysis
Number of patients	50	40
Age, years		
Mean (SD)	61.9 (8.6)	61.1 (8.0)
Range	36–81	36–78
Sex, n (%)		
Male	47 (94.0)	37 (92.5)
Female	3 (6.0)	3 (7.5)
Race, n (%)		
White	49 (98.0)	39 (97.5)
Black	1 (2.0)	1 (2.5)
Length of BE (cm)		
Median (IQR)	3.5 (2.0–5.0)	3.0 (2.0–5.5)
Range	1.0–12.0	1.0–12.0
Treatment number		
Median (IQR)	3.0 (2.0–5.0)	3.0 (2.0–5.0)
Range	1.0–12.0	1.0–12.0
Endoscopic resection before treatment, n (%)	14 (28.0%)	11 (27.5%)
Endoscopic resection for adenocarcinoma stage pT1a before treatment, n (%)	4 (8.0%)	2 (5.0%)
Duration of follow-up, months		
Mean (SD)	64.6 (15.5)	69.7 (13.8)
Range	36.6–106.0	53.8–106.0

SD, standard deviation; *BE*, Barrett's esophagus; *IQR*, interquartile range