# ***Policy Replaced with LCD L34434 Effective February 26, 2018***

BlueCross BlueShield of Alabama

**Name of Blue Advantage Policy:**

# Endoscopic Radiofrequency Ablation or Cryoablation for Barrett's Esophagus

Policy #: 417
Category: Surgery

Latest Review Date: December 2017
Policy Grade: B

## Background:

***Blue Advantage*** *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*

    - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
    - *Furnished in a setting appropriate to the patient's medical needs and condition;*
    - *Ordered and furnished by qualified personnel;*
    - *One that meets, but does not exceed, the patient's medical need; and*
    - *At least as beneficial as an existing and available medically appropriate alternative.*

**Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare*** *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

## Description of Procedure or Service:

### Barrett Esophagus and the Risk of Esophageal Carcinoma

The esophagus is normally lined by squamous epithelium. Barrett's esophagus (BE) is a condition in which the normal squamous epithelium is replaced by specialized columnar-type epithelium known as intestinal metaplasia, in response to irritation and injury caused by gastroesophageal reflux disease (GERD). Barrett's esophagus occurs in the distal esophagus, may be of any length, focal or circumferential, and can be visualized by the endoscopist as being a different color than the background squamous mucosa. Confirmation of Barrett's esophagus requires biopsy of the columnar epithelium and microscopic identification of intestinal metaplasia.

Intestinal metaplasia is a precursor to esophageal adenocarcinoma, which is thought to result from a stepwise accumulation of genetic abnormalities in the specialized epithelium, which results in the phenotypic expression of histologic features of low-grade dysplasia to high-grade dysplasia to carcinoma. Two large epidemiologic studies published in 2011 reported the risk of progression to cancer in patients with Barrett's esophagus. One study reported the rate of progression to cancer in more than 8,000 patients with a mean duration of follow-up of seven years (range 1-20 years). The de novo progression to cancer from Barrett's esophagus at one year was 0.13%. The risk of progression was reported as 1.4% per year in patients with low grade dysplasia and 0.17% per year in patients without dysplasia. This incidence translates into a risk of ten to eleven times that of the general population. The other study identified over 11,000 patients with Barrett's esophagus and after a median follow-up of 5.2 years, reported that the annual risk of esophageal adenocarcinoma was 0.12%. Detection of low-grade dysplasia on index endoscopy was associated with an incidence rate for adenocarcinoma of 5.1 cases per 1000 person years. Risk estimates for patients with high-grade dysplasia were slightly higher.

The reported risk of progression to cancer in Barrett's esophagus in older studies was much higher, with an annual incidence of risk of 0.4-0.5% per year, with risk estimated at 30-40 times the general population. Current surveillance recommendations have been based on these higher estimates.

### Management of BE

The management of Barrett's esophagus includes treatment of GERD, and surveillance endoscopy to detect progression to high-grade dysplasia or adenocarcinoma. The finding of high-grade dysplasia or early-stage adenocarcinoma warrants mucosal ablation or resection (either endoscopic mucosal resection [EMR] or esophagectomy).

EMR, either focal or circumferential, provides a histologic specimen for examination and staging (unlike ablative techniques). A recent study published by Ell et al provided long-term results for EMR in 100 consecutive patients with early Barrett's associated adenocarcinoma (limited to the mucosa). The five-year overall survival (OS) was 98% and metachronous lesions were observed in 11% of patients after a mean of 36.7 months. In a review by Pech et al, it is stated that circumferential EMR of the entire segment of Barrett's leads to a stricture rate of 50%, and recurrences occur at a rate of up to 11%.

**Ablation techniques**
Mucosal ablation techniques that are available consist of one of several thermal (multipolar electrocoagulation [MPEC], argon plasma coagulation [APC], heater probe, Nd:YAG laser, KTP-YAG laser, diode laser, argon laser, and cryoablation) or nonthermal (5-aminolevulinic acid [5-ALA] and photofrin photodynamic therapy [PDT]) techniques. PDT has been shown in a randomized Phase III trial to significantly decrease the risk of carcinoma in Barrett's esophagus. (PDT therapy for Barrett's esophagus is discussed in a separate policy, MP# 337-*Oncologic Applications of Photodynamic Therapy, Including Barrett's Esophagitis*).

The CryoSpray Ablation™ System uses a low-pressure spray for spraying liquid nitrogen through an upper endoscope. Cryotherapy allows for treatment of uneven surfaces, however, disadvantages include the uneven application inherent in spraying the cryogen.

The HALO System uses radiofrequency energy and consists of two components: an energy generator and an ablation catheter. The generator provides rapid (i.e., less than one second) delivery of a predetermined amount of radiofrequency energy to the catheter. Both the HALO90 and HALO360 are inserted into the esophagus with an endoscope, using standard endoscopic techniques. The HALO90 catheter is plate-based and used for focal ablation of areas of Barrett's esophagus up to 3cm. The HALO360 uses a balloon catheter that is sized to fit the individual esophagus, and is inflated to allow for circumferential ablation.

Ablation with radiofrequency affects only the most superficial layer of the esophagus (the mucosa), leaving the underlying tissues unharmed. Efficacy measures of the procedure include eradication of intestinal metaplasia without leaving behind microscopic (or "buried") foci and post-ablation regrowth of the normal squamous epithelium. Reports of the efficacy of the HALO system in ablating Barrett's esophagus have been as high as 70% (comparable to alternative methods of ablation [e.g., APC and MPEC]), and even higher in some reports. The incidence of leaving behind "buried" foci of intestinal metaplasia has been reported to be 20%–44% with APC and 7% with MPEC; reports using the HALO system have been 0%. Another potential advantage to the HALO system is that because it is automated, it eliminates operator-dependent error that may be seen with APC and MPEC.

