Name of Policy:
Endoscopic Radiofrequency Ablation or Cryoablation for Barrett’s Esophagus

Policy #: 417       Latest Review Date: April 2014
Category: Surgery       Policy Grade: B

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**
Barrett's esophagus (BE) is a condition in which the normal squamous epithelium is replaced by specialized columnar-type epithelium, known as intestinal metaplasia. Intestinal metaplasia is a precursor to adenocarcinoma and may be treated with mucosal ablation techniques such as radiofrequency ablation (RFA) or cryoablation.

**BE and the Risk of Esophageal Carcinoma**
The esophagus is normally lined by squamous epithelium. Barrett’s esophagus 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, and patients with Barrett’s esophagus are at a 40-fold increased risk for developing this disease compared to the general population. Esophageal adenocarcinoma 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 10-11 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. It is upon these higher risk estimates that current surveillance recommendations have been based.

**Management of BE**
The current management of Barrett’s esophagus includes treatment of GERD, and surveillance endoscopy to detect progression to high-grade dysplasia or adenocarcinoma. The finding of low-grade dysplasia typically warrants only follow-up and surveillance biopsies, whereas 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%.

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 the only therapy shown in a randomized Phase III trial to significantly decrease the risk of carcinoma in Barrett’s esophagus. Two hundred and eight patients with high-grade dysplasia were randomized to PDT and omeprazole versus omeprazole alone. At 24 months’ follow-up, 77% of patients treated with PDT had complete ablation of high-grade dysplasia versus 39% in the control group (p<0.0001) and occurrence of adenocarcinoma within a follow-up time of 3.6 years was 13% in the PDT group versus 20% in the control group (p<0.006) (PDT therapy for Barrett’s esophagus is discussed in a separate policy 8.01.06). However, the use of PDT for Barrett’s esophagus with high-grade dysplasia has decreased dramatically recently, due to the fact that is relatively expensive and associated with a high complication rate, including photosensitivity and esophageal stricture formation in up to 30% of patients treated with this method.

The CryoSpray Ablation™ System (formerly the SprayGenix™ Cryo Ablation System, CSA Medical, Inc.) 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.

Treating high-grade dysplasia (HGD) or mucosal cancer solely with ablative techniques risks under treating the approximately 10% of patients who have undetected submucosal cancer, in whom esophagectomy would have been required.

The HALO System from BÂRRX™ Medical, Inc. (Sunnyvale, Calif. – acquired by Covidien in 2012 and now known as the Barrx line of products) 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.

**Policy:**

**Radiofrequency ablation meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for **Barrett’s esophagus with dysplasia**

**Radiofrequency ablation does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for **Barrett’s esophagus without dysplasia** and is considered investigational.

**Cryoablation does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for **Barrett’s esophagus, with or without dysplasia** and is considered investigational.

Blue Cross and Blue Shield of Alabama 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 Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate 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:**

**RFA versus surgical resection for Barrett Esophagus**
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.

In 2014 Chadwick et al reported on a systematic review which compared RFA and complete endoscopic resection (ER) for Barrett esophagus (BE). Twenty studies (22 articles) were reviewed including two randomized controlled trials (RCT), ten cohort studies on ER and eight cohort studies on RFA. The only study that compared RFA and ER 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 ER 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 ER and RFA eradicated BE dysplasia in 95% and 92%, respectively. Eradication was maintained in 95% of ER 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 ER (12%). Esophageal strictures requiring additional treatment occurred in 4% of RFA patients and 38% of complete ER 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 ER 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 event 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.

van Vilsteren et al reported on the results of a multicenter, randomized trial which compared the safety of stepwise radical endoscopic resection (SRER) versus focal ER 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 ER. Patients in the ER/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. 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%) ER/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.

RFA is a less-invasive alternative to surgical mucosal resection (SMR) and/or esophagectomy. 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**

One randomized multicenter, sham-controlled trial has been published that compares RFA to surveillance alone in BE with dysplasia. This trial 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 (\(<4\text{cm}\) or \(4-8\text{cm}\)). 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.

**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 Shaheen RCT 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.

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. Evidence from one RCT reports that progression from HGD to cancer is reduced by approximately 90% following RFA, with rates of esophageal strictures of 6%.

