2.01.80 Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus			
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Policy Statement

Radiofrequency ablation (RFA) may be considered **medically necessary** for the treatment of Barrett esophagus (BE) with **either** of the following:

I. High-grade dysplasia (HGD)
II. Low-grade dysplasia (LGD), when the initial diagnosis of low-grade dysplasia is confirmed by 2 pathologists.

Radiofrequency ablation is considered **investigational** for the treatment of Barrett esophagus when the above criteria are not met, including but not limited to Barrett esophagus in the absence of dysplasia.

Cryoablation is considered **investigational** for the treatment of Barrett esophagus, with or without dysplasia.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

High-grade Dysplasia

Radiofrequency ablation for Barrett esophagus with high-grade dysplasia may be used in combination with endoscopic mucosal resection (EMR) of nodular or visible lesions. The diagnosis of high-grade dysplasia should be confirmed by 2 pathologists before initiating radiofrequency ablation. The American Society for Gastrointestinal Endoscopy and the American Gastroenterological Association both recommend that a reading of high-grade dysplasia (HGD) should be confirmed by an experienced gastrointestinal pathologist.[1,2] Two cohort studies found that reevaluation of HGD after an initial evaluation resulted in 40% to 53% of patients receiving a lower-grade evaluation on repeat endoscopy, highlighting the need for confirmation by an expert center.[3,4] Additionally for HGD, it is important to rule out adenocarcinoma; referral to an expert center that can conduct high-definition white-light endoscopy and other diagnostic techniques has been found to increase the rate of adenocarcinoma detection and proper referral for endoscopic mucosal resection.[5]

Low-grade Dysplasia

There is considerable interobserver variability in the diagnosis of low-grade dysplasia (LGD), and the potential exists for overdiagnosis of LGD by nonexpert pathologists (overdiagnosis is due primarily to the difficulty in distinguishing inflammatory changes from LGD). There is evidence in the literature that expert gastrointestinal (GI) pathologists will downgrade a substantial portion of biopsies that are initially read as LGD by nonexperts (Curvers et al [2010]; Kerkhof et al [2007]).[6,7] As a result, it is ideal that 2 experts in gastrointestinal pathology agree on the diagnosis to confirm LGD; this may result in greater than 75% of initial diagnoses of LGD being downgraded to nondysplasia (Curvers et al [2010]). A review by a single expert gastrointestinal pathologist will also result in a large number of LGD diagnoses being downgraded, although probably not as many as achieved using 2 expert pathologists (Kerkhof et al, 2007).

Coding

There is no CPT code specific to radiofrequency ablation or cryoablation of tissue in the esophagus. These procedures would likely be coded using one of the following 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)

- **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)

Description

In Barrett esophagus (BE), 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.

Related Policies

- Confocal Laser Endomicroscopy
- Oncologic Applications of Photodynamic Therapy, Including Barrett Esophagus

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In 2005, the HALO360 (now Barrx™ 360 RFA Balloon Catheter; Barrx Medical; 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. The FDA labeled indications are for use in coagulation of bleeding and nonbleeding sites in the gastrointestinal tract and include the treatment of BE.[12,] Other focal ablation devices from Barrx include the Barrx™ 60 RFA Focal Catheter, the Barrx™ Ultra Long RFA Focal Catheter, the Barrx™ Channel RFA Endoscopic Catheter.[13,]

FDA product code: GEI.

In 2007, the CryoSpray Ablation™ System (formerly the SprayGenix Cryo Ablation system; CSA Medical) was cleared for marketing by the 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."[14,] The CryoBalloon Ablation System has also been cleared by the FDA through the 510(k) process for use as a cryosurgical tool in surgery for endoscopic applications, including ablation of BE with dysplasia.[15,]

FDA product code: GEH.

In 2002, the Polar Wand® device (Chek-Med Systems), a cryosurgical device that uses compressed carbon dioxide, was cleared for marketing by the 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."[16,]

Rationale

Background

Management of Barrett Esophagus

The management of Barrett Esophagus (BE) includes the treatment of gastroesophageal reflux disease and surveillance endoscopy to detect progression to high-grade dysplasia (HGD) or adenocarcinoma. The finding of HGD or early-stage adenocarcinoma warrants mucosal ablation or resection (either endoscopic mucosal resection [EMR] or esophagectomy).

EMR, either focal or circumferential, provide a histologic specimen for examination and staging (unlike ablative techniques). One 2007 study provided long-term results for EMR in 100 consecutive patients with early Barrett-associated adenocarcinoma (limited to the mucosa).[8] The 5-year overall survival was 98% and, after a mean of 36.7 months, metachronous lesions were observed in 11% of patients. In a review by Pech and Ell (2009), the authors stated that circumferential EMR of the entire segment of BE leads to a stricture rate of 50%, and recurrences occur at a rate of up to 11%.[9]

Ablative Techniques

Available mucosal ablation techniques include several thermal (multipolar electrocoagulation [MPEC], argon plasma coagulation [APC], heater probe, neodymium-doped yttrium aluminum garnet [Nd:YAG] laser, potassium titanyl phosphate[KTP]-YAG laser, diode laser, argon laser, cryoablation) or nonthermal (5-aminolevulinic acid, photodynamic therapy) techniques. In a randomized phase 3 trial reported by Overholt et al (2005), photodynamic therapy was shown to decrease significantly the risk of adenocarcinoma in BE.[10] (Photodynamic therapy for BE is discussed in Blue Shield of California Medical Policy: Oncologic Applications of Photodynamic Therapy, Including Barrett Esophagus.)

The CryoSpray Ablation system uses a low-pressure spray for applying liquid nitrogen through an upper endoscope. Cryotherapy allows for the treatment of uneven surfaces; however, a disadvantage of the treatment is the uneven application inherent in spraying the cryogen.