Treating HGD or mucosal cancer solely with ablative techniques risks undertreating the approximately 10% of patients who have undetected submucosal cancer, in whom esophagectomy would have been required.

## Policy:

**Effective for dates of service on or after February 26, 2018 refer to LCD L34434**

**Effective for dates of service on or after May 22, 2010 and prior to February 26, 2018:**
**Blue Advantage** will treat **radiofrequency ablation** as a **covered** benefit for **Barrett's esophagus with dysplasia.**

**Blue Advantage** will treat **radiofrequency ablation** as a **non-covered** benefit including, but not limited to **Barrett's esophagus without dysplasia** and as **investigationa**l.

**Blue Advantage** will treat **cryoablation** as a **non-covered** benefit for **Barrett's esophagus, with or without dysplasia** and as **investigational**.

*Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

## Key Points:

The most recent update covers the period through September 14, 2017.

**Radiofrequency Ablation for Barrett Esophagus**

Radiofrequency Ablation (RFA) versus Surgical Resection for Barrett Esophagus with Dysplasia

Radiofrequency ablation (RFA) has been accepted as a less invasive alternative to surgical mucosal resection or esophagectomy, based on the results of randomized and nonrandomized trials. Early single-arm trials reported high rates of success in eradication of dysplastic and metaplastic tissue, with low rates of adverse effects.

Systematic Reviews

In 2014 Chadwick et al reported on a systematic review which compared RFA and complete endoscopic mucosal resection (EMR) for Barrett esophagus (BE). Twenty studies (22 articles) were reviewed including two randomized controlled trials (RCT), ten cohort studies on EMR and eight cohort studies on RFA. The only study that compared RFA and EMR was the RCT by van Vilsteren (described next). The other RCT was by Shaheen et al (also described next). The studies were heterogeneous in design. Included in the studies reviewed was a total of 1087 (532 EMR and 555 RFA) patients with either high-grade dysplasia (HGD) or intramucosal cancer. The median number of resections or RFA sessions required for BE eradication was two. Complete EMR and RFA eradicated BE dysplasia in 95% and 92%, respectively. Eradication was maintained in 95% of EMR patients at a median follow-up of 23 months and in 94% of RFA patients at a median follow-up of 21 months. Fewer RFA patients experienced short-term

adverse effects (2.5%) versus complete EMR (12%). Esophageal strictures requiring additional treatment occurred in 4% of RFA patients and 38% of complete EMR patients.

In 2013 Orman et al reported on a systematic review and meta-analysis of 24 studies with a total of 4342 patients treated with RFA for BE dysplasia and intestinal metaplasia. Included in the review were the van Vilsteren and Shaheen studies. The studies were heterogeneous in design and contained a mix of nondysplastic and LGD and HGD. The use of EMR varied in the studies with a range of 0% to 96%. Patients were followed for a median of 20.5 months (range, 12-31 months). For patients treated with RFA, complete eradication of dysplasia occurred in 91% (95% CI, 87% to 95%), and complete eradication of intestinal metaplasia occurred in 78% (95% CI, 70% to 86%). Intestinal metaplasia recurred in 13% (95% CI, 9% to 18%) after eradication. In patients with complete eradication of intestinal metaplasia, 0.2% and 0.7% progressed to cancer during treatment and after treatment, respectively. The most frequent adverse even was esophageal stricture, which occurred in 5% of patients (95% CI, 3% to 7%).

Semlitsch et al reported a systematic review of this evidence for RFA of BE based on a total of nine observational studies and 429 patients. Inclusion criteria for the systematic review required that studies include patients with BE and metaplasia or dysplasia for which RFA was the intervention (with or without endoscopic mucosal resection) and have a minimum follow-up period of 12 months. In seven of the studies, the patients were treated with circumferential ablation followed by focal ablation, whereas two studies used only the circumferential method. The maximum number of ablations performed was reported in seven studies and ranged from two to five. Complete eradication of BE with dysplasia and metaplasia was achieved in 71 to 100% and 46 to 100% of patients, respectively. Six cases of esophageal stenosis and one case of buried intestinal metaplasia were reported among all patients.

*Randomized Controlled Trials*

Van Vilsteren et al (2011) reported on the results of a multicenter, randomized trial which compared the safety of stepwise radical endoscopic resection (SRER) versus focal EMR followed by RFA for complete eradication of BE ≤5cm containing HGD/early cancer. Patients in the SRER group underwent piecemeal ER of 50% of BE followed by serial EMR. Patients in the EMR/RFA group underwent focal ER for visible lesions followed by serial RFA. Follow-up endoscopy with biopsies (4-quadrant/2cm BE was performed at six and 12 months and then annually. The main outcome measures were: stenosis rate, complications, complete histologic response for neoplasia (CR-neoplasia); and complete histologic response for intestinal metaplasia (CR-IM). CR-neoplasia was achieved in 25/25 (100%) SRER and in 21/22 (96%) ER/RFA patients. CR-IM was achieved in 23 (92%) SRER and 21 (96%) EMR/RFA patients. The stenosis rate was significantly higher in SRER (88%) versus ER/RFA (14%; $p<0.001$), resulting in more therapeutic sessions in SRER (6 vs 3; $p<0.001$) due to dilations. After median follow-up of 24 months, one SRER patient had recurrence of early cancer, requiring endoscopic resection. This study confirmed that both techniques achieve comparably high rates of CR-IM and CR-neoplasia but that SRER was associated with a higher number of complications and therapeutic sessions.