RFA for LGD
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. Additional studies were selected for inclusion if they were full-length, peer-reviewed articles in English, and studied BE treated with RFA in a comparative study of any size, or a single-arm study of at least 40 patients. The conclusions of the Assessment were that among patients with nondysplastic or low-grade dysplastic BE the evidence was insufficient to permit conclusions. Since the TEC Assessment a randomized controlled trial of RFA versus surveillance in patients with LGD has been published. 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 study 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%). There are challenges in diagnostic differentiation between nondysplastic BE and BE with LGD that are important in the consideration of treatment for LGD. Both sampling bias and interobserver variability have been shown to be problematic. Therefore, analysis of progression to carcinoma in BE with intestinal metaplasia versus LGD is a challenge. Initial diagnosis of BE can be a challenge with respect to histologic grading because inflammation and LGD can share similar histologic characteristics.

One approach to risk-stratify patients with an initial diagnosis of low-grade dysplasia has been to use multiple pathologists, including experts in gastrointestinal (GI) histopathology, to confirm the initial diagnosis of LGD. There is a high degree of intraobserver variability in pathologists’ reading of LGD versus inflammatory changes, and this variability in pathology diagnosis may contribute to the variable rates of progression of LGD reported in the literature. Kerkhof et al reported that in patients with an initial pathologic diagnosis of LGD, review by an expert pathologist will result in downgrading the initial diagnosis to non-dysplasia in up to 50% of cases. Curvers et al tested this hypothesis in 147 patients with BE who were given an initial diagnosis of LGD. All pathology slides were then read by two expert GI pathologists with extensive experience in BE, with disagreements among experts resolved by consensus. After review by expert pathologists, 85% of initial diagnoses of LGD were downgraded to non-dysplasia, leaving a total of only 22/147 patients (15%) with a confirmed diagnosis of LGD. All patients were followed for a mean of 5.1 years for progression to HGD or cancer. For patients with confirmed LGD, the rate of progression was 13.4%, compared with a rate of 0.5% for patients who had been downgraded to nondysplasia.

The strategy of having LGD confirmed by expert pathologists is supported by the results of the RCT by Phoa et al, which required confirmation of LGD by a central expert panel following initial diagnosis by a local pathologist. Of 511 patients with an initial diagnosis of LGD, 264 (52%) were excluded because the central expert panel reassigned classification of LGD, most often from LGD to indefinite or non-dysplasia.
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 two years. One RCT of 136 patients reported a lower rate of progression to high-grade dysplasia or adenocarcinoma for patients treated with RFA who had confirmed LGD. This trial supports the strategy of selecting a population that has a higher risk of progression by subjecting the initial pathologic diagnosis of LGD to review by an expert in GI pathology. Expert review has been reported to reduce the number of patients diagnosed with LGD by 50% to 75%, presumably by reducing the number of patients with inflammatory changes who are mislabeled as having LGD.

**RFA for Non-Dysplastic BE**
There are no RCTs 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.

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. It is possible that the risk of RFA exceeds the benefit in this population, owing to the low underlying rates of progression and the reported rates of esophageal strictures following RFA.
**RFA versus 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.

There is limited evidence to compare RFA with PDT for treatment of BE and no controlled trials. While evidence supports greater eradication rates with RFA over PDT, these data are not sufficient to determine the comparative efficacy of RFA compared with PDT.

**Cryoablation**

Published efficacy data for cryoablation in Barrett’s esophagus are limited. Johnston et al. 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.

An 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 who 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 strictures 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 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).

There is limited evidence on the use of cryoablation for treatment of BE and no controlled trials. 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
Barrett’s esophagus (BE) is a condition in which the normal squamous epithelium is replaced by specialized columnar-type epithelium, known as intestinal metaplasia. Intestinal metaplasia is a precursor to adenocarcinoma and may be treated with mucosal ablation techniques such as radiofrequency ablation (RFA) or cryoablation.

Radiofrequency ablation (RFA) of high-grade dysplasia (HGD) in Barrett’s esophagus has been shown to be 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. Therefore, RFA may be considered medically necessary for patients with Barrett’s esophagus (BE) and HGD.

For patients with low-grade dysplasia (LGD), one RCT has reported that RFA reduces progression to high-grade dysplasia and adenocarcinoma in patients with confirmed LGD. Based on the results of this RCT, other available evidence, specialty society guidelines, and the results of clinical vetting, it is possible to define a population with a higher risk of progression by having the initial LGD diagnosis confirmed by an additional pathologist who is an expert in gastrointestinal (GI) pathology. In this subpopulation of patients with an initial diagnosis of LGD, the benefit of treatment outweighs the risk. As a result, RFA of LGD may be considered medically necessary for patients with LGD when the initial diagnosis of LGD is confirmed by an expert in GI pathology.