The HALO system uses radiofrequency energy and consists of 2 components: an energy generator and an ablation catheter. The generator provides rapid (i.e., <1 second) delivery of a predetermined amount of radiofrequency energy to the catheter. The HALO90 or the HALO360 is 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 BE up to 3 cm. HALO360 uses a balloon catheter that is sized to fit the individual's esophagus and is inflated to allow for circumferential ablation.

Radiofrequency ablation affects only the most superficial layer of the esophagus (i.e., the mucosa), leaving the underlying tissues unharmed. Measures of efficacy for the procedure are the eradication of intestinal metaplasia and the postablation regrowth of the normal squamous epithelium. (Note: The eradication of intestinal metaplasia does not leave behind microscopic foci). Reports of the efficacy of the HALO system in ablating BE have been as high as 70% (comparable with alternative methods of ablation [e.g., APC, MPEC]), and even higher in some reports. The incidence of leaving behind microscopic foci of intestinal metaplasia has been reported to be between 20% and 44% with APC and 7% with MPEC; studies using the HALO system have reported 0%.[11] Another potential advantage of the HALO system is that it is an automated process that eliminates operator-dependent error, which may be seen with APC or MPEC.

The risk of treating HGD or mucosal cancer solely with ablative techniques is undertreatment for approximately 10% of patients with undetected submucosal cancer, in whom esophagectomy would have been required.[9]

Literature Review

This review was influenced in part by a Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment (2010) that assessed the use of radiofrequency ablation (RFA) for treating nondysplastic Barrett esophagus (BE) or BE with low-grade dysplasia (LGD).[17]

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Barrett Esophagus and Risk of Esophageal Carcinoma

The esophagus is normally lined by squamous epithelium. 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. Occurring in the distal esophagus, BE may be of any length; it may be focal or circumferential and can be seen on endoscopy as being a different color than the background squamous mucosa. Confirmation of BE requires a 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, resulting in the phenotypic expression of histologic features from LGD, to high-grade dysplasia (HGD), to carcinoma. Two large epidemiologic studies published in 2011 reported the risk of progression to cancer in patients with BE. One reported the rate of progression to cancer in more than 8000 patients with a mean duration of follow-up of 7 years (range, 1-20 years).[18] The de novo progression to cancer from BE at 1 year was 0.13%. The risk of progression was reported as 1.4% per year in patients with LGD and 0.17% per year in patients without dysplasia. This incidence translates into a risk of 10 to 11 times that of the general population. The other study identified more than 11000 patients with BE and, after a median follow-up of 5.2 years, it reported that the annual risk of esophageal adenocarcinoma was 0.12%.[19] Detection of LGD on index endoscopy was associated with an incidence rate for adenocarcinoma of 5.1 cases per 1000 person-years, and the incidence rate among patients without dysplasia was 1.0 case per 1000 person-years. Risk estimates for patients with HGD were slightly higher. The reported risk of progression to cancer in BE in older studies was much higher, with an annual incidence of risk of 0.4% to 0.5% per year, with risk estimated at 30 to 40 times that of the general population. Current surveillance recommendations have been based on these higher risk estimates.

There are challenges in diagnostically differentiating between nondysplastic BE and BE with LGD; they are important when considering treatment for LGD.[20,21] Both sampling bias and inter-observer variability have been shown to be problematic. Therefore, analysis of progression to carcinoma in BE with intestinal metaplasia versus LGD is difficult. Initial diagnosis of BE can also

be a challenge with respect to histologic grading because inflammation and LGD can share similar histologic characteristics.[22]

One approach to risk-stratify patients with an initial diagnosis of LGD has been to use multiple pathologists, including experts in gastrointestinal histopathology, to confirm the initial diagnosis of LGD. There is a high degree of interobserver variability among the pathology readings of LGD versus inflammatory changes, and the resultant variability in pathology diagnosis may contribute to the variable rates of progression of LGD reported in the literature.[17] Kerkhof et al (2007) reported that, in patients with an initial pathologic diagnosis of LGD, review by an expert pathologist would result in the initial diagnosis being downgraded to nondysplasia in up to 50% of cases.[7] Curvers et al (2010) tested this hypothesis in 147 patients with BE who were given an initial diagnosis of LGD.[6] All pathology slides were read by 2 expert gastrointestinal pathologists with extensive experience in BE; disagreements among experts in the readings were resolved by consensus. Once this process was completed, 85% of initial diagnoses of LGD were downgraded to nondysplasia, leaving 22 (15%) of 147 patients 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 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 an RCT by Phoa et al (2014), which required confirmation of LGD by a central expert panel following initial diagnosis by a local pathologist.[23] Of 511 patients with an initial diagnosis of LGD, 264 (52%) were excluded because the central expert panel reassigned the classification of LGD, most often from LGD to indefinite or nondysplasia. These findings were further confirmed in a retrospective cohort study by Duits et al (2015) who reported on 293 BE cases with LGD diagnosed over an 11-year period and submitted for expert panel review.[24] In this sample, 73% of subjects were downstaged.

Radiofrequency Ablation for Barrett Esophagus With High-Grade Dysplasia
Clinical Context and Therapy Purpose
In patients diagnosed with BE with HGD, the risk of progression to cancer is relatively high, and esophageal adenocarcinoma is associated with high morbidity and a 5-year survival rate of up to 13%.[25] Therefore, intervention with esophagectomy or RFA may be strongly indicated.

The purpose of endoscopic RFA in patients who have BE with HGD is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of RFA improve the net health outcome in patients with BE with HGD?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients with BE with HGD.

Interventions
The therapy being considered is endoscopic RFA.

Comparators
The following therapies and practices are currently being used to treat BE: esophagectomy, endoscopic mucosal resection (EMR), and surveillance.

Outcome
The general outcomes of interest are symptoms (e.g., pain) and functional outcomes (including swallowing).