*Noncomparative Studies*
Since publication of the systematic reviews described above, individual noncomparative studies have described outcomes after use of combined EMR with RFA to treat BE with HGD and any early cancer, if any present. In 2016, Phoa et al reported on a prospective, single-arm interventional study with 132 subjects that evaluated the use of combined EMR with RFA for BE with HGD and/or early cancer. At baseline endoscopy, all visible abnormalities were removed at a single endoscopic resection for histologic staging. After 2 mapping endoscopies, patients underwent the first RFA treatment for circumferential or focal ablation, after which they underwent RFA treatment every 3 months until visible BE was cleared. Complete eradication of neoplasia (absence of all HGD and early cancer on biopsy and endoscopic clearance of BE) and complete eradication of intestinal metaplasia were achieved in 92% (95% CI, 83% to 93%) and 87% (95% CI, 80% to 92%), respectively, of all patients who began the study in intention-to-treat (ITT) analysis.

Section Summary: Radiofrequency Ablation vs Surgical Resection for Barrett Esophagus with Dysplasia
RFA is a less-invasive alternative to EMR and/or esophagectomy for BE with dysplasia. Available research supports that RFA results in similar efficacy for disease that has not extended into the submucosa, with fewer complications.

RFA versus surveillance alone in BE
*RFA for Dysplastic BE*
One randomized multicenter, sham-controlled trial has been published that compares RFA to surveillance alone in BE with dysplasia. This trial, reported by Shaheen et al, included patients with both HGD and LGD. A total of 127 patients with dysplastic BE were randomized in a 2:1 ratio to receive RFA or a sham procedure. The groups were randomly assigned according to the grade of dysplasia (low-grade [n=64] or high-grade [n=63]) and length of the BE (<4cm or 4-8cm). Patients in the RFA group could receive up to four ablation sessions, performed at baseline and at two, four, and nine months. Primary outcomes were the proportion of patients who had complete eradication of dysplasia at 12 months and the proportion of all patients who had complete eradication of intestinal metaplasia at 12 months. The proportion of patients who had progression of dysplasia was a secondary outcome, this included progression of LGD to HGD or cancer, and the progression of HGD to cancer. This trial was included in the 2010 TEC Assessment and was rated fair on formal quality assessment according to the U.S. Preventive Services Task Force system (USPSTF). The only obstacles to a good rating were missing details about random sequence generation and concealment of allocation.

Overall, complete eradication of intestinal metaplasia was 77.4% in the ablation group compared with 2.3% of the control group ($p<0.001$). Patients who did not receive RFA were more likely to have disease progression (16.3%) than those who received RFA (3.6%; $p=0.03$). Three serious adverse events occurred in the RFA group, including one episode of upper gastrointestinal hemorrhage, which was treated endoscopically, one overnight hospitalization for new-onset chest pain eight days after RFA, and one night of hospitalization for an episode of chest discomfort and nausea immediately after RFA. No adverse events were observed in the control group. No esophageal perforations or procedure-related deaths occurred. Among

patients in the RFA group, esophageal stricture developed in five patients (6%), all of whom successfully underwent dilated endoscopy.

In 2011, two- and three-year results of this trial were reported. Subjects were followed for a mean time of 3.05 years, with 106/127 (83%) patients included in the analysis. Outcomes included eradication of dysplasia or intestinal metaplasia after two and three years, durability of response, disease progression, and adverse events. After two years, 101 of 106 patients had complete eradication of all dysplasia (95%) and 99 of 106 had eradication of intestinal metaplasia (93%). Serious adverse events occurred in four of 119 subjects (3.4%). No perforations or procedure-related deaths occurred. The rate of esophageal stricture was 7.6%. The rate of esophageal adenocarcinoma was one per 181 patient-years (0.55%/patient-years); there was no cancer-related morbidity or mortality. The annual rate of any neoplastic progression was one per 73 patient-years (1.37%/ patient-years). The authors concluded that, for patients with dysplastic BE, RFA is durable and associated with a low rate of disease progression for up to three years.

Section Summary: RFA for Dysplastic BE

The most direct evidence related to the efficacy of RFA for BE with dysplasia comes from one small-to-moderate, reasonably well-designed RCT comparing RFA with surveillance only in patients with both LGD and HGD. RFA was associated with lower risk of disease progression, compared with surveillance.

*RFA for HGD*

In patients diagnosed with BE with HGD, risk of progression to cancer is relatively high and esophageal adenocarcinoma is associated with poor morbidity and a five-year survival rate of 13% or less. Therefore, intervention with esophagectomy or RFA may be strongly indicated.

The 2009 RCT conducted by Shaheen et al, reported that RFA was successful in eradicating HGD, with complete eradication achieved in 81% of the ablation group versus 19% in the control group ($p<0.001$) at 12 months. This trial also confirmed a high risk of progression to cancer in patients with HGD and established that this progression was significantly reduced in patients treated with RFA. Among 63 patients with HGD in that trial, 19% in the control group progressed to cancer versus 2.4% in the RFA group ($p=0.04$). This represented a nearly 90% relative risk (RR) reduction for progression to cancer (RR=0.1, 95% CI, 0.01 to 1.0, $p=0.04$), and a number needed to treat of 6.0 to prevent one case of cancer over a one-year period.

Longer-term follow-up at two to three years reported that complete eradication of dysplasia was maintained in most participants with initial HGD. For 54 patients with HGD available for follow-up, all dysplasia was eradicated in 50 of 54 (93%), and all intestinal metaplasia was eradicated in 48 of 54 (89%). After three years, dysplasia was eradicated in 55 of 56 of subjects (98%), and all intestinal metaplasia was eradicated in 51 of 56 (91%). More than 75% of high-grade patients remained free of intestinal metaplasia with a follow-up of longer than three years, with no additional therapy.