For patients with non-dysplastic BE, it cannot be concluded that the benefit of RFA outweighs the risk, and therefore RFA is considered investigational for this population. Data for the efficacy of cryoablation of BE with or without dysplasia are limited. The studies consist of small numbers of patients with short-term follow-up, and therefore cryoablation of BE is considered investigational.
**Practice Guidelines and Position Statements**

*The American Gastroenterological Association (AGA)*

The AGA 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.

*American College of Gastroenterology (ACG)*

The ACG published updated guidelines for the management of BE in 2008. The following recommendations were included:

- Any initial diagnosis of dysplasia, both HGD and LGD, requires confirmation by an expert in GI pathology.
- HGD, when confirmed by an expert, represents a threshold for intervention.
- LGD, when confirmed by an expert, requires more frequent endoscopy and biopsy.

*Society of the American Gastrointestinal and Endoscopic Surgeons*

The Society of the American Gastrointestinal and Endoscopic Surgeons published guidelines on the surgical treatment of GERD, which included recommendations for the treatment of BE. These guidelines included the following statements:

- High-grade dysplasia and intramucosal carcinoma can be effectively treated with endoscopic therapy including photodynamic therapy (PDT), endoscopic mucosal resection (EMR), and RFA, alone or in combination (grade B).
- Antireflux surgery may be performed in a patient with non-neoplastic intestinal metaplasia, indeterminate dysplasia, or low-grade dysplasia, 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 (grade B).
National Comprehensive Cancer Network Guidelines
NCCN guidelines for esophageal cancer indicate resection is the preferred treatment choice for Barrett’s esophagus but ablative therapy such as RFA is listed as an alternative option to resection for Barrett’s esophagus with high-grade dysplasia. NCCN guidelines state that, for primary treatment, endoscopic mucosal resection or ablative therapy may be appropriate for Barrett’s esophagus associated with Tis (HGD or carcinoma in-situ). Patients with superficial T1a disease should have ablation (preferred) or esophagectomy performed following mucosal resection. For post-treatment surveillance, the guidelines state that ablation of residual flat or recurrent high-grade and low-grade dysplasia using RFA or cryoablation should be considered. Ablation of non-dysplastic Barrett’s esophagus is not recommended.

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

Approved by Governing Bodies:
The HALO360 (now Barrx™ 360 RFA Balloon Catheter) received FDA 510(k) clearance for marketing in 2005 and the HALO90 (now Barrx™ 90 RFA Focal Catheter) in 2006. FDA-labeled indications are for use in coagulation of bleeding and nonbleeding sites in the gastrointestinal tract (GI), and include the treatment of BE.

The CryoSpray Ablation™ System received FDA 510(k) marketing clearance in December 2007 for use as a “cryosurgical tool for destruction of unwanted tissue in the field of general surgery, specifically for endoscopic applications.”

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

ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

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)

43257 Upper gastrointestinal endoscopy including esophagus, stomach and either the duodenum and/or jejunum as appropriate; with delivery of thermal
energy to the muscle of lower esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease

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

**Previous Coding:**

43228  Esophagoscopy, rigid or flexible; with ablation of tumor(s), polyp(s), or other lesion(s), not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique *(Deleted effective 01/01/2014)*

43258  Upper Gastrointestinal Endoscopy including esophagus, stomach, and either the duodenum and/or Jejunum as appropriate; with ablation of tumor(s), polyp(s), or other lesion(s), not amendable to removal by hot biopsy forceps, bipolar cautery or snare technique ) *(Deleted effective 01/01/14)*

**References:**

2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Radiofrequency ablation of nondysplastic or low-grade dysplastic Barrett’s esophagus. TEC Assessments 2010; Volume 25, Tab 5.
**Policy History:**
Medical Policy Panel, December 2009
Medical Policy Group, March 2010 (2)
Medical Policy Administration Committee, April 2010
Available for comment April 7-May 21, 2010
Medical Policy Group, June 2010 (3)
Medical Policy Administration Committee, July 2010
Available for comment July 2-August 16, 2010
Medical Policy Group April 2011: Added 2011 Key Points and Reference
Medical Policy Group, September 2011 (1): Update to Key Points and References
Medical Policy Group, April 2012 (3): 2012 Update to Description, Key Points and References
Medical Policy Panel, April 2013
Medical Policy Group, April 2013 (3): 2013 Update to Description, Key Points and References
Medical Policy Group, December 2013 (3): 2014 Coding Update – added new codes 43229 and 43270 (effective 01/01/14); moved to previous coding 43228 and 43258 (deleted effective 01/01/14)
Medical Policy Panel, April 2014
Medical Policy Group, April 2014 (3): 2014 Update to Description, Key Points, Governing Bodies & References; no change in policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. 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.