Beneficial outcomes include reductions in progression to carcinoma and longer-term maintenance of eradication of dysplasia.

Harmful outcomes include damage to the esophagus resulting in difficulty swallowing.

Morbidity from treatment would be assessed within 30 days after the procedure.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Chadwick et al (2014) reported on a systematic review that compared RFA with complete EMR for the treatment of BE.[26] Twenty studies (22 articles) were reviewed, including 2 RCTs, 10 cohort studies on EMR, and 8 cohort studies on RFA. The only study that compared RFA with EMR was an RCT by van Vilsteren et al (2011)[27]; the other RCT was by Shaheen et al (2009, 2011; see below).[28,29] The studies were heterogeneous in design. A total of 1,087 (532 EMR, 555 RFA) patients with HGD or intramucosal carcinoma were included in the studies reviewed. The median number of resections or RFA sessions required for the eradication of BE was 2. Complete EMR and RFA eradicated BE dysplasia in 95% and 92% of patients, 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 events (2.5%) than those who received complete EMR (12%). Esophageal strictures requiring additional treatment occurred in 4% of RFA patients and 38% of complete endoscopic resection patients.

Randomized Controlled Trials

RFA may be used alongside focal endoscopic resection. In the intention-to-treat analysis of a prospective interventional study by Phoa et al (2016) that included 132 subjects with BE and HGD or early cancer treated with endoscopic resection followed by RFA, complete eradication of neoplasia and complete eradication of intestinal metaplasia occurred in 92% and 87% of subjects, respectively.[30] At a median follow-up of 27 months, neoplasia and intestinal metaplasia had recurred in 4% and 8% of subjects, respectively.

Van Vilsteren et al (2011) reported on the results of a multicenter randomized trial that compared the safety of stepwise radical endoscopic resection (SRER) with focal EMR followed by RFA for complete eradication of BE 5 cm or less with HGD or early cancer.[27] Patients in the SRER group underwent a piecemeal EMR of 50% of BE followed by serial EMR. Patients in the EMR plus RFA group underwent focal EMR for visible lesions followed by serial RFA. Follow-up endoscopy with biopsies (4-quadrant/2 cm BE) was performed at 6 and 12 months and then annually. The main outcome measures were: stenosis rate; complications; complete histologic response for neoplasia; and complete histologic response for intestinal metaplasia (CR-IM). Complete histologic response for neoplasia was achieved in 25 (100%) of 25 SRER patients and in 21 (96%) of 22 patients receiving EMR plus RFA. CR-IM was achieved in 23 (92%) SRER patients and 21 (96%) patients receiving EMR plus RFA. The stenosis rate was significantly higher with SRER (88%) than with EMR plus RFA (14%; p<.001), resulting in more therapeutic sessions in SRER (6 vs 3; p<.001) due to dilations. After a median follow-up of 24 months, 1 SRER patient had a recurrence of early cancer, requiring endoscopic resection. This trial confirmed that both techniques achieved comparably high rates of CR-IM and complete histologic response for neoplasia but found that SRER was associated with more complications and therapeutic sessions.

The randomized multicenter, sham-controlled trial by Shaheen et al (2009) compared RFA with surveillance alone in patients with BE and dysplasia.[28] RFA was successful in eradicating HGD, with complete eradication at 12 months achieved in 81% of the ablation group versus 19% in the control group (p<.001).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 the trial, 19% in the control group progressed to cancer versus 2.4% in the RFA group (p=.04). This represented a nearly 90% relative risk reduction for progression to cancer (relative risk, 0.1; 95% confidence interval [CI], 0.01 to 1.0, p=.04), and a number needed to treat of 6.0 to prevent 1 case of cancer over a 1-year period.

Longer-term follow-up at 2 to 3 years reported that complete eradication of dysplasia was maintained in most participants with initial HGD.[29] For 54 patients with HGD available for follow-up, all dysplasia was eradicated in 50 (93%) of 54, and all intestinal metaplasia was eradicated in 48 (89%) of 54. After 3 years, dysplasia was eradicated in 55 (98%) of 56 of subjects, and all intestinal metaplasia was eradicated in 51 (91%) of 56. More than 75% of patients with HGD remained free of intestinal metaplasia with a follow-up of longer than 3 years, with no additional therapy.

Section Summary: Radiofrequency Ablation for Barrett Esophagus With High-Grade Dysplasia
For patients who have BE with 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 2 years. One RCT demonstrated that, following RFA, the progression from HGD to cancer is reduced by approximately 90%, with rates of esophageal strictures of 6%.

Radiofrequency Ablation for Barrett Esophagus With Low-Grade Dysplasia
Clinical Context and Therapy Purpose
The purpose of endoscopic RFA in patients who have BE with LGD is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of RFA improve the net health outcome in patients with BE with LGD?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients with BE with LGD.

Interventions
The therapy being considered is endoscopic RFA.

Comparators
The following practice is currently being used to treat BE with LGD: surveillance by gastroenterologists.

Outcome
The general outcomes of interest are symptoms (e.g., pain) and functional outcomes (including swallowing)

Beneficial outcomes include reductions in progression to HGD or carcinoma and longer-term maintenance of eradication of dysplasia.

Harmful outcomes include damage to the esophagus resulting in difficulty swallowing.

Morbidity would be assessed within 30 days after the procedure. Conversion to HGD would be measured at 2 to 5 years.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Klair et al (2021) performed a systematic review and meta-analysis of comparative studies of RFA versus endoscopic surveillance in patients with BE with LGD.[31] The primary outcome was risk of progression to HGD or esophageal adenocarcinoma. The meta-analysis included 4 studies (N=543), including 2 retrospective studies and 2 RCTs. Compared with endoscopic surveillance, RFA was associated with lower odds of progression to either HGD or esophageal adeno-carcinoma (odds ratio [OR], 0.17; 95% CI, 0.04 to 0.65). Individually, the progression to HGD maintained significance compared with endoscopic surveillance (OR, 0.23; 95% CI, 0.08 to 0.61), while progression to adenocarcinoma was numerically lower (OR, 0.44; 95% CI, 0.17 to 1.16). However, the findings indicated moderate heterogeneity (I^2=0.63) and evidence of publication bias.