RFA may be used along with focal endoscopic resection. In the ITT analysis of a prospective interventional study that included 132 subjects with BE and HGD or early cancer treated with

endoscopic resection followed by RFA, in intention-to-treat analysis, complete eradication of neoplasia and complete eradication of intestinal metaplasia occurred in 92% and 87% of subjects, respectively. Neoplasia or intestinal metaplasia recurred in 4% and 8% of subjects, respectively, at a median follow-up of 27 months.

Barret et al (2016) retrospectively analyzed a prospectively enrolled cohort including 40 patients with early BE who had a visible lesion and required EMR for the visible early neoplasia lesion, followed by RFA for the residual BE, which was done at the same procedure. Follow-up was available for 34 patients at a median of 19 months. For the study's primary outcome (complete remission of dysplasia), in the ITT analysis, remission was achieved in 85% of cohort participants; complete remission of intestinal metaplasia was achieved in 82.5% of cohort participants.

Section Summary: RFA for HGD

For patients with BE and HGD, there is a relatively high risk of progression to cancer, and interventions to prevent progression are warranted. RFA results in high rates of complete eradication of dysplasia that is durable for at least two years. One RCT demonstrated that progression from HGD to cancer is reduced by approximately 90% following RFA, with rates of esophageal strictures of 6%.

*RFA for LGD*

In 2014, Almond et al reported results of a meta-analysis of studies of endoscopic therapy in the treatment of BE with LGD. The analysis included 37 studies, nine of which evaluated RFA alone, including the Shaheen et al RCT. Most studies were small, with the Shaheen et al RCT representing the largest study (52 with LGD treated with RFA). For patients treated with RFA, the pooled incidence of cancer or HGD was 10.77 per 1000 patient-years (95% CI, 2.22 to 31.48 per 1000 patient-years). For RFA-treated patients, pooled rates of complete eradication of intestinal metaplasia and complete eradication of dysplasia were 87.2% (95% CI, 76.2% to 93.5%) and 90.6% (95% CI, 81.0% to 95.6%), respectively.

A 2010 TEC Assessment on the use of RFA plus surveillance versus surveillance alone in the treatment of nondysplastic and LGD BE included the Shaheen et al randomized trial and four single-arm studies. It was determined that the evidence was insufficient to permit conclusions for the use of RFA for patients with nondysplastic or LGD BE.

Since the TEC Assessment and the 2014 Almond et al systematic review, a randomized controlled trial of RFA versus surveillance in patients with LGD has been published by Phoa et al. This trial randomized 140 patients with BE and confirmed LGD; four patients were excluded after randomization due to not meeting study inclusion criteria at further review, leaving a total of 136 patients in the modified intention-to-treat analysis. "Confirmed" LGD was defined as a diagnosis of LGD by the local pathologist with confirmation by a centralized expert panel of pathologists convened for the trial. The primary outcome measure was the occurrence of either high-grade dysplasia or adenocarcinoma up to three years following randomization. Secondary outcomes were complete eradication of dysplasia, the absence of intestinal metaplasia, and adverse events.

The trial was terminated early due to interim analysis that determined superiority of RFA. At the time of termination all patients had reached the 24 month follow-up time point and the median follow-up was 36 months. The occurrence of adenocarcinoma was significantly lower in the RFA group (1.5%) compared to the surveillance group (8.8%, $p<0.03$), and the occurrence of high-grade dysplasia was also significantly lower for the RFA group (1.5%) compared to the surveillance group (26.5%, $p<0.001$). For patients treated with RFA, complete eradication of dysplasia during follow-up was 98.4% and the absence of metaplasia was 90.0%. There were three serious adverse events in two patients who received RFA (one abdominal pain requiring hospitalization, one bleeding episode, one episode of fever/chills following dilation for stricture), and a total of 12 other adverse events (eight strictures requiring dilation, three mucosal lacerations, one retrosternal pain).

In the Shaheen RCT, there were 64 patients with LGD and subgroup analysis was reported for these patients. At 12 months follow-up, the dysplasia was completely eradicated in 90.5% of those in the RFA group, compared with 22.7% of those in the control group ($p<0.001$). There were no patients in the LGD group who progressed to cancer over the initial 12 months. Progression to HGD was noted in 2/42 (5%) of patients in the RFA group, compared with 3/22 (14%) in the control group. The difference in rates of progression to HGD did not reach statistical significance (RR: 0.3, 95% CI, 0.1-1.9, $p=0.33$). After two years, there were 52 subjects available who had initial LGD treated with RFA. Progression from LGD to HGD or cancer occurred in one patient, for an estimated rate of 2.0% per patient per year. In patients with initial LGD, all dysplasia was eradicated in 51 of 52 (98%), and all intestinal metaplasia was eradicated in 51 of 52 (98%).

Section Summary: RFA for LGD

The risk of progression from LGD to cancer is not well-defined, with highly variable rates reported in the published literature. Evidence from randomized and nonrandomized studies has established that RFA can achieve complete eradication of dysplasia in patients with LGD that is durable for at least 2 years. One RCT of 136 subjects reported a lower rate of progression to HGD or adenocarcinoma for patients who had confirmed LGD treated with RFA.

*RFA for Non-Dysplastic BE*

There are no RCTs identified that evaluate treatment of nondysplastic BE with RFA. The evidence on this question consists of single-arm trials that report outcomes of RFA. This evidence can provide useful data on the success in eradicating dysplasia, but cannot provide high-quality evidence on the comparative efficacy of RFA versus surveillance alone. Progression to cancer in nondysplastic BE is lower than that for LGD or HGD, with rates in the literature ranging from 0.05% to 0.5%.

