

<b>2.01.80</b>		<b>Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus</b>	
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<b>Section:</b>	2.0 Medicine	<b>Page:</b>	Page 1 of 22

## Policy Statement

- I. Radiofrequency ablation (RFA) may be considered **medically necessary** for the treatment of Barrett esophagus (BE) with **either** of the following:
  - A. High-grade dysplasia ([HGD](#))
  - B. Low-grade dysplasia ([LGD](#)), when the initial diagnosis of low-grade dysplasia is confirmed by 2 pathologists.
- II. Radiofrequency ablation is considered **investigational** for the treatment of BE when the above criteria are not met, including but not limited to BE in the absence of dysplasia.
- III. Cryoablation is considered **investigational** for the treatment of BE, 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 (HGD) may be used in combination with endoscopic mucosal resection (EMR) of nodular or visible lesions. The diagnosis of HGD 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 HGD should be confirmed by an experienced gastrointestinal pathologist [Wani et. al., 2018, PMID 29397943; Sharma et. al. 2020, PMID 31730766]. Two cohort studies found that reevaluation of HGD after an initial evaluation resulted in 40% to 53% of individuals receiving a lower-grade evaluation on repeat endoscopy, highlighting the need for confirmation by an expert center [Sangle et. al., 2015, PMID 25676554; Verbeek et. al, 2014; PMID 24388501]. 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 EMR [Cameron et. al., 2014; PMID 24929493].

### 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 pathologists will downgrade a substantial portion of biopsies that are initially read as LGD by nonexperts (Curvers et al [2010], PMID 20461069; Kerkhof et al [2007], PMID 17543082). 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 [now Medtronic]) 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.<sup>15</sup> The FDA labeled indications are for use in coagulation of bleeding and nonbleeding sites in the gastrointestinal tract and include the treatment of BE. 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.

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."<sup>16</sup> 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.<sup>17</sup> The next-generation C2 CryoBalloon Ablation System was introduced in 2018.<sup>18</sup> 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."<sup>19</sup>

## Rationale

### Background

#### Barrett Esophagus and Risk of Esophageal Carcinoma

The esophagus is normally lined by squamous epithelium. Barrett Esophagus (BE) is a condition in which the normal squamous epithelium is replaced by specialized columnar-type epithelium, known as intestinal metaplasia, in response to irritation and injury caused by gastroesophageal reflux disease. 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 low grade dysplasia (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 to 20 years).<sup>1</sup> 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 11,000 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%.<sup>2</sup> 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.<sup>3,4</sup> 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 difficult. Initial diagnosis of BE can also be a challenge with respect to histologic grading because inflammation and LGD can share similar histologic characteristics.<sup>5</sup>

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.<sup>6</sup> 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.<sup>7</sup> Curvers et al (2010) tested this hypothesis in 147 patients with BE who were given an initial diagnosis of LGD.<sup>8</sup> 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 a randomized controlled trial by Phoa et al (2014), which required confirmation of LGD by a central expert panel following initial diagnosis by a local pathologist.<sup>9</sup> 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.<sup>10</sup> In this sample, 73% of subjects were downstaged.

### Management of Barrett Esophagus

The management of BE includes the treatment of gastroesophageal reflux disease and surveillance endoscopy to detect progression to 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, provides 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).<sup>11</sup> 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%.<sup>12</sup>

### 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.<sup>13</sup> (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%.<sup>14</sup> 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.<sup>12</sup>

### **Literature Review**

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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

### **Radiofrequency Ablation for Barrett Esophagus With High-Grade Dysplasia Clinical Context and Therapy Purpose**

In patients diagnosed with BE with high-grade dysplasia (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%.<sup>20</sup> Therefore, intervention with esophagectomy or RFA may be strongly indicated.