In their meta-analysis, Pandey et al (2018) evaluated RCTs and observational studies to determine the efficacy of RFA in treating BE with LGD compared with surveillance.[32] The 8 studies in the meta-analysis included 619 patients followed up for a median of 26 months. The overall pooled rate of complete eradication of intestinal metaplasia after RFA was 88.17% (95% CI, 88.13% to 88.20%; p<.001); the rate of complete eradication of dysplasia was 96.69% (95% CI, 96.67% to 96.71%; p<.001). Compared with surveillance, the rates of progression to HGD or cancer were significantly lower with RFA (OR, 0.07; 95% CI, 0.02 to 0.22). The pooled recurrence rate of intestinal metaplasia was 5.6% (95% CI, 5.57% to 5.63%; p<.001) and 9.66% (95% CI, 9.61% to 9.71%; p<.001) for dysplasia. Although the analysis was limited by its inclusion of observational cohort studies and the sample sizes of patients receiving RFA were all less than 100 patients, all studies supported the use of RFA for LGD BE. The authors concluded that RFA is safe and effective for eradicating intestinal metaplasia and dysplasia and reducing progression from LDG to HGD or cancer in the short term. Longer-term outcomes, however, warrant further research.

Almond et al (2014) reported on the results of a meta-analysis of studies using endoscopic therapy to treat BE with LGD.[33] The analysis included 37 studies, 9 of which evaluated RFA alone, including the RCT by Shaheen et al (2009). Most studies were small, with the Shaheen et al (2009) RCT representing the largest study (52 with LGD treated with RFA). For patients treated with RFA, the pooled incidence of cancer or progression to 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.

Randomized Controlled Trials

Several RCTs comparing RFA with surveillance in patients with BE with LGD have been published that were not included in the systematic reviews by Klair et al (2021), Pandey et al (2018), and Almond et al (2014), and the TEC Assessment (2010). Barret et al (2020) performed an RCT that randomized 82 patients with confirmed LGD at 14 centers in France to RFA or surveillance.[34] Of 40 patients randomized to RFA, 37 actually received treatment. The primary outcome (prevalence of LGD 3 years after randomization) was significantly improved with RFA in the per-protocol analysis (40.5% vs. 67.5%; OR, 0.33; 95% CI, 0.13 to 0.83), but not in the intention-to-treat

analysis (34.3% vs. 58.1%; OR, 0.38; 95% CI, 0.14 to 1.02). The secondary outcome of neoplastic progression rate to HGD or early adenocarcinoma with RFA versus surveillance was 12.5% versus 26.2% (p=.15), respectively, in the ITT analysis.

Phoa et al (2014) also conducted an RCT comparing RFA with surveillance in patients with LGD; this RCT was included in the meta-analysis by Klair et al.[23] This trial randomized 140 patients with BE and confirmed LGD; 4 patients were excluded after randomization for not meeting study inclusion criteria at further review, leaving 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 HGD or adenocarcinoma up to 3 years after randomization. Secondary outcomes were the complete eradication of dysplasia, the absence of intestinal metaplasia, and adverse events.

The trial was terminated early after an interim analysis determined the superiority of RFA.[23] At 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%) than in the surveillance group (8.8%; p<.03), and the occurrence of HGD was also significantly lower for the RFA group (1.5%) than for the surveillance group (26.5%; p<.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 3 serious adverse events in 2 patients who received RFA (1 case each of abdominal pain requiring hospitalization, bleeding, fever/chills following dilation for stricture), and 12 other adverse events (8 strictures requiring dilation, 3 mucosal lacerations, 1 retrosternal pain).

The long-term follow-up results of the Phoa et al (2014) study were reported in Pouw et al (2020).[35] After a median follow-up of 73 months, no additional patients showed progression to HGD in the RFA group from the original study, while 5 additional patients in the surveillance group progressed to HGD (n=4) or intramucosal cancer (n=1). Overall, during the initial study period and long-term follow-up, progression to HGD/cancer was observed in 1.5% of patients in the RFA group compared to 33.8% in the surveillance group, translating to a number needed to treat of 3.1 (95% CI, 2.3 to 4.5). Of the 83 patients treated with RFA (68 patients in the original study plus 15 patients in the original surveillance group who received RFA after study closure), 75 (90%) achieved complete clearance of BE and dysplasia.

Section Summary: Radiofrequency Ablation for Barrett Esophagus With Low-Grade 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 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. This trial supported the strategy of selecting a population at a higher risk of progression by subjecting the initial pathologic diagnosis of LGD to review by an expert in GI pathology. The expert review has reduced the number of patients diagnosed with LGD by 50% to 75%, presumably by reducing the number of patients with inflammatory changes who are miscategorized as having LGD.

Radiofrequency Ablation for Barrett Esophagus Without Dysplasia
Clinical Context and Therapy Purpose
The purpose of endoscopic RFA in patients who have BE without dysplasia is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of RFA improve the net health outcome in patients with BE without dysplasia?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients with BE without dysplasia.

Interventions
The therapy being considered is endoscopic RFA.

Comparators
The following practice is currently being used to treat BE without dysplasia: surveillance by gastroenterologists.

Outcome
The general outcomes of interest are symptoms (e.g., pain) and functional outcomes (including swallowing).

Beneficial outcomes include reductions in progression to dysplasia or carcinoma and longer-term maintenance of eradication of dysplasia.

Harmful outcomes include damage to the esophagus resulting in difficulty swallowing.