Fleischer et al reported the five-year follow-up of a single-arm study of patients with nondysplastic BE treated with RFA. The original study included 70 patients who underwent circumferential RFA and CR-IM; defined as complete eradication of nondysplastic BE, CR-IM was seen in 70% of patients at one-year follow-up; patients with persistent BE underwent focal RFA. At the 2.5 year follow-up, CR-IM was found in 60 of 61 patients (98%). At five-year follow-up, four-quadrant biopsies were obtained from every 1cm of the original extent of BE, and the authors reported the proportion of patients demonstrating CR-IM. If nondysplastic BE

was identified at the five-year follow-up, focal RFA was performed one month later and re-biopsy two months after to assess histologic response. Primary outcomes were the proportion of patients demonstrating CR-IM at five-year biopsy or after single session focal RFA. For the five-year follow-up, there were 60 eligible patients, 50 (83%) of whom were willing to participate. Forty-six of 50 patients (92%) showed CR-IM at the five-year biopsy visit. The four patients found to have BE at five years underwent a single session of RFA one month after biopsy, and all were found to have CR-IM at subsequent rebiopsy two months after RFA. No strictures were noted. The authors concluded that this first report of five-year CR-IM outcomes lends support to the safety, efficacy, cost-utility, and reduction in neoplastic progression in treating nondysplastic BE with RFA.

Section Summary: RFA for Nondysplastic BE

Nondysplastic BE has a relatively low rate of progression to cancer. Although available research reports that nondysplastic metaplasia can be eradicated by RFA, the risk/benefit ratio and the net effect on health outcomes is uncertain.

RFA versus Photodynamic Therapy (PDT) for BE

In 2013 Ertan et al reported on a series of 86 consecutive patients treated with either PDT or RFA by a single investigator. RFA was administered to 47 patients with LGD and six patients with HGD. PDT was administered to 33 patients with HGD. Average time from ablative therapy to follow-up biopsy was 33 months (range, 24-48) for RFA and 44 months (range, 24-60) for PDT. RFA resulted in significantly more complete eradication than PDT (88.7% vs 54.5%, respectively, p=0.001). However, interpretation of this study is limited by its nonrandomized nature and differences in the type of dysplasia between groups.

In a retrospective observational study, David et al compared several endovascular therapies, including RFA, RFA and endoscopic mucosal resection, and PDT, among patients with BE with HGD or adenocarcinoma. Of the 342 patients included, 98 underwent endoscopic mucosal resection plus RFA, 119 RFA alone, and 125 PDT. Patients treated with PDT were typically older and had more advanced stages of Barrett's disease and more comorbidities. In multivariable analysis, complete remission of intestinal metaplasia was more likely in PDT patients than those treated with endoscopic mucosal resection with RFA (RR 2.69, P<0.001) or with RFA alone (RR 4.47, P<0.001). However, the multivariable analysis did not adjust for a history of esophageal cancer, esophagectomy, or warfarin use. Among 121 patients who had at least 1 follow-up after complete remission of intestinal metaplasia was established, the disease recurrence rate was 32.2%, which did not differ across treatment groups.

Section Summary: RFA vs Photodynamic Therapy for BE

There is limited evidence to compare RFA with PDT for treatment of BE and no controlled trials. Evidence from nonrandomized studies have mixed findings about the comparative efficacy of RFA compared with PDT.

**Cryoablation of BE**

Published efficacy data for cryoablation in Barrett's esophagus are limited. Johnston et al (2015) conducted a prospective, single-center pilot study in 11 men with Barrett's esophagus and degrees of dysplasia ranging from none to multifocal high-grade dysplasia. The mean

length of Barrett's was 4.6cm (range: 1–8cm). After six months' follow-up, complete histologic eradication of Barrett's esophagus was achieved in seven of the nine patients (78%), completing the protocol.

A 2009 open-label, single-center, prospective, nonrandomized cohort study assessed the safety of cryoablation as a treatment option for Barrett's esophagus with high-grade dysplasia or early cancer (intramucosal carcinoma). Thirty patients who were either deemed high-risk surgical candidates or who refused esophagectomy underwent cryoablation. Twenty-seven patients (90%) had downgrading of pathology stage after treatment. After a median follow-up period of 12 months, elimination of cancer or downgrading of high-grade dysplasia was 68% for high-grade dysplasia and 80% for intramucosal cancer.

Greenwald et al reported the safety, tolerability, and efficacy of low-pressure liquid nitrogen spray cryotherapy in 77 patients from multiple institutions that underwent a total of 377 procedures for Barrett's esophagus with HGD (58.4%), intramucosal carcinoma (16.9%), invasive carcinoma (13%), Barrett's esophagus without dysplasia (9.1%), and severe squamous dysplasia (2.6%). The main outcome measurement was the incidence of serious adverse events and side effects from treatments. No side effects were reported by 28.6% of patients. The most common side effects were chest pain (18%), dysphagia (13%), odynophagia (12.1%), and sore throat (9.6%). Esophageal stricture occurred in three patients, all of which were successfully treated with dilation, and gastric perforation occurred in one patient. Complete response for HGD, all dysplasia, intestinal metaplasia, and cancer were assessed in patients completing therapy during the study period and having at least one follow-up endoscopy with biopsy for assessment of histologic regression of the underlying lesion (n=23). For patients with HGD (n=17), complete response (CR) of the HGD, any dysplasia, and intestinal metaplasia was 94%, 88% and 53%, respectively. For patients with intramucosal carcinoma (n=4), 100% had complete response of the cancer, HGD, and any dysplasia, and 75% had complete response of intestinal metaplasia. For the patients with invasive cancer (n=3), 100% had complete response of the cancer, HGD, and any dysplasia, and 67% of intestinal metaplasia.