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

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

#### ***Populations***

The relevant population of interest is individuals 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.<sup>21</sup> 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)<sup>22</sup>; the other RCT was by Shaheen et al (2009, 2011; see below).<sup>23,24</sup> The studies were heterogeneous in design. A total of 1087 (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.<sup>25</sup> 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.<sup>22</sup> 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.<sup>23</sup> 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.<sup>24</sup> 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 subjects, and all intestinal metaplasia was eradicated in 51 (91%) of 56 subjects. 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 individuals who have BE with LGD is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

#### ***Populations***

The relevant population of interest is individuals 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

Wang et al (2022) performed a meta-analysis of 3 RCTs (N=282) comparing RFA with surveillance in patients with LGD.<sup>26</sup> Nearly 90% of the patients enrolled were male; other demographic information was not reported. The primary outcome was risk of progression to HGD or esophageal adenocarcinoma. Compared with endoscopic surveillance, RFA was associated with lower odds of progression to either HGD or esophageal adenocarcinoma (risk ratio [RR], 0.25; 95% CI, 0.07 to 0.93;  $p=.04$ ). The findings had moderate heterogeneity ( $I^2=55\%$ ), and the risk of bias was considered low. When analyzed separately, the risk of progression to HGD was significantly reduced with RFA (RR, 0.25; 95% CI, 0.07 to 0.71;  $p=.01$ ;  $I^2=15\%$ ); however, the results for progression to esophageal adenocarcinoma were not significant (RR, 0.56; 95% CI, 0.05 to 6.76;  $p=.65$ ).

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.<sup>27</sup> 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 adenocarcinoma (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 both RCTs and observational studies to determine the efficacy of RFA in treating BE with LGD compared with surveillance.<sup>28</sup> 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 LGD to HGD or cancer in the short term. Longer-term outcomes, however, warrant further research.

### 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. Combined rates of progression to HGD or esophageal adenocarcinoma are lower in patients with LGD treated with RFA compared with surveillance.

## Radiofrequency Ablation for Barrett Esophagus Without Dysplasia

### Clinical Context and Therapy Purpose

The purpose of endoscopic RFA in individuals who have BE without dysplasia is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

### *Populations*

The relevant population of interest is individuals 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%.<sup>1,2</sup>

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.<sup>29,30</sup> The original study included 70 patients who underwent circumferential RFA and CR-IM, defined as complete eradication of nondysplastic BE.<sup>29</sup> 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.<sup>29</sup> 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.<sup>30</sup> 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 individuals who have BE is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

#### ***Populations***

The relevant population of interest is individuals 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.<sup>31</sup> 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.<sup>32</sup> 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-naïve.<sup>33</sup> 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 Systematic Reviews and Meta-Analyses**

Study	Tariq et al (2020) <sup>31</sup>	Westerveld et al (2020) <sup>32</sup>	Hamade et al (2019) <sup>33</sup>
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)	●		

**Table 2. Systematic Review and Meta-Analysis Characteristics**

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Tariq et al (2020) <sup>31</sup>	2006-2016	14	Patients with biopsy-confirmed dysplastic or neoplastic BE who underwent $\geq 1$ session of cryotherapy	405 (20 to 81)	Retrospective, prospective observational	Range, 3 to 54 months

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Westerveld et al (2020) <sup>32</sup>	2015-2019	7	Patients with BE treated with cryoablation	272 (5 to 120)	Retrospective, prospective observational	NR
Hamade et al (2019) <sup>33</sup>	NR	6	Treatment-naive patients with BE treated with cryotherapy	282 (22 to 81)	Retrospective observational	Range, 24 to 65 months

BE: Barrett's esophagus; NR: not reported.

**Table 3. Systematic Review and Meta-Analysis Results**

Study	Complete eradication of dysplasia	Complete eradication of intestinal metaplasia
<b>Tariq et al (2020)<sup>31</sup></b>		
Total N	405	393
Pooled effect (95% CI)	84.8% (72.2 to 94.4)	64.2% (52.9 to 74.8)
<i>P</i> (%)	88.3	77.9
<b>Westerveld et al (2020)<sup>32</sup></b>		
Total N	262	272
Pooled effect (95% CI)	93.8% (85.5 to 98.7)	85.8% (77.8 to 92.2)
<i>P</i> (%)	74.2	55
<b>Hamade et al (2019)<sup>33</sup></b>		
Total N	282	282
Pooled effect (95% CI)	90.6% (83.7 to 97.4)	69.35% (52.1 to 86.5)
<i>P</i> (%)	75.7	89.3

CI: confidence interval.