Morbidity would be assessed within 30 days after the procedure. Conversion to dysplasia would be measured at 2 to 5 years.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Nonrandomized Trials
No RCTs were identified that evaluated RFA treatment of BE without dysplasia. The evidence on this issue consists of single-arm trials that have reported outcomes of RFA. There is no high-quality evidence on the comparative efficacy of RFA versus surveillance alone. Progression to cancer in cases of nondysplastic BE is lower than that for LGD or HGD, with rates in the literature ranging from 0.05% to 0.5%.[18,19]

Fleischer et al (2008, 2010) reported on the 5-year follow-up of a single-arm study of patients with nondysplastic BE treated with RFA.[36,37] The original study included 70 patients who underwent circumferential RFA and CR-IM, defined as complete eradication of nondysplastic BE.[36] CR-IM was seen in 70% of patients at 1-year follow-up; patients with persistent BE underwent focal RFA. At the 2.5-year follow-up, CR-IM was found in 60 (98%) of 61 patients.[36] At 5-year follow-up, 4-quadrant biopsies were obtained from every 1 cm of the original extent of BE, and the authors reported the proportion of patients demonstrating CR-IM.[37] If nondysplastic BE was identified at the 5-year follow-up, focal RFA was performed 1 month later, and biopsies were repeated 2 months afterward to assess histologic response. Primary outcomes were the proportion of patients demonstrating CR-IM at a 5-year biopsy or after a single session of focal RFA. For the 5-year follow-up, there were 60 eligible patients, 50 (83%) of whom participated. Forty-six (92%) of 50 patients showed CR-IM at the 5-year biopsy visit. The 4 patients found to have BE at 5 years underwent a single session of RFA 1 month after biopsy; all 4 patients had CR-IM at subsequent rebiopsy 2 months after RFA. No strictures were noted. The authors concluded that this first report of 5-year CR-IM outcomes supported the safety, efficacy, and reduction in neoplastic progression in treating nondysplastic BE with RFA.

Section Summary: Radiofrequency Ablation for Barrett Esophagus Without Dysplasia
Nondysplastic BE has a relatively low rate of progression to cancer. Although available research has indicated that nondysplastic metaplasia can be eradicated by RFA, the risk-benefit ratio and the net effect on health outcomes is uncertain.

Cryoablation of Barrett Esophagus
Clinical Context and Therapy Purpose
The purpose of endoscopic cryoablation in patients who have BE is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of cryoablation improve the net health outcome in patients with BE?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients with BE with or without dysplasia.

Interventions
The therapy being considered is endoscopic cryoablation.

Comparators
The following therapies and practices are currently being used to treat BE: esophagectomy, EMR, and surveillance.

Outcomes
The general outcomes of interest are symptoms (e.g., pain) and functional outcomes (including swallowing).

Beneficial outcomes include reductions in progression to HGD or carcinoma and longer-term maintenance of eradication or dysplasia.

Harmful outcomes include damage to the esophagus resulting in difficulty swallowing.

Morbidity would be assessed within 30 days after the procedure.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
Several meta-analyses have evaluated the efficacy of cryotherapy in patients with BE (Tables 1, 2, and 3). Tariq et al (2021) performed a meta-analysis of 14 retrospective and prospective observational studies (N=405) of patients with BE who were treated with cryotherapy.[38.] The primary outcome of proportions of patients achieving complete eradication of dysplasia and complete eradication of intestinal metaplasia were 84.8% (95% CI, 72.2% to 94.4%) and 64.2% (95% CI, 52.9% to 74.8%), respectively. Both outcomes had a high degree of heterogeneity (I^2 of 88.3% and 77.9%, respectively). Subgroup analyses of only high-quality studies revealed rates of 91.3% (95% CI, 83.0% to 97.4%; I^2=69.5) and 71.6% (95% CI, 59.0% to 82.9%, I^2=80.9%), respectively.

In their meta-analysis, Westerveld et al (2020) evaluated 7 prospective and retrospective cohort studies that reported outcomes of balloon cryoablation across 272 patients with BE; 3 of the included studies were previously reported in abstract form only.[39] The pooled proportion for complete eradication of intestinal metaplasia was 85.8% (95% CI, 77.8% to 92.2%). Among 262 patients with BE with dysplasia, 238 reported complete eradication of dysplasia after cryoablation (pooled proportion, 93.8%; 95% CI, 85.5% to 98.7%). Both outcomes had a high degree of heterogeneity (I^2 of 55% and 74.2%, respectively). However, when 2 low quality studies were excluded from the analysis results were consistent with the primary analysis. Adverse events were reported in 12.5% of patients, representing 34 adverse events. Half of the adverse events (n=16) were post-ablation stricture formation (5.8%).

Hamade et al (2019) evaluated the use of cryotherapy for BE in patients who were previously treatment-naive.[40] Six uncontrolled trials were included in the systematic review, which included 232 patients overall. Complete eradication of intestinal metaplasia was achieved in 69.35% of cases (95% CI, 52.1% to 86.5%; I^2 = 89.3%). Complete eradication of dysplasia was achieved in 90.6% of cases (95% CI, 83.7% to 97.4%; I^2 = 75.7%). Progression to cancer occurred in 4% of cases (9/225). The pooled recurrence rate of intestinal metaplasia was 19.1 per 100 patient-years. The post-procedure stricture formation rate was 4.9% and 3.9% of patients reported postprocedural pain.