Shaheen et al (2010) reported a multicenter, retrospective cohort study of 98 consecutive patients with Barrett's esophagus with HGD treated with spray cryotherapy to assess the safety and efficacy. A total of 333 treatments (mean 3.4 per patient) were performed, and cryotherapy was performed with the intent to eradicate all Barrett's esophagus. Sixty patients completed all planned cryotherapy treatments and were assessed for efficacy with follow-up endoscopy sessions with four quadrant biopsies performed every 1-2cm. Fifty-eight patients (97%) had complete eradication of HGD, 52 (87%) had complete eradication of all dysplasia with persistent nondysplastic intestinal metaplasia, and 34 (57%) had complete eradication of all intestinal metaplasia. There were no esophageal perforations, and esophageal stricture occurred in three patients. The authors noted the limitations of the study as it was nonrandomized, retrospective without a control group, lacked centralized pathology, used surrogate outcomes for decreased cancer risk, and had a short follow-up (10.5 months).

In 2015, Canto et al reported on a retrospective, single-center study evaluated a carbon dioxide cryosurgery device for treatment of with neoplasia or HGD who were treatment-naïve or who had persistent or recurrent neoplasia after initial treatment. The study's analysis included 68

patients who were offered treatment with cryoablation for either initial therapy (n=21) or after previous therapy with any ablative technique (n=47). At one year, complete response for dysplasia was 89% (57/64) overall and 95% (19/20) and 86% (38/44) in treatment-naïve and previously treated patients, respectively. Over a median follow-up of 4.2 years, the complete response for HGD at three years or study end was not statistically significantly different between treatment-naïve and previously treated patients (100% for treatment-naïve and 84% for previously treated; P=0.08).

Also in 2015, Sengupta et al evaluated cryoablation among 16 patients who failed RFA in a retrospective, single-center study. The cohort of 16 patients was derived from an original cohort of 121 patients who underwent RFA for BE with LGD, HCD, or IMC. After a median three RFA treatments, 91 subjects had complete eradication of dysplasia. Of 21 patients offered cryotherapy, 16 underwent cryotherapy and had adequate follow-up. Fourteen of those who did not have complete eradication and two patients who had recurrence of dysplasia underwent salvage cryotherapy. Over a median follow-up of 2.5 months, and with a median three cryotherapy treatments, 12 patients (75%) had complete eradication of dysplasia after cryotherapy and 14 (88%) had some improvement in pathology after cryotherapy.

Section Summary: Cryoablation of BE

There are no controlled trials evaluating the treatment of BE. The evidence from uncontrolled studies report high rates of success in eradicating dysplasia, with low rates of complications. These data are not sufficient to determine the comparative efficacy of cryoablation compared to RFA.

**Summary of Evidence**

For individuals who have Barrett Esophagus with dysplasia who receive endoscopic radiofrequency ablation (RFA), the evidence includes RCTs, a number of observational studies and systematic reviews. Relevant outcomes include overall survival, change in disease status, morbid events, and treatment-related morbidity and mortality. The available evidence indicates that using RFA to treat BE with high-grade dysplasia (HGD) is at least as effective in eradicating high-grade dysplasia as other ablative techniques with a lower progression rate to cancer and may be considered as an alternative to esophagectomy. Evidence from at least one RCT demonstrates higher rates of eradication than surveillance alone. For low-grade dysplasia, evidence from one RCT has suggested that RFA reduces progression to HGD and adenocarcinoma. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have BE without dysplasia who receive endoscopic RFA, the evidence includes single-arm studies reporting outcomes after RFA. Relevant outcomes include overall survival, change in disease status, morbid events, and treatment-related morbidity and mortality. The available studies suggest that nondysplastic metaplasia can be eradicated by RFA. However, the risk/benefit ratio and the net effect of RFA on health outcomes are unknown. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have BE with or without dysplasia who receive endoscopic cryoablation, the evidence includes noncomparative studies reporting outcomes after cryoablation. Relevant

outcomes include overall survival, change in disease status, morbid events, and treatment-related morbidity and mortality. These studies generally demonstrate high rates of eradication of dysplasia. However, the available evidence does not allow comparisons with surgical care or RFA. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Practice Guidelines and Position Statements**

American College of Gastroenterology

In 2016, the American College of Gastroenterology (ACG) issued guidelines for the diagnosis and management of Barrett esophagus (BE), which makes statements about endoscopic therapies in general, as outlined in Table 1.

**Table 1: American College of Gastroenterology Guidelines**

| Guidelines | Recommendation Strength | Level of Evidence |
|---|---|---|
| Patients with nodularity in the BE segment should undergo endoscopic mucosal resection of the nodular lesion(s) as the initial diagnostic and therapeutic maneuver…. Histologic assessment of the EMR specimen should guide further therapy. In subjects with EMR specimens demonstrating HGD, or IMC, endoscopic ablative therapy of the remaining BE should be performed. | Strong | High |
| In patients with EMR specimens demonstrating neoplasia at a deep margin, residual neoplasia should be assumed, and surgical, systemic, or additional endoscopic therapies should be considered | Strong | Low |
| Endoscopic ablative therapies should not be routinely applied to patients with nondysplastic BE because of their low risk of progression to EAC. Endoscopic eradication therapy is the procedure of choice for patients with confirmed LGD, and confirmed HGD, as noted above | Strong | Very low |
| In patients with T1a EAC, endoscopic therapy is the preferred therapeutic approach, being both effective and well tolerated | Strong | Moderate |
| In patients with T1b EAC, consultation with multidisciplinary surgical oncology team should occur before embarking on endoscopic therapy. In such patients, endoscopic therapy may be an alternative strategy to esophagectomy, especially in those with superficial (sm1) disease with a well-differentiated neoplasm lacking lymphovascular invasion, as well as those who are poor surgical candidates | Strong | Low |
| Routine staging of patients with nodular BE with EUS or other imaging modalities before EMR has no demonstrated benefit. Given the possibility of over- and under-staging, findings of these modalities should not preclude the performance of EMR to stage-early neoplasia | Strong | Moderate |
| In patients with known T1b disease, EUS may have a role in assessing and sampling regional lymph nodes, given the increased prevalence of lymph node involvement in these patients compared with less advanced disease | Strong | Moderate |
| In patients with dysplastic BE who are to undergo endoscopic ablative therapy for nonnodular disease, radiofrequency ablation is currently the preferred endoscopic ablative therapy | Strong | Moderate |