### Prospective and Retrospective Studies

Several small prospective and retrospective uncontrolled studies of cryoablation 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.<sup>34</sup> 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.<sup>35</sup> A total of 333 cryotherapy treatments (mean, 3.4 per patient) were performed, each 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: the study was nonrandomized and retrospective without a control group, lacked centralized pathology, used surrogate outcomes for decreased cancer risk, and 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.<sup>36</sup> 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.

Two retrospective cohort studies compared RFA and cryotherapy in patients with BE undergoing endoscopic eradication therapy. Fasullo et al (2022) compared 100 RFA-treated patients with 62 cryotherapy-treated patients.<sup>37</sup> The majority of patients included in the study were white males, and cryotherapy was performed with liquid nitrogen spray. The rate of complete eradication of dysplasia was similar between groups (81% with RFA vs. 71% with cryotherapy;  $p=.14$ ), and complete eradication of intestinal metaplasia was also similar between groups (64% with RFA and 66% with cryotherapy;  $p=.78$ ). However, more sessions were required for complete eradication with cryotherapy, and treatment failure was also more common with cryotherapy (73.3% vs. 53.3%). Agarwal et al (2022) evaluated a cohort of 311 patients with BE undergoing endoscopic eradication therapy with either cryoballoon ablation (CBA) or RFA.<sup>38</sup> For the primary outcome of complete eradication of intestinal metaplasia, CBA versus RFA had similar outcomes (hazard ratio [HR], 1.19; 95% CI, 0.82 to 1.73;  $p=.36$ ). Patients treated with CBA had more strictures (10.4%) compared with RFA (4.4%;  $p=.04$ ).

**Table 4. Summary of Key Nonrandomized Studies**

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
Agarwal et al (2022) <sup>38</sup>	Retrospective, observational	US	2014-2020	Patients who underwent RFA or cryotherapy for dysplastic BE	Cryoablation or RFA	Median, 1.5 years in RFA group and 2 years in the cryoablation group
Fasullo et al (2022) <sup>37</sup>	Retrospective, observational	US	2009-2020	Patients who underwent RFA or cryotherapy for BE with LGD, HGD, or intramucosal adenocarcinoma	Cryoablation or RFA	>12 months
Sengupta et al (2015) <sup>34</sup>	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) <sup>35</sup>	Retrospective, observational	US	2007-2009	Patients who had BE with HGD	Cryoablation	Mean, 10.5 months
Dumot et al (2009) <sup>36</sup>	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
Agarwal et al (2022) <sup>38</sup>	N=311; n=226 RFA and 85 cryoablation			
Cryotherapy, %	85.7	69.8	NR	NR

Study	Complete eradication of dysplasia	Complete eradication of intestinal metaplasia	Downgrading of pathology stage	Elimination of cancer or downgrading of HGD
RFA, %	78.3	57.3	NR	NR
Fasullo et al (2022) <sup>37</sup> .	N=162; n=100 RFA and 62 cryoablation			
Cryotherapy, n %	44 (71)	41 (66.1)	NR	NR
RFA, n %	81 (81)	64 (64)	NR	NR
Sengupta et al (2015) <sup>34</sup> .	N=121			
Cryotherapy, n (%)	91 (75)	NR	NR	NR
Shaheen et al (2010) <sup>35</sup> .	N=60			
Cryotherapy, n (%)	58 (97)	34 (57)	NR	NR
Dumot et al (2009) <sup>36</sup> .	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; RFA: radiofrequency ablation.

### 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. In observational studies comparing RFA with cryoablation for patients with BE, similar outcomes have been noted; however, RCTs are lacking. These data are not sufficient to determine the comparative efficacy of cryoablation and RFA.

### 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, input was received from reviewers at 6 academic medical centers and from 1 subspecialty medical society while this policy was under review 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, input was received from 3 academic medical centers and 1 subspecialty medical society (with 12 reviewers) while this policy was under review 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 2022, the American College of Gastroenterology (ACG) updated guidelines on the diagnosis and management of BE, which made statements about ablation techniques<sup>39</sup>. The ACG recommends ablation of remaining BE tissue when endoscopic eradication therapy is chosen for patients with LGD, HGD, or intramucosal carcinoma. Both RFA and cryoablation are discussed in the ACG guideline without a specific recommendation; however, the guideline notes the lack of randomized controlled trials (RCTs) for cryoablation methods and the more established evidence for RFA. The ACG does recommend cryotherapy as an alternative in patients unresponsive to RFA.

#### 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.<sup>40</sup> This best practice document was not based on a formal systematic review; thus, no ratings for strength of recommendation and quality of evidence were 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."

#### 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.<sup>41</sup> 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 6).

**Table 6. Guidelines on Use of Endoscopy for Barrett Esophagus and Intramucosal Cancer**

Recommendation	SOR	QOE <sup>a</sup>
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

Recommendation	SOR	QOE <sup>a</sup>
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; GI: gastrointestinal; HGD: high-grade dysplasia; IMC: intramucosal cancer; LGD: low-grade dysplasia; QOE: quality of evidence; SOR: strength of recommendation.

<sup>a</sup>Quality assessed using GRADE system.

### National Comprehensive Cancer Network

National Comprehensive Cancer Network Guidelines (v.3.2023) Esophageal and Esophagogastric Cancers make recommendations about BE and early-stage esophageal adenocarcinomas.<sup>42</sup> 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 pre-neoplastic tissue (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 7.

**Table 7. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT02514525 <sup>a</sup>	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	Jun 2023
<i>Unpublished</i>			
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 Jan 2022)
NCT02558504	Clinical and Medico-economic Evaluation of Radiofrequency Ablation Versus Oesophagectomy in the Treatment of High-Grade Dysplasia in Barrett's Oesophagus	87	Jan 2021 (Last update posted Apr 2022)

NCT: national clinical trial.

<sup>a</sup>Denotes industry sponsored or co-sponsored trial.

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41. Wani S, Qumsey B, Sultan S, et al. Endoscopic eradication therapy for patients with Barrett's esophagus-associated dysplasia and intramucosal cancer. *Gastrointest Endosc.* Apr 2018; 87(4): 907-931.e9. PMID 29397943
42. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers. Version 3.2023. [https://www.nccn.org/professionals/physician\\_gls/PDF/esophageal.pdf](https://www.nccn.org/professionals/physician_gls/PDF/esophageal.pdf). Accessed September 14, 2023.

### 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)
- Treatment plan including treatment modality (radiofrequency or cryoablation, etc.)

**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)

Type	Code	Description
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.
01/01/2023	Annual review. No change to policy statement. Policy guidelines and literature updated
01/01/2024	Annual review. No change to policy statement. Literature review 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 and Feedback (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](http://www.blueshieldca.com/provider).

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: [MedPolicy@blueshieldca.com](mailto:MedPolicy@blueshieldca.com)

*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 (No changes)	
BEFORE	AFTER
<p><b>Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus 2.01.80</b></p> <p><b>Policy Statement:</b></p> <ul style="list-style-type: none"> <li>I. Radiofrequency ablation (RFA) may be considered <b>medically necessary</b> for the treatment of Barrett esophagus (BE) with <b>either</b> of the following:                             <ul style="list-style-type: none"> <li>A. High-grade dysplasia (<a href="#">HGD</a>)</li> <li>B. Low-grade dysplasia (<a href="#">LGD</a>), when the initial diagnosis of low-grade dysplasia is confirmed by 2 pathologists.</li> </ul> </li> <li>II. Radiofrequency ablation is considered <b>investigational</b> for the treatment of BE when the above criteria are not met, including but not limited to BE in the absence of dysplasia.</li> <li>III. Cryoablation is considered <b>investigational</b> for the treatment of BE, with or without dysplasia.</li> </ul>	<p><b>Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus 2.01.80</b></p> <p><b>Policy Statement:</b></p> <ul style="list-style-type: none"> <li>I. Radiofrequency ablation (RFA) may be considered <b>medically necessary</b> for the treatment of Barrett esophagus (BE) with <b>either</b> of the following:                             <ul style="list-style-type: none"> <li>A. High-grade dysplasia (<a href="#">HGD</a>)</li> <li>B. Low-grade dysplasia (<a href="#">LGD</a>), when the initial diagnosis of low-grade dysplasia is confirmed by 2 pathologists.</li> </ul> </li> <li>II. Radiofrequency ablation is considered <b>investigational</b> for the treatment of BE when the above criteria are not met, including but not limited to BE in the absence of dysplasia.</li> <li>III. Cryoablation is considered <b>investigational</b> for the treatment of BE, with or without dysplasia.</li> </ul>