Table 1. Comparison of Studies Included in SR & M-As

Study	Tariq et al (2020)[38]	Westerveld et al (2020)[39]	Hamade et al (2019)[40]
Canto et al (2019)		●	
Canto et al (2018)	●	●	●
Canto et al (2015)	●		●
Cheng et al (2013)	●		
Eluri et al (2017)	●		
Goldberg et al (2012)	●		
Gosaine et al (2013)	●		●
Greenwald et al (2010)	●		
Halsey et al (2011)	●		
Johnston et al (2013)	●		
Kunzli et al (2016)		●	
Ramay et al (2017)	●		●
Scholvinck et al (2015)		●	
Sitaraman et al (2016)		●	
Trindade et al (2017)	●		●
Thota et al (2018)	●		●
Van Munster et al (2018)		●	
Verbeek et al (2015)	●		
Wang et al (2015)		●	
Wani et al (2012)	●		

M-A: meta-analysis; SR: systematic review.

Table 2. SR & M-A Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Tariq et al (2020)[38]	2006-2016	14	Patients with biopsy-confirmed dysplastic or neoplastic BE who underwent ≥1 session of cryotherapy	405 (20-81)	Retrospective, prospective observational	Range, 3-54 months

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Westerveld et al (2020)[39.]	2015-2019	7	Patients with BE treated with cryoablation	272 (5-120)	Retrospective, prospective observational	NR
Hamade et al (2019)[40.]	NR	6	Treatment-naive patients with BE treated with cryotherapy	282 (22-81)	Retrospective observational	Range, 24 to 65 months

BE: Barrett's esophagus; NR: not reported; M-A: meta-analysis; SR: systematic review.

Table 3. SR & M-A Results

Study	Complete eradication of dysplasia	Complete eradication of intestinal metaplasia
Tariq et al (2020)[38.]		
Total N	405	393
Pooled effect (95% CI)	84.8% (72.2-94.4)	64.2% (52.9-74.8)
I^2 (%)	88.3	77.9
Westerveld et al (2020)[39.]		
Total N	262	272
Pooled effect (95% CI)	93.8% (85.5-98.7)	85.8% (77.8-92.2%)
I^2 (%)	74.2	55
Hamade et al (2019)[40.]		
Total N	282	282
Pooled effect (95% CI)	90.6 (83.7-97.4)	69.35 (52.1-86.5)
I^2 (%)	75.7	89.3

CI: confidence interval; M-A: meta-analysis; SR: systematic review.

Prospective and Retrospective Studies

Several small prospective and retrospective uncontrolled studies of cryoablation studies have been published (Tables 4 and 5). These studies are heterogenous in the proportion of patients with prior BE treatment, cryoablation techniques used, and follow-up duration. Below is a summary of studies that were not included in the above-described systematic reviews and/or have notable characteristics (*i.e.,* focus on subpopulations, have long-term follow-up).

A retrospective, single-center study by Sengupta et al (2015) evaluated cryoablation among 16 patients who failed RFA.[41.] The cohort of 16 patients was derived from an original cohort of 121 patients who underwent RFA for BE with LGD, HGD, or intramucosal carcinoma. After a median of 3 treatments with RFA, 91 subjects had complete eradication of dysplasia. Of 21 patients offered cryotherapy, 16 underwent cryotherapy and had an adequate follow-up. Fourteen of those who did not have complete eradication and 2 who had a recurrence of dysplasia underwent salvage cryotherapy. Over a median follow-up of 2.5 months, and with a median of 3 cryotherapy treatments, 12 (75%) patients had complete eradication of dysplasia after cryotherapy, and 14 (88%) had some improvement in pathology after cryotherapy.

Shaheen et al (2010) reported on a multicenter, retrospective cohort study that assessed the safety and efficacy of spray cryotherapy in 98 consecutive patients who had BE with HGD.[42.] A total of 333 cryotherapy treatments (mean 3.4 per patient) were performed, all with the intent to eradicate all BE. Sixty patients completed all planned cryotherapy treatments and were assessed for efficacy at follow-up endoscopy sessions with 4-quadrant biopsies performed every 1 to 2 cm. Fifty-eight (97%) patients 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 3 patients. The authors noted several study limitations: it was nonrandomized and retrospective without a control group, it lacked centralized pathology, it used surrogate outcomes for decreased cancer risk, and it had a short follow-up (10.5 months).

An open-label, single-center, prospective, nonrandomized cohort study by Dumot et al (2009) assessed the safety of cryoablation as a treatment option for BE with HGD or intramucosal carcinoma.[43] Thirty patients who were either deemed high-risk surgical candidates or who refused esophagectomy underwent cryoablation. Twenty-seven (90%) patients had their pathology stage downgraded after treatment. After a median follow-up of 12 months, elimination of cancer or downgrading of HGD was 68% for HGD and 80% for intramucosal carcinoma. The authors noted the heterogeneous nature of the patient sample (high-risk, nonsurgical group of patients), which limited generalizability to patients in most BE ablation trials.

Table 4. Summary of Key Nonrandomized Studies

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
Sengupta et al (2015)[41]	Retrospective, observational	US	2006-2013	Patients who underwent RFA for BE with LGD, HGD, or intramucosal carcinoma	Cryoablation	Median, 2.5 months
Shaheen et al (2010)[42]	Retrospective, observational	US	2007-2009	Patients who had BE with HGD	Cryoablation	Mean, 10.5 months
Dumot et al (2009)[43]	Prospective, observational	US	2005-2008	Patients who had BE with HGD or intramucosal carcinoma	Cryoablation	Median, 12 months

BE: Barrett's esophagus; HGD: high-grade dysplasia; LGD: low-grade dysplasia; RFA: radiofrequency ablation.

Table 5. Summary of Key Nonrandomized Study Results

Study	Complete eradication of dysplasia	Complete eradication of intestinal metaplasia	Downgrading of pathology stage	Elimination of cancer or downgrading of HGD
Sengupta et al (2015)[41]	N=121			
Cryotherapy, n (%)	91 (75)	NR	NR	NR
Shaheen et al (2010)[42]	N=60	N=60		
Cryotherapy, n (%)	58 (97)	34 (57)	NR	NR
Dumot et al (2009)[43]			N=30	N=30
Cryotherapy, n (%)	NR	NR	27 (90)	Patients with HGD: 20 (68) Patients with intramucosal carcinoma: 24 (80)

HGD: high-grade dysplasia; NR: not reported.