BE: Barrett esophagus; EAC: esophageal adenocarcinoma; EMR: endoscopic mucosal resection; EUS: endoscopic ultrasound; HGD: high grade dysplasia; IMC: intramucosal carcinoma; LGD: low- grade dysplasia.

British Society of Gastroenterology

In 2014, the British Society of Gastroenterology issued guidelines on the diagnosis and management of BE which make the following recommendations on management of dysplasia and early cancer (see table 2).

**Table 2: British Society of Gastroenterology Guidelines**

| Guidelines | Recommendation |
|---|---|
| Management of low-grade dysplasia (LGD) is unclear in view of limited data about the natural history. It is essential that the diagnosis is confirmed by two pathologists, and patients should be surveyed endoscopically at 6 monthly intervals. Currently, ablation therapy cannot be recommended routinely until more data are available | C |
| For HGD and Barrett's-related adenocarcinoma confined to the mucosa, endoscopic therapy is referred over oesophagectomy or endoscopic surveillance | B |
| In the presence of HGD or intramucosal cancer without visible lesions (flat HGD/intramucosal cancer), these should be managed with an endoscopic ablative technique | A |
| There are few comparative data among ablative techniques, but RFA currently has a better safety and side-effect profile and comparable efficacy | C |
| Eradication of residual Barrett's esophagus after focal ER reduces the risk of metachronous neoplasia and is recommended | B |

ER: endoscopic resection; HGD: high-grade dysplasia; RFA: radiofrequency ablation.

American Society for Gastrointestinal Endoscopy

In 2012, the American Society for Gastrointestinal Endoscopy issued a guideline on the role of endoscopy in BE and other premalignant conditions of the esophagus. These guidelines make the following recommendations on ablative therapies (see table 3).

**Table 3: British American Society for Gastrointestinal Endoscopy Guidelines**

| Guidelines | Evidence Quality |
|---|---|
| We suggest that ablation be considered in select patients with LGD. Appropriate surveillance intervals after ablation are unknown | Low |
| We recommend that endoscopic resection of nodular dysplastic BE be performed to determine the stage of dysplasia before considering other ablative endoscopic therapy | Moderate |
| We suggest that local staging with EUS ± FNA is an option in select patients being considered for endoscopic ablative therapy | Very low |
| We recommend that eradication with endoscopic resection or RFA be considered for flat HGD in select cases because of its superior efficacy (compared with surveillance) and side effect profile (compared with esophagectomy) | Moderate |

BE: Barrett esophagus; EUS: endoscopic ultrasound; FNA: fine needle aspiration; HGD: high-grade dysplasia; LGD: low-grade dysplasia; RFA: radiofrequency ablation.
[a] Quality assessed using GRADE system.

American Gastroenterological Association (AGA)

In 2015, the American Gastroenterological Association (AGA) published consensus recommendations for the management of BE, dysplasia, and esophageal adenocarcinoma. (See Table 4)

**Table 4. Recommendations on Management of BE, Dysplasia, and Esophageal Adenocarcinoma**

| Recommendation | Agreement | Strongly Agree | Agree | Neither | Disagree | Strongly Disagree |
|---|---|---|---|---|---|---|
| **Statements with ≥80% consensus agreement but generally low-quality evidence relevant to RFA for BE** | | | | | | |
| In patients with BE undergoing endoscopic therapy, endoscopic resection of more than two-thirds of the circumference is not generally recommended due to the risk of stricture. | 83 | 13 | 70 | 17 | | |
| RFA is an acceptable treatment option for BE patients with flat mucosa containing HGD without any visible lesions confirmed by high-resolution, high-definition endoscopy. | 87 | 35 | 52 | 13 | | |
| **Statements with consensus agreement <80% relevant to RFA for BE** | | | | | | |
| In patients with BE, all cases of possible dysplasia (indefinite, low grade, high grade) should be reviewed by at least 2 additional pathologists with specific expertise in Barrett's pathology. | 60.8 | | | 8.7 | 26.1 | 4.3 |

Values are percent.
BE: Barrett esophagus; RFA: radiofrequency ablation. HGD: high-grade dysplasia

A 2011 American Gastroenterological Association Medical Position Statement on the management of Barrett's esophagus recommends endoscopic eradication therapy with RFA [radiofrequency ablation], photodynamic therapy or endoscopic mucosal resection rather than surveillance for treatment of patients with confirmed high-grade dysplasia within Barrett's esophagus. They also state that:

- Although endoscopic eradication therapy is not suggested for the general population of patients with Barrett's esophagus in the absence of dysplasia, they suggest that RFA, with or without endoscopic mucosal resection, should be a therapeutic option for select individuals with non-dysplastic Barrett's esophagus who are judged to be at increased risk for progression to high-grade dysplasia or cancer but that specific criteria that identify this population have not been fully defined at this time.
- Endoscopic eradication therapy with RFA should also be a therapeutic option for treatment of patients with confirmed low-grade dysplasia in Barrett's esophagus.