Section Summary: Cryoablation of Barrett Esophagus
No controlled trials have evaluated cryoablation for the treatment of BE. The evidence from uncontrolled studies has reported high rates of success in eradicating dysplasia, with low rates of complications. These data are not sufficient to determine the comparative efficacy of cryoablation and RFA.

Summary of Evidence
For individuals who have BE with HGD who receive endoscopic RFA, the evidence includes a RCT comparing radical endoscopic resection with focal endoscopic resection followed by RFA, an RCT comparing RFA with surveillance alone, and a systematic review evaluating RCTs and a number of observational studies, some of which compared RFA with other endoscopic treatment modalities. Relevant outcomes are change in disease status, morbid events, and treatment-related morbidity and mortality. The available evidence has shown that using RFA to treat BE with HGD is at least as effective in eradicating HGD as other ablative techniques, with a lower progression rate to cancer, and may be considered an alternative to esophagectomy.

Evidence from at least 1 RCT has demonstrated higher rates of eradication than surveillance alone. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have BE with LGD who receive endoscopic RFA, the evidence includes at least 2 RCTs comparing RFA with surveillance alone, a number of observational studies, and systematic reviews of these studies. Relevant outcomes are change in disease status, morbid events, and treatment-related morbidity and mortality. For patients with confirmed LGD, evidence from an RCT has suggested that RFA reduces progression to HGD and adenocarcinoma. Challenges exist in differentiating between nondysplastic BE and BE with LGD; thus, a correct diagnosis has important implications for LGD treatment decisions. One of the available RCTs required that LGD be confirmed by an expert panel, which supports the use of having a gastrointestinal pathologist confirm LGD before treatment of BE with LGD can begin. The evidence is sufficient to determine that the technology results in an 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 are change in disease status, morbid events, and treatment-related morbidity and mortality. The available studies have suggested 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 that the technology results in an improvement in the net health outcome.

For individuals who have BE with or without dysplasia who receive endoscopic cryoablation, the evidence includes noncomparative studies and systematic reviews of those studies reporting outcomes after cryoablation. Relevant outcomes include change in disease status, morbid events, and treatment-related morbidity and mortality. These studies have generally demonstrated high rates of eradication of dysplasia. However, the available evidence does not compare cryoablation with surgical care or RFA. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2012 Input
In response to requests from Blue Cross Blue Shield Association, input was received from reviewers at 6 academic medical centers and from 1 subspecialty medical society in 2012. Input related to the treatment of low-grade dysplasia (LGD) was mixed, with 2 reviewers stating that radiofrequency ablation (RFA) for LGD should be investigational, 3 indicating that it should be medically necessary, and 2 indicating that it was a split decision. There was a general consensus among reviewers that there are subsets of patients with LGD who have a higher risk and should, therefore, be treated. Reviewers mentioned that factors useful in defining higher risk populations for whom treatment is warranted are the confirmation of LGD diagnosis by multiple pathologists and/or the application of clinical high-risk factors such as lesion length.

2009 Input
In response to requests from Blue Cross Blue Shield Association, input was received from 3 academic medical centers and 1 subspecialty medical society (with 12 reviewers) in 2009. All

reviewers agreed that RFA (cryoablation was not included in the request) should be considered medically necessary for the treatment of Barrett esophagus (BE) with high-grade dysplasia (HGD). Reviewers were split for the use of RFA for LGD, with 9 considering it medically necessary and 4 considering it investigational.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Gastroenterology

In 2016, the American College of Gastroenterology issued guidelines on the diagnosis and management of BE, which made statements about endoscopic therapies in general, as outlined in Table 6.[44]

Table 6. Guidelines on the Diagnosis and Management of Barrett Esophagus

Recommendation	SOR	LOE
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 understaging, 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; LOE: level of evidence; SOR: strength of recommendation.

American Society for Gastrointestinal Endoscopy

In 2018, the American Society for Gastrointestinal Endoscopy issued guidelines on the role of endoscopy in BE-associated dysplasia and intramucosal cancer.[1] These guidelines made the following recommendations on endoscopic eradication therapy, consisting of endoscopic mucosal resection of visible lesions and ablative techniques that include RFA and cryotherapy (see Table 7).

Table 7. Guidelines on Use of Endoscopy for Barrett Esophagus and Intramucosal Cancer

Recommendation	SOR	QOE[a]
In BE patients with LGD and HGD being considered for EET, we suggest confirmation of diagnosis by at least 1 expert GI pathologist or panel of pathologists compared with review by a single pathologist.	Conditional	Low
In BE patients with LGD, we suggest EET compared with surveillance; however, patients who place a high value on avoiding adverse events related to EET may choose surveillance as the preferred option.	Conditional	Moderate
In BE patients with confirmed HGD, we recommend EET compared with surveillance	Strong	Moderate
In BE patients with HGD/IMC, we recommend against surgery compared with EET	Strong	Very low quality
In BE patients referred for EET, we recommend endoscopic resection of all visible lesions compared with no endoscopic resection of visible lesions.	Strong	Moderate
In BE patients with visible lesions who undergo endoscopic resection, we suggest ablation of the remaining Barrett's segment compared with no ablation.	Conditional	Low
In BE patients with dysplasia and IMC referred for EET, we recommend against routine complete endoscopic resection of entire Barrett's segment compared with endoscopic resection of visible lesion followed by ablation of remaining Barrett's segment.	Strong	Very low
In BE patients with dysplasia and IMC who have achieved CE-IM after EET, we suggest surveillance endoscopy versus no surveillance.	Conditional	Very low

BE: Barrett esophagus; CE-IM: complete eradication of intestinal metaplasia; EET: endoscopic eradication therapy; HGD: high-grade dysplasia; LGD: low-grade dysplasia; IMC: intramucosal cancer; QOE: quality of evidence; SOR: strength of recommendation.
[a] Quality assessed using GRADE system.

American Gastroenterological Association

In 2020, the American Gastroenterological Association published a best practice clinical update on the role of endoscopic therapy in patients with BE with dysplasia and/or early cancer.[2] This best practice document was not based on a formal systematic review; thus, no ratings for strength of recommendation and quality of evidence were not provided.

For BE with LGD, best practice advice included the following:

- "The reading of LGD in BE should be confirmed by an experienced gastrointestinal pathologist."
- "In BE patients with confirmed LGD, a repeat examination within 3–6 months with HD-WLE [high-definition white-light endoscopy] and preferably optical chromoendoscopy should be performed to rule out the presence of a visible lesion, which should prompt endoscopic resection (see section on HGD)."
- "Both BET [Barrett's endoscopic therapy] and continued surveillance are reasonable options for the management of BE patients with confirmed and persistent LGD."

For BE with HGD, best practice advice included the following:

- "The reading of HGD in BE should be confirmed by an experienced gastrointestinal pathologist."
- "The diagnosis of flat HGD should prompt a repeat HD-WLE (6–8 weeks) to evaluate for the presence of a visible lesion; these visible lesions should be removed by EMR [endoscopic mucosal resection]."
- "BET is the preferred treatment, over esophagectomy, for BE patients with HGD."

Society of American Gastrointestinal and Endoscopic Surgeons

In 2010, the Society of American Gastrointestinal and Endoscopic Surgeons published guidelines on the surgical treatment of gastroesophageal reflux disease, which included recommendations for the treatment of BE (see Table 8).[45]

Table 8. Guidelines on Surgical Treatment of Gastroesophageal Reflux Disease

Recommendation	GOR
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 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; GOR: grade of recommendation; HGD: high-grade dysplasia; IM: intestinal metaplasia; IMC: intramucosal carcinoma; IND: indeterminate dysplasia; LGD: low-grade dysplasia; PDT: photodynamic therapy; RFA: radiofrequency ablation.

National Comprehensive Cancer Network

National Comprehensive Cancer Network Guidelines (v.4.2021) Esophageal and Esophago-gastric Cancers make recommendations about BE and early-stage esophageal adeno-carcinomas.[46,] For primary treatment; "The goal of endoscopic therapy [by 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 LVI] and Barrett esophagus."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 9.

Table 9. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02514525	Multi-center Clinical Study to Evaluate the C2 CryoBalloon Focal Ablation System for the Treatment of Patients With Previously Untreated Dysplastic Barrett's Epithelium	150	May 2022
NCT02793479	National Registry for Radiofrequency Ablation in Patients With Barrett's Esophagus	500	Dec 2021
NCT02514525	Multi-center Clinical Study to Evaluate the C2 CryoBalloon Focal Ablation System for the Treatment of Patients With Previously Untreated Dysplastic Barrett's Epithelium	150	May 2022
Unpublished			
NCT01961778	Prospective Randomized Trial Comparing Radiofrequency Ablation (Barrx™) and Cryotherapy (truFreeze™) for the Treatment of Barrett's Esophagus With High-Grade Dysplasia and/or Early Adenocarcinoma	50	Feb 2020 (Last update posted 2017)
NCT02558504	Clinical and Medico-economic Evaluation of Radiofrequency Ablation Versus Oesophagectomy in the Treatment of High-Grade Dysplasia in Barrett's Oesophagus	250	Nov 2018 (Last update posted 2015)

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes
- Pathology report(s), including documentation of high-grade or low-grade dysplasia (confirmed by two expert GI pathologists)

Post Service (in addition to the above, please include the following):

- Procedure report

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement

policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	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)
	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)
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
07/01/2011	BCBSA Medical Policy adoption
10/05/2012	Policy revision without position change
09/27/2013	Policy revision with position change
03/07/2014	Coding and Administrative Update
07/31/2015	Coding update
08/31/2015	Policy revision with position change
05/01/2016	Policy revision without position change
01/01/2017	Policy revision without position change
01/01/2018	Policy revision without position change
01/01/2019	Policy revision without position change
01/01/2019	Policy revision without position change
01/01/2020	Annual review. No change to policy statement. Literature review updated.
01/01/2021	Annual review. Policy statement, guidelines and literature updated.
01/01/2022	Annual review. Policy statement, guidelines and literature updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment,

procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE **Red font: Verbiage removed**	**AFTER**
Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus 2.01.80 **Policy Statement:** Radiofrequency ablation (RFA) may be considered **medically necessary** for the treatment of Barrett esophagus (BE) with **either** of the following: I. High-grade dysplasia (HGD) (see Policy Guidelines section) II. Low-grade dysplasia (LGD), when the initial diagnosis of low-grade dysplasia is confirmed by 2 pathologists (see Policy Guidelines section) Radiofrequency ablation is considered **investigational** for the treatment of Barrett esophagus when the above criteria are not met, including but not limited to Barrett esophagus in the absence of dysplasia. Cryoablation is considered **investigational** for the treatment of Barrett esophagus, with or without dysplasia.	**Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus 2.01.80** **Policy Statement:** Radiofrequency ablation (RFA) may be considered **medically necessary** for the treatment of Barrett esophagus (BE) with **either** of the following: I. High-grade dysplasia (HGD) II. Low-grade dysplasia (LGD), when the initial diagnosis of low-grade dysplasia is confirmed by 2 pathologists. Radiofrequency ablation is considered **investigational** for the treatment of Barrett esophagus when the above criteria are not met, including but not limited to Barrett esophagus in the absence of dysplasia. Cryoablation is considered **investigational** for the treatment of Barrett esophagus, with or without dysplasia.