The current literature is inadequate to recommend endoscopic eradication therapy with cryotherapy for patients with confirmed low-grade or high-grade dysplasia within Barrett's esophagus or patients judged to be at high risk for progression to high-grade dysplasia or esophageal carcinoma. Further studies are needed to assess whether reversion to squamous epithelium can persist long-term after cryotherapy.

Society of American Gastrointestinal and Endoscopic Surgeons

In 2010, the Society of American Gastrointestinal and Endoscopic Surgeons published guidelines on the surgical treatment of GERD, which included recommendations for the treatment of BE. (see table 5)

**Table 5: Society of American Gastrointestinal and Endoscopic Surgeons Guidelines**

| Guidelines | Grade |
|---|---|
| HGIN and IMC can be effectively treated with endoscopic therapy including PDT, EMR, and RFA, alone or in combination | B |
| Antireflux surgery may be performed in a patient with non-neoplastic IM, IND, or LGIN, with or without endoscopic therapy to eradicate the Barrett's tissue. Specifically, RFA has been shown to be safe, clinically effective, and cost-effective in these disease states and may be performed in eligible patients before, during, or after antireflux surgery | B |

EMR: endoscopic mucosal resection; HGIN: high-grade dysplasia; IM: intestinal metaplasia; IMC: intramucosal carcinoma; IND: indeterminate dysplasia; LGIN: low-grade dysplasia; PDT: photodynamic therapy; RFA: radiofrequency ablation.

National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines (v.2.2017) for esophageal cancer make the following recommendations about BE and early-stage esophageal adenocarcinomas:

Primary Treatment

> "The goal of endoscopic therapy, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and/or ablation, is the complete removal or eradication of early-stage disease (pTis, pT1a, and selected superficial pT1b without lymphovascular invasion (LVI)) and pre-neoplastic tissue (Barrett's esophagus).
>
> In early stage disease, Barrett's esophagus associated with flat high-grade dysplasia (HGD) should be treated by endoscopic resection (ER) as it provides more accurate histologic assessment of the lesion. Larger flat lesions (>2 cm) can be treated effectively by ER, but this is associated with greater risk of complications. Such lesions can be effectively treated by ablation alone, but there are very limited data on treating squamous cell HGD by ablation alone.
>
> Lesions that are found to be pathologically limited to the lamina propria or muscularis mucosae (pT1a), or the superficial submucosa (pT1b), in the absence of evidence of lymph node metastases, LVI, or poor differentiation grade can be treated with full ER. Ablative therapy of residual Barrett's esophagus should be performed following ER. Complete eradication of Barrett's esophagus can also be performed with more aggressive application of EMR (wide field EMR) or ESD at the initial intervention, if necessary to completely resect an area of superficial tumor or mucosal nodularity less than or equal to 2 cm in maximal dimension."

Post-Treatment Surveillance

> "Ablative therapy of residual Barrett's esophagus should be performed following ER. Complete eradication of Barrett's esophagus can also be performed with more aggressive application of EMR (wide field EMR) or ESD at the initial intervention, if necessary to

completely resect an area of superficial tumor or mucosal nodularity less than or equal to 2 cm in maximal dimension."

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

## Key Words:
Radiofrequency ablation, Cryoablation, Barrett's Esophagus, HALO360, CryoSpray Ablation

## Approved by Governing Bodies:
In 2005, the HALO360 (now Barrx™ 360 RFA Balloon Catheter; Barrx Medical, Sunnyvale, CA; acquired by Covidien in 2012) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process and, in 2006, the HALO90 (now Barrx™ 90 RFA Focal Catheter) received clearance. FDA-labeled indications are for use in coagulation of bleeding and nonbleeding sites in the gastrointestinal tract, and include the treatment of Barrett esophagus.

In December 2007, the CryoSpray Ablation™ System (formerly the SprayGenix Cryo Ablation system; CSA Medical, Lutherville, MD) was cleared for marketing by FDA through the 510(k) process for use as a "cryosurgical tool for destruction of unwanted tissue in the field of general surgery, specifically for endoscopic applications."

In July 2002, the Polar Wand® device (Chek Med Systems, Willington, CT), a cryosurgical device that uses compressed carbon dioxide, was cleared for marketing by FDA through the 510(k) process. Indications for use are, "ablation of unwanted tissue in the fields of dermatology, gynecology, general surgery, urology, and gastroenterology."

## Benefit Application:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

## Current Coding:
There are no specific CPT codes for radiofrequency or cryoablation of tissue in the esophagus.

CPT Codes:

| | |
|---|---|
| **43229** | Esophagoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed) **(Effective 01/01/2014)** |
| **43270** | Esophagogastroduodenoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post- |

| | |
|---|---|
| | dilation and guide wire passage, when performed) **(Effective 01/01/2014)** |
| **43499** | unlisted procedure, esophagus |

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## Policy History:

Adopted for Blue Advantage, March 2010
Available for comment April 7-May 21, 2010
Medical Policy Group, June 2010
Available for comment July 2-August 16, 2010
Medical Policy Group April 2011
Medical Policy Group, September 2011
Medical Policy Group, April 2012
Medical Policy Group, April 2013
Medical Policy Group, December 2013
Medical Policy Group, April 2014
Medical Policy Group, November 2014
Medical Policy Group, May 2015
Medical Policy Group, November 2015
Medical Policy Group, March 2016
Medical Policy Group, November 2016
Medical Policy Group, December 2016
Medical Policy Group, December 2017
Medical Policy Group, February 2018

*Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.*

*This